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REVIEW

Myeloid cells: key players in tumor microenvironments

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Abstract **Cancer is the result of evolving crosstalk between neoplastic cell and its immune microenvironment. In recent years, immune therapeutics targeting T lymphocytes, such as immune checkpoint blockade (ICB) and CAR-T, have made significant progress in cancer treatment and validated targeting immune cells as a promising approach to fight human cancers. However, responsiveness to the current immune therapeutic agents is limited to only a small proportion of solid cancer patients. As major components of most solid tumors, myeloid cells played critical roles in regulating the initiation and sustentation of adaptive immunity, thus determining tumor progression as well as therapeutic responses. In this review, we discuss emerging data on the diverse functions of myeloid cells in tumor progression through their direct effects or interactions with other immune cells. We explain how different metabolic reprogramming impacts the characteristics and functions of tumor myeloid cells, and discuss recent progress in revealing different mechanisms—chemotaxis, proliferation, survival, and alternative sources—involved in the infiltration and accumulation of myeloid cells within tumors. Further understanding of the function and regulation of myeloid cells is important for the development of novel strategies for therapeutic exploitation in cancer.**

Keywords myeloid cells; ICB treatment; immune therapy; tumor microenvironments

Introduction

Cancer results from the evolving crosstalk between neoplastic cell and its immune microenvironment, of which T lymphocytes have been regarded as key players [1,2]. Accordingly, immune therapeutics targeting T lymphocytes, such as immune checkpoint blockade (ICB) and CAR-T, have made significant progress in cancer treatment. However, responsiveness to the current immune therapeutic agents is limited to only a small proportion of solid cancer patients. One of the major reasons for that lies in the lack of consideration of immune system as a complex interactive network which comprises both T lymphocytes and large amounts of myeloid cells [3–5]. As major components of most solid tumors, myeloid cells played critical roles in regulating the initiation and sustentation of adaptive immunity, tumor angiogenesis, matrix remodeling, as well as cancer cell biology, thus determining tumor progression as well as therapeutic responses [6–10]. A renewed focus on myeloid cells in cancer research has yielded significant new insight into the critical roles of these cells in cancer therapies.

Myeloid cells belong to the innate arm of immune system. They harbor a broad specificity toward pathogens and constitute the "first-line" defense against infections [11]. As a heterogeneous group of populations, myeloid cells consist of monocytes, macrophages, granulocytes (which include neutrophils, basophils, eosinophils and mast cells), dendritic cells (DCs), and myeloid-derived suppressor cells (MDSCs, which are further categorized into monocytic MDSCs or granulocytic/polymorphonuclear (PMN) MDSCs in both mouse and human) [12–16]. Many markers have been applied to distinguish different myeloid cell subsets. For example, combinations of CD11c, CD14, CD68, Fcγ RIII/CD16, Fc gamma RI/CD64, and CCR5 are regarded as DC markers, and cell surface markers used to identify human and mouse macrophages include CD11b/Integrin alpha M, CD14, CD68, Fcγ RIII/CD16, Fc gamma RI/CD64, and CCR5, along with F4/80 in mouse [17,18]. While

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$CD11b^+Gr1^+Ly\text{-}6C^-Ly\text{-}6G^+$ and $CD11b^+Gr1^+Ly\text{-}6C^+Ly\text{-}6G^{-/low}$ could be generally used to distinguish mouse PMN MDSCs and monocytic MDSCs, markers for human MDSCs vary across different tumor types. $CD11b^+CD14^-CD15^+/CD66b^+$ and $CD14^+CD15^-HLA\text{-}DR^{-/low}$ could be used to identify human PMN MDSCs and monocytic MDSCs, and lectin-type oxidized low-density lipoprotein receptor 1 has emerged as a specific human PMN MDSCs marker [9,19]. Of note, some researches proposed that the most viable standard to define MDSCs is their ability to inhibit immune responses [9,20,21].

Recent years have seen large amounts of publications revealing roles of myeloid cells in tumor microenvironments (TME). This review will briefly discuss the diverse functions of myeloid cells in tumor progression through their direct effects or interactions with other immune cells, and then explore how different metabolic pathways shift and impact the characteristics of tumor myeloid cells. We also discuss how different mechanisms—chemotaxis, proliferation, survival, and alternative origins—contribute to the infiltration and accumulation of myeloid cells within tumors. For simplicity and clarity, we mainly focus on monocytes/macrophages and MDSCs. Other myeloid cells such as granulocytes and DCs have been reviewed elsewhere and have not been discussed in this review.

Functions of TAM and MDSC in tumor microenvironments

A majority of tumor-associated macrophages (TAMs) originate from bone marrow (BM)-derived monocytic precursors, but tissue-resident macrophages originate from embryonic precursors that seed organs in embryonic life also contribute to sustaining macrophage levels within tumors [12]. In contrast, it has been proposed that pathological activation arising from persistent stimulation of the myeloid cell compartment owing to the prolonged presence of myeloid growth factors and inflammatory signals in the settings of cancer, chronic infections or inflammation, gives rise to MDSCs [9]. While monocytes/macrophages are double-edged swords with dual potential in cancer, MDSCs were generally regarded as pro-tumor populations [9,12,22,23].

Direct effects on tumor cells

Macrophages can directly impact different characteristics of cancer cells. For instance, high densities of $CD68^+$ cells had been associated with improved survival in colon, gastric and endometrial cancer [7,24]. Macrophages could directly kill cancer cells through the release of nitric oxide, reactive oxygen species (ROS), and tumor necrosis factor (TNF). When appropriately activated, macrophages could mediate phagocytosis of cancer cells and cytotoxic tumor killing [12,25]. Recent studies found that Kupffer cell lineage-determining factor ID3 endowed Kupffer cells, but not monocyte-derived TAMs, with the ability to phagocytose live cancer cells and orchestrate the recruitment, proliferation and activation of immune effector cells in the liver to restrict the tumor growth [26,27]. Interestingly, whole beta-glucan particle could lead to a trained immunity phenotype in lung interstitial macrophages, resulting in inhibition of tumor metastasis and survival prolongation in multiple mouse models of metastasis [28].

However, within many tumors, macrophages often exhibited pro-tumor functions and their infiltration had been a negative prognostic factor [7,29]. Cytokines and growth factors, such as IL-6, TNF, EGF, creatine released by TAMs supported the survival and proliferation of cancer cells [7,30,31]. TAMs also produced large amounts of proteases such as matrix metalloproteinases (MMPs) or cathepsins that degraded collagen fibers, and cross-linking enzymes that modulated the stiffness of the extracellular matrix [7,30,32]. TAMs-derived TGF-β, CCL18, and Cathepsin B facilitate the epithelial-to-mesenchymal transition (EMT) of cancer cells to promote metastasis [7,30,33]. In hepatocellular carcinoma (HCC), we previously found that tumor necrosis factor alpha (TNF-α) and IL-1β derived from tumor-activated monocytes synergistically induced cancer cell autophagy in the invading edges, which facilitated the EMT of cancer cells and promoted tumor metastasis [34]. Moreover, TAMs played important roles in promoting tumor angiogenesis through vascular endothelial growth factor (VEGF), IL-8, and SEMA4D. It has been reported that TAMs expressing the angiopoietin receptor Tie2 accumulated at the perivascular areas, where they supported angiogenesis and tumor growth [7,23,30,35]. Monocytes/macrophages were also involved in the process of pre-metastatic niche formation. Once activated by tumor-derived cues, tissue resident macrophages helped establish a pro-tumoral environment by enhancing cancer cell extravasation, transmitting survival signals to support cancer cell survival, promoting inflammation, suppressing anti-tumor immune responses, or inducing endothelial cell-mediated production of niche components, thus creating a favorable environment for disseminating cancer cells. Premetastatic niches continually recruited monocytes to replenish local macrophages, facilitating a positive pro-metastatic feedback loop [30,36–39]. Similar effects on cancer cell transformation and the establishment of premetastatic niche could also be observed in MDSCs. MDSCs could stimulate cancer cell stemness and EMT via production of IL-6 and TGFβ as well as cancer cell invasion and dissemination via secretion of MMPs [40]. Furthermore, MDSCs could promote metastasis by enhancing the

engraftment by circulating tumor cells, escorting tumor cells into the circulation, promoting their metastatic potential, inhibiting their killing by immune cells, and promoting their extravasation into the tissues [9,20,40].

It should be noted that the different functions exhibited by TAMs can be attributed to distinct macrophage subsets with different origins, or the same population changing its phenotypes according to different environmental cues or from different developmental stages. Progress in single cell analysis technique in recent years has provided more sensitive characterization of TAM phenotypes and functions across various cancer types, but protein level analysis is warranted for the validation and proper interpretation of scRNA-seq data [41,42].

Modulation of tumor microenvironments

In addition to direct interactions with tumor cells, myeloid cells can also orchestrate multiple immune cells, especially effector T cells, within the TME to influence tumor progression [38,43]. The immune modulation by tumor-associated myeloid cells is supported by a diverse array of molecular mechanisms. These mechanisms span from the depletion of critical nutrients within the tumor microenvironment, providing cytokine signals, to cell-to-cell interaction. Here, we described the multifaceted roles of myeloid cells in promoting or inhibiting tumor progression through their interactions with TME components.

It is well-established that TAMs and MDSCs can produce high levels of immunoregulatory enzymes that deplete essential nutrients for T cells [44]. Arginase 1 (Arg1) served as a marker of alternatively activated macrophages [45] and exhibited high expression levels in MDSCs [46]. It catalyzed the conversion of L-arginine into urea and L-ornithine. By depleting L-arginine, myeloid cells suppressed CD3ε re-expression and inhibited antigen-specific T cell proliferation, fostering an immunosuppressive TME [47]. Similarly, TAMs and MDSCs utilized indoleamine 2,3-dioxygenase (IDO) to deplete L-tryptophan [48]. Moreover, the resultant L-kynurenine inhibited the proliferation and function of T and NK cells [49–51], and supported the expansion of Treg cells [52]. In addition to depriving lymphocytes of essential nutrients, myeloid cells also suppressed anti-tumor immune responses by inducing an oxidative stress milieu through the expression of inducible nitric oxide synthase (iNOS) and the production of ROS [53–55]. iNOS-mediated nitric oxide production led to peroxynitrite formation, which disrupted the interaction between the T cell receptor (TCR) and the major histocompatibility complex (MHC) by nitrating tyrosine residues in the TCR-CD8 complex [56]. Consequently, this nitration impeded antigen recognition and hindered effective immune activation. Synergizing with iNOS, ROS contributed to the suppression of T cell responses [56]. ROS could downregulate CD3ζ expression in T cells [57], impairing T cell activation and cytokine production [58], thereby promoting tumor immune evasion [59,60]. Moreover, both TAMs and MDSCs could convert extracellular adenosine triphosphate (ATP) to adenosine via the ectonucleotidases CD39 and CD73, leading to an immunosuppressive milieu [61,62].

Myeloid cells shaped adaptive immune responses not only by altering the metabolic microenvironment but also by delivering immunosuppressive cytokine signals. IL-10, an important immunomodulatory cytokine, was notably produced by TAMs and MDSCs [63–65]. In addition to its inhibitory effects on antigen-presenting cells and $CD4^+$ T cells [63,66,67], IL-10 directly modulated $CD8^+$ T cells by increasing N-glycan branching on their surface glycoproteins, resulting in reduced antigen sensitivity [68]. Moreover, TAMs and MDSCs released TGF-β, which suppressed the cytotoxic activity of T cells and NK cells, and induced Treg generation [69–73]. $TREM2^+$ monocyte-derived macrophages impaired NK cell function and recruitment by secreting IL-18BP to intercept IL-18 and the infiltration of TAMs was associated with a decreased number and dysfunction of NK cells in various human cancers [70,74,75].

Additionally, tumor-associated myeloid cells could suppress anti-tumor function of lymphocytes through direct cell-to-cell contact. By expressing immune checkpoint ligands including B7-H4, programmed cell death ligand 1 (PD-L1), and PD-L2, TAMs interacted with the related receptors on T cells and suppressed adaptive immune responses [40,76]. Within the tumor tissue, TAMs regulated $CD8^+$ T cell exhaustion by forming antigen-specific and long-lasting synapses, especially within the tumor hypoxia region [77]. In addition to promoting T cell exhaustion, recently identified $Tim\text{-}4^+$ macrophages could selectively sequester viable and cytotoxic T cells by interacting with phosphatidylserine, thereby preventing their infiltration into the tumor to exert anti-tumoral effects [78].

In addition to T cells and NK cells, research on human ovarian cancer has highlighted that within TME, large stromal leukocyte aggregates featured a dynamic intermingling of T cells, tumor-infiltrating B cells, and macrophages [79]. There was a reciprocal regulatory relationship between tumor-infiltrating myeloid cells and B cells during tumor progression and immunotherapy [80–83]. In HCC and colorectal cancer liver metastasis, TAMs selectively recruited IgG^+ plasma cells, which in turn, fostered the polarization of protumorigenic macrophages within the HCC [81]. Moreover, distinct myeloid cell subsets could be colocalized within specific tumor regions to amplify immunosuppression and accelerate tumor progression [84,85]. Depending on cell contact, tumor-induced MDSCs could reduce the IL-12

production by macrophages, while simultaneously increasing their own secretion of anti-inflammatory cytokine IL-10 [86,87]. The interactions between MDSCs and macrophages could also lead to decreased MHC II expression in macrophages, potentially regulated by IL-10 through the induced expression of MARCH1 [88]. Interestingly, under the condition of tumor hypoxia, M-MDSCs could differentiate into TAMs with a more immunosuppressive phenotype [89,90]. These mutual interactions could be further enhanced by the chemotaxis among myeloid subsets [84].

Although current research on TAMs predominantly highlights their protumorigenic roles, emerging studies have identified that in certain tumor types and tissue regions, TAMs may also fulfill protective roles for the host. In human HCC tissues, $CD169^+$ macrophage was a potential anti-tumor subset with high expression levels of HLA-DR and CD86 [91]. Moreover, in primary breast tumors, a distinct population of human tissue-resident $FOLR2^+$ macrophages has recently been identified to exhibit anti-tumor properties [92]. $PD\text{-}L1^+$ macrophages were predominantly recognized for their role in dampening immune responses within TME. Nonetheless, in human HCC and breast cancer tumors, PD-L1 expression on macrophages was correlated with an active immune microenvironment and better prognosis [93,94]. These $PD\text{-}L1^+$ macrophages in breast cancer tumor tissue exhibit closer spatial contact with $CD8^+$ T cells compared to $PD\text{-}L1^-$ macrophages and were able to enhance T cell proliferation and cytotoxic activity [94]. That could reflect the nature of macrophages that activated cells also highly express inhibitory molecules, e.g. PD-L1 [59,60]. Therefore, even among myeloid cells with the same phenotype, their functions could vary dramatically in different tissue types and TME, influenced by local environmental signals and neighboring cells, including the expression pattern of receptors on target cells that transduce either pro- or anti-tumor functions of macrophages. Integrating high-throughput *in situ* detection and analysis techniques is warranted to enhance our understanding of the true roles of myeloid cells within the tumor milieu.

The metabolic rewiring of TAM and MDSC

Immunometabolism describes the changes in intracellular metabolic pathways in immune cells during their growth, differentiation, and function [95]. Solid tumors are fast-growing and metabolically demanding tissues, and this largely influences the features in the TME, including altered nutrient availability, hypoxia and immunosuppressive metabolite production. These changes could induce immune cell metabolic rewiring, then affect their survival and function, and eventually regulate tumor progression. In light of recent progress in the field, we discuss the metabolic landscape of TAMs and MDSCs, including the immunoregulatory roles of glucose, fatty acids, and amino acids. A binary metabolic schema is currently used to characterize macrophages immunological phenotypes: glycolysis promotes the activation of classic M1 macrophage, which generates ROS and other inflammatory factors, whereas oxidative phosphorylation (OXPHOS) stimulates alternative M2 macrophage to support tissue repair and immunosuppression. However, this classification likely underestimates the variety of states *in vivo*. Understanding these nuances will be significant when developing interventional metabolic strategies.

Glucose metabolism

Glucose was usually metabolized through glycolysis, the Krebs or tricarboxylic acid (TCA) cycle and the pentose phosphate pathway (PPP). Glucose metabolism led to the accumulation of metabolites such as lactate and succinate that could regulate epigenetic remodeling and signaling transduction [96]. Therefore, glucose metabolism in tumor associated myeloid cells coordinated an intrinsic immune-metabolism crosstalk via integrating gene-, protein-, and metabolite-based regulatory mechanisms, consequently determining the function of TAMs and MDSCs [96] (Fig. 1).

Glucose uptake (GLUT1)

In TME, myeloid cells had the greatest capacity to uptake glucose and maintained a higher glycolysis rate than tumor-infiltrating T cells and cancer cells [97]. M2-like TAMs were recently shown to be the subset of immune cells with the strongest glucose uptake capacity [33], suggesting that nutrient acquisition and metabolism preferences between macrophages and tumor cells were complex. Macrophages sensed the glucose concentration and took glucose into the cytoplasm through glucose transporter protein 1 (GLUT1) and specific deletion of GLUT1 in macrophages dramatically decreased glycolysis and tumor burden [98]. However, in the murine mammary tumor model, a subset of MDSCs suppressed antitumor immunity by overexpressing GLUT3 [99]. GLUT3 knockdown significantly triggered apoptosis and reduced glucose uptake in these cells [99].

Glycolysis

With the glucose uptake capacity increased, the levels of glycolysis in TAMs were further enhanced [100]. Inhibiting glycolysis in TAMs with a competitive inhibitor to hexokinase-2, 2-deoxyglucose, was sufficient to disrupt their pro-metastatic phenotype. Tumor-derived soluble factors, including hyaluronan fragments, could

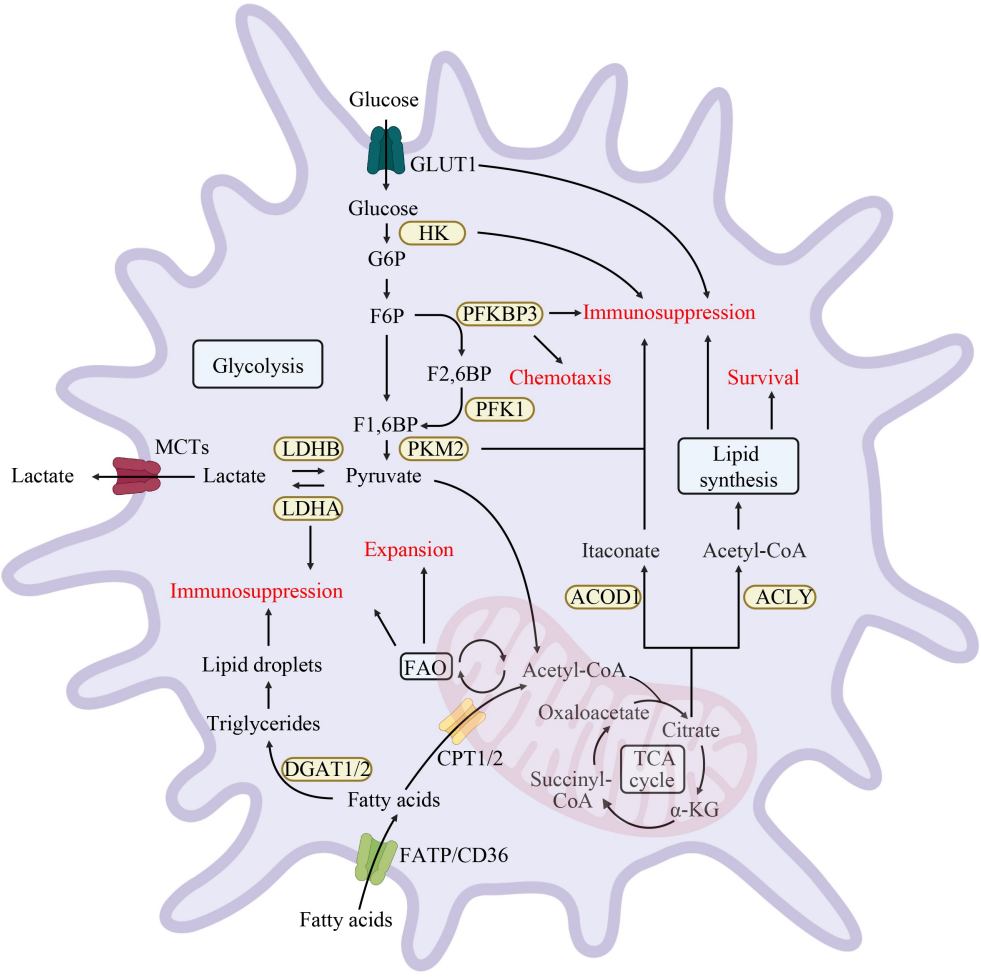

Fig. 1 The glucose and lipid metabolic landscape of tumor-associated myeloid cells. The diagram depicts the different metabolic pathways in myeloid cells, especially, glycolysis, lipid accumulation and oxidation are frequently upregulated in tumor associated myeloid cells, coordinated with their infiltration and protumor function (highlighted in red). G6P, glucose-6-phosphate; F6P, fructose-6-phosphate; F1,6BP, fructose-1,6-bisphosphate; F2,6BP, fructose-2,6-bisphosphate. This figure was created using BioRender.com.

significantly enhance glycolysis by upregulating a key glycolytic enzyme, PFKFB3, in TAMs. This enzyme modulated the cellular metabolic switch and mediated the increased expression of PD-L1 on macrophages, subsequently attenuating anti-tumoral responses. Consistently, the levels of PFKFB3^{+} TAMs infiltration were negatively correlated with overall survival in patients with HCC [101]. The activation of glycolysis also led to the production of large amounts of CXCL2 and CXCL8, which effectively recruited peripheral neutrophils and sustained their survival, subsequently facilitating disease progression in human HCC [84]. PFKFB3 overexpression in TAMs was indicative of a higher risk of tumor relapse in patients with colon cancer [102]. As the enzyme that regulates the final rate-limiting step of glycolysis, pyruvate kinase M2 exerted control over TAM expression of PD-L1 in pancreatic cancer, while also supporting tumor cell growth, exemplifying the dual benefit of glycolytic perturbation [103]. Thus, M2-like TAMs could be highly glycolytic and utilize glucose to support their maintenance and suppressive activity. However, the macrophage anti-tumor response also depended on glycolysis, at least in some circumstances. Wenes *et al.* reported that enhanced glycolysis in hypoxic TAMs could reduce endothelial glucose availability and promote the formation of an organized tumor vasculature, which helped to restore oxygenation and prevented metastasis in subcutaneous lung cancer and orthotopic mammary tumor mouse models [104]. There was no coincidence that chloroquine reprogrammed macrophage metabolism toward glycolysis and induced TAMs proinflammatory polarization to ameliorate TME in mice bearing subcutaneous melanoma or hepatocarcinoma ascites [105].

