Neuroinflammation in retinitis pigmentosa: Therapies targeting the innate immune system

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Retinitis pigmentosa (RP) is an important cause of irreversible blindness worldwide and lacks effective treatment strategies. Although mutations are the primary cause of RP, research over the past decades has shown that neuroinflammation is an important cause of RP progression. Due to the abnormal activation of immunity, continuous sterile inflammation results in neuron loss and structural destruction. Therapies targeting inflammation have shown their potential to attenuate photoreceptor degeneration in preclinical models. Regardless of variations in genetic background, inflammatory modulation is emerging as an important role in the treatment of RP. We summarize the evidence for the role of inflammation in RP and mention therapeutic strategies where available, focusing on the modulation of innate immune signals, including TNFα signaling, TLR signaling, NLRP3 inflammasome activation, chemokine signaling and JAK/STAT signaling. In addition, we describe epigenetic regulation, the gut microbiome and herbal agents as prospective treatment strategies for RP in recent advances.

KEYWORDS
retinal inflammation, innate immune, gut microbiome, trained immunity, epigenetic modification, retinitis pigmentosa

1 Introduction
1.1 Retinal inflammation and RP

Retinitis pigmentosa (RP) is a category of inherited retinal dystrophies marked by vision loss and, ultimately, blindness. More than 3000 mutations in over 80 distinct genes or loci have been identified as causes of non-syndromic RP (1, 2). These mutations can be transmitted in an autosomal-dominant, autosomal-recessive, or X-linked manner. There are also syndromic forms of RP, such as Usher syndrome and Bardet-Biedl syndrome (3). The prevalence of RP is reported to be 1/3,000 to 1/5,000 (https://www.orpha.net/consor/cgi-bin/index.php?lng=EN). Early in the progression of RP, patients experience night blindness and difficulty with dark adaptation. They gradually lose peripheral vision and...
develop tunnel vision as the disease advances, indicating the loss of rod function. Cone involvement contributes to visual acuity decline over time, and finally, typically in middle age, central vision loss occurs (2). Due to its clinical and genetic heterogeneity, RP has limited therapeutic options. It has long been recognized that inflammation and immune responses are associated with RP, and this theme has recently gained increasing attention (4–6). Greater understanding of the molecular processes driving RP inflammation is expected to provide new therapeutic approaches independent of the genetic background.

Inflammation activation is a prominent feature of RP. In RP, inflammation is characterized by activation of the innate immune system, including dysfunction of the immune barrier, activation and infiltration of immune cells, and upregulation of topical and peripheral inflammatory factors. Bone-spicule pigmentation, attenuated retinal vessels and waxy pallor of the optic disc are typical clinical manifestations of RP. In addition, inflammatory cells are commonly observed in the vitreous due to the collapse of the blood–retina barrier (BRB). Higher cell density correlates with younger age and impaired visual function (6). In addition, it has been reported that increased aqueous flare in RP patients correlates closely with visual function and the extent of global retinal degeneration (7–11). Aqueous flare is generally seen in individuals with inflammatory ocular disorders, indicating deficits of the blood–aqueous barrier and inflammatory protein/cell leakage (12, 13). BRB disruption begins early in the disease. Prior to the infiltration of inflammatory cells and photoreceptor (PR) starvation, the tight junctions of the retinal pigment epithelium (RPE) and the retinal vasculature become leaky, thereby promoting the formation of an inflammatory milieu and the degeneration of PRs (14–17).

Microglia are essential components of the retinal innate immune system and play a pivotal role in retinal inflammatory responses. Gupta et al. reported that microglial activation is engaged in human RP. With thinning of the PR layer, microglia are maintained throughout life independent of circulating monocytes and by self-renewal (34, 40, 41). Microglia express a variety of receptors (e.g., CX3CR1, TLRs, IL-1R, and TNFR) that allow them to detect environmental changes and initiate the inflammatory signal cascade (42). Microglia activation induces a robust inflammatory response, including the release of proinflammatory factors, phagocytosis, and inflammatory cell recruitment. Excessive microglial phagocytosis contributes to local inflammation and neurodegeneration (43, 44).

Classically, activated microglia were categorized into two groups: M1 (classically activated) and M2 (alternatively activated), with the belief that M1 microglia secrete proinflammatory factors such as TNFα, IL-1β, IL-6, and inducible nitric oxide synthase (iNOS) that fuel inflammation, whereas M2 microglia produce anti-inflammatory cytokines (e.g., IL-4, IL-10, IL-13, IL-18) that are beneficial for damage repair (45). Recent research, however, suggests that the microglial phenotype varies in response to environmental changes (46).

