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REVIEW

Immune cells in diabetic wound repair: the key to better wound management

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Abstract **Chronic diabetic ulcers (DUs) pose a significant clinical challenge with high amputation and mortality rates, impacting over 131 million people worldwide and incurring approximately $755 billion in annual healthcare costs. Immune cells play indispensable roles in orchestrating wound healing; however, existing reviews often overlook the temporal heterogeneity of immune cell subsets in DUs. To bridge this gap, this review comprehensively examines the roles and characteristics of immune cells in DUs healing, involving monocytes, macrophages, dendritic cells, neutrophils, mast cells, B cells, T cells, and natural killer cells, with a focus on their distribution and dysregulation throughout different stages of wound healing. Furthermore, we highlight advances in immune cell-targeted modulation and the emerging therapeutic promise of topical anti-cytokine biologics in diabetic wound care. We uniquely emphasize the dynamic transitions of monocyte subsets and offer a systematic evaluation of the controversial roles of macrophage M1/M2 polarization. This review underscores emerging therapeutic strategies that leverage immune cell modulation, offering insights into more effective DU management.**

Keywords diabetic ulcers; macrophages; neutrophils; wound healing; targeted therapies

Introduction

Diabetes-related lower extremity complications impact nearly 131 million people worldwide, comprising 1.8% of the global population; diabetic ulcers (DUs) draw significant attention due to their high rates of amputation and mortality [1]. The five-year survival rate of diabetic foot ulcers (DFUs) is only 50%, and over 70% of amputees die within five years, with the mortality rate surpassing that of several cancers [2,3]. Diabetes-related amputations place the largest economic burden in chronic wound care [2]. Annual expenditures for diabetic lower limb complications reach approximately $60 billion in the United States [4], while the cost is estimated at $54.14 billion in China [5,6]. Despite advancements in dressings, cell therapies, and hyperbaric oxygen therapy, clinical outcomes remain unsatisfactory, underscoring an urgent need for innovative approaches that target the underlying immune-pathological mechanisms of DU wounds.

Wound healing progresses through four distinct yet overlapping phases: hemostasis, inflammation, proliferation, and remodeling [7]. During hemostasis, platelets release chemokines to recruit immune cells [8]. In the inflammatory phase, neutrophils arrive first, followed by macrophages, which transition from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype [9–11]. Macrophages and neutrophils orchestrate angiogenesis by releasing vascular endothelial growth factor (VEGF) during the proliferative phase [12]. In the remodeling phase, M2 macrophages regulate extracellular matrix (ECM) turnover by secreting matrix metalloproteinases (MMPs), ensuring optimal tissue recovery with minimal scarring [13,14]. Moreover, regulatory T cells (Tregs) and mast cells modulate wound healing by suppressing excessive inflammation and enhancing neutrophil recruitment [15,16]. Therefore,

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immune cells play an indispensable role in orchestrating multiple aspects of wound healing, from initial inflammatory responses to tissue repair and remodeling.

However, the temporal transitions of immune cell subpopulations in DUs during different wound-healing phases remain unclear. Existing studies often focus on summarizing broad immune cell categories rather than the dynamic changes and plasticity of immune cells in diabetic wounds. In this review, we focus on these underexplored and controversial aspects of immune cell behavior in DU healing. With the summarization of the immune cell subsets in DUs, we sought to refine clinical treatment protocols and facilitate the translation of therapies into clinical practice.

Dysregulation of immune cells in DUs

In the following section, we summarize the functions of immune cells over time in DU repair, introducing each major immune cell type in the order of their temporal involvement. Altered cellular activities and impaired immune coordination will also be explored in DUs.

Mast cells: degranulation and dysfunction

Mast cells originate from hematopoietic stem cells (HSCs) along the myeloid lineage [17]. They play roles in allergic responses and participate in all stages of wound healing with their mediators [18]. Besides, mast cells are involved in the pathogenesis of diabetes and its complications [18]. In the early phase of injury, mast cells release histamine rapidly, promote vasodilation, increase vascular permeability, and recruit immune cells. In the later stage, mast cells stimulate the proliferation of keratinocytes, endothelial cells, and fibroblasts by secreting growth factors, and further enhance the angiogenesis and re-epithelialization [19–21]. Excessive mast cell degranulation has been observed in diabetic wounds; however, if this aberration persists, it may hinder the wound healing process.

Studies have reported that elevated total and degranulated mast cells were found in skin tissues of diabetic patients compared to non-diabetic controls [22,23]. Although the total count of mast cells was unchanged in diabetic foot, activated mast cells increased, correlating with elevated pro-inflammatory cytokine levels [23]. Animal models demonstrate elevated baseline levels of mast cells in wounds, resulting in impaired re-epithelialization, reduced angiogenesis, and delayed wound healing [23,24]. This aberrant pre-activation of mast cells likely compromises the acute responsiveness of mast cells to injury. Nevertheless, prolonged mast cell infiltration and sustained degranulation were observed in the later stage of DUs healing in STZ-induced rats and mice, indicating the persistent dysregulated inflammatory response [23–28]. Application of mast cell stabilizers could enhance wound recovery and promote M2 polarization in STZ-induced mice [24]. Furthermore, mast cell-deficient mice ($Kit^{W}/Kit^{W\text{-}v}$) consistently displayed delayed healing irrespective of diabetes, underscoring the indispensable role of mast cells in tissue reparation. *In vitro* studies further revealed that high glucose alone could not trigger mast cell degranulation, which could suppress VEGF secretion and increase IL-8 production [24]. Overall, diabetes-related hyperglycemia exacerbates wound healing by disrupting mast cell abundance, activation dynamics, and functional output.

Neutrophils: variation in number and characteristic

Neutrophils originate from HSCs in the bone marrow (BM) and mature into fully segmented granulocytes [29]. As the first responders in innate immunity, they eliminate pathogens via phagocytosis, degranulation, and formation of neutrophil extracellular traps (NETs) (they extrude DNA structures coated with antimicrobial proteins to trap and kill pathogens) [9,30–32]. In normal wound healing, they quickly infiltrate injury sites, initiate inflammation, and facilitate tissue repair [33]. However, excessive and prolonged neutrophil activity can damage host tissue and impair healing, especially in DUs [34].

DFU patients often exhibit elevated peripheral neutrophil counts or neutrophil-to-lymphocyte ratios, which correlate with prolonged hospital stays and an increased risk of amputation [35–37]. Paradoxically, despite this systemic neutrophilia, the actual recruitment of neutrophils into the wound site is impaired in diabetes [38]. The reduced activity of FOXM1 (a transcription factor essential for leukocyte migration) was found in DFU tissues, with decreases in neutrophil infiltration [38]. Thus, more neutrophils in circulation do not translate to effective local immune defense in diabetic wounds.