MDSCs also had high glucose and glutamine uptake rates, a reduced oxygen consumption rate and most of the ATP generated was obtained through a glycolysis-dependent mechanism. A high glycolytic flux was needed

for the maturation and survival of MDSCs and suggested an indirect mechanism by which the consumption of carbon sources by MDSCs results in the suppression of effector T cells [9]. Although MDSCs were also shown to use OXPHOS, under hypoxic conditions, the activation of hypoxia-inducible factor 1α (HIF-1α) induced the switch from OXPHOS to glycolysis in MDSCs [9]. As a critical regulator of MDSCs in the TME, HIF-1α could not only facilitate the differentiation of MDSCs [90]; but also enhance immunosuppressive function of MDSCs via glycolysis [106]. Deleting HIF-1α in MDSCs reactivated antitumor T cell responses and effectively impaired tumor radioresistance [107]. However, MDSCs isolated from tumor tissue of patients with HCC had a dormant metabolic phenotype and failed to utilize glucose [108]. This peculiar metabolic phenotype was mediated by the accumulation of methylglyoxal in MDSCs and MDSCs suppressed T cell activation by transferring methylglyoxal to T cells [108]. Whether these findings could be recapitulated in other conditions remains to be determined.

Lactate

Lactic acid production from the end product of glycolysis, pyruvate, by the enzyme lactate dehydrogenase A was associated with immune suppressive TME in certain tumors. Lactate could promote HIF-1α stabilization and M2 polarization in the absence of IL-4. In addition, exposure of mouse BM-derived macrophages to an acidic pH (6.8) *in vitro* increased the expression of anti-inflammatory genes [109]. Consistently, depletion of lactate dehydrogenase A in myeloid cells skewed M1-like polarization of macrophages with reduced pro-angiogenic VEGF expression and triggered antitumor properties. Conversely, LDHB could transform lactate to pyruvate and its expression was downregulated in TAMs. LDHB downregulation increased aerobic glycolysis and lactogenesis in TAMs and subsequent tumor growth [110].

Lactate was transported across the plasma membrane by proton-linked monocarboxylate transporters (MCTs) such as MCT1 (mainly lactate import) and MCT4 (mainly lactate export) [111]. High levels of circulating lactate caused expansion of MDSCs and such effect was significantly reduced by inhibition of MCT1 [112]. Lactate transporter MCT2 transcription downregulation led to reduced intracellular lactate levels, blunted MDSCs differentiation, and enhanced TAMs maturation [113]. Besides, lactate-enhanced tumor-promoting activity of MDSCs contributed to the radioresistance of pancreatic cancer [107]. Therefore, lactic acid could foster an immunosuppressive environment by modulating the differentiation and function of myeloid cells.

Lactate also served as a key bridge linking glucose metabolism and epigenetics in TAMs. Lactate derived lactylation of histone lysine residues in macrophages could directly stimulate gene transcription [114]. For example, histone lactylation in M1 macrophages induced expressions of homeostatic genes, including VEGF and Arg1, and promoted M1 to M2 macrophage transition [114]. Tumor-derived factors induced high glycolysis and lactate production in TAMs, and intracellular lactate-driven histone lactylation promoted IL-10 expression [100]. Another study showed that tumor derived lactate mediated H3K18 lactylation was also important for IL-6 expression in TAMs, which endowed macrophages with tumor-promoting functions via activation of signal transducer and activator of transcription 3 (STAT3) signaling in tumor cells [115]. These studies pointed out different ways by which lactate production was linked to epigenetic remodeling for the direction of TAMs polarization and tumor progression. The discrepancy might be related to a dynamic change in glucose supply and metabolism in TME during different stages of tumor development, which resulted in differential patterns of epigenetic regulation of gene expression in TAMs.

TCA cycle/Krebs cycle

During proinflammatory macrophage activation, there was an accumulation of the TCA cycle intermediates succinate and citrate, and the TCA cycle-derived metabolite itaconate. In TAMs, high OXCT1 expression induced the accumulation of succinate, which promoted Arg1 transcription and $CD8^+$ T cell exhaustion [116]. Myeloid-specific Bmal1 knockout rendered TAMs aberrant HIF-1α activation and metabolic shift for glycolytic metabolism and succinate accumulation, contributing to an immunosuppressive TME [117]. Besides, itaconate produced by aconitate decarboxylase 1 (ACOD1) inhibited the expression of inflammatory genes in TAMs and the infiltration of $CD8^+$ T cells into tumor sites [118]. Deletion of aconitate decarboxylase 1 in mice suppressed the growth of multiple tumors and enhanced the efficacy of anti-PD-(L)1 immunotherapy [118]. Similarly, metabolic reprogramming via aconitate decarboxylase 1 depletion enhanced function of human induced pluripotent stem cell-derived CAR-macrophages in solid tumors [119]. These studies suggested succinate and itaconate maybe immunosuppressive regulators of TAMs.

However, the role of the TCA cycle in tumor associated MDSCs was still unclear. Dihydrolipoamide succinyl transferase, a subunit of α-ketoglutarate decarboxylase complex in the TCA cycle, was found to be the most significantly elevated gene in tumor-primed myeloid cells [120]. The inhibition of dihydrolipoamide succinyl transferase reduced OXPHOS, immunosuppressive marker expression and function in myeloid cells [120]. Triggering STAT3 signaling via β2-adrenergic receptor

activation enhanced glutamine consumption via the TCA cycle in MDSCs [121]. Then the metabolized glutamine generated itaconate could downregulate mitochondrial ROS and the oxidative stress response to promote MDSC survival [122].

Hexosamine biosynthetic pathway

The hexosamine biosynthetic pathway was a glucose metabolic pathway essential for the synthesis of UDP-GlcNAc, which regulated protein N-glycosylation and O-GlcNAcylation. Recently, Cao *et al.* revealed that TAMs increased glycolysis through the hexosamine biosynthetic pathway and O-GlcNAcylation to promote tumor metastasis and chemoresistance [33]. Consistently, glucose flux promoted O-GlcNAcylation in TAMs and induced an M2-like phenotype in patients with hyperglycemia [123]. Hedgehog signaling enhanced UDP-GlcNAc biosynthesis and STAT6 O-GlcNAcylation to promote the immune suppressive polarization of TAMs [124]. Given that TAMs had the strongest glucose uptake capacity in the TME, it was important to further identify how O-GlcNAcylation linked glucose uptake and utilization in TAMs to their tumor-promoting functions.

The product of hexokinase enzymes, glucose-6-phosphate, could be metabolized through glycolysis or directed to alternative metabolic routes, such as the PPP to generate anabolic intermediates. Although glycolysis and the PPP were indispensable in the activation of inflammatory macrophages, the role of PPP in tumor associated myeloid cells still needs to be illustrated.

Lipid metabolism

In response to different stimulus, cellular lipid metabolism could be dynamically altered and influence the heterogeneity of TAMs and MDSCs from several aspects [125]. Not only as an important energy source, lipids could also serve as essential components of cell membranes and as signaling molecules to modulate various myeloid cell functions. Besides, lipids modified proteins to regulate cell functions and acted as ligands for some key transcription factors (Fig. 1).

Lipid synthesis

Tumor-exposed macrophages had a strong upregulation of lipid biosynthesis pathways, an increased total lipid content and enriched levels of intracellular lipids. Inhibition of lipid biosynthesis by the FASN inhibitor C75 in TAMs significantly reversed the increased inflammatory cytokines and the capacity to produce ROS [126]. The disruption of SREBP1-dependent *de novo* fatty acids synthesis could impede TAMs survival and their tumor-promoting activity. Targeting SREBP1 pathway could improve anti-PD1 treatment efficacy in tumor-bearing mice [127]. However, *de novo* lipogenesis, not exogenous fatty acids, was also critical for CpG-activated macrophages anti-tumoral activity [128].

Lipid synthesis also influenced MDSCs. Ginger polysaccharide could decrease MDSCs proliferation and promote their apoptosis by inhibiting expression of FASN and diacylglycerol acyltransferase 2 [129]. The downregulation of RIPK3 in tumor-infiltrating MDSCs potentiated NF-κB activation, cyclooxygenase-2 expression and the release of the immunosuppressive mediator, prostaglandin E2 (PGE2). PGE2, in turn, further reduced RIPK3 and promoted the immunosuppressive activity of MDSCs and tumorigenesis [130]. Thus, enhanced lipid synthesis in TAMs and MDSCs could promote their survival and protumor characteristics.

Fatty acid oxidation

Fatty acid oxidation (FAO) mainly occurred in mitochondrial matrix and was a source of ATP, especially when glucose availability was limited. In addition to bioenergetics, FAO may produce multiple metabolites that influence signal transduction and/or gene regulation [125]. Oxidative stress-induced oncogenic KRAS protein released from pancreatic cancer cells was essential for TAMs polarization via STAT3-dependent FAO [131]. Peroxisome proliferator-activated receptor γ (PPARγ)-dependent fatty acid absorption and FAO induction could enhance protumor macrophage polarization, regulated by S100A4 or Hedgehog signaling [124,132]. Nevertheless, FAO was also critical for stimulating anti-tumorigenic functions in macrophages [128,133].

MDSCs relied on FAO as the major metabolic fuel for their immunosuppressive function. The increased fatty acid uptake and activated FAO were found in both peripheral blood MDSCs from patients with cancer and tumor-infiltrating MDSCs in murine tumor models. FAO inhibition blocked tumor-infiltrating MDSCs immunosuppressive effects and induced a significant antitumor effect [134]. scRNA sequencing analysis also showed that immunosuppressive myeloid cells with characteristics of fatty acid oxidative metabolism dominated the immune-cell landscape in ICB-resistant subjects. Furthermore, PIM1, a serine/threonine kinase, was confirmed in regulating MDSCs lipid oxidative metabolism and their immunosuppressive function via PPARγ-mediated activities. PIM kinase inhibition not only improved the efficacy of PD-L1 blockade but also overcame ICB resistance in nonresponders [135]. Besides, β2-adrenergic receptor signaling triggered by stress was an important physiologic regulator of OXPHOS and FAO in tumor-infiltrating MDSCs, which increased expression of fatty acid transporter CPT1A and PGE2 production [136]. Although targeting FAO maybe

a useful approach to limit the immune-suppressive function of TAMs and MDSCs, the specific factors responsible for this shift among the TCA, glycolysis, and FAO pathways in the TME and the molecular networks involved in the energy metabolic reprogramming of TAMs and MDSCs are still unknown.

Lipid droplet

Several studies revealed that lipid-associated macrophages were present in the TME, normally showed high cellular granularity and enriched lipid droplets and lipid metabolism related genes. These cells could exert immune-suppressive activities and support tumor growth and progression. Our recent study found LDs-laden macrophages were enriched in HCC tissues and associated with disease progression. These TAMs displayed immunosuppressive phenotypes and attenuated the antitumor activities of $CD8^+$ T cells. LDs prolonged their survival and promoted CCL20 secretion, which further recruited $CCR6^+$ Tregs to HCC tissue. Inhibiting these TAMs formation by targeting diacylglycerol acyltransferase 1 and diacylglycerol acyltransferase 2, which catalyze the synthesis of triglycerides, significantly reduced Treg recruitment and delayed tumor growth [137]. TAMs and MDSCs highly expressed scavenge receptor CD36 that was implicated in lipid scavenging and accumulation, and consequently augmented FAO and OXPHOS to fuel their protumorigenic functionality [138]. Although CD36 acted as a central regulator of both immune and metabolic pathways mainly through transporting of long-chain fatty acids, there were other lipid receptors to be revealed. Lipid receptor TREM2 drove a gene expression program involved in phagocytosis and lipid metabolism, the accumulation of $TREM2^+$ TAMs was confirmed using scRNA-seq analysis and immunohistochemistry [139]. Furthermore, a subpopulation of monocyte-derived $STAB1^+TREM2^{high}$ TAMs with immune suppressive capacities was expanded and correlated to ICB resistance in patients with triple-negative breast cancer. These TAMs were induced by cancer-associated fibroblast-driven CXCL12-CXCR4 axis. $TREM2^+$ TAMs were also significantly increased in pulmonary breast cancer metastasis lesions, and showed enrichment of genes implicated in lipid metabolism, extracellular matrix remodeling and immunosuppression, but reduced capacity for phagocytosis [140]. As a sensor for β-glucosylceramide, Mincle was essential for lipid accumulation, pro-tumorigenic properties and suppressive activity of TAMs in mouse melanoma model [141]. In prostatic adenocarcinoma, the formation of lipid-loaded TAMs was dependent on Marco-mediated oxidized low-density lipoprotein (LDL) uptake [142]. Fatty acid transport protein 2 promoted lipid accumulation and suppressive activity of MDSCs [143]. The accumulated lipids could generate oxidized lipids via myeloperoxidase (MPO) in MDSCs. The transfer of oxidized lipids from MDSCs to DCs was implicated in the negative regulation of tumor-associated antigen cross-presentation *in vivo* by DCs, which was substantially improved in MDSC-depleted or MPO-deficient tumor-bearing mice [144]. The release of oxygenated lipids from MDSCs induced by ferroptosis could limit T cells activity [145]. If lipid accumulation became an established feature of TAMs and MDSCs, the mechanisms of lipid intake and the source of lipids still need to be fully illustrated.

Cholesterol metabolism

Cholesterol homeostasis was a dynamic process, involving synthesis, influx, efflux and esterification, which was implicated in the regulation of cell growth and differentiation. Moreover, it has been reported that the TCA cycle might be the possible intracellular source of acetyl-CoA for cholesterol synthesis [125]. Many cancers rewired cholesterol metabolism to support tumor progression and therapeutic resistance [146]. Notably, cholesterol metabolism could also impact TME and anti-tumor immune responses. The cholesterol metabolism feature and its potential role in tumor associated myeloid cells has recently been explored (Fig. 2).

Hypoxia induced nuclear translocation and activation of sterol regulatory element binding protein 2 (SREBP2) in monocytes, an essential regulator of cholesterol biosynthesis. In tumor-bearing mouse models, inhibiting cholesterol biosynthesis with atorvastatin significantly reduced tumor growth, angiogenesis, infiltration of monocytes/macrophages, and expression of Ccl2 [147]. A novel potent colony-stimulating factor 1 receptor (CSF1R) inhibitor, PXB17, significantly reprogramed TAMs to M1 phenotype. Compared with M2 macrophages, PXB17-treated cells showed reduction of cholesterol content and downregulation of cholesterol biosynthesis related genes, including 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), squalene epoxidase (SQLE) and SREBP2 [148]. DHCR7, another key enzyme in cholesterol biosynthesis, was significantly elevated in tumor-supportive macrophages. DHCR7 ablation in macrophages effectively suppressed cholesterol supply and activated T cell immunity [149]. SQLE catalyzed the stereospecific oxidation of squalene to (S)-2,3-epoxysqualene and was a rate-limiting enzyme in cholesterol biosynthesis. Dysregulation of SQLE resulted in altered cholesterol metabolism in TAMs and an immune suppressive TME, favorable for tumor growth and progression [150]. However, Liu *et al.* showed that β-glucan-induced antitumor activity of macrophages in a melanoma mouse model required SQLE-catalyzed squalene epoxidation, which not only produced 24(S),25-epoxycholesterol for liver X receptor (LXR) activation

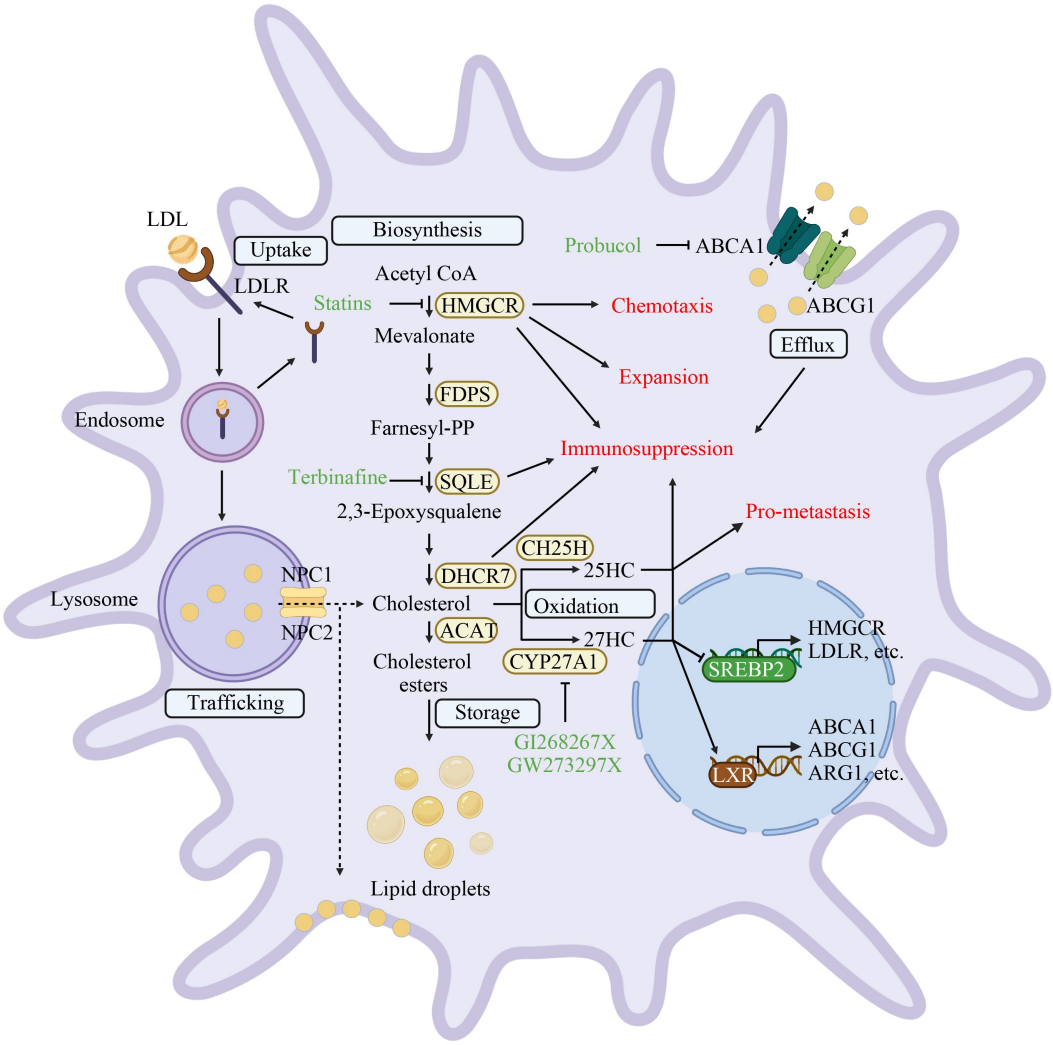

Fig. 2 Cholesterol metabolism in tumor-associated myeloid cells. Cholesterol is synthesized with acetyl-CoA from the TCA cycle, using HMGCR, farnesyl diphosphate synthase (FDPS), SQLE and DHCR7 as the rate-limiting enzymes (highlighted in blue). In addition to *de novo* biosynthesis, cholesterol carried by LDL particles can be taken up by LDL receptor. Excess cholesterol is exported to the blood by ABCA1 and ABCG1. Cholesterol can also be fluxed into cholesterol ester by ACAT (or SOAT) for storage in lipid droplets. Besides, cholesterol can further be converted into 25-hydroxycholesterol by CH25H or 27-hydroxycholesterol (27HC) by CYP27A1. These oxysterols can decrease cholesterol synthesizing genes by inhibiting SREBP2 and activating LXR-mediated cholesterol efflux. Moreover, cholesterol synthesis, oxidation and efflux are frequently upregulated in tumor associated myeloid cells, coordinated with their infiltration and protumor function (highlighted in red). This figure was created using BioRender.

and ensuing reprogramming of histone modification and chromatin accessibility but also generated ROS for glycolytic induction [151].

Cholesterol production might promote the expansion and immunosuppressive activity of MDSCs. In tumor-bearing mouse models, cholesterol promoted BM cell immature differentiation into MDSCs, and increased the levels of MDSC signature molecules, PD-L1 and ROS. The inhibition of cholesterol biosynthesis by HMGCR knockdown resulted in a reduction in cholesterol levels as well as the expression of PD-L1 and ROS in MDSCs [152]. However, RIPK3 deficiency led to cholesterol abrogation in MDSCs, which induced the translocation of LXRβ into nuclear to transcript Arg1, consequently, cholesterol deficiency profoundly elevated the immunosuppressive activity of tumor-infiltrating MDSCs [153]. PD-1 ablation in myeloid cells skewed the fate of myeloid cells away from immunosuppressive MDSCs, but toward a functional effector monocyte/macrophage and DC differentiation, which was associated with cholesterol accumulation [154]. Therefore, the exact role of cholesterol in MDSCs should be further illustrated.

Oxysterols, the oxidized forms of cholesterol or its precursors, could also modulate tumor immunity. Xiao *et al*. show that TAMs exhibited elevated expression of cholesterol-25-hydroxylase (Ch25h), resulting in lysosome-accumulated 25-hydroxycholesterol that activates AMPKα to promote STAT6-dependent Arg1

production. CH25H-deficient macrophages switched "cold tumors" into "hot tumors" and improved anti-PD1 treatment efficacy [155]. In human breast cancer specimens, TAMs highly elevated the CYP27A1 expression and the conversion of cholesterol to 27-hydroxycholesterol (27HC), which promoted tumor growth and metastasis. Besides, 27HC-treated macrophages exhibited a strong immunosuppressive effect on T cell activation and function in an LXR-dependent manner [156]. It was worth noting that MDSCs were also required for the pro-metastatic effects of 27HC [157].

Although myeloid cells could produce cholesterol, they could not catabolize the molecule and therefore needed to dispose of the excess out of the cell or store it as cholesteryl esters in LDs. ATP binding cassette subfamily A member 1 (ABCA1) and ATP binding cassette subfamily G member 1 (ABCG1) were responsible for cholesterol efflux, which regulated plasma membrane cholesterol levels and profoundly influenced macrophage responses to extracellular stimuli. For example, ABCG1 deficiency in macrophages increased their pro-inflammatory phenotype and reduced tumor growth [158]. In a mouse model of metastatic ovarian cancer, tumor cells promoted membrane cholesterol efflux and depletion of lipid rafts from macrophages. Genetic deletion of ABCA1 and ABCG1 could revert the tumor-promoting functions of TAMs and reduce tumor progression [159]. Granulocyte-macrophage colony-stimulating factor (GM-CSF)/PPARγ signaling increased fatty acid synthesis and cholesterol efflux, yet decreased cholesterol esterification in TAMs from lung adenocarcinoma. TAMs transferred cholesterol to lung adenocarcinoma cells, which increased EGFR phosphorylation and promoted tumor progression. Macrophages could also transfer cholesterol to prostate tumor cells, enhancing androgen receptor activation *in vitro* [160]. Cholesterol depletion was a key feature of TAMs in human lung adenocarcinoma and HCC. Li *et al.* observed that the coordination of exogenous cholesterol and tumor-derived factors promoted ABCA1-mediated cholesterol efflux and decreased cellular cholesterol levels in human primary monocytes/macrophages, resulting in immature and immunosuppressive macrophages. High numbers of $ABCA1^+$ TAMs in HCC were correlated with reduced $CD8^+$ T cell infiltration and poor clinical outcome [161]. These studies suggested selective modulation of cholesterol metabolism in TAMs may represent a novel strategy for cancer treatment.

