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From Location To Lesion: Regional Microglial Signatures And Pathogenic Pathways In Retinal Degeneration

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Abstract: Microglia are a key and spatially regulated component of the complicated neuroinflammatory process that causes retinal degeneration. Retinal microglia are resident immune cells of the central nervous system that show significant regional variation. Their distinct morphologies, migration processes and signal programs are controlled by local retinal micro environments. New studies indicate that the arrangement of microglia within specific layers in the retina can have a major effect on their output functions that may be chronic neurotoxicity in the pathology or synaptic reliance and clearance of debris under normal conditions. Microglia migrate specifically from synaptic layers into neuronal compartments like the outer nuclear layer during degenerative conditions, where ongoing activation intensifies inflammatory cascades and speeds up photoreceptor loss. This review summarizes recent discoveries that connect pathogenic signaling pathways, such as NF-κB activation, NLRP3 inflammasome signaling, purinergic P2X7 receptor activation, complement-mediated synapse elimination, oxidative stress pathways, and dysregulated CX3CL1–CX3CR1 and TREM2 signaling, to microglial spatial identity. We also investigate the convergence of these pathways in key retinal degenerative illnesses, including as glaucoma, diabetic retinopathy, age-related macular degeneration, retinitis pigmentosa, and Stargardt disease. Lastly, we address new treatment techniques that take advantage of microglial regional specificity, emphasizing targeted intranasal and intravitreal delivery methods, exosome-mediated immunomodulation, and dendrimer-based nanomedicine. A fundamental assumption for precision immunotherapy that aims to minimize associated neuroinflammation while maintaining retinal structure and function is provided by an understanding of how microglial location controls lesion formation.

Key Words: Retinal microglia, chronic neurotoxicity, IPL, OPL, Photoreceptor loss, Signaling pathways, Targeted-intranasal, intravitreal, exosome, dentrimers, neuroinflammation.

I. INTRODUCTION

Neurons and glial cells, such as oligodendrocytes, astrocytes, and microglia, make up the majority of the brain. The blood–brain barrier (BBB), which restricts the entry of soluble substances and peripheral immune cells, makes the central nervous system (CNS) an immune-privileged organ[(1)] About 5–20% of all glial cells are microglia, which are the major immunological effector cells and resident mononuclear phagocytes of the central nervous system. In both healthy and pathological circumstances, they are essential for preserving CNS homeostasis, neurogenesis, neurodevelopment, and inflammatory reaction[(2,3)] Historically, they were described as reactive neuroglia by Nissl and later identified by Ramón y Cajal and del Río Hortega as a distinct, migratory, and phagocytic glial cell type[(4)]The formation of microglia, distinct tissue-resident macrophages, is intimately associated with BBB maturation. The BBB becomes impervious to small molecules by E14.5 and less permeable to large molecules from E12.5 during embryogenesis, allowing controlled admission of microglial progenitors and safeguarding the neuronal environment. The origin of