DUs models demonstrate the “slow-in, slow-out” pattern of neutrophil infiltration, characterized by delayed initial recruitment and prolonged persistence compared to normal wounds [39–48]. Mechanistically, neutrophils from *db*/*db* mice display reduced adhesion and migration receptors (such as CD54, CXCR4), impairing their effective entry into wound sites [49]. Hyperglycemia further exacerbates neutrophil dysfunction by disrupting formyl peptide receptor-mediated chemotaxis, delaying migration, and impairing phagocytic capacity against pathogens [41,43,50]. Concurrently, diabetic conditions prolong neutrophil survival in wounds by inhibiting apoptosis and compromising their clearance through macrophage-mediated efferocytosis [39,41,51]. Notably, the uptake of apoptotic neutrophils by macrophages is a key trigger of the M1-to-M2 phenotypic switch [41]. These early defects in neutrophil chemotaxis,

phagocytosis, and clearance not only precede the dysregulation of other immune subsets but also initiate the prolonged inflammatory state observed in DUs, suggesting that neutrophil dysfunction may be a primary immunological event in DU pathogenesis.

Elevated release of NETs in DUs microenvironment

DFUs are associated with excessive NETs in both blood and wound tissues [52,53]. Elevated levels of citrullinated histone H3 (CitH3) correlate with ulcer severity, delayed healing, and higher amputation risk [52–54]. NETs thus serve not only as indicators of disease progression but also as contributors to pathological inflammation. Mechanistically, diabetic neutrophils exhibit a lower threshold for NETs release [52]. For instance, plasma and platelets from DFU patients, especially those sourced from ulcer-associated vessels, stimulate higher NETs release in healthy neutrophils compared to plasma and platelets from healthy controls [53]. Hyperglycemia enhances NET formation through reactive oxygen species (ROS)-dependent pathways (PKC-ERK1/2-NADPH oxidase) [55]. NET-derived proteases and inflammatory mediators may injure endothelial cells or even induce endothelial-to-mesenchymal transition, thereby reducing functional blood vessel growth [53,56].

Excessive formation of NETs in DUs disrupts the function of fibroblasts and macrophages, perpetuating a highly inflammatory microenvironment detrimental to wound healing. For instance, IL-8 derived from diabetic neutrophils and NETs amplifies MMP-9 production, accelerating ECM degradation, impairing fibroblast migration, and hindering wound contraction [57]. Moreover, direct exposure to NETs could induce ferroptosis in fibroblasts via endoplasmic reticulum stress, resulting in decreased collagen synthesis and compromised tissue regeneration [58]. NETs also obstruct inflammation resolution by inhibiting PI3K/Rac1 signaling needed for macrophage efferocytosis, leading to debris accumulation and prolonged inflammation [59]. Additionally, NETs activate the NLRP3 inflammasome in macrophages, drive IL-1β secretion, and exacerbate chronic inflammation [60]. Furthermore, NET-derived DNA promotes macrophage polarization toward a pro-inflammatory M1 phenotype through NF-κB pathway activation [55]. Collectively, these NET-mediated processes critically undermine the reparative capacity of diabetic wounds.

DUs exhibit profound quantitative and functional abnormalities in neutrophils. Increased neutrophil counts and NET levels were found in the peripheral blood of DUs patients, with inadequate neutrophil recruitment and prolonged, unproductive inflammation in their wounds paradoxically. Neutrophils in diabetic tissues persist longer and release excessive NETs, contributing to sustained inflammation and impairments in key healing processes like angiogenesis and ECM deposition. Moreover, coordinated interactions between neutrophils and other key wound-healing cells (such as endothelial cells, macrophages, and fibroblasts) are disrupted, further exacerbating the breakdown of reparative homeostasis.

NK cells: dysregulation and functional impairment

NK cells, derived from HSCs in the BM, can also mature in secondary lymphoid tissues, acquiring adaptive traits like memory formation [61]. As innate lymphocytes, NK cells rapidly eliminate infected or damaged cells and coordinate immune responses through cytokine secretion [62–64]. In normal wounds, early NK cell infiltration aids infection control and tissue clearance, while their prolonged presence could delay healing paradoxically. Systemic NK depletion in C57BL/6J mice accelerates wound repair by enhancing re-epithelialization and collagen deposition, without altering neutrophil or monocyte/macrophage accumulation, but reducing pro-inflammatory cytokine levels significantly [65]. Recent evidence has identified that HIF-1α in NK cells is a critical regulator in balancing antimicrobial defense and wound healing; deletion of HIF-1α could accelerate healing but weaken antibacterial responses, whereas its activation could enhance pathogen clearance but delay repair [66].

However, this NK cell-mediated balance is disrupted in diabetic wounds. DFU patients display reduced circulating NK cells compared to healthy individuals, and higher peripheral NK cell levels are associated with improved healing outcomes [67,68]. Paradoxically, wounds in STZ-induced BALB/c mice exhibit increased NK cell infiltration [69]; however, transcriptomic analyses reveal a predominance of resting NK cells and attenuated activation signatures in DFU tissues [70,71]. Therefore, DUs maintain NK cells that are abundant but functionally impaired, perpetuating chronic inflammation and delayed healing. Future studies should clarify NK cell dysfunction mechanisms and explore therapeutic strategies to explore its reparative functions in DUs.

Mononuclear phagocytes: variation in number and characteristic

Mononuclear phagocytes comprise monocytes, macrophages, and dendritic cells (DCs). Monocytes and macrophages arise from both embryonic yolk sac-derived and adult BM-derived hematopoiesis, while most DCs develop from BM-derived precursors [72]. Circulating monocytes differentiate into macrophages upon tissue infiltration and respond to local cues [73–75].

Monocytes: infection and inflammation

Under homeostatic conditions, circulating monocyte counts remain relatively constant. However, circulating monocyte levels and monocyte-to-lymphocyte ratios are significantly elevated in DFU patients, especially those with infections, and positively correlating with ulcer occurrence and severity [76,77]. Peripheral monocytes isolated from infected DFU patients demonstrate increased expression of Toll-like receptors (TLR2 and TLR4), which enhance IL-6 secretion and subsequent $CD8^+$ T cell activation through innate-adaptive immune interplay [76,78]. Suggesting that monocytes play crucial roles in amplifying inflammation during DFU infection.

Similar disruptions in monocyte homeostasis occur in diabetic animal models. The proportion of pro-inflammatory ($Ly6C^{+Hi}$) monocytes in both *db*/*db* and STZ-induced C57BL/6 mice is elevated in both circulation and wound sites, while the proportion of anti-inflammatory ($Ly6C^{low/-}$) monocytes is significantly reduced compared to control mice in circulation [47,49,79–82]. Elevated monocyte accumulation in DUs results from increased BM-derived monocyte production and impaired local differentiation [83,84]. Specifically, common myeloid progenitors from *db*/*db* mice produce more monocytes compared to C57BL/6 mice but exhibit impaired maturation into functional macrophages, causing excessive monocyte accumulation and persistent inflammation [83,84].

