Role of microglia/macrophage polarisation in intraocular diseases (Review)

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Abstract. Macrophages form a crucial component of the innate immune system, and their activation is indispensable for various aspects of immune and inflammatory processes, tissue repair, and maintenance of the balance of the body's state. Macrophages are found in all ocular tissues, spanning from the front surface, including the cornea, to the posterior pole, represented by the choroid/sclera. The neural retina is also populated by specialised resident macrophages called microglia. The plasticity of microglia/macrophages allows them to adopt different activation states in response to changes in the tissue microenvironment. When exposed to various factors, microglia/macrophages polarise into distinct phenotypes, each exhibiting unique characteristics and roles. Furthermore, extensive research has indicated a close association between microglia/macrophage polarisation and the development and reversal of various intraocular diseases. The present article provides a review of the recent findings on the association between microglia/macrophage polarisation and ocular pathological processes (including autoimmune uveitis, optic neuritis, sympathetic ophthalmia, retinitis pigmentosa, glaucoma, proliferative vitreoretinopathy, subretinal fibrosis, uveal melanoma, ischaemic optic neuropathy, retinopathy of prematurity and choroidal neovascularization). The paradoxical role of microglia/macrophage polarisation in retinopathy of prematurity is also discussed. Several studies have shown that microglia/macrophages are involved in the pathology of ocular diseases. However, it is required to further explore the relevant mechanisms and regulatory processes. The relationship between the functional diversity displayed by microglia/macrophage polarisation and intraocular diseases may provide a new direction for the treatment of intraocular diseases.

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Abbreviations: RPE, retinal pigment epithelium; HIF-1α, hypoxia-inducible factor-α; TNF-α, tumor necrosis factor-α; LPS, lipopolysaccharide; TLR, Toll-like receptor; PPARγ, peroxisome proliferator-activated receptor γ; NO, nitric oxide; iNOS, inducible NO synthase; VEGF, vascular endothelial growth factor; EAU, experimental autoimmune uveitis; MDSCs, myeloid-derived suppressor cells; ROS, reactive oxygen species; AhR, aryl hydrocarbon receptor; BMDMs, bone marrow-derived macrophages; MS, multiple sclerosis; RGCs, retinal ganglion cells; EAE, experimental autoimmune encephalomyelitis; CNS, central nervous system; FA, fatty acids; SO, sympathetic ophthalmia; RP, retinitis pigmentosa; PONT, partial optic nerve transection; LBP, *Lycium barbarum*; PACAP, pituitary adenylate cyclase-activating polypeptide; PVR, proliferative vitreoretinopathy; CNV, choroidal neovascularization; nAMD, neovascular age-related macular degeneration; ECM, extracellular matrix; Arg-1, Arginase-1; NAION, nonarteritic anterior ischemic optic neuropathy; rAION, rat AION; ROP, retinopathy of prematurity; HUVEC, human umbilical vein endothelial cell; CSF1/M-CSF, macrophage colony-stimulating factor 1; CSF2/(GM)-CSF, granulocyte-macrophage colony-stimulating factor 2

Key words: microglia/macrophage polarization, ocular disease, retinopathy of prematurity, choroidal neovascularization, autoimmune uveitis, proliferative vitreoretinopathy, subretinal fibrosis, diabetic retinopathy

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1. Introduction

Macrophages are vital components of the innate immune system and are ubiquitous throughout the body. First identified and elucidated by Metchnikoff in the 19th century, macrophages have been recognised for their pivotal roles in the phagocytosis and elimination of microorganisms (1). Their multifaceted functions encompass the maintenance of tissue equilibrium, orchestration and resolution of immune responses during pathogenic assaults and the facilitation of tissue repair and restructuring in both developmental and injury-induced contexts (2,3). Furthermore, macrophages exhibit diverse

cellular responses and adapt to distinct stimuli or sources within tissues or the environment. For instance, exposure to microbial stimulation triggers an M1 or inflammatory state in macrophages, which is characterised by increased production of pro-inflammatory cytokines and microbe eradication. Conversely, during helminthic or parasitic infections, macrophages transition to an M2 or alternative state, specialising in tissue regeneration and remodelling (4).

The eye is a remarkably specialised sensory organ that encompasses several intricately interconnected tissue types, each of which is pivotal for the formation of clear visual images by the neural retina. Among the intraocular tissues, the pigmented iris, ciliary body and choroid collectively form the uvea. Similar to the brain, the retina represents neural tissue sheltered by the blood-eye barrier, comprising a complex network of interconnected neurons. Positioned adjacent to the neural retina, the choroid, a highly vascularised connective tissue, serves a crucial role in providing metabolic and nutritional support to the outer retina. In the unique microenvironment of intraocular tissue, there are different populations of resident tissue macrophages that are adept at maintaining tissue homeostasis and coordinating inflammatory responses when encountering abnormal stimuli.

The neural retina contains specialised resident macrophages known as microglia (5). Originating early in embryogenesis from precursor cells in the embryonic yolk sac, microglia migrate to specific regions within the central nervous system (CNS) at approximately embryonic day 8.5 (6,7). Their developmental pathways overlap with those of tissue macrophages. In cases of radiation-induced complete microglial apoptosis, bone marrow-derived macrophages (BMDMs) can supplement and express a phenotype similar to that of microglia. However, these cells constitute a distinct population capable of self-renewal and are not typically substituted for BMDMs (8). In the retina, microglia are primarily found in three specific locations: The nerve fibre, inner and outer plexiform layers (5).

Macrophages are crucial components of the innate immune system and exhibit various functions. They serve as a primary defence against microorganisms and orchestrate adaptive immune responses. Apart from generating essential pro-inflammatory cytokines and chemokines, macrophages also have pivotal roles in phagocytosis, clearing apoptotic cells and tissue debris (9). In addition, macrophages engage in immune regulation by expressing anti-inflammatory cytokines like interleukin (IL)-10, transforming growth factor (TGF-β) and lipid mediators, such as lipoxins. Macrophages are implicated in tissue remodelling and the development of various organs, such as the breast tissue, bones, kidneys and brain (10). Macrophage dysregulation may trigger autoimmune conditions and persistent inflammatory diseases (11).

In the CNS, microglia constitute 5-12% of total brain cells and share functional similarities with peripheral macrophages. Microglia actively contribute to synaptic plasticity and debris clearance in the healthy brain (12,13). Studies revealed that even in a relatively quiescent state, microglia have pivotal roles in tissue repair and infection control (14). Following injury or infection, microglia in the CNS promptly respond to stimuli by releasing cytokines that induce phagocytosis and direct cytotoxicity (15). Peripheral macrophages can replenish the microglia. Although microglia and macrophages share several functions, such as antigen presentation and production of cytokines, including oxidative free radicals, chemokines and nitric oxide (NO), they possess distinct characteristics. In the initial stages of CNS inflammatory responses, microglia demonstrate lower cytokine production levels (CD45, C-C chemokine receptor type (CCR)1 and CCR5) alongside higher TGF-β expression. Conversely, infiltrating macrophages exhibit elevated expression of CD45, CCR1, CCR2 and CCR5, accompanied by reduced TGF-β expression (6,16). These differences in biomarker profiles aid in distinguishing the CNS-resident microglia from the infiltrating macrophages (17). Nonetheless, both resident microglia and infiltrating macrophages have analogous roles in the CNS during inflammatory responses.

Macrophages demonstrate responsiveness to endogenous signals after infection or injury, assuming both pathogenic and protective roles (2,18,19). Upon appropriate stimulation, M1 macrophages serve as the frontline defence of the innate immune system during the early stages of a disease. Microglia share phenotypic traits with peripheral macrophages and detect detrimental stimuli through various immune receptors, including Toll-like receptors (TLRs), nucleotide-binding oligomerisation domains (NODs) and NOD-like receptors (20,21). Microglia exhibit different activation states within injured tissues (22,23). Upon injury, microglia or macrophages infiltrating from the circulation polarise toward a pro-inflammatory (M1) phenotype upon exposure to pro-inflammatory cytokines such as interferon-γ (IFN-γ) and tumour necrosis factor (TNF)-α.

Typically, M1 classically activated macrophages express TNF-α, IL-1α, IL-1β, IL-6, IL-12, IL-23, C-X-C motif chemokine ligand (CXCL)9, CXCL10 and other cytokines and chemokines. They are distinguished by their high secretion ratio of IL-12 and IL-23 but produce relatively less IL-10. Furthermore, M1 macrophages engage in the type I T-helper cell (Th1) immune response as both inducer and effector cells, apart from their roles in defence against parasites and tumours (24-26). Similar to infiltrating macrophages, microglia respond by producing M1-associated factors, including pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, IL-12, IL-23 and TNF-α), chemokines, redox molecules [e.g. NADPH oxidase and inducible NO synthase (iNOS)], macrophage receptors with collagen structure, costimulatory proteins (CD40) and major histocompatibility complex class II (18,21,27-30).

M2 macrophages have multifaceted roles in allergic responses, parasite clearance, inflammation suppression, tissue remodelling, angiogenesis, immune regulation and tumour promotion (31). Within this subset, M2 macrophages consist of four distinct subpopulations: i) M2a, predominantly induced by IL-4 and IL-13; ii) M2b, primarily triggered by immune complexes, IL-1β and TLR ligands; iii) M2c macrophages, produced in response to IL-10, glucocorticoids and TGF-β (25,32-36); and iv) M2d, primarily induced by TLR antagonists (33). The polarisation of microglia toward the M2 phenotype mirrors that of peripheral macrophages (37-40), leading to distinctive mRNA profiles following stimulation with IL-4 and IL-10, including the expression of arginase 1 (Arg-1), chitinase-like protein 3, Fizz1 and peroxisome proliferator-activated receptor (PPAR) (41). Although these connections have been demonstrated *in vitro*, the induction

Table I. Phenotypes, inducible factors, surface markers and functions of macrophage polarization.

Cell type	Inducible factor	Surface marker	Phenotype	Function	(Refs.)
M1	IFN-γ, TNF-α, (GM)-CSF, LPS	TLR-2, TLR-4, CD80, CD86, iNOS, MHC-II	TNF-α, IL-1α, IL-1β, IL-6, IL-12, IL-23, CXCL1-3, CXCL8-10, CCL2-5, CCL11	Th1 immune reaction, proinflammation, anti-tumor	(24-26)
M2					
M2a	IL-4, IL-13	CD206, MHC-II, IL-1R, Arg-1, Ym1/2, FIZZ1	TGF-β, Arg-1, IL-10, CCL17, CCL22, CCL18	Cell growth, anti-inflammation, tissue repair, Th2 immune response, anaphylaxis, fibrosis	(25,35,36)
M2b	Immune complex, TLR, IL-1β	CD206, MHC-II, CD86, IL-10R, IL-12R, IL-6R	TNF-α, IL-1β, IL-10, IL-6, IL-12	Regulation of immune responses, inflammatory reactions	(32,35,36)
M2c	IL-10, glucocorticoids, TGF-β	CD206, CD163, TLR-1, TLR-8, Arg-1	IL-10, TGF-β, Arg-1, CXCL13, CCL16, CCL18	Phagocytosis, immuno-suppression, tissue remodeling	(34-36)
M2d	TLR antagonists	CD206, IL-10R, IL-12R	VEGF, TNF-α, IL-10, IL-12	Promotion of angiogenesis and tumor progression	(33,35,36)

LPS, lipopolysaccharide, TLR, Toll-like receptor; (GM)-CSF, granulocyte-macrophage colony-stimulating factor; MHC, major histocompatibility complex; iNOS, inducible nitric oxide synthase; CCL-2, C-C motif chemokine ligand 2; CXCL13, C-X-C motif chemokine ligand 13; Th1, type 1 T-helper cell; Arg-1, Arginase-1.

of M2 occurs *in vivo* in sterile wounds, even in the absence of IL-4 or IL-13 (42). In this model, M2 macrophages were observed to originate from M1 macrophages transitioning into repair-oriented macrophages within the tissue after recruitment from circulation (43). As a result, the intrinsic phenotype of these cells may diverge based on their origin and local microenvironment.

By contrast, although M2 macrophages are divided into different subpopulations, they share a common phenotype characterised by low production of IL-12 and IL-23 but a high release of IL-10. M2a macrophages express IL-10, TGF-β, C-C motif chemokine ligand (CCL1)7, CCL22 and other cytokines. In general, M2 macrophages are unique in that they release a low proportion of pro-inflammatory cytokines, such as IL-1, TNF-α and IL-6. However, M2b subpopulations are distinctive for high expression of IL-10 and CD86 but low production of IL-12 and Arg-1. Like M1 macrophages, they are proficient producers of IL-1, TNF-α and IL-6 (35,36). Furthermore, M2b macrophages express high levels of reactive nitrogen intermediates and iNOS (35,36).

M2c macrophages, also known as inactivated macrophages, secrete IL-10, TGF-β, CCL16 and CCL18, having a key role in the phagocytosis of apoptotic cells (34). In addition, M2d macrophages induce IL-10 and vascular endothelial growth factor (VEGF) production, thereby promoting angiogenesis and pathological tumour processes (33). The phenotypes, inducer factors, surface markers and functions of macrophage polarisation are shown in Table I, and a schematic diagram of the M1 and M2 macrophage subsets is shown in Fig. 1.

2. Intraocular inflammation-related diseases

Macrophages have pivotal roles in maintaining tissue homeostasis and regulating inflammation (44,45). M1 macrophages undergo polarisation triggered by lipopolysaccharide (LPS) alone or in conjunction with Th1 cytokines such as IFN-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF). Consequently, M1 macrophages secrete pro-inflammatory cytokines, including IL-1β, IL-6, IL-12, IL-23 and TNF-α, through the activation of various transcription factors, such as signal transducer and activator of transcription (STAT)1, nuclear factor κB (NF-κB) and IFN regulatory factor 5. Thus, M1 macrophages are characterised by a pro-inflammatory phenotype (46). Conversely, M2 macrophages receive polarisation signals primarily from Th2 cytokines, such as IL-4 and IL-13, and exhibit anti-inflammatory and immunomodulatory phenotypes (47). M2 macrophages produce anti-inflammatory cytokines, including IL-10 and TGF-β, by activating multiple transcription factors such as STAT3, STAT6, IFN regulatory factor 4 and PPAR-γ (48). The association between macrophage polarisation and inflammatory cytokine levels is illustrated in Fig. 2

Autoimmune uveitis. The experimental autoimmune uveitis (EAU) model is a noninfectious uveitis animal model that closely resembles human uveitis in both clinical and histological features (49-51). EAU in mice is induced through the subcutaneous injection of an emulsified antigen, which disrupts immune tolerance within the body. Following immunisation, naïve T cells receive antigens delivered by presenting cells.

