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Macrophage polarization in diabetic vascular complications: mechanistic insights and therapeutic targets

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Abstract

Diabetes mellitus, particularly type 2 diabetes mellitus, is a widespread chronic metabolic disorder characterized by persistent hyperglycemia and low-grade chronic inflammation. This sustained inflammatory state is a major driver of both macrovascular and microvascular complications. Among immune cells, macrophages play a central role as effectors and regulators of chronic inflammation. In the diabetic milieu, they respond to diverse microenvironmental cues and polarize into distinct functional phenotypes, thereby contributing to both the progression and potential resolution of diabetes-associated vascular damage. This review examines the mechanisms of macrophage polarization in diabetic vascular complications, elucidates key signaling pathways and their interactions with metabolic dysfunction, and summarizes current regulatory strategies and emerging therapeutic targets. Particular emphasis is placed on recent pharmacological approaches that modulate macrophage polarization, highlighting their potential as novel strategies to delay or prevent the onset and progression of vascular complications in diabetes.

Keywords Macrophages, Macrophage polarization, M1-polarized macrophages, M2-polarized macrophages, Diabetic vascular complications, Therapeutics

Introduction

Diabetes is a chronic metabolic disorder characterized by persistent hyperglycaemia arising from either absolute insulin deficiency (type 1 diabetes mellitus, T1DM) or insulin resistance (type 2 diabetes mellitus, T2DM) [1]. According to the International Diabetes Federation (IDF), the global prevalence of diabetes currently approaches 500 million individuals and is projected to rise to 700 million by 2045, making diabetes a major global health threat in terms of both morbidity and mortality [2].

Chronic, low-grade inflammation is a defining feature of diabetes, particularly T2DM. In the setting of obesity, macrophages infiltrate key metabolic organs, including adipose tissue, liver, and skeletal muscle. They also secrete abundant proinflammatory cytokines that disrupt

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insulin receptor signaling, thereby driving both local and systemic inflammation and promoting the development of insulin resistance [3–6]. Clinical studies in T2DM patients and corresponding animal models reveal an increased accumulation of islet-associated macrophages [4, 7]. Moreover, elevated concentrations of circulating free fatty acids and glucose under obese conditions induce a proinflammatory polarization of macrophages, enhancing the production of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and other inflammatory mediators, which further impair pancreatic β-cell function and viability [8–10]. As a result, controlling inflammation has emerged as a vital strategy for metabolic protection.

Over time, inflammation driven by metabolic dysregulation becomes a central driver of diabetes-related complications, which are broadly classified into macrovascular complications (e.g., cardiovascular disease) and microvascular complications (e.g., retinopathy, nephropathy, and neuropathy) [11–14].

Macrophage polarization plays a pivotal role in the onset and progression of T2DM and its associated complications [15, 16]. Chronic inflammation and metabolic stress frequently induce maladaptive shifts in macrophage phenotypes. Although the classical M1/M2 dichotomy oversimplifies macrophage heterogeneity, it remains a valuable framework for interpreting their functional roles in metabolic diseases [17].

In this review, we synthesize current insights into how macrophage polarization contributes to the pathogenesis of diabetic vascular complications. Relevant literature was searched in the Web of Science, PubMed, and ScienceDirect databases between December 2002 and April 2025 and cited accordingly. Current treatment of diabetes primarily emphasizes glycemic control through insulin therapy, dietary regulation, and exercise, alongside management of associated complications. However, these approaches remain insufficient to halt the progression of advanced diabetic vascular lesions, highlighting an urgent unmet need for innovative therapeutic strategies capable of directly targeting the pathological development of diabetic vascular complications. We emphasize the key signaling pathways and microenvironmental cues that govern macrophage phenotypes and discuss emerging therapeutic strategies aimed at modulating polarization. Such interventions hold significant promise as innovative approaches for managing diabetes-related vascular complications.

Macrophage polarization and function are reliant on signaling pathways and stimuli

Inflammation is the body's primary defense against exogenous pathogens and endogenous tissue injury, proceeding through four sequential stages: initiation, progression, resolution, and tissue reconstruction [18, 19]. Macrophages play indispensable roles during both the initiation and resolution phases. They are ubiquitously distributed across organs and tissues, where they perform immune surveillance and orchestrate defensive responses [1, 20].

During embryogenesis, macrophages originate from the yolk sac and fetal liver [1], differentiating into tissue-resident populations with specialized local identities that are essential for development, remodeling, and homeostasis. After birth, these resident pools are supplemented by monocytes recruited from the bone marrow [21–23]. Under steady-state conditions, macrophages constitute approximately 10–15% of total cells in many tissues and maintain their numbers through limited self-renewal [24]. In response to inflammatory stimuli, macrophage populations expand via both monocyte recruitment and proliferation of resident cells. However, uncontrolled or chronic inflammation can inflict severe tissue and organ damage, contributing to diseases such as sepsis, T2DM, atherosclerosis, and autoimmune disorders [4, 25–28]. Thus, the timely phenotypic switch from a proinflammatory (M1) state to an anti-inflammatory (M2) state is critical for rapid restoration of tissue homeostasis [22, 29].

Macrophage functional heterogeneity is determined by local microenvironmental cues and activation of specific signaling pathways. Inflammatory stimuli, such as microbial components or proinflammatory cytokines, induce M1 polarization, characterized by elevated production of IL-1β, TNF-α, and inducible nitric oxide synthase (iNOS). In contrast, anti-inflammatory signals, including IL-4 and IL-13, drive M2 polarization, which promotes tissue repair and exerts immunosuppressive functions [30–32] (Fig. 1).

M1 macrophages

M1 macrophages are chiefly responsible for cytotoxic and proinflammatory functions. In vitro, M1 polarization is induced by bacterial lipopolysaccharide (LPS) or Th1-associated cytokines such as interferon-γ (IFN-γ) [32, 33]. Upon activation, M1 macrophages secrete high levels of proinflammatory cytokines, including TNF-α, IL-1β, and IL-6, and generate reactive oxygen species (ROS) and iNOS, all of which contribute to pathogen elimination [34–36]. They also release matrix metalloproteinases (MMPs) [37] that degrade extracellular matrix components and exhibit robust phagocytic capacity to clear senescent, damaged, and degenerative cells. These characteristics underpin the potent antimicrobial and antitumor activities of M1 macrophages.

The polarization process involves several key signaling cascades. IFN-γ binding to its receptor activates the Janus kinase (JAK)/signal transducer and activator of transcription 1 (STAT1) pathway, whereas LPS engagement of Toll-like receptor 4 (TLR4) triggers nuclear

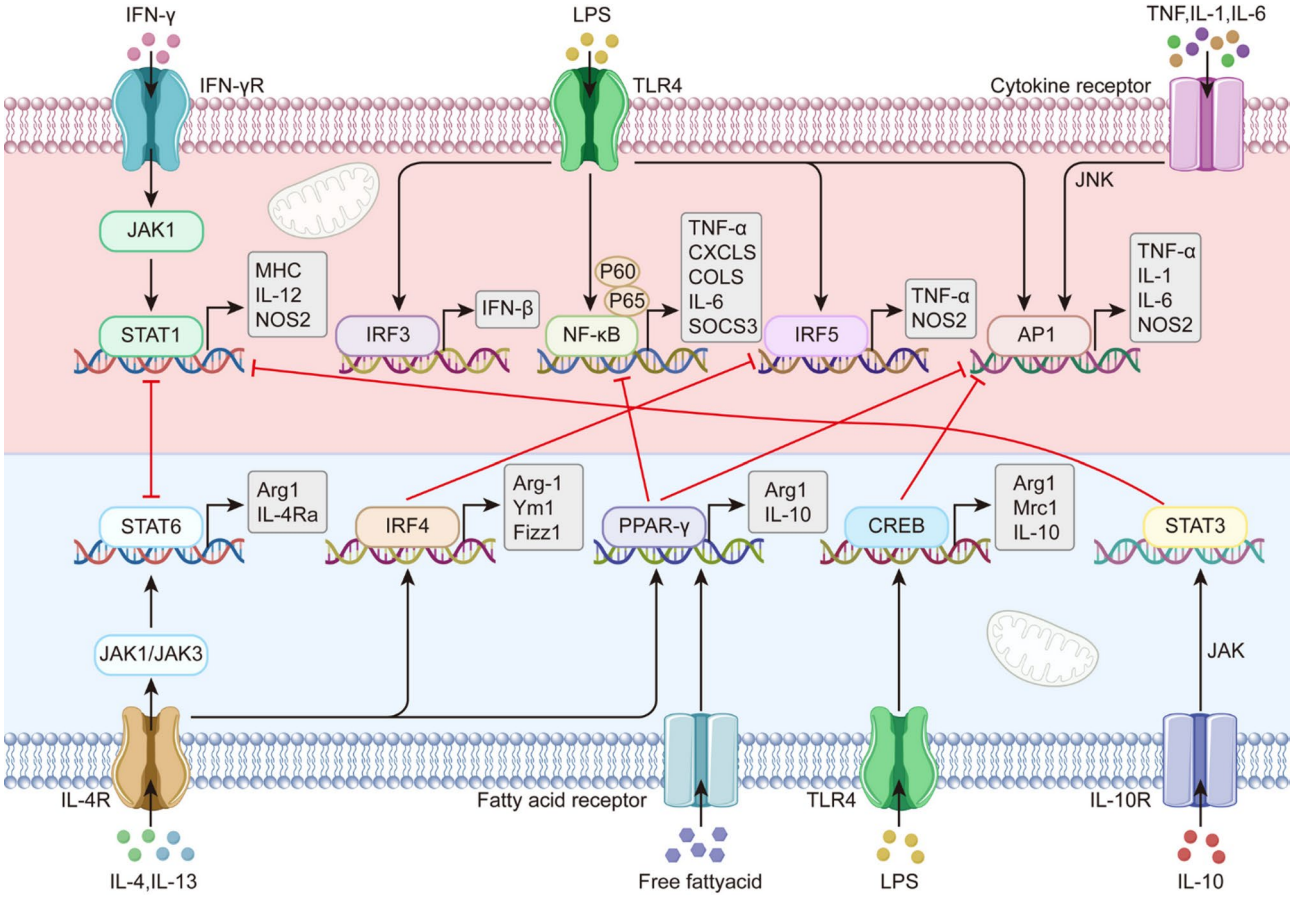

Fig. 1 Signaling pathways involved in macrophage polarization. This figure illustrates the key signaling cascades required for macrophage polarization and highlights the feedback regulation between M1 and M2 pathways. Several transcription factor pairs including STAT1-STAT6/STAT3, IRF5-IRF4, NF-κB-PPARγ, AP-1-CREB, and AP-1-PPARγ act as reciprocal regulators to finely tune macrophage phenotype and function. These signaling networks collectively modulate the dynamic balance between pro-inflammatory M1 and anti-inflammatory M2 states, ensuring context-dependent immune responses

factor kappa-B (NF-κB), interferon regulatory factor 3 (IRF3), and mitogen-activated protein kinase (MAPK) pathways, collectively driving inflammatory mediator expression [32, 38]. However, persistent M1 activation can impair tissue regeneration and delay wound healing, underscoring the need to facilitate a transition toward the M2 phenotype to resolve chronic inflammation [39].

M2 macrophages

Alternatively activated M2 macrophages mediate immunosuppression, promote tissue repair, and, in certain contexts, facilitate tumor progression. In vitro, M2 polarization is classically induced by Th2-type cytokines, interleukin-4 (IL-4) and interleukin-13 (IL-13) [39], which trigger the secretion of anti-inflammatory mediators such as interleukin-10 (IL-10), interleukin-12 (IL-12), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) [40]. These cells also efficiently clear apoptotic cells and debris, thereby supporting angiogenesis and extracellular matrix remodeling. In pathological settings, M2 macrophages contribute to tumor growth, metastasis, and fibrotic processes [41, 42].