Monocyte-macrophage-mediated phenotypic transitions

The transcriptome of $Ly6C^{+Hi}$ cells isolated from normal murine wounds is closely resemble to *in vitro*-cultured M1 macrophages, while $Ly6C^{low/-}$ cells are more likely to differentiate into M2 macrophages in wound tissues [79,84,85]. Pro-inflammatory monocytes are recruited to injury sites and differentiated into M1 macrophages, and anti-inflammatory monocytes were differentiated into M2 macrophages; increased M1 macrophages and reduced M2 macrophages were found in *db*/*db* mice wounds [79]. Collectively, the diabetic state promotes pro-inflammatory monocytes recruitment and inhibits anti-inflammatory monocytes, increasing blood-derived M1 macrophages and reducing M2 macrophages in wounds, ultimately delaying healing [47,49,79–82,84,86].

Monocytes and macrophages (Mo/MΦ) are essential producers of both pro-inflammatory and pro-healing factors, which balance the inflammation, clear debris/dead cells, and secrete cytokines and growth factors [87,88]. In normal wounds, both the total Mo/MΦ population and the pro-inflammatory $Ly6C^{+Hi}$ subset show increased apoptosis as healing progresses, while $Ly6C^{+Hi}$ Mo/MΦ transition into the regenerative $Ly6C^{+Lo}$ phenotype [84,89]. In contrast, diabetic mice wounds exhibit low apoptosis levels and a secondary influx of $Ly6C^{+Hi}$ cells, which fail to transition into the $Ly6C^{+Lo}$ phenotype [84,89]. Furthermore, Mo/MΦ display an undifferentiated phenotype in DUs of *db*/*db* mice, characterized by high *Ly6C* mRNA and low *F4/80* mRNA levels [90]. Consequently, reduced Mo/MΦ apoptosis and impaired transition from pro-inflammatory to pro-healing phenotypes lead to the accumulation of pro-inflammatory Mo/MΦ in diabetic wounds.

Macrophages: characteristics and functional impairments

The chronic non-healing nature of DUs has been partly attributed to macrophage dysfunction and an imbalanced inflammatory milieu. Excessive inflammation is often characterized by heightened M1 macrophage infiltration and impaired M2 responses [71,91–94]. Clinically, DFU lesions display elevated M1/M2 macrophage ratios, increased pro-inflammatory cytokines (such as IL-1β, IL-18, and TNF-α), and reduced anti-inflammatory factors (such as IL-10) [71,91–94], indicating sustained inflammation. Higher M2 macrophage numbers and lower M1/M2 ratios correlate positively with healing outcomes, highlighting the importance of transitioning from an M1-dominated inflammatory phase to an M2-driven reparative phase [22,95].

Alternatively, some studies suggest DFUs exhibit an immunosuppressive microenvironment, featuring attenuated inflammatory responses and impaired immune activation [22,96–98]. DFU non-healers can show reduced overall macrophage activation, with macrophages expressing anti-inflammatory and diminished pro-inflammatory responses [96]. DFU-healer wounds exhibit enhanced macrophage density, particularly M1 phenotypes, in contrast to DFU non-healers [96–98]. Pro-inflammatory responses are not inherently detrimental; rather, they may exert phase-specific reparative roles when properly regulated. A recent study demonstrated that during the early inflammatory phase, pro-inflammatory macrophages promote keratinocyte migration by secreting paracrine signals (such as EREG, CXCL1, and CXCL5), thereby facilitating re-epithelialization [98]. Therefore, the DFU microenvironment is thought to be dysregulated, characterized by prolonged inflammation that is not effectively resolved, but in some cases also showing pockets of immune paralysis. This duality underscores why therapies should be timed and targeted to restore immune balance.

Macrophage infiltration also exhibits a “slow-in, slow-out” pattern in DU animal models. Diabetic wounds exhibit impaired early macrophage recruitment followed by persistent inflammation due to prolonged macrophage retention differ from the rapid and coordinated

macrophage influx of normal wounds [99–102]. Impaired macrophage migration in diabetic wounds is closely associated with reduced early expression of macrophage chemokines, and remain elevated in later stages [50,103,104]. Moreover, the inflammatory phase features impaired M1 macrophage recruitment and reduced pro-inflammatory mediator expression [41,46,103,105], while the proliferative phase shows persistent M1 infiltration, fewer M2 macrophages, and a pro-inflammatory milieu [99–102]. Persistent M1 macrophages exacerbate tissue damage through elevated MMPs and ROS, impairing granulation tissue formation, while reduced M2 populations lead to inadequate growth factor production essential for angiogenesis and tissue rebuilding [106–109].

High glucose levels/diabetic conditions promote M1 polarization in macrophages while suppressing pro-healing traits. For instance, THP-1 monocytes differentiated into M0 macrophages using phorbol 12-myristate 13-acetate exhibit increased levels of M1 markers and reduced levels of M2 markers under high glucose conditions [92,103,110,111]. Additionally, BM-derived macrophages from *db*/*db* mice exhibit impaired migration and enhanced adhesion to endothelial cells, contributing to vascular dysfunction and delayed wound infiltration [95]. The angiogenic potential of vascular endothelial cells diminishes with M1 macrophage coculture but increases with M2 macrophage coculture [103]. Reduced VEGF secretion, coupled with an M1-over-M2 polarization imbalance, further exacerbates defective angiogenesis in diabetic wounds. Recent evidence indicates that macrophages in *db*/*db* mouse wounds undergo inflammasome-mediated pyroptosis, triggering IL-18 and IL-1β secretion that sustains chronic inflammation [112]. Furthermore, diabetic macrophages exhibit impaired phagocytosis, particularly efferocytosis (clearance of apoptotic cells) and autophagy (intracellular degradation and recycling of damaged components) [44,45,51,113,114]. Reduced macrophage autophagy impairs pathogen clearance and worsens infection management [113,115], whereas defective efferocytosis causes apoptotic debris accumulation, amplifying inflammation through secondary necrosis [104,116].

Therefore, diabetic macrophages are often caught in a dysfunctional state: biased M1 polarization, diminished pro-healing capabilities, impaired migration and angiogenesis, elevated inflammasome-mediated pyroptosis, and defective clearance of apoptotic debris and pathogens. Collectively, these abnormalities sustain a chronic inflammatory state, directly contributing to the delayed healing that characterizes DUs.