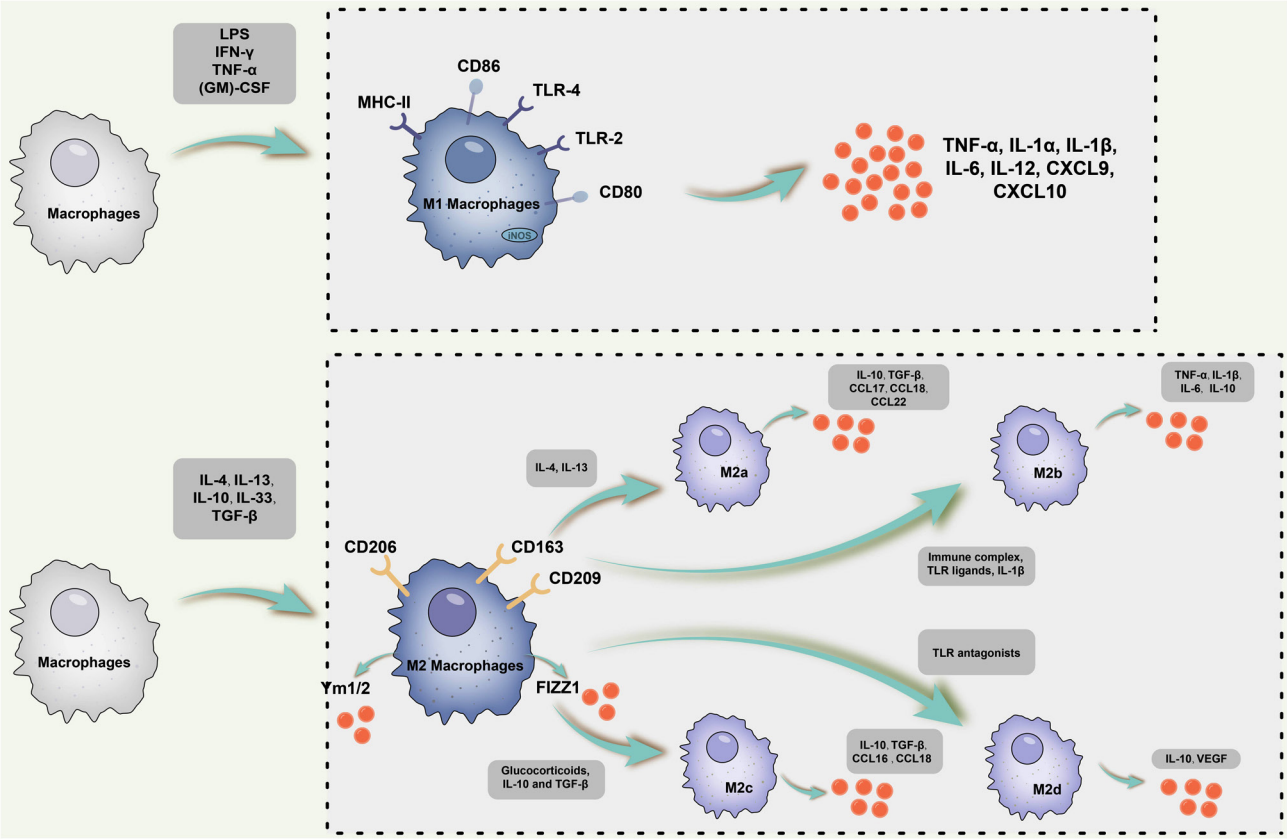

Figure 1. Schematic diagram of M1 and M2 macrophage subsets. Typically, M1-classically activated macrophages are polarized in response to IFN-γ, TNF-α and other cytokines, and express TNF-α, IL-1α, IL-1β, IL-6, IL-12, IL-23, CXCL9, CXCL10 and other cytokines and chemokines. M2 macrophages consist of four distinct subpopulations: i) M2a, induced primarily by IL-4 and IL-13; ii) M2b is mainly triggered by immune complexes, IL-1β and TLR ligands; iii) M2c macrophages, produced in response to IL-10, glucocorticoids and TGF-β; iv) M2d, induced primarily by TLR antagonists. Although M2 macrophages are divided into distinct subpopulations, they share a common phenotype characterized by low production of IL-12 and IL-23 but high release of IL-10. M2a macrophages express IL-10, TGF-β, CCL17 as well as CCL22 and other cytokines. However, the M2b subpopulation is unique in its high expression of IL-10 and CD86 but lower production of IL-12 and Arg-1. Like M1 macrophages, they are capable of producing IL-1, TNF-α and IL-6. In addition, M2b macrophages express high levels of RNI and iNOS. As for M2c macrophages, also known as inactivated macrophages, these cells secrete IL-10, TGF-β, CCL16 and CCL18 and have a key role in the phagocytosis of apoptotic cells. Furthermore, M2d macrophages induce IL-10 and VEGF production, thereby promoting angiogenesis and tumor pathological processes. CXCL9, C-X-C motif chemokine ligand 9; TLR, Toll-like receptor; iNOS, inducible nitric oxide synthase; RNI, reactive nitrogen intermediates; (GM)-CSF, granulocyte-macrophage colony-stimulating factor; MHC, major histocompatibility complex; LPS, lipopolysaccharide; Arg-1, Arginase-1.

Subsequently, these cells are converted into Th0 cells, and T-cell subpopulations such as Th1 and Th17 differentiated from these cells have important functions in numerous autoimmune diseases, including EAU (52,53). These T cells multiply in the peripheral system and translocate to the retina, where they release inflammatory factors and promote macrophage migration, causing tissue damage (50).

Diverse immune-cell infiltration is a hallmark of the EAU retina, involving macrophages, neutrophils, dendritic cells and other immune cells (54). Furthermore, the proportions of various immune cells were observed to vary across different phases of EAU. During the acute EAU phase, macrophages accounted for 40% of all retinal immune cells. However, in the late chronic stage, the percentage decreased to 19%. By contrast, the percentage of immune cells, such as CD8 T cells and myeloid-derived suppressor cells (MDSCs), increased during the transition from the acute to the chronic phase (54).

In addition, the phenotypes of immune constituents infiltrating different EAU stages undergo dynamic changes. For instance, in the acute phase, most macrophages exhibit the M1 phenotype, whereas in the chronic (angiogenic) phase, M2 macrophages are predominant (55). These results suggest that the retinal microenvironment under inflammatory conditions determines the subsets of infiltrating cells, in addition to controlling the phenotypes of different types of immune cell.

Studies have underscored the involvement of innate immune cells, particularly macrophages and microglia, in antigen presentation in EAU (56). Macrophages are recognised as crucial effector cells in EAU and contribute to the inflammatory process by releasing inflammatory cytokines (57). Retinal microglia exhibit phagocytic and pathogenic characteristics similar to those of macrophages. Upon activation, both macrophages and retinal microglia release pathogenic factors such as TNF-α and iNOS, resulting in the nitration of cytochrome c, which is known to cause EAU-cell apoptosis (58-60).

The aryl hydrocarbon receptor (AhR), a high-molecular-weight transcription factor, has been demonstrated to exert a negative regulatory effect on LPS-mediated inflammatory responses in macrophages (61). This suggests that AhR may be involved in the negative regulation of M1 polarisation. After EAU induction, AhR-/- mice had more severe

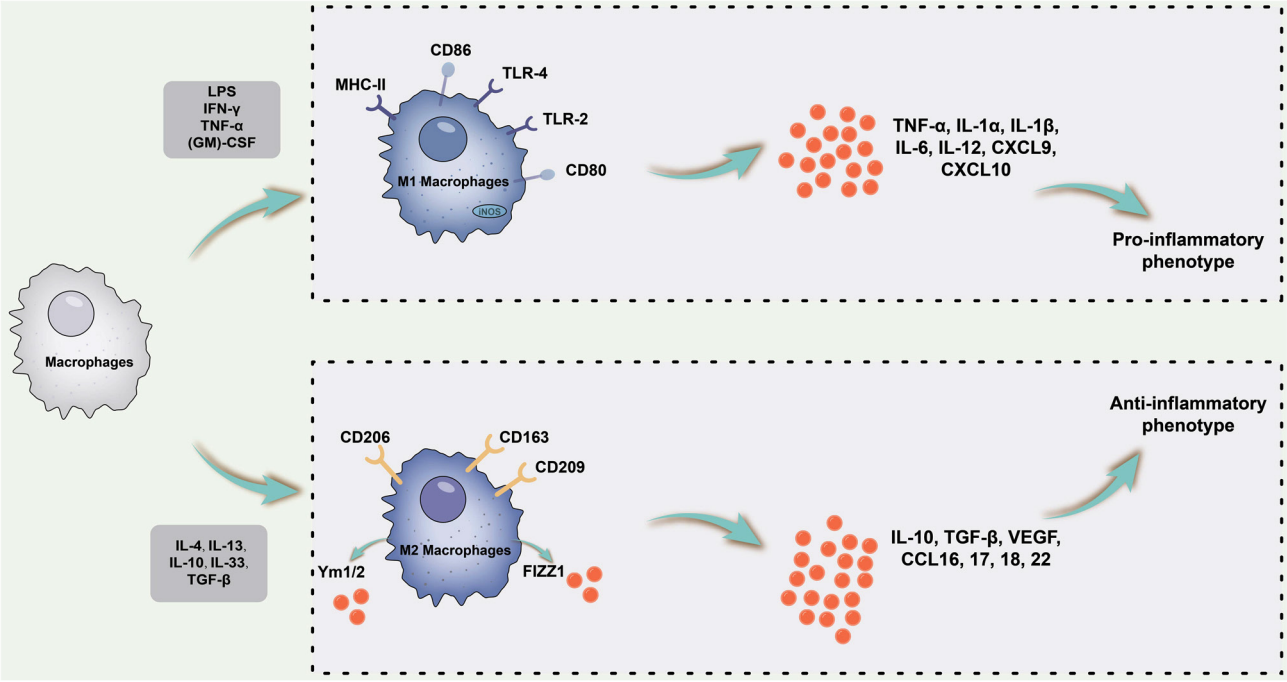

Figure 2. Schematic diagram of the association between macrophage polarization and inflammatory cytokines. M1 macrophage polarization is primarily triggered by LPS alone or in combination with Th1 cytokines, such as IFN-γ and GM-CSF. M1 macrophages are characterized by a pro-inflammatory phenotype and secrete pro-inflammatory cytokines, including IL-1β, IL-6, IL-12, IL-23 and TNF-α. By contrast, M2 macrophages primarily receive polarizing signals from Th2 cytokines, such as IL-4 and IL-13, exhibiting an anti-inflammatory and immunomodulatory phenotype. M2 macrophages produce anti-inflammatory cytokines including IL-10 and TGF-β. MHC, major histocompatibility complex; LPS, lipopolysaccharide; Th1, type 1 T-helper cell; CXCL9, C-X-C motif chemokine ligand 9; TLR, Toll-like receptor; (GM)-CSF, granulocyte-macrophage colony-stimulating factor; iNOS, inducible nitric oxide synthase.

clinical and histopathological manifestations of uveitis than AhR mice. Compared with AhR EAU mice, AhR+/+-/- EAU mice showed evidence of a significant increase in macrophages/microglia and a greater polarisation of phenotypes from M2 to M1 (62).

Furthermore, research has shown that the use of 2,3,7,8-tetrachlorodibenzo-p-dioxin (an AhR activator) can activate AhR through the NF-κB, STAT1 and STAT3 signalling pathways. This induces macrophage M2 polarisation, reducing the production of apoptotic cells and the release of pro-inflammatory factors. Consequently, the clinical manifestations of EAU are alleviated (62).

IL-33 is a member of the IL-1 cytokine family and signals through a heterodimeric receptor composed of suppression of tumorigenicity 2 (ST2) and IL-1R accessory protein (63). Studies have highlighted the crucial role of the IL-33/ST2 pathway in enhancing the polarisation of alternatively activated macrophages (M2) (64).

Following 21 days of EAU induction, ST2-deficient mice showed worse clinical symptoms than non-knockout mice, whereas treatment of wild-type (WT) mice with IL-33 significantly improved uveitis lesions. This improvement was accompanied by a significant increase in the proportion of CD206 and CD273 cells, suggesting that the upregulation of the IL-33/ST2 signalling pathway drives macrophage (M2) polarisation, thus attenuating the clinical manifestations of EAU (65).

Furthermore, glucocorticoids have been reported to mediate the P38-MAPK/myocyte enhancer factor-2c axis, thereby promoting the polarisation transition of macrophages from M2 to M1 and the release of anti-inflammatory factors. Consequently, this process inhibits EAU and fosters the healing of damaged eye tissue (66).

Suppressor of cytokine signalling (SOCS) proteins, particularly SOCS1 and SOCS3, regulate macrophage polarisation and cytokine expression. For instance, in BMDMs, SOCS3 acts as a negative regulator of GM-CSF-induced expression of CCL2, Arg-1 and matrix metallopeptidase 12 (67,68). $LysM^{Cre/+}SOCS3^{fl/fl}$ mice ($LysM^{Cre/+}SOCS3^{fl/fl}$ mice were obtained by crossing $SOCS3^{fl/fl}$ mice with LysM-Cre mice, a type of mouse with SOCS3 deficiency in myeloid cells) showed an increased proportion of GM-CSF in the intraretinal milieu, which may have triggered the release of CCL2 and Arg-1 from macrophages.

Research has demonstrated that mice deficient in SOCS3 ($LysM^{Cre/+}SOCS3^{fl/fl}$) experience enhanced retinal degeneration and accelerated retinal angiogenesis owing to inflammation (69). In the acute phase of EAU, $LysM^{Cre/+}SOCS3^{fl/fl}$ mice exhibited increased numbers of infiltrating neutrophils and decreased numbers of macrophages compared to WT mice. Real-time reverse transcription PCR analysis revealed a significant upregulation in the release of TNF-α, IL-1β, IFN-γ, GM-CSF and Arg-1 in the retina of $LysM^{Cre/+}SOCS3^{fl/fl}$ mice compared to that in WT mice. Furthermore, the percentage of Arg-1+ infiltrating cells was notably higher in $LysM^{Cre/+}SOCS3^{fl/fl}$ EAU retinas than in WT EAU retinas. In the absence of SOCS3, both macrophages and neutrophils expressed higher levels of Arg-1, CCL2, IL-6 and VEGF, promoting angiogenesis, suggesting that deletion of SOCS3 partially induced M2 polarisation. Both isoforms of

arginase have been implicated in vascular cell dysfunction and vessel wall remodelling in various diseases (70). Arg-1 is a characteristic marker of M2-type macrophages. To treat EAU, researchers utilised an Arg inhibitor, amino-2-borono-6-hexanoic acid, which effectively inhibits retinal angiogenesis without improving inflammation (69). This suggests that the development of retinal fibrovascular membranes in EAU is associated with the polarisation of macrophages to the M2 phenotype.

Optic neuritis. Optic neuritis, an acute inflammatory demyelinating disease of the optic nerve, is an initial symptom of multiple sclerosis (MS). It is characterised by optic nerve degeneration and loss of retinal ganglion cells (RGCs), resulting in permanent visual impairment; however, reliable treatments for this condition are currently lacking. The well-established experimental autoimmune encephalomyelitis (EAE) mouse model used for studying MS has also proven useful for investigating optic neuritis. The mouse model is characterised by the upregulation of molecules involved in inflammation, gliosis and macrophage infiltration (71). Accumulation of inflammatory factors leads to macrophage infiltration, which subsequently produces a large number of potentially harmful cytokines, further fuelling the inflammatory process (72).

EAE, triggered primarily by autoimmune Th1 and Th17 cells, is an inflammatory disease of the CNS (73). These cells produce various cytokines, including IFN-γ, TNF and GM-CSF, which participate in the M1 polarisation process of macrophages. Approximately 70% of the immune cells in the inner environment of the CNS in an inflammatory state are macrophages that are responsible for most neuronal tissue damage by releasing TNF, NO and other inflammatory factors (74-77). During EAE pathology, macrophages exhibit a dual-activated phenotype that expresses both M1 and M2 markers, such as CD86 and chitinase-like protein 3 (78). During EAE, both M1 (IFN-γ) and M2 (IL-4) cytokines are present in the inflamed CNS. Therefore, promoting the conversion of M1 subpopulation macrophages to the M2 subpopulation can promote the repair of MS-related damage and ameliorate functional impairment (6). Studies have demonstrated that fatty acids (FAs) have a positive impact on neuronal rescue by modulating macrophage phenotypes, reducing pro-inflammatory capacity and enhancing tissue recovery capacity (79).

Among M1-related factors, IL-12 and IL-23 are largely involved in the progression of EAE (80) by inducing macrophage recruitment through the upregulation of CXCL-10 and CXCL-11 release (81). Conversely, M2-related markers, such as CCL-2, promote the repair of neuronal axons in the EAE model (82), and CCL-22 upregulates the migration of anti-inflammatory immune cells during EAE progression (83). Furthermore, studies have demonstrated that treatment with ω-3 FAs reduces RGC damage by regulating the conversion of the M1 to the M2 subpopulation (84).

In the context of optic neuritis in an EAE model, suppressing M1 subpopulations and activating M2 subpopulations can effectively prevent retinal inflammatory processes (85). This intervention holds promise for hindering optic nerve damage and protecting RGCs from death.

Sympathetic ophthalmia (SO). SO is a type of uveitis characterised by granulomatous lesions that occur after ocular surgery or penetrating trauma (86). It appears to occur as a delayed-type hypersensitivity reaction to antigens in tissues exposed to traumatic events (87,88). The histopathology of SO is often characterised by choroidal capillary involvement, the presence of eosinophils, inflammation within the scleral canal, and substantial infiltration by B lymphocytes and macrophages (89,90).