Amino acid metabolism

Amino acids played a major role in regulating important cellular events including hormones and peptides synthesis, signal transduction and regulation of gene expression. In myeloid cells, the consumption of amino acids and their availability were key drivers of cellular identity impacting development, functional polarization, and interaction with other cells [162]. Here, we discussed recent progress and emerging concepts in our understanding of the impact amino acid availability and consumption had on myeloid cell phenotype, with a major focus on three amino acids: arginine, glutamine and tryptophan.

Arginine metabolism

Arginine could be degraded by Arg1. It was highly expressed in TAMs, which was in part dependent on HIF-1α signaling, lactate, GM-CSF and creatine [163]. Arg1-expressing myeloid cells could inhibit T cell proliferation in an *in vitro* culture system. SLC7A2-mediated arginine uptake in tumor myeloid cells also suppressed T cell proliferation *ex vivo* [164]. Those observations suggested that the Arg1-mediated arginine consumption in TAMs and MDSCs might have an immunosuppressive function. Arginase inhibition enhanced arginine concentration and cytotoxic immune cell infiltration and delayed tumor development [165]. Moreover, studies in pancreatic cancer identified arginine as the most depleted metabolite [166], and Arg1 deletion in myeloid cells suppressed murine tumor progression, which was associated with increased cytotoxic $CD8^+$ T cell infiltration and activation [167]. The arginine-polyamine pathway was induced in myeloid cells to promote their survival, and depletion of polyamine prolonged tumor-bearing mouse survival [168]. Myeloid cells also produced creatine from arginine to feed tumor cells to allow their survival in the hypoxic niche [31]. Arginine was also a substrate for proline, which promoted the production of collagen fibrils and subsequent fibrosis, leading to the immune exclusion from tumors [169].

Arginine catabolism through nitric oxide synthase 2 (NOS2) was another key suppressive mechanism of TAMs or MDSCs. Their release of nitric oxide or peroxynitrite could induce T cells apoptosis as well as T cell function and migration inhibition [9,31]. Traditional Chinese medicine saposhnikovia root extract Prim-O-glucosylcimifugin could inhibit the proliferation, metabolism and immunosuppressive ability of MDSCs by inhibiting arginine metabolism and the TCA cycle. Prim-O-glucosylcimifugin could also increase $CD8^+$ T cell infiltration in the tumors and enhance the antitumor effect of PD-1 inhibitor [170]. These observations suggested that different arginine catabolism pathways coordinated its pro-tumor phenotype, but the exact mechanisms and functions of such metabolic rewiring in TAMs and MDSCs remained to be investigated.

Glutamine metabolism

As a major source of carbon and nitrogen, glutamine was

essential for production of amino acids, purine, pyrimidines, and lipids. Additionally, glutamine-derived glutamate could be utilized in synthesis of glutathione, which was used to neutralize ROS and maintain redox balance. Glutamine-derived α-KG was required for the differentiation of macrophages to an anti-inflammatory, immunosuppressive phenotype [171]. Glutamine deprivation and glutaminolysis inhibition decreased expression of immunosuppressive genes while upregulating inflammatory genes in macrophages [172]. Therefore, glutamine metabolism contributed to the polarization of macrophages toward an immunosuppressive phenotype like those of TAMs in the TME. Our previous work found that human suppressive immature myeloid cells from colon and breast tumor tissues exhibited high glycolytic metabolism [173]. However, the generation of immature myeloid cells relied on glutaminolysis, regardless of glucose availability. Glutamine metabolism not only supported the expansion of immature myeloid cells with glutamine-derived α-KG but also regulated the suppressive capacity through the glutamate–NMDA receptor axis. Moreover, inhibition of glutaminase GLS1 enhanced the therapeutic efficacy of anti–PD-L1 treatment, with reduced $Arg1^+$ myeloid cells, increased $CD8^+$, $IFN\gamma^+$ and granzyme B^+ T cells, and delayed tumor growth in an ICB-resistant mouse model [173]. Tumor-primed myeloid cells showed increased immunosuppressive marker expression and OXPHOS fueled by glutamine, inhibiting the glutamine metabolic pathway decreased OXPHOS and immunosuppressive activity [120]. These findings suggest a tumor-promoting role of myeloid glutamine/glutamate catabolism, but its specific function in TAMs and MDSCs remains to be determined.

Glutamine metabolism was a promising target for sensitizing tumors and their immunosuppressive microenvironments toward immunotherapy. JHU083, a prodrug version of the glutamine antagonist 6-diazo-5-oxo-Lnorleucine, was a glutamine metabolism inhibitor that was selectively activated in the TME to mitigate toxicity; it was shown to inhibit tumor growth and promote survival in tumor-bearing mice, particularly in combination with immunotherapy [174]. Administration of this prodrug augmented endogenous antitumor immunity, as it promoted activation, proliferation, and memory in tumor-infiltrating lymphocytes [174]. Additionally, JHU083 inhibited the recruitment of immunosuppressive MDSCs to the TME and induced their apoptosis, simultaneously reprogramming MDSCs and TAMs to a proinflammatory antitumor phenotype [175]. Notably, glutamine inhibition via JHU083 increased the effectiveness of anti-PD1 and anti-CTLA4 checkpoint blockade in tumors that did not benefit from monotherapy [175].

Tryptophan metabolism

IDO was an intracellular, tryptophan-metabolizing enzyme that functions through its catalysis of the rate-limiting step of the kynurenine pathway. IDO was highly expressed in TAMs and MDSCs in the TME and played a role in tumor immune escape. Our previous study found that activated $CD69^+$ T cells fostered immune privilege by upregulating IDO expression in TAMs [176]. Tryptophan metabolism and subsequent depletion via IDO expression in macrophages had been shown to inhibit antigen-specific T cell proliferation and activation [48]. Additionally, kynurenine had been shown to activate the aryl hydrocarbon receptor (AhR), and this activation led to the generation of immunosuppressive Tregs and the resistance of solid tumors to oncolytic adenoviruses treatments [52]. IL-4-induced-1 (IL4I1), an L-amino-acid oxidase, had recently been identified as a potent activator of the AhR pathway by promoting tryptophan catabolism to indole metabolites and kynurenic acid [177]. $IL4I1^+$ TAMs could prevent T cell proliferation and cytokine production, decrease the $CD8^+$ T cell response, and promote the differentiation of naive $CD4^+$ T cells into Tregs. In addition to suppressing the antitumoral T cell response, IL4I1 expression was also shown to recruit immunosuppressive MDSCs to the TME [178]. scRNA-seq analyses revealed that an enriched $IL4I1^+IDO^+PD\text{-}L1^+$ TAMs subset was associated with T cell dysfunction in multiple human tumors [179]. In addition to AhR, kynurenine was also bound to the cell surface receptor G-protein coupled receptor 35 (GPR35), GPR35 depletion in myeloid cells suppressed tumor development in genetic and carcinogen-induced tumor models [180].

MDSCs also decreased levels of tryptophan via the expression of IDO in the external environment to impair cytotoxic T cell responses and survival. In patients with breast cancer, increased IDO-expressing MDSC populations were correlated with increased amounts of Tregs and a poor prognosis [181]. In fact, IDO^+ MDSCs tended to be more suppressive than their IDO^- counterparts. Moreover, a recent study showed that IDO vaccine ablated immune-suppressive myeloid populations and enhanced antitumor effects [182].

Current clinical therapeutics targeting myeloid cell metabolism

At present, several clinical trials are underway to evaluate the efficacy of targeting the aforementioned metabolic pathways in various cancers (Table 1). IM156 and IACS-010759, small molecules targeting the OXPHOS pathway, were primarily in Phase I clinical trials (NCT03291938, NCT03272256 and NCT05497778). Cyclooxygenase-2, a rate-limiting enzyme involved in the synthesis of PGE2, is currently being explored as a

Table 1 Therapeutic approaches targeting metabolism pathway in myeloid cells

Targets	Drug type	Drug name	Phase	Trial identifier	Combination regimen	Targeted disease	Clinical outcomes
Oxidative phosphorylation pathway inhibitor	Small molecule	IACS-010759	I	NCT03291938	Monotherapy	With advanced solid tumors and lymphoma	No results posted
	Small molecule	IM156	I	NCT03272256	Monotherapy	Advanced solid tumors and lymphoma	No results posted
	Small molecule	IM156	I	NCT05497778	Gemcitabine and nab-paclitaxel	Advanced pancreatic cancer	No results posted
Cyclooxygenase-2 inhibitor	Small molecule	Celecoxib	II	NCT03026140	Ipilimumab and nivolumab	With stage 1–3 adenocarcinoma of the colon with no signs of distant metastases	No results posted
	Small molecule	Celecoxib	II	NCT03926338	Toripalimab	Mismatch-repair deficient or microsatellite instability-high locally advanced colorectal cancer	No results posted
E-type prostanoid receptor 4 antagonist	Small molecule	TPST-1495	I	NCT04344795	Monotherapy and with pembrolizumab	Advanced solid tumors	No results posted
Glutaminase inhibitor	Small molecule	CB-839	I/II	NCT02861300	Capecitabine chemotherapy	Colon cancer, rectal cancer, and other solid tumors	Results submitted
	Small molecule	CB-839	I	NCT03944902	Niraparib	Platinum-resistant BRCA wild-type ovarian cancer patients	No results posted
Arginase 1 inhibitor	Small molecule	INCB001158	I	NCT02903914	Monotherapy and with pembrolizumab	Advanced/metastatic solid tumors	Well tolerated with early responses observed in pretreated MSS CRC patients
NOS2 inhibitor	Small molecule	L-NMMA	I	NCT03236935	Pembrolizumab	Unresectable or metastatic tumor mutational burden-high solid tumors	No results posted
Aryl Hydrocarbon Receptor (AHR) Inhibitor	Small molecule	IK-175	I	NCT04200963	Monotherapy and with nivolumab	Locally advanced or metastatic solid tumors and urothelial carcinoma	No results posted
	Small molecule	BAY2416964	I	NCT04069026	Monotherapy	Advanced solid tumors	No results posted
	Small molecule	BAY2416964	I	NCT04999202	Pembrolizumab	Advanced solid cancers including head and neck cancer, lung cancer and bladder cancer	No results posted
IDO1 inhibitor	Small molecule	NLG802	I	NCT03164603	Monotherapy	Recurrent advanced solid tumors	No results posted
	Small molecule	D-1MT	I	NCT00739609	Monotherapy	Relapsed or refractory solid tumors	No results posted

Abbreviations: IACS, inhibitor of ATP synthase complex; CRC, colorectal cancer; MSS, microsatellite stable; BRCA, breast cancer susceptibility gene; NOS2, nitric oxide synthase 2; AHR, aryl hydrocarbon receptor; IDO1, indoleamine 2,3-dioxygenase 1; NCT, national clinical trial identifier; MSS CRC, microsatellite stable colorectal cancer; SC, subcutaneous; IV, intravenous.

therapeutic target in several clinical trials (NCT03026140 and NCT03926338). PGE2, in turn, reprogramed myeloid cells toward an immunosuppressive function via interaction with the E-type prostanoid receptor 4. The E-type prostanoid receptor 4 antagonist TPST-1495 was still undergoing clinical trials as both a monotherapy and in combination with pembrolizumab (NCT04344795). Other clinical trials concerning amino acid metabolism pathways included those targeting glutaminase (NCT02861300 and NCT03944902), arginase 1 (NCT02903914) and NOS2 (NCT03236935). The AHR inhibitor IK-175 associated with tryptophan metabolism was undergoing Phase I clinical trials as a monotherapy and in combination with nivolumab in solid tumors and urothelial carcinoma (NCT04200963). Another AhR inhibitor BAY2416964 has been evaluated as a monotherapy (NCT04069026) or in combination with pembrolizumab (NCT04999202) in advanced solid cancers including head and neck cancer, lung cancer and bladder cancer. While Phase II clinical trials showed that the combination of IDO inhibitors and immune checkpoint blockade was well tolerated and achieved an

objective response rate of 55% [183], this combination therapy failed in Phase III trials [184,185]. Additionally, metabolic pathways concerning iron metabolism were also being investigated as novel therapeutic targets.

To be noted, in the TME, myeloid cells exhibit plasticity and heterogeneity, rather than binary polarization. Therefore, there is a pressing need to comprehensively explore the metabolic networks among these diverse myeloid subsets. Additionally, most metabolic pathways currently under clinical investigation are not exclusive to myeloid cells, and the same metabolic products may lead to opposite effects depending on their interactions with different cell types such as T cells or tumor cells. This complexity presents challenges but also opportunities for developing therapeutic strategies that selectively target myeloid cell metabolism.

The accumulation of TAM and MDSC

Given that cells of the myeloid compartment were generally short-lived, this growing and fast-turnover pool of tumor-associated myeloid cells needed prompt and continuous regeneration, which could be achieved by enhancing peripheral recruitment, promoting survival and proliferation within the tumor, and biasing host hematopoietic activity toward myeloid cells differentiation.

Chemotaxis

Different immune cells traffic into the TME and modulate immune responses in primary tumors and metastatic sites. Chemokines, small secreted proteins, are pivotal in immune cell trafficking and lymphoid tissue development. In the TME, chemokines can be expressed by tumor cells as well as immune and stromal cells. In response to specific chemokines, different immune cell subsets migrate into the TME and regulate tumor immune responses in a spatiotemporal manner [186] (Fig. 3).

Monocytes continuously egressed from the BM in a strictly CCR2-dependent manner, initially circulating in the bloodstream as classical or "inflammatory" CCR2^{hi} monocytes with a half-life of approximately one day [187]. Under steady-state conditions, these monocytes could be recruited at a low rate to tissues, differentiating into macrophages that supplement the tissue-resident macrophages established during embryogenesis to maintain tissue homeostasis. However, in the context of the tumor milieu, tumor cells employed various mechanisms to upregulate chemokine expression, thereby enhancing the recruitment of monocytes, which subsequently differentiated into TAMs. The chemokine C-C motif ligand 2 (CCL2), also known as monocyte chemoattractant protein 1 (MCP-1), facilitated the migration of monocytes into the tumor sites by binding to its receptor CCR2. Elevated levels of CCL2 have been observed in several malignancies, including HCC [188,189], breast cancer [190], and colorectal cancer [191]. Blockade of the CCL2/CCR2 signaling pathway inhibited the recruitment of monocytes and their subsequent M2 polarization, generally enhancing T cell immunity and reducing the growth of various tumors, which indicated that their pro-tumoral activities most often outweigh their anti-tumoral ones [189,192–195]. CCL2 also facilitated the recruitment of MDSCs to tumors. Studies across numerous animal models and cancer patient samples have demonstrated that increased CCL2 levels correlate with heightened MDSCs accumulation in the TME, thereby promoting tumor progression [196–199]. This indicated that, in addition to CCR2, other receptors expressed on TAMs and MDSCs, such as CCR1, CCR5, CXCR1, and CXCR2, may serve as alternative mechanisms for tumor infiltration. This provided opportunities to reduce the accumulation of these cells in the TME by interfering with these receptors

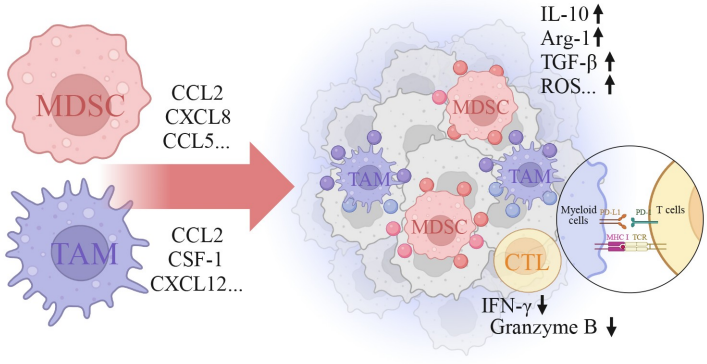

Fig. 3 Tumor-driven recruitment of tumor-associated myeloid cells. Tumor-derived chemokines such as CCL2, CXCL8, CXCL12, and CSF-1 recruit MDSCs and TAMs into the TME. These myeloid cells contribute to immune evasion by producing immunosuppressive mediators and upregulating PD-L1, suppressing CTL effector functions and facilitating tumor progression. This figure was created using BioRender.com.

or their ligands' signaling. For instance, the MDSCs attractant CXCL8, whose receptors were CXCR1 or CXCR2, was found to be elevated in various cancer types, such as breast, colon, ovarian, pancreatic, prostate, and several hematological malignancies [200]. The inhibition of CXCR1 or CXCR2 has shown a potential to enhance sensitivity to ICB therapy and restrict tumor metastasis [201,202]. In a recent study, CAR T cells engineered with CXCR1 or CXCR2 demonstrated increased accumulation within tumors, leading to a significant reduction in tumor burden [203]. CCR5 is also expressed in both monocytes and MDSCs. Therefore, CCR5, along with its associated ligands, is a key element in the recruitment program of monocytes and MDSCs. Meanwhile, CCR5 was also expressed in cytotoxic T lymphocytes (CTLs), which were a major source of its ligand CCL5 [204] and were often considered as part of the type 1 immune response. This suggested that these chemokine-receptor signaling pathways facilitate T cell interactions with monocytes or macrophages in inflamed tissue environments. Additionally, CCR5 expressed on $CD8^+$ T cells in immunogen-draining lymph nodes permitted these cells to be guided to sites of DCs-$CD4^+$ T cell interaction where the cognate chemokines CCL3 and CCL4 were produced [205]. Finally, activated CTLs could produce CCR5 ligands CCL3 and CCL4. This accelerated the recruitment of distant $CCR5^+$ T cells and further speeded up swarming behavior [206]. Further investigation is required to elucidate the role of CCR5 in distinct immune cell types within the TME, including its function on TAMs and T cells.

In addition to chemokine-receptor signaling pathways, the signaling factor CSF-1 (also known as colony-stimulating factor-1 or M-CSF) served as a critical attractant for macrophages. The interaction of CSF-1 with its receptor CSF-1R orchestrated a cascade of downstream signaling pathways involving the phosphoinositide 3-kinase (PI3K)-AKT pathway, mitogen-activated protein kinase (MAPK) pathway, and JAK-STAT pathway. These pathways collectively regulated macrophage activation, polarization, and proliferation, illustrating that CSF1 function governs macrophage biology and diseases involving macrophage dysfunction. CSF-1 was highly expressed in multiple tumors and subsequently enhanced the accumulation and migration of TAMs. Recent research has shown that IL-1β enhances the expression of HIF-1α, PD-L1, and CSF1, facilitating the infiltration of TAMs and MDSCs through the CSF-1/CSF1R axis. Knockdown of CSF1 attenuated intra-tumoral TAMs and MDSCs infiltration and HCC metastasis [207]. In some studies, CSF-1 has been found to elevate the expression of CCL2 in macrophages [208]. Given that CSF-1/CSF1R signaling was instrumental in shifting macrophage polarization toward a tumor-promoting phenotype, targeting the CSF-1/CSF-1R axis emerged as a promising therapeutic strategy.

Survival

Tumors possess a unique physicochemical environment that differs significantly from that of normal tissues, resulting in complex metabolic patterns such as hypoxia, elevated lactate levels, and reduced glucose availability. These features collectively create an adverse environment that impairs the survival and function of recruited immune cells. Despite their typically short lifespan, their substantial presence in tumor tissues indicates that these cells have developed intricate mechanisms to adapt to the tumor-specific environment. Understanding how tumor-associated myeloid cells survived in the inhospitable TME is of significant importance [15] (Fig. 4).

Circulating monocytes play a crucial role in innate immune surveillance. In a steady-state, these monocytes have a short lifespan, with most either leaving the circulation or undergoing apoptosis. However, in an inflammatory environment, chemokines and pathogen signals guide monocytes across blood vessels into damaged or infected tissue areas, where they rapidly differentiate into macrophages or dendritic cells to perform their respective immune functions. Unlike monocytes, macrophages have a significantly extended lifespan, ranging from months to years. Cytokines such as M-CSF, GM-CSF, and IL-34 were crucial for the survival and proliferation of macrophages, stimulating at least three signaling pathways: the PI3K pathway, the MAPK pathway, and the JAK-STAT pathway. Mice lacking M-CSF showed deficiencies in most tissue-resident macrophages [209], while IL-34-deficient mice displayed selective reductions in Langerhans cells and microglia [210]. Thus, targeting M-CSF or its corresponding receptor was an effective strategy for depleting macrophages within the TME in cancer therapy. This approach could reduce the recruitment of macrophages and increase the apoptosis of existing TAMs. Previous studies have shown that RG7155 was a selective inhibitor of CSF-1R dimerization, effectively blocking both ligand-dependent and ligand-independent receptor activation. Administration of RG7155 to patients led to significant reductions in $CSF\text{-}1R^+CD163^+$ macrophages in various solid malignancies, which also altered the T cell composition and contributed to a more favorable immune response against the tumors [211]. Additionally, inhibiting the CSF-1/CSF-1R signaling pathway could enhance the effectiveness of various immunotherapies, including CD40 agonists [212], PD-1 inhibitors [213], CTLA-4 antagonists [214], and adoptive T cell therapies [215]. Therapeutic blockade of GM-CSF effectively depleted TAMs by reducing their viability and altering their polarization, which was correlated with decreased STAT5 phosphorylation. This strategy functionally

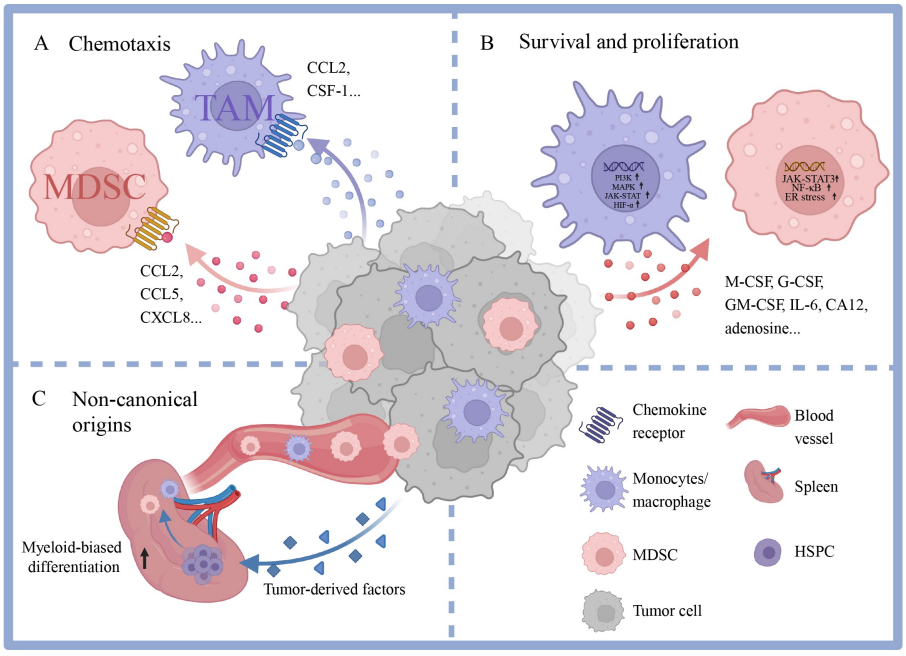

Fig. 4 Different mechanisms mediate the accumulation of TAMs and MDSCs in TME. The accumulation of tumor-associated myeloid cells can be facilitated through several mechanisms: (A) enhancing the recruitment of myeloid cells from peripheral sources, (B) promoting their survival and proliferation within TME, and (C) skewing host hematopoietic activity toward the differentiation of myeloid cells. This figure was created using BioRender.com.

reprogramed myeloid cells, resulting in enhanced cytotoxic T cell engagement [216].