microglia can be explained by embryonic haematopoiesis. Three hematopoietic waves occur in mice: definitive (E10.5, AGM, producing hematopoietic stem cells), transitory definitive (E8.25–E9, yolk sac and AGM), and primitive (E7.5, yolk sac)[5]. Early in development, microglia emerge from yolk sac progenitors and continue to exist as a self-renewing population separate from adult bone marrow(2).Activated astrocytes, invading immune cells, and dysregulated pro-inflammatory microglial activity all contribute to persistent neuroinflammation, which is the foundation of neurodegenerative processes [6]. A specific subset of macrophages found in the brain and neural retina are called microglia. Three discrete non-microglial macrophage subsets have been found in the eye by fate-mapping and multiparameter flow cytometry investigations. These subsets differ in their MHC class II expression and developmental origins. These results demonstrate that the retina contains a varied network of macrophages in addition to microglia. When combined, these observations suggest that the microglia and macrophage phenotypes and functions respond differently to differences in the microenvironment, even though they both have a common embryonic origin[7]. Regular monitoring of tissue In the normal retina the microglia keep a constant check on the situation In the normal retina, microglia take care of tissue homeostasis by constantly inspecting the microenvironment[7]. At late embryonic development, retinal progenitor cells form a neuroblast layer (NbL). These progenitors differentiate in a highly regulated order to produce all forms of retinal cells. During the neonatal and adult stages, the retina evolves into a fully developed and highly specialized circuitry comprising of nuclear and plexiform layers, alternating. The main populations of neurons will be located in the ONL, INL, and GCL, respectively, and they will include rod receptors, cone receptors, bipolar cells, and ganglion cells[8]). It is well organized laminated, which enables effective processing of signals and transmission of synapses. The retinal neurons are connected with each other forming synaptic links in two adjacent layers that are referred to as the outer plexiform layer (OPL) and inner plexiform layer (IPL). An integrated neurovascular and immunological unit is formed across the retina by the distribution of astrocytes, microglial cells, and the retinal vasculature, which is made up of endothelial cells and pericytes.Both innate and adaptive immunity depend on a healthy inflammatory response for host defense, tissue repair, and homeostasis maintenance[9].However, to avoid lasting neuronal injury in a sensitive neural tissue like the retina, inflammatory responses must be strictly controlled. Modern neuroscience has strengthened this concept using lesion–symptom mapping and neuroimaging correlations, making “location to lesion” analysis a powerful tool in both researchandclinicaldiagnosis.[4]

MICROGLIAL REGIONAL IDENTITY IN THE RETINA

Retinal microglia represent a specialized population of tissue-resident macrophages whose spatial organization, migratory behavior, and functional phenotype are tightly regulated by local retinal microenvironments. Their “regional identity” is reflected in their laminar distribution, morphology, gene expression, and responses to injury. This regional specialization allows microglia to perform surveillance, synaptic remodelling, and immune defense in a layer-specific manner. Single-cell transcriptomic and histological studies have shown that retinal microglia adapt their molecular signatures according to retinal layer and pathological status, emphasizing the importance of linking location to function and lesion development in retinal disease models[10,11]

a) Developmental origin of retinal microglia

Retinal microglia originate from primitive macrophages derived from the yolk sac during early embryogenesis rather than from bone marrow–derived hematopoietic stem cells.Microglia arise from erythromyeloid progenitors that migrate into the developing neural tube before the formation of the blood–brain barrier, establishing a long-lived, self-renewing population[12].In the retina, microglial precursors enter through the optic cup and colonize the neural retina in a highly regulated temporal pattern.Hence it is reported that retinal microglia appear during early embryonic development and expand through local proliferation rather than peripheral monocyte recruitment under physiological conditions[13].More importantly demonstrated that microglia are involved in the refinement of synapses in development, meaning that they must be properly formed in the early location of the retinal circuit[14].

b) Microglial distribution in the normal retina

Microglia are highly organized in lamella formation, mainly found in the synaptic layers in the healthy retina. They have a ramified morphology and possess long motile processes that are in permanent scanning of their local environment[15].

Inner Plexiform Layer (IPL)

The IPL has a high concentration of microglia, which indicates the high level of the synapses between bipolar cells, amacrine cells and ganglion cells. The retinal microglia of the IPL are highly active in this atmosphere and are tightly linked to the terminals of synapses and they are involved in the maintenance and pruning of the synapses[16].Microglia of the IPL are also immune surveillance and neurotrophic-supportive genes, which implies that their presence in this layer plays a vital role in maintaining the homeostasis of neurons[17].

Outer Plexiform Layer (OPL)

Another major location of the localization of the microglial under normal conditions is the OPL. Photoreceptors and bipolar or horizontal cells synaptic with each other are found in this layer. Microglia in this case are thought to maintain synaptic stability and react to micro metabolic stress. Microglia in the OPL reportedly are in tight contact with photoreceptor synapses and participate in the clearance of debris that is produced in the normal process of photoreceptor turnover. This is a solid indication of the contribution of OPL microglia in maintaining the integrity of the outer retina.

c) Microglial migration during degeneration

In pathological cases, there is the dramatic redistribution of retinal microglia, which is formerly located in the plexiform layer to degenerating layers of neurons. This is the migration reaction of retinal injury and degeneration.[18]

Outer Nuclear Layer (ONL)