In healthy retinas, microglia tile the inner and outer plexiform layers without overlapping (37), where they are ramified cells responsible for immune surveillance and maintenance of synaptic structure and transmission (47–50). In response to insults, microglia rapidly change into an amoeboid appearance and migrate into lesion areas, removing dead/dying neurons and neuronal debris while concurrently releasing proinflammatory factors as well as protective cytokines and trophic factors to repair damage and restore...
homeostasis (51), after which microglia recover to the “resting” state; this process usually results in minimal retinal remodeling.

In RP retinas, initial mutation-driven PR degeneration increases extracellular signal molecules (e.g., ATP, HSPs, HMGB1, DNA, and many others) termed damage-associated molecular patterns (DAMPs) (52–56). The “eat-me” signal, phosphatidylserine, appears on stressed rods (19). Microglia proliferate and infiltrate the PR layer and subretinal space, where they function as reactive phagocytes, phagocytose dead and stressed PRs, secrete proinflammatory cytokines (e.g., TNFα and IL-1β) and chemokines (e.g., CCL2 and RANTES), and recruit infiltrating immune cells (19, 24, 57, 58). Due to this mutant genetic background, however, microglial activation persists, and the continuous production of inflammatory and cytotoxic factors exacerbates PR loss until the late stage, at which point PRs mostly die and the retinal structure is severely damaged (59).

Müller glia are another group of retinal cells engaged in degeneration. Müller glia are retinal macroglia that provide homeostasis, metabolism, and functional support for neurons (60). Depending on the severity, the Müller glial response to injury refers to reactive gliosis accompanied by Müller proliferation or not. Reactive gliosis can be beneficial because it releases protective factors such as neurotrophic factors, whereas prolonged gliosis is detrimental and generally results in neurodegeneration (61). Müller glia are potential modulators of retinal inflammation. Upon BRB disruption, Müller glia compensate for RPE deficiency by sealing the leaky choroid and inducing claudin-5 expression (14). Müller glia share characteristics with immune cells. Müller glia express multiple cytokine receptors and are a major source of cytokines and inflammatory factors (62). Proteomic evidence supports the capacity of Müller glia for antigen presentation and inflammatory signaling transduction in response to immune stimulation (63, 64). Müller glia contribute to the phagocytic clearance of dead PRs (65). Moreover, the interaction between Müller glia and microglia modulates retinal inflammation and degeneration (66–68).

As the predominant glial population of the retina, Müller glia are abundant and widely distributed. Müller glia traverse the thickness of the neuroretina structurally, allowing them to keep touch with all types of retinal cells. Due to its neurotrophic function and regeneration potential, the Müller cell has been studied in a variety of degenerative retinal disorders (69). In actuality, Müller glia are also intimately linked to retinal inflammation. For more information about how Müller glia interact with the innate immune system and monitor retinal inflammation, we refer the reader to this article (70).

Complicated mechanisms are involved in the regulation of retinal inflammation in RP. Microglia and Müller glia are major cellular populations that express and modulate these signaling pathways (Figure 1). Here, we review treatment strategies from the perspective of inflammation management (Table 1), focus on molecular mechanisms related to immunomodulation, and discuss new findings regarding epigenetic modification and the gut microbiome as novel therapies for RP.

2 Mechanisms related to inflammation in RP

2.1 TNFα signaling

Tumor necrosis factor α (TNFα) is a strong proinflammatory cytokine that plays vital roles in immune modulation, cell proliferation, differentiation, and apoptosis. TNFα is produced predominantly by T and innate immune cells and is initially synthesized as transmembrane protein (tmTNFα), a precursor that requires proteolytic cleavage by TNFα-converting enzyme (also ADAM17) to release a soluble form (sTNFα) (124). Both tmTNFα and sTNFα are implicated in the inflammatory response.

TNFα initiates a signal cascade by binding to its receptors, TNFR1 and TNFR2. TNFR1 is activated by both tmTNFα and sTNFα, whereas TNFR2 is proposed to be fully activated primarily by tmTNFα (125). Ligand binding to TNFR1 recruits the adaptor molecule TNFR1-associated death domain protein, which then leads to the assembly of several signaling complexes known as complexes I, IIA, IIB, and IIC. Complex I formation stimulates nuclear factor kappa B (NF-kB) and mitogen-activated protein kinases (MAPKs). Complex IIA and IIB assembly activates caspase-8 and facilitates apoptosis, and complex IIC formation activates the mixed lineage kinase domain-like protein and induces necroptosis and inflammation. TNFR2 stimulation activates NF-kB, MAPKs, and protein kinase B (125).