The metabolic state of macrophages significantly influences their survival and function under various physiologic and pathological conditions. Research has shown that transient glycolytic activation of peritumoral monocytes can induce carbonic anhydrase 12 upregulation in both monocytes and macrophages through HIF-1α and an autocrine cytokine-dependent pathway. This mechanism supports the survival of monocytes and macrophages in acidic microenvironments and may help explain the relatively high levels of infiltration of these cells observed in HCC tumor tissues [217]. Another study demonstrated that β-glucosylceramide derived from tumor cells drove the reshuffling of lipid composition and saturation in the endoplasmic reticulum membrane of macrophages. This process promoted pro-tumorigenic polarization in macrophages, enhancing their survival capacity within the TME [141]. Similarly, recent research has shown that tumor-induced lipid reshuffling and TNF-α-mediated uptake of tumoral fatty acids contribute to the formation of lipid droplets in TAMs, thereby extending their survival [218]. A detailed understanding of the signaling pathways and metabolic states regulating TAMs survival could lead to novel therapeutic strategies to control their accumulation.

MDSCs generally have a short lifespan; however, their survival dynamics vary considerably across different pathological contexts and tissue environments. A critical regulator of MDSC survival is the STAT3 signaling pathway, which is activated by tumor-derived factors like G-CSF, GM-CSF, and IL-6. Activated STAT3 orchestrated essential functions in MDSCs, including cell survival, proliferation, differentiation, and apoptosis regulation. It upregulates key proteins like MYC, cyclin D1, and B cell lymphoma-extra large, which resisted cell death and contributed to the expansion and maintenance of MDSCs. In addition to STAT-related signaling pathways, the NF-κB pathway plays a significant role in the survival and activation of MDSCs. This pathway is activated by inflammatory cytokines, such as TNF-α, which binds to TNF receptor-2. This interaction upregulates c-FLIP expression and inhibits caspase-8 activity, thereby promoting the survival of MDSCs in murine models [219]. A distinguishing characteristic of MDSCs, compared to monocytes and neutrophils, is the activation of the ER stress pathway [220,221]. This activation leads to the upregulation of DR5, a key receptor in the TRAIL pathway [221], providing a potential therapeutic target for selectively inducing apoptosis in MDSCs. For instance, the agonistic DR5 antibody DS-8273a has been tested in phase I clinical trials, showing potential for selectively inducing MDSCs apoptosis and enhancing antitumor immunity [222]. Recent research indicated that autophagy might also play a role in the survival of MDSCs. Inhibition of autophagy increased the apoptosis of MDSCs, indicating that autophagy enhanced their survival. This process was

mediated by HMGB1 and highlighted the role of autophagy in sustaining MDSCs viability [223]. Collectively, these insights underscored the complex regulation of TAMs and MDSCs survival. Therapeutic strategies targeting molecules like M-CSF/CSF-1R and STAT3 to modulate TAMs and MDSCs functions hold promise for disrupting their pro-tumor functions and enhancing immune therapy efficacy.

Proliferation

In addition to the recruitment of myeloid cells, the proliferation of pre-existing myeloid cells within tissues also contributes significantly to the abundance of myeloid cells in the TME. This local expansion of myeloid cells is driven by various factors, including cytokines, growth factors, and other signaling molecules secreted by tumor and stromal cells. These factors not only attract myeloid cells to the tumor site but also stimulate their proliferation and survival once they arrive. This dual mechanism ensures a continuous supply of myeloid cells, which play crucial roles in supporting tumor growth, suppressing anti-tumor immune responses, and promoting metastasis (Fig. 4).

It was long believed that TAMs primarily originated from circulating monocytes. However, recent evidence suggested that some macrophages in tissues such as the liver and brain were established from progenitors derived from the yolk sac and fetal liver. The pool of macrophage could be maintained through monocytes input and proliferation. Adenosine, a metabolic product of ATP conversion to AMP, typically accumulates in tumors due to increased CD73 expression during tumor growth. While adenosine is essential for maintaining tissue homeostasis and preventing excessive immune responses during inflammation and infection, it can also hinder immune responses against tumor cells by disrupting cytotoxic anti-tumor immune responses. Recent studies indicated that HCC-derived adenosine could induce TAMs proliferation via the adenosine/A2A pathway [224]. Both *in vitro* and *in vivo* models showed that PD-L1 antibody treatment enhanced spontaneous proliferation, survival, and activation of mouse and human macrophages, which was linked to the upregulation of mTOR pathway. These findings suggested that targeting PD-L1 signaling in macrophages could reverse their immune-suppressive state and boost antitumor activity [225]. Previous research has shown that phosphoglycerate dehydrogenase (PHGDH), the first rate-limiting enzyme in the serine synthesis pathway, was activated in IL-4 induced M2 macrophages and was critical for their anti-inflammatory function. High levels of PHGDH expression have been observed in TAMs isolated from murine orthotopic lung tumors. Inhibiting PHGDH has been found to reduce IL-4-induced M2 polarization and macrophage proliferation. These findings suggest that PHGDH could be a potential target for modulating TAM infiltration to enhance the body's immune response against tumors [226].

The same growth factors that facilitated regular myelopoiesis in the BM, namely GM-CSF, G-CSF, and CSF1, also promoted the accumulation of MDSCs [227]. Therefore, the dysregulated production of such growth factors and the constant presence of inflammatory mediators in the context of chronic inflammation and tumor resulted in the expansion and accumulation of MDSCs. The activation of mTOR signaling in tumor cells has also been described as a major driver of this process through increased secretion of G-CSF [228]. In addition to the growth factors mentioned above, VEGF was a potent stimulator of MDSCs expansion owing to its ability to inhibit the differentiation of immature myeloid cells [229–231]. The JAK/STAT3 pathway was crucial for promoting the expansion of MDSCs. Consequently, cytokines that activated this pathway, including GM-CSF, G-CSF, and IL-6, were key contributors to MDSC proliferation [227]. On the one hand, STAT3 activation upregulated MYC, B cell lymphoma-extra large, and cyclin D1, which were essential for the proliferation and survival of MDSCs. On the other hand, STAT3 also promoted MDSCs proliferation by upregulating the expression of S100A8 and S100A9, whose receptors were also present on the surface of MDSCs. The STAT3-inducible upregulation of S100A9 in myeloid progenitor cells inhibited the differentiation of DCs and macrophages, leading to the accumulation and expansion of MDSCs. Conversely, MDSCs expansion was not observed in S100A9-deficient mice following tumor challenge [232]. IL-6 was also reported as an important cytokine mediating MDSCs expansion via STAT3. In mice, the overexpression of PPARγ, which was defined as an anti-inflammatory molecule, upregulated IL-6 levels to activate STAT3 and expand MDSCs [233]. Further study demonstrated that in a mouse model of breast cancer, MDSCs secreted IL-6 at the tumor site, thus inducing pSTAT3 expression by tumor cells and promoting tumor progression and metastasis [234].

Non-canonical origins

The BM was the primary hematopoietic organ, playing a crucial role in maintaining homeostasis and responding to pathological conditions. Under homeostasis, BM tightly regulated the process of hematopoiesis, generating various blood cells, including erythrocytes, leukocytes, and platelets. Hematopoietic stem and progenitor cells (HSPCs) were central to this process, possessing the abilities of self-renewal and multipotent differentiation. At a steady-state, HSPCs resided primarily in the BM and remained largely quiescent, only entering the cell cycle

when needed to produce specific lineages of blood cells. This regulation ensured a balanced production of blood cells, meeting the physiologic demands of the organism without exhausting the HSPCs pool. In recent years, studies have found that HSPCs could directly sense environmental signals and pro-inflammatory cytokines, allowing them to actively participate in initiating the immune response. These mechanisms provided a basis for tumor-regulated emergency myelopoiesis, which altered BM niche and HSPCs activity by a range of factors, such as cytokines and chemokines. Emergency myelopoiesis became crucial in tumors where the short lifespan of myeloid cells necessitated rapid and sustained regeneration from HSPCs, biased toward generating myeloid cells with tumor-promoting properties. Studies across various solid tumors, including hepatocellular, breast, cervical, esophageal, gastrointestinal, lung, and ovarian cancers, consistently showed circulating HSPCs skewed toward granulocytic differentiation [235]. Both human and murine studies provided evidence supporting the generality and importance of hematopoietic skewing observed in cancers [235–239].

Hematopoietic alteration was not restricted to BM, it has also been observed in multiple extramedullary organs. Recent research underscored the spleen as a pivotal site of extramedullary hematopoiesis. The spleen was primarily known for its roles in blood filtration, differentiation, and activation of T cells and B cells, as well as for antibody production. In addition to studies on the expansion of myeloid precursors in the spleen [240–242], the spleen had been found to be the reservoir of a large number of HSPCs, including HSCs and granulocyte/macrophage progenitors (GMPs). Their descendants, including monocytes and neutrophils, were relocated to tumor sites and exerted tumor-promoting functions [236,243]. It suggested that splenic monocytes and granulocytes might have received distinct signals compared to those in the BM. Although phenotypically and functionally, there were no notable differences between the two counterparts, this mechanism could not be formally excluded. Consistently, our investigation revealed that the spleen accumulated a population of HSPCs that was functionally distinct from those in the BM, profoundly expanding and supporting myeloid-biased myelopoiesis in various types of solid tumors [238]. These findings suggested the generality of splenic myelopoiesis. The mechanisms underlying the activity of splenic HSPCs and the adaptation of the extramedullary hematopoiesis niche to the organism's environment remained not fully elucidated. However, these processes are likely attributed to two key factors. On one hand, there may be selective recruitment of HSPCs to the spleen, potentially mediated by pathways like the CCL2/CCR2 axis. On the other hand, HSPCs might engage in a dynamic interplay with their niche through the secretion of various cytokines that regulate their own function. This HSPCs-niche interaction could be crucial in adapting to the demands of the microenvironment [244]. Understanding the regulatory mechanisms of splenic myelopoiesis was vital for controlling myeloid cell responses and fostering tumor suppression. Thus, targeting splenic myelopoiesis presented substantial potential for inhibiting tumor-promoting myeloid cell responses and shifting the balance toward tumor suppression. A comprehensive understanding of the functional specialization and regulatory mechanisms of splenic myelopoiesis will be essential for managing myeloid cell responses at their origin.

It was also noteworthy that the conventional understanding was that myeloid cells primarily developed from HSPCs originating in the BM or migrating to the spleen via myelopoiesis. In normal physiology, HSPCs differentiated into common myeloid progenitors, which then further differentiated into GMPs or megakaryocyte/erythrocyte progenitors (MEPs), ultimately giving rise to myeloid cells or erythrocytes/platelets. Such studies have convincingly demonstrated that lineage fate may be predetermined earlier than the common myeloid progenitors stage with advancements in single-cell sequencing, lineage tracing, and other technologies. Zhu *et al*. found that tumor-derived GM-CSF mediated the transdifferentiation of $CD45^+$ erythroid progenitor cells ($CD45^+Ter119^+CD71^+$, EPCs) into the myeloid lineage, known as erythroid-derived myeloid cells (EDMCs), thereby supporting and supplementing tumor-promoting myeloid cell generation at its source [245,246]. Interestingly, Cao *et al*. reported one population of tumor-inducible, erythroblast-like cells (Ter-cells, $CD45^-Ter119^+CD71^+$) deriving from megakaryocyte-erythroid progenitor cells. Ter-cells that were enriched in the enlarged spleen of hosts bearing advanced tumors produced artemin, a neurotrophic factor, and facilitated tumor progression [247]. Given the powerful immunosuppressive capabilities of EPCs in the TME, further understanding of the tumor-induced erythrocyte immune regulation mechanisms and investigating their developmental origins are crucial from a therapeutic standpoint.

Current clinical therapeutics targeting myeloid cell accumulation

In clinical research, one strategy for targeting myeloid cells is to inhibit their infiltration into tumors. Targeting these chemotaxis-related pathways reduced myeloid cell infiltration and increased anti-tumoral immunity in preclinical studies [248–250]. Accordingly, a broad range of clinical trials was initiated to explore the inhibition of myeloid cell chemotactic pathways (Table 2), including those mediated by CCL2–CCR2, CCL5–CCR5, CSF1–CSF1R, CXCR1, CXCR2, CXCR4, and IL-8 in

Table 2 Therapeutic approaches targeting myeloid cells accumulation

Therapeutic target	Drug type	Drug name	Phase	Trial identifier	Combination regimen	Targeted disease	Clinical outcomes
CSF1R antagonists	Small molecule	AMG 820	Ib/II	NCT02713529	Pembrolizumab	Select advanced solid tumors	Limited clinical activity but was well tolerated at the recommended dose of 1100 mg AMG 820 with 200 mg pembrolizumab
	Small molecule	ARRY-382 (PF-07265804)	Ib/II	NCT02880371	Pembrolizumab	PD1/PDL1-refractory tumors, platinum-refractory ovarian cancer, and PDAC	Despite limited clinical benefits, the combination was well tolerated
	Small molecule	ARRY-382 (PF-07265804)	I	NCT01316822	Monotherapy	Solid tumors	No results posted
	Small molecule	Pexidartinib (PLX3397)	I	NCT01790503	Radiotherapy and temozolomide	Recurrent glioblastoma	Safety and efficacy data reported. Minimal impact observed on PFS and OS
	Small molecule	Pexidartinib (PLX3397)	I	NCT02777710	Durvalumab	CRC, PDAC, metastatic cancer, advanced cancer	No results posted
	Small molecule	Pexidartinib (PLX3397)	I	NCT02452424	Pembrolizumab	Melanoma and other solid tumors	Terminated for lack of clinical efficacy
	Small molecule	Pexidartinib (PLX3397)	I/II	NCT01596751	Eribulin	Metastatic breast cancer	Well tolerated at 1000 mg/day, but with limited efficacy
	Antibody	LY3022855 (Lilly)	I	NCT02718911	Durvalumab or tremelimumab	Advanced solid tumors	No efficacy, but well tolerated
	Antibody	LY3022855 (Lilly)	I	NCT02265536	Monotherapy	Breast and prostate cancer	Well tolerated with evidence of immune modulation; limited clinical efficacy observed
	Antibody	LY3022855 (Lilly)	I	NCT03153410	Cyclophosphamide, GVAX and pembrolizumab	PDAC	No results posted
	Antibody	LY3022855 (Lilly)	I/II	NCT03101254	Cobimetinib and vemurafenib	Melanoma	Poorly tolerated; limited efficacy. Phase II halted
	Antibody	Cabiralizumab (BMS-986227, FPA008)	II	NCT04050462	Nivolumab	HCC	No results posted
	Antibody	Cabiralizumab (BMS-986227, FPA008)	I/II	NCT03335540	Nivolumab	Solid tumors	No results posted
	Antibody	Cabiralizumab (BMS-986227, FPA008)	II	NCT03336216	Nivolumab with and without chemotherapy	PDAC	Limited efficacy
	Antibody	Cabiralizumab (BMS-986227, FPA008)	II	NCT03697564	Nivolumab and gemcitabine	PDAC	No results posted
	Antibody	Cabiralizumab (BMS-986227, FPA008)	II	NCT03768531	Nivolumab	Biliary tract cancer	Withdrawn
	Antibody	Cabiralizumab (BMS-986227, FPA008)	II	NCT03927105	Nivolumab	Relapsed/refractory T cell lymphoma	Safety data reported
	Antibody	Cabiralizumab (BMS-986227, FPA008)	I	NCT03431948	Nivolumab and radiotherapy	Advanced metastatic cancers	No results posted
CSF1 antagonists	Antibody	Lacnotuzumab (MCS110)	I/II	NCT02807844	PDR001	Solid tumors	Safety reported
	Antibody	Lacnotuzumab (MCS110) (Novartis)	II	NCT02435680	Carboplatin and gemcitabine	TNBC	Safety reported, no efficacy

(*Continued*)

Therapeutic target	Drug type	Drug name	Phase	Trial identifier	Combination regimen	Targeted disease	Clinical outcomes
	Antibody	Lacnotuzumab (MCS110) (Novartis)	I/II	NCT03742349	Spartalizumab and LAG525	TNBC	No results posted
	Antibody	Lacnotuzumab (MCS110)	I/II	NCT02807844	PDROO1	Solid tumors	Preliminary safety and limited efficacy
	Antibody	Lacnotuzumab (MCS110)	II	NCT02435680	Carboplatin and gemcitabine	TNBC	Safe, limited efficacy
	Antibody	Lacnotuzumab (MCS110)	I/II	NCT03742349	Spartalizumab and LAG525	TNBC	No results posted
CCR2 antagonists	Small molecule	PF-04136309 (PF-6309)	Ib/II	NCT01413022	FOLFIRINOX	PDAC	Potential efficacy signal
	Small molecule	PF-04136309 (PF-6309)	Ib/II	NCT02732938	Nab-paclitaxel	PDAC	No efficacy signal and increased toxicity
	Small molecule	BMS-813160 (BMS CCR2/5 inhibitor)	II	NCT04123379	Nivolumab	HCC/NSCLC	No results posted
	Small molecule	BMS-813160 (BMS CCR2/5 inhibitor)	I/II	NCT03767582	GVAX, radiotherapy and nivolumab	PDAC	No results posted
	Small molecule	BMS-813160 (BMS CCR2/5 inhibitor)	I/II	NCT03496662	Gemcitabine, paclitaxel and nivolumab	PDAC	Results reported in *ClinicalTrials.gov*
CXCR2/IL-8 antagonists	Small molecule	AZDS5069 (AstraZeneca)	I/II	NCT02499328	Durvalumab	HNSCC	Safety data reported, no efficacy
	Small molecule	AZDS5069 (AstraZeneca)	I/II	NCT02583477	Durvalumab	PDAC	Minimal efficacy observed
	Small molecule	AZDS5069 (AstraZeneca)	I/II	NCT03177187	Enzalutamide	Metastatic castrate-resistant prostate cancer	Terminated
	Antibody	BMS-986253 (HuMax-IL8)	I/II	NCT03689699	Nivolumab and degarelix	Hormone-sensitive prostate cancer	No results posted
	Antibody	BMS-986253 (HuMax-IL8)	I/II	NCT04050462	Nivolumab	HCC	No results posted
	Antibody	BMS-986253 (HuMax-IL8)	I	NCT04123379	Nivolumab	HCC, NSCLC	No results posted
	Antibody	BMS-986253 (HuMax-IL8)	I/II	NCT03400332	Nivolumab or nivolumab and ipilimumab	Metastatic or unresectable solid tumors	No results posted
	Antibody	BMS-986253 (HuMax-IL8)	I	NCT04572451	Radiotherapy and nivolumab	Metastatic solid tumors	No results posted
CXCR4 antagonists	Small molecule	USL311	I/II	NCT02765165	Monotherapy or with lomustine	Advanced solid tumors; relapsed/recurrent glioblastoma multiforme	Due to early termination of study in phase 1, efficacy outcomes were not analyzed for subjects in part 1a or part 1b
	Peptide	LY2510924	I	NCT02737072	Durvalumab	Advanced refractory solid tumors	No dose-limiting toxicities observed. Recommended phase 2 dose: 40 mg LY2510924 SC daily with 1500 mg durvalumab IV, showing acceptable safety and tolerability
	Peptide-drug conjugate	MB1707 conjugated CXCR4 peptide antagonist	I	NCT05465590	Conjugated with paclitaxel	Advanced cancer	Withdrawn

Abbreviations: CSF1R, colony-stimulating factor 1 receptor; PD1, programmed cell death protein 1; PDL1, programmed death-ligand 1; PDAC, pancreatic ductal adenocarcinoma; CRC, colorectal cancer; TNBC, triple-negative breast cancer; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; GVAX, granulocyte-macrophage colony stimulating factor vaccine; CTLA4, cytotoxic T-lymphocyte antigen 4; HNSCC, head and neck squamous cell carcinoma; IL-8, interleukin 8; GBM, glioblastoma multiforme; SC, subcutaneous; IV, intravenous; FOLFIRINOX, combination chemotherapy regimen (5-FU, leucovorin, irinotecan, and oxaliplatin).

various types of solid cancer [14].

Preclinical studies have shown enhanced efficacy of CCR2 inhibition in various cancer treatments including chemotherapy and immunotherapy [251–255]. A phase 1b study of CCR2 inhibition with the small molecule inhibitor PF-04136309 combined with FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) chemotherapy showed an increase in efficacy over the group with FOLFIRINOX alone (NCT01413022). Although CCL2–CCR2 blockade could impair the recruitment of circulating monocytes, the tissue resident macrophages in PDAC were demonstrated as key regulators in cancer progression [256] and should be considered as therapeutic targets. Interestingly, despite the improved efficacy, patients receiving CCR2 inhibition showed increased tumor-infiltrating $CXCR2^+$ TAN following treatment. This compensatory recruitment of alternative myeloid subsets may lead to a persistent immunosuppressive TME, highlighting the potential consideration of combined inhibition of myeloid cell chemotactic pathways [257]. In various cancers, inhibitors AMG 820 targeting the CSF1R as monotherapy or combination with pembrolizumab (NCT02713529) had not shown significant anti-tumor effects [258]. The limitations in the efficacy of CSF1R inhibitors might be due to insufficient depletion of heterogeneous protumoral macrophage populations and diverse protumorigenic compensatory mechanisms. In colorectal cancer, anti-CSF1R therapy selectively targeted and reduced the number of pro-inflammatory macrophages within the tumor, while a population of pro-angiogenic macrophages persisted [259]. Moreover, inhibition of CSF1R conversely caused the recruitment of PMN-MDSCs and was accompanied by the accumulation of $Foxp3^+$ regulatory T cells, which limited the efficacy of the treatment [260,261]. Similar compensatory mechanism was observed in the treatment of small-molecule inhibitor of CXCR1 and CXCR2, possibly due to co-expression of CXCR1 and CSF1R on macrophages [262]. These observations underscored the need for further investigation into the potential benefits of the combination of targeting multiple chemotaxis-related pathways.

Despite the association of TAM and MDSC infiltration in tumors with poor prognosis and treatment resistance, the clinical translation of therapies that solely inhibit overall myeloid cell infiltration remains challenging. This may be primarily due to the heterogeneity of tumor-associated myeloid cells. The pro- and anti-tumor myeloid subtypes often simultaneously coexist within the tumor milieu, potentially competing for the balance of the local myeloid response. Our recent studies revealed that the balance of microenvironmental myeloid cell response significantly impacts the TIME status, tumor progression, and efficacy of immunotherapy in both mice and patients [263,264]. Therefore, further understanding the environmental factors and key subsets involved in pro-tumor myeloid responses may provide an alternative approach to tipping the balance of myeloid response toward tumor suppression, thereby enhancing the benefits of myeloid-targeted therapy.