To further investigate the role of macrophages in the inflammatory process of SO, researchers have performed immunohistochemical staining of choroid tissue obtained from patients clinically diagnosed with SO. Their analysis revealed a significant presence of infiltrating CD68 cells, along with the infiltration of TNF-α, INF-γ and other cytokines (91). These findings strongly suggest that macrophages are involved in the pathological processes underlying SO.

The presence of Dalen-Fuchs nodules suggests granulomatous inflammation in the middle of the retinal pigment epithelial (RPE) and Bruch's zones (88,89,92). Granulomas primarily consist of activated macrophages (93,94) and may arise within the retina. Studies have shown that M1 macrophage-specific cytokines, such as IL-23 and CCL19, account for a large proportion of granulation tissue in SO (93), suggesting that most inflammatory cells in SO Dalen-Fuchs nodules and granulation tissue are M1 macrophages.

Retinitis pigmentosa (RP). RP is a retinal degenerative disease accompanied by the apoptosis of photoreceptor cells, often leading to severe visual impairment. Degeneration of photoreceptors is initiated by microglial activation, infiltration of macrophages, and accumulation of immunoglobulins and complement factors, resulting in persistent inflammation, proliferation of macroglial cells and progressive apoptosis of retinal neurons (95,96). Consequently, it is crucial to explore avenues for RP intervention therapy that involve the regulation of microglial activation and suppression of the inflammatory response.

As RP advances, the blood-retinal barrier becomes disrupted, leading to the recruitment of macrophages into the retina. This recruitment has an important role in activating immune cells and triggering the release of pro-inflammatory factors, which further exacerbates disease progression and ultimately leads to the loss of the retinal photoreceptor layer (97). Blood-borne immune cells have a significant role in the microenvironment associated with RP and are considered key mediators of the development of neurodegenerative diseases (98,99).

Resident microglia and invading macrophages coordinate responses to CNS injury by restoring tissue loss and causing neuroinflammation (14,100). These immune cells have distinct phenotypes, such as M1 macrophages that foster inflammation and M2 macrophages that facilitate tissue repair and regeneration (101). Given the contrasting roles of these macrophage subsets, recent therapeutic approaches to nervous system inflammation are being tuned from immune cell suppression to achieving a balance through molecules that regulate the M1/M2 phenotypic polarisation switch (102).

Studies have demonstrated that olfactory ensheathing cell transplantation holds promise for regulating the polarisation of retinal macrophages from M1 to M2 in Royal College of

Surgeons rats via the JAK2/STAT3 pathway. This approach reduces the infiltration of activated M1 macrophages and fosters a less inflammatory microenvironment (103). Significant improvements in both the functional and structural aspects of vision can be achieved through this intervention. Similarly, essential FA supplementation improves retinal dysfunction and degeneration by reducing inflammation and microglial activation, weakening M1 markers, and inducing the transformation of rd10 mice (a model of autosomal recessive RP) retinas and LPS-stimulated BV10 cells to the M2 phenotype (104).

Glaucoma. Glaucoma is a neurodegenerative disease characterised by optic nerve atrophy and irreversible loss of RGCs (105). Secondary degeneration of RGCs has a critical role in the progression of glaucomatous damage (106), as RGC apoptosis may continue even after intraocular pressure is reduced. Hence, delaying secondary RGC degeneration holds promise as a potential therapeutic approach for glaucoma treatment.

Damage to RGCs can be categorised as primary (resulting from direct injury to the axon or cell body, such as axonal extrusion or transection) or secondary (resulting from the release of toxic effectors from adjacent dying cells) (107-110). To investigate the secondary degeneration of RGCs, researchers have developed the partial optic nerve transection (PONT) model. In comparison with the complete optic nerve transection and optic nerve crush models, which damage all axons simultaneously, the PONT model offers an advantage, as it only damages a portion of the inner axons of the optic nerve, leaving others intact. This enables the separation of the primary from the secondary injury (111).

In glaucoma, the mechanisms leading to the death of RGCs are multifaceted and encompass the activation of microglia/macrophages, autophagy, disturbances in calcium regulation, apoptosis, oxidative stress, expression of pro-apoptotic proteins and neurotrophic deprivation (112). Microglia and macrophages have essential roles in inflammation, tissue restoration and homeostasis regulation following inflammation or CNS injury (113). Various subsets of macrophages contribute to the pro-inflammatory, anti-inflammatory, cell growth and tissue repair processes. Therefore, manipulating the activation state of microglia/macrophage subsets to foster favourable cytoprotection in response to injury may be a promising approach for glaucoma treatment.

The study revealed a significant increase in the release of CD68, iNOS and Arg-1 one week after PONT modelling, indicating an increase in M1 microglia/macrophages, which may contribute to RGC death. However, researchers found that polysaccharides extracted from *Lycium barbarum* could delay RGC degeneration by four weeks after PONT. This delay was accompanied by an increase in the number of activated microglia/macrophages and a higher count of M2-type microglia/macrophages. This suggests that *L. barbarum* regulates microglia/macrophage phagocytic activity and induces M2 polarisation, ultimately leading to delayed RGC damage (111).

Furthermore, in a glaucoma ganglion cell injury model (N-methyl-D-aspartic acid-induced retinal injury model), studies demonstrated that pituitary adenylate cyclase-activating polypeptide (PACAP) increased the proportion of M2 subpopulations. In addition, PACAP promoted the release of factors such as TGF-β1 and IL-10 mRNA (112), both of which are markers of the M2 subtype of microglia/macrophages. The M2 subtype is associated with an acquired inactive state and is linked to reduced tissue damage, enhanced phagocytosis, increased synthesis of trophic factors, and decreased secretion of pro-inflammatory cytokines (25). These findings suggest that PACAP regulates the activation of microglia/macrophages toward the M2 subtype, thereby offering retinal protection against damage.

Ischaemic optic neuropathy. Clinically, non-arteritic anterior ischaemic optic neuropathy (NAION) often presents as optic disc oedema accompanied by acute painless visual loss (114). NAION is thought to arise from ischaemic damage to the optic nerve, which triggers an inflammatory response and oedema (115,116).

The optic nerve head is highly sensitive to changes in blood flow and is easily affected by factors such as autoregulation, vasospasm and systemic vascular diseases (117). In the context of NAION, inflammation is thought to be partially responsible for optic nerve damage (115,118). In a rat model of anterior ischaemic optic neuropathy (rAION), extracellular macrophages in the hypoxic region were recruited early and activated the resident microglia (119). Macrophages improve neuronal survival by secreting relevant factors and effectively phagocytosing myelin components to promote axonal regeneration (120). Furthermore, activated M2 microglia/macrophages have been linked to neuroprotection (121). However, it is important to acknowledge that in CNS diseases, activated microglia/macrophages may also release harmful factors, including pro-inflammatory cytokines and free radicals, which can cause damage to the nervous system (72). The proportion and subpopulation type of M2 microglia/macrophages in different pathological states may have distinct effects on the survival of RGCs and/or axon repair.

Research findings indicate that early treatment of the rAION model with G-CSF stabilises optic nerve vascular permeability, reduces macrophage recruitment near the optic nerve and induces M2 microglia/macrophage polarisation within the optic nerve (122). This treatment approach subsequently leads to a decreased expression of pro-inflammatory factors, prevents apoptosis induced by such factors and exerts neuroprotective effects in the rAION model.

Another study demonstrated that the binding complex of icariin and CCAAT enhancer-binding protein β significantly induces endogenous G-CSF expression by promoting alternative phosphorylation of IκB kinase-β, inhibitor of NF-κB (123). The elevated G-CSF expression then triggers noncanonical NF-κB activation, which further activates the PI3K/serine/threonine protein kinase B-a (AKT1) signalling pathway and promotes M2 microglia/macrophage polarisation, thereby preventing neuroinflammation and RGC apoptosis after optic nerve infarction in a rAION. In addition, ω-3 polyunsaturated FAs have also been found to possess neuroprotective effects in rAION by promoting the transformation of M1 macrophages into M2 macrophages. This transformation subsequently reduces the release of pro-inflammatory factors, such as TNF-a, iNOS and IL-1β, exerting anti-inflammatory

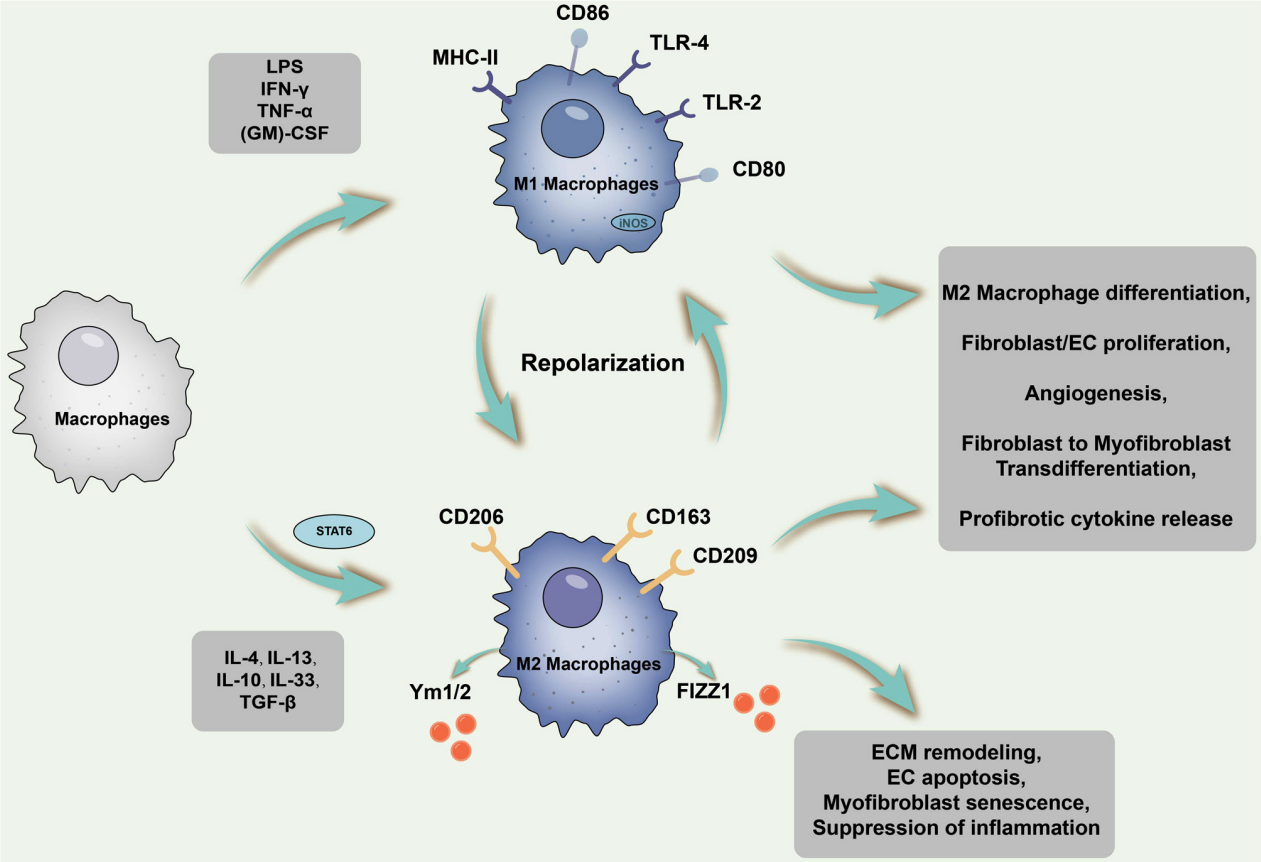

Figure 3. Schematic diagram of the processes related to macrophage polarization and fibrosis. During tissue remodeling and profibrotic phases, M2 macrophages emerge through differentiation of recruited infiltrating monocytes or polarization of infiltrating M1 macrophages. STAT6 is activated during this period to promote IL-4/IL-13-mediated M2 macrophage differentiation by upregulating the expression of Arg-1 and various other pro-fibrotic phenotype genes. M2 macrophages exhibit an anti-inflammatory phenotype and stimulate fibroblasts to enhance ECM production, among other effects. ECM, extracellular matrix; MHC, major histocompatibility complex; LPS, lipopolysaccharide; TLR, Toll-like receptor; (GM)-CSF, granulocyte-macrophage colony-stimulating factor; iNOS, inducible nitric oxide synthase; STAT6, signal transducer and activator of transcription 6; Arg-1, Arginase-1; EC, endothelial cell.

effects that mitigate cytokine-induced optic nerve damage and help maintain RGC survival after infarction (84).

Furthermore, puerarin treatment has been found to stimulate the PI3K-AKT signalling pathway and sustain AKT1 activation, resulting in microglia/macrophages releasing CCAAT enhancer-binding protein β and hallmark M2 markers, such as Arg-1 and IL-10 (124,125). Polarisation of M1 microglia/macrophages into M2 microglia/macrophages reduces the proportion of TNF-α and IL-1β after optic nerve infarction, effectively preventing subsequent cytokine-induced optic nerve injury.

3. Intraocular fibrosis-related diseases

Intraocular fibrosis-related diseases exhibit molecular mechanisms similar to fibrosis in organs, including the lungs, liver, kidneys, heart and skin (126). Following tissue injury, epithelial cells have a pivotal role in the recruitment and activation of inflammatory cells, endothelial cells and fibroblasts. Furthermore, epithelial cells undergo epithelial-mesenchymal transition (EMT), facilitating their transdifferentiation into myofibroblasts (127,128). These myofibroblasts are responsible for extracellular matrix (ECM) production, proliferation and migration across the basal layer, facilitating the coverage and regeneration of damaged tissue.

During this stage, M2 macrophages emerge either through the differentiation of recruited infiltrating monocytes or through the polarisation of infiltrating M1 macrophages. STAT6 activation occurs during this period, fostering IL-4/IL-13-mediated M2 macrophage differentiation by upregulating the expression of Arg-1 and various other profibrotic phenotype genes. M2 macrophages exhibit an anti-inflammatory phenotype and stimulate fibroblasts to enhance ECM production (129). The processes related to macrophage polarisation and fibrosis are illustrated in Fig. 3.

Proliferative vitreoretinopathy (PVR). PVR is characterised by extensive proliferation and shrinkage of cell tissues at the posterior interface of the vitreous and inner surface of the retina (130). Shrinkage of these cell membranes can lead to traction retinal detachment or the reopening of previously treated retinal tears, resulting in severe visual impairment. Although the exact pathogenesis of PVR remains to be fully elucidated, the prevailing view is that it is a long-term injury repair process involving the activation of inflammatory cells, cytokine production, ocular cell proliferation and scarring (131).

A pivotal characteristic of PVR is the formation of myofibroblast membranes from transdifferentiated RPE cells and other cell types, including macrophages (132). Macrophages

are considered one of the most crucial inflammatory cell types (133). By comparing vitreous samples from patients with PVR and uncomplicated retinal detachment, researchers have noted a significant increase in the number of monocytes/macrophages in vitreous samples from patients with PVR. Monocytes/macrophages were found to peak in the first 30 days after symptom onset in PVR and gradually decline over the subsequent three months (134). The abundance of macrophages in the intraocular microenvironment in the early stages of PVR and their sustained presence during progression underscore their vital role in the pathological process of PVR.

Macrophages have an irreplaceable role in the development of PVR through their ability to phagocytose damaged cells and tissues and release various growth factors and cytokines that mediate fibroblast chemotaxis and proliferation (135). Among the macrophage subsets, M2 macrophages, identified by the expression of Arg-1 and CD206, are particularly important in tissue repair and fibrogenesis (136).

In studies conducted in a rabbit model of PVR (137), researchers observed a swift onset of intense inflammation within the initial two weeks following PVR induction, with inflammation continuing to escalate until the 4-week mark post-induction. After the inflammatory phase, RPE cells undergo EMT, transitioning into fibroblast-like cells, which then give rise to contractile membranes. Throughout this process, the levels of growth factors, such as IFN-γ, VEGF, platelet-derived growth factor BB, placental growth factor and angiopoietin-2, surge, potentially fostering the survival, proliferation and EMT of RPE cells. The formation of contractile membranes and the secretion of growth factors are closely linked to M2 macrophages (133,138). Studies based on vitreous samples from human patients have indicated that M2 macrophage-derived microparticles can stimulate the proliferation and migration of RPE cells by activating the PI3K/AKT/mTOR signalling pathway (139), thereby contributing to the pathogenesis of vitreoretinal diseases.