Activation of the STAT6 signaling pathway by IL-4 and IL-13 constitutes the canonical mechanism driving M2 polarization [32, 43]. Additional transcription factors, such as peroxisome proliferator-activated receptor-γ (PPAR-γ) and cAMP response element-binding protein (CREB), also reinforce the anti-inflammatory program of M2 macrophages [38]. Notably, M2 macrophages can be subdivided into distinct subphenotypes based on their inducing stimuli and functions: M2a macrophages are induced by IL-4 or IL-13 and primarily mediate anti-inflammatory responses and tissue remodeling via TGF-β secretion; despite their reparative role, they exhibit relatively limited phagocytic capacity [44]. M2b macrophages are regulated by Toll-like receptor (TLR) and IL-1 receptor signaling and co-secrete both pro- and anti-inflammatory cytokines, thereby modulating immune responses and promoting a Th2-type environment [45]. M2c macrophages are activated by glucocorticoids or IL-10 and display pronounced immunosuppressive and

efferocytic activities; they aid in inflammation resolution by engulfing apoptotic cells and upregulating matrix-remodeling enzymes. M2d macrophages, also known as tumor-associated macrophages (TAMs), facilitate tumor progression by producing pro-angiogenic factors such as VEGF and TGF-β [41, 46]. Although M2 macrophages functionally counter many actions of M1 macrophages, their activation is governed by distinct signaling networks rather than by simple inhibition of M1 polarization [19] (Table 1).

Diabetes, vascular disease and macrophages

Diabetes is not merely a condition characterized by elevated blood glucose levels but a metabolic disorder resulting from sustained hyperglycaemia-induced cellular dysfunction, ultimately contributing to diabetic complications [47]. Among the key immune cells involved, macrophages are central mediators linking metabolic dysregulation to vascular injury [48, 49]. In the diabetic milieu, stimuli such as high glucose (HG), advanced glycation end-products (AGEs), and dyslipidaemia drive macrophage polarization toward the proinflammatory M1 phenotype. This polarization induces the release of cytokines, such as TNF-α and IL-1β, that further exacerbate endothelial dysfunction and impede vascular repair. In contrast, M2 macrophages exert anti-inflammatory effects, facilitate vascular remodeling, and promote tissue regeneration, making enhancement of M2 polarization a promising therapeutic strategy [50, 51].

Dysregulated lipid metabolism also significantly contributes to diabetic vascular disease [52–54]. Insulin resistance promotes the release of free fatty acids (FFAs), increases hepatic triglyceride synthesis, and drives overproduction of very low-density lipoprotein (VLDL) [55]. Excess VLDL alters high-density lipoprotein (HDL) stability [56, 57], and leads to the formation of modified low-density lipoprotein (LDL) particles, such as glycated LDL and oxidized LDL (ox-LDL). These modified LDL particles are engulfed by macrophages, resulting in foam cell formation and further vascular inflammation[55].

Chronic hyperglycaemia induces mitochondrial dysfunction and oxidative stress, leading to elevated production of ROS [12]. These ROS not only damage endothelial cells but also activate macrophages via the DNA damage-PARP-GAPDH signaling pathway, thereby amplifying M1 macrophage responses and accelerating the progression of diabetic vascular complications [58, 59]. In parallel, the upstream accumulation of glycolytic intermediates drives multiple pathogenic mechanisms implicated in vascular injury, including enhanced intracellular formation of AGEs, activation of the diacylglycerol-protein kinase C (DAG-PKC) pathway, increased flux through the hexosamine biosynthetic pathway, and upregulated activity of the polyol pathway [60, 61]. Consequently, targeting macrophage polarization alongside these metabolic derangements is a promising strategy to mitigate vascular injury in diabetes.

Table 1 Summary of the different macrophage subsets

Subtypes	Stimuli	Markers	Secretions	Function	Refs
M1	IFN-γ, LPS, ox-LDL	CD80, CD86, MHC-II, TLR-4	IL-1β, IL-6, TNF-α, NO, iNOS	Proinflammatory activity, tissue damage	[16, 228, 229]
M2 M2a	IL-4, IL-13	CD206, CD163, MHC-II, Arg-1,	Fibronectin, TGF-β, IGF, IL-10,	Anti-inflammatory responses and tissue remodel	[230, 231]
M2b	Immune complexes, TLR ligands, IL-1R agonists	CD86, MHC-II, MR	IL-01β, IL-6, TNF-α, IL-10, CCL1, CCL20	Anti-inflammatory and immunodulatory properties	[232]
M2c	Glucocorticoids, IL-10	CD163, TLR1/8	IL-10, TGF-β, CCL18, MMPs	Immunosuppression, efferocytic activities,	[233–235]
M2d	TLR, adenosine $A_{2A}R$ agonists	CD163	IL-10, VEGF, TGF-β	Angiogensis and tumor progression	[228, 234]

Regulation of macrophage polarization in diabetic macrovascular complications

Cardiovascular disease is the leading cause of death among diabetic patients worldwide, with approximately 29.1% of individuals with T2DM developing AS [62, 63]. Studies indicate that the risk of vascular complications and mortality is inversely correlated with age at diagnosis [64]. Even under strict glycemic control, the deleterious effects of macrovascular complications endure over the long term, a phenomenon termed "metabolic memory" [65]. Diabetes and AS are interconnected through multiple pathological mechanisms, notably dysregulated fatty acid metabolism, dyslipidemia, and insulin resistance, all of which drive the progression of atherosclerotic lesions [66–68]. Accelerated AS is now understood to result, in part, from alterations in monocyte and macrophage function and phenotype; shifts in macrophage subtype balance are strongly associated with disease progression and exacerbate vascular inflammation (Fig. 2). Consequently, targeting macrophage polarization emerges as a promising strategy to delay the development of macrovascular complications in diabetes [69–71].

Progression of diabetic macrovascular complications

These mechanisms are intricately interconnected. Under their combined influence, low-density lipoprotein cholesterol (LDL-C) infiltrates sites of vascular endothelial

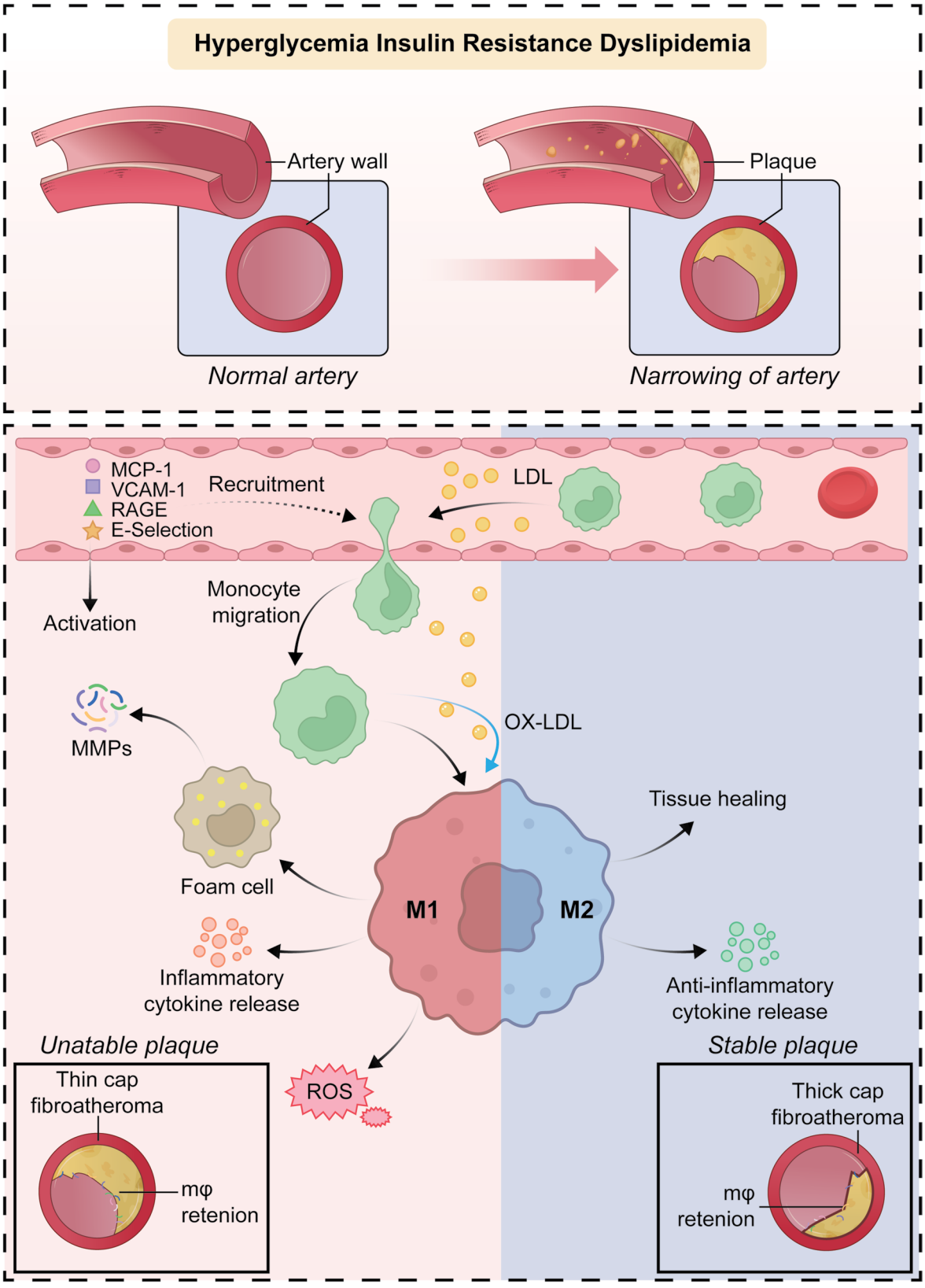

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Fig. 2 Macrophage phenotypes and metabolic mechanisms in diabetic macroangiopathy. In the early stages of atherosclerosis, hyperglycemia and other risk factors induce vascular endothelial injury, thereby facilitating the adhesion of circulating monocytes to endothelial cells and their subsequent transmigration into the intima, where they differentiate into macrophages. These macrophages engulf oxidized low-density lipoprotein (ox-LDL) and transform into foam cells, which represent a critical driver of plaque progression. Foam cells exacerbate local inflammatory responses and promote the development of lipid-rich or necrotic cores that are covered by a fibrous cap composed of extracellular matrix, thereby accelerating plaque formation. During the initial phase of lesion development, M2-polarized macrophages predominate within the plaque, exerting anti-inflammatory and tissue-repair functions that contribute to plaque stability. However, as the disease progresses, the proportion of M2 macrophages decreases, while M1 macrophages gradually become dominant. M1 macrophages secrete large amounts of proinflammatory cytokines and MMPs, leading to extracellular matrix degradation and thinning of the fibrous cap. This transition renders the plaque prone to rupture, which in turn triggers thrombosis and vascular occlusion

injury, where ROS oxidatively modify it to form ox-LDL. This modified lipoprotein activates endothelial cells to secrete adhesion molecules and chemokines, recruiting circulating monocytes that adhere to the vessel wall and transmigrate into the subendothelial space. As the disease progresses, both these monocytes and smooth muscle cell (SMC)-derived M1 macrophages engulf ox-LDL and transform into foam cells, which is an essential step in the early formation of atherosclerotic plaques [14, 72, 73].

As the lesion advances, immune and SMC-derived responses promote plaque stabilization by secreting collagen, which assembles into a fibrous cap that isolates the plaque core from the bloodstream [74]. In advanced stages, however, macrophages that continuously ingest lipoproteins undergo apoptosis, giving rise to a soft, unstable lipid core. Simultaneously, M1 macrophages secrete MMPs that degrade collagen and other extracellular matrix components, resulting in fibrous cap thinning [75–77]. The eventual rupture and hemorrhage of these unstable plaques precipitate acute cardiovascular events [78].