Conclusions and perspective

In addition to their tumor-promoting activities, myeloid cells are also critical players in mediating the immune surveillance and therapeutic efficacy against tumors. That could explain that direct targeting myeloid cells or lineages failed to achieve therapeutic benefit. Recent studies, especially those concerning the metabolic rewiring (involving multiple metabolic pathways) and accumulation (including the non-canonical mechanisms) of myeloid cells within tumors, have greatly advanced our understanding about the diverse routes leading to the specific characteristics and functions of these cells, thus providing novel targets for stand-alone or combinational anti-tumor treatments.

Myeloid cells might simultaneously exhibit activatory and inhibitory properties. For example, activated monocytes/macrophages often express high levels of PD-L1 in many tissues. The ultimate functions of these cells depend on the composition of and receptors expressed by their surrounding cells. Therefore, deciphering the interaction network between regional myeloid and non-myeloid cells is of utmost importance to determine the key molecules/pathways in regulating their functions. In addition, as proposed by Song *et al.* in their new concept of onco-spheres in cancer ecosystem, cancer cells should be conceived as “living organisms” and it is important to explore their interacting with cellular or noncellular components in the host internal environment, not only within local TME, but also with distant organ niche, host’s nervous, endocrine and immune systems [106]. Technologies including scRNA-seq, multiplex IHC, and mass cytometry, have greatly improved our ability to explore the diversity of tumor-associated myeloid cells, and future advances in the field will provide more insights to build up myeloid-based models for precision medicine. Future studies will also enable the next wave of cancer immunotherapy agents that will selectively target pro-tumoral myeloid cell subsets, while leaving those anti-tumoral ones unimpacted, to further enhance the clinical outcomes for patients.

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Compliance with ethics guidelines

Conflicts of interest Qiaomin Hua, Zhixiong Li, Yulan Weng, Yan Wu, and Limin Zheng have declared that no conflict of interest exists.

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References

1. de Visser KE, Joyce JA. The evolving tumor microenvironment from cancer initiation to metastatic outgrowth. Cancer Cell 2023; 41(3): 374–403
2. Mellman I, Chen DS, Powles T, Turley SJ. The cancer-immunity cycle: indication, genotype, and immunotype. Immunity 2023; 56(10): 2188–2205
3. Kubli SP, Berger T, Araujo DV, Siu LL, Mak TW. Beyond immune checkpoint blockade: emerging immunological strategies. Nat Rev Drug Discov 2021; 20(12): 899–919
4. Morad G, Helmink BA, Sharma P, Wargo JA. Hallmarks of response, resistance, and toxicity to immune checkpoint blockade. Cell 2022; 185(3): 576
5. Topalian SL, Forde PM, Emens LA, Yarchoan M, Smith KN, Pardoll DM. Neoadjuvant immune checkpoint blockade: a window of opportunity to advance cancer immunotherapy. Cancer Cell 2023; 41(9): 1551–1566
6. Cassetta L, Pollard JW. Targeting macrophages: therapeutic approaches in cancer. Nat Rev Drug Discov 2018; 17(12): 887–904
7. Engblom C, Pfirschke C, Pittet MJ. The role of myeloid cells in cancer therapies. Nat Rev Cancer 2016; 16(7): 447–462
8. Mantovani A, Marchesi F, Jaillon S, Garlanda C, Allavena P. Tumor-associated myeloid cells: diversity and therapeutic targeting. Cell Mol Immunol 2021; 18(3): 566–578
9. Veglia F, Sanseviero E, Gabrilovich DI. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. Nat Rev Immunol 2021; 21(8): 485–498
10. Cheng J, Huo DH, Kuang DM, Yang J, Zheng L, Zhuang SM. Human macrophages promote the motility and invasiveness of osteopontin-knockdown tumor cells. Cancer Res 2007; 67(11): 5141–5147
11. Mantovani A, Garlanda C. Humoral innate immunity and acute-phase proteins. N Engl J Med 2023; 388(5): 439–452
12. Mantovani A, Allavena P, Marchesi F, Garlanda C. Macrophages as tools and targets in cancer therapy. Nat Rev Drug Discov 2022; 21(11): 799–820
13. van Vlerken-Ysla L, Tyurina YY, Kagan VE, Gabrilovich DI. Functional states of myeloid cells in cancer. Cancer Cell 2023; 41(3): 490–504
14. Barry ST, Gabrilovich DI, Sansom OJ, Campbell AD, Morton JP. Therapeutic targeting of tumour myeloid cells. Nat Rev Cancer 2023; 23(4): 216–237
15. Goswami S, Anandhan S, Raychaudhuri D, Sharma P. Myeloid cell-targeted therapies for solid tumours. Nat Rev Immunol 2023; 23(2): 106–120
16. Chen S, Saeed AFUH, Liu Q, Jiang Q, Xu H, Xiao GG, Rao L, Duo Y. Macrophages in immunoregulation and therapeutics. Signal Transduct Target Ther 2023; 8(1): 207
17. Lazarov T, Juarez-Carreño S, Cox N, Geissmann F. Publisher correction: physiology and diseases of tissue-resident macrophages. Nature 2023; 619(7970): E51
18. Guilliams M, Mildner A, Yona S. Developmental and functional heterogeneity of monocytes. Immunity 2018; 49(4): 595–613
19. Youn JI, Collazo M, Shalova IN, Biswas SK, Gabrilovich DI. Characterization of the nature of granulocytic myeloid-derived suppressor cells in tumor-bearing mice. J Leukoc Biol 2012; 91(1): 167–181
20. Grover A, Sanseviero E, Timosenko E, Gabrilovich DI. Myeloid-derived suppressor cells: a propitious road to clinic. Cancer Discov 2021; 11(11): 2693–2706
21. Tcyganov E, Mastio J, Chen E, Gabrilovich DI. Plasticity of myeloid-derived suppressor cells in cancer. Curr Opin Immunol 2018; 51: 76–82
22. Xiang XN, Wang J, Lu D, Xu X. Targeting tumor-associated macrophages to synergize tumor immunotherapy. Signal Transduct Target Ther 2021; 6(1): 75
23. Christofides A, Strauss L, Yeo A, Cao C, Charest A, Boussiotis VA. The complex role of tumor-infiltrating macrophages. Nat Immunol 2022; 23(8): 1148–1156
24. Wang B, Xu D, Yu X, Ding T, Rao H, Zhan Y, Zheng L, Li L. Association of intra-tumoral infiltrating macrophages and regulatory T cells is an independent prognostic factor in gastric cancer after radical resection. Ann Surg Oncol 2011; 18(9): 2585–2593
25. Li J, Ye Y, Liu Z, Zhang G, Dai H, Li J, Zhou B, Li Y, Zhao Q, Huang J, Feng J, Liu S, Ruan P, Wang J, Liu J, Huang M, Liu X, Yu S, Liang Z, Ma L, Gou X, Zhang G, Chen N, Lu Y, Di C, Xia Q, Pan J, Feng R, Cai Q, Su S. Macrophage mitochondrial fission improves cancer cell phagocytosis induced by therapeutic antibodies and is impaired by glutamine competition. Nat Can 2022; 3(4): 453–470
26. Deng ZH, Loyher PL, Lazarov T, Li L, Shen Z, Bhinder B, Yang H, Zhong Y, Alberdi A, Massague J, Sun JC, Benezra R, Glass CK, Elemento O, Iacobuzio-Donahue CA, Geissmann F. The nuclear factor ID3 endows macrophages with a potent anti-tumour activity. Nature 2024; 626(8000): 864–873
27. Goubet AG, Pittet MJ. Unveiling the antitumor function of ID3 in liver macrophages. Nat Immunol 2024; 25(3): 394–395
28. Ding CL, Shrestha R, Zhu X, Geller AE, Wu S, Woeste MR, Li W, Wang H, Yuan F, Xu R, Chariker JH, Hu X, Li H, Tieri D, Zhang HG, Rouchka EC, Mitchell R, Siskind LJ, Zhang X, Xu XG, McMasters KM, Yu Y, Yan J. Inducing trained immunity in pro-metastatic macrophages to control tumor metastasis. Nat Immunol 2023; 24(2): 239–254
29. Kuang DM, Wu Y, Chen N, Cheng J, Zhuang SM, Zheng L. Tumor-derived hyaluronan induces formation of immunosuppressive macrophages through transient early

activation of monocytes. Blood 2007; 110(2): 587–595
30. Bied M, Ho WW, Ginhoux F, Blériot C. Roles of macrophages in tumor development: a spatiotemporal perspective. Cell Mol Immunol 2023; 20(9): 983–992
31. Rashidi A, Billingham LK, Zolp A, Chia T, Silvers C, Katz JL, Park CH, Delay S, Boland L, Geng Y, Markwell SM, Dmello C, Arrieta VA, Zilinger K, Jacob IM, Lopez-Rosas A, Hou D, Castro B, Steffens AM, McCortney K, Walshon JP, Flowers MS, Lin H, Wang H, Zhao J, Sonabend A, Zhang P, Ahmed AU, Brat DJ, Heiland DH, Lee-Chang C, Lesniak MS, Chandel NS, Miska J. Myeloid cell-derived creatine in the hypoxic niche promotes glioblastoma growth. Cell Metab 2024; 36(1): 62–77.e8
32. Zhao L, Wu Y, Xie XD, Chu YF, Li JQ, Zheng L. c-Met identifies a population of matrix metalloproteinase 9-producing monocytes in peritumoural stroma of hepatocellular carcinoma. J Pathol 2015; 237(3): 319–329
33. Shi QZ, Shen Q, Liu Y, Shi Y, Huang W, Wang X, Li Z, Chai Y, Wang H, Hu X, Li N, Zhang Q, Cao X. Increased glucose metabolism in TAMs fuels O-GlcNAcylation of lysosomal Cathepsin B to promote cancer metastasis and chemoresistance. Cancer Cell 2022; 40(10): 1207–1222.e10
34. Chen DP, Ning WR, Li XF, Wei Y, Lao XM, Wang JC, Wu Y, Zheng L. Peritumoral monocytes induce cancer cell autophagy to facilitate the progression of human hepatocellular carcinoma. Autophagy 2018; 14(8): 1335–1346
35. Xu ZQ, Zhao L, Zhu LY, He M, Zheng L, Wu Y. MicroRNA-17, 20a regulates the proangiogenic function of tumor-associated macrophages via targeting hypoxia-inducible factor 2α. PLoS One 2013; 8(10): e77890
36. Hongu T, Pein M, Insua-Rodríguez J, Gutjahr E, Mattavelli G, Meier J, Decker K, Descot A, Bozza M, Harbottle R, Trumpp A, Sinn HP, Riedel A, Oskarsson T. Perivascular tenascin C triggers sequential activation of macrophages and endothelial cells to generate a pro-metastatic vascular niche in the lungs. Nat Can 2022; 3(4): 486–504
37. Mirzapour MH, Heidari-Foroozan M, Razi S, Rezaei N. The pro-tumorigenic responses in metastatic niches: an immunological perspective. Clin Transl Oncol 2023; 25(2): 333–344
38. DeNardo DG, Ruffell B. Macrophages as regulators of tumour immunity and immunotherapy. Nat Rev Immunol 2019; 19(6): 369–382
39. Morrissey SM, Zhang F, Ding C, Montoya-Durango DE, Hu X, Yang C, Wang Z, Yuan F, Fox M, Zhang H, Guo H, Tieri D, Kong M, Watson CT, Mitchell RA, Zhang X, McMasters KM, Huang J, Yan J. Tumor-derived exosomes drive immunosuppressive macrophages in a pre-metastatic niche through glycolytic dominant metabolic reprogramming. Cell Metab 2021; 33(10): 2040–2058.e10
40. Lasser SA, Ozbay Kurt FG, Arkhypov I, Utikal J, Umansky V. Myeloid-derived suppressor cells in cancer and cancer therapy. Nat Rev Clin Oncol 2024; 21(2): 147–164
41. Liu ZD, Zhang ZM. Mapping cell types across human tissues. Science 2022; 376(6594): 695–696
42. Xue RD, Zhang Q, Cao Q, Kong R, Xiang X, Liu H, Feng M, Wang F, Cheng J, Li Z, Zhan Q, Deng M, Zhu J, Zhang Z, Zhang N. Liver tumour immune microenvironment subtypes and neutrophil heterogeneity. Nature 2022; 612(7938): 141–147
43. Kuang DM, Zhao Q, Xu J, Yun JP, Wu C, Zheng L. Tumor-educated tolerogenic dendritic cells induce CD3ε down-regulation and apoptosis of T cells through oxygen-dependent pathways. J Immunol 2008; 181(5): 3089–3098
44. Geiger R, Rieckmann JC, Wolf T, Basso C, Feng Y, Fuhrer T, Kogadeeva M, Picotti P, Meissner F, Mann M, Zamboni N, Sallusto F, Lanzavecchia A. L-arginine modulates T cell metabolism and enhances survival and anti-tumor activity. Cell 2016; 167(3): 829–842.e13
45. Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: time for reassessment. F1000Prime Rep 2014; 6: 6
46. Raber P, Ochoa AC, Rodríguez PC. Metabolism of L-arginine by myeloid-derived suppressor cells in cancer: mechanisms of T cell suppression and therapeutic perspectives. Immunol Invest 2012; 41(6-7): 614–634
47. Rodriguez PC, Quiceno DG, Zabaleta J, Ortiz B, Zea AH, Piazuelo MB, Delgado A, Correa P, Brayer J, Sotomayor EM, Antonia S, Ochoa JB, Ochoa AC. Arginase I production in the tumor microenvironment by mature myeloid cells inhibits T-cell receptor expression and antigen-specific T-cell responses. Cancer Res 2004; 64(16): 5839–5849
48. Munn DH, Shafizadeh E, Attwood JT, Bondarev I, Pashine A, Mellor AL. Inhibition of T cell proliferation by macrophage tryptophan catabolism. J Exp Med 1999; 189(9): 1363–1372
49. Frumento G, Rotondo R, Tonetti M, Damonte G, Benatti U, Ferrara GB. Tryptophan-derived catabolites are responsible for inhibition of T and natural killer cell proliferation induced by indoleamine 2, 3-dioxygenase. J Exp Med 2002; 196(4): 459–468
50. Munn DH, Sharma MD, Baban B, Harding HP, Zhang Y, Ron D, Mellor AL. GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2, 3-dioxygenase. Immunity 2005; 22(5): 633–642
51. Chiesa MD, Carlomagno S, Frumento G, Balsamo M, Cantoni C, Conte R, Moretta L, Moretta A, Vitale M. The tryptophan catabolite L-kynurenine inhibits the surface expression of NKp46-and NKG2D-activating receptors and regulates NK-cell function. Blood 2006; 108(13): 4118–4125
52. Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. J Immunol 2010; 185(6): 3190–3198
53. Movahedi K, Laoui D, Gysemans C, Baeten M, Stangé G, Van den Bossche J, Mack M, Pipeleers D, In't Veld P, De Baetselier P, Van Ginderachter JA. Different tumor microenvironments contain functionally distinct subsets of macrophages derived from Ly6C (high) monocytes. Cancer Res 2010; 70(14): 5728–5739
54. Marigo I, Zilio S, Desantis G, Mlecnik B, Agnellini AHR, Ugel S, Sasso MS, Qualls JE, Kratochvill F, Zanovello P, Molon B, Ries CH, Runza V, Hoves S, Bilocq AM, Bindea G, Mazza EMC, Bicciato S, Galon J, Murray PJ, Bronte V. T cell cancer therapy requires CD40–CD40L activation of tumor necrosis factor and inducible nitric-oxide-synthase-producing dendritic cells. Cancer Cell 2016; 30(3): 377–390
55. Kusmartsev S, Gabrilovich DI. STAT1 signaling regulates tumor-associated macrophage-mediated T cell deletion. J Immunol 2005; 174(8): 4880–4891
56. Nagaraj S, Gupta K, Pisarev V, Kinarsky L, Sherman S, Kang L, Herber DL, Schneck J, Gabrilovich DI. Altered recognition of

antigen is a mechanism of $CD8^+$ T cell tolerance in cancer. Nat Med 2007; 13(7): 828–835
57. Schmielau J, Finn OJ. Activated granulocytes and granulocyte-derived hydrogen peroxide are the underlying mechanism of suppression of t-cell function in advanced cancer patients. Cancer Res 2001; 61(12): 4756–4760
58. Corzo CA, Cotter MJ, Cheng P, Cheng F, Kusmartsev S, Sotomayor E, Padhya T, McCaffrey TV, McCaffrey JC, Gabrilovich DI. Mechanism regulating reactive oxygen species in tumor-induced myeloid-derived suppressor cells. J Immunol 2009; 182(9): 5693–5701
59. Hamilton MJ, Bosiljcic M, LePard NE, Halvorsen EC, Ho VW, Banáth JP, Krystal G, Bennewith KL. Macrophages are more potent immune suppressors *ex vivo* than immature myeloid-derived suppressor cells induced by metastatic murine mammary carcinomas. J Immunol 2014; 192(1): 512–522
60. OuYang LY, Wu XJ, Ye SB, Zhang R, Li ZL, Liao W, Pan ZZ, Zheng LM, Zhang XS, Wang Z, Li Q, Ma G, Li J. Tumor-induced myeloid-derived suppressor cells promote tumor progression through oxidative metabolism in human colorectal cancer. J Transl Med 2015; 13(1): 1–12
61. Antonioli L, Pacher P, Vizi ES, Haskó G. CD39 and CD73 in immunity and inflammation. Trends Mol Med 2013; 19(6): 355–367
62. Takenaka MC, Gabriely G, Rothhammer V, Mascanfroni ID, Wheeler MA, Chao CC, Gutiérrez-Vázquez C, Kenison J, Tjon EC, Barroso A, Vandeventer T, de Lima KA, Rothweiler S, Mayo L, Ghannam S, Zandee S, Healy L, Sherr D, Farez MF, Prat A, Antel J, Reardon DA, Zhang H, Robson SC, Getz G, Weiner HL, Quintana FJ. Control of tumor-associated macrophages and T cells in glioblastoma via AHR and CD39. Nat Neurosci 2019; 22(5): 729–740
63. Ruffell B, Chang-Strachan D, Chan V, Rosenbusch A, Ho CMT, Pryer N, Daniel D, Hwang ES, Rugo HS, Coussens LM. Macrophage IL-10 blocks $CD8^+$ T cell-dependent responses to chemotherapy by suppressing IL-12 expression in intratumoral dendritic cells. Cancer Cell 2014; 26(5): 623–637
64. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol 2001; 19(1): 683–765
65. Hart KM, Byrne KT, Molloy MJ, Usherwood EM, Berwin B. IL-10 immunomodulation of myeloid cells regulates a murine model of ovarian cancer. Front Immunol 2011; 2: 29
66. Ip WE, Hoshi N, Shouval DS, Snapper S, Medzhitov R. Anti-inflammatory effect of IL-10 mediated by metabolic reprogramming of macrophages. Science 2017; 356(6337): 513–519
67. Krawczyk CM, Holowka T, Sun J, Blagih J, Amiel E, DeBerardinis RJ, Cross JR, Jung E, Thompson CB, Jones RG, Pearce EJ. Toll-like receptor–induced changes in glycolytic metabolism regulate dendritic cell activation. Blood 2010; 115(23): 4742–4749
68. Smith LK, Boukhaled GM, Condotta SA, Mazouz S, Guthmiller JJ, Vijay R, Butler NS, Bruneau J, Shoukry NH, Krawczyk CM, Richer MJ. Interleukin-10 directly inhibits $CD8^+$ T cell function by enhancing N-glycan branching to decrease antigen sensitivity. Immunity 2018; 48(2): 299–312.e5
69. Li H, Han Y, Guo Q, Zhang M, Cao X. Cancer-expanded myeloid-derived suppressor cells induce anergy of NK cells through membrane-bound TGF-β1. J Immunol 2009; 182(1): 240–249
70. Peng L, Zhang J, Teng Y, Zhao Y, Wang T, Mao F, Lv Y, Cheng P, Li W, Chen N, Duan M, Chen W, Guo G, Zou Q, Zhuang Y. Tumor-associated monocytes/macrophages impair NK-cell function via TGFβ1 in human gastric cancer. Cancer Immunol Res 2017; 5(3): 248–256
71. Batlle E, Massague J. Transforming growth factor-beta signaling in immunity and cancer. Immunity 2019; 50(4): 924–940
72. Ma X, Gao Y, Chen Y, Liu J, Yang C, Bao C, Wang Y, Feng Y, Song X, Qiao S. M2-type macrophages induce tregs generation by activating the TGF-β/Smad signalling pathway to promote colorectal cancer development. OncoTargets Ther 2021; 14: 5391–5402
73. Kos K, Salvagno C, Wellenstein MD, Aslam MA, Meijer DA, Hau CS, Vrijland K, Kaldenbach D, Raeven EAM, Schmittnaegel M, Ries CH, de Visser KE. Tumor-associated macrophages promote intratumoral conversion of conventional $CD4^+$ T cells into regulatory T cells via PD-1 signalling. OncoImmunology 2022; 11(1): 2063225
74. Wu Y, Kuang DM, Pan WD, Wan YL, Lao XM, Wang D, Li XF, Zheng L. Monocyte/macrophage-elicited natural killer cell dysfunction in hepatocellular carcinoma is mediated by CD48/2B4 interactions. Hepatology 2013; 57(3): 1107–1116
75. Park MD, Reyes-Torres I, LeBerichel J, Hamon P, LaMarche NM, Hegde S, Belabed M, Troncoso L, Grout JA, Magen A, Humblin E, Nair A, Molgora M, Hou J, Newman JH, Farkas AM, Leader AM, Dawson T, D'Souza D, Hamel S, Sanchez-Paulete AR, Maier B, Bhardwaj N, Martin JC, Kamphorst AO, Kenigsberg E, Casanova-Acebes M, Horowitz A, Brown BD, De Andrade LF, Colonna M, Marron TU, Merad M. TREM2 macrophages drive NK cell paucity and dysfunction in lung cancer. Nat Immunol 2023; 24(5): 792–801
76. Kuang DM, Xiao X, Zhao Q, Chen MM, Li XF, Liu RX, Wei Y, Ouyang FZ, Chen DP, Wu Y, Lao XM, Deng H, Zheng L. B7–H1-expressing antigen-presenting cells mediate polarization of protumorigenic Th22 subsets. J Clin Invest 2014; 124(10): 4657–4667
77. Kersten K, Hu KH, Combes AJ, Samad B, Harwin T, Ray A, Rao AA, Cai E, Marchuk K, Artichoker J, Courau T, Shi Q, Belk J, Satpathy AT, Krummel MF. Spatiotemporal co-dependency between macrophages and exhausted $CD8^+$ T cells in cancer. Cancer Cell 2022; 40(6): 624–638.e9
78. Chow A, Schad S, Green MD, Hellmann MD, Allaj V, Ceglia N, Zago G, Shah NS, Sharma SK, Mattar M, Chan J, Rizvi H, Zhong H, Liu C, Bykov Y, Zamarin D, Shi H, Budhu S, Wohlhieter C, Uddin F, Gupta A, Khodos I, Waninger JJ, Qin A, Markowitz GJ, Mittal V, Balachandran V, Durham JN, Le DT, Zou W, Shah SP, McPherson A, Panageas K, Lewis JS, Perry JSA, de Stanchina E, Sen T, Poirier JT, Wolchok JD, Rudin CM, Merghoub T. Tim-4^+ cavity-resident macrophages impair anti-tumor $CD8^+$ T cell immunity. Cancer Cell 2021; 39(7): 973–988.e9
79. Laumont CM, Banville AC, Gilardi M, Hollern DP, Nelson BH. Tumour-infiltrating B cells: immunological mechanisms, clinical impact and therapeutic opportunities. Nat Rev Cancer 2022; 22(7): 414–430
80. Wu RQ, Lao XM, Chen DP, Qin H, Mu M, Cao WJ, Deng J,