Furthermore, studies based on vitreous samples from human patients suggested that M2 macrophages may contribute to the development of fibrovascular membranes in diabetic proliferative retinopathy (140). In a mouse model of PVR, CD206-positive M2 macrophages were found near the surface of the fibrous proliferation membrane, and the γ-secretase inhibitor DAPT was shown to inhibit RPE cell-induced PVR formation (decreased α-smooth muscle actin expression) and inhibit the infiltration of M2 macrophages by specifically targeting the Notch signalling pathway, thereby ameliorating PVR (141). These findings underscore the critical involvement of M2 macrophages in the pathogenesis of PVR and present a potential therapeutic target for intervention.

Subretinal fibrosis. Choroidal neovascularisation (CNV) is the primary cause of vision loss in neovascular age-related macular degeneration (nAMD), with CNV possibly progressing to end-stage fibrous plaques and disc scarring (142). In nAMD, the accumulation of drusen may lead to reduced oxygen diffusion in the choriocapillary plexus, eventually culminating in CNV. The subsequent growth of new abnormal blood vessels in the subretinal space often results in haemorrhage, triggering a wound-healing response that eventually leads to subretinal fibrosis (126).

Fibrosis is a healing process that occurs in response to tissue injury (128). During the healing phase, angiogenesis is triggered to facilitate tissue repair, enhance oxygen supply and facilitate the migration of inflammatory cells to the lesion area (143). In nAMD, CNV develops in the subretinal and/or subpigmented epithelial spaces, causing haemorrhages and leaks that ultimately lead to subretinal fibrosis. This process involves the recruitment and/or migration of various cell types. These cells interact with inflammatory factors, causing significant remodelling of the ECM (144).

Histopathological examination of human eyes revealed significant recruitment of macrophages during CNV, where they have a role in the development of pathological neovascularisation, drusen formation and fibroblast scaffolds (145). Direct anatomical and functional evidence suggests that circulating macrophages rather than resident macrophages are responsible for laser-induced CNV. To construct subretinal fibrosis models, researchers commonly use a laser-induced acute wound-healing model of CNV (146,147). In this experimental setup, macrophages were found to promote the formation of fibroblast scaffolds during the early wound-healing response of laser-affected CNV lesions, with most macrophages at the laser injury sites being activated M2 macrophages (147). CNV membranes infiltrated by M2 macrophages were more susceptible to fibrosis than those with M1 macrophage infiltration (148).

Studies based on the laser-induced subretinal fibrosis model have demonstrated that inhibiting macrophage transition to the M2 subpopulation via the PI3K/Akt axis contributes to the improvement of fibrotic lesions in subretinal fibrosis (146). In addition, the application of triptolide has shown promise in reducing subretinal fibrosis by inhibiting the polarisation of M2 subpopulations and suppressing the activation of the TGF-β1/Smad axis, thereby downregulating TGF-β1-induced EMT/endothelial-MT (149).

4. Intraocular malignancy

Macrophage phagocytic activity has a crucial role in clearing dead and dying cells. However, tumours can regulate macrophage function, thwart macrophage-triggered inflammation and kill tumour cells. This metabolic reprogramming drives the transformation of macrophages into either the M1 or M2 subpopulations, which are influenced by various cytokine stimuli. Although tumour-associated macrophages do not strictly conform to the M1 and M2 subpopulations, they often have similarities to M2 and actively promote tumour growth by upregulating immunosuppression (150).

Research indicates that, in the tumour microenvironment, M1-polarised macrophages primarily depend on glucose flux and the conversion of glucose to lactate, along with the production of reactive oxygen species and NO to combat tumours. Conversely, M2-polarised macrophages predominantly rely on FA β-oxidation and the tricarboxylic acid cycle while stimulating the production of polyamines and L-proline to facilitate tumour growth (150). Macrophage polarisation and tumour-related processes are shown in Fig. 4.

Uveal melanoma. Uveal melanoma is the most prevalent primary intraocular malignancy in adults, with an incidence of ~6-7 new cases per million individuals (151). The current

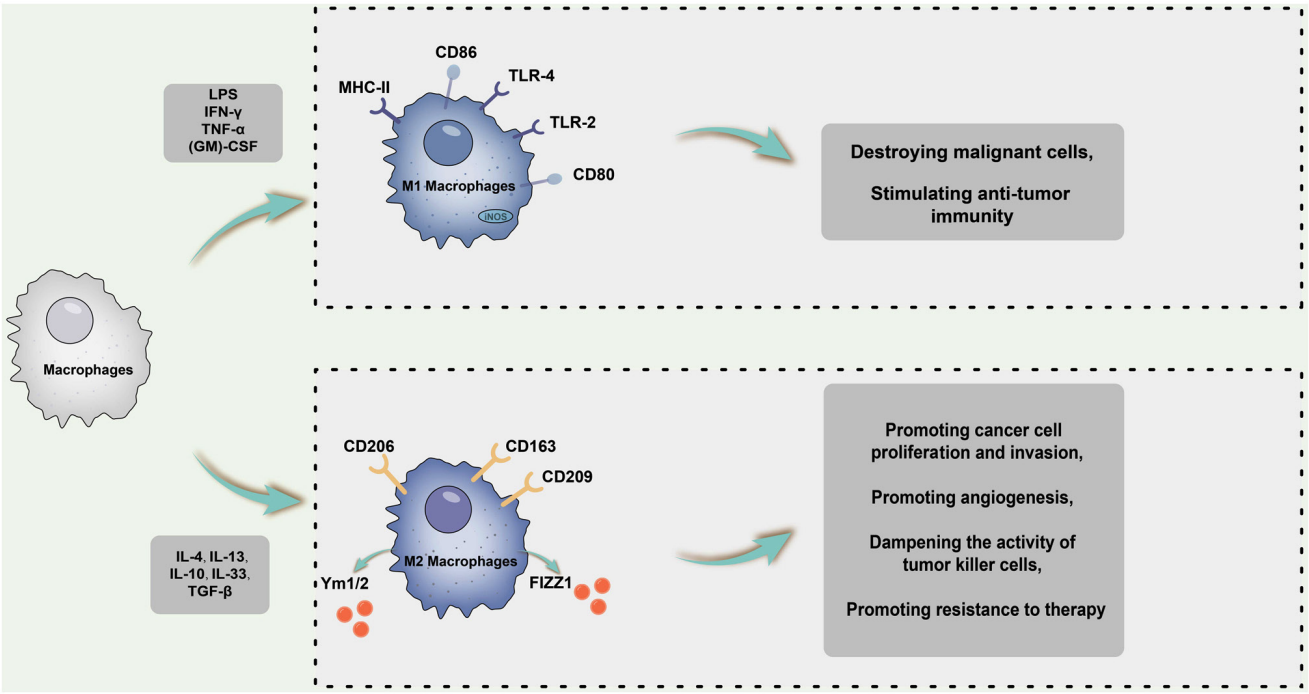

Figure 4. Schematic diagram of macrophage polarization and tumor-related processes. In the tumor microenvironment, M1-polarized macrophages fight tumors primarily by killing tumor cells and stimulating anti-tumor inflammation. By contrast, M2-polarized macrophages promote tumor growth mainly by promoting tumor cell proliferation and invasion and promoting angiogenesis. Although tumor-associated macrophages do not strictly fit into the M1 and M2 subpopulations, they often resemble M2 and actively promote tumor growth by upregulating immunosuppression. LPS, lipopolysaccharide; TLR, Toll-like receptor; (GM)-CSF, granulocyte-macrophage colony-stimulating factor; iNOS, inducible nitric oxide synthase.

treatment modalities include enucleation and radiation therapy. Although these treatments can curtail primary tumour growth, they remain ineffective in preventing tumour metastasis, leading to death within ~1-3 years (152).

Studies have provided compelling evidence for the pivotal role of macrophages in melanoma growth and survival. Melanoma-derived exosomes have also been identified as mediators of immunosuppression (153). These exosomes exert their effects by directly interacting with and suppressing various lymphocytes or by inducing MDSCs. In turn, MDSCs promote M2 subset transformation and recruit tumour-promoting regulatory T cells (154).

Researchers have postulated that lysing IFN-γ released by both tumour cells and immune cells in the microenvironment may be a contributing factor in transforming macrophages from a tumour-promoting M2 phenotype to an anti-tumour M1 phenotype, primarily through the IFN-γ/JAK-STAT1 pathway (155,156). In a mouse xenograft model, treatment with the oncolytic herpes simplex virus 1-enhanced green fluorescence protein through vitrectomy injection led to increased IFN-γ levels, an elevation in M1 macrophages and a reduction in M2 macrophages in peripheral blood, intraocular sites and distant tumours. *In vitro* experiments have further demonstrated a significant increase in IFN-γ at both the RNA and protein levels following oncolytic virus infection (157). Consequently, this treatment approach effectively reduced intraocular and subcutaneous tumours throughout the body.

However, it has been observed that melanoma exosomes can induce both M1 and M2 representative factors, namely TNF-α and IL-10, respectively (154). Furthermore, macrophage function assays have revealed an increasing trend from iNOS (M1) to Arg-1 (M2) activity, indicating that melanoma exosomes can induce a 'mixed' M1 and M2 tumour-promoting macrophage activation phenotype. Thus, in the pathological progression of uveal melanoma, M1 and M2 macrophage subpopulations seem to have flexible adaptability to tumour survival.

5. Intraocular neovascularisation-related diseases

Macrophages have a role in angiogenesis, albeit to a limited extent, by promoting the production of pro-angiogenic and growth factors, such as VEGF-A and fibroblast growth factor 2 (FGF2). Research indicates that M1 macrophages may facilitate vascular sprouting through the secretion of VEGF, IL-1β and TNF-α (158). Conversely, investigations have demonstrated that M2 macrophages, rather than M1 macrophages, enhance angiogenesis *in vivo* with increased expression of VEGF, FGF2, insulin-like growth factor 1, CCL2 and placental growth factor (33,159). Furthermore, a study determined that M2-polarised macrophages exhibit greater angiogenic potential than other subpopulations (159). However, the precise mechanisms underlying macrophage-mediated angiogenesis and the cellular interactions between endothelial cells and macrophage subsets remain to be fully elucidated. Although the categorisation of macrophages into distinct subpopulations offers a simplified overview of their intricate functional activities in the body, the specific mechanisms involved have not been determined. Macrophage polarisation and angiogenesis-related cytokines are shown in Fig. 5.

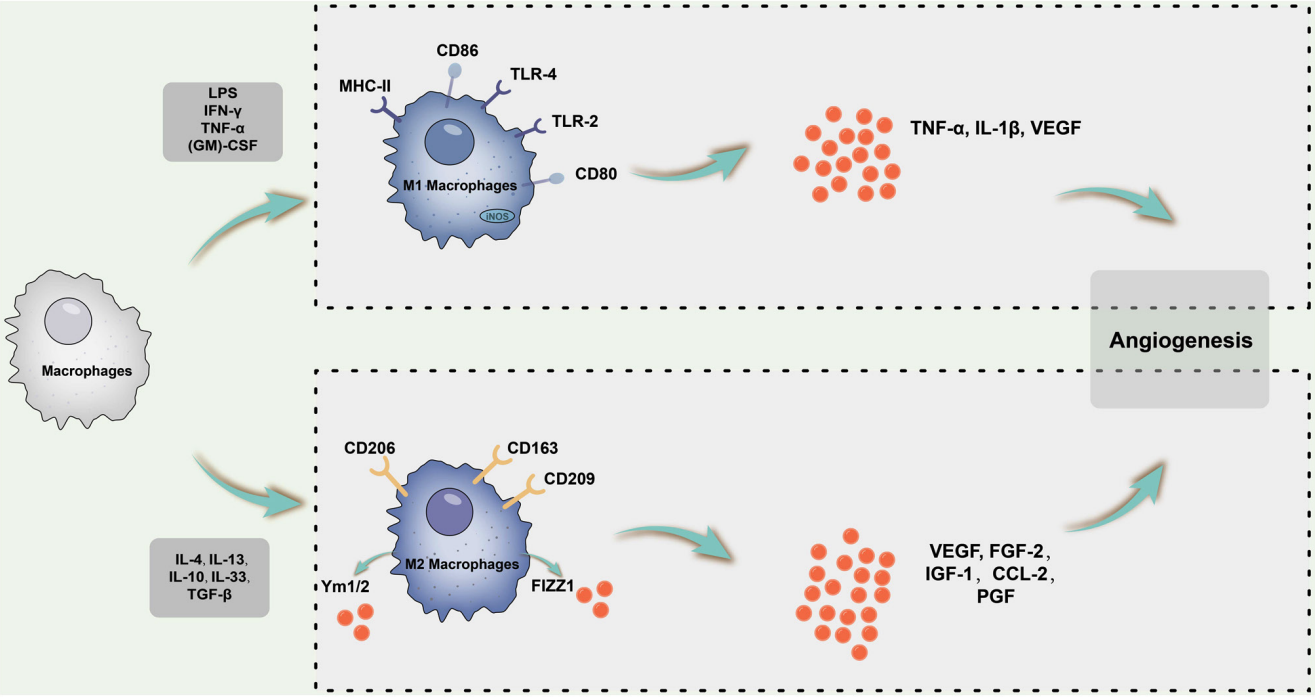

Figure 5. Schematic diagram of the macrophage polarization process and angiogenesis-related cytokines. M1 macrophages may promote vascular sprouting by secreting VEGF, IL-1β and TNF-α. By contrast, M2 macrophages enhance angiogenesis *in vivo* and enhance the expression of VEGF, FGF-2, IGF-1, CCL-2 and PGF. LPS, lipopolysaccharide; TLR, Toll-like receptor; (GM)-CSF, granulocyte-macrophage colony-stimulating factor; iNOS, inducible nitric oxide synthase; IGF, insulin-like growth factor; CCL2, C-C motif chemokine ligand 2; FGF, fibroblast growth factor; PGF, placental growth factor.

Diabetic retinopathy (DR). Diabetes is a metabolic disorder primarily characterised by hyperglycaemia stemming from abnormal insulin secretion and insulin resistance. Among patients with DR, microvascular complications are the most common manifestation. DR is categorised into non-proliferative DR (non-PDR) and PDR (PDR), with a distinction based on the presence of retinal neovascularisation (160). Non-PDR is typically characterised by asymptomatic microvascular changes, whereas PDR is involved in angiogenesis (161). DR is characterised by the abnormal growth and leakage of small blood vessels, leading to local oedema and associated tissue dysfunction. Dysregulation of vascular regeneration and inflammation are thought to be involved in the pathogenesis of DR (162,163).

Researchers have observed that upon high-glucose stimulation, microglia initially polarise toward the M2a phenotype, a response that initially mitigates tissue damage (164). However, as time progresses, there is an escalation in the production of M1 pro-inflammatory factors, accompanied by a decrease in the production of M2 anti-inflammatory factors, gradually shifting the macrophages toward the M2b phenotype. In advanced stages, microglia tend to exhibit an M1 phenotype with pronounced pro-inflammatory effects. In a rat model of streptozotocin-induced DR, there was an increase in M1 polarisation and a decrease in M2 polarisation, and microglia tended toward M1 polarisation with increasing glucose concentrations (165). The levels of iNOS (an M1 marker) and Arg-1 (an M2 marker) were higher in the retinas of db/db mice at five weeks of age. However, at eight weeks of age, iNOS levels continue to increase, whereas Arg-1 levels return to baseline (166).

It has been indicated that melatonin inhibits the excessive activation of microglia in the retina of diabetic rats by inhibiting the PI3K/AKT/Stat3/NF-κB signalling pathway, i.e., reducing the number of microglia cells and promoting their anti-inflammatory properties (167). It was speculated that this is related to melatonin promoting the transformation of microglia from pro-inflammatory (M1) to anti-inflammatory (M2) cells. Similarly, it was demonstrated that inhibiting M1 polarisation and promoting M2 polarisation of retinal microglia in DR rats through the TLR4/MyD88/NF-κB p65 pathway can effectively improve early DR (168).