Infiltration of DCs and langerhans cells in DUs

DCs, professional antigen-presenting cells, detect pathogens through pattern-recognition receptors such as Toll-like receptors and are categorized into plasmacytoid DCs, conventional DCs, monocyte-derived DCs, and epidermal Langerhans cells [117,118]. DCs and Langerhans cells sustain immune surveillance by capturing pathogens or apoptotic cells, migrating to lymph nodes, and activating T cells [119,120]. Beyond antigen presentation, DCs support wound repair. Murine burn models show that DC depletion impairs wound closure and angiogenesis, whereas DC expansion promotes healing [121]. Langerhans cells, epidermis-resident DCs, maintain skin homeostasis, regulate keratinocyte activity, and promote angiogenesis during tissue regeneration [119,122,123].

In DUs, DC functions are notably impaired despite increased numbers [47,124–126]. Diabetic DCs exhibit reduced expression of activation markers (CD40, CD86) and impaired efferocytosis, limiting antigen presentation and prolonging inflammation [47,124–126]. Recent experimental studies demonstrate that restoring DC function promotes angiogenesis and accelerates wound closure in DU models, highlighting their therapeutic potential [126–128].

The specific role of Langerhans cells in diabetic wound healing warrants further clarification. Clinical studies report that increased Langerhans cell density in DFU patient wounds positively correlates with improved healing outcomes, suggesting beneficial roles in controlling infection and inflammation [129,130]. Consistent with this protective role, experimental studies have found reduced Langerhans cell numbers in *db*/*db* mice wounds compared to the sustained Langerhans cell presence in normal controls [48]. Conversely, a study involving acute wounds indicated that depletion of langerin-positive cells (including Langerhans cells) could accelerate wound closure, suggesting context-dependent inhibitory roles under certain conditions [131]. Collectively, these observations imply that Langerhans cells support wound repair processes in chronic diabetic contexts. Future targeted investigations, employing conditional Langerhans cell depletion and single-cell transcriptomics, are essential to clearly define their therapeutic potential in DUs.

Dynamics of T cells in DU healing

T cells ($CD3^+$), originating from HSCs, differentiate into two main subsets: αβ and γδ T cells [132]. In DUs, overall T cell dynamics are notably altered. Clinically, DFU patients show reduced naive and early differentiated T cell subsets in peripheral circulation, alongside increased activated effector populations [133]. Notably, DFU-healing patients have a higher proportion of naive and early-differentiated progenitor T cells, whereas non-healers display abundant cytotoxic natural killer T cells,

indicating chronic activation and exhaustion [96]. DFU lesions often exhibit elevated dermal $CD3^+$ T cells accompanied by increased IL-17 and IFN-γ expression [134,135], the same with other studies reporting higher circulating $CD3^+$ T cell counts [67,136]. However, other research has noted reduced $CD3^+$ T cell infiltration in chronic DFU patient wounds compared to acute wounds, reflecting complex and variable immune dynamics potentially influenced by patient-specific factors and ulcer severity [137].

$CD4^+$ T cells, derived from thymic double-positive αβ precursors, act as helper cells coordinating immune responses by activating other immune cells [138,139]. Normally, $CD4^+$ T cell depletion in thymectomized rats impairs wound strength and delays closure, highlighting their essential role in tissue repair [140]. In DFU patients, circulating naive and non-polarized central memory $CD4^+$ T cells are significantly decreased, and activated effector subsets accumulated in both blood and wound tissues [96,133,137]. Elevated inflammatory cytokines could decrease chemokine receptor expression, impair $CD4^+$ T cell migration, and compromise local immune function [133]. Consistently, DFU biopsies confirm reduced $CD4^+$ T cell infiltration [137]. This imbalance between depleted naive cells and hyperactive effector subsets perpetuates chronic inflammation and hinders regeneration.

Tregs, a specialized $Foxp3^+$ subset of $CD4^+$ T cells, normally resolve inflammation and support tissue regeneration by secreting IL-10, TGF-β, and amphiregulin during late-stage wound repair [141–143]. Tregs appear to exert a double-edged influence in DUs. Clinical studies report that therapies expanding Tregs (such as maggot debridement) could enhance DFU healing [144], a finding supported by animal studies where lipoic acid treatment increased Treg levels and improved wound closure in STZ-induced diabetic mice [145]. Conversely, Treg depletion in alloxan-induced diabetic mice accelerated local wound repair but worsened systemic diabetes, emphasizing the importance of localized modulation [146]. This duality likely reflects the intricate balance Tregs maintain between anti-inflammatory actions and potential pro-fibrotic effects within diabetic wounds [133].

$CD8^+$ T cells, also originating from double-positive αβ precursors, function primarily as cytotoxic lymphocytes targeting infected or malignant cells [138,139]. Normal wound healing is accelerated by $CD8^+$ T cell depletion, suggesting these cells generally constrain repair through inflammation [140]. However, $CD8^+$ dynamics in DFU patients are highly heterogeneous. Clinical and animal studies have documented increased $CD8^+$ infiltration in both wounds and peripheral blood, especially during late-stage healing, potentially exacerbating chronic inflammation [46,67,147]. Single-cell analysis identifies enriched $GZMA^+$ $CD8^+$ subsets in chronic DFU patient wounds, which secrete granzyme A and IFN-γ, likely promoting epidermal inflammation and impairing re-epithelialization [148]. Conversely, other studies show reduced $CD8^+$ T cells in both wounds and circulation of DFU non-healers compared to healers, indicative of immune exhaustion [68,96]. Healing DFU patients exhibit $CD8^+$ T cells enriched with central memory phenotypes ($CD27^+$), characterized by reduced immediate cytotoxicity but enhanced plasticity, facilitating balanced inflammation and repair [96,149]. In contrast, persistent non-healing ulcers accumulate exhausted and terminally differentiated $CD8^+$ effectors that sustain destructive inflammation [96,133,149]. These discrepancies underline the complex, context-specific roles of $CD8^+$ T cells in diabetic wound pathology.

γδ T cells, originating from double-negative thymic precursors without CD4 or CD8 expression, provide rapid immune responses crucial for tissue repair [149]. Dendritic epidermal T cells (DETCs, a specialized γδ T cell subset exclusive to murine epidermis) serve as valuable models to understand γδ T cell roles in human epithelial regeneration [150]. Under normal conditions, DETCs rapidly secrete growth factors (IGF-1, KGF-1/2) essential for keratinocyte function and rapid re-epithelialization [149,151]. Clinically, γδ T cell levels are reduced in DFUs compared to normal wounds [152]. In STZ-induced mice, γδ T cells (including DETCs) are significantly reduced in both intact skin and wound margins, coupled with reduced IL-17 and key cytokine expression (NKG2D, JAML, KGF, IGF-1), impairing neutrophil recruitment, angiogenesis, macrophage M2 polarization, and keratinocyte responses [152–156]. Taken together, marked reductions in γδ T cells and DETC activity in diabetic wounds are accompanied by impaired cytokine production, compromised keratinocyte activation, and delayed re-epithelialization.