The ONL, comprising photoreceptor nuclei, is normally free of microglia. But, in the case of retinal degeneration, the microglia enter into this layer in great numbers. Therefore, it was found that microglial proliferation in the ONL is associated with photoreceptor breakdown and augmented generation of inflammatory agents[19]. Depreeding photoreceptors deactivate chemotactic signals including CCL2, ATP, which bring microglia to ONL. At that point, microglia can assume two functions, as they can remove apoptotic debris, but at the same time, they can intensify the inflammation by producing cytokines and reactive oxygen species[17] The persistent presence of microglia in the ONL leads to the secondary neuronal damage and makes a once protective process neurotoxic. In such a way, migration to the ONL is a change in microglial regional identity with homeostatic surveillance giving way to activated, disease associated phenotype[18].

FUNCTIONAL SIGNATURES OF REGION-SPECIFIC RETINAL MICROGLIA:

Retinal microglia demonstrate functional heterogeneity and this is contingent on its laminar localization and activation state. Their functional signatures involve homeostatic surveillance, inflammatory and neuroprotective responses and this plasticity have a major role in retinal integrity, as well as disease progression.1. Homeostatic and elimination of cellular debris.In this case it showed that microglia play a role in synaptic pruning in neural development by complement-dependent engagements with weak or redundant synapses, and thus neural circuit sculpture[20]. Even though they carried out their study in the CNS, equivalent processes have now been identified in the retina where microglia concentrate on the synaptic layers to a large extent, to control the process of synaptic remodelling. The extension and contraction of retinal microglia processes is a dynamic process that helps sample the extracellular environment and eliminate apoptotic cells and metabolic waste before they can build up and cause toxic damage to neuronal functioning[21].Moreover, that effective clearance of photoreceptor debris by microglia is crucial in the maintenance of retinal homeostasis particularly in the outer retina where photoreceptor

turnover is rapid. These are studies that collectively uphold the notion that retinal microglia are housekeeping processes that maintain the viability of neurons[22].

2. Pro-inflammatory functions

Upon retinal injury or degeneration, microglia rapidly transform from a ramified, surveillant phenotype into an amoeboid, activated state characterized by the release of inflammatory mediators. It showed that activated retinal microglia produce high levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and nitric oxide, which amplify local inflammatory cascades and contribute to neuronal stress[23]. Early inflammatory processes in retinal degenerative diseases involve microglial activation which continues over time, facilitating infiltration by leukocytes and sustaining tissue damage[24] Pro-inflammatory microglia have the ability to combat the blood retinal barrier, which enhances tissue injury. These results suggest that although inflammation is a protective mechanism, the persistent pro-inflammatory microglial response is the primary cause of retinal pathology[25].

3. Phagocytic and neuroprotective roles

Neuroprotective functions Microglia also participate in removing the dying cells of retinal ganglia and releasing neurotrophic molecules including, but confined to neurotrophic factor-BDNF and insulin-like growth factor-IGF-1 to promote neuronal survival and regeneration[26,27].The microglial phagocytic suppression in the retina aggravates retinal degeneration, which means that the proper elimination of dying photoreceptors is protective but not detrimental in the initial stage of diseases[28].

4. M1/M2 imbalance

Microglia polarization is described as functional polarization; it is functional M1 (pro-inflammatory) and M2 (anti-inflammatory/neuroprotective). Though it is a simplified version of classification, it still helps to explain the imbalance in microglial functions in case of retinal diseases. M1-like microglia secrete cytotoxic mediators such as IL-6, TNF-α, and reactive oxygen species, whereas M2-like microglia release anti-inflammatory cytokines (IL-10, TGF-β) and growth factors that promote tissue repair[29].The degenerative states in the retinal context lead to the polarization of microglium to the dominant M1 phenotype, leading to inflammation chronicity, and eventual loss of retinal photoreceptors[30]Polarization of microglium to predominantly M2 phenotype is shown to have a major effect of reducing retinal degeneration and maintenance of vision[31].