Retinopathy of prematurity (ROP). ROP is characterised by impaired retinal blood vessel growth and development in preterm infants, which frequently leads to visual impairment and blindness (169). The pathological process of ROP is divided into two stages: An initial phase marked by delayed vascular growth after birth accompanied by vascular regression, followed by a second phase of hypoxia-induced pathological angiogenesis (170). An abnormal vascular state disrupts the inner retinal environment, thereby exacerbating the ischaemic state and leading to retinal leakage, scarring and eventually blindness. Although treatments such as laser and cryotherapy have improved ROP-related blindness, visual outcomes remain suboptimal for treated patients. Laser treatment has been successful in resolving most threshold ROP cases (171) and 100% of pre-threshold ROP cases (172). However, eyes treated with cryofixation or laser photocoagulation often manifest structural sequelae (171), underscoring the pressing need for preventive and less invasive therapeutic approaches.

Vascular abnormalities and inflammatory cell recruitment are primary contributors to the progression of abnormal retinal vascular diseases, including PDR and ROP (173). Studies have shown that macrophages have a role in promoting abnormal angiogenesis during pathological retinal vessel growth and

that M1 and M2 subpopulations of macrophages are present in the intraretinal environment of ROP (174).

Studies have demonstrated that microglia/macrophages are activated after P12 once oxygen-induced retinopathy (OIR) models are established. M1 microglia/macrophages were observed in neovascular tufts located in the retina, starting at P12 and reaching their peak at P17 upon returning to normoxic conditions. At this time-point, the NF-κB/STAT3 axis is triggered, which results in an increased proportion of M1 microglia/macrophages and an enhanced proportion of TNF-α and IL-6. Consequently, the neovascular clusters exhibit a progressive increase in volume from P12 to P17. However, a shift to M2-type microglia/macrophage activity occurs from P17 onwards during the advanced stages of OIR. The IL-4/STAT6/PPAR-γ axis is triggered from P17 and reaches its maximum at P20, promoting M2 microglia/macrophage transformation. This, in turn, results in a decrease in inflammatory factors and regression of neovascular clusters (175).

Furthermore, investigations have revealed that cytokines TNF-α and VEGF, released by the M1 subpopulation, promote abnormal angiogenesis through interactions with endothelial cells. By contrast, M2 macrophages promote vascular anastomosis. The involvement of Notch1 signalling has been reported, although the exact secretory factors remain to be elucidated (176). These findings underscore the coordinated engagement of M1 and M2 macrophage subsets in guiding retinal neovascularisation.

Promoting macrophage transition from the M1 to the M2 phenotype during the pathological process of OIR is thought to have anti-angiogenic benefits. To investigate this, Marchetti *et al* (177) used human umbilical cord blood to obtain enriched progeny CD14(+) cell populations, which were then injected into the eyes of OIR mice. The results demonstrated that only CD14(+) cells polarised into M2-type macrophages could promote the normalisation of retinal vasculature and control pathological neovascularisation. Consequently, areas of vascular occlusion and associated tissue hypoxia were reduced. A separate study found that in the OIR retina, activated microglia/macrophages were predominantly of the M1 type rather than the M2 type. Treatment with ferulic acid was shown to decrease the proportion of iNOS+ microglia/macrophages while increasing the release of Arg-1, suggesting its potential to transform microglia/macrophages from the M1 type (expressing iNOS, CD86, IL-6 and TNF-α) to the M2 type (expressing Arg-1, IL-10 and CD206), thus exerting a strong anti-angiogenic effect (178).

It has been demonstrated that blocking the activation of NF-κB signalling can effectively promote the transformation of M1 macrophages into the M2 phenotype in OIR mice and subsequently reduce the number of neovascular clusters (179). In addition, IL-17A neutralisation attenuates ocular neovascularisation by increasing the proportion of M2 macrophages and downregulating the release of VEGF from M1 macrophages (180).

To explore macrophage polarisation in an OIR mouse model, researchers assessed the retina and found a significant increase in both M1- and M2-like macrophages compared to normal controls. Both M1 and M2 macrophages exhibit a pro-angiogenic effect, promoting human umbilical vein endothelial cell (HUVEC) proliferation and contributing to retinal pathological neovascularisation (181). Similarly, Ma *et al* (174) investigated patients with advanced ROP and revealed a pro-angiogenic and pro-inflammatory microenvironment, with M1 macrophages predominant over M2.

In studies focusing on the role of pigment epithelium-derived factor, it was shown to inhibit macrophage polarisation in the retinas of an OIR mouse model through the regulation of adipose triglyceride lipase in the MAPK and Notch1 pathways. Specifically, pigment epithelium-derived factor suppressed the Notch1 and MAPK signalling pathways by inhibiting adipose triglyceride lipase, leading to a significant reduction in the release of iNOS and Arg-1, which are characteristic factors of M1 macrophages and M2 subpopulations, respectively. This ultimately resulted in a reduction in retinal neovascularisation (181).

Consequently, the role of macrophages in neovascularisation in OIR models remains a subject of debate, as both M1 and M2 macrophages may be involved. On the one hand, in the OIR model, retinal neovascularisation can manifest in two forms: Pathological neovascularisation, characterised by the emergence of abnormal blood vessels sprouting from the retinal surface into the vitreous, and physiological revascularisation, which involves the restoration of avascular regions with functional intraretinal vessels (182). Therefore, their proportions at different pathological stages may have contradictory effects. Ritter *et al* (183) found that a large number of migrating cells were localised in the retinal ischaemic area with a large loss of microglia, which may replace the function of microglia and promote vascular remodelling in the damaged area by releasing an appropriate amount of VEGF. Therefore, their location within the retina may also be one of the reasons for their contradictory roles in OIR models.

CNV. Wet AMD is a disease that causes vision loss due to the growth of CNV in the macula (184). Aberrant neovascularisation initially proliferates under the RPE band and then breaches the RPE band, causing intraocular haemorrhage and exudative serous retinal detachment, and later, discoid scarring (126). This localised loss of the retinal photoreceptor layer and RPE zone results in irreversible macular function loss and vision impairment.

CNV is considered involved in the submacular healing process (126,144). Angiogenesis has a crucial role in this process, and current clinical strategies predominantly focus on reducing the levels of VEGF, which is the primary factor that promotes angiogenesis (185,186). However, despite these efforts, only ~30% of patients with exudative AMD experience a three-line improvement in visual acuity, and ~15% of patients experience progressive deterioration, leading to legal blindness, even after receiving VEGF-inhibiting drugs (187-189). These results were expected, considering angiogenesis is an integral part of the complex healing phase. Hence, the search for alternative therapeutic approaches for CNV beyond anti-angiogenic treatments continues.

Multiple studies have explored AMD pathology and identified inflammation as a key driver of neovascular AMD progression (99,126,144,190,191). AMD is characterised by a chronic inflammatory response. Within this inflammatory milieu, macrophage recruitment and cytokine regulation are key mediators of CNV development (191).

Studies have indicated that macrophages are involved in abnormal angiogenesis in the pathology of CNV. M1 macrophages, characterised by specific markers such as iNOS, IL-6 and TNF-α, have been shown to inhibit angiogenesis (159). Conversely, M2 macrophages, identified using specific markers such as Arg-1, CD206 and CD163, promote pathological angiogenesis in CNV (192). Nakamura *et al* (193) revealed that increased IL-10 release in the eyes of aged mice activates associated signalling pathways, resulting in an increased proportion of M2 macrophages and the activation of vascular proliferative processes. Macrophage polarisation has emerged as a potential therapeutic target for CNV treatment.

In laser-impacted CNV, dynamic patterns of M1 macrophages and M2 subpopulations were observed, showing an early and immediate shift to M1, followed by a sustained shift to M2. M1 macrophages appear to be involved in the initial stages of CNV, whereas M2 macrophages have a critical role in the middle and late stages of CNV development and remodelling (194). For instance, during experimental CNV, upregulation of M1 signature factors (TNF-α and iNOS) was observed at day 3, suggesting inflammation at the onset of CNV lesions. By contrast, CD206 reached its maximum expression on day 7 of CNV formation, whereas CD86 and CD163 reached their maximum expression on day 14 of lesion formation. These marker genes represent different M2 macrophage subpopulations, suggesting that different macrophage subtypes have distinct roles at different time-points during the pathological process of CNV. Specifically, M2a macrophages may be associated with neovascularisation, whereas M2b and M2c macrophages may be involved in fibrous scarring (195).

CSF1, also known as macrophage CSF, has a crucial role in macrophage recruitment (196) and the transition to the M2 subpopulation (197). When the CSF1 receptor receives CSF1, the PI3K/AKT/forkhead box (FOX)O1 axis is activated, promoting M2 polarisation. Furthermore, under hypoxic conditions, HUVECs release more CSF1, thereby promoting macrophage migration and transition to the M2 subpopulation by upregulating the PI3K/AKT/FOXO1 axis. In a CSF1/CSF1 receptor (CSF1R)-associated manner, the M2 subpopulation upregulates the proliferation, recruitment and lumen formation of HUVECs. Inhibition of the CSF/CSFR axis has been shown to suppress M2 polarisation of macrophages and attenuate laser-induced CNV formation in mice (198).

In addition, studies have revealed that long non-coding RNA nuclear paraspeckle assembly transcript 1 (NEAT1) promotes the expression of M2 macrophage markers by targeting phosphatase and tensin homolog via microRNA (miR)-148a-3p. Downregulation of NEAT1 can effectively inhibit CNV by suppressing the transformation of M2 macrophage subsets (199).

Researchers have proposed that the Rho-associated protein kinase (ROCK) signalling pathway is a key pathway in regulating macrophage polarisation, and that the expression of ROCK pathway-related factors and pathway signal transduction processes affect the pathological process of CNV. They conducted experiments by differentiating mouse BMDMs into M1 or M2 phenotypes and injecting them into the eyeballs of laser-modelled WT mice. They observed that CNV lesions were not altered by native-morphological macrophages but that M2 subpopulation macrophages promoted lesion progression, which was reversed in ROCK2 inhibitor-treated animals. By contrast, the M1 subpopulation ameliorated the damage caused by the CNV. Further intravitreal injection of the M1 subpopulation in laser-modelled mice treated with a ROCK2 inhibitor did not ameliorate CNV-induced damage, confirming that ROCK2 inhibits CNV lesions *in vivo* by promoting the polarisation transition of macrophages to M1 (200). Ras homolog family member A (RhoA) expression and myosin phosphatase target subunit 1 and myosin light chain phosphorylation are also upregulated in CNV and decreased by melatonin administration (201). The RhoA/ROCK axis promotes the transition of macrophages to the M2 subpopulation and prevents conversion of the M1 subpopulation, thereby triggering CNV lesions. Melatonin converts M2 microglia/macrophages to the M1 subset by inhibiting the RhoA/ROCK axis, resulting in the downregulation of CNV lesions, reduced associated vascular leakage and inhibition of abnormal vascular status in laser-affected CNV lesions.

Other studies have shown that miR-505 is abnormally upregulated in laser-induced CNV lesions. Transmembrane protein 229 B (TMEM229B) was identified as a direct target of miR-505-5p, and administration of an miR-505 inhibitor significantly upregulated the expression of endogenous TMEM229B in CNV mice. This specific inhibition of M2 polarisation in mice with CNV led to reduced VEGF expression and suppressed CNV formation. *In vitro* experiments further demonstrated that exogenous TMEM229B significantly inhibited the expression of the M2-specific markers Ym-1 and Arg-1 (202).

In addition, the IL-4 mutant protein IL-4/Q116E was found to regulate the inflammatory response of laser-induced CNV through the Notch/delta-like canonical Notch ligand 4/monocyte to macrophage differentiation-associated signalling pathway, increasing the expression of CD68 and CD80 and reducing the expression of Arg-1 in RPE choroidal tissue. Induction of macrophage polarisation from M2 to M1 attenuated CNV development (203).

Furthermore, in the context of a laser-induced CNV model, injured RPE upregulated 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3)-driven glycolysis in macrophages, resulting in the induction of hypoxia-inducible factor (HIF)-1α/HIF-2α and NF-κB. This subsequently induced the expression of macrophage subset-associated signature factors and pro-angiogenic factors, ultimately promoting the transformation of the M1 subpopulation of macrophages into the M2 subpopulation and promoting CNV development. However, the PFKFB3 inhibitor AZ67 effectively downregulated the expression of HIF-1α/HIF-2α and NF-κB signalling and largely prevented laser-affected CNV lesions (204).

Furthermore, researchers have used small interfering RNAs (siRs) to suppress TIMP metallopeptidase inhibitor 3 (TIMP-3) expression in BMDMs and RPE/choroidal tissues in a laser-induced mouse model of CNV. They found that the release of M2 biomarkers CD206, CD163, Arg-1 and Ym-1 was correspondingly upregulated *in vitro* and *in vivo* in the siR-TIMP-3 group, indicating that a lack of TIMP-3 may promote M2 macrophage differentiation. Furthermore, intraocular injection of siR-TIMP-3 was shown to upregulate the progression of CNV lesions, as detected using optical coherence tomography angiography, suggesting that TIMP-3

inhibition is associated with the M2 macrophage subset and has a key role in CNV formation (205).

Finally, studies have shown a greater proportion of M2 macrophages compared with the M1 subpopulation during three and seven days of buffer treatment in a laser-induced mouse model (206). Triptolide significantly downregulated the accumulation of the M2 subpopulation at the lesion site over the 3 and 7-day periods. Triptolide also reduced the proportion of M2 macrophages during the same periods. In addition, triptolide decreased the release of VEGF, intercellular adhesion molecule 1 and TNF-α in local CNV injury, consistent with a reduction in the total number of aggregated macrophages and a lower ratio of the M2 subpopulation. Consequently, intraperitoneal injection of triptolide inhibited the transformation of the M2 subpopulation in CNV focal lesion areas, resulting in the downregulation of inflammatory and angiogenic factors, thereby inhibiting CNV progression and macrophage infiltration in CNV focal areas (207).

6. Conclusion

The present review provides an overview of key findings on the role of microglia/macrophage polarisation in intraocular diseases. It also provides ideas for further research on macrophage polarisation and the role of different subpopulations in intraocular diseases and a summary of the association between macrophage polarisation and different diseases. In intraocular tissues, there are not only BMDMs but also specialised resident macrophages called microglia, which provide the initial defence against microorganisms and participate in immune regulation. They have key roles in phagocytosis by clearing apoptotic cells and tissue debris. Dysfunction of macrophages/microglia may lead to autoimmune and persistent inflammatory diseases. An increasing number of studies have shown that macrophage or microglial polarisation has a key role in the pathological process of intraocular diseases and that regulating the polarisation process can effectively delay the progression of related diseases.

The present study provides the first review of the association between macrophage polarisation and intraocular disease. Although studies have been published on the relationship between macrophage polarisation and intraocular neovascular diseases, the publication time was relatively early and the literature included was not comprehensive. Simultaneously, there is a lack of an overview of the relationship between macrophage polarisation and intraocular fibrosis- and inflammation-related diseases. In addition, the present review covers, as much as possible, the typical literature on the association between intraocular disease and macrophage polarisation to provide a more comprehensive overview.

The present study also has certain limitations. On the one hand, certain studies have divided macrophages into different subgroups during the study to simplify their complex functional activities in the body, but not enough to elucidate the specific mechanisms involved. In addition, most studies simply divided macrophages into M1/M2 subgroups and did not further subdivide M2a, M2b or other subgroups in terms of research methods. Therefore, only we can an overview of the relevant mechanisms can be provided, rather than discussing them in depth. Although all attempts were made to unify the differences in research models in the process of literature inclusion, there may still be differences in methods among certain studies. Different models can only simulate the pathological process of diseases locally, which may lead to differences in the relevant research conclusions. In the present study, it was attempted to determine the association between macrophage polarisation and intraocular diseases. Therefore, the discussion section provided a simplified overview of the mechanism and did not discuss its relevance to other cell types (neutrophils, T cells, fibroblasts, etc.) in depth. Furthermore, because there are few clinical studies on the association between macrophage polarisation and intraocular diseases, it is difficult to collect clinical literature on the pathogenesis of diseases.

As mentioned earlier, the current study lacks further delineation of the macrophage subsets; therefore, future studies need to identify the macrophage subsets involved in the disease process to further elucidate the specific mechanisms involved. Although numerous basic studies are related to intraocular diseases, relevant clinical studies are still lacking. Therefore, in the future, more clinical studies on the association between macrophage polarisation and intraocular diseases are required to further explore the disease mechanism.