Reduced B cell levels in DU healing

B cells originate from HSCs within the BM, which is a beneficial actor in wound healing [157–158]. A recent study indicates that recruited B cells accumulate at wound sites, driving macrophage polarization toward the M2 phenotype, which could promote tissue reparation [159]. Decreased B cell infiltration was observed in DUs. Clinically, DFU patients exhibit reduced peripheral B cell counts compared to those with diabetes alone, and even lower B cell levels observed in non-healing DFU patients compared to healing ones [68]. Bioinformatics analyses highlight that B cells are predominantly enriched in healthy skin and DFU tissues associated with favorable healing outcomes [68]. A recent study demonstrates that topical application of purified mature naive B cells to wounds could accelerate closure, enhance collagen deposition and maturation, reduce scarring, increase

angiogenesis, and promote nerve regeneration in both healthy and *db*/*db* mice [158]. Additionally, elevated expression of *CXCR5* and *MS4A1* genes in healing DFU tissues emphasizes the critical roles of B cell migration and activation [160].These findings underscore the therapeutic potential of enhancing mature B cell responses to improve healing outcomes in DUs.

Collectively, leukocytes exhibit elevated counts but impaired functionality in DUs, with notably compromised phagocytic and cytocidal abilities, particularly in polymorphonuclear leukocytes [161–166]. Similarly, lymphocyte dynamics in DUs are complex and paradoxical; diabetic animal models deficient in lymphocytes (including T cells, B cells, and innate lymphoid cells) show delayed wound closure, heightened pro-inflammatory macrophage ratios, and increased oxidative stress [167]. These findings indicate that immune cells infiltrate diabetic wounds in greater numbers, but their intrinsic functional impairments (including heightened inflammatory polarization, diminished phagocytic and antimicrobial effectiveness, impaired pro-healing phenotype transitions, and reduced secretion of regenerative factors) drive persistent inflammation and impaired repair in DU pathogenesis (Table 1, Fig. 1). Importantly, indiscriminate elimination or systemic suppression of these immune cells may be counterproductive. The following sections explore therapeutic strategies aimed at restoring immune cell function and re-establishing effective reparative processes in diabetic wounds.

Immune-targeted therapies for DUs

Targeting innate and adaptive immune cells offers promising therapeutic opportunities for diabetic wound management. In DUs, excessive mast cell degranulation drives chronic inflammation and impairs healing, making mast cell stabilization a compelling therapeutic strategy. Preclinical studies have shown that cromolyn sodium, a classical mast cell stabilizer, accelerates wound closure in STZ-induced diabetic mice by preventing premature degranulation and promoting M2 macrophage polarization [168]. Similarly, topical application of a mast cell stabilizer inhibits mast cell degranulation and improves healing outcomes, achieving effects comparable to those of systemic mast cell stabilizers [168]. In addition, omega-3 fatty acid supplementation indirectly modulates mast cells by reducing their infiltration, thereby enhancing wound healing in diabetic rats [169]. Although clinical evidence remains limited, these findings highlight mast cell stabilization as a viable and translatable strategy for diabetic wound therapy.

Targeting neutrophil-driven NETosis has shown substantial therapeutic potential in preclinical models of DUs. Study have demonstrate that the ablation of NET formation could degrade extracellular NETs and effectively restore wound healing in STZ-induced diabetic mice [34]. Beyond direct NET degradation, other strategies (such as using IL-8 monoclonal antibodies and MMP-9 inhibitors) that mitigate NET-mediated ECM breakdown and fibroblast dysfunction still under investigation [57]. These approaches could modulate neutrophil activity, attenuate their destructive effects, and preserve antimicrobial function, aiming to promote inflammation resolution and facilitate the transition of DUs into the regenerative phase.

Targeting monocyte/macrophage dysfunction emerges as a promising strategy for DUs therapy. Various approaches aim to restore the disrupted M1-to-M2 polarization balance in response to the chronic

Table 1 Characteristics of immune microenvironment in diabetic wound

Phases	Immune cells	Immune cell subsets	Pathways	Cell cytokines	References
Inflammation	Leukocyte ↑, monocytes ↑, Mo/MΦ ↑, macrophages (paradox), neutrophils ↑, mast cells ↑, DCs ↑, lymphocytes (paradox), B cells ↓, T cells (paradox), NK cells (paradox)	$Ly6C^{+Hi}$ monocytes ↑, $Ly6C^{+Hi}$ Mo/MΦ ↑, M1 ↑, Langerhans cells (paradox), Tregs (paradox), $CD8^+$ T cells (paradox), γδ T cells ↓, DETCs ↓	NF-κB pathway ↑, TLR signaling pathway ↑, PKC-ERK1/2-NADPH-ROS pathway ↑, NETosis ↑	IL-1β ↑, TNF-α ↑, IL-12 ↑, IL-6 ↑, MMP-9 ↑, ROS ↑, NETs ↑, Histamine ↑	[76,84,88–90,161, 164–166,181]
Proliferation	Monocytes ↑, Macrophages (impaired), Neutrophils ↑, Mast cells ↑	$Ly6C^{low/-}$ monocytes ↓, $Ly6C^{+Lo}$ Mo/MΦ ↓, M2 ↓, Tregs (paradox), γδ T cells ↓, DETCs ↓	Wnt signaling ↓	IL-10 ↓, TGF-β ↓, VEGF ↓, EGF ↓, KGF ↓, IGF-1 ↓, FGF ↓	[41,44–45,51,76,95, 103,112,181–183]
Remodeling	Macrophages (impaired)	M2 ↓	TGF-β signaling ↓	IL-10 ↓, TGF-β ↓, IGF-1 ↓, VEGF ↓, FGF ↓	[41,71,91–94,99]

These changes reflect the dysregulated immune response that contributes to impaired healing in diabetic wounds. Upward arrows (↑) indicate increased levels or activation, downward arrows (↓) indicate decreased levels or activation, and "paradox" indicates conflicting evidence in the literature. DETCs, dendritic epidermal T cells; DCs, dendritic cells; EGF, epidermal growth factor; FGF, fibroblast growth factor; IGF-1, insulin-like growth factor 1; IL, interleukin; KGF, keratinocyte growth factor; $Ly6C^{+Hi}$ Mo/MΦ, Ly6C-high monocytes/macrophages; $Ly6C^{+Lo}$ Mo/MΦ, Ly6C-low monocytes/macrophages; M1, M1 macrophages; M2, M2 macrophages; MMP-9, matrix metalloproteinase 9; NETs, neutrophil extracellular traps; NK, natural killer; ROS, reactive oxygen species; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; Tregs, regulatory T cells; Mo/MΦ, monocyte/macrophage.