The polarization mechanism of M1/M2 macrophages in diabetic macrovascular complications

Macrophages are central effectors in AS, playing critical roles in both its initiation and progression. In response to local microenvironmental cues, they adopt distinct phenotypes, and the relative abundance of each subtype within plaques profoundly influences plaque size and stability. Both M1 and M2 macrophages coexist in AS lesions; notably, the shoulder regions, areas most prone to rupture, exhibit strong immunopositivity for M1 markers CD11c and CD68, whereas the fibrous cap shows comparable expression of M1 and M2 markers [79, 80]. These observations implicate M1 macrophages in plaque destabilization, while lesions enriched in M2 cells tend to be more stable [81, 82]. Importantly, macrophage polarization remains dynamic throughout both plaque progression and regression [83]. In advanced AS, M1 macrophages localize predominantly to the necrotic core, whereas M2 macrophages are enriched in regions of neovascularization. Thus, therapeutic strategies that targeting specific macrophage subsets according to their spatial distribution and the stage of disease stage may represent an effective means of slowing AS progression [84].

In peripheral blood mononuclear cells (PBMCs) from obese patients with T2DM, $CD14^{+}$ cells exhibit reduced expression of the M2-associated markers CD163 and IL-10, alongside elevated levels of M1 markers and proinflammatory cytokines. This skewed M1/M2 ratio correlates with increased arterial stiffness [85]. Furthermore, elevated plasma BMP-2 in T2DM activates the PI3K/p38/MAPK signaling cascade, which both promotes monocyte migration and differentiation into macrophages and suppresses M2 polarization, thereby amplifying inflammatory responses [86]. Chronic hyperglycaemia also drives the overproduction of AGEs, which induce hypoxia-inducible factor-1α (HIF-1α) and trigger the pyruvate dehydrogenase kinase 4 (PDK4) pathway, further skewing macrophage polarization toward the proinflammatory M1 phenotype [87].

Endothelial dysfunction also plays a critical role in diabetes-related complications [88, 89]. LPS and high-glucose (25 mM)-stimulated macrophages differentiated from THP-1 cells induce damage and apoptosis in human umbilical vein endothelial cells (HUVECs). Astragalus polysaccharides reverse this effect by reducing ROS production in M1 macrophages, suppressing inflammatory cytokine expression, and promoting M2 polarization through activation of the Nrf2/HO-1 pathway [90].

In addition, HG/ox-LDL-induced endothelial cell–derived exosomes exhibit elevated NEDD4L expression, which accelerates M1 polarization via ubiquitination of IκBα/PPARγ and phosphorylation of Smad1/2, thereby enhancing ox-LDL uptake and foam cell formation and promoting diabetic AS [91]. In $Trail^{-/-}ApoE^{-/-}$ mice, treatment with recombinant HDL not only modulates macrophage phenotypes within atherosclerotic plaques but also reduces macrophage accumulation and increases insulin secretion from pancreatic β-cells [92].

Xia et al. demonstrated that hyperglycaemia-induced methylation reduces TFPI2 expression, disrupting activator protein-2α (AP-2α)/PPARγ binding and driving M1 macrophage activation, which contributes to AS development [93]. Li et al. showed that diabetes activates the PARP-1/STAT1/Runx2 pathway, promoting M1 polarization and exacerbating calcification in both macrophages and vascular smooth muscle cells [94]. Furthermore,

hyperglycaemia-regulated miR-32-5p, carried in extracellular vesicles, inhibits VSMC autophagy and accelerates vascular calcification in T2DM by skewing macrophages toward the M1 phenotype [95].

ApoE$^{-/-}$ diabetic mice develop more severe AS, likely due to diminished Mer tyrosine kinase (MerTK) expression in macrophages, which impairs efferocytosis. These mice show increased CD68^{+}/TUNEL^{+} staining and elevated mRNA levels of proinflammatory M1 cytokines within plaques [96]. Liu et al. demonstrated that diabetes alters Golgi structure in plaque-associated macrophages, where elevated phosphatidylinositol 4-phosphate (PI4P) levels recruit ASC and activate the NLRP3 inflammasome, thereby upregulating M1 markers and exacerbating AS [97]. Wang et al. further reported that several saturated fatty acids elevated in T2DM patients and murine models correlate with plaque vulnerability. Notably, palmitic acid activates the TLR4/ERK/FOXC2 pathway, driving M1 polarization and increased Dll4 expression in macrophages, which in turn induces vascular smooth muscle cell senescence and compromises plaque stability [67].

Overall, an imbalance between M1 and M2 macrophage phenotypes permeates every stage of diabetes-related macrovascular complications, and strategies that promote M2 polarization while suppressing M1 activation may facilitate AS regression.

Regulation of macrophage polarization in diabetic microangiopathy

Macrophage polarization and diabetic nephropathy

Diabetic nephropathy (DN) is a leading cause of end-stage renal disease. Despite glycemic and blood pressure management, DN frequently progresses to irreversible kidney failure [98, 99], underscoring the need for novel therapeutic strategies. As a multifactorial disorder, its pathogenesis centers on inflammation: hyperglycaemia and elevated AGEs promote both the infiltration of circulating macrophages and activation of resident renal macrophages, which drive glomerular hypertrophy, basement membrane thickening, and mesangial expansion [100]. Indeed, macrophage accumulation occurs in the glomeruli and interstitium at all stages of DN [101], with the extent of infiltration correlating closely with renal injury severity and functional decline. In T2DM db/db mice, nephropathy progression parallels renal macrophage accumulation [102].

Intercellular adhesion molecule-1 (ICAM-1) is critical for macrophage recruitment in the diabetic kidney. Patients with microalbuminuria exhibit significantly elevated serum ICAM-1 levels compared with healthy controls [103], and ICAM-1 expression is likewise increased in the glomeruli and interstitium of db/db mice. Conversely, ICAM-1 deficiency in diabetic db/db mice markedly ameliorates renal damage and fibrosis [104]. Hyperglycaemia-induced ROS and inflammatory cytokines upregulate ICAM-1 expression [105], facilitating leukocyte adhesion and transmigration into glomerular and tubular compartments. This cascade of rolling, firm adhesion, and endothelial inflammation exacerbates glomerular and tubular endothelial injury, ultimately leading to proteinuria.

Monocyte chemoattractant protein-1 (MCP-1) is a critical mediator of macrophage infiltration. By binding to G-protein-coupled receptors on monocytes, MCP-1 activates the MCP-1/CCR2 axis, which, through PKC-mediated NF-κB stimulation, upregulates motility-associated genes and induces Rho family proteins. This coordinated response enhances monocyte migration into the renal parenchyma, thereby driving kidney inflammation [106, 107]. MCP-1 is considered a key marker throughout all stages of DN, with peak expression in renal tubules that correlates positively with tubular injury [108]. In animal models, elevated renal MCP-1 levels are tightly associated with macrophage accumulation and fibrosis, whereas administration of the CCR2 antagonist RS102895 significantly reduces both macrophage infiltration and renal fibrosis [109]. In streptozotocin (STZ)-induced DN models, MCP-1$^{-/-}$mice likewise exhibit markedly decreased macrophage infiltration and activation in glomeruli and interstitium, accompanied by attenuated histological renal damage [110].

Proinflammatory M1 macrophages play a pivotal role in DN progression. Under hyperglycaemic conditions, activation of the TAB1/NF-κB/HIF-1α pathway promotes glycolysis and skews macrophages toward the M1 phenotype [111], while TLR2/MyD88 signaling similarly drives M1 polarization and contributes to early DN development [112]. Transwell co-culture studies demonstrate that high-glucose–treated podocytes secrete increased MCP-1, which in turn induces M1 macrophage migration and compromises podocyte barrier integrity. Sunilkumar S. further reported that hyperglycaemia-induced REDD1 expression in podocytes activates NF-κB signaling, amplifies cytokine and chemokine release, triggers pyroptosis, and recruits M1 macrophages, thereby exacerbating podocyte injury [113].

Overexpression of Tim-3 in diabetic renal tissue activates NF-κB/TNF-α signaling, thereby promoting M1 polarization. Hyperglycaemia also induces RAGE overexpression and downregulates the glucagon-like peptide-1 receptor (GLP-1R), further enhancing M1 macrophage activation and accelerating DN progression [114]. Immunofluorescence co-staining of F4/80 with CD86 and CD32/16 in the kidneys of db/db mice reveals an increased density of M1 macrophages, accompanied by elevated serum and renal levels of TNF-α and IL-1β [115].

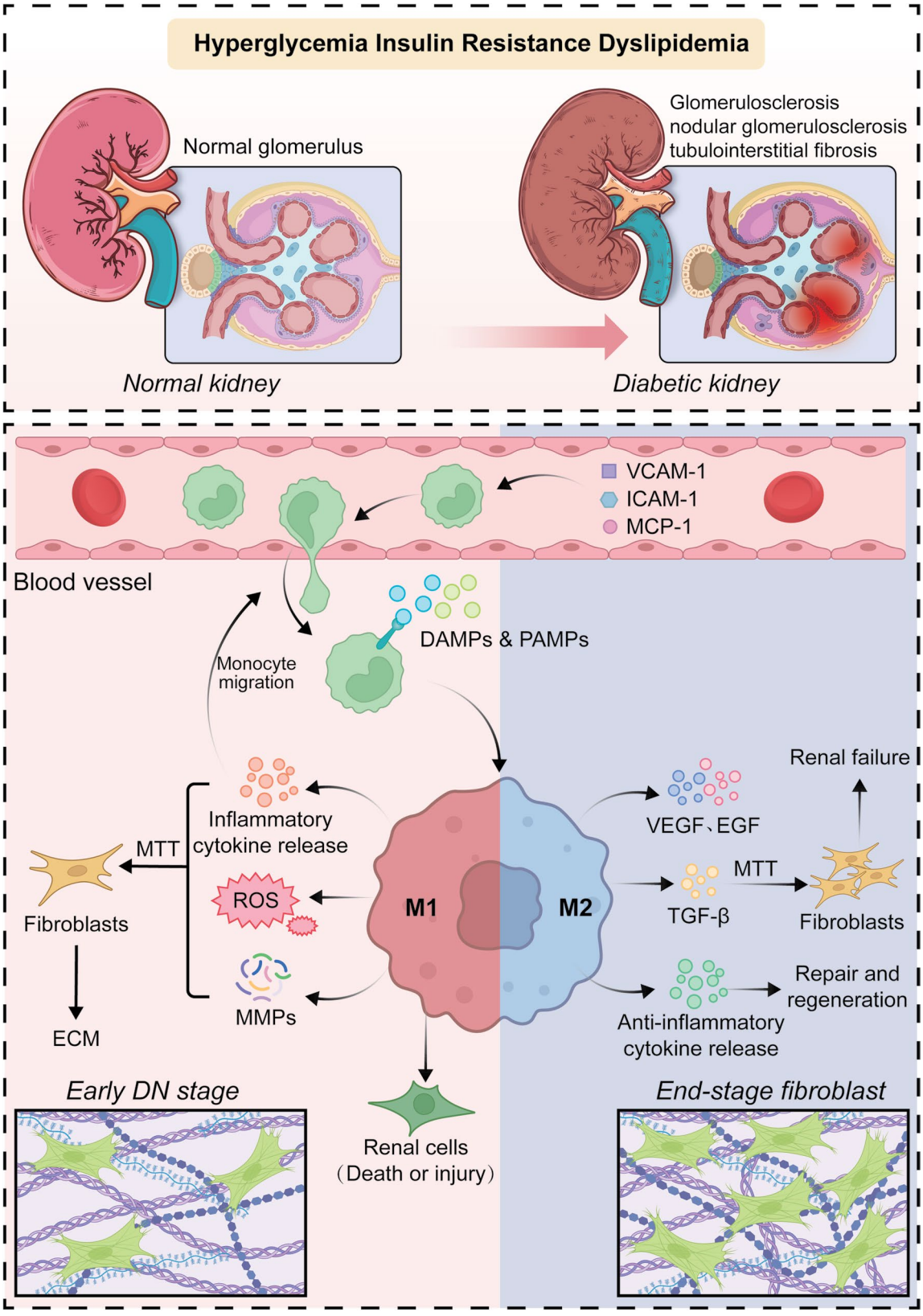

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Fig. 3 Macrophage phenotypes and metabolic mechanisms in DKD. Persistent hyperglycemia induces injury to mesangial cells, podocytes, and tubular epithelial cells, leading to the release of chemokines such as MCP-1, which recruit circulating monocytes into the renal tissue. These monocytes differentiate into M0 macrophages and subsequently polarize toward the M1 phenotype within the inflammatory microenvironment. M1 macrophages secrete large amounts of pro-inflammatory cytokines, ROS, and MMPs, which disrupt the extracellular matrix and exacerbate renal cell injury. This process establishes a positive feedback loop that sustains immune cell infiltration and chronic renal inflammation. Under these conditions, fibroblasts are activated and differentiate into myofibroblasts (MMT), resulting in excessive production and deposition of collagen and fibronectin, thereby contributing to tubulointerstitial fibrosis and glomerulosclerosis. As chronic kidney disease (CKD) progresses, macrophages gradually shift toward the M2 phenotype, which helps to resolve inflammation and promote tissue repair. However, excessive secretion of pro-fibrotic growth factors such as VEGF and EGF by M2 macrophages further enhances collagen deposition and matrix remodeling. This maladaptive repair response ultimately aggravates renal fibrosis and accelerates the progression of CKD toward end-stage renal disease