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Authors' contributions

HL analyzed and summarized the literature on the association of macrophage polarization with intraocular disease and was a major contributor in writing the manuscript. BL is responsible for the search and collection of literature related to macrophage polarization and intraocular diseases. YLZ optimized the writing structure and developed the idea of the article. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Yan J and Horng T: Lipid metabolism in regulation of macrophage functions. Trends Cell Biol 30: 979-989, 2020.
2. Wynn TA, Chawla A and Pollard JW: Macrophage biology in development, homeostasis and disease. Nature 496: 445-455, 2013.
3. Murray PJ and Wynn TA: Protective and pathogenic functions of macrophage subsets. Nat Rev Immunol 11: 723-737, 2011.
4. Murray PJ: Macrophage polarization. Annu Rev Physiol 79: 541-566, 2017.
5. Chinnery HR, McMenamin PG and Dando SJ: Macrophage physiology in the eye. Pflugers Arch 469: 501-515, 2017.
6. Chu F, Shi M, Zheng C, Shen D, Zhu J, Zheng X and Cui L: The roles of macrophages and microglia in multiple sclerosis and experimental autoimmune encephalomyelitis. J Neuroimmunol 318: 1-7, 2018.
7. Norden DM, Muccigrosso MM and Godbout JP: Microglial priming and enhanced reactivity to secondary insult in aging, and traumatic CNS injury, and neurodegenerative disease. Neuropharmacology 96: 29-41, 2015.
8. Kabba JA, Xu Y, Christian H, Ruan W, Chenai K, Xiang Y, Zhang L, Saavedra JM and Pang T: Microglia: Housekeeper of the central nervous system. Cell Mol Neurobiol 38: 53-71, 2018.
9. Das A, Sinha M, Datta S, Abas M, Chaffee S, Sen CK and Roy S: Monocyte and macrophage plasticity in tissue repair and regeneration. Am J Pathol 185: 2596-2606, 2015.
10. Biswas SK, Chittezhath M, Shalova IN and Lim JY: Macrophage polarization and plasticity in health and disease. Immunol Res 53: 11-24, 2012.
11. Strauss O, Dunbar PR, Bartlett A and Phillips A: The immunophenotype of antigen presenting cells of the mononuclear phagocyte system in normal human liver-a systematic review. J Hepatol 62: 458-468, 2015.
12. McMurran CE, Jones CA, Fitzgerald DC and Franklin RJ: CNS remyelination and the innate immune system. Front Cell Dev Biol 4: 38, 2016.
13. Tay TL, Hagemeyer N and Prinz M: The force awakens: Insights into the origin and formation of microglia. Curr Opin Neurobiol 39: 30-37, 2016.
14. Subramaniam SR and Federoff HJ: Targeting microglial activation states as a therapeutic avenue in Parkinson's disease. Front Aging Neurosci 9: 176, 2017.
15. Du L, Zhang Y, Chen Y, Zhu J, Yang Y and Zhang HL: Role of microglia in neurological disorders and their potentials as a therapeutic target. Mol Neurobiol 54: 7567-7584, 2017.
16. Jiang HR, Milovanović M, Allan D, Niedbala W, Besnard AG, Fukada SY, Alves-Filho JC, Togbe D, Goodyear CS, Linington C, *et al*: IL-33 attenuates EAE by suppressing IL-17 and IFN-gamma production and inducing alternatively activated macrophages. Eur J Immunol 42: 1804-1814, 2012.
17. Butovsky O, Landa G, Kunis G, Ziv Y, Avidan H, Greenberg N, Schwartz A, Smirnov I, Pollack A, Jung S and Schwartz M: Induction and blockage of oligodendrogenesis by differently activated microglia in an animal model of multiple sclerosis. J Clin Invest 116: 905-915, 2006.
18. Boche D, Perry VH and Nicoll JA: Review: Activation patterns of microglia and their identification in the human brain. Neuropath Appl Neuro 39: 3-18, 2013.
19. Mills CD: M1 and M2 macrophages: Oracles of health and disease. Crit Rev Immunol 32: 463-488, 2012.
20. Ransohoff RM and Brown MA: Innate immunity in the central nervous system. J Clin Invest 122: 1164-1171, 2012.
21. Ransohoff RM and Perry VH: Microglial physiology: Unique stimuli, specialized responses. Annu Rev Immunol 27: 119-145, 2009.
22. Graeber MB: Changing face of microglia. Science 330: 783-788, 2010.
23. Stout RD, Jiang C, Matta B, Tietzel I, Watkins SK and Suttles J: Macrophages sequentially change their functional phenotype in response to changes in microenvironmental influences. J Immunol 175: 342-349, 2005.
24. Wang N, Liang H and Zen K: Molecular mechanisms that influence the macrophage m1-m2 polarization balance. Front Immunol 5: 614, 2014.
25. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A and Locati M: The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol 25: 677-686, 2004.
26. Gordon S: Alternative activation of macrophages. Nat Rev Immunol 3: 23-35, 2003.
27. Varnum MM and Ikezu T: The classification of microglial activation phenotypes on neurodegeneration and regeneration in Alzheimer's disease brain. Arch Immunol Ther Exp (Warsz) 60: 251-266, 2012.
28. Colton C and Wilcock DM: Assessing activation states in microglia. CNS Neurol Disord Drug Targets 9: 174-191, 2010.
29. Henkel JS, Beers DR, Zhao W and Appel SH: Microglia in ALS: The good, the bad, and the resting. J Neuroimmune Pharm 4: 389-398, 2009.
30. Hanisch UK and Kettenmann H: Microglia: Active sensor and versatile effector cells in the normal and pathologic brain. Nat Neurosci 10: 1387-1394, 2007.
31. Sica A and Mantovani A: Macrophage plasticity and polarization: In vivo veritas. J Clin Invest 122: 787-795, 2012.
32. Wang LX, Zhang SX, Wu HJ, Rong XL and Guo J: M2b macrophage polarization and its roles in diseases. J Leukoc Biol 106: 345-358, 2019.
33. Ferrante CJ, Pinhal-Enfield G, Elson G, Cronstein BN, Hasko G, Outram S and Leibovich SJ: The adenosine-dependent angiogenic switch of macrophages to an M2-like phenotype is independent of interleukin-4 receptor alpha (IL-4Rα) signaling. Inflammation 36: 921-931, 2013.
34. Zizzo G, Hilliard BA, Monestier M and Cohen PL: Efficient clearance of early apoptotic cells by human macrophages requires M2c polarization and MerTK induction. J Immunol 189: 3508-3520, 2012.
35. Mosser DM and Edwards JP: Exploring the full spectrum of macrophage activation. Nat Rev Immunol 8: 958-969, 2008.
36. Edwards JP, Zhang X, Frauwirth KA and Mosser DM: Biochemical and functional characterization of three activated macrophage populations. J Leukoc Biol 80: 1298-1307, 2006.
37. Chhor V, Le Charpentier T, Lebon S, Oré MV, Celador IL, Josserand J, Degos V, Jacotot E, Hagberg H, Sävman K, *et al*: Characterization of phenotype markers and neuronotoxic potential of polarised primary microglia in vitro. Brain Behav Immun 32: 70-85, 2013.
38. Freilich RW, Woodbury ME and Ikezu T: Integrated expression profiles of mRNA and miRNA in polarized primary murine microglia. PLoS One 8: e79416, 2013.
39. Fenn AM, Henry CJ, Huang Y, Dugan A and Godbout JP: Lipopolysaccharide-induced interleukin (IL)-4 receptor-α expression and corresponding sensitivity to the M2 promoting effects of IL-4 are impaired in microglia of aged mice. Brain Behav Immun 26: 766-777, 2012.
40. Liu HC, Zheng MH, Du YL, Wang L, Kuang F, Qin HY, Zhang BF and Han H: N9 microglial cells polarized by LPS and IL4 show differential responses to secondary environmental stimuli. Cell Immunol 278: 84-90, 2012.
41. Michelucci A, Heurtaux T, Grandbarbe L, Morga E and Heuschling P: Characterization of the microglial phenotype under specific pro-inflammatory and anti-inflammatory conditions: Effects of oligomeric and fibrillar amyloid-beta. J Neuroimmunol 210: 3-12, 2009.
42. Crane MJ, Daley JM, van Houtte O, Brancato SK, Henry WJ Jr and Albina JE: The monocyte to macrophage transition in the murine sterile wound. PLoS One 9: e86660, 2014.
43. Italiani P, Mazza EM, Lucchesi D, Cifola I, Gemelli C, Grande A, Battaglia C, Bicciato S and Boraschi D: Transcriptomic profiling of the development of the inflammatory response in human monocytes in vitro. PLoS One 9: e87680, 2014.
44. Orecchioni M, Ghosheh Y, Pramod AB and Ley K: Macrophage polarization: Different gene signatures in M1(LPS+) vs. classically and M2(LPS-) vs. alternatively activated macrophages. Front Immunol 10: 1084, 2019.
45. Watanabe S, Alexander M, Misharin AV and Budinger GRS: The role of macrophages in the resolution of inflammation. J Clin Invest 129: 2619-2628, 2019.
46. Atri C, Guerfali FZ and Laouini D: Role of human macrophage polarization in inflammation during infectious diseases. Int J Mol Sci 19: 1801, 2018.
47. Shapouri-Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, Mardani F, Seifi B, Mohammadi A, Afshari JT and Sahebkar A: Macrophage plasticity, polarization, and function in health and disease. J Cell Physiol 233: 6425-6440, 2018.
48. He C and Carter AB: The metabolic prospective and redox regulation of macrophage polarization. J Clin Cell Immunol 6: 371, 2015.
49. Bansal S, Barathi V, Iwata D and Agrawal R: Experimental autoimmune uveitis and other animal models of uveitis: An update. Indian J Ophthalmol 63: 211-218, 2015.

50. Meng X, Fang S, Zhang Z, Wang Y, You C, Zhang J and Yan H: Preventive effect of chrysin on experimental autoimmune uveitis triggered by injection of human IRBP peptide 1-20 in mice. Cell Mol Immunol 14: 702-711, 2017.
51. Bousquet E, Camelo S, Leroux Les Jardins G, Goldenberg B, Naud MC, Besson-Lescure B, Lebreton L, Annat J, Behar-Cohen F and de Kozak Y: Protective effect of intravitreal administration of tresperimus, an immunosuppressive drug, on experimental autoimmune uveoretinitis. Invest Ophthalmol Vis Sci 52: 5414-5423, 2011.
52. Haruta H, Ohguro N, Fujimoto M, Hohki S, Terabe F, Serada S, Nomura S, Nishida K, Kishimoto T and Naka T: Blockade of interleukin-6 signaling suppresses not only th17 but also interphotoreceptor retinoid binding protein-specific Th1 by promoting regulatory T cells in experimental autoimmune uveoretinitis. Investigative Invest Ophthalmol Vis Sci 52: 3264-3271, 2011.
53. Luger D, Silver PB, Tang J, Cua D, Chen Z, Iwakura Y, Bowman EP, Sgambellone NM, Chan CC and Caspi RR: Either a Th17 or a Th1 effector response can drive autoimmunity: Conditions of disease induction affect dominant effector category. J Exp Med 205: 799-810, 2008.
54. Zhao J, Chen M and Xu H: Experimental autoimmune uveoretinitis (EAU)-related tissue damage and angiogenesis is reduced in CCL2-/-CX3CR1gfp/gfp mice. Invest Ophthalmol Vis Sci 55: 7572-7582, 2014.
55. Chen M, Copland DA, Zhao J, Liu J, Forrester JV, Dick AD and Xu H: Persistent inflammation subverts thrombospondin-1-induced regulation of retinal angiogenesis and is driven by CCR2 ligation. Am J Pathol 180: 235-245, 2012.
56. Lipski DA, Dewispelaere R, Foucart V, Caspers LE, Defrance M, Bruyns C and Willermain F: MHC class II expression and potential antigen-presenting cells in the retina during experimental autoimmune uveitis. J Neuroinflamm 14: 136, 2017.
57. Miura-Takeda S, Tashiro-Yamaji J, Oku H, Takahashi T, Shimizu T, Sugiyama T, Ikeda T, Kubota T and Yoshida R: Experimental autoimmune uveoretinitis initiated by non-phagocytic destruction of inner segments of photoreceptor cells by Mac-1(+) mononuclear cells. Microbiol Immunol 52: 601-610, 2008.
58. Niven J, Hoare J, McGowan D, Devarajan G, Itohara S, Gannagé M, Teismann P and Crane I: S100B up-regulates macrophage production of IL1β and CCL22 and influences severity of retinal inflammation. PLoS One 10: e132688, 2015.
59. Nguyen AM and Rao NA: Oxidative photoreceptor cell damage in autoimmune uveitis. J Ophthalmic Inflamm Infect 1: 7-13, 2010.
60. Wu GS, Lee TD, Moore RE and Rao NA: Photoreceptor mitochondrial tyrosine nitration in experimental uveitis. Invest Ophthalmol Vis Sci 46: 2271-2281, 2005.
61. Kimura A, Naka T, Nakahama T, Chinen I, Masuda K, Nohara K, Fujii-Kuriyama Y and Kishimoto T: Aryl hydrocarbon receptor in combination with Stat1 regulates LPS-induced inflammatory responses. J Exp Med 206: 2027-2035, 2009.
62. Huang Y, He J, Liang H, Hu K, Jiang S, Yang L, Mei S, Zhu X, Yu J, Kijlstra A, *et al*: Aryl hydrocarbon receptor regulates apoptosis and inflammation in a murine model of experimental autoimmune uveitis. Front Immunol 9: 1713, 2018.
63. Chackerian AA, Oldham ER, Murphy EE, Schmitz J, Pflanz S and Kastelein RA: IL-1 receptor accessory protein and ST2 comprise the IL-33 receptor complex. J Immunol 179: 2551-2555, 2007.
64. Kurowska-Stolarska M, Stolarski B, Kewin P, Murphy G, Corrigan CJ, Ying S, Pitman N, Mirchandani A, Rana B, van Rooijen N, *et al*: IL-33 amplifies the polarization of alternatively activated macrophages that contribute to airway inflammation. J Immunol 183: 6469-6477, 2009.
65. Barbour M, Allan D, Xu H, Pei C, Chen M, Niedbala W, Fukada SY, Besnard AG, Alves-Filho JC, Tong X, *et al*: IL-33 attenuates the development of experimental autoimmune uveitis. Eur J Immunol 44: 3320-3329, 2014.
66. Qu R, Zhou M, Qiu Y, Peng Y, Yin X, Liu B, Bi H, Gao Y and Guo D: Glucocorticoids improve the balance of M1/M2 macrophage polarization in experimental autoimmune uveitis through the P38MAPK-MEF2C axis. Int Immunopharmacol 120: 110392, 2023.
67. Tortorella C, Simone O, Piazzolla G, Stella I and Antonaci S: Age-related impairment of GM-CSF-induced signalling in neutrophils: Role of SHP-1 and SOCS proteins. Ageing Res Rev 6: 81-93, 2007.
68. Jost MM, Ninci E, Meder B, Kempf C, Van Royen N, Hua J, Berger B, Hoefer I, Modolell M and Buschmann I: Divergent effects of GM-CSF and TGFbeta1 on bone marrow-derived macrophage arginase-1 activity, MCP-1 expression, and matrix metalloproteinase-12: A potential role during arteriogenesis. FASEB J 17: 2281-2283, 2003.
69. Chen M, Zhao J, Ali IHA, Marry S, Augustine J, Bhuckory M, Lynch A, Kissenpfennig A and Xu H: Cytokine signaling protein 3 deficiency in myeloid cells promotes retinal degeneration and angiogenesis through arginase-1 up-regulation in experimental autoimmune uveoretinitis. Am J Pathol 188: 1007-1020, 2018.
70. Benitez JT and Bouchard KR: Brain stem auditory evoked response correlates in patients with spinocerebellar lesions. Am J Otol 7: 183-187, 1986.
71. Horstmann L, Schmid H, Heinen AP, Kurschus FC, Dick HB and Joachim SC: Inflammatory demyelination induces glia alterations and ganglion cell loss in the retina of an experimental autoimmune encephalomyelitis model. J Neuroinflamm 10: 120, 2013.
72. Cui Q, Yin Y and Benowitz LI: The role of macrophages in optic nerve regeneration. Neuroscience 158: 1039-1048, 2009.
73. Starossom SC, Veremeyko T, Yung AWY, Dukhinova M, Au C, Lau AY, Weiner HL and Ponomarev ED: Platelets play differential role during the initiation and progression of autoimmune neuroinflammation. Circ Res 117: 779-792, 2015.
74. Martinez FO and Gordon S: The M1 and M2 paradigm of macrophage activation: Time for reassessment. F1000Prime Rep 6: 13, 2014.
75. McGeachy MJ: GM-CSF: The secret weapon in the T(H)17 arsenal. Nat Immunol 12: 521-522, 2011.
76. Ponomarev ED, Shriver LP, Maresz K, Pedras-Vasconcelos J, Verthelyi D and Dittel BN: GM-CSF production by autoreactive T cells is required for the activation of microglial cells and the onset of experimental autoimmune encephalomyelitis. J Immunol 178: 39-48, 2007.
77. Ponomarev ED, Shriver LP, Maresz K and Dittel BN: Microglial cell activation and proliferation precedes the onset of CNS autoimmunity. J Neurosci Res 81: 374-389, 2005.
78. Ponomarev ED, Maresz K, Tan Y and Dittel BN: CNS-derived interleukin-4 is essential for the regulation of autoimmune inflammation and induces a state of alternative activation in microglial cells. J Neurosci 27: 10714-10721, 2007.
79. Zhang HL, Hassan MY, Zheng XY, Azimullah S, Quezada HC, Amir N, Elwasila M, Mix E, Adem A and Zhu J: Attenuated EAN in TNF-α deficient mice is associated with an altered balance of M1/M2 macrophages. PLoS One 7: e38157, 2012.
80. Kroenke MA, Carlson TJ, Andjelkovic AV and Segal BM: IL-12- and IL-23-modulated T cells induce distinct types of EAE based on histology, CNS chemokine profile, and response to cytokine inhibition. J Exp Med 205: 1535-1541, 2008.
81. Ha Y, Liu H, Zhu S, Yi P, Liu W, Nathanson J, Kayed R, Loucas B, Sun J, Frishman LJ, *et al*: Critical Role of the CXCL10/C-X-C chemokine receptor 3 axis in promoting leukocyte recruitment and neuronal injury during traumatic optic neuropathy induced by optic nerve crush. Am J Pathol 187: 352-365, 2017.
82. Kwon MJ, Shin HY, Cui Y, Kim H, Thi AH, Choi JY, Kim EY, Hwang DH and Kim BG: CCL2 mediates neuron-macrophage interactions to drive proregenerative macrophage activation following preconditioning injury. J Neurosci 35: 15934-15947, 2015.
83. Butti E, Bergami A, Recchia A, Brambilla E, Del Carro U, Amadio S, Cattalini A, Esposito M, Stornaiuolo A, Comi G, *et al*: IL4 gene delivery to the CNS recruits regulatory T cells and induces clinical recovery in mouse models of multiple sclerosis. Gene Ther 15: 504-515, 2008.
84. Georgiou T, Wen YT, Chang CH, Kolovos P, Kalogerou M, Prokopiou E, Neokleous A, Huang CT and Tsai RK: Neuroprotective effects of Omega-3 polyunsaturated fatty acids in a rat model of anterior ischemic optic neuropathy. Invest Ophthalmol Vis Sci 58: 1603-1611, 2017.
85. Locri F, Cammalleri M, Pini A, Dal Monte M, Rusciano D and Bagnoli P: Further evidence on efficacy of diet supplementation with fatty acids in ocular pathologies: Insights from the EAE model of optic neuritis. Nutrients 10: 1447, 2018.
86. Sen HN and Nussenblatt RB: Sympathetic ophthalmia: What have we learned? Am J Ophthalmol 148: 632-633, 2009.
87. Castiblanco CP and Adelman RA: Sympathetic ophthalmia. Graefes Arch Clin Exp Ophthalmol 247: 289-302, 2009.