PATHOGENIC SIGNALING PATHWAYS LOCATION TO RETINAL LESIONS LINKING MICROGLIAL:

1) NF-κB signalling and cytokine storm:

NF-κB is a master transcriptional regulator of inflammatory responses in retinal microglia. Once activated, it induces the expression of TNF-α, IL-1β, IL-6, iNOS, and COX-2. NF-KB is promptly activated in microglia through retinal ischemia reperfusion injury that results in an explosion of inflammatory cytokines, which directly mediates the loss of ganglion cells [32].NF-kB signalling in the retinal microglia remains chronic in diabetic retinopathy models, and is associated with long-term inflammatory damage and vascular permeability[33].

2) NLRP3 inflammasome and pyroptosis

The NLRP3 inflammasome is a cytosolic complex that activates caspase-1 and promotes maturation of IL-1β and IL-18, driving pyroptotic cell death. NLRP3 is strongly upregulated in activated retinal microglia in age-related macular degeneration (AMD), where it contributes to photoreceptor degeneration[34]. Microglial NLRP3 activation induces a feed-forward loop of inflammation that worsens retinal damage[35].

3) P2X7 receptor and ATP-mediated toxicity

Extracellular ATP released from dying neurons activates the P2X7 receptor on microglia, triggering calcium influx, inflammasome activation, and cell death signaling. P2X7 stimulation converts microglia into a highly cytotoxic phenotype capable of amplifying neuronal injury [36]The blockage of the P2X7

receptors in models of retinal degeneration decreases migration of the microglia to the ONL and retains photoreceptors[37] Accordingly, the ATP also serves as a spatial danger cue which connects lesion areas to microglial toxicity.

4) MAPK pathways (p38 / JNK / ERK)

The microglial proliferation, cytokine production, and migration are managed by MAPK signaling pathways that are activated by p38 MAPK in the retinal microglia in response to the optic nerve damage [38]In the 2nd study, JNK signaling can contribute to microglial neurotoxicity, but ERK signaling can contribute to microglial proliferation and chemotaxis[39]. These pathways are based on a mechanistic answer to why microglia located in the vicinity of lesions show an enhanced inflammatory response.

5) TLR4 / MyD88 innate immune activation

TLR4 recognizes damage-associated molecular patterns (DAMPs) released from injured retinal neurons. Once activated, it signals through MyD88 to induce NF-κB and MAPK pathways. TLR4 knockout mice display reduced retinal inflammation and diminished microglial activation after endotoxin challenge[40]. In photoreceptor degeneration, That TLR4 signalling in microglia accelerates neuronal loss by promoting cytokine and ROS production[41]

6) Oxidative stress signaling (ROS and NO)

Activated microglia produce reactive oxygen species (ROS) and nitric oxide (NO), which damage lipids, proteins, and DNA. Microglial oxidative stress is a major contributor to neurodegeneration[42].In the retina, oxidative stress generated by activated microglia exacerbates photoreceptor death in light-induced degeneration[43]

7) Complement cascade (C1q, C3)

The complement system is a powerful mediator of synapse elimination and neuronal injury. C1q and C3 tag synapses for microglial phagocytosis[44] In the retina, complement activation precedes photoreceptor degeneration and that C3 deficiency confers neuroprotection[45]

8) CX3CL1–CX3CR1 axis

The fractalkine receptor CX3CR1 controls microglial migration and activation. CX3CR1 deficiency causes exaggerated microglial neurotoxicity[46]. In retinal degeneration, loss of CX3CR1 leads to excessive subretinal microglial accumulation and accelerated photoreceptor loss[47]

9) TREM2 signaling dysfunction

TREM2 regulates microglial phagocytosis and metabolic fitness. TREM2 deficiency impairs microglial energy metabolism and promotes a neurotoxic phenotype[48].In retinal pathology, reduced TREM2 signaling compromises microglial debris clearance and intensifies inflammatory damage[49]

10) JAK/STAT pathway in microglial expansion

JAK/STAT signalling controls microglial proliferation and cytokine responsiveness. STAT3 activation drives inflammatory amplification in glial cells[50].In retinal injury models, JAK/STAT inhibition reduces microglial accumulation and protects retinal neurons[51]

Summary Table: Pathogenic Signalling Pathways Linking Microglial Location to Retinal Lesions