Wan CC, Zhan WY, Wang JC, Xu L, Chen MS, Gao Q, Zheng L, Wei Y, Kuang DM. Immune checkpoint therapy-elicited sialylation of IgG antibodies impairs antitumorigenic type I interferon responses in hepatocellular carcinoma. Immunity 2023; 56(1): 180–192.e11

81. Chen Z, Zhang G, Ren X, Yao Z, Zhou Q, Ren X, Chen S, Xu L, Sun K, Zeng Q, Kuang M, Kuang DM, Peng S. Cross-talk between myeloid and B cells shapes the distinct microenvironments of primary and secondary liver cancer. Cancer Res 2023; 83(21): 3544–3561
82. Shaul ME, Zlotnik A, Tidhar E, Schwartz A, Arpinati L, Kaisar-Iluz N, Mahroum S, Mishalian I, Fridlender ZG. Tumor-associated neutrophils drive B-cell recruitment and their differentiation to plasma cells. Cancer Immunol Res 2021; 9(7): 811–824
83. Wang Y, Schafer CC, Hough KP, Tousif S, Duncan SR, Kearney JF, Ponnazhagan S, Hsu HC, Deshane JS. Myeloid-derived suppressor cells impair B cell responses in lung cancer through IL-7 and STAT5. J Immunol 2018; 201(1): 278–295
84. Peng ZP, Jiang ZZ, Guo HF, Zhou MM, Huang YF, Ning WR, Huang JH, Zheng L, Wu Y. Glycolytic activation of monocytes regulates the accumulation and function of neutrophils in human hepatocellular carcinoma. J Hepatol 2020; 73(4): 906–917
85. Matusiak M, Hickey JW, van IJzendoorn DGP, Lu G, Kidziński L, Zhu S, Colburg DRC, Luca B, Phillips DJ, Brubaker SW, Charville GW, Shen J, Loh KM, Okwan-Duodu DK, Nolan GP, Newman AM, West RB, van de Rijn M. Spatially segregated macrophage populations predict distinct outcomes in colon cancer. Cancer Discov 2024; 14(8): 1418–1439
86. Sinha P, Clements VK, Bunt SK, Albelda SM, Ostrand-Rosenberg S. Cross-talk between myeloid-derived suppressor cells and macrophages subverts tumor immunity toward a type 2 response. J Immunol 2007; 179(2): 977–983
87. Bunt SK, Clements VK, Hanson EM, Sinha P, Ostrand-Rosenberg S. Inflammation enhances myeloid-derived suppressor cell cross-talk by signaling through Toll-like receptor 4. J Leukoc Biol 2009; 85(6): 996–1004
88. Thibodeau J, Bourgeois-Daigneault MC, Huppé G, Tremblay J, Aumont A, Houde M, Bartee E, Brunet A, Gauvreau ME, de Gassart A, Gatti E, Baril M, Cloutier M, Bontron S, Früh K, Lamarre D, Steimle V. Interleukin-10-induced MARCH1 mediates intracellular sequestration of MHC class II in monocytes. Eur J Immunol 2008; 38(5): 1225–1230
89. Kwak T, Wang F, Deng H, Condamine T, Kumar V, Perego M, Kossenkov A, Montaner LJ, Xu X, Xu W, Zheng C, Schuchter LM, Amaravadi RK, Mitchell TC, Karakousis GC, Mulligan C, Nam B, Masters G, Hockstein N, Bennett J, Nefedova Y, Gabrilovich DI. Distinct populations of immune-suppressive macrophages differentiate from monocytic myeloid-derived suppressor cells in cancer. Cell Rep 2020; 33(13): 108571
90. Corzo CA, Condamine T, Lu L, Cotter MJ, Youn JI, Cheng P, Cho HI, Celis E, Quiceno DG, Padhya T, McCaffrey TV, McCaffrey JC, Gabrilovich DI. HIF-1α regulates function and differentiation of myeloid-derived suppressor cells in the tumor microenvironment. J Exp Med 2010; 207(11): 2439–2453
91. Zhang Y, Li JQ, Jiang ZZ, Li L, Wu Y, Zheng L. CD169 identifies an anti-tumour macrophage subpopulation in human hepatocellular carcinoma. J Pathol 2016; 239(2): 231–241
92. Nalio Ramos R, Missolo-Koussou Y, Gerber-Ferder Y, Bromley CP, Bugatti M, Núñez NG, Tosello Boari J, Richer W, Menger L, Denizeau J, Sedlik C, Caudana P, Kotsias F, Niborski LL, Viel S, Bohec M, Lameiras S, Baulande S, Lesage L, Nicolas A, Meseure D, Vincent-Salomon A, Reyal F, Dutertre CA, Ginhoux F, Vimeux L, Donnadieu E, Buttard B, Galon J, Zelenay S, Vermi W, Guermonprez P, Piaggio E, Helft J. Tissue-resident FOLR2^{+} macrophages associate with CD8^{+} T cell infiltration in human breast cancer. Cell 2022; 185(7): 1189–1207.e25.
93. Liu CQ, Xu J, Zhou ZG, Jin LL, Yu XJ, Xiao G, Lin J, Zhuang SM, Zhang YJ, Zheng L. Expression patterns of programmed death ligand 1 correlate with different microenvironments and patient prognosis in hepatocellular carcinoma. Br J Cancer 2018; 119(1): 80–88
94. Wang L, Guo W, Guo Z, Yu J, Tan J, Simons DL, Hu K, Liu X, Zhou Q, Zheng Y, Colt EA, Yim J, Waisman J, Lee PP. PD-L1-expressing tumor-associated macrophages are immunostimulatory and associate with good clinical outcome in human breast cancer. Cell Rep Med 2024; 5(2): 101420
95. O'Neill LAJ, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. Nat Rev Immunol 2016; 16(9): 553–565
96. Liu J, Cao X. Glucose metabolism of TAMs in tumor chemoresistance and metastasis. Trends Cell Biol 2023; 33(11): 967–978
97. Reinfeld BI, Madden MZ, Wolf MM, Chytil A, Bader JE, Patterson AR, Sugiura A, Cohen AS, Ali A, Do BT, Muir A, Lewis CA, Hongo RA, Young KL, Brown RE, Todd VM, Huffstater T, Abraham A, O'Neil RT, Wilson MH, Xin F, Tantawy MN, Merryman WD, Johnson RW, Williams CS, Mason EF, Mason FM, Beckermann KE, Vander Heiden MG, Manning HC, Rathmell JC, Rathmell WK. Cell-programmed nutrient partitioning in the tumour microenvironment. Nature 2021; 593(7858): 282–288
98. Penny HL, Sieow JL, Gun SY, Lau MC, Lee B, Tan J, Phua C, Toh F, Nga Y, Yeap WH, Janela B, Kumar D, Chen H, Yeong J, Kenkel JA, Pang A, Lim D, Toh HC, Hon TLK, Johnson CI, Khameneh HJ, Mortellaro A, Engleman EG, Rotzschke O, Ginhoux F, Abastado JP, Chen J, Wong SC. Targeting glycolysis in macrophages confers protection against pancreatic ductal adenocarcinoma. Int J Mol Sci 2021; 22(12)
99. Fu C, Fu Z, Jiang C, Xia C, Zhang Y, Gu X, Zheng K, Zhou D, Tang S, Lyu S, Ma S. CD205^{+} polymorphonuclear myeloid-derived suppressor cells suppress antitumor immunity by overexpressing GLUT3. Cancer Sci 2021; 112(3): 1011–1025
100. De Leo A, Ugolini A, Yu X, Scirocchi F, Scocozza D, Peixoto B, Pace A, D'Angelo L, Liu JKC, Etame AB, Rughetti A, Nuti M, Santoro A, Vogelbaum MA, Conejo-Garcia JR, Rodriguez PC, Veglia F. Glucose-driven histone lactylation promotes the immunosuppressive activity of monocyte-derived macrophages in glioblastoma. Immunity 2024; 57(5): 1105–1123.e8
101. Chen DP, Ning WR, Jiang ZZ, Peng ZP, Zhu LY, Zhuang SM, Kuang DM, Zheng L, Wu Y. Glycolytic activation of peritumoral monocytes fosters immune privilege via the PFKFB3-PD-L1 axis in human hepatocellular carcinoma. J Hepatol 2019; 71(2): 333–343
102. Larionova I, Patysheva M, Iamshchikov P, Kazakova E, Kazakova A, Rakina M, Grigoryeva E, Tarasova A, Afanasiev S,

Bezgodova N, Kiselev A, Dobrodeev A, Kostromitskiy D, Cherdyntseva N, Kzhyshkowska J. PFKFB3 overexpression in monocytes of patients with colon but not rectal cancer programs pro-tumor macrophages and is indicative for higher risk of tumor relapse. Front Immunol 2023; 13: 1080501

103. Chen M, Liu H, Li Z, Ming AL, Chen H. Mechanism of PKM2 affecting cancer immunity and metabolism in tumor microenvironment. J Cancer 2021; 12(12): 3566–3574
104. Wenes M, Shang M, Di Matteo M, Goveia J, Martín-Pérez R, Serneels J, Prenen H, Ghesquière B, Carmeliet P, Mazzone M. Macrophage metabolism controls tumor blood vessel morphogenesis and metastasis. Cell Metab 2016; 24(5): 701–715
105. Chen D, Xie J, Fiskesund R, Dong W, Liang X, Lv J, Jin X, Liu J, Mo S, Zhang T, Cheng F, Zhou Y, Zhang H, Tang K, Ma J, Liu Y, Huang B. Chloroquine modulates antitumor immune response by resetting tumor-associated macrophages toward M1 phenotype. Nat Commun 2018; 9(1): 873
106. Zhang Z, Zheng Y, Chen Y, Yin Y, Chen Y, Chen Q, Hou Y, Shen S, Lv M, Wang T. Gut fungi enhances immunosuppressive function of myeloid-derived suppressor cells by activating PKM2-dependent glycolysis to promote colorectal tumorigenesis. Exp Hematol Oncol 2022; 11(1): 88
107. Yang X, Lu Y, Hang J, Zhang J, Zhang T, Huo Y, Liu J, Lai S, Luo D, Wang L, Hua R, Lin Y. Lactate-modulated immunosuppression of myeloid-derived suppressor cells contributes to the radioresistance of pancreatic cancer. Cancer Immunol Res 2020; 8(11): 1440–1451
108. Baumann T, Dunkel A, Schmid C, Schmitt S, Hiltensperger M, Lohr K, Laketa V, Donakonda S, Ahting U, Lorenz-Depiereux B, Heil JE, Schredelseker J, Simeoni L, Fecher C, Körber N, Bauer T, Hüser N, Hartmann D, Laschinger M, Eyerich K, Eyerich S, Anton M, Streeter M, Wang T, Schraven B, Spiegel D, Assaad F, Misgeld T, Zischka H, Murray PJ, Heine A, Heikenwälder M, Korn T, Dawid C, Hofmann T, Knolle PA, Höchst B. Regulatory myeloid cells paralyze T cells through cell-cell transfer of the metabolite methylglyoxal. Nat Immunol 2020; 21(5): 555–566
109. El-Kenawi A, Gatenbee C, Robertson-Tessi M, Bravo R, Dhillon J, Balagurunathan Y, Berglund A, Vishvakarma N, Ibrahim-Hashim A, Choi J, Luddy K, Gatenby R, Pilon-Thomas S, Anderson A, Ruffell B, Gillies R. Acidity promotes tumour progression by altering macrophage phenotype in prostate cancer. Br J Cancer 2019; 121(7): 556–566
110. Frank AC, Raue R, Fuhrmann DC, Sirait-Fischer E, Reuse C, Weigert A, Lütjohann D, Hiller K, Syed SN, Brüne B. Lactate dehydrogenase B regulates macrophage metabolism in the tumor microenvironment. Theranostics 2021; 11(15): 7570–7588
111. Apostolova P and Pearce EL. Lactic acid and lactate: revisiting the physiological roles in the tumor microenvironment. Trends Immunol 2022; 43(12): 969–977
112. Barbato A, Giallongo C, Giallongo S, Romano A, Scandura G, Concetta S, Zuppelli T, Lolicato M, Lazzarino G, Parrinello N, Del Fabro V, Fontana P, Aguennoz M, Li Volti G, Palumbo GA, Di Raimondo F, Tibullo D. Lactate trafficking inhibition restores sensitivity to proteasome inhibitors and orchestrates immuno-microenvironment in multiple myeloma. Cell Prolif 2023; 56(4): e13388
113. Zhao JL, Ye YC, Gao CC, Wang L, Ren KX, Jiang R, Hu SJ, Liang SQ, Bai J, Liang JL, Ma PF, Hu YY, Li BC, Nie YZ, Chen Y, Li XF, Zhang W, Han H, Qin HY. Notch-mediated lactate metabolism regulates MDSC development through the Hes1/MCT2/c-Jun axis. Cell Rep 2022; 38(10): 110451
114. Zhang D, Tang Z, Huang H, Zhou G, Cui C, Weng Y, Liu W, Kim S, Lee S, Perez-Neut M, Ding J, Czyz D, Hu R, Ye Z, He M, Zheng YG, Shuman HA, Dai L, Ren B, Roeder RG, Becker L, Zhao Y. Metabolic regulation of gene expression by histone lactylation. Nature 2019; 574(7779): 575–580
115. Li XM, Yang Y, Jiang FQ, Hu G, Wan S, Yan WY, He XS, Xiao F, Yang XM, Guo X, Lu JH, Yang XQ, Chen JJ, Ye WL, Liu Y, He K, Duan HX, Zhou YJ, Gan WJ, Liu F, Wu H. Histone lactylation inhibits RARγ expression in macrophages to promote colorectal tumorigenesis through activation of TRAF6-IL-6-STAT3 signaling. Cell Rep 2024; 43(2): 113688
116. Zhu CX, Yan K, Chen L, Huang RR, Bian ZH, Wei HR, Gu XM, Zhao YY, Liu MC, Suo CX, Li ZK, Yang ZY, Lu MQ, Hua XF, Li L, Zhao ZB, Sun LC, Zhang HF, Gao P, Lian ZX. Targeting OXCT1-mediated ketone metabolism reprograms macrophages to promote antitumor immunity via $CD8^+$ T cells in hepatocellular carcinoma. J Hepatol. 2024; 81(4): 690–703
117. Alexander RK, Liou YH, Knudsen NH, Starost KA, Xu C, Hyde AL, Liu S, Jacobi D, Liao NS, Lee CH. Bmal1 integrates mitochondrial metabolism and macrophage activation. eLife 2020; 9: e54090
118. Chen YJ, Li GN, Li XJ, Wei LX, Fu MJ, Cheng ZL, Yang Z, Zhu GQ, Wang XD, Zhang C, Zhang JY, Sun YP, Saiyin H, Zhang J, Liu WR, Zhu WW, Guan KL, Xiong Y, Yang Y, Ye D, Chen LL. Targeting IRG1 reverses the immunosuppressive function of tumor-associated macrophages and enhances cancer immunotherapy. Sci Adv 2023; 9(17): eadg0654
119. Wang X, Su S, Zhu Y, Cheng X, Cheng C, Chen L, Lei A, Zhang L, Xu Y, Ye D, Zhang Y, Li W, Zhang J. Metabolic Reprogramming via ACOD1 depletion enhances function of human induced pluripotent stem cell-derived CAR-macrophages in solid tumors. Nat Commun 2023; 14(1): 5778
120. Udumula MP, Sakr S, Dar S, Alvero AB, Ali-Fehmi R, Abdulfatah E, Li J, Jiang J, Tang A, Buekers T, Morris R, Munkarah A, Giri S, Rattan R. Ovarian cancer modulates the immunosuppressive function of $CD11b^+Gr1^+$ myeloid cells via glutamine metabolism. Mol Metab 2021; 53: 101272
121. Daneshmandi S, Choi JE, Yan Q, MacDonald CR, Pandey M, Goruganthu M, Roberts N, Singh PK, Higashi RM, Lane AN, Fan TWM, Wang J, McCarthy PL, Repasky EA, Mohammadpour H. Myeloid-derived suppressor cell mitochondrial fitness governs chemotherapeutic efficacy in hematologic malignancies. Nat Commun 2024; 15(1): 2803
122. Zhao H, Teng D, Yang L, Xu X, Chen J, Jiang T, Feng AY, Zhang Y, Frederick DT, Gu L, Cai L, Asara JM, Pasca di Magliano M, Boland GM, Flaherty KT, Swanson KD, Liu D, Rabinowitz JD, Zheng B. Myeloid-derived itaconate suppresses cytotoxic $CD8^+$ T cells and promotes tumour growth. Nat Metab 2022; 4(12): 1660–1673
123. Rodrigues Mantuano N, Stanczak MA, Oliveira IA, Kirchhammer N, Filardy AA, Monaco G, Santos RC, Fonseca AC, Fontes M, Bastos CS Jr, Dias WB, Zippelius A, Todeschini AR, Läubli H. Hyperglycemia enhances cancer immune evasion by inducing alternative macrophage polarization through increased O-GlcNAcylation. Cancer Immunol Res 2020; 8(10): 1262–1272

124. Hinshaw DC, Hanna A, Lama-Sherpa T, Metge B, Kammerud SC, Benavides GA, Kumar A, Alsheikh HA, Mota M, Chen D, Ballinger SW, Rathmell JC, Ponnazhagan S, Darley-Usmar V, Samant RS, Shevde LA. Hedgehog signaling regulates metabolism and polarization of mammary tumor-associated macrophages. Cancer Res 2021; 81(21): 5425–5437
125. Yan J, Horng T. Lipid metabolism in regulation of macrophage functions. Trends Cell Biol 2020; 30(12): 979–989
126. Rabold K, Aschenbrenner A, Thiele C, Boahen CK, Schiltmans A, Smit JWA, Schultze JL, Netea MG, Adema GJ, Netea-Maier RT. Enhanced lipid biosynthesis in human tumor-induced macrophages contributes to their protumoral characteristics. J Immunother Cancer 2020; 8(2): e000638
127. Liu C, Chikina M, Deshpande R, Menk AV, Wang T, Tabib T, Brunazzi EA, Vignali KM, Sun M, Stolz DB, Lafyatis RA, Chen W, Delgoffe GM, Workman CJ, Wendell SG, Vignali DAA. Treg cells promote the SREBP1-dependent metabolic fitness of tumor-promoting macrophages via repression of $CD8^+$ T cell-derived interferon-γ. Immunity 2019; 51(2): 381–397.e6
128. Liu M, O'Connor RS, Trefely S, Graham K, Snyder NW, Beatty GL. Metabolic rewiring of macrophages by CpG potentiates clearance of cancer cells and overcomes tumor-expressed CD47-mediated 'don't-eat-me' signal. Nat Immunol 2019; 20(3): 265–275
129. Song C, Ji Y, Wang W, Tao N. Ginger polysaccharide promotes myeloid-derived suppressor cell apoptosis by regulating lipid metabolism. Phytother Res 2023; 37(7): 2894–2901
130. Yan G, Zhao H, Zhang Q, Zhou Y, Wu L, Lei J, Wang X, Zhang J, Zhang X, Zheng L, Du G, Xiao W, Tang B, Miao H, Li Y. A RIPK3–PGE2 circuit mediates myeloid-derived suppressor cell-potentiated colorectal carcinogenesis. Cancer Res 2018; 78(19): 5586–5599
131. Dai E, Han L, Liu J, Xie Y, Kroemer G, Klionsky DJ, Zeh HJ, Kang R, Wang J, Tang D. Autophagy-dependent ferroptosis drives tumor-associated macrophage polarization via release and uptake of oncogenic KRAS protein. Autophagy 2020; 16(11): 2069–2083
132. Liu S, Zhang H, Li Y, Zhang Y, Bian Y, Zeng Y, Yao X, Wan J, Chen X, Li J, Wang Z, Qin Z. S100A4 enhances protumor macrophage polarization by control of PPAR-γ-dependent induction of fatty acid oxidation. J Immunother Cancer 2021; 9(6): e002548
133. Liu PS, Chen YT, Li X, Hsueh PC, Tzeng SF, Chen H, Shi PZ, Xie X, Parik S, Planque M, Fendt SM, Ho PC. CD40 signal rewires fatty acid and glutamine metabolism for stimulating macrophage anti-tumorigenic functions. Nat Immunol 2023; 24(3): 452–462
134. Hossain F, Al-Khami AA, Wyczechowska D, Hernandez C, Zheng L, Reiss K, Valle LD, Trillo-Tinoco J, Maj T, Zou W, Rodriguez PC, Ochoa AC. Inhibition of fatty acid oxidation modulates immunosuppressive functions of myeloid-derived suppressor cells and enhances cancer therapies. Cancer Immunol Res 2015; 3(11): 1236–1247
135. Xin G, Chen Y, Topchyan P, Kasmani MY, Burns R, Volberding PJ, Wu X, Cohn A, Chen Y, Lin CW, Ho PC, Silverstein R, Dwinell MB, Cui W. Targeting PIM1-mediated metabolism in myeloid suppressor cells to treat cancer. Cancer Immunol Res 2021; 9(4): 454–469
136. Mohammadpour H, MacDonald CR, McCarthy PL, Abrams SI, Repasky EA. β2-adrenergic receptor signaling regulates metabolic pathways critical to myeloid-derived suppressor cell function within the TME. Cell Rep 2021; 37(4): 109883
137. Wang Y, Chen W, Qiao S, Zou H, Yu X, Yang Y, Li Z, Wang J, Chen M, Xu J, Zheng L. Lipid droplet accumulation mediates macrophage survival and Treg recruitment via the CCL20/CCR6 axis in human hepatocellular carcinoma. Cell Mol Immunol 2024; 21(10): 1120–1130
138. Yang P, Qin H, Li Y, Xiao A, Zheng E, Zeng H, Su C, Luo X, Lu Q, Liao M, Zhao L, Wei L, Varghese Z, Moorhead JF, Chen Y, Ruan XZ. CD36-mediated metabolic crosstalk between tumor cells and macrophages affects liver metastasis. Nat Commun 2022; 13(1): 5782
139. Zhou L, Wang M, Guo H, Hou J, Zhang Y, Li M, Wu X, Chen X, Wang L. Integrated analysis highlights the immunosuppressive role of $TREM2^+$ macrophages in hepatocellular carcinoma. Front Immunol. 2022; 13: 848367.
140. Huggins DN, LaRue RS, Wang Y, Knutson TP, Xu Y, Williams JW, Schwertfeger KL. Characterizing macrophage diversity in metastasis-bearing lungs reveals a lipid-associated macrophage subset. Cancer Res 2021; 81(20): 5284–5295
141. Di Conza G, Tsai CH, Gallart-Ayala H, Yu YR, Franco F, Zaffalon L, Xie X, Li X, Xiao Z, Raines LN, Falquet M, Jalil A, Locasale JW, Percipalle P, Masson D, Huang SCC, Martinon F, Ivanisevic J, Ho PC. Tumor-induced reshuffling of lipid composition on the endoplasmic reticulum membrane sustains macrophage survival and pro-tumorigenic activity. Nat Immunol 2021; 22(11): 1403–1415
142. Masetti M, Carriero R, Portale F, Marelli G, Morina N, Pandini M, Iovino M, Partini B, Erreni M, Ponzetta A, Magrini E, Colombo P, Elefante G, Colombo FS, den Haan JMM, Peano C, Cibella J, Termanini A, Kunderfranco P, Brummelman J, Chung MWH, Lazzeri M, Hurle R, Casale P, Lugli E, DePinho RA, Mukhopadhyay S, Gordon S, Di Mitri D. Lipid-loaded tumor-associated macrophages sustain tumor growth and invasiveness in prostate cancer. J Exp Med 2022; 219(2): e20210564
143. Veglia F, Tyurin VA, Blasi M, De Leo A, Kossenkov AV, Donthireddy L, To TKJ, Schug Z, Basu S, Wang F, Ricciotti E, DiRusso C, Murphy ME, Vonderheide RH, Lieberman PM, Mulligan C, Nam B, Hockstein N, Masters G, Guarino M, Lin C, Nefedova Y, Black P, Kagan VE, Gabrilovich DI. Fatty acid transport protein 2 reprograms neutrophils in cancer. Nature 2019; 569(7754): 73–78
144. Ugolini A, Tyurin VA, Tyurina YY, Tcyganov EN, Donthireddy L, Kagan VE, Gabrilovich DI, Veglia F. Polymorphonuclear myeloid-derived suppressor cells limit antigen cross-presentation by dendritic cells in cancer. JCI Insight. 2020; 5(15): e138581
145. Kim R, Hashimoto A, Markosyan N, Tyurin VA, Tyurina YY, Kar G, Fu S, Sehgal M, Garcia-Gerique L, Kossenkov A, Gebregziabher BA, Tobias JW, Hicks K, Halpin RA, Cvetesic N, Deng H, Donthireddy L, Greenberg A, Nam B, Vonderheide RH, Nefedova Y, Kagan VE, Gabrilovich DI. Ferroptosis of tumour neutrophils causes immune suppression in cancer. Nature 2022; 612(7939): 338–346
146. Gao C, Huang Q, Liu C, Kwong CHT, Yue L, Wan JB, Lee SMY, Wang R. Treatment of atherosclerosis by macrophage-biomimetic nanoparticles via targeted pharmacotherapy and