88. Jakobiec FA, Marboe CC, Knowles DN II, Iwamoto T, Harrison W, Chang S and Coleman DJ: Human sympathetic ophthalmia. An analysis of the inflammatory infiltrate by hybridoma-monoclonal antibodies, immunochemistry, and correlative electron microscopy. Ophthalmology 90: 76-95, 1983.
89. Shah DN, Piacentini MA, Burnier MN, McLean IW, Nussenblatt RB and Chan CC: Inflammatory cellular kinetics in sympathetic ophthalmia a study of 29 traumatized (exciting) eyes. Ocul Immunol Inflamm 1: 255-262, 1993.
90. Abu El-Asrar AM, Struyf S, Van den Broeck C, Van Damme J, Opdenakker G, Geboes K and Kestelyn P: Expression of chemokines and gelatinase B in sympathetic ophthalmia. Eye (Lond) 21: 649-657, 2007.
91. Aziz HA, Flynn HW Jr, Young RC, Davis JL and Dubovy SR: Sympathetic ophthalmia: Clinicopathologic correlation in a consecutive case series. Retina 35: 1696-1703, 2015.
92. Chan CC, Nussenblatt RB, Fujikawa LS, Palestine AG, Stevens G Jr, Parver LM, Luckenbach MW and Kuwabara T: Sympathetic ophthalmia. Immunopathological findings. Ophthalmology 93: 690-695, 1986.
93. Furusato E, Shen D, Cao X, Furusato B, Nussenblatt RB, Rushing EJ and Chan CC: Inflammatory cytokine and chemokine expression in sympathetic ophthalmia: A pilot study. Histol Histopathol 26: 1145-1151, 2011.
94. Marak GE Jr: Recent advances in sympathetic ophthalmia. Surv Ophthalmol 24: 141-156, 1979.
95. Ben M'Barek K and Monville C: Cell therapy for retinal dystrophies: From cell suspension formulation to complex retinal tissue bioengineering. Stem Cells Int 2019: 4568979, 2019.
96. Athanasiou D, Aguila M, Bellingham J, Li W, McCulley C, Reeves PJ and Cheetham ME: The molecular and cellular basis of rhodopsin retinitis pigmentosa reveals potential strategies for therapy. Prog Retin Eye Res 62: 1-23, 2018.
97. Kyger M, Worley A and Adamus G: Autoimmune responses against photoreceptor antigens during retinal degeneration and their role in macrophage recruitment into retinas of RCS rats. J Neuroimmunol 254: 91-100, 2013.
98. Sevenich L: Brain-resident microglia and blood-borne macrophages orchestrate central nervous system inflammation in neurodegenerative disorders and brain cancer. Front Immunol 9: 697, 2018.
99. Xu H, Chen M and Forrester JV: Para-inflammation in the aging retina. Prog Retin Eye Res 28: 348-368, 2009.
100. Wohleb ES: Neuron-microglia interactions in mental health disorders: 'For better, and for worse'. Front Immunol 7: 544, 2016.
101. Edholm ES, Rhoo KH and Robert J: Evolutionary aspects of macrophages polarization. Results Probl Cell Differ 62: 3-22, 2017.
102. Neves J, Zhu J, Sousa-Victor P, Konjikusic M, Riley R, Chew S, Qi Y, Jasper H and Lamba DA: Immune modulation by MANF promotes tissue repair and regenerative success in the retina. Science 353: aaf3646, 2016.
103. Xie J, Li Y, Dai J, He Y, Sun D, Dai C, Xu H and Yin ZQ: Olfactory ensheathing cells grafted into the retina of RCS rats suppress inflammation by down-regulating the JAK/STAT pathway. Front Cell Neurosci 13: 341, 2019.
104. Olivares-González L, Velasco S, Gallego I, Esteban-Medina M, Puras G, Loucera C, Martínez-Romero A, Peña-Chilet M, Pedraz JL and Rodrigo R: An SPM-enriched marine oil supplement shifted microglia polarization toward M2, ameliorating retinal degeneration in rd10 mice. Antioxidants (Basel) 12: 98, 2022.
105. Quigley HA, Nickells RW, Kerrigan LA, Pease ME, Thibault DJ and Zack DJ: Retinal ganglion cell death in experimental glaucoma and after axotomy occurs by apoptosis. Invest Ophthalmol Vis Sci 36: 774-786, 1995.
106. Levkovitch-Verbin H, Dardik R, Vander S, Nisgav Y, Kalev-Landoy M and Melamed S: Experimental glaucoma and optic nerve transection induce simultaneous upregulation of proapoptotic and prosurvival genes. Invest Ophthalmol Vis Sci 47: 2491-2497, 2006.
107. Prilloff S, Henrich-Noack P and Sabel BA: Recovery of axonal transport after partial optic nerve damage is associated with secondary retinal ganglion cell death in vivo. Invest Ophthalmol Vis Sci 53: 1460-1466, 2012.
108. Levkovitch-Verbin H, Quigley HA, Martin KRG, Zack DJ, Pease ME and Valenta DF: A model to study differences between primary and secondary degeneration of retinal ganglion cells in rats by partial optic nerve transection. Invest Ophthalmol Vis Sci 44: 3388-3393, 2003.
109. Levkovitch-Verbin H, Quigley HA, Kerrigan-Baumrind LA, D'Anna SA, Kerrigan D and Pease ME: Optic nerve transection in monkeys may result in secondary degeneration of retinal ganglion cells. Invest Ophthalmol Vis Sci 42: 975-982, 2001.
110. Yoles E and Schwartz M: Degeneration of spared axons following partial white matter lesion: Implications for optic nerve neuropathies. Exp Neurol 153: 1-7, 1998.
111. Li HY, Huang M, Luo QY, Hong X, Ramakrishna S and So KF: *Lycium barbarum* (wolfberry) increases retinal ganglion cell survival and affects both microglia/macrophage polarization and autophagy after rat partial optic nerve transection. Cell Transplant 28: 607-618, 2019.
112. Wada Y, Nakamachi T, Endo K, Seki T, Ohtaki H, Tsuchikawa D, Hori M, Tsuchida M, Yoshikawa A, Matkovits A, *et al*: PACAP attenuates NMDA-induced retinal damage in association with modulation of the microglia/macrophage status into an acquired deactivation subtype. J Mol Neurosci 51: 493-502, 2013.
113. Schwartz M: Macrophages and microglia in central nervous system injury: Are they helpful or harmful? J Cereb Blood Flow Metab 23: 385-394, 2003.
114. Hayreh SS: Ischemic optic neuropathy. Prog Retin Eye Res 28: 34-62, 2009.
115. Salgado C, Vilson F, Miller NR and Bernstein SL: Cellular inflammation in nonarteritic anterior ischemic optic neuropathy and its primate model. Arch Ophthalmol 129: 1583-1591, 2011.
116. Zhang C, Guo Y, Miller NR and Bernstein SL: Optic nerve infarction and post-ischemic inflammation in the rodent model of anterior ischemic optic neuropathy (rAION). Brain Res 1264: 67-75, 2009.
117. Nicholson JD, Leiba H and Goldenberg-Cohen N: Translational preclinical research may lead to improved medical management of non-arteritic anterior ischemic optic neuropathy. Front Neurol 5: 122, 2014.
118. Hayreh SS and Zimmerman MB: Nonarteritic anterior ischemic optic neuropathy: Natural history of visual outcome. Ophthalmology 115: 298-305.e2, 2008.
119. Bernstein SL, Johnson MA and Miller NR: Nonarteritic anterior ischemic optic neuropathy (NAION) and its experimental models. Prog Retin Eye Res 30: 167-187, 2011.
120. Yin Y, Cui Q, Li Y, Irwin N, Fischer D, Harvey AR and Benowitz LI: Macrophage-derived factors stimulate optic nerve regeneration. J Neurosci 23: 2284-2293, 2003.
121. Orihuela R, McPherson CA and Harry GJ: Microglial M1/M2 polarization and metabolic states. Brit J Pharmacol 173: 649-665, 2016.
122. Wen YT, Huang TL, Huang SP, Chang CH and Tsai RK: Early applications of granulocyte colony-stimulating factor (G-CSF) can stabilize the blood-optic-nerve barrier and ameliorate inflammation in a rat model of anterior ischemic optic neuropathy (rAION). Dis Model Mech 9: 1193-1202, 2016.
123. Desai TD, Wen YT, Daddam JR, Cheng F, Chen CC, Pan CL, Lin KL and Tsai RK: Long term therapeutic effects of icariin-loaded PLGA microspheres in an experimental model of optic nerve ischemia via modulation of CEBP-β/G-CSF/noncanonical NF-κB axis. Bioeng Transl Med 7: e10289, 2022.
124. Nguyen Ngo Le MA, Wen YT, Ho YC, Kapupara K and Tsai RK: Therapeutic effects of puerarin against anterior ischemic optic neuropathy through antiapoptotic and anti-inflammatory actions. Invest Ophthalmol Vis Sci 60: 3481-3491, 2019.
125. Arranz A, Doxaki C, Vergadi E, Martinez de la Torre Y, Vaporidi K, Lagoudaki ED, Ieronymaki E, Androulidaki A, Venihaki M, Margioris AN, *et al*: Akt1 and Akt2 protein kinases differentially contribute to macrophage polarization. Proc Natl Acad Sci USA 109: 9517-9522, 2012.
126. Friedlander M: Fibrosis and diseases of the eye. J Clin Invest 117: 576-586, 2007.
127. Kalluri R and Weinberg RA: The basics of epithelial-mesenchymal transition. J Clin Invest 119: 1420-1428, 2009.
128. Wynn TA: Common and unique mechanisms regulate fibrosis in various fibroproliferative diseases. J Clin Invest 117: 524-529, 2007.
129. Wermuth PJ and Jimenez SA: The significance of macrophage polarization subtypes for animal models of tissue fibrosis and human fibrotic diseases. Clin Transl Med 4: 2, 2015.
130. Pastor JC, de la Rúa ER and Martin F: Proliferative vitreoretinopathy: Risk factors and pathobiology. Prog Retin Eye Res 21: 127-144, 2002.
131. Cordeiro MF, Schultz GS, Ali RR, Bhattacharya SS and Khaw PT: Molecular therapy in ocular wound healing. Br J Ophthalmol 83: 1219-1224, 1999.

