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REVIEW

Research progress on FASN and MGLL in the regulation of abnormal lipid metabolism and the relationship between tumor invasion and metastasis

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Abstract **Tumorigenesis involves metabolic reprogramming and abnormal lipid metabolism, which is manifested by increased endogenous fat mobilization, hypertriglyceridemia, and increased fatty acid synthesis. Fatty acid synthase (FASN) is a key enzyme for the *de novo* synthesis of fatty acids, and monoacylglycerol esterase (MGLL) is an important metabolic enzyme that converts triglycerides into free fatty acids. Both enzymes play an important role in lipid metabolism and are associated with tumor-related signaling pathways, the most common of which is the PI3K–AKT signaling pathway. They can also regulate the immune microenvironment, participate in epithelial–mesenchymal transition, and then regulate tumor invasion and metastasis. Current literature have shown that these two genes are abnormally expressed in many types of tumors and are highly correlated with tumor migration and invasion. This article introduces the structures and functions of FASN and MGLL, their relationship with abnormal lipid metabolism, and the mechanism of the regulation of tumor invasion and metastasis and reviews the research progress of the relationship of FASN and MGLL with tumor invasion and metastasis.**

Keywords FASN; MGLL; lipid metabolism; tumor invasion; metastasis

Introduction

Fatty acid synthase (FASN) and monoacylglycerol esterase (MGLL) are critical enzymes related to fatty acid metabolism. FASN catalyzes the *de novo* synthesis of fatty acids, whereas MGLL is involved in the conversion of fat to free fatty acids (FFAs). They synthesize FFAs in different ways; thus, they provide raw materials for the synthesis of cell membrane phospholipids and signal molecules and supply energy to the body. Studies have found that FASN and MGLL play an important role in tumorigenesis and metastasis.

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Structure and function of FASN and MGLL

FASN is a key enzyme in the *de novo* synthesis of long-chain fatty acids that catalyzes the decarboxylation condensation of acetyl CoA, malonyl-CoA, and other small carbon units to form palmitate in the presence of NADPH. Human *FASN* gene is located in region 2, band 5 (17q25) of the long arm of chromosome 17, has a total length of about 20 kb, and contains 43 exons and 42 introns. FASN is a multifunctional enzyme complex with a relative molecular mass of 25.0×10^4–27.0×10^4. In animals, the FASN complex integrates seven enzyme activities, including condensation, transacylation, reduction, and dehydration, as well as an acyl carrier protein (ACP). FASN is a dimer with two identical polypeptide chains by the head–tail way. This dimer structure affects the activity of the enzyme, that is, the depolymerization of the dimer leads to the disappearance of the enzyme activity. The core part of FASN is located at the C-terminal, which contains about 600 residues of four structural domains

(enol reduction region, β-ketoacyl reduction region, ACP, and thioester region), and the other three domains (β-ketoacyl synthesis area and the acetic acid/malonyl monoacid transfer and dehydration zones) are located at the N-terminal.

MGLL is a peripheral membrane enzyme in the serine hydrolase superfamily. As an important fatty acid-metabolizing enzyme, MGLL can catalyze the conversion of monoglyceride to FFAs and glycerol. The *MGLL* gene is located in region 2, band 1 (3q21.3) of the long arm of chromosome 3 and contains 13 exons. Mouse *Mgll* gene contains the coding sequence of MGLL in seven exons, including about 2.6 kb large-end exon, termination codon, and 30 complete untranslated regions. The amino acid sequence of human MGLL cDNA clone is 84% the same as that of mouse MGLL [1]. MGLL is a 33 kDa protein that contains the most common serine hydrolase of the classical GXSXG consensus sequence and the α/β-hydrolase fold of sequence homology. The fold consists of a central β-fold surrounded by an indefinite number of α-helices. The catalytic triplets are Ser122, His269, and Asp239 [2].

FASN has two main functions under physiologic conditions: one is to store excess energy in fat tissue in the form of triglycerides, and the other is to synthesize phospholipids for cell membrane and alveolar surfactant. Fatty acids come from exogenous diet; FASN expression *in vivo* is low when the synthesis level of endogenous fatty acids is low. FASN also plays a role in some pathological processes, such as diabetes, inflammation, and tumor development. FASN overexpression is related to glomerulosclerosis and inflammation in diabetic nephropathy [3]. In a diabetic model, the FASN of macrophage promotes the inflammatory process and insulin resistance induced by high-fat diet [4]. FASN is increased in breast cancer [5], colorectal cancer [6], liver cancer [7], lung cancer [8], and other tumors and promotes the proliferation and invasion of tumor cells.