sequestration of proinflammatory cytokines. Nat Commun 2020; 11(1): 2622

147. Nakahara R, Aki S, Sugaya M, Hirose H, Kato M, Maeda K, Sakamoto DM, Kojima Y, Nishida M, Ando R, Muramatsu M, Pan M, Tsuchida R, Matsumura Y, Yanai H, Takano H, Yao R, Sando S, Shibuya M, Sakai J, Kodama T, Kidoya H, Shimamura T, Osawa T. Hypoxia activates SREBP2 through Golgi disassembly in bone marrow-derived monocytes for enhanced tumor growth. EMBO J 2023; 42(22): e114032
148. Lv Q, Zhang Y, Gao W, Wang J, Hu Y, Yang H, Xie Y, Lv Y, Zhang H, Wu D, Hu L, Wang J. CSF1R inhibition reprograms tumor-associated macrophages to potentiate anti-PD-1 therapy efficacy against colorectal cancer. Pharmacol Res 2024; 202: 107126
149. Dong Y, Zhang J, Wang Y, Zhang Y, Rappaport D, Yang Z, Han M, Liu Y, Fu Z, Zhao X, Tang C, Shi C, Zhang D, Li D, Ni S, Li A, Cui J, Li T, Sun P, Benny O, Zhang C, Zhao K, Chen C, Jiang X. Intracavitary spraying of nanoregulator-encased hydrogel modulates cholesterol metabolism of glioma-supportive macrophage for postoperative glioblastoma immunotherapy. Adv Mater 2024; 36(13): e2311109
150. Ye Z, Ai X, Yang K, Yang Z, Fei F, Liao X, Qiu Z, Gimple RC, Yuan H, Huang H, Gong Y, Xiao C, Yue J, Huang L, Saulnier O, Wang W, Zhang P, Dai L, Wang X, Wang X, Ahn YH, You C, Xu J, Wan X, Taylor MD, Zhao L, Rich JN, Zhou S. Targeting microglial metabolic rewiring synergizes with immune-checkpoint blockade therapy for glioblastoma. Cancer Discov 2023; 13(4): 974–1001
151. Liu Y, Wang Z, Jin H, Cui L, Huo B, Xie C, Li J, Ding H, Zhang H, Xiong W, Li M, Zhang H, Guo H, Li C, Wang T, Wang X, He W, Wang Z, Bei JX, Huang P, Liu J, Xia X. Squalene-epoxidase-catalyzed 24(S), 25-epoxycholesterol synthesis promotes trained-immunity-mediated antitumor activity. Cell Rep 2024; 43(4): 114094
152. Wu L, Liu X, Lei J, Zhang N, Zhao H, Zhang J, Deng H, Li Y. Fibrinogen-like protein 2 promotes tumor immune suppression by regulating cholesterol metabolism in myeloid-derived suppressor cells. J Immunother Cancer 2023; 11(12): e008081
153. Chen Y, Xu Y, Zhao H, Zhou Y, Zhang J, Lei J, Wu L, Zhou M, Wang J, Yang S, Zhang X, Yan G, Li Y. Myeloid-derived suppressor cells deficient in cholesterol biosynthesis promote tumor immune evasion. Cancer Lett 2023; 564: 216208
154. Strauss L, Mahmoud MAA, Weaver JD, Tijaro-Ovalle NM, Christofides A, Wang Q, Pal R, Yuan M, Asara J, Patsoukis N, Boussiotis VA. Targeted deletion of PD-1 in myeloid cells induces antitumor immunity. Sci Immunol 2020; 5(43): eaay1863
155. Xiao J, Wang S, Chen L, Ding X, Dang Y, Han M, Zheng Y, Shen H, Wu S, Wang M, Yang D, Li N, Dong C, Hu M, Su C, Li W, Hui L, Ye Y, Tang H, Wei B, Wang H. 25-hydroxycholesterol regulates lysosome AMP kinase activation and metabolic reprogramming to educate immunosuppressive macrophages. Immunity 2024; 57(5): 1087–1104.e7
156. Ma L, Wang L, Nelson AT, Han C, He S, Henn MA, Menon K, Chen JJ, Baek AE, Vardanyan A, Shahoei SH, Park S, Shapiro DJ, Nanjappa SG, Nelson ER. 27-Hydroxycholesterol acts on myeloid immune cells to induce T cell dysfunction, promoting breast cancer progression. Cancer Lett 2020; 493: 266–283
157. Baek AE, Yu YRA, He S, Wardell SE, Chang CY, Kwon S, Pillai RV, McDowell HB, Thompson JW, Dubois LG, Sullivan PM, Kemper JK, Gunn MD, McDonnell DP, Nelson ER. The cholesterol metabolite 27 hydroxycholesterol facilitates breast cancer metastasis through its actions on immune cells. Nat Commun 2017; 8(1): 864
158. Sag D, Cekic C, Wu R, Linden J, Hedrick CC. The cholesterol transporter ABCG1 links cholesterol homeostasis and tumour immunity. Nat Commun 2015; 6(1): 6354–6367
159. Goossens P, Rodriguez-Vita J, Etzerodt A, Masse M, Rastoin O, Gouirand V, Ulas T, Papantonopoulou O, Van Eck M, Auphan-Anezin N, Bebien M, Verthuy C, Vu Manh TP, Turner M, Dalod M, Schultze JL, Lawrence T. Membrane cholesterol efflux drives tumor-associated macrophage reprogramming and tumor progression. Cell Metab 2019; 29(6): 1376–1389
160. El-Kenawi A, Dominguez-Viqueira W, Liu M, Awasthi S, Abraham-Miranda J, Keske A, Steiner KLK, Noel L, Serna AN, Dhillon J, Gillies RJ, Yu X, Koomen JM, Yamoah K, Gatenby RA, Ruffell B. Macrophage-derived cholesterol contributes to therapeutic resistance in prostate cancer. Cancer Res 2021; 81(21): 5477–5490
161. Li Z, Wang Y, Xing R, Zeng H, Yu XJ, Zhang Y, Xu J, Zheng L. Cholesterol efflux drives the generation of immunosuppressive macrophages to promote the progression of human hepatocellular carcinoma. Cancer Immunol Res 2023; 11(10): 1400–1413
162. Halaby MJ, McGaha TL. Amino acid transport and metabolism in myeloid function. Front Immunol 2021; 12: 695238
163. Zhang X, Ji L, Li MO. Control of tumor-associated macrophage responses by nutrient acquisition and metabolism. Immunity 2023; 56(1): 14–31
164. Cimen Bozkus C, Elzey BD, Crist SA, Ellies LG, Ratliff TL. Expression of cationic amino acid transporter 2 is required for myeloid-derived suppressor cell-mediated control of T cell immunity. J Immunol 2015; 195(11): 5237–5250
165. Steggerda SM, Bennett MK, Chen J, Emberley E, Huang T, Janes JR, Li W, MacKinnon AL, Makkouk A, Marguier G, Murray PJ, Neou S, Pan A, Parlati F, Rodriguez MLM, Van de Velde LA, Wang T, Works M, Zhang J, Zhang W, Gross MI. Inhibition of arginase by CB-1158 blocks myeloid cell-mediated immune suppression in the tumor microenvironment. J Immunother Cancer 2017; 5(1): 101
166. Sullivan MR, Danai LV, Lewis CA, Chan SH, Gui DY, Kunchok T, Dennstedt EA, Vander Heiden MG, Muir A. Quantification of microenvironmental metabolites in murine cancers reveals determinants of tumor nutrient availability. eLife 2019; 8: e44235
167. Menjivar RE, Nwosu ZC, Du W, Donahue KL, Hong HS, Espinoza C, Brown K, Velez-Delgado A, Yan W, Lima F, Bischoff A, Kadiyala P, Salas-Escabillas D, Crawford HC, Bednar F, Carpenter E, Zhang Y, Halbrook CJ, Lyssiotis CA, Pasca di Magliano M. Arginase 1 is a key driver of immune suppression in pancreatic cancer. Elife. 2023; 12: e80721
168. McCubbrey AL, McManus SA, McClendon JD, Thomas SM, Chatwin HB, Reisz JA, D'Alessandro A, Mould KJ, Bratton DL, Henson PM, Janssen WJ. Polyamine import and accumulation causes immunomodulation in macrophages engulfing apoptotic cells. Cell Rep. 2022; 38(2): 110222
169. Horn LA, Chariou PL, Gameiro SR, Qin H, Iida M, Fousek K, Meyer TJ, Cam M, Flies D, Langermann S, Schlom J, Palena C. Remodeling the tumor microenvironment via blockade of LAIR-1

and TGF-β signaling enables PD-L1-mediated tumor eradication. J Clin Invest 2022; 132(8): e155148

170. Gao W, Zhang X, Yang W, Dou D, Zhang H, Tang Y, Zhong W, Meng J, Bai Y, Liu Y, Yang L, Chen S, Liu H, Yang C, Sun T. Prim-O-glucosylcimifugin enhances the antitumour effect of PD-1 inhibition by targeting myeloid-derived suppressor cells. J Immunother Cancer 2019; 7(1): 231
171. Jha AK, Huang SCC, Sergushichev A, Lampropoulou V, Ivanova Y, Loginicheva E, Chmielewski K, Stewart KM, Ashall J, Everts B, Pearce EJ, Driggers EM, Artyomov MN. Network integration of parallel metabolic and transcriptional data reveals metabolic modules that regulate macrophage polarization. Immunity 2015; 42(3): 419–430
172. Liu PS, Wang H, Li X, Chao T, Teav T, Christen S, Di Conza G, Cheng WC, Chou CH, Vavakova M, Muret C, Debackere K, Mazzone M, Huang HD, Fendt SM, Ivanisevic J, Ho PC. α-ketoglutarate orchestrates macrophage activation through metabolic and epigenetic reprogramming. Nat Immunol 2017; 18(9): 985–994
173. Wu WC, Sun HW, Chen J, OuYang HY, Yu XJ, Chen HT, Shuang ZY, Shi M, Wang Z, Zheng L. Immunosuppressive immature myeloid cell generation is controlled by glutamine metabolism in human cancer. Cancer Immunol Res 2019; 7(10): 1605–1618
174. Leone RD, Zhao L, Englert JM, Sun IM, Oh MH, Sun IH, Arwood ML, Bettencourt IA, Patel CH, Wen J, Tam A, Blosser RL, Prchalova E, Alt J, Rais R, Slusher BS, Powell JD. Glutamine blockade induces divergent metabolic programs to overcome tumor immune evasion. Science 2019; 366(6468): 1013–1021
175. Oh MH, Sun IH, Zhao L, Leone RD, Sun IM, Xu W, Collins SL, Tam AJ, Blosser RL, Patel CH, Englert JM, Arwood ML, Wen J, Chan-Li Y, Tenora L, Majer P, Rais R, Slusher BS, Horton MR, Powell JD. Targeting glutamine metabolism enhances tumor-specific immunity by modulating suppressive myeloid cells. J Clin Invest 2020; 130(7): 3865–3884
176. Zhao Q, Kuang DM, Wu Y, Xiao X, Li XF, Li TJ, Zheng L. Activated CD69^{+} T cells foster immune privilege by regulating IDO expression in tumor-associated macrophages. J Immunol 2012; 188(3): 1117–1124
177. Sadik A, Somarribas Patterson LF, Öztürk S, Mohapatra SR, Panitz V, Secker PF, Pfänder P, Loth S, Salem H, Prentzell MT, Berdel B, Iskar M, Faessler E, Reuter F, Kirst I, Kalter V, Foerster KI, Jäger E, Guevara CR, Sobeh M, Hielscher T, Poschet G, Reinhardt A, Hassel JC, Zapatka M, Hahn U, von Deimling A, Hopf C, Schlichting R, Escher BI, Burhenne J, Haefeli WE, Ishaque N, Böhme A, Schäuble S, Thedieck K, Trump S, Seiffert M, Opitz CA. IL4I1 is a metabolic immune checkpoint that activates the AHR and promotes tumor progression. Cell 2020; 182(5): 1252–1270.e34
178. Bod L, Lengagne R, Wrobel L, Ramspott JP, Kato M, Avril MF, Castellano F, Molinier-Frenkel V, Prévost-Blondel A. IL4-induced gene 1 promotes tumor growth by shaping the immune microenvironment in melanoma. OncoImmunology 2017; 6(3): e1278331
179. Mulder K, Patel AA, Kong WT, Piot C, Halitzki E, Dunsmore G, Khalilnezhad S, Irac SE, Dubuisson A, Chevrier M, Zhang XM, Tam JKC, Lim TKH, Wong RMM, Pai R, Khalil AIS, Chow PKH, Wu SZ, Al-Eryani G, Roden D, Swarbrick A, Chan JKY, Albani S, Derosa L, Zitvogel L, Sharma A, Chen J, Silvin A, Bertoletti A, Blériot C, Dutertre CA, Ginhoux F. Cross-tissue single-cell landscape of human monocytes and macrophages in health and disease. Immunity 2021; 54(8): 1883–1900.e5
180. Pagano E, Elias JE, Schneditz G, Saveljeva S, Holland LM, Borrelli F, Karlsen TH, Kaser A, Kaneider NC. Activation of the GPR35 pathway drives angiogenesis in the tumour microenvironment. Gut 2022; 71(3): 509–520
181. Li F, Zhao Y, Wei L, Li S, Liu J. Tumor-infiltrating Treg, MDSC, and IDO expression associated with outcomes of neoadjuvant chemotherapy of breast cancer. Cancer Biol Ther 2018; 19(8): 695–705
182. Nandre R, Verma V, Gaur P, Patil V, Yang X, Ramlaoui Z, Shobaki N, Andersen MH, Pedersen AW, Zocca MB, Mkrtichyan M, Gupta S, Khleif SN. IDO vaccine ablates immune-suppressive myeloid populations and enhances antitumor effects independent of tumor cell IDO status. Cancer Immunol Res. 2022; 10(5): 571–580
183. Mitchell TC, Hamid O, Smith DC, Bauer TM, Wasser JS, Olszanski AJ, Luke JJ, Balmanoukian AS, Schmidt EV, Zhao Y, Gong X, Maleski J, Leopold L, Gajewski TF. Epacadostat plus pembrolizumab in patients with advanced solid tumors: phase I results from a multicenter, open-label phase I/II trial (ECHO-202/KEYNOTE-037). J Clin Oncol 2018; 36(32): 3223–3230
184. Mariotti V, Han H, Ismail-Khan R, Tang SC, Dillon P, Montero AJ, Poklepovic A, Melin S, Ibrahim NK, Kennedy E, Vahanian N, Link C, Tennant L, Schuster S, Smith C, Danciu O, Gilman P, Soliman H. Effect of taxane chemotherapy with or without indoximod in metastatic breast cancer: a randomized clinical trial. JAMA Oncol 2021; 7(1): 61–69
185. Long GV, Dummer R, Hamid O, Gajewski TF, Caglevic C, Dalle S, Arance A, Carlino MS, Grob JJ, Kim TM, Demidov L, Robert C, Larkin J, Anderson JR, Maleski J, Jones M, Diede SJ, Mitchell TC. Epacadostat plus pembrolizumab versus placebo plus pembrolizumab in patients with unresectable or metastatic melanoma (ECHO-301/KEYNOTE-252): a phase 3, randomised, double-blind study. Lancet Oncol 2019; 20(8): 1083–1097
186. Nagarsheth N, Wicha MS, Zou W. Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. Nat Rev Immunol 2017; 17(9): 559–572
187. Patel AA, Zhang Y, Fullerton JN, Boelen L, Rongvaux A, Maini AA, Bigley V, Flavell RA, Gilroy DW, Asquith B, Macallan D, Yona S. The fate and lifespan of human monocyte subsets in steady state and systemic inflammation. J Exp Med 2017; 214(7): 1913–1923
188. Chen J, Ji K, Gu L, Fang Y, Pan M, Tian S. HMGA1 promotes macrophage recruitment via activation of NF-κB-CCL2 signaling in hepatocellular carcinoma. J Immunol Res 2022; 2022: 4727198
189. Li X, Yao W, Yuan Y, Chen P, Li B, Li J, Chu R, Song H, Xie D, Jiang X, Wang H. Targeting of tumour-infiltrating macrophages via CCL2/CCR2 signalling as a therapeutic strategy against hepatocellular carcinoma. Gut 2017; 66(1): 157–167
190. Wang YF, Yu L, Hu Z, Fang Y, Shen Y, Song M, Chen Y. Regulation of CCL2 by EZH2 affects tumor-associated macrophages polarization and infiltration in breast cancer. Cell Death Dis 2022; 13(8): 748
191. Tu W, Gong J, Zhou Z, Tian D, Wang Z. TCF4 enhances hepatic

metastasis of colorectal cancer by regulating tumor-associated macrophage via CCL2/CCR2 signaling. Cell Death Dis 2021; 12(10): 882