Therapeutic modulation of macrophage polarization has yielded promising results. Administration of $1,25(OH)_2D3$ in STZ-induced DN rats rebalances M1/M2 phenotypes and alleviates podocyte injury [116]. Xu et al. demonstrated that myricetin promotes the M1-to-M2 transition in renal macrophages of db/db mice, reducing inflammation and renal damage [117]. Ma et al. found that macrophage infiltration in both the glomeruli and tubules of db/db mice is predominantly M1, with M2 macrophages being scarce; hyperglycaemia-induced activation of Notch/NF-κB signaling in tubular cells correlates with vacuolar degeneration, necrosis, and detachment. Both macrophage depletion and Notch pathway inhibition ameliorate DN pathology [118]. In CD11b-DTR mice, diphtheria toxin-mediated macrophage ablation following STZ induction significantly reduces renal injury and fibrosis [119].

These findings illustrate the dynamic interplay between M1 and M2 polarization in DN. Strategies that suppress M1 activation or facilitate M1-to-M2 conversion can mitigate renal damage; however, because M2 macrophages may also contribute to fibrosis, targeted macrophage depletion could represent a viable therapeutic approach for DN (Fig. 3).

Macrophage polarization and diabetic retinopathy

Diabetic retinopathy (DR), a prevalent microvascular complication of diabetes, is a leading cause of vision impairment worldwide [120]. In its early non-proliferative stage (NPDR), sustained hyperglycaemia induces vascular dilation, increased blood flow, heightened permeability, and capillary occlusion, clinically manifesting as microaneurysms, dot-blot haemorrhages, and hard exudates composed of lipids and proteins [121]. As ischaemia and hypoxia worsen, hypoxia-inducible factor-1 (HIF-1) and VEGF become upregulated, driving pathological neovascularization. The emergence of fragile new vessels marks progression to proliferative diabetic retinopathy (PDR), which can culminate in vitreous haemorrhage and retinal detachment [122, 123].

Although fundamentally a vascular disorder, DR is initiated by metabolic derangements such as excess flux through the polyol pathway, accumulation of AGEs, activation of PKC, and increased hexosamine biosynthetic pathway activity, all of which generate oxidative stress and chronic low-grade inflammation targeting retinal microvascular endothelial cells [124, 125]. Early histopathological changes include pericyte loss, endothelial apoptosis, basement membrane thickening, and pericyte dropout, leading to capillary degeneration, disruption of the blood–retinal barrier (BRB), and neurotrophic deficits [126–128]. Persistent inflammation, driven by ongoing microglial proliferation, monocyte recruitment, and upregulation of proinflammatory cytokines and adhesion molecules, is closely linked to both microvascular dysfunction and neuronal degeneration [129–131].

Retinal resident macrophages (microglia) derive from the embryonic yolk sac and reside predominantly in the inner retina. Functionally analogous to peripheral macrophages, microglia maintain retinal homeostasis via self-renewal and replenishment by circulating monocytes, and they mount immune defenses in response to injury or infection [132]. In reaction to local environmental cues, microglia assume either a pro-inflammatory M1 phenotype or an anti-inflammatory M2 phenotype, shaping the course of DR progression [133].

In STZ-induced rat models of DR, microglial polarization becomes imbalanced, with a progressive rise in M1 markers and a decline in M2 markers. In vitro, high-glucose treatment of BV2 cells demonstrated that ALKBH5-mediated m^6A modification of A20 promotes M1 polarization [117]. High-glucose-treated microglia also exhibit elevated mm9_circ_014863 expression, which activates the NF-κB pathway and drives M1 polarization; inhibition of mm9_circ_014863 restores the M1/M2 balance and slows DR progression [134]. Co-staining of retinal macrophages/microglia with IBA-1 and isolectin B4 in db/db mice reveals an M1-like morphology, whereas PEG-Arg-1 treatment reduces retinal inflammation and iNOS expression, reinstates continuous ZO-1 and CD31 localization, and diminishes albumin leakage, thereby preserving blood-retinal barrier integrity [135]. Furthermore, Elena et al. found that extracellular vesicles from M1-activated microglia contain elevated levels of CCL2, MMPs, and VCAM-1, contributing to barrier disruption and inducing retinal endothelial and pericyte secretion of proinflammatory and pro-angiogenic factors [136, 137].

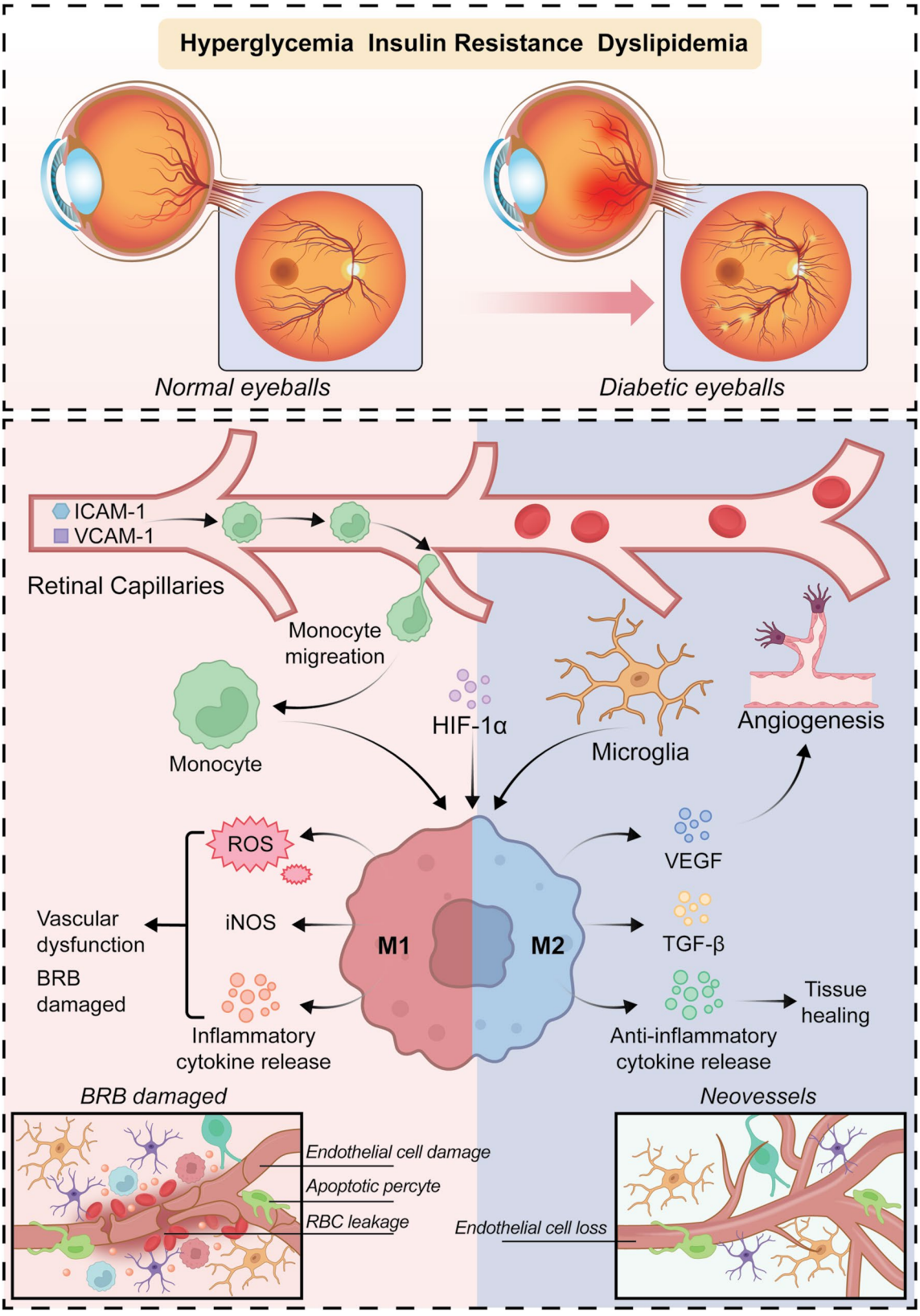

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Fig. 4 Macrophage phenotypes and metabolic mechanisms in diabetic DR. Under hyperglycemic conditions, macrophages preferentially polarize toward the pro-inflammatory M1 phenotype, releasing abundant cytokines and ROS. This process disrupts the BRB, enhances vascular permeability, and exacerbates neuroinflammation. Such pathological alterations accelerate disease progression and promote aberrant neovascularization, as observed in PDR. In contrast, M2 macrophages secrete anti-inflammatory mediators such as IL-10 and TGF-β, which suppress inflammation and facilitate tissue repair. However, in advanced stages of diabetic retinopathy, excessive M2 activation may drive fibrotic remodeling and pathological angiogenesis, ultimately resulting in retinal structural damage and functional impairment

Using single-cell RNA sequencing, Wang et al. showed that Egr2$^+$ M1 macrophages upregulate inflammatory cytokines via the RAGE/NF-κB pathway as early as two weeks in diabetic rats, with further amplification through MAPK and JAK/STAT pathways by week four [138]. Ma et al. reported that reduced scavenger receptor A (SR-A) expression in DR macrophages, combined with AGE-RAGE axis activation of the MKK7/JNK/NF-κB pathway, favors M1 polarization, increases vascular permeability, and disrupts the blood-retinal barrier [139].

Fu et al. observed that M1-polarized CD16$^+$ microglia in DR mice express higher levels of IL-1β, IL-6, and TNF-α, while M2 markers (CD206$^+$) and cytokines (TGF-β, IL-4, IL-10) are diminished. These changes are mediated by Müller cell-derived exosomes under hyperglycaemic conditions, involving miR-320-3p regulation of aldose reductase (AR), miR-221-3p targeting PFKFB3, and miR-574-5p modulating GLUT1 [140]. Finally, LPS stimulation of BV2 cells, mimicking the DR microenvironment, elevates TNF-α, IL-1β, and IL-6, whereas treatment with (S_S)-DS-ONJ upregulates the M2 marker arginase-1 and alleviates retinal gliosis in BB rats with type 1 diabetes [141].