MGLL is expressed in adipose tissue, muscle, liver, kidney, ovary, and testis. In the central nervous system, MGLL acts on the endogenous cannabinoid system to catalyze the hydrolysis of 2-arachidonylglycerol (2-AG) and plays a key role in physiologic processes, such as pain and perception. In lipid metabolism, MGLL, together with hormone-sensitive lipase, hydrolyzes triglycerides in fat cells and other cells into fatty acids and glycerin. MGLL can also supplement lipoprotein lipase to complete the hydrolysis of monoglycerides caused by the degradation of lipoprotein triglycerides. The cellular metabolism process that involves FASN and MGLL is provided in Fig. 1. MGLL also plays a role in some pathological processes, including liver injury, inflammation, nerve injury diseases, and malignant tumors. MGLL is a critical step in the regulation of endogenous cannabinoid and eicosane-like signaling pathways, which promote liver injury, and blocks this pathway to protect mice from liver injury [9]. MGLL inhibitors have anti-anxiety and anti-inflammatory effects in various neuro degenerative animal models, including Parkinson's disease, Alzheimer's disease, and acute brain injury [10]. MGLL also contributes to tumor occurrence and metastasis. MGLL is upregulated in many types of cancers, including melanoma, ovarian cancer, and breast cancer and promotes cancer cell proliferation [11].

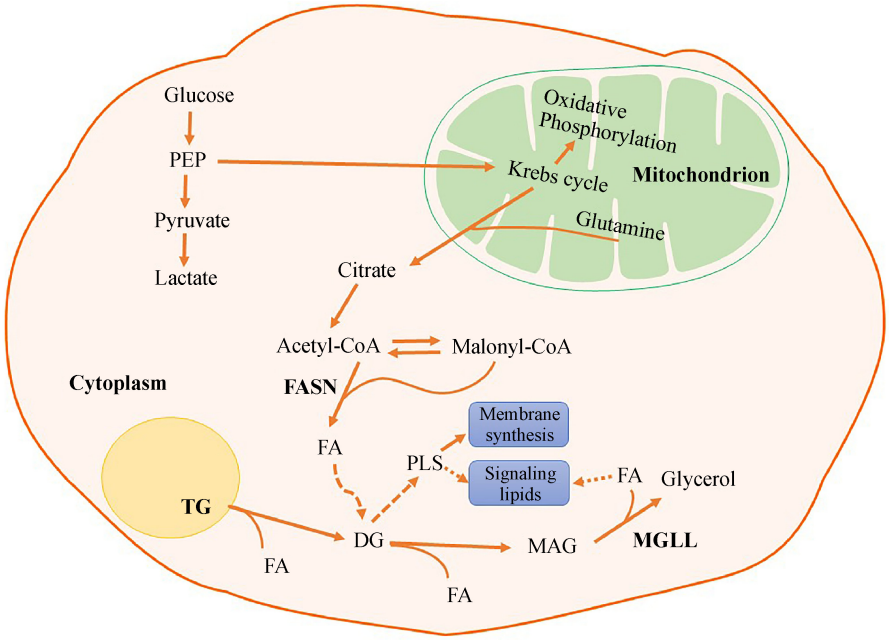

Fig. 1 Cellular metabolism process involving FASN and MGLL.

However, other literatures have shown that MGLL expression is low or absent in colorectal cancer [12], hepatocellular carcinoma (HCC) [12,13], breast cancer, intestinal adenomas, and lung cancer [14] and inhibits tumor progression.

FASN, MGLL, and abnormal tumor metabolism

Tumor cells have metabolic reprogramming as characterized by abnormal glycolysis pathway, active glutamine metabolism, and abnormal lipid metabolism [15]. Tumor cells can re-adapt to the environment through metabolic reprogramming in an unfavorable living environment to maintain their growth advantage, continuous proliferation, metastasis, and invasion.

Tumor occurrence and development are a multi-factor and multi-stage process. In malignant transformation, tumor cells lose their normal regulation and control and gain the ability of unlimited proliferation, invasion, and metastasis. Energy metabolism provides the basis for the occurrence and development of tumor cells. Warburg proposed that unlike normal cell metabolism, tumor cells will give priority to glycolysis even in the presence of sufficient oxygen to provide energy for tumor cells; this phenomenon is known as the Warburg effect [16]. In mammalian cells, glutamine is the main energy substrate that produces α-ketoglutaric acid through its metabolism and enters the Krebs cycle. Its product, citric acid, can enter the cytoplasm and produce fatty acids under the catalysis of a series of enzymes, including FASN. Active glutamine metabolism is a common metabolic abnormality in tumors that provides a metabolic substrate for FASN-catalyzed *de novo* synthesis of fatty acids and thus promotes tumor occurrence and development.