Pathway	Trigger	Microglial Response	Retinal Outcome
NF-Kb	DAMPs, cytokines	Cytokine storm	Neuronal apoptosis
NLRP3	ATP, ROS	Pyroptosis, IL-1β release	Photoreceptor degeneration
P2X7	Extracellular ATP	Ca^{2+} influx, toxicity	Lesion expansion
MAPK	Stress signals	Cytokines, migration	Neuroinflammation
TLR4/MyD88	DAMPs	Innate immune activation	Accelerated degeneration
ROS/NO	Microglial activation	Oxidative damage	DNA and lipid injury
Complement	C1q/C3	Synapse removal	Neurodegeneration
CX3CL1–CX3CR1	Neuron–microglia signalling	Migration control	Lesion localization
TREM2	Lipid debris	Phagocytic regulation	Repair vs toxicity
JAK/STAT	Cytokines	Microglial expansion	Chronic inflammation

Microglial Pathways in Major Retinal Degenerative Disorders

1) Age-Related Macular Degeneration (AMD)

AMD is marked by progressive degeneration of photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris. Microglial accumulation in the subretinal space is a pathological hallmark of AMD.Human AMD specimens, microglia migrate from the inner retina into the subretinal region where they exhibit an activated phenotype and express pro-inflammatory cytokines, including IL-1β and TNF-α, linking their spatial relocation to outer retinal damage[52].Oxidative stress in the outer retina promotes microglial recruitment and activation, leading to enhanced production of ROS and complement factors that exacerbate photoreceptor injury[53].In a mouse model of AMD,subretinal microglia express high levels of complement C3 and VEGF, contributing to both inflammation and neovascularization[54].Furthermore, inflammasome signalling in retinal immune cells amplifies RPE degeneration, suggesting that microglial NLRP3 activation is an upstream event in AMD pathogenesis[55].

2) Retinitis Pigmentosa (RP)

RP is characterized by genetically driven photoreceptor death, followed by secondary inflammatory responses dominated by microglial activation. Microglial infiltration into the ONL is an early event in RP models and correlates spatially with photoreceptor apoptosis[56].In a transgenic RP mouse model, that activated microglia produce TNF-α and IL-6 in degenerating retinal regions, accelerating rod and cone loss [57].Pharmacological inhibition of microglial activation significantly delays photoreceptor degeneration, indicating that microglia are not merely reactive but actively pathogenic in RP[58].Additionally, found that microglial NADPH oxidase activity increases oxidative stress in RP, linking microglial metabolic pathways to lesion expansion [59].

3) Diabetic Retinopathy (DR)

DR is now recognized as a chronic inflammatory neurovascular disease. Microglial activation precedes overt vascular pathology. Microglia become activated in the diabetic retina before endothelial dysfunction appears, indicating that neuroinflammation is an initiating factor [60].High glucose directly activates retinal microglia, inducing NF-κB signalling and release of IL-1β and MCP-1, which promote vascular leakage and neuronal injury[61]In streptozotocin-induced diabetic mice, observed increased microglial density in the inner retina along with elevated iNOS expression, linking microglial oxidative stress pathways to neuronal apoptosis[62].Moreover, reported that suppression of microglial activation prevents retinal capillary degeneration and preserves visual function[63].

4) Stargardt Disease

Stargardt disease is an inherited macular dystrophy caused by mutations in ABCA4, leading to lipofuscin accumulation and RPE toxicity. Microglial involvement is increasingly recognized as a contributor to disease progression. Toxic BI retinoids released from degenerating RPE cells act as chemotactic signals

that attract microglia into the subretinal space [64].In ABCA4 knockout mice, demonstrated that microglial infiltration into the outer retina is accompanied by increased expression of inflammatory mediators and complement factors [65].Further, reported that suppression of microglial activation reduces photoreceptor loss and inflammatory cytokine expression in Stargardt disease models[66].