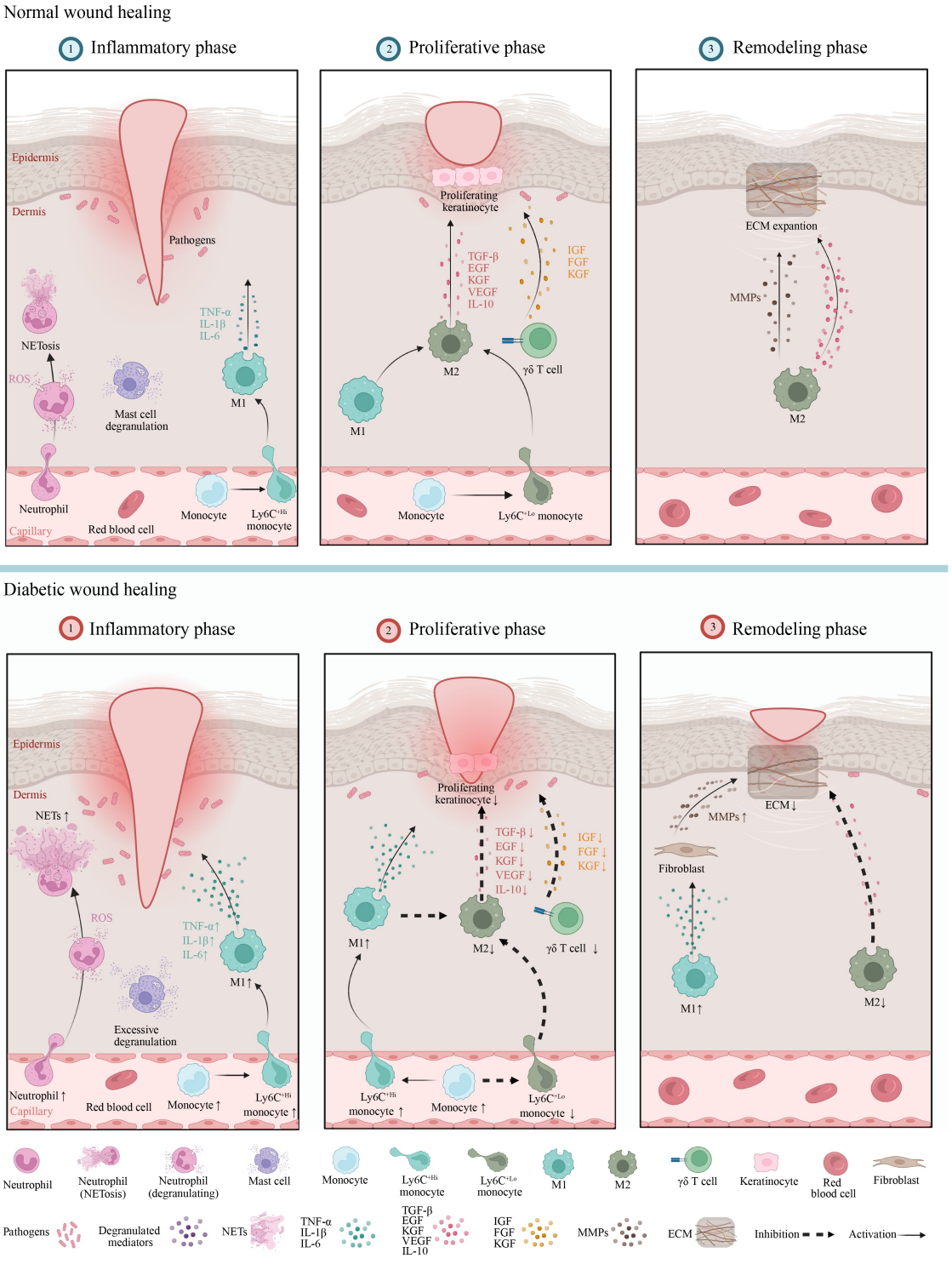

Fig. 1 Diagram of the immune cell distribution and function during normal and diabetic wound healing. In normal wound healing, mast cells degranulation releasing histamine, neutrophils infiltration performing NETosis and phagocytosis, pro-inflammatory Ly6C^{+Hi} monocytes were recruited and differentiate into M1 macrophages (the inflammatory phase); then transition to Ly6C^{+Lo} monocytes and M2 macrophages, γδ T cells promote keratinocyte proliferation and re-epithelialization (the proliferative phase); extracellular matrix (ECM) remodeled by M2 macrophage-secreted MMPs and limited scar formation (the remodeling phase). In diabetic wound healing, excessive mast cells degranulation, delayed/increased neutrophils infiltration, elevated pro-inflammatory Ly6C^{+Hi} monocytes, with impaired neutrophils and macrophages (the inflammatory phase); reduced anti-inflammatory Ly6C^{+Lo} monocytes with decreased M2 differentiation, persistent M1 polarization and diminished M2 phenotype, reduced γδT cell infiltration impair the angiogenesis, keratinocyte proliferation and re-epithelialization (the proliferative phase); the dysregulated ECM remodeling resulting in impaired tissue repair (the remodeling phase). Designed using BioRender.

inflammatory milieu of DUs. ON101 (a macrophage-targeted topical agent) could promote M2 polarization, which demonstrates superior healing efficacy over standard dressings in randomized trials and has been approved for clinical use in Taiwan and other regions [170]. ON101 represents a rare case of macrophage-directed immunotherapy translated into diabetic wound care. While other macrophage-targeted strategies remain in preclinical stages, they show considerable translational potential. These strategies include pro-resolving cytokine supplementation (such as IL-4, IL-13, IL-27) to promote M2 polarization [171–172] and inhibiting pro-inflammatory pathways (such as NF-κB, NLRP3 inflammasome, the cGAS–STING axis) to attenuate M1 macrophage activation and downstream cytokine release [56,173–174]. Nanomaterial of MMP-9 responsive hydrogel has been designed to release M2 macrophage-derived exosomes at inflamed sites, providing on-demand anti-inflammatory signals and enhancing re-epithelialization in *db*/*db* mice wounds [175]. Collectively, these approaches underscore the translational promise of harnessing macrophage plasticity through cytokines, small-molecule inhibitors, or advanced biomaterials.

Targeting DC dysfunction through cellular reprogramming has shown promising potential in diabetic wound therapy. One strategy involves modulating metabolic pathways to enhance DC efferocytosis and reparative capacity. For instance, inhibiting the membrane transporter SLC7A11 in DCs could enhance efferocytosis and promote wound healing in *db*/*db* mice by reducing apoptotic burden and triggering the release of pro-healing factors [126]. Similarly, treatment with the flavonoid isoliquiritigenin improves glycolytic metabolism and efferocytosis in DCs, thereby stimulating angiogenesis and accelerating wound closure in *db*/*db* mice [127]. Beyond metabolic modulation, genetic approaches such as *Ndrg2* knockout maintain DCs in an immature, pro-regenerative state. When delivered via hydrogel scaffolds, these engineered DCs promote neovascularization and tissue regeneration in both diabetic and non-diabetic wounds [128]. Collectively, restoring DC function through metabolic or cellular reprogramming offers a viable and translational strategy to reverse immune dysfunction in DUs.