However, in oxygen-induced retinopathy (OIR) mouse models, M2-polarized microglia and macrophages have been shown to drive pathological neovascularization. Immunostaining revealed an enrichment of CD206$^+$ cells surrounding neovessels, and intravitreal administration of bone marrow-derived M2 macrophages further exacerbated aberrant angiogenesis in both avascular and neovascular retinal regions [142, 143]. Consistent with these findings, Muneo et al. observed a predominance of M1 microglia and macrophages in ischemic retinal zones, whereas M2 cells localized primarily around neovessels [144]. Furthermore, Shen et al. demonstrated that succinate accumulation elevates the M2/M1 ratio, which in turn promotes endothelial migration, invasion, and neovascular proliferation [145].

These results suggest that, during the proliferative stage of diabetic retinopathy, targeted depletion of M2 macrophages may offer a therapeutic approach to suppress aberrant neovascularization (Fig. 4).

Macrophage polarization and diabetic peripheral neuropathy

Diabetic peripheral neuropathy (DPN) is a common diabetic complication characterized by peripheral nerve dysfunction, with distal symmetric polyneuropathy (DSPN) being the most prevalent form. Current treatments primarily target glycaemic control and pain management, whereas options for non-painful symptoms remain limited [146]. The pathogenesis of DPN is multifactorial, involving axonal degeneration, Schwann cell dysfunction, and microvascular compromise [147]. Histopathological analyses of patient biopsies reveal nerve fiber degeneration, disorganization of the myelin sheath, disruption of the nodes of Ranvier, and abnormal distribution of sodium and potassium channels [148]. Given the peripheral nervous system's unique architecture, where nerve fibers are encased by the perineurium and supplied by only a few transperineurial arterioles, any microvascular disturbance readily impairs nutrient delivery to neurons and Schwann cells [149]. Consequently, microangiopathy can precede overt neuropathy, with the severity of vascular lesions correlating positively with DPN progression [150, 151].

Inflammation emerges early in diabetes, even during the insulin-resistant phase [152], and subclinical damage to small nerve fibers and endothelial cells is detectable before chronic hyperglycaemia develops [153, 154]. A cross-sectional study found significantly increased macrophage density in skin biopsies from DPN patients compared to healthy controls, suggesting a role for macrophages in neuropathic pain [155]. Transcriptomic profiling of dorsal root ganglia similarly indicated macrophage recruitment [156]. In DPN patients, macrophages adopt a pro-inflammatory phenotype, with elevated secretion of TNF-α, MCP-1, and IL-6 [157]. In the endoneurial compartment of T2DM patients, marked infiltration by macrophages and T cells accompanies a reduction in capillary lumen area and thickening of the basement membrane, likely driven by CD40-mediated upregulation of HIF-1α and PTEN [158]. Likewise, in T1DM mouse models, a progressive increase in CD11b$^+$ cells within the spinal cord reflects ongoing peripheral macrophage infiltration, which may act alongside resident glia to exacerbate neuropathic pain [159].

In mice deficient in macrophage monocarboxylate transporter 1 (MCT1), peripheral nerve tissues exhibit elevated expression of inflammatory cytokines and a pronounced shift toward the M1 phenotype, resulting in impaired nerve regeneration, a finding that was corroborated in vitro [160]. In the diabetic neuropathy (DNP) model, lncRNA HCG18 was shown to regulate

the miR-146a/TRAF6 axis, thereby driving M1 polarization and exacerbating DNP progression [161]. Under high-glucose conditions, microglia downregulate Sirtuin 3 (Sirt3) expression and increase glycolytic flux, which aggravates neuroinflammation in DNP [162]. Throughout the course of diabetic peripheral neuropathy (DPN), early-stage sciatic nerves display a marked increase in M1 macrophage infiltration, whereas chronic stages are characterized by a disrupted M1/M2 balance, suggesting a transition from acute to chronic inflammation that underlies persistent nerve damage and regenerative failure [163].

AGEs accumulation is a pivotal mechanism in diabetic complications [164]; AGE-RAGE signaling enhances M1-associated gene expression while suppressing M2 markers, promotes tissue inflammation, and impairs neuronal growth and axonal regeneration, thereby precipitating early DPN onset [165]. In diabetic RAGE-null mice, increased M2 polarization in the distal sciatic nerve, as evidenced by elevated Arg-1 and CD206 levels, correlates with axonal regeneration and greater myelin density [166]. Conversely, heightened proinflammatory mediator release and M1 macrophage infiltration in the sciatic nerve intensify neuropathic pain in T2DM mice [167]. Likewise, STZ-treated rats exhibit increased M1 microglial markers in the spinal cord, which associate with diabetic neuropathic pain [168].

Administration of MSC-derived exosomes in db/db mice significantly reduced $CD68^{+}$ macrophage infiltration in the sciatic nerve and lowered serum TNF-α and IL-1β levels, thereby ameliorating neuroinflammation and microvascular dysfunction in diabetic peripheral nerves [169]. Similarly, the TLR2 antagonist CU-CPT22 markedly decreased M1 marker and proinflammatory cytokine expression in the sciatic nerve of T2DM mice, shifted the balance toward M2 macrophages, and alleviated neuropathic pain [167]. MicroRNA-146a mimics exert their therapeutic effect not by lowering blood glucose but by reprogramming macrophage polarization, completely reversing diabetes-induced increases in M1 markers and decreases in M2 marker genes, thus enhancing peripheral nerve perfusion and promoting neurovascular remodeling [170]. Finally, IL-35 improves DNP by inhibiting JNK signaling and activating the JAK2/STAT6 axis, converting microglia from an M1 to an M2 phenotype and delivering both anti-inflammatory and analgesic benefits [171]. (Fig. 5).

Therapeutic perspectives: targeting macrophage polarization in diabetic vascular complications

Diabetes mellitus-accelerated AS

Gliclazide, a second-generation sulfonylurea antidiabetic agent, attenuates the proinflammatory M1 phenotype induced by AGEs through inhibition of the RAGE/TLR4/NF-κB signaling axis [172]. Metformin likewise ameliorates mitochondrial dysfunction in ox-LDL-stimulated RAW264.7 macrophages, shifting their metabolism toward oxidative phosphorylation via upregulation of phosphorylated Akt [173]. The GLP-1 receptor agonist liraglutide promotes M2 macrophage polarization and IL-10 secretion in THP-1 cells and bone marrow-derived macrophages, concurrently suppressing MCP-1 expression, and in $ApoE^{-/-}$ mice enhances M2 marker expression in bone marrow cells to inhibit AS progression [174]. Similarly, the GLP-1 analogue lixisenatide reprograms macrophages toward an M2 phenotype by modulating STAT signaling in $ApoE^{-/-}Irs2^{+/-}$ mice, leading to plaque stabilization, reduced inflammatory cell infiltration, and diminished necrotic core formation, while also attenuating peripheral lymphocyte and T-cell activation [175]. Prostaglandin E_2 activates the CREB/BDNF/TrkB cascade to upregulate M2-associated markers (Fizz1, Ym1, Arg-1) and delay disease progression in diabetic AS-prone mice [176]. Inhibition of DPP-4 by sitagliptin stimulates the SDF-1/CXCR4 pathway, enhances M2 polarization within the aortic wall, and thereby mitigates atherosclerotic lesion development [177]. The antioxidant Sestrin2 regulates the AMPK/mTOR pathway to downregulate iNOS, TNF-α, IL-6, and CD80/CD68 expression in THP-1 macrophages exposed to HG or ox-LDL [178]. The SGLT2 inhibitor Dapagliflozin exerts anti-inflammatory effects by modulating the TLR4/NF-κB axis, upregulating miR-146a and downregulating miR-155, thereby reversing M1 polarization induced by LPS and HG [179]. Another SGLT2 inhibitor, Luseogliflozin, also suppressed inflammation related mRNA expression in NA and STZ induced $ApoE^{-/-}$ mice [180].

In high-fat diet–induced $ApoE^{-/-}$ mice, exogenous insulin administration enhanced AKT phosphorylation and eNOS activation, shifted the macrophage polarization balance toward the M2 phenotype, lowered circulating VLDL and LDL levels, and ameliorated endothelial dysfunction [181].

Mesenchymal stem cells (MSCs) -derived extracellular vesicles have demonstrated therapeutic potential by modulating the AMPK/mTOR signaling axis, inhibiting M1 polarization, upregulating arginase-1 (Arg-1), and reducing macrophage infiltration and migration, thereby attenuating diabetes-exacerbated AS[182]. Ginsenoside Rg3, a bioactive saponin from Panax ginseng, exerts well-established anti-inflammatory and antioxidant effects in metabolic and cardiovascular disease settings [183]. By enhancing PPARγ signaling, Rg3 suppresses AGE-induced M1 polarization in bone marrow–derived macrophages and limits the release of proinflammatory and chemotactic factors; in diabetic $ApoE^{-/-}$mice, Rg3 treatment reduced the M1/M2 macrophage ratio within atherosclerotic plaques, conferring significant

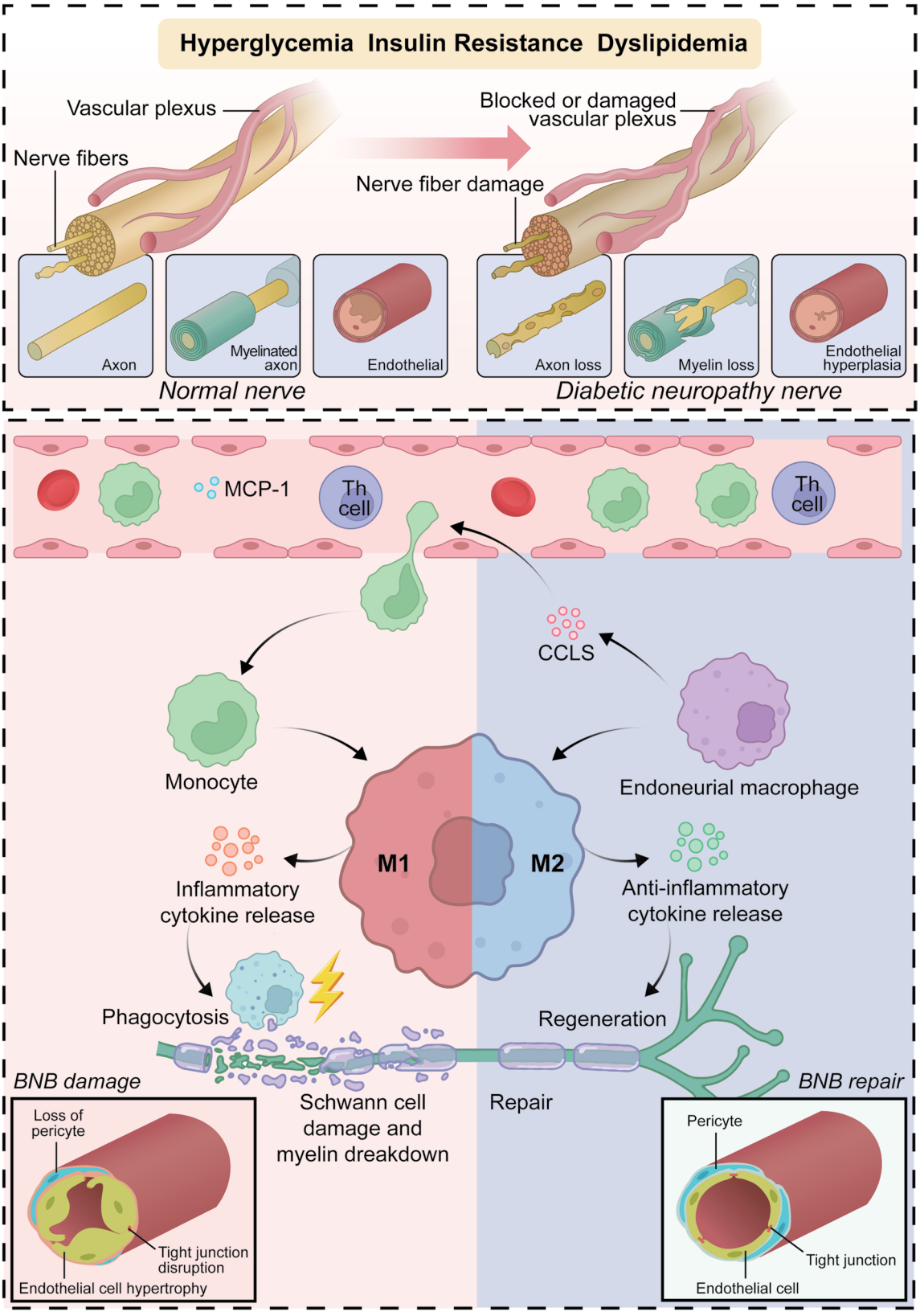

Fig. 5 Macrophage phenotypes and metabolic mechanisms in diabetic DPN. Hyperglycemia induces non-neuronal cells to release mediators that alter the activity of endoneurial macrophages and recruit circulating monocytes. These monocytes differentiate into M1 macrophages, which release pro-inflammatory cytokines that damage neurovascular structures, including axonal degeneration, endothelial dysfunction, and myelin degradation, ultimately impairing nerve regeneration. In contrast, M2 macrophages suppress inflammation and support tissue repair, thereby attenuating DPN progression

vascular protection [184]. Osmotin, a novel plant-derived protein from Nicotiana tabacum, prevents atherosclerotic lesion formation by inhibiting M1 polarization in THP-1–derived macrophages and foam cell development [185]. Matrine, an alkaloid extracted from the root of Sophora flavescens, effectively suppresses M1 polarization and cytokine production via inhibition of the RAGE/TLR4/STAT1 axis while enhancing antioxidant capacity through upregulation of glutathione peroxidase-1 (GPX1) [186] (Table 2).