5) Glaucoma

Microglial activation is a significant pathogenesis of glaucoma, and microglial neurotoxicity is proved to be directly caused by TNF-A.In an experimental glaucoma disease model, it is shown that activity of the complement pathway by microglia is directly neurotoxic to retinal ganglion cells and induces degeneration of axons[67,68]. The activation of microglial complement pathway is a putative initiator of glaucomatous neurodegeneration[69,70]

THERAPEUTIC IMPLICATIONS:

1)Pathway-Specific Drug Targeting in Retinal Microglia

NF-KB, NLRP3 inflammasome, P2X7 receptor signaling, complement activation, and JAK/STAT cascades modulation have been demonstrated to have considerable potential as microglial pathogenicity in experimental retinal disease models and are shown to both protect neurons and inhibit inflammatory injury.

1.1 NF-κB Inhibition

The Activation of NF-κB drives TNF-α, IL-1β, and IL-6 expression, contributing to neuronal apoptosis and lesion expansion in the retina.NF- kB pharmacological inhibition with pyrrolidine dithiocarbamate (PDTC) was found to significantly preserve retinal neurons in an ischemic injury model. NF- κB inhibition not only decreased the levels of cytokines but also preserved retinal structure, which underlines the importance of specificity of transcriptional regulator inhibition to prevent microglia-induced neurotoxicity without impairment of their homeostatic surveillance roles[71].

1.2 NLRP3 Inflammasome Blockade

The NLRP3 inflammasome is involved in the maturation of IL-1 loop and IL-18 mediated by caspase-1, which results in pyroptotic neuronal death of the retina in murine models, and this effect was blocked by pharmacological inhibition of NLRP3. The results of this study offer strong grounds that inflammasome blockage can be selective to disrupt the destructive microglial signaling without affecting the essential clearance roles of microglia [72]

1.3. P2X7 Receptor Antagonism

The role of selective P2X7 antagonists is to decrease microglial activation, as well as restrict neurotoxicity, in neuroinflammation models. P2X7 blockade also suppresses neuron protection by inhibiting ATP-mediated excessive activation of microglia as well as the heightening of local inflammatory responses[73]

1.4. Complement C3 Inhibition

Activation of C3 causes over synapse loss and neuronal loss in models of retinal degeneration. Pharmacological blocking of complement C3 in a model of retinal degeneration spared photoreceptor loss and decreased microglial phagocytic death. The above-mentioned approach focuses on the possibility of controlling microglial effector functions without globally inhibiting their immune surveillance[74].

1.5. JAK/STAT Pathway Modulation

Selective JAK/STAT inhibition suppresses microglial proliferation, reduces IL-6 and TNF-α levels, and mitigates neuroinflammatory damage in retinal injury models. These findings suggest that targeting intracellular signalling hubs like JAK/STAT[75].

2) DENDRIMERS AS TARGETED THERAPEUTIC APPROACH:

2.1. Selective Accumulation in Activated Retinal Microglia

Preferential localization in activated microglia and sparing of quiescent microglia and other types of cells in the retina is one of the most important properties of dendrimers. Their study demonstrated that microglia, which reside in the inflamed and damaged neural areas such as the retina, accumulated hydroxyl-terminated PAMAM dendrimers selectively because endocytosis of dendrimers was enhanced and the dynamics of the membrane of activated microglial cells was altered. It was proved that in the microinflammatory pathology dendrimers can be targeted in specific areas, which makes the work highly effective[(76)]

2.2. Dendrimer–Drug Conjugates for Neuroprotection

Beyond passive targeting, dendrimers can be chemically conjugated with therapeutic agents to form stable nanoconjugates that release drugs intracellularly following microglial uptake. Dendrimer–N-acetylcysteine (NAC) conjugate designed to deliver antioxidant therapy directly to activated microglia in retinal degeneration models[(77)]The study further demonstrated that dendrimer conjugation enhanced the intracellular availability of NAC within microglia, allowing effective suppression of reactive oxygen species and downstream inflammatory cascades at doses far lower than those required with conventional systemic therapy[(78).]