192. Yao W, Ba Q, Li X, Li H, Zhang S, Yuan Y, Wang F, Duan X, Li J, Zhang W, Wang H. A natural CCR2 antagonist relieves tumor-associated macrophage-mediated immunosuppression to produce a therapeutic effect for liver cancer. EBioMedicine 2017; 22: 58–67
193. Cho HR, Kumari N, Thi Vu H, Kim H, Park CK, Choi SH. Increased antiangiogenic effect by blocking CCL2-dependent macrophages in a rodent glioblastoma model: correlation study with dynamic susceptibility contrast perfusion MRI. Sci Rep 2019; 9(1): 11085
194. Teng KY, Han J, Zhang X, Hsu SH, He S, Wani NA, Barajas JM, Snyder LA, Frankel WL, Caligiuri MA, Jacob ST, Yu J, Ghoshal K. Blocking the CCL2–CCR2 axis using CCL2-neutralizing antibody is an effective therapy for hepatocellular cancer in a mouse model. Mol Cancer Ther 2017; 16(2): 312–322
195. Tu MM, Abdel-Hafiz HA, Jones RT, Jean A, Hoff KJ, Duex JE, Chauca-Diaz A, Costello JC, Dancik GM, Tamburini BAJ, Czerniak B, Kaye J, Theodorescu D. Inhibition of the CCL2 receptor, CCR2, enhances tumor response to immune checkpoint therapy. Commun Biol 2020; 3(1): 720
196. Chang AL, Miska J, Wainwright DA, Dey M, Rivetta CV, Yu D, Kanojia D, Pituch KC, Qiao J, Pytel P, Han Y, Wu M, Zhang L, Horbinski CM, Ahmed AU, Lesniak MS. CCL2 produced by the glioma microenvironment is essential for the recruitment of regulatory T cells and myeloid-derived suppressor cells. Cancer Res 2016; 76(19): 5671–5682
197. Hale M, Itani F, Buchta CM, Wald G, Bing M, Norian LA. Obesity triggers enhanced MDSC accumulation in murine renal tumors via elevated local production of CCL2. PLoS One 2015; 10(3): e0118784
198. Liang H, Deng L, Hou Y, Meng X, Huang X, Rao E, Zheng W, Mauceri H, Mack M, Xu M, Fu YX, Weichselbaum RR. Host STING-dependent MDSC mobilization drives extrinsic radiation resistance. Nat Commun 2017; 8(1): 1736
199. Chun E, Lavoie S, Michaud M, Gallini CA, Kim J, Soucy G, Odze R, Glickman JN, Garrett WS. CCL2 promotes colorectal carcinogenesis by enhancing polymorphonuclear myeloid-derived suppressor cell population and function. Cell Rep 2015; 12(2): 244–257
200. Liu Q, Li A, Tian Y, Wu JD, Liu Y, Li T, Chen Y, Han X, Wu K. The CXCL8-CXCR1/2 pathways in cancer. Cytokine Growth Factor Rev 2016; 31: 61–71
201. Steele CW, Karim SA, Leach JDG, Bailey P, Upstill-Goddard R, Rishi L, Foth M, Bryson S, McDaid K, Wilson Z, Eberlein C, Candido JB, Clarke M, Nixon C, Connelly J, Jamieson N, Carter CR, Balkwill F, Chang DK, Evans TRJ, Strathdee D, Biankin AV, Nibbs RJB, Barry ST, Sansom OJ, Morton JP. CXCR2 inhibition profoundly suppresses metastases and augments immunotherapy in pancreatic ductal adenocarcinoma. Cancer Cell 2016; 29(6): 832–845
202. Han ZJ, Li YB, Yang LX, Cheng HJ, Liu X, Chen H. Roles of the CXCL8-CXCR1/2 Axis in the tumor microenvironment and immunotherapy. Molecules 2021; 27(1): 137
203. Jin L, Tao H, Karachi A, Long Y, Hou AY, Na M, Dyson KA, Grippin AJ, Deleyrolle LP, Zhang W, Rajon DA, Wang QJ, Yang JC, Kresak JL, Sayour EJ, Rahman M, Bova FJ, Lin Z, Mitchell DA, Huang J. CXCR1- or CXCR2-modified CAR T cells co-opt IL-8 for maximal antitumor efficacy in solid tumors. Nat Commun 2019; 10(1): 4016
204. Halama N, Zoernig I, Berthel A, Kahlert C, Klupp F, Suarez-Carmona M, Suetterlin T, Brand K, Krauss J, Lasitschka F, Lerchl T, Luckner-Minden C, Ulrich A, Koch M, Weitz J, Schneider M, Buechler MW, Zitvogel L, Herrmann T, Benner A, Kunz C, Luecke S, Springfeld C, Grabe N, Falk CS, Jaeger D. Tumoral immune cell exploitation in colorectal cancer metastases can be targeted effectively by anti-CCR5 therapy in cancer patients. Cancer Cell 2016; 29(4): 587–601
205. Castellino F, Huang AY, Altan-Bonnet G, Stoll S, Scheinecker C, Germain RN. Chemokines enhance immunity by guiding naive $CD8^+$ T cells to sites of $CD4^+$ T cell-dendritic cell interaction. Nature 2006; 440(7086): 890–895
206. Galeano Niño JL, Pageon SV, Tay SS, Colakoglu F, Kempe D, Hywood J, Mazalo JK, Cremasco J, Govendir MA, Dagley LF, Hsu K, Rizzetto S, Zieba J, Rice G, Prior V, O'Neill GM, Williams RJ, Nisbet DR, Kramer B, Webb AI, Luciani F, Read MN, Biro M. Cytotoxic T cells swarm by homotypic chemokine signalling. eLife 2020; 9: e56554
207. He Q, Liu M, Huang W, Chen X, Zhang B, Zhang T, Wang Y, Liu D, Xie M, Ji X, Sun M, Tian D, Xia L. IL-1β-induced elevation of solute carrier family 7 member 11 promotes hepatocellular carcinoma metastasis through up-regulating programmed death ligand 1 and colony-stimulating factor 1. Hepatology 2021; 74(6): 3174–3193
208. Sierra-Filardi E, Nieto C, Domínguez-Soto Á, Barroso R, Sánchez-Mateos P, Puig-Kroger A, López-Bravo M, Joven J, Ardavín C, Rodríguez-Fernández JL, Sánchez-Torres C, Mellado M, Corbí ÁL. CCL2 shapes macrophage polarization by GM-CSF and M-CSF: identification of CCL2/CCR2-dependent gene expression profile. J Immunol 2014; 192(8): 3858–3867
209. Dai XM, Ryan GR, Hapel AJ, Dominguez MG, Russell RG, Kapp S, Sylvestre V, Stanley ER. Targeted disruption of the mouse colony-stimulating factor 1 receptor gene results in osteopetrosis, mononuclear phagocyte deficiency, increased primitive progenitor cell frequencies, and reproductive defects. Blood 2002; 99(1): 111–120
210. Wang Y, Szretter KJ, Vermi W, Gilfillan S, Rossini C, Cella M, Barrow AD, Diamond MS, Colonna M. IL-34 is a tissue-restricted ligand of CSF1R required for the development of Langerhans cells and microglia. Nat Immunol 2012; 13(8): 753–760
211. Ries CH, Cannarile MA, Hoves S, Benz J, Wartha K, Runza V, Rey-Giraud F, Pradel LP, Feuerhake F, Klaman I, Jones T, Jucknischke U, Scheiblich S, Kaluza K, Gorr IH, Walz A, Abiraj K, Cassier PA, Sica A, Gomez-Roca C, de Visser KE, Italiano A, Le Tourneau C, Delord JP, Levitsky H, Blay JY, Rüttinger D. Targeting tumor-associated macrophages with anti-CSF-1R antibody reveals a strategy for cancer therapy. Cancer Cell 2014; 25(6): 846–859
212. Wiehagen KR, Girgis NM, Yamada DH, Smith AA, Chan SR, Grewal IS, Quigley M, Verona RI. Combination of CD40 agonism and CSF-1R blockade reconditions tumor-associated macrophages and drives potent antitumor immunity. Cancer Immunol Res 2017; 5(12): 1109–1121

213. Neubert NJ, Schmittnaegel M, Bordry N, Nassiri S, Wald N, Martignier C, Tillé L, Homicsko K, Damsky W, Maby-El Hajjami H, Klaman I, Danenberg E, Ioannidou K, Kandalaft L, Coukos G, Hoves S, Ries CH, Fuertes Marraco SA, Foukas PG, De Palma M, Speiser DE. T cell-induced CSF1 promotes melanoma resistance to PD1 blockade. Sci Transl Med 2018; 10(436): eaan3311
214. Zhu Y, Knolhoff BL, Meyer MA, Nywening TM, West BL, Luo J, Wang-Gillam A, Goedegebuure SP, Linehan DC, DeNardo DG. CSF1/CSF1R blockade reprograms tumor-infiltrating macrophages and improves response to T-cell checkpoint immunotherapy in pancreatic cancer models. Cancer Res 2014; 74(18): 5057–5069
215. Mok S, Koya RC, Tsui C, Xu J, Robert L, Wu L, Graeber TG, West BL, Bollag G, Ribas A. Inhibition of CSF-1 receptor improves the antitumor efficacy of adoptive cell transfer immunotherapy. Cancer Res 2014; 74(1): 153–161
216. Ruffolo LI, Jackson KM, Kuhlers PC, Dale BS, Figueroa Guilliani NM, Ullman NA, Burchard PR, Qin SS, Juviler PG, Keilson JM, Morrison AB, Georger M, Jewell R, Calvi LM, Nywening TM, O'Dell MR, Hezel AF, De Las Casas L, Lesinski GB, Yeh JJ, Hernandez-Alejandro R, Belt BA, Linehan DC. GM-CSF drives myelopoiesis, recruitment and polarisation of tumour-associated macrophages in cholangiocarcinoma and systemic blockade facilitates antitumour immunity. Gut 2022; 71(7): 1386–1398
217. Ning WR, Jiang D, Liu XC, Huang YF, Peng ZP, Jiang ZZ, Kang T, Zhuang SM, Wu Y, Zheng L. Carbonic anhydrase XII mediates the survival and prometastatic functions of macrophages in human hepatocellular carcinoma. J Clin Invest 2022; 132(7): e153110
218. Wang Y, Chen W, Qiao S, Zou H, Yu X, Yang Y, Li Z, Wang J, Chen M, Xu J, Zheng L. Lipid droplet accumulation mediates macrophage survival and Treg recruitment via the CCL20/CCR6 axis in human hepatocellular carcinoma. Cell Mol Immunol 2024; 21(10): 1120–1130
219. Zhao X, Rong L, Zhao X, Li X, Liu X, Deng J, Wu H, Xu X, Erben U, Wu P, Syrbe U, Sieper J, Qin Z. TNF signaling drives myeloid-derived suppressor cell accumulation. J Clin Invest 2012; 122(11): 4094–4104
220. Thevenot PT, Sierra RA, Raber PL, Al-Khami AA, Trillo-Tinoco J, Zarreii P, Ochoa AC, Cui Y, Del Valle L, Rodriguez PC. The stress-response sensor chop regulates the function and accumulation of myeloid-derived suppressor cells in tumors. Immunity 2014; 41(3): 389–401
221. Condamine T, Kumar V, Ramachandran IR, Youn JI, Celis E, Finnberg N, El-Deiry WS, Winograd R, Vonderheide RH, English NR, Knight SC, Yagita H, McCaffrey JC, Antonia S, Hockstein N, Witt R, Masters G, Bauer T, Gabrilovich DI. ER stress regulates myeloid-derived suppressor cell fate through TRAIL-R-mediated apoptosis. J Clin Invest 2014; 124(6): 2626–2639
222. Dominguez GA, Condamine T, Mony S, Hashimoto A, Wang F, Liu Q, Forero A, Bendell J, Witt R, Hockstein N, Kumar P, Gabrilovich DI. Selective targeting of myeloid-derived suppressor cells in cancer patients using DS-8273a, an agonistic TRAIL-R2 antibody. Clin Cancer Res 2017; 23(12): 2942–2950
223. Parker KH, Horn LA, Ostrand-Rosenberg S. High-mobility group box protein 1 promotes the survival of myeloid-derived suppressor cells by inducing autophagy. J Leukoc Biol 2016; 100(3): 463–470
224. Wang J, Wang Y, Chu Y, Li Z, Yu X, Huang Z, Xu J, Zheng L. Tumor-derived adenosine promotes macrophage proliferation in human hepatocellular carcinoma. J Hepatol 2021; 74(3): 627–637
225. Hartley GP, Chow L, Ammons DT, Wheat WH, Dow SW. Programmed cell death ligand 1 (PD-L1) signaling regulates macrophage proliferation and activation. Cancer Immunol Res 2018; 6(10): 1260–1273
226. Cai Z, Li W, Hager S, Wilson JL, Afjehi-Sadat L, Heiss EH, Weichhart T, Heffeter P, Weckwerth W. Targeting PHGDH reverses the immunosuppressive phenotype of tumor-associated macrophages through alpha-ketoglutarate and mTORC1 signaling. Cell Mol Immunol 2024; 21(5): 448–465
227. Condamine T, Mastio J, Gabrilovich DI. Transcriptional regulation of myeloid-derived suppressor cells. J Leukoc Biol 2015; 98(6): 913–922
228. Welte T, Kim IS, Tian L, Gao X, Wang H, Li J, Holdman XB, Herschkowitz JI, Pond A, Xie G, Kurley S, Nguyen T, Liao L, Dobrolecki LE, Pang L, Mo Q, Edwards DP, Huang S, Xin L, Xu J, Li Y, Lewis MT, Wang T, Westbrook TF, Rosen JM, Zhang XHF. Oncogenic mTOR signalling recruits myeloid-derived suppressor cells to promote tumour initiation. Nat Cell Biol 2016; 18(6): 632–644
229. Gabrilovich D, Ishida T, Oyama T, Ran S, Kravtsov V, Nadaf S, Carbone DP. Vascular endothelial growth factor inhibits the development of dendritic cells and dramatically affects the differentiation of multiple hematopoietic lineages *in vivo*. Blood 1998; 92(11): 4150–4166
230. Gabrilovich DI, Chen HL, Girgis KR, Cunningham HT, Meny GM, Nadaf S, Kavanaugh D, Carbone DP. Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. Nat Med 1996; 2(10): 1096–1103
231. Rivera LB, Bergers G. Intertwined regulation of angiogenesis and immunity by myeloid cells. Trends Immunol 2015; 36(4): 240–249
232. Cheng P, Corzo CA, Luetteke N, Yu B, Nagaraj S, Bui MM, Ortiz M, Nacken W, Sorg C, Vogl T, Roth J, Gabrilovich DI. Inhibition of dendritic cell differentiation and accumulation of myeloid-derived suppressor cells in cancer is regulated by S100A9 protein. J Exp Med 2008; 205(10): 2235–2249
233. Wu L, Yan C, Czader M, Foreman O, Blum JS, Kapur R, Du H. Inhibition of PPARγ in myeloid-lineage cells induces systemic inflammation, immunosuppression, and tumorigenesis. Blood 2012; 119(1): 115–126
234. Oh K, Lee OY, Shon SY, Nam O, Ryu PM, Seo MW, Lee DS. A mutual activation loop between breast cancer cells and myeloid-derived suppressor cells facilitates spontaneous metastasis through IL-6 trans-signaling in a murine model. Breast Cancer Res 2013; 15(5): R79
235. Wu WC, Sun HW, Chen HT, Liang J, Yu XJ, Wu C, Wang Z, Zheng L. Circulating hematopoietic stem and progenitor cells are myeloid-biased in cancer patients. Proc Natl Acad Sci USA 2014; 111(11): 4221–4226
236. Cortez-Retamozo V, Etzrodt M, Newton A, Rauch PJ, Chudnovskiy A, Berger C, Ryan RJH, Iwamoto Y, Marinelli B, Gorbatov R, Forghani R, Novobrantseva TI, Koteliansky V,

Figueiredo JL, Chen JW, Anderson DG, Nahrendorf M, Swirski FK, Weissleder R, Pittet MJ. Origins of tumor-associated macrophages and neutrophils. Proc Natl Acad Sci USA 2012; 109(7): 2491–2496

237. Casbon AJ, Reynaud D, Park C, Khuc E, Gan DD, Schepers K, Passegué E, Werb Z. Invasive breast cancer reprograms early myeloid differentiation in the bone marrow to generate immunosuppressive neutrophils. Proc Natl Acad Sci USA 2015; 112(6): E566–E575
238. Wu C, Ning H, Liu M, Lin J, Luo S, Zhu W, Xu J, Wu WC, Liang J, Shao CK, Ren J, Wei B, Cui J, Chen MS, Zheng L. Spleen mediates a distinct hematopoietic progenitor response supporting tumor-promoting myelopoiesis. J Clin Invest 2018; 128(8): 3425–3438
239. Ugel S, Peranzoni E, Desantis G, Chioda M, Walter S, Weinschenk T, Ochando JC, Cabrelle A, Mandruzzato S, Bronte V. Immune tolerance to tumor antigens occurs in a specialized environment of the spleen. Cell Rep 2012; 2(3): 628–639
240. Almand B, Clark JI, Nikitina E, van Beynen J, English NR, Knight SC, Carbone DP, Gabrilovich DI. Increased production of immature myeloid cells in cancer patients: a mechanism of immunosuppression in cancer. J Immunol 2001; 166(1): 678–689
241. Bronte V, Apolloni E, Cabrelle A, Ronca R, Serafini P, Zamboni P, Restifo NP, Zanovello P. Identification of a CD11b$^+$/Gr-1$^+$/CD31$^+$ myeloid progenitor capable of activating or suppressing CD8$^+$ T cells. Blood 2000; 96(12): 3838–3846
242. Marigo I, Bosio E, Solito S, Mesa C, Fernandez A, Dolcetti L, Ugel S, Sonda N, Bicciato S, Falisi E, Calabrese F, Basso G, Zanovello P, Cozzi E, Mandruzzato S, Bronte V. Tumor-induced tolerance and immune suppression depend on the C/EBPβ transcription factor. Immunity 2010; 32(6): 790–802
243. Cortez-Retamozo V, Etzrodt M, Newton A, Ryan R, Pucci F, Sio SW, Kuswanto W, Rauch PJ, Chudnovskiy A, Iwamoto Y, Kohler R, Marinelli B, Gorbatov R, Wojtkiewicz G, Panizzi P, Mino-Kenudson M, Forghani R, Figueiredo JL, Chen JW, Xavier R, Swirski FK, Nahrendorf M, Weissleder R, Pittet MJ. Angiotensin II drives the production of tumor-promoting macrophages. Immunity 2013; 38(2): 296–308
244. Bronte V, Pittet MJ. The spleen in local and systemic regulation of immunity. Immunity 2013; 39(5): 806–818
245. Long H, Jia Q, Wang L, Fang W, Wang Z, Jiang T, Zhou F, Jin Z, Huang J, Zhou L, Hu C, Wang X, Zhang J, Ba Y, Gong Y, Zeng X, Zeng D, Su X, Alexander PB, Wang L, Wang L, Wan YY, Wang XF, Zhang L, Li QJ, Zhu B. Tumor-induced erythroid precursor-differentiated myeloid cells mediate immunosuppression and curtail anti-PD-1/PD-L1 treatment efficacy. Cancer Cell 2022; 40(6): 674–693.e7
246. Zhao L, He R, Long H, Guo B, Jia Q, Qin D, Liu SQ, Wang Z, Xiang T, Zhang J, Tan Y, Huang J, Chen J, Wang F, Xiao M, Gao J, Yang X, Zeng H, Wang X, Hu C, Alexander PB, Symonds ALJ, Yu J, Wan Y, Li QJ, Ye L, Zhu B. Late-stage tumors induce anemia and immunosuppressive extramedullary erythroid progenitor cells. Nat Med 2018; 24(10): 1536–1544
247. Han Y, Liu Q, Hou J, Gu Y, Zhang Y, Chen Z, Fan J, Zhou W, Qiu S, Zhang Y, Dong T, Li N, Jiang Z, Zhu H, Zhang Q, Ma Y, Zhang L, Wang Q, Yu Y, Li N, Cao X. Tumor-induced generation of splenic erythroblast-like Ter-cells promotes tumor progression. Cell 2018; 173(3): 634–648.e12
248. Cannarile MA, Weisser M, Jacob W, Jegg AM, Ries CH, Rüttinger D. Colony-stimulating factor 1 receptor (CSF1R) inhibitors in cancer therapy. J Immunother Cancer 2017; 5(1): 53
249. Chaib M, Chauhan SC, Makowski L. Friend or foe? Recent strategies to target myeloid cells in cancer. Front Cell Dev Biol 2020; 8: 351
250. Jahchan NS, Mujal AM, Pollack JL, Binnewies M, Sriram V, Reyno L, Krummel MF. Tuning the tumor myeloid microenvironment to fight cancer. Front Immunol 2019; 10: 1611
251. Mitchem JB, Brennan DJ, Knolhoff BL, Belt BA, Zhu Y, Sanford DE, Belaygorod L, Carpenter D, Collins L, Piwnica-Worms D, Hewitt S, Udupi GM, Gallagher WM, Wegner C, West BL, Wang-Gillam A, Goedegebuure P, Linehan DC, DeNardo DG. Targeting tumor-infiltrating macrophages decreases tumor-initiating cells, relieves immunosuppression, and improves chemotherapeutic responses. Cancer Res 2013; 73(3): 1128–1141
252. Kalbasi A, Komar C, Tooker GM, Liu M, Lee JW, Gladney WL, Ben-Josef E, Beatty GL. Tumor-derived CCL2 mediates resistance to radiotherapy in pancreatic ductal adenocarcinoma. Clin Cancer Res 2017; 23(1): 137–148
253. Connolly KA, Belt BA, Figueroa NM, Murthy A, Patel A, Kim M, Lord EM, Linehan DC, Gerber SA. Increasing the efficacy of radiotherapy by modulating the CCR2/CCR5 chemokine axes. Oncotarget 2016; 7(52): 86522–86535
254. Fridlender ZG, Buchlis G, Kapoor V, Cheng G, Sun J, Singhal S, Crisanti MC, Wang LCS, Heitjan D, Snyder LA, Albelda SM. CCL2 blockade augments cancer immunotherapy. Cancer Res 2010; 70(1): 109–118
255. Flores-Toro JA, Luo D, Gopinath A, Sarkisian MR, Campbell JJ, Charo IF, Singh R, Schall TJ, Datta M, Jain RK, Mitchell DA, Harrison JK. CCR2 inhibition reduces tumor myeloid cells and unmasks a checkpoint inhibitor effect to slow progression of resistant murine gliomas. Proc Natl Acad Sci USA 2020; 117(2): 1129–1138
256. Zhu Y, Herndon JM, Sojka DK, Kim KW, Knolhoff BL, Zuo C, Cullinan DR, Luo J, Bearden AR, Lavine KJ, Yokoyama WM, Hawkins WG, Fields RC, Randolph GJ, DeNardo DG. Tissue-resident macrophages in pancreatic ductal adenocarcinoma originate from embryonic hematopoiesis and promote tumor progression. Immunity. 2017; 47(2): 323–338.e6
257. Nywening TM, Belt BA, Cullinan DR, Panni RZ, Han BJ, Sanford DE, Jacobs RC, Ye J, Patel AA, Gillanders WE, Fields RC, DeNardo DG, Hawkins WG, Goedegebuure P, Linehan DC. Targeting both tumour-associated CXCR2$^+$ neutrophils and CCR2$^+$ macrophages disrupts myeloid recruitment and improves chemotherapeutic responses in pancreatic ductal adenocarcinoma. Gut 2018; 67(6): 1112–1123
258. Papadopoulos KP, Gluck L, Martin LP, Olszanski AJ, Tolcher AW, Ngarmchamnanrith G, Rasmussen E, Amore BM, Nagorsen D, Hill JS, Stephenson J Jr. First-in-human study of AMG 820, a monoclonal anti-colony-stimulating factor 1 receptor antibody, in patients with advanced solid tumors. Clin Cancer Res 2017; 23(19): 5703–5710
259. Zhang L, Li Z, Skrzypczynska KM, Fang Q, Zhang W, O'Brien SA, He Y, Wang L, Zhang Q, Kim A, Gao R, Orf J, Wang T, Sawant D, Kang J, Bhatt D, Lu D, Li CM, Rapaport AS, Perez K, Ye Y, Wang S, Hu X, Ren X, Ouyang W, Shen Z, Egen JG, Zhang Z, Yu X. Single-cell analyses inform mechanisms of

myeloid-targeted therapies in colon cancer. Cell. 2020; 181(2): 442–459.e29

260. Kumar V, Donthireddy L, Marvel D, Condamine T, Wang F, Lavilla-Alonso S, Hashimoto A, Vonteddu P, Behera R, Goins MA, Mulligan C, Nam B, Hockstein N, Denstman F, Shakamuri S, Speicher DW, Weeraratna AT, Chao T, Vonderheide RH, Languino LR, Ordentlich P, Liu Q, Xu X, Lo A, Puré E, Zhang C, Loboda A, Sepulveda MA, Snyder LA, Gabrilovich DI. Cancer-associated fibroblasts neutralize the anti-tumor effect of CSF1 receptor blockade by inducing PMN-MDSC infiltration of tumors. Cancer cell 2017; 32(5): 654–668.e5
261. Gyori D, Lim EL, Grant FM, Spensberger D, Roychoudhuri R, Shuttleworth SJ, Okkenhaug K, Stephens LR, Hawkins PT. Compensation between CSF1R$^+$ macrophages and Foxp3$^+$ Treg cells drives resistance to tumor immunotherapy. JCI Insight 2018; 3(11): e120631
262. Sun L, Clavijo PE, Robbins Y, Patel P, Friedman J, Greene S, Das R, Silvin C, Van Waes C, Horn LA, Schlom J, Palena C, Maeda D, Zebala J, Allen CT. Inhibiting myeloid-derived suppressor cell trafficking enhances T cell immunotherapy. JCI Insight 2019; 4(7): e126853
263. Wu C, Lin J, Weng Y, Zeng DN, Xu J, Luo S, Xu L, Liu M, Hua Q, Liu CQ, Li JQ, Liao J, Sun C, Zhou J, Chen MS, Liu C, Guo Z, Zhuang SM, Huang JH, Zheng L. Myeloid signature reveals immune contexture and predicts the prognosis of hepatocellular carcinoma. J Clin Invest 2020; 130(9): 4679–4693
264. Liu M, Wu C, Luo S, Hua Q, Chen HT, Weng Y, Xu J, Lin H, Wang L, Li J, Zhu L, Guo Z, Zhuang SM, Kang T, Zheng L. PERK reprograms hematopoietic progenitor cells to direct tumor-promoting myelopoiesis in the spleen. J Exp Med 2022; 219(4): e20211498