Diabetic Nephropathy

Liraglutide has been shown to suppress MCP-1 expression and promote M2 macrophage polarization within renal tissues, thereby ameliorating podocyte injury and improving kidney function in models of DN [114]. Dapagliflozin, a sodium–glucose co-transporter 2 inhibitor, reverses macrophage apoptosis and M1 polarization and reduces inflammatory cytokine expression in T2DM mice by inhibiting the PI3K/AKT pathway [187]. Active vitamin D functions as an immunomodulator and exerts renoprotective effects in DN rats via regulation of the STAT-1/TREM-1 signaling pathway, upregulation of mineralocorticoid receptor expression, and reduction of iNOS levels [188]. Similarly, the vitamin D analogue paricalcitol suppresses proinflammatory cytokine release and facilitates the M1-to-M2 transition by modulating the VDR/CYP2J2 axis in high-glucose/LPS-stimulated macrophages and in DN mice [189]. In diabetic $ApoE^{-/-}$ mice, the selective endothelin A receptor antagonist atrasentan restores the M1/M2 balance, normalizes the glomerular endothelial glycocalyx barrier, and decreases albuminuria [190].

Targeted therapies further demonstrate efficacy in mitigating DN-associated damage. Tonabersat inhibits connexin 43–mediated ATP release and NLRP3 inflammasome activation in high-glucose- and cytokine-stimulated renal proximal tubular epithelial cells and macrophages, concurrently reducing MCP-1 expression and M1 polarization [191]. The VEGFR-3 inhibitor SAR131675 downregulates MCP-1 and TNF-α expression, suppresses M1 macrophage infiltration, and attenuates proinflammatory lymphangiogenesis and renal injury in DN [192].

Small non-coding RNAs, notably microRNAs (miRNAs), have emerged as promising therapeutic targets. For example, miR-146a-5p modulates TRAF6 to drive M2 polarization, thereby attenuating inflammatory cytokine production and improving renal function in DN rats [193], while miR-486-5p regulates the PI3K/AKT pathway to restore the M2/M1 balance, enhancing renal morphology and function [194].

Mesenchymal stem cells (MSCs) therapy likewise confers renoprotection in DN mouse models by reprogramming macrophages toward an M2 phenotype through restoration of lysosomal autophagy and mitochondrial function [195]. Furthermore, mitochondrial transfer from MSCs to macrophages activates the PGC-1α/TFEB pathway, reinforcing M2 polarization and sustaining anti-inflammatory responses [196].

Traditional Chinese medicine offers additional macrophage-targeting strategies. Hyperoside, isolated from Cuscuta chinensis, ameliorates renal injury in db/db mice by rebalancing M1/M2 macrophage polarization and correcting Th2/Treg imbalances [197]. Tectorigenin promotes AMPKα phosphorylation in LPS-stimulated RAW264.7 macrophages, suppressing NF-κB p65 signaling, inhibiting M1 polarization, and mitigating glucolipotoxic endothelial injury [198]. At high concentrations, myricetin inhibits M1 activation via the PTEN/PI3K/AKT pathway [199], while hirudin from Hirudo medicinalis reduces macrophage infiltration and pro-inflammatory cytokine levels to prevent podocyte apoptosis in DN rats [200]. Loganin suppresses MCP-1/CCR2 signaling, decreases M1 macrophage infiltration and iNOS/CD16/32 expression, and alleviates renal histopathological damage and extracellular matrix deposition [201]. Additionally, Trichosanthes kirilowii downregulates Notch/NICD1/Hes1 expression to enhance M2 polarization, restoring podocyte proliferation and ameliorating STZ-induced renal injury [202], and Yi-Shen-Hua-Shi granules protect against high-glucose-induced podocyte damage by reducing exosomal miR-21a-5p from M1 macrophages, thereby reversing podocyte apoptosis [203](Table 3).

Diabetic Retinopathy

DR, a leading cause of vision loss in diabetic patients, is driven by chronic inflammation and dysregulated microglial/macrophage polarization within the retina. Strategies that shift the M1/M2 balance toward the anti-inflammatory state have therefore emerged as promising avenues for restoring retinal homeostasis and preserving blood–retinal barrier integrity. The ATP-sensitive potassium channel opener pinacidil upregulates Kir6.1 in retinal microglia, promoting their M2 polarization while simultaneously inhibiting Müller cell proliferation; pinacidil also enhances Kir4.1 in Müller cells, exerting a bidirectional modulatory effect on retinal glia [204]. Melatonin similarly protects the BRB by blocking the PI3K/Akt/STAT3/NF-κB signaling cascade, thereby suppressing M1 microglial activation and safeguarding both endothelial cells and pericytes [205].

The small molecule (S_S)-DS-ONJ markedly attenuates NLRP3 inflammasome activation and NF-κB signaling in LPS-stimulated BV-2 microglia, driving M2 polarization and reducing retinal inflammation in DR rat models [141]. Exosomes derived from M2-polarized microglia

Table 2 The role of macrophage polarization in Diabetes mellitus-accelerated AS

Interventions	Subject	Dose	Targets/pathways/mechanisms	Effects	Refs
Gliclazide	Raw 264.7	In vitro: 250 nmol/L	(–) RAGE/NF-κB/iNOS	Promotes M2 and suppressing M1, IL-1β, IL-6, and TNF-α, $NO^{\cdot}$↓	[172]
Metformin	Raw 264.7	In vitro: 15 μmol/L	(+) p-Akt (Ser^{473})/p-AS160	Towards alternatively activated M2 cells mitochondrial function, ATP↑, ROS↓ JC-1 Red/JC-1 Green↑ IL-10, Retnla↑	[173]
Liraglutide	HFSCD-$ApoE^{-/-}$mice human PBMCs, THP-1 Murine BMDMs	In vivo: 0.3 g/kg	(–) p-STAT1/STAT1	Attenuates M1 and promotes M2 M1 monocytes and macrophages from bone marrow-derived cells↓ M2 (Arg-1, IL-10, MR, CD163) ↑ M1 (CCR7, iNOS, TNF-alpha, IL-6) ↓	[174]
lixisenatide	$ApoE^{-/-}$Irs2 $^{+/-}$ mice, BMDMs	In vivo: 0.1 g/kg	(+) STAT3 (–) STAT1	Reprogramming macrophages towards an M2 phenotype, proinflammatory $Ly6C^{high}$ monocytes and activated T cells M2 (Arg-1) ↑, M1 (iNOS, IL-6) ↓	[175]
Prostaglandin E2	ALX-$LDLR^{-/-}$mice, PBMCs	In vivo: 200 μg/kg	(+) CREB/BDNF/TrkB	M1(TNF-α and NOS2) ↓ M2(Fizz1, Ym1, Arg-1) ↑	[176]
Sitagliptin	$ApoE^{-/-}$mice	In vivo: 500 mg/kg	(+) SDF-1/CXCR4	Activates M2 M2 macrophage accumulation is based on local macrophage priming rather than preferential recruitment of circulating monocyte subtypes	[177]
sestrin2	THP-1, HUVECs	-	(+) AMPK (–) mTOR	M1/M2↓ reduced foam cell formation	[178]
Dapagliflozin	HUVECs, Human PBMCs	In vitro: 0.5 μM	(–) TLR4/NF-κB (–) miR-155, miR-146a	Diminish the number of M1 polarized macrophages while increasing M2 polarized ones reducing M1/M2 ratio IL-1β, IL-6, IL-8 and TNF-α↓	[179]
Luseogliflozin	NA/STZ-$ApoE^{-/-}$ mice	In vivo mixing it into the diet at a concentration of 0.1%	Prevention of inflammation rather than of hyperlipidemia	M1↓ IL-1β, IL-6, TNF-α, ICAM-1, MMP9 and MMP2 mRNA↓	[180]
Insulin	HFD-$ApoE^{-/-}$ mice	In vivo: 0.1 U/day	(+) p-AKT	eNOS/NO↑, M1/M2↓ IL6, TNFα and VCAM-1↓	[181]
BMSC-EVs	STZ-$ApoE^{-/-}$mice, Raw 264.7	In vivo: 100 μg	(–) AMPK/mTOR	Inhibits M1 polarization and promotes M2 polarization iNOS, CD68↓, Arg-1↑ Inhibit Raw 264.7 cellular migration, proliferation, foam cell formation	[182]
Ginsenoside Rg3	STZ-$ApoE^{-/-}$mice, BMDMs, THP-1	In vivo: 10 mg/kg In vitro: 25 μM	(+) PPARγ	Reverses the M1 polarization to the M2 phenotype iNOS↓, Arg-1↑	[184]
Osmotin	$ApoE^{-/-}$mice HUVECs, THP-1, HASMCs	In vivo: 100 ng/kg	(+) PPARγ (–) ERK1/2/NF-κB	HUVECs: TNF-α, MCP-1, VCAM-1, ICAM-1↓ THP-1: suppressed the inflammatory M1 phenotype, foam cell formation, ACAT1↓, ABCA1 HASMCs: Collagen-1, FN, MMP2↓ without inducing apoptosis reductions of fasting plasma glucose, and insulin resistance	[185]
Matrine	Primary peritoneal macrophages	In vitro: 2.0 mM	(–) RAGE/TLR4/STAT1	Inhibits AGEs- induced macrophage M1 polarization iNOS, IL-1β, IL-6, TNF-α↓ reduce DNMT3a/b-mediated GPX1 promoter DNA methylation	[186]