Targeting γδ T cells and DETCs has emerged as a novel immunotherapeutic avenue in DUs management. Recombinant IL-15 therapy, which restores DETC activation and IGF-1 output, has shown robust efficacy in STZ-induced diabetic mice, accelerating wound closure and epithelial regeneration [156]. IL-17A supplementation transiently promotes inflammation and healing in early stages, though its dual role necessitates precise temporal control [154]. These cytokine-based approaches have translational potential, offering prospects for repurposing in wound care [176]. Cell-based strategies are also gaining momentum. A recent study demonstrated that hydrogel dressings loaded with *ex vivo*-expanded DETCs not only restored local growth factor levels but also reprogrammed macrophages toward an M2 phenotype, improving healing in a chronic pressure ulcers animal model and underscoring the feasibility of γδ T cell augmentation via bioengineered scaffolds [177]. Overall, these studies provided that supplementing γδ T cell supportive cytokines and enhancing γδ T cell activity could improve DUs healing.

Beyond immune cell-specific interventions, targeting pro-inflammatory cytokines represents a promising translational strategy for DUs therapy. IL-1β, a key driver of chronic inflammation, is markedly upregulated in diabetic wounds. IL-1β receptor antagonist anakinra (an FDA-approved biologic for systemic inflammatory conditions) has demonstrated therapeutic efficacy in *db*/*db* mice models, where local administration could accelerate wound closure and reduce immune cell infiltration [178]. TNF-α emerges as a promising target as well, which systemic administration of anti-TNF-α antibodies could reduce healing time in diabetic mice [179]. Notably, topical infliximab (an anti-TNF-α monoclonal antibody) demonstrated marked efficacy in a case series of patients with chronic, treatment-refractory lower extremity ulcers, supporting its potential for repurposing in wound care [180]. Collectively, we found the feasibility of translating existing anti-cytokine biologics into topical therapeutics for DUs management. Those strategies underscore the emerging potential of immune-targeted therapies for DUs management (Fig. 2, Table 2).

Conclusions

The discrepancy in cell distribution and discordance in DUs may be attributed to patient heterogeneity, sample differences, and methodological inconsistencies across studies. In the early stage of DUs, the immune microenvironment is marked by fewer immune cells and essential immune-related molecules, which is detrimental to eliminate pathogens; in the later stage, excessive immune cell accumulation, impaired immune function, and intensified pro-inflammatory responses hinder keratinocyte proliferation and tissue repair [46,98]. Importantly, many studies rely on biopsies obtained at unknown time points, introducing temporal heterogeneity that complicates direct comparisons with the well-defined phases of normal wound healing. To reconcile these conflicting findings and advance understanding of DU pathogenesis, future research should establish standardized protocols, apply advanced analytical methods, and adopt a systematic research approach (Fig. 3).

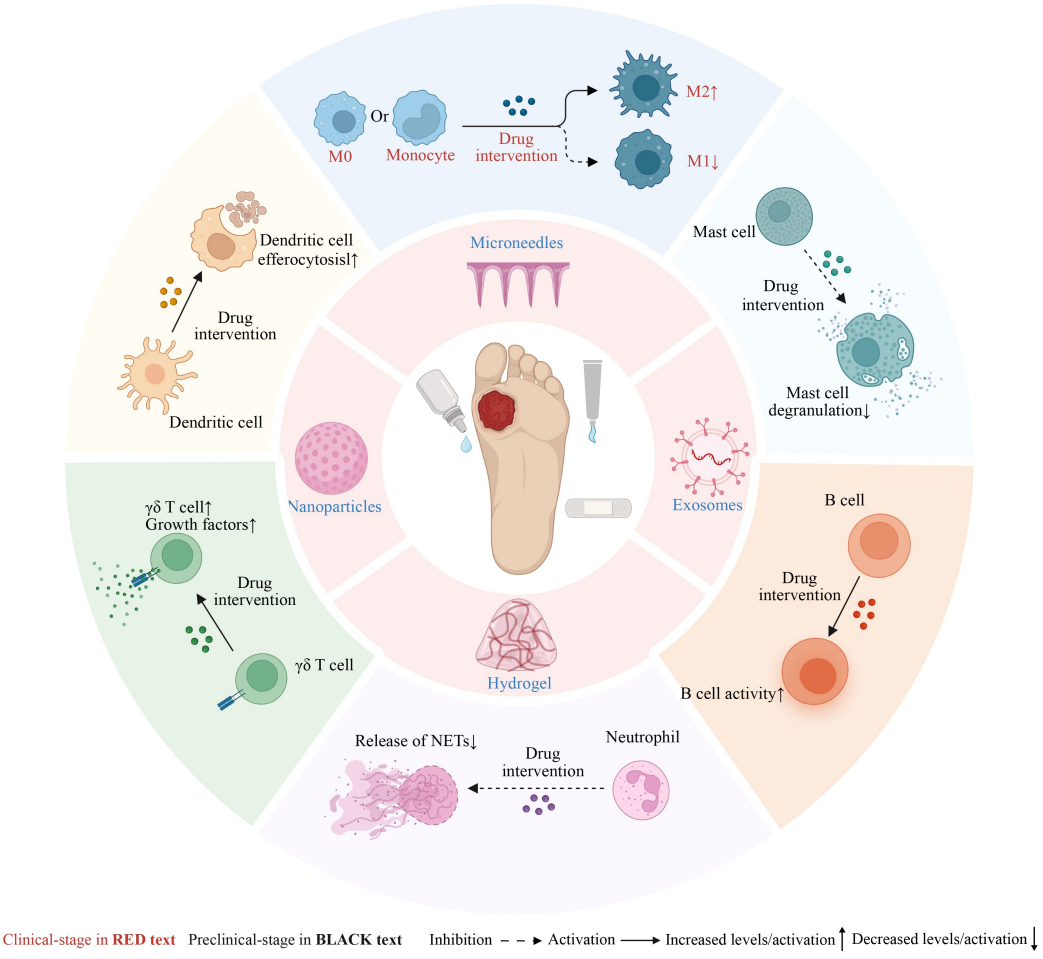

Fig. 2 Potential immune cell-targeted therapies for DUs. Monocyte/macrophage-based interventions that applying macrophages to cutaneous wounds were approached in clinical-stage (in red text). Other paths toward reducing mast cell degranulation, enhancing dendritic cell efferocytosis, increasing γδ T cell counts and their growth factor production, promoting B cell activity, and decreasing neutrophil NETs formation were still in pre-clinical study stages (in black text). At present, microneedles, exosomes, nanoparticles, and hydrogel could be used as promising targeted drug delivery method. Designed using BioRender.