Abnormal fat metabolism in patients with tumors is characterized by increased endogenous fat mobilization, hypertriglyceridemia, and increased fatty acid synthesis. Fatty acids are the main energy substances in tumor-bearing body that support the growth of tumor cells by providing metabolic substrates for energy production. Exogenous glucose cannot inhibit the continuous decomposition and oxidation of fat in the body. In tumor cells, 90% of fat synthesis come from *ab initio* fatty acid synthesis, which is catalyzed by FASN. The rapid proliferation of tumor cells consumes a lot of energy. In the state of energy stress, fatty acids can provide the energy needed by tumor cells through β-oxidative decomposition. MGLL catalyzes another way of fatty acid synthesis, that is, the conversion of monoacylglycerol esters to FFAs and glycerol.

FASN and MGLL catalyze the synthesis of fatty acids, and fatty acids can promote malignant biological behaviors, such as tumor cell proliferation, invasion, and metastasis, by participating in tumor cell membrane phospholipid synthesis, energy supply, and the synthesis of important tumor-promoting lipid signal molecules.

Mechanism of FASN and MGLL in regulating tumor invasion and metastasis

FASN expression is remarkably increased in colorectal cancer, breast cancer, liver cancer, osteosarcoma, ovarian cancer, lung cancer, nephroblastoma, and other malignant tumors [5–8,17–19]. MGLL expression is also abnormal in melanoma, gastrointestinal stromal tumor, colon cancer, liver cancer, ovarian cancer, and breast cancer [11,12,20,21]. The regulation of these two key genes of lipid metabolism on tumor can be explained from three aspects: tumor-related signal pathway, immune microenvironment, and epithelial–mesenchymal transformation (EMT).

FASN and MGLL participate in signal pathway

The expression of FASN in tumor tissues involves a variety of regulatory mechanisms, including sterol regulatory element binding protein (SREBP), phosphatidylinositol-3-kinase (PI3K)/AKT kinase, and Wnt/β-catenin signal. Human epidermal growth factor receptor 2 (HER2) can regulate the malignant phenotype of colorectal cancer cells through the PI3K–AKT–FASN axis. Silencing HER2 can downregulate the expression of FASN and decrease cell proliferation and migration [6]. FASN is also stimulated by SREBP precursor to regulate *ab initio* fat synthesis. As a transcriptional coactivator, spindling-1 (SPIN1) can co-stimulate SREBP1c to promote FASN expression. SPIN1/SREBP1c/FASN signal regulates abnormal lipid metabolism and promotes the growth of HCC cells [22]. FASN activity is closely related to receptor tyrosine kinase (RTK), PI3K–AKT–mTOR, and MAPK signal pathways, and the activation of these pathways is a sign of tumor cell growth [23]. *FASN* gene expression is activated downstream of the PI3K–AKT–mTOR signal transduction pathway in response to cell metabolism and growth signals and is driven by SREBP-1, ZBTB7A, and the p53 family transcription factors. The reprogramming of tumor cell mitochondrial metabolism can directly meet the energy needs of tumor cell growth and proliferation through growth factor signal transduction and the PI3K–AKT–mTOR pathway. TVB-3166, a FASN inhibitor, can quickly stop the synthesis of new palmitates. When palmitates are exhausted, the gene expression in tumor cells changes, the lipid raft structure is destroyed, and the PI3K–AKT–mTOR and β-catenin signal transduction pathways are inhibited. Finally, tumor cells die through apoptosis [24].