132. Agrawal RN, He S, Spee C, Cui JZ, Ryan SJ and Hinton DR: In vivo models of proliferative vitreoretinopathy. Nat Protoc 2: 67-77, 2007.
133. Esser P, Heimann K and Wiedemann P: Macrophages in proliferative vitreoretinopathy and proliferative diabetic retinopathy: Differentiation of subpopulations. Br J Ophthalmol 77: 731-733, 1993.
134. Martin F, Pastor JC, De La Rúa ER, Mayo-Iscar A, García-Arumí J, Martínez V, Fernández N and Saornil MA: Proliferative vitreoretinopathy: Cytologic findings in vitreous samples. Ophthalmic Res 35: 232-238, 2003.
135. Garweg JG, Tappeiner C and Halberstadt M: Pathophysiology of proliferative vitreoretinopathy in retinal detachment. Surv Ophthalmol 58: 321-329, 2013.
136. Biswas SK and Mantovani A: Macrophage plasticity and interaction with lymphocyte subsets: Cancer as a paradigm. Nat Immunol 11: 889-896, 2010.
137. Wong CW, Cheung N, Ho C, Barathi V, Storm G and Wong TT: Characterisation of the inflammatory cytokine and growth factor profile in a rabbit model of proliferative vitreoretinopathy. Sci Rep 9: 15419, 2019.
138. Ishikawa K, Kannan R and Hinton DR: Molecular mechanisms of subretinal fibrosis in age-related macular degeneration. Exp Eye Res 142: 19-25, 2016.
139. Song Y, Liao M, Zhao X, Han H, Dong X, Wang X, Du M and Yan H: Vitreous M2 macrophage-derived microparticles promote RPE cell proliferation and migration in traumatic proliferative vitreoretinopathy. Invest Ophthalmol Vis Sci 62: 26, 2021.
140. Kobayashi Y, Yoshida S, Nakama T, Zhou Y, Ishikawa K, Arita R, Nakao S, Miyazaki M, Sassa Y, Oshima Y, *et al*: Overexpression of CD163 in vitreous and fibrovascular membranes of patients with proliferative diabetic retinopathy: possible involvement of periostin. Br J Ophthalmol 99: 451-456, 2015.
141. Zhang J, Zhou Q, Yuan G, Dong M and Shi W: Notch signaling regulates M2 type macrophage polarization during the development of proliferative vitreoretinopathy. Cell Immunol 298: 77-82, 2015.
142. Lim LS, Mitchell P, Seddon JM, Holz FG and Wong TY: Age-related macular degeneration. Lancet 379: 1728-1738, 2012.
143. Greaves NS, Ashcroft KJ, Baguneid M and Bayat A: Current understanding of molecular and cellular mechanisms in fibroplasia and angiogenesis during acute wound healing. J Dermatol Sci 72: 206-217, 2013.
144. Kent D and Sheridan C: Choroidal neovascularization: A wound healing perspective. Mol Vis 9: 747-755, 2003.
145. Cherepanoff S, McMenamin P, Gillies MC, Kettle E and Sarks SH: Bruch's membrane and choroidal macrophages in early and advanced age-related macular degeneration. Br J Ophthalmol 94: 918-925, 2010.
146. Bo Q, Shen M, Xiao M, Liang J, Zhai Y, Zhu H, Jiang M, Wang F, Luo X and Sun X: 3-Methyladenine alleviates experimental subretinal fibrosis by inhibiting macrophages and M2 polarization through the PI3K/Akt pathway. J Ocul Pharmacol Ther 36: 618-628, 2020.
147. He L and Marneros AG: Macrophages are essential for the early wound healing response and the formation of a fibrovascular scar. Am J Pathol 182: 2407-2417, 2013.
148. Cao X, Shen D, Patel MM, Tuo J, Johnson TM, Olsen TW and Chan CC: Macrophage polarization in the maculae of age-related macular degeneration: A pilot study. Pathol Int 61: 528-535, 2011.
149. Lai K, Li Y, Li L, Gong Y, Huang C, Zhang Y, Cheng L, Xu F, Zhao H, Li C, *et al*: Intravitreal injection of triptolide attenuates subretinal fibrosis in laser-induced murine model. Phytomedicine 93: 153747, 2021.
150. Mehla K and Singh PK: Metabolic regulation of macrophage polarization in cancer. Trends Cancer 5: 822-834, 2019.
151. Egan KM, Seddon JM, Glynn RJ, Gragoudas ES and Albert DM: Epidemiologic aspects of uveal melanoma. Surv Ophthalmol 32: 239-251, 1988.
152. Johnson DB and Daniels AB: Continued poor survival in metastatic uveal melanoma: Implications for molecular prognostication, surveillance imaging, adjuvant therapy, and clinical trials. JAMA Ophthalmol 136: 986-988, 2018.
153. Hood JL: The association of exosomes with lymph nodes. Semin Cell Dev Biol 67: 29-38, 2017.
154. Bardi GT, Smith MA and Hood JL: Melanoma exosomes promote mixed M1 and M2 macrophage polarization. Cytokine 105: 63-72, 2018.
155. Delwar ZM, Kuo Y, Wen YH, Rennie PS and Jia W: Oncolytic virotherapy blockade by microglia and macrophages requires STAT1/3. Cancer Res 78: 718-730, 2018.
156. Zhou D, Huang C, Lin Z, Zhan S, Kong L, Fang C and Li J: Macrophage polarization and function with emphasis on the evolving roles of coordinated regulation of cellular signaling pathways. Cell Signal 26: 192-197, 2014.
157. Liu S, Zhang J, Fang S, Zhang Q, Zhu G, Tian Y, Zhao M and Liu F: Macrophage polarization contributes to the efficacy of an oncolytic HSV-1 targeting human uveal melanoma in a murine xenograft model. Exp Eye Res 202: 108285, 2021.
158. Spiller KL, Anfang RR, Spiller KJ, Ng J, Nakazawa KR, Daulton JW and Vunjak-Novakovic G: The role of macrophage phenotype in vascularization of tissue engineering scaffolds. Biomaterials 35: 4477-4488, 2014.
159. Jetten N, Verbruggen S, Gijbels MJ, Post MJ, De Winther MPJ and Donners MMPC: Anti-inflammatory M2, but not pro-inflammatory M1 macrophages promote angiogenesis in vivo. Angiogenesis 17: 109-118, 2014.
160. Cheung N, Mitchell P and Wong TY: Diabetic retinopathy. Lancet 376: 124-136, 2010.
161. Jenkins AJ, Joglekar MV, Hardikar AA, Keech AC, O'Neal DN and Januszewski AS: Biomarkers in diabetic retinopathy. Rev Diabet Stud 12: 159-195, 2015.
162. Wu JH, Li YN, Chen AQ, Hong CD, Zhang CL, Wang HL, Zhou YF, Li PC, Wang Y, Mao L, *et al*: Inhibition of Sema4D/PlexinB1 signaling alleviates vascular dysfunction in diabetic retinopathy. EMBO Mol Med 12: e10154, 2020.
163. Madonna R, Balistreri CR, Geng YJ and De Caterina R: Diabetic microangiopathy: Pathogenetic insights and novel therapeutic approaches. Vasc Pharmacol 90: 1-7, 2017.
164. Chen C, Wu S, Hong Z, Chen X, Shan X, Fischbach S and Xiao X: Chronic hyperglycemia regulates microglia polarization through ERK5. Aging (Albany NY) 11: 697-706, 2019.
165. Chen T, Zhu W, Wang C, Dong X, Yu F, Su Y, Huang J, Huo L and Wan P: ALKBH5-mediated m^6A modification of A20 regulates microglia polarization in diabetic retinopathy. Front Immunol 13: 813979, 2022.
166. Yao Y, Li J, Zhou Y, Wang S, Zhang Z, Jiang Q and Li K: Macrophage/microglia polarization for the treatment of diabetic retinopathy. Front Endocrinol (Lausanne) 14: 1276225, 2023.
167. Tang L, Zhang C, Lu L, Tian H, Liu K, Luo D, Qiu Q, Xu GT and Zhang J: Melatonin maintains inner blood-retinal barrier by regulating microglia via inhibition of PI3K/Akt/Stat3/NF-κB signaling pathways in experimental diabetic retinopathy. Front Immunol 13: 831660, 2022.
168. Fang M, Wan W, Li Q, Wan W, Long Y, Liu H and Yang X: Asiatic acid attenuates diabetic retinopathy through TLR4/MyD88/NF-κB p65 mediated modulation of microglia polarization. Life Sci 277: 119567, 2021.
169. Good WV, Hardy RJ, Dobson V, Palmer EA, Phelps DL, Quintos M and Tung B; Early Treatment for Retinopathy of Prematurity Cooperative Group: The incidence and course of retinopathy of prematurity: Findings from the early treatment for retinopathy of prematurity study. Pediatrics 116: 15-23, 2005.
170. Dogra MR, Katoch D and Dogra M: An update on retinopathy of prematurity (ROP). Indian J Pediatr 84: 930-936, 2017.
171. Dhawan A, Dogra M, Vinekar A, Gupta A and Dutta S: Structural sequelae and refractive outcome after successful laser treatment for threshold retinopathy of prematurity. J Pediatr Ophthalmol Strabismus 45: 356-361, 2008.
172. Katoch D, Sanghi G, Dogra MR, Beke N and Gupta A: Structural sequelae and refractive outcome 1 year after laser treatment for type 1 prethreshold retinopathy of prematurity in Asian Indian eyes. Indian J Ophthalmol 59: 423-426, 2011.
173. Lee J, Kim KE, Choi DK, Jang JY, Jung JJ, Kiyonari H, Shioi G, Chang W, Suda T, Mochizuki N, *et al*: Angiopoietin-1 guides directional angiogenesis through integrin αvβ5 signaling for recovery of ischemic retinopathy. Sci Transl Med 5: 203ra127, 2013.
174. Ma J, Mehta M, Lam G, Cyr D, Ng TF, Hirose T, Tawansy KA, Taylor AW and Lashkari K: Influence of subretinal fluid in advanced stage retinopathy of prematurity on proangiogenic response and cell proliferation. Mol Vis 20: 881-893, 2014.
175. Li J, Yu S, Lu X, Cui K, Tang X, Xu Y and Liang X: The phase changes of M1/M2 phenotype of microglia/macrophage following oxygen-induced retinopathy in mice. Inflamm Res 70: 183-192, 2021.

176. Outtz HH, Tattersall IW, Kofler NM, Steinbach N and Kitajewski J: Notch1 controls macrophage recruitment and Notch signaling is activated at sites of endothelial cell anastomosis during retinal angiogenesis in mice. Blood 118: 3436-3439, 2011.
177. Marchetti V, Yanes O, Aguilar E, Wang M, Friedlander D, Moreno S, Storm K, Zhan M, Naccache S, Nemerow G, *et al*: Differential macrophage polarization promotes tissue remodeling and repair in a model of ischemic retinopathy. Sci Rep 1: 76, 2011.
178. Sun X, Ma L, Li X, Wang J, Li Y and Huang Z: Ferulic acid alleviates retinal neovascularization by modulating microglia/macrophage polarization through the ROS/NF-κB axis. Front Immunol 13: 976729, 2022.
179. Sui A, Chen X, Demetriades AM, Shen J, Cai Y, Yao Y, Yao Y, Zhu Y, Shen X and Xie B: Inhibiting NF-κB signaling activation reduces retinal neovascularization by promoting a polarization shift in macrophages. Invest Ophthalmol Vis Sci 61: 4, 2020.
180. Zhu Y, Tan W, Demetriades AM, Cai Y, Gao Y, Sui A, Lu Q, Shen X, Jiang C, Xie B and Sun X: Interleukin-17A neutralization alleviated ocular neovascularization by promoting M2 and mitigating M1 macrophage polarization. Immunology 147: 414-428, 2016.
181. Gao S, Li C, Zhu Y, Wang Y, Sui A, Zhong Y, Xie B and Shen X: PEDF mediates pathological neovascularization by regulating macrophage recruitment and polarization in the mouse model of oxygen-induced retinopathy. Sci Rep 7: 42846, 2017.
182. Zhou Y, Yoshida S, Nakao S, Yoshimura T, Kobayashi Y, Nakama T, Kubo Y, Miyawaki K, Yamaguchi M, Ishikawa K, *et al*: M2 macrophages enhance pathological neovascularization in the mouse model of oxygen-induced retinopathy. Invest Ophthalmol Vis Sci 56: 4767-4777, 2015.
183. Ritter MR, Banin E, Moreno SK, Aguilar E, Dorrell MI and Friedlander M: Myeloid progenitors differentiate into microglia and promote vascular repair in a model of ischemic retinopathy. J Clin Invest 116: 3266-3276, 2006.
184. Fine SL, Berger JW, Maguire MG and Ho AC: Age-related macular degeneration. New Engl J Med 342: 483-492, 2000.
185. Rosenfeld PJ, Shapiro H, Tuomi L, Webster M, Elledge J and Blodi B; MARINA and ANCHOR Study Groups: Characteristics of patients losing vision after 2 years of monthly dosing in the phase III ranibizumab clinical trials. Ophthalmology 118: 523-530, 2011.
186. CATT Research Group; Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL and Jaffe GJ: Ranibizumab and bevacizumab for neovascular age-related macular degeneration. New Engl J Med 364: 1897-1908, 2011.
187. Takeda A, Baffi JZ, Kleinman ME, Cho WG, Nozaki M, Yamada K, Kaneko H, Albuquerque RJ, Dridi S, Saito K, *et al*: CCR3 is a target for age-related macular degeneration diagnosis and therapy. Nature 460: 225-230, 2009.
188. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY and Kim RY; MARINA Study Group: Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 355: 1419-1431, 2006.
189. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP and Schneider S; ANCHOR Study Group: Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 355: 1432-1444, 2006.
190. Grisanti S and Tatar O: The role of vascular endothelial growth factor and other endogenous interplayers in age-related macular degeneration. Prog Retin Eye Res 27: 372-390, 2008.
191. Zarbin MA: Current concepts in the pathogenesis of age-related macular degeneration. Arch Ophthalmol 122: 598-614, 2004.
192. He L and Marneros AG: Doxycycline inhibits polarization of macrophages to the proangiogenic M2-type and subsequent neovascularization. J Biol Chem 289: 8019-8028, 2014.
193. Nakamura R, Sene A, Santeford A, Gdoura A, Kubota S, Zapata N and Apte RS: IL10-driven STAT3 signalling in senescent macrophages promotes pathological eye angiogenesis. Nat Commun 6: 7847, 2015.
194. Yang Y, Liu F, Tang M, Yuan M, Hu A, Zhan Z, Li Z, Li J, Ding X and Lu L: Macrophage polarization in experimental and clinical choroidal neovascularization. Sci Rep 6: 30933, 2016.
195. Wang C, Zhang R, Zhang Q, Jin H, Wei C, Wu C, Mei L, Liu Y and Zhang P: Cytokine profiles and the effect of intravitreal aflibercept treatment on experimental choroidal neovascularization. Ophthalmic Res 65: 68-76, 2022.
196. Manthey CL, Moore BA, Chen Y, Loza MJ, Yao X, Liu H, Belkowski SM, Raymond-Parks H, Dunford PJ, Leon F, *et al*: The CSF-1-receptor inhibitor, JNJ-40346527 (PRV-6527), reduced inflammatory macrophage recruitment to the intestinal mucosa and suppressed murine T cell mediated colitis. PLoS One 14: e223918, 2019.
197. Braza MS, Conde P, Garcia M, Cortegano I, Brahmachary M, Pothula V, Fay F, Boros P, Werner SA, Ginhoux F, *et al*: Neutrophil derived CSF1 induces macrophage polarization and promotes transplantation tolerance. Am J Transplant 18: 1247-1255, 2018.
198. Zhou Y, Zeng J, Tu Y, Li L, Du S, Zhu L, Cang X, Lu J, Zhu M and Liu X: CSF1/CSF1R-mediated crosstalk between choroidal vascular endothelial cells and macrophages promotes choroidal neovascularization. Invest Ophthalmol Vis Sci 62: 37, 2021.
199. Zhang P, Lu B, Zhang Q, Xu F, Zhang R, Wang C, Liu Y, Wei C and Mei L: LncRNA NEAT1 sponges MiRNA-148a-3p to suppress choroidal neovascularization and M2 macrophage polarization. Mol Immunol 127: 212-222, 2020.
200. Zandi S, Nakao S, Chun KH, Fiorina P, Sun D, Arita R, Zhao M, Kim E, Schueller O, Campbell S, *et al*: ROCK-isoform-specific polarization of macrophages associated with age-related macular degeneration. Cell Rep 10: 1173-1186, 2015.
201. Xu Y, Cui K, Li J, Tang X, Lin J, Lu X, Huang R, Yang B, Shi Y, Ye D, *et al*: Melatonin attenuates choroidal neovascularization by regulating macrophage/microglia polarization via inhibition of RhoA/ROCK signaling pathway. J Pineal Res 69: e12660, 2020.
202. Zhao S, Lu L, Liu Q, Chen J, Yuan Q, Qiu S and Wang X: MiR-505 promotes M2 polarization in choroidal neovascularization model mice by targeting transmembrane protein 229B. Scand J Immunol 90: e12832, 2019.
203. Gao L, Jiang W, Liu H, Chen Z and Lin Y: Receptor-selective interleukin-4 mutein attenuates laser-induced choroidal neovascularization through the regulation of macrophage polarization in mice. Exp Ther Med 22: 1367, 2021.
204. Liu Z, Mao X, Yang Q, Zhang X, Xu J, Ma Q, Zhou Y, Da Q, Cai Y, Sopeyin A, *et al*: Suppression of myeloid PFKFB3-driven glycolysis protects mice from choroidal neovascularization. Br J Pharmacol 179: 5109-5131, 2022.
205. Cheng Y, Cheng T and Qu Y: TIMP-3 suppression induces choroidal neovascularization by moderating the polarization of macrophages in age-related macular degeneration. Mol Immunol 106: 119-126, 2019.
206. Lai K, Gong Y, Zhao W, Li L, Huang C, Xu F, Zhong X and Jin C: Triptolide attenuates laser-induced choroidal neovascularization via M2 macrophage in a mouse model. Biomed Pharmacother 129: 110312, 2020.
207. Chanmee T, Ontong P, Konno K and Itano N: Tumor-associated macrophages as major players in the tumor microenvironment. Cancers (Basel) 6: 1670-1690, 2014.