Table 3 The role of macrophage polarization in DN

Interventions	Subject	Dose	Targets/pathways/mechanisms	Effects	Refs
Liraglutide	$Ins2^{Akita}$ mice	In vivo: 50 μg/kg	(–) RAGE/NF-κB (+) PKA	Promotes M2 macrophage phenotype TGF-β, MCP-1, NLRP3 ↓, IL-10↑	[114]
Dapagliflozin	STZ-C57BL/6J THP-1	In vivo: 10 mg/kg In vitro: 100 μM	(–) P13K/AKT	Impedes cellular M1 polarization Caspase 3, Apoptosis rate↓, BCL2↑ iNOS, CD86, TNF-α, IL-1β and IL-6↓	[187]
Active vitamin D	STZ-SD rats Raw 264.7	In vivo: 0.1 μg/kg In vitro: 10^{-8} mol/L	(–) p-STAT-1/TREM-1	Inhibits M1 iNOS and TNF-α↓ mannose receptor↑	[188]
Paricalcitol	Human PBMCs STZ-C57BL/6J	In vitro: 1 mM	(+) VDR/CYP2J2	Promotes M2 polarization. EETs↑ TNF-α, IL-1β, MCP-1, and IL6↓	[189]
Atrasentan	STZ-$ApoE^{-/-}$ KO mice HUVECs	In vitro: 0.5 μM In vivo: 7.5 mg/kg	-	Restores glycocalyx thickness on Endothelial Cells F4/80-CD206↑, HPSE, CTSL↓	[190]
Tonabersat	RPTECs, MDMs	In vitro: 50 μM	(–) Cx43 hemichannel/NLRP3	RPTECs: MCP-1, CX3CL1, CXCL12↓ MDMs:M1(IL-1α, CD80, STAT1) ↓ M2(IL-10, CD206, STAT6) ↓	[191]
SAR131675	db/db mice Raw 264.7	In vivo: 30 mg/kg	(–) lipotoxicity (FFA, TG, TC)	Decrease M1 infiltration TNF-α, MCP-1↓ F4/80, CD68, iNOS,Arg-II↓ VEGF-C-VEGFR-3, TGF-β↓ ROS, apoptosis↓	[192]
miRNA-146a-5p	STZ-SD rats THP-1, Raw 264.7	In vivo: 2×10^6 UC-MSCs	(–) TRAF6-STAT1	Facilitates M2 polarization TNF-α, IL-1β and IL6↓ IL10↑ iNOS↓, Arg-I↑	[193]
miR486-5p	UCMSCs db/db mice	In vivo: 150 μg	(+) PI3K/Akt	Enhances suppression of M1 and augmented induction of M2 TNF-α, MCP-1, iNOS↓ Arg-1, CD206, IL-10↑	[194]
MSCs	STZ-BALB/c mice Raw 264.7	In vivo: 5×10^5 cells	(+) TFEB	Elicites Mφ into M2 phenotype M1(F4/80 CD11c) ↓M2(F4/80 CD206) ↑ TNF-α, MCP-1and IL-1β↓, IL-10↑	[195]
MSCs-mito	STZ-C57BL/6 J mice Raw 264.7	In vitro: 1×10^7 In vivo: 2×10^6	(+) PGC-1α/TFEB	M1(F4/80 CD11c) ↓, M2 (F4/80 CD206) ↑ energy metabolism↑ lysosomal function and autophagy↑ TNF-α, IL-1β↓	[196]
Hyperoside	db/db mice BMDMs	In vivo: 40, 80 mg/kg In vitro: 12.5-50uM	_	Induces M2 macrophage MCP-1, IFN-γ, iNOS, IL-17, TNF-α↓ IL-10, Arg-1↑	[197]
Tectorigenin	HRGECs, THP-1 db/db mice	In vivo: 75 mg/kg	(–) TGF-β/SMAD (+) AdipoR1/2/AMPKα/PPARα	Promotes M1 macrophage switch into M2 phenotype TNFα, CXCL1 and IL-6↓ Mgl2, Arg1 and IL-10↑ TG, LDL-C↓, eNOS↑	[198]
Myricetin	db/db mice Raw 264.7	In vivo: 50, 100 mg/kg	(+) P-Akt	TNF-α, IL-1β and IL6↓IL-10↑ collagen-1a1↓	[199]
Hirudin	STZ-SD rat	In vivo: 5U	(–) p38 MAPK/NF-κB	Podocyte apoptosis CD68, TNF-α, IL-1β and IL-6↓	[200]
Loganin	KK/Ay mice, GMCs, Raw 264.7	In vivo: 50,100 mg/kg In vitro: 0.1, 1.0 and 10.0 μmol/L	(–) MCP-1/CCR2	iNOS and CD16/32 (M1 markers) ↓, Arg-1 and CD206 (M2 markers) ↑, FN, COL-IV, IL-12and TGF-β↓ IL-10↑	[201]
Trichosanthes	STZ-wistar rat	In vivo: 200,400 and 800 mg/kg	(–) Notch/Hes 1	CD80, CD86, TNF-α, iNOS↓ CD163, CD206, Arg-1, IL-10↑	[202]

Table 3 (continued)

Interventions	Subject	Dose	Targets/pathways/mechanisms	Effects	Refs
Yi-Shen-Hua-Shi granules	db/db mice	In vivo: 0.5, 0.25, 0.125 g/ml	(–) macrophage-derived exosomal miR-21a-5p	Inhibits macrophage M1 glomerular structural lesions and glomerular cell apoptosis↓	[203]

also confer protection to retinal endothelial cells and pericytes in oxygen-induced retinopathy and STZ-induced DR models by reinforcing anti-inflammatory signaling and restoring BRB function [206]. MicroRNA-based interventions further demonstrate therapeutic potential: miR-130a-3p enhances macrophage autophagy through upregulation of LC3II/I and Beclin-1 while repressing YY1, thereby inhibiting M1 polarization under high-glucose conditions and slowing DR progression [207]. Finally, exogenous beta-hydroxybutyrate (BHB) activates BDNF/PI3K signaling, reverses M1 microglial activation, and normalizes autophagy-related proteins such as LC3B and ATG14, alleviating aberrant autophagy and preserving retinal cell integrity [208].

MSCs represent a promising cell-based therapy for DR. MSCs have been shown to inhibit the HMGB1/TLR4/p-NF-κB signaling cascade while activating the PI3K/Akt pathway, thereby reversing M1 polarization in retinal microglia and AGEs-stimulated BV-2 cells. These effects preserve blood-retinal barrier integrity and retinal architecture in diabetic rat models [209]. Human umbilical cord blood (hUCB), a rich source of hematopoietic stem cells, provides $CD14^+$ cells that differentiate into M2 macrophages, which inhibit pathological neovascularization in OIR mice and accelerate retinal tissue repair [210].

Natural products have likewise demonstrated therapeutic potential. Asiatic acid attenuates M1 microglial polarization in both diabetic rats and LPS/high-glucose–treated BV-2 cells by suppressing the TLR4/MyD88/NF-κB pathway and upregulating tight-junction proteins, thereby maintaining blood–retinal barrier function [211]. Rhein, an active anthraquinone from Rheum species, when encapsulated in GFFYE nanofibers (Rhein-GFFYE NFs), reprograms bone marrow-derived macrophages toward an M2 phenotype via NF-κB and STAT3 inhibition. These nanofibers also reduce oxidative stress in R28 retinal cells under hypoxia-high-glucose conditions and, in retinal ischemia-reperfusion rats, suppress M1 microglial activation and retinal ganglion cell apoptosis, ultimately preserving visual function [212](Table 4).

Diabetic Peripheral Neuropathy (DPN)

DPN is among the most prevalent microvascular complications of diabetes and is closely associated with immune dysregulation and chronic inflammation, particularly involving dynamic macrophage and microglial polarization. TLRs, as key innate immune sensors, recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), thereby initiating inflammatory cascades. In T2DM murine models, antagonism of TLR2 with CU-CPT22 reprograms sciatic nerve macrophages toward an M2 phenotype and alleviates neuropathic pain [167]. Likewise, intrathecal administration of recombinant IL-35 suppresses JNK signaling and activates STAT6, promoting M2 polarization of spinal microglia and attenuating DPN-associated neuroinflammation [171].

MSCs and their derived exosomes also exhibit potent immunomodulatory effects in DPN therapy. MSC-derived exosomes inhibit M1 marker expression and proinflammatory cytokine production in the sciatic nerves of db/db mice, thereby preserving myelinated fibers, improving nerve conduction velocity, and mitigating microvascular dysfunction [169]. Exosomes from M2-polarized macrophages further downregulate NF-κB/IKBα phosphorylation in spinal microglia, fostering M2 polarization and conferring analgesic benefits [212, 213]. Dental pulp stem cells (DPSCs), a specialized MSC subset, enhance nerve conduction velocity and restore sciatic nerve blood flow in STZ-induced diabetic rats, likely through elevated secretion of M2-inducing cytokines [214]. MicroRNA-based interventions show similar promise: miR-146a mimics modulate the IRAK1/TRAF6–NF-κB axis in the sciatic nerves of db/db mice, reversing diabetes-induced upregulation of M1 markers and downregulation of M2 markers, while enhancing blood flow in the sciatic nerve and plantar region to restore neurovascular function [170]. Koumine, an alkaloid from Gelsemium elegans Benth., inhibits the Notch–RBP-Jκ pathway to suppress M1 polarization of spinal microglia and normalize mechanical withdrawal thresholds in DPN rats without affecting glycaemia or body weight [168]. Similarly, the traditional Chinese formulation Jinmaitong downregulates JAK2/STAT3 signaling in the spinal cord, curbing excessive M1 microglial activation and mitigating neuroinflammation in diabetic rats [215] (Table 5).

Progress of Clinical Studies Involving Macrophage Polarization

Researchers have increasingly investigated agents capable of modulating macrophage polarization as a means to mitigate diabetic vascular complications. Preclinical studies indicate that various pharmacological compounds, natural products, and biological interventions can regulate macrophage polarization, thereby reducing

Table 4 The role of macrophage polarization in DR

Interventions	Subject	Dose	Targets/pathways/mechanisms	Effects	Refs
Pinacidil	STZ-SD rats Müller cell,Microglia cell	In vivo: 30 mg/kg	Müller cell: (+) Kir4.1 Microglia cell: (+) Kir6.1	Enhances the M2 transition CD86↓, CD206↑ GFAP, IBA-1, VEGF, TNF-α, IL-1β↓ Arg-1↑	[204]
Melatonin	STZ-SD rats Bv.2 cells, HRMECs,HBVPs	In vivo: 30 μg In vitro: 100 μM	(–) PI3K/Akt/STAT3/NF-κB	Protects the barrier function IBA-1, Albumin↓, NG2, Claudin-5, ZO-1↑ CCL-3, CCL-5, CXCL-10, TNF-α, iNOS and IL-1β↓ Arg-1, CD206 and TGF-β↑	[205]
(S_S)-DS-ONJ	Bv.2 cells, BB rats	In vitro: 10 μM In vivo: 20 μM	(–) JNK/NF-κB (–) NLRP3/ASC/Caspase-1	Increases anti-inflammatory M2 response nitrites production↓ iNOS, Nos2, TNFα, IL-1β, IL-6↓ HO-1, IL-10, Arg-1↑	[141]
M2-exo	STZ-C57BL/6 J mice HERCs,pericytes	In vitro: 100 μg/mL	-	Promotes microglia M2 polarization Protective BRB, vascular endothelial cell and pericyte, ZO-1↑, apoptosis ↓	[206]
miR-130a-3p	STZ-C57BL/6 J mice THP-1	In vivo: 20 μM	(–) YY1/PI3K/AKT/mTOR	Inhibits M1 polarization, TNF-α,IL-6, iNOS,CRR7↓, IL-10, Arg-1, CD206↑ LC3II/I, Beclin1↑P62↓	[207]
Beta-hydroxybutyrate	STZ-C57BL/6 J mice	In vivo: 25,50,100 mg/kg	(+) BDNF	Reduces M1 Microglial within the ONL ATG14 (autophagy-related 14 protein) ↓	[208]
MSCs	STZ-SD rats BV-2 cells	In vivo: 2×10^5 MSCs	(–) HMGB1/TLR4 (+) p-PI3K/p-AKT	Alleviates BRB Damage in DR, M1($iNOS^+$/$Iba\text{-}1^+$) microglia ↓, M2($Arg\text{-}1^+$/$Iba\text{-}1^+$) microglia ↑, TNF-α, MCP-1, IL-6, iNOS, CD16↓ TGF-β, IL-4, IL-10, Arg-1, CD206↑	[209]
Human umbilical cord blood	C57BL/6 J mice	In vivo: 250,000/ 0,5 μl	-	Induce the polarization of resident M2 macrophages expression of genes that regulate oxidative stress, apoptosis and control of inflammation and angiogenesis	[210]
Asiatic acid	STZ-SD rats BV-2 cells HERCs, ARPE-19	In vivo: 37.5, 75 mg/kg In vitro: 1 μM or 10 μM	(–) TLR-4/MyD88/NF-κB	Arg-1 /IBA1↑ occludin, claudin-5, ZO-1↑ TNF-α, IL-6↓, IL-4, IL-10↑	[211]
Rh-GFFYE	R28 cells,BMDMs RIR rats	In vitro: 10, 20, 40 μM In vivo: 20 μM	(–) TLR4/IκBα/NF-κB (–) p-STAT3 (+) PI3K/AKT/mTOR	Transformation to the M2 phenotype apoptosis↓ (BRN3A, β-III-TUBULIN↑) IBA-1, GFAP ↓ IL-1β, IL-6 ↓CD206/CD86 ↑	[212]

vascular inflammation and endothelial dysfunction. For instance, GLP-1 receptor agonists, DPP-4 inhibitors, and PPARγ agonists exert anti-inflammatory effects in part through modulation of macrophage phenotypes. Similarly, natural compounds such as loganin, quercetin, and ginsenosides have been shown to promote M2 polarization while suppressing M1-driven inflammatory responses in experimental models. In addition, emerging strategies, including mesenchymal stem cell-derived exosomes and miRNA-based therapies, hold promise as novel approaches to reprogram macrophage polarization.