MGLL can regulate the malignant behavior of tumors through Krueppel-like factor 4 (KLF4)–MGLL and NF-κB

signaling pathways in tumor tissues with different results. The expression of MGLL in HCC is decreased, MGLL overexpression can inhibit cell migration, KLF4 is the key factor that regulates MGLL expression, and the KLF4–MGLL axis plays an important role in inhibiting the migration of HCC cells [25]. However, another study on HCC showed that the expression of MGLL in HCC tissues is considerably higher than that in para-carcinoma tissues, is associated with poor prognosis, and promotes HCC invasion and metastasis through the NF-κB pathway [21]. Sun *et al*. reported that the expression of MGLL is low or absent in primary colorectal cancer, and MGLL interacts with a variety of phospholipids, among which PI(3,4,5)P3 has the strongest effect. Lentiviral interference was used to knockout the *MGLL* gene in HT29 colon cancer cells and MDA-MB-231 breast cancer cells, and the result proved that MGLL may structurally inhibit AKT phosphorylation. Furthermore, MGLL knockdown can alleviate this inhibitory effect, which in turn leads to AKT activation. In conclusion, MGLL has a potential negative regulatory effect on the PI3K–AKT pathway [12].

Interestingly, FASN and MGLL are involved in the PI3K–AKT signaling pathway. The PI3K–AKT pathway is the most commonly activated pathway in human cancers [26]. This pathway plays a crucial role in regulating diverse cellular functions, including metabolism, growth, proliferation, survival, transcription, and protein synthesis [27]. Under physiologic conditions, this pathway is activated in response to insulin, cytokines, and growth factors and regulates key metabolic processes [28,29], including glucose metabolism, macromolecule biosynthesis, and maintenance of redox balance, to support systemic metabolic homeostasis and the growth and metabolism of individual cells. The oncogenic activation of the PI3K–AKT pathway in cancer cells reprogrammed cellular metabolism by augmenting the activity of nutrient transporters and metabolic enzymes to support the anabolic demands of aberrantly growing cells [30,31]. The specific process of the PI3K–AKT pathway is shown in Fig. 2. No literatures has studied the upstream and downstream regulatory relationships of MGLL and FASN in the PI3K–AKT pathway. The PI3K–AKT may be a potential regulatory pathway for abnormal tumor lipid metabolism.

FASN and MGLL participate in EMT

EMT is a process that endows cancer cells with stem cell-like properties, including self-renewal, enhanced survival, and anchored independent growth. EMT plays an important role in cancer development and metastasis [32]. Studying the effect of metabolism on EMT is helpful to further understand the mechanism of tumor development. FASN and MGLL can promote the growth and invasion of tumor cells by participating in EMT induction.

In breast cancer cells, hyperglycemia can induce EMT, which promotes the Warburg effect by upregulating

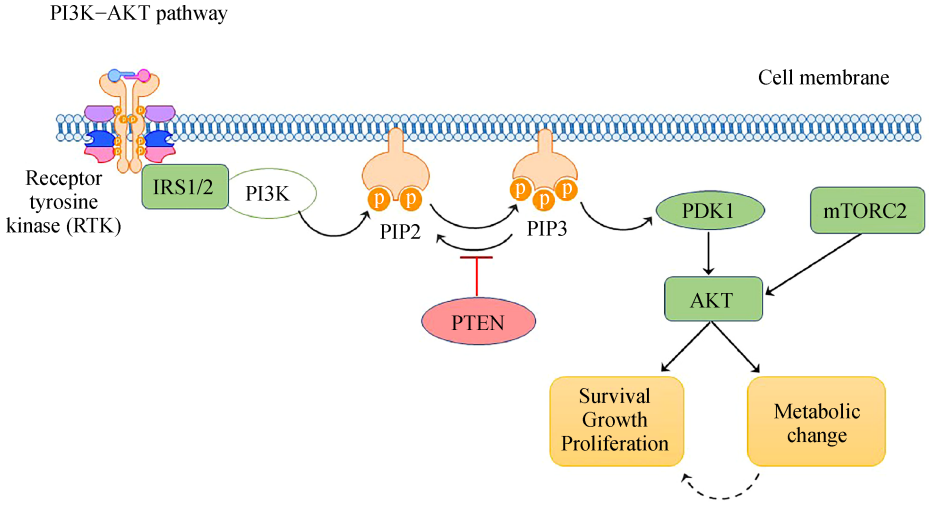

Fig. 2 PI3K–AKT pathway. RTK will create binding sites that recruit the lipid kinase phosphatidylinositol 3-kinase (PI3K) to the plasma membrane. Phosphatidylinositol (PI) 4,5-bisphosphate (PIP2) is the main phosphoinositide at the cell membrane. PI3K phosphorylates PIP2 and yields PI 3,4,5-triphosphate (PIP3). Phosphatase and tensin homolog (PTEN) counteracts the action of PI3K by dephosphorylating PIP3 to PIP2. PIP3 acts as a second messenger to recruit the serine/threonine protein kinase AKT to the plasma membrane, where it is fully activated by phosphoinositide-dependent protein kinase 1 (PDPK1) and the mechanistic target of rapamycin complex 2 (mTORC2). AKT signal transduction promotes cell survival, growth, and proliferation in part by inducing various changes in cell metabolism.