3. Exosomes as Targeted Therapeutic Platforms for Modulating Retinal Microglia:

Exosomes are nanosized extracellular vesicles (30-150 nm) discharged by nearly every type of cell and serve as a natural mechanism of transporting proteins, lipids, and nucleic acids to control intercellular communication. Exosomes have earned special consideration in the retinal neuroinflammation setting due to their cross-biological barrier properties, inherent biocompatibility, and the ability to control the microglial activation phenotype. In comparison with synthetic nanoparticles, exosomes are of biological origin and have endogenous surface markers that can be used to target cells making them exceptionally applicable in targeted therapy of retinal degenerative diseases. This finding gave the conceptual basis of utilizing exosomes as therapeutic agents to re-program the actions of microglials in disease conditions[(79)]

3.1. Exosome-Mediated Regulation of Microglial Phenotype

In retinal degeneration, microglia often transition into a pro-inflammatory state characterized by excessive production of TNF-α, IL-1β, and reactive oxygen species. This pathological trigger can be inhibited through exosomes that transfer regulatory microRNAs that downregulate the inflammatory transcription factors and signal cascades. This effect causes the microglia to shift away and return to a less cytotoxic state and promote survival of neurons [(79)]

3.2. MSC-Derived Exosomes in Retinal Neuroprotection

Exosomes produced by mesenchymal stem cell (MSC) have strong neuroprotective effects in the retinal degeneration and optic nerve injury models. Their results revealed that exosomes generated by MSCs maintained the survival of the retinal ganglion cells, lessened microglial activation as opposed to neuronal replacement or differentiation. A key result of their work was that MSC-derived exosomes acted by inhibiting microglial activation and not via neuronal replacement or differentiation. Exosomes therapy lessened the thickness of activated microglia and changed their morphology pointing to the restoration of homeostatic microglial work [(80).]

4) INTRANASAL AND INTRAVITREAL STRATEGIES FOR TARGETING RETINAL MICROGLIAL PATHWAYS:

Effective delivery of drugs across biological barriers is key to the success of therapies that will regulate the activity of microglial processes in retinal degenerative diseases. These regulate the systemic drug delivery to the retina, since blood-retinal barrier prevents the release of pathogenic microglial signals in the retina (Bloom, 2016).These two methods are complementary and highly translational in nature; they can be used to achieve targeted retina immunotherapy.[(81)]

4.1. Intranasal Modulation of Neuroinflammation and Microglial Activation

Retinal microglia activated release cytokines, chemokines, reactive oxygen species, and inflammasome products which cause further neuronal [81]damage. Direct exposures of neural tissues to therapeutic agents suppressing these inflammatory cascades can be achieved through intranasal delivery. Drugs delivered in the form of intranasal only distributes them to neural tissues, not to peripheral organs, which has a greater therapeutic index when used to treat the retina [82].

4.2. Intravitreal Delivery: Direct and Precise Retinal Targeting

Intravitreal injection is the most efficient way of obtaining high local drug concentrations in the retina and immediate high local drug concentrations. This pathway circumvents all systemic and vascular it can guide therapeutics directly to the microglia located in the inner plexiform layer, outer plexiform layer, and outer nuclear layer and inhibition of microglial activation by intravitreal delivery is a potent protective factor against inflammatory retinol neurons[83]

4.3. Intravitreal Targeting of Inflammasome Pathways in AMD

Inflammasome activation is a central mechanism linking microglial inflammation to retinal degeneration, particularly in AMD.Inflammasome-mediated production of IL-1β and IL-18 in retinal immune cells drives chronic inflammation and photoreceptor loss. Intravitreal delivery was found the best pathway in order to reach adequate levels of drugs in the subretinal bed, where microglial inflammasome is one of the direct causes of disease pathology[84].

CHALLENGES AND TRANSLATIONAL LIMITATIONS:

Blood–Retinal Barrier (BRB) Penetration:

One of the most significant obstacles in retinal drug development is the presence of the blood–retinal barrier, a highly specialized vascular interface that tightly regulates molecular transport into neural tissues. Structurally and functionally analogous to the blood–brain barrier, the BRB severely restricts the entry of most systemically administered therapeutic agents, particularly large molecules and nanocarriers. Tight junction proteins such as claudins and occludins form a highly selective endothelial barrier that excludes over 98% of small-molecule drugs and nearly all biologics from entering neural tissues under physiological conditions this limitation directly affects microglial-targeted therapy Their review emphasized that localized delivery of inflammasome inhibitors is essential to suppress these pathways without impairing systemic immune defense[85].Even during retinal degeneration, when BRB integrity becomes partially compromised, drug penetration remains unpredictable and spatially heterogeneous breakdown varies between patients and disease stages, making systemic dosing unreliable for consistent microglial modulation[86].While intravitreal and intranasal strategies partially overcomes this limitation, these approaches introduce new challenges including invasiveness, patient compliance issues, and regional variability in drug diffusion across retinal layers[87].