Notably, clinical evidence has begun to emerge. The LIRAFLAME trial (NCT03449654) demonstrated that liraglutide treatment in patients with T2DM reduced coronary uptake of [^{64}Cu]Cu-DOTATATE PET/CT, a marker of M1 macrophage activation, thereby highlighting the feasibility of noninvasive imaging for monitoring therapeutic effects[216]. Similarly, a clinical study (n = 48) reported that the DPP-4 inhibitor sitagliptin decreased systemic inflammatory markers (CRP, TNF-α), increased IL-10 expression, and promoted monocyte polarization toward an M2 phenotype, supporting its anti-inflammatory benefits beyond glycemic control[217]. In contrast, a randomized, double-blind, placebo-controlled trial in patients with T2DM and high-risk ASCVD (NCT03829046) found that treatment with a PCSK9 inhibitor did not significantly reduce systemic inflammatory markers. However, compared with placebo, PBMCs

Table 5 The role of macrophage polarization in DPN

Interventions	Subject	Dose	Targets/pathways/mechanisms	Effects	Refs
CU-CPT22	HFD-C57BL/6 mice BMDMs	In vivo: 0.01 mg In vitro: 20 μM	(–) TLR2	Promotes M2 phenotype macrophages CD86, IL-1β, CCL3↓, CD206, Arg-1, IL-10↑	[167]
IL-35	STZ-SD rats HAPI	In vivo: 5 μg/kg In vitro: 0,10, 20, and 40 ng/mL	(+) JAK2/STAT6 (–) JNK	Promotes microglial M2 polarization CD68, iNOS, TNF-α, IL-6↓ CD206, Arg-1, IL-10↑	[171]
MSCs-Exo	db/db mice	In vivo: 1×10^9 particles	(–) TLR4/NF-κB	Decreases and increased M1 and M2, Arg-1, TGF-β, IL-10↑ $CD68^+$, TNF-α, IL-1β, iNOS↓	[169]
M2-exo	STZ-SD rats	In vivo: 20 μg	(–) NF-κB/p-IKBα	Convert the M1 to the M2 Arg-1, IL-10↑, IL-1β, iNOS↓	[212, 213]
Dental pulp stem cells	STZ-SD rats Raw 264.7	In vivo: 1×10^6 cell	-	Promotes M2 phenotypes TNF-α↓, CD206, M-CSF, IL-10↑	[214]
miRNA-146a	db/db mice	In vivo: 5, 10 mg/kg	(–) IRAK1/TRAF6/ADAMTS3	Reverses increased M1 reduced M2 TNF-α, IL-1β, iNOS↓, Ym1↑	[170]
Koumine	STZ-SD rats	In vivo: 0.28, 1.4, 7 mg/kg	(–) Notch-1/RBP-Jκ	Inhibits microglial M1 polarization CD86, CD68, TNF-α, IL-1β↓	[168]
Jinmaitong	ZDF model rats	In vivo: 11.6, 23.2, 46.4 g/kg	(–) JAK2/STAT3	inhibits microglia activation TNF-α, IL-1β, IL-6, IL-12, iNOS, CCL3, CCL5 and CXCL12↓ IL-10, Arg-1, TGF-β↑	[215]

Table 6 Macrophage polarization targeting therapeutic strategies in clinical trials

Related drugs	Effects on macrophages	Targeted diseases	Trial ID	Phase	Last update	Status
Telmisartan	[236–238]	DN	NCT02768948	Not Applicable	2022-05-19	Competed
Cocarnit	[239, 240]	DPN	NCT03877523	Not Applicable	2019-03-21	Competed
Victoza	[114, 241]	T2DM with obese	NCT02650206	Phase 1	2020-06-09	Competed
		Diabetes mellitus-accelerated AS	NCT03449654	Phase 4	2020-06-11	Competed
Sitagliptin	[177, 242–244]	T2DM	UMIN R000006517	Not applicable	2013-03-21	Competed
Pioglitazone	[245]	T2DM	NCT00108615 NCT00470262	Phase 4	2016-07-21	Competed
Evolocumab	[246]	T2DM with ASCVD	NCT03829046	Phase 4	2023-03-08	Competed

isolated from treated subjects exhibited pronounced transcriptional responses upon LPS stimulation, underscoring the pivotal role of monocyte "stress" responses in immune regulation [218](Table 6).

Conclusions and future prospects

With the global rise in diabetes prevalence, the incidence of both macrovascular and microvascular complications has escalated. Current therapies predominantly target glycaemic control, through insulin administration, dietary adjustments, and exercise, and address individual sequelae [219]. However, these measures often fail to halt disease progression in advanced stages of diabetic vascular pathology. Consequently, there is an urgent need for novel interventions that directly mitigate the vascular consequences of diabetes. Mounting evidence implicates chronic inflammation as a central driver of both diabetes onset and its vascular complications, suggesting that anti-inflammatory strategies could complement existing treatments [14, 220–222]. Yet, the heterogeneity and complexity of inflammatory responses in diabetes pose significant challenges to the development of personalized therapeutic approaches.

Macrophage polarization underpins the inflammatory landscape of diabetic vascular disease by modulating the balance between proinflammatory and reparative processes. Persistent hyperglycaemia and metabolic dysregulation foster a sustained inflammatory environment that directs macrophages toward either a classically activated, proinflammatory M1 phenotype or an alternatively activated, anti-inflammatory M2 phenotype [6, 29]. These reversible phenotypic transitions critically influence endothelial function, vascular integrity, and extracellular matrix remodeling [223, 224]. As such, targeting macrophage polarization represents a promising immunomodulatory approach for preventing and treating diabetes-related vascular complications.

Importantly, distinct diabetic vascular complications exhibit characteristic macrophage polarization profiles. In AS, M1 macrophages predominate during early lesion

formation and drive plaque instability, whereas M2 macrophages support repair and fibrous cap formation [79, 80]. In DN, M1 cells drive initial glomerular inflammation, while excessive M2 activation contributes to tubulointerstitial fibrosis [225]. In diabetic retinopathy and peripheral neuropathy, both M1 and M2 phenotypes are present, and disruption of their balance compromises neurovascular integrity [165, 226]. These disease-specific patterns highlight the importance of context-dependent intervention strategies.

Despite advances in macrophage biology, several challenges impede the translation of polarization-targeted therapies. First, the complex interplay among hyperglycemia-induced metabolic dysregulation, inflammatory cascades, and imbalances in macrophage polarization makes the identification of a single therapeutic target particularly challenging. Second, the high plasticity and heterogeneity of macrophage subsets often give rise to mixed or intermediate phenotypes. Their interactions with tissue-specific microenvironments further shape functional responses, highlighting the need for a nuanced understanding of macrophage lineage commitment and specialization[227]. Third, achieving an optimal therapeutic balance remains difficult: excessive suppression of M1-driven inflammation may compromise host defense, whereas unchecked M2 polarization can promote pathological fibrosis, particularly in the kidney and heart, highlighting the need for modulation rather than binary switching of macrophage states. Finally, the lack of reliable in vivo biomarkers to accurately reflect macrophage polarization status limits the ability to monitor therapeutic efficacy and disease progression.

Given the central role of macrophages in chronic inflammation, a comprehensive understanding of their diverse functions and precise regulatory mechanisms is essential for developing promising therapeutic interventions. Future research should focus on the following aspects: integrate cutting-edge single-cell RNA sequencing, lineage tracing, and spatial transcriptomics to delineate functionally distinct macrophage subsets across diabetic tissues. Concurrently, the design of phenotype-selective delivery platforms, ranging from targeted nanoparticles and antibody–drug conjugates to precision gene-editing systems, offers the potential to modulate macrophage behavior in situ with unprecedented specificity. Real-time monitoring of macrophage dynamics may be achieved through liquid biopsy approaches that leverage exosomal cargos or soluble cytokine profiles.

Equally critical is the transition from preclinical studies to rigorous, large-scale, multicenter clinical trials capable of establishing the safety, efficacy, and optimal timing of macrophage-targeted therapies. The integration of gene-editing techniques with nanotechnology offers strong potential for the precise delivery of macrophage-modulating agents. Furthermore, noninvasive imaging modalities, such as PET and MRI tracers of macrophage activation, may enable more accurate in vivo assessment of therapeutic efficacy. Within this framework, natural products and traditional medicine–derived compounds, owing to their multitarget mechanisms and favorable toxicity profiles, may serve as valuable adjuncts to modern immunotherapeutic strategies. Ultimately, personalized, organ-specific approaches to macrophage modulation hold the greatest promise for transforming the prevention and treatment of diabetic vascular complications.

Limitations

This review has several limitations. The literature discussed was limited to English publications, and recent studies may not yet fully reflect their academic impact. Moreover, most of the current evidence comes from preclinical research, and a lack of robust clinical data restricts the translational value of the conclusions. Future work should incorporate broader literature sources and well-designed clinical trials to enhance the reliability and applicability of the findings.

Abbreviations

AGEs	Advanced glycation end products
AP-2α	Activator protein 2α
AS	Atherosclerosis
BMDMs	Bone marrow-derived macrophages
BRB	Blood-retinal barrier
CREB	CAMP response element-binding protein
DAMPs	Damage-associated molecular patterns
DN	Diabetic nephropathy
DPN	Diabetic peripheral neuropathy
DR	Diabetic retinopathy
eNOS	Endothelial NO synthase
EVs	Extracellular vesicles
GLP-1R	Glucagon-like peptide-1 receptor
HG	High glucose
HIF-1α	Hypoxia-inducible factor-1α
ICAM-1	Intercellular adhesion molecule-1
IFN	Interferon
IL	Interleukin
iNOS	Inducible NO synthase
IRF	Interferon regulatory factor
JAK	Janus Kinase
LDL-C	Low-density lipoprotein cholesterol
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
MCT1	Macrophage monocarboxylate transporter 1
MerTK	Mer tyrosine kinase
miRNAs	MicroRNAs
MMPs	Metalloproteinases
MCs	Mesenchymal stem cells
NF-κB	Nuclear factor kappa-B
NPDR	Non-proliferative diabetic retinopathy
OIR	Oxygen-induced retinopathy
PAMPs	Pathogen-associated molecular patterns
PDR	Proliferative diabetic retinopathy
PDGF	Platelet-derived growth factor
PPAR-γ	Peroxisome proliferator-activated receptor-γ
RIR	Retinal ischemia–reperfusion
ROS	Reactive oxygen species
SMC	Smooth muscle cell

STAT	Signal Transducers and Activators of Transcription
STZ	Streptozotocin
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TGF-β	Transforming growth factor-β

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