glucose uptake, lactate release, and specific glycolytic enzymes and transporters. However, FASN silencing can reverse the effect of hyperglycemia on the level of EMT markers, increase E-cadherin expression, decrease vimentin and fibronectin, promote stroma-to-epithelium transformation, and inhibit the growth of tumor cells [33]. MGLL is highly expressed in HCC with high malignancy, and the upregulation of MGLL can induce EMT through the NF-κB signal pathway, which endows HCC cells with mesenchymal-like properties and promotes the growth and invasion of HCC cells [21].

FASN and MGLL regulate immunity

FASN is a key metabolic enzyme in the formation of new fat and can directly provide cancer cells the ability to proliferate and metastasize. However, the effect of the abnormal activation of lipogenic enzyme on the host antitumor immune environment is still unknown. FASN expression is increased in ovarian cancer, and the constitutive activation of FASN in tumor cells leads to abnormal lipid accumulation and inhibits the ability of tumor-infiltrating dendritic cells (DC) to resist tumor T cells; therefore, FASN promotes the development of ovarian cancer by weakening antitumor immunity [18]. Interestingly, Xiang *et al.* found that MGLL expression is decreased in tumor-associated macrophages (TAMs), which have antitumor effect. The lack of MGLL in TAMs leads to lipid accumulation in inoculated and genetic cancer models and the activation of macrophages to M2 phenotype through TAMs' endogenous 2-AG–cannabinoid type 2 (CB2) signal. The TAM–MGLL–CB2 axis regulates the activation of tumor-related $CD8^+$ T cells and the progression of various cancers [34].

Research status of FASN and MGLL in tumor invasion and metastasis

Tumor cells often need higher metabolic efficiency to support their rapid proliferation. Besides glycolysis, lipid metabolism can also provide energy for the malignant behavior of tumors. Fatty acids can participate in the biosynthesis of cell membrane and signal molecules and can also provide energy through oxidative decomposition. A large number of studies have shown that abnormal lipid metabolism may be related to tumor invasion and metastasis. The unpublished single-cell RNA-seq and Bulk-seq experiments of our group suggested that FASN and MGLL are abnormally expressed in invasive micropapillary carcinoma (IMPC), which is a highly invasive malignant breast cancer. Current studies have shown that FASN and MGLL are highly correlated with the migration and invasion of various tumor types. The details are provided in Table 1.

FASN and tumor migration and invasion

The increased expression of FASN in breast cancer has been reported many times. Huang *et al.* showed that in breast cancer MCF-7 cells, estradiol or insulin stimulation can increase the pAKT/AKT ratio and the expression of p-SREBP-1, m-SREBP-1, and FASN and promote cell proliferation, whereas docosahexaenoic acid (DHA) can inhibit pAKT signal and thus reduce these effects. Therefore, as a natural anti-breast cancer supplement, DHA may have the potential to inhibit cancer growth [5]. Wang *et al.* proved that miR-15a and miR-16-1 can inhibit FASN expression in breast cancer cells, and FASN can be used as a target for breast cancer therapy [36]. Besides, the *AKT* gene can substantially increase the FASN expression in mouse liver, increase the accumulation of abnormal lipids in liver tissue, and promote the occurrence and development of liver cancer in mice [37]. In addition, some studies have shown that FASN overexpression is closely related to the occurrence, development, and distant metastasis of osteosarcoma. Qiu and Zhao studied the correlation between the PI3K/AKT signal pathway and FASN overexpression in osteosarcoma and found that AKT and FASN expression were upregulated in osteosarcoma and related to soft tissue infiltration and metastasis. The upregulation of FASN expression could upregulate the expression of mTOR, which is an important downstream molecule of the PI3K/AKT signal pathway [17]. FASN is also overexpressed in non-small-cell lung cancer (NSCLC) and leads to poor prognosis. Chang *et al.* demonstrated that the downregulation of FASN could inhibit the invasion and migration of A549 cells *in vitro*, whereas the inhibition of FASN leads to a remarkable shrinkage of animal tumors *in vivo*. Thus, FASN may be a key regulator of the migration and invasion of NSCLC cells [8].