Microglial Specificity and Cellular Off-Target Effects:

The other main restriction is that the selective targeting of the microglia without compromising other retinal immune and neural cell groups is not easily obtained. Many surface receptors/signaling pathways of microglia are shared with infiltrating macrophages, Muller glia, and astrocytes, which complicates cell-specific design of a therapeutic strategy. Recurring microglia marker proteins like Iba1, CD11b, and CX3CR1 are also expressed by peripheral monocytes and tissue macrophages in an inflammatory state. Consequently, treatments aimed at inhibiting the activity of microglia will also have the undesirable outcome of suppressing protective immune responses or interference with important glial support functions[88]

Long-Term Safety and Immune Homeostasis:

Long-term inhibition of microglial signaling lowers the process of synaptic remodelling, and predisposes neurons to subsequent damage [89] Long term impairment of microglia in test models results in distorted retinal circuitry and visual processing[90]

FUTURE PERSPECTIVES

The latest developments underline that the emerging direction in future retinal therapy should be the evolution of the concept of general immunosuppression to the individual regulation of the microglial signaling pathway. Microglia show highly dynamic transcriptional profiles whose characteristics vary with disease-stage, indicating that therapeutic interventions should also focus on molecular program of interest, as opposed to generally inhibiting the activity of microglia[91]. This finding indicates that precision targeting must be guided by the identification of signaling pathways selectively activated in pathogenic microglial states, such as inflammasome activation, NF-κB signalling, and oxidative stress responses. These findings justify the establishment of therapies targeting the specific interference with microglial pathways that are linked to the disease and do not disrupt more fundamental physiology, such as the clearance of debris and the maintenance of the synapses. Precision targeting is thus logically the most appropriate approach to achieve the greatest neuroprotection at the lowest possible adverse effects of unselective immune suppression[92].

CONCLUSION:

As homeostatic regulators and pathological drivers of retinal degeneration, microglia are increasingly recognized as being a spatially organized neuroimmune disease. Laminar location, local neuronal signals, and disease stage have a close control over microglial behavior instead of being uniform throughout the retina. The synaptic layers of microglia support the retinal integrity in physiological environments through the process of surveillance, synaptic perfecting, as well as the removal of debris. Nevertheless, during degeneration, the targeted migration into neuronal layers represents an important transition to maladaptive inflammatory phenotypes that strengthen tissue injury and promote lesion progression.

This review illustrates the relationship between the spatial redistribution of microglia and neuronal vulnerability by region-specific engagement of signaling pathways like NF-KB, NLRP3 inflammasome, MAPK cascades, purinergic signaling, complement activation, and oxidative stress responses. Their overlap in a range of retinal diseases indicates that the chronic activation and microglial mislocalization are not abnormalities of the disease, but they are everywhere, ubiquitous pathogenic factors. Eventually, immune homeostasis, synaptic stability, and neuronal survival are all undermined in case of inflammation failure to be addressed.

Regarding treatment, these findings point out the disadvantages of global immunosuppression and the need to be specific to these treating pathways which address pathogenic microglial pathways without disrupting essential physiological functions. Despite the ongoing problem of cellular specificity, penetration of the bloodretinal barrier, and long-term immune control, the use of dendrimer-based drug delivery, exosome-mediated immune control, and intranasal or intravitreal targeted delivery is promising as an avenue towards spatially localized microglial targeting.

Putting everything mentioned aside, a reinterpretation of retinal degeneration as a location-to-lesion paradigm provides a consistent framework through the help of which the microglial regional identity can be linked to the progression of the disease and new opportunities offered to pursue focused neuroprotective therapies aimed at preserving vision and regenerating retinal immune responses.

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