TNFα is postulated to participate in the pathogenesis of RP (74). TNFα and TNF expression levels are elevated in the retina of RP models and in the aqueous humor of RP patients (24, 74, 126–128); microglia (129) and Müller glia (130, 131) are the primary cellular sources of TNFα. TNFα signaling has been found to mediate PR death via RIP1/3-related necrosis and caspase3/7-dependent apoptosis, in addition to triggering proinflammatory signaling in the RP retina (73, 126).

2.1.1 NGF receptor and TNFα production

Increased TNFα expression in the retina is linked to nerve growth factor (NGF) receptor activation. Müller glia in rhodopsin mutant RP model RHO3P347S mice upregulate the expression of TrkC. T1, a truncated TrkC receptor isoform, and its ligand NT-3. TrkC.T1 increases local TNFα production by activating MAPK/Erk, ultimately leading to PR death. This process can be reversed by genetic knockdown of TrkC.T1, TrkC antagonism, or MAPK/Erk inhibition (71). Similarly, TrkC.T1 knockout (KO) and TrkC inhibition increased retinal
ganglion cell survival in a mouse model of glaucoma by reducing TNFα production (132), implying that TrkC.T1 is upstream of TNFα.

It has been reported that microglia-derived proNGF facilitates PR death via p75NTR (133), proNGF binding to p75NTR in Müller glia induces robust expression of TNFα and TNFα-dependent neuron death in rodent retina (131, 134), the expression levels of proNGF and p75NTR are increased in the retina of rd10 at early degenerative stages, pharmacological antagonism of p75NTR with THX-B ((1,3-diisopropyl-1-[2-(1,3-dimethyl-2,6-dioxo-1,2,3,6tetrahydro-purin-7-yl)-acetyl]-urea) affords neuroprotection to PRs, and the treatment also mediates reduction of TNFα production, microglial activation, and reactive gliosis (72).
### TABLE 1  Treatments for retinitis pigmentosa and related mechanisms.

| Mechanism | Approach | Gene/molecule/agent | Effect | Model | Ref. |
|-----------|----------|---------------------|--------|-------|------|
| TNFα signal | Genetic KD | TrkC T1, KB1368 | Suppress p-ERK activation and TNFα production | RHOP347S mouse | (71) |
| | p75NTR antagonism | THX-B | Inhibit reactive gliosis and TNF secretion | Rd10, RHOP347S mouse | (72) |
| | Genetic KD | Tnfα | Decrease proinflammatory factors (IL-1β, IL-6, IL-17, RANTES, CCL2) as well anti-inflammatory factor (IL-10 and IL-13) | T17MRHO mouse | (73) |
| | TNFα blockade | Infliximab | Decrease caspase-3 activation and reactive gliosis | Zaprinast-induced degeneration of porcine retina | (74) |
| | | | | | |
| TLR signal | Genetic KO | Th2 | Suppress microglial activation and infiltration | Rd10, P23H mouse | (76) |
| | Genetic KO | Th4 | Reduce CCL2 expression, microglia activation and gliosis | LD Abca4−/−, Rdh8−/− mouse | (77) |
| | | Minocycline | Suppress microglial activation and migration | P23H-1, RCS rat, Prph2 R22/ R22 mouse | (78, 79) |
| | | Minocycline | Decrease microglial activation and proinflammatory gene transduction | LD mouse retina | (80, 81) |
| | | Myd88 | Reduce chemokine (CCL2, CCL4, CCL7 and CXCL10) expression and microglial activation | Rd10 mouse | (82) |
| | Myd88 inhibitor peptide | Myd88 inhibitor peptide | Suppress microglia infiltration, increase neuroprotective microglia, expression of MCP-1, IL-27 and crystalline | Rd10 mouse | (84, 85) |
| | AMWAP | AMWAP | Blockade TLR-mediated NF-κB activation | 661W cell-microglia co-culture | (86) |
| NLRP3 signal | NLRP3 inhibition | N-acetylcysteine | Decrease NLRP3 expression and microglial infiltration | Rd10 mouse, P23H rat | (24, 87) |
| | P2X7R blockade | PPADS | Promote photoreceptor survival | Rd1 mouse | (88) |
| | IL-1β blockade | BBG | Decrease inflammasome components (NLRP3, cleaved caspase-1 and mature IL-1β proteins) | P23H rat | (87) |
| | CX3CL1/CX3CR1 supplement | CX3CL1 | Decrease microglial infiltration, phagocytosis and activation | Rd10 mouse | (89) |
| | | AA-V8-CX3CL1 | Improve cone survival | Rd1, rd10 and rhodopsin null mouse | (90) |
| | | Norgestrel | Upregulate CX3CL1/CX3CR1 signal | Rd10 mouse | (91, 92) |
| | CCL2/CCR2 | Lecithin-bound iodine | Suppress CCR2 positive macrophage invasion | Merk mouse | (93, 94) |
| | Genetic KO | Ccl2 | Reduce apoptosis | Rd10 | (95) |
| | Genetic KD | CCL2 siRNA | Decrease macrophage/microglia infiltration | LD rat retina | (97) |
| JAK/STAT pathway | JAK/STAT inhibition | AG490 | Improve PR survival | LD mouse retina | (98) |
| | JAK/STAT activation | OECs transplantation | Inhibit JAK2/STAT3 activity and increase SOCS3 | RCS rat | (99) |
| | pMSC-RGC transplantation | pMSc-RPGs | Activate JAK/STAT, improve retinal structure and function | Rd12 | (100) |
| | CNTF supplement | rAAV2/2-hCNTF | Upregulate STAT3, SOCS3, SOCS3 and complement factor (C3, C4a, C1b) expression | Rhodopsin null mouse | (101) |
| | LV-hCNTF | Stimulate expression of LIF, Ecdn2; activate gp130/JAK/STAT | Rd1/peripherin P216L transgenic mice | (102) |