MGLL and tumor invasion and migration

MGLL promotes the invasion and migration of malignant melanoma, ovarian cancer, and breast cancer [11]. MGLL can control the level of FFAs in tumor cells by hydrolyzing monoacylglycerol, and the MGLL–FFA pathway can regulate a variety of lipid networks rich in original tumorigenic signaling molecules and promote the growth and migration of tumors. JZL184, a highly efficient selective inhibitor of MGLL, can be fully inactivated in central and peripheral tissues. Monoacylglycerol activity is remarkably increased in cancer cells whereas FFA level is considerably reduced after the action of JZL184 on invasive cancer cells. The addition of JZL184 restrains the *in vitro* migration of cancer cells and affects the tumor growth *in vivo*, both of which can be saved by exogenous FFAs (including high-fat diet).

Interestingly, MGLL showed the opposite effect in other cancerous tissues. For example, *MGLL* plays a role as a

Table 1 Expression and function of FASN and MGLL in different tumor types

Gene	Cancer type	Expression	Function and mechanism	Reference
FASN	Breast cancer	Elevated	Oncogene	[5,35,36]
	HCC	Elevated	Oncogene AKT–FASN SPIN1–SREBP1C–FASN Osthole–AKT–FASN axis	[37] [22] [7]
	Osteosarcoma	Elevated	Oncogene PI3K–AKT pathway	[17]
	NSCLC	Elevated	Oncogene AKT/ERK	[8]
	Colorectal cancer	Elevated	Oncogene HER2–PI3K–AKT–FASN axis	[6]
	Ovarian cancer	Elevated	Oncogene Blunts antitumor immunity PI3K–AKT pathway	[18] [38]
	Wilms tumor	Elevated	Oncogene	[19]
	Prostate cancer	Elevated	Oncogene Modifies Rho GTPases	[39,40]
	Salivary adenoid cystic carcinoma	Elevated	Oncogene PRRX1/Wnt/β-catenin pathway	[41]
	Acute lymphoblastic leukemia	Elevated	Oncogene	[42]
MGLL	Aggressive melanoma	Elevated	Oncogene MGLL–FFA	[11]
	Gastrointestinal stromal tumor	Elevated	Oncogene	[20]
	Primary colorectal cancers	Absent or reduced	Tumor suppressor gene Negatively regulates PI3K–AKT signaling	[12]
	HCC	Reduced	Tumor suppressor gene KLF4–MGLL axis SND1–MGLL–AKT axis	[25] [13]
		Elevated	NF-κB-mediated EMT	[21]
	Aggressive ovarian cancer	Elevated	Oncogene MGLL–FFA	[11]
	Breast cancer	Reduced	Tumor suppressor gene	[14]
	Aggressive breast cancer	Elevated	Oncogene MGLL–FFA	[11]
	Intestinal adenomas	Elevated	Tumor suppressor gene	[14]
	Primary lung cancer	Reduced	Tumor suppressor gene	[14]
	Neuroblastoma	Reduced	Tumor suppressor gene	[43]
	TAMs	Reduced	Tumor suppressor gene Attenuates endogenous CB2 signaling	[34]

tumor suppressor gene in colorectal cancer, liver cancer, neuroblastoma, and melanoma [12,25,43]. MGLL is speculated to play a tissue-specific role in promoting or suppressing cancer. Sun *et al.* reported that MGLL expression is lost or decreased in carcinomatous epithelial cells in human primary colorectal cancer. MGLL overexpression can inhibit the colony formation of tumor cell lines and play a negative regulatory role in the PI3K/AKT signal pathway and tumor growth [12]. MGLL expression decreased in TAMs in the melanoma mouse model established by Xiang W. MGLL overexpression could stimulate macrophages through the TLR4–Sirpa axis, enhance the tumor phagocytosis of macrophages, and remarkably inhibit the progression of subcutaneously transplanted tumor [44].

Prospects

People know more about the relationship between the abnormal lipid metabolism and malignant behavior of tumors with the deepening of research. *FASN* and *MGLL* are the key genes in tumor lipid metabolism. In our study, we found the abnormal expression of FASN and MGLL in

IMPC using single-cell sequencing method. This finding is consistent with the results of other researchers in other types of malignant tumors. However, the mechanism of the high expression of FASN and MGLL in IMPC is not clear. FASN and MGLL are likely to be highly related to the malignant invasion and metastasis of IMPC, which will be the direction of our future research.

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Compliance with ethics guidelines

Jingyue Zhang, Yawen Song, Qianqian Shi, and Li Fu declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol that require the approval of relevant institutional review board or ethics committee.

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