Table 2 Immunotherapy development in DUs

Development stage	Therapeutic strategy	Specific drug or method	Evidence and progress	References
Marketed	Macrophage M2 polarization modulation	ON101 topical cream	Completed phase III RCT (approved in Chinese Taiwan and Chinese mainland)	[170]
Small-scale clinical study	Anti-cytokine antibodies	Infliximab (anti-TNF-α antibody), topical application	Clinical case report	[180]
Preclinical animal studies	Mast cell stabilizer	Cromolyn sodium, MCS-01 (topical)	Animal experiment	[168,168]
	NETs inhibition	DNase I, anti-IL-8 monoclonal antibody, and MMP-9 inhibitor		[34,57]
	Inhibition of M1 macrophage activation	NF-κB, NLRP3 inflammasome, and cGAS-STING inhibitors		[56,173–174]
	M2 macrophage-derived exosome delivery	MMP-9 responsive hydrogel		[175]
	Dendritic cell reprogramming	SLC7A11 inhibitor, isoliquiritigenin, and hydrogel-based delivery of pro-regenerative dendritic cells		[126–128]
	γδ T cell activation	Recombinant IL-15, IL-17A, and γδ T cell-loaded hydrogel		[154,156,177]
	B cell therapy	Topical application of mature naive B cells		[158]
	IL-1β receptor antagonist	Anakinra (topical)		[178]

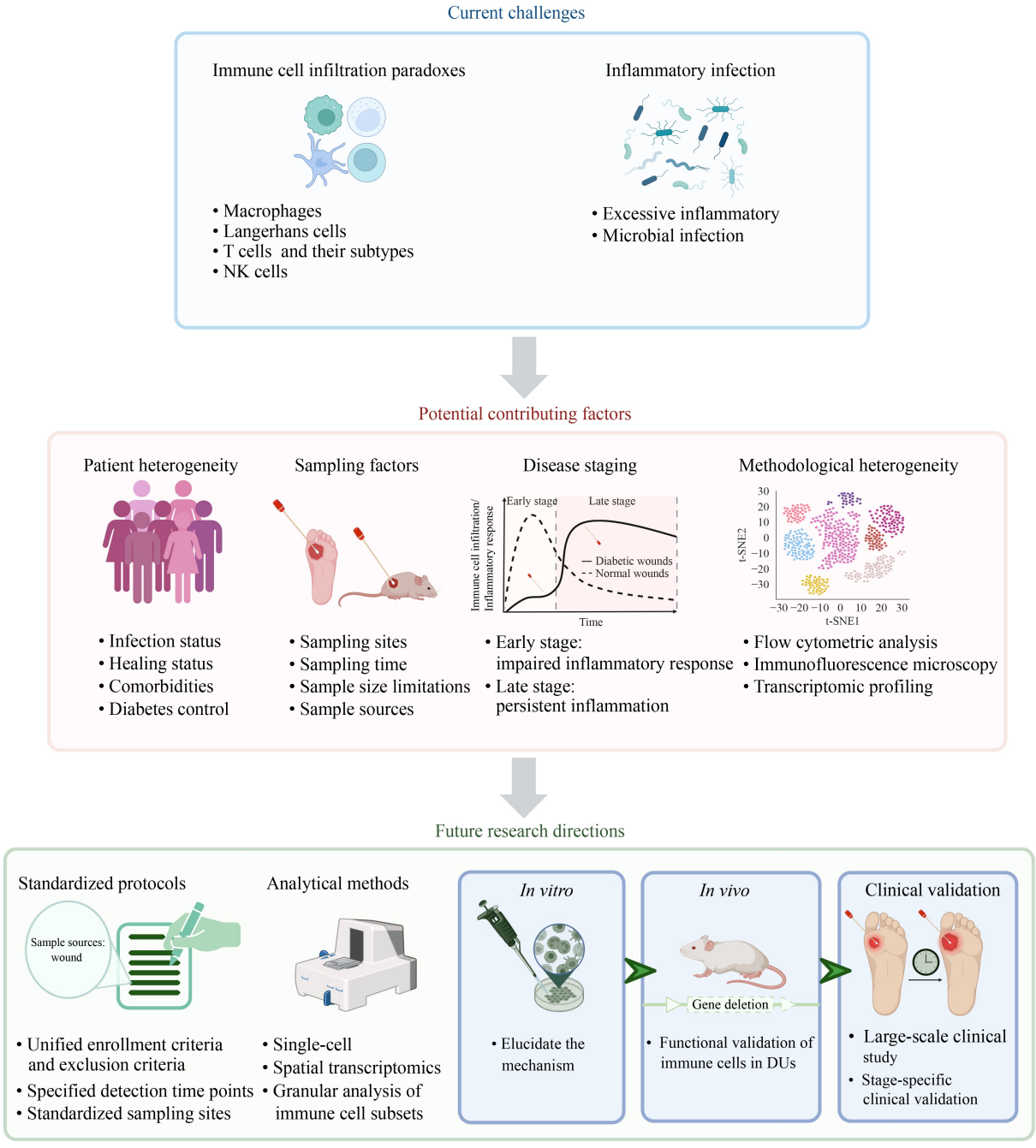

Fig. 3 Research challenges and future directions in understanding immune cell dysregulation in DUs. The exact expression of many immune cell infiltration remains inconclusive (such as macrophages, Langerhans cells, T cells and natural killer cells), and the inflammatory microbial infection are the current challenges of diabetic ulcer healing. Besides, the technical heterogeneity may come from differences in the diseases reported, sampling types, and methods. Future researches and techniques should be unified. Designed using BioRender.

Addressing DUs requires a multifaceted approach that not only involves excessive immune activation but also impaired inflammatory responses. Tailored immune cell-targeting strategies, informed by patients' specific inflammatory profiles and immune status, are indispensable for guiding effective clinical interventions. The clinical approval of ON101 marks a significant step forward in translating immune-targeted therapies into practice. Moving forward, broader clinical applications of these emerging immunotherapies are highly anticipated and hold great promise for improving diabetic wound management.

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Compliance with ethics guidelines

Conflicts of interest Yi Ru, Yunxi Cai, Guangyuan Cheng, Xiaoxuan Ma, Jingsi Jiang, Jiankun Song, Ying Luo, Ying Zhang, Qi Zheng, Mingxia Wang, Chunjie Gao, Bin Li, Le Kuai, Yue Luo, and Zhan Zhang declare that they have no conflict of interest.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

Data availability and compliance statement

The authors declare that the acquisition and subsequent use of all data presented in this manuscript comply fully with all relevant local, national, and international laws, regulations, ethical guidelines, and the terms of use associated with the original data sources.

The authors bear full legal responsibility for ensuring the legality of data acquisition and all subsequent uses.

Data sharing is not applicable to this article, as no new data were created or analyzed in this study.

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