(Continued)
TABLE 1 Continued

| Mechanism                  | Approach            | Gene/molecule/agent | Effect                                                                 |
|----------------------------|---------------------|---------------------|------------------------------------------------------------------------|
| Epigenetic modification    | HDACi               | HDACi               | Decrease activity of PARP, preserve cone morphology                     |
|                           | JQ1                 | JQ1                 | Suppress microglial proliferation, migration, and cytokine production   |
|                           | LSD1 inhibition     | Tranylcypromine; GSK2879552 | Inhibit transcription of inflammatory genes and inflammation |
|                           | H3K27me3 inhibition | DZNep               | Improve PR survival                                                     |
| miRNA inhibition           | AAV-miRNA modulator of miR-6937 | Improve ONL thickness and ERG response  |
| miRNA supplement           | AAV- miR-204        | AAV- miR-204        | Suppress microglia activation                                           |
| Herbal agent               | Curcumin            | Inhibit microglial activation and expression of CCL2, TIMP-1, improves retinal morphology |
|                           | Lycium barbarum polysaccharides | Inhibit NF-kB and HIF-1α expression          |
|                           | Zeaxanthin dipalmitate | Inhibit STAT3, CCL2, MAPF pathways           |
|                           | Saffron             | P2X7R signaling blockade, decrease vascular disruption |
|                           | Resveratrol         | Downregulate microglial migratory, phagocytic, and proinflammatory cytokine production |
|                           | JC19                | Improve PR survival, sirtuin1 activation may be the protective mechanisms |
| THX-B, (1,3-diisopropyl-1-[(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-yl)-acetyl]-urea; KD, knock down; KO, knock out; LD, light damage; MyD88, myeloid differentiation factor 88; AMWAP, activated microglia/macrophage whey acidic protein; PPADS, pyridoxal-phosphate-6-azolonic acid; RING, Brilliant Blue G; AAAD, adeno-associated virus; siRNA, small interfering RNA; PR, photoreceptor; OECs, olfactory ensheathing cells; SOCS, suppressor of cytokine signaling; pMSC-RPCs, primitive mesenchymal stem cell-derived retinal progenitor cells; rAAV2/2, recombinant adeno-associated virus serotype 2; LV, lentiviral vector; LIF, leukemia inhibitory factor; Edn2, endonulcin2, HDACs, histone deacetylase inhibition; BET, bromodomain and extraterminal domain; LSD1, lysine demethylase 1; miRNA, microRNA; ONL, outer nuclear layer; ERG, electroretinogram; TIMP-1, tissue inhibitor of metalloproteinases |

2.1.2 TNFα inhibition

TNFα knockdown in the T17M rhodopsin mutant mouse model reduces PR death and PR-related functional loss, and this neuroprotective effect is associated with reductions in proinflammatory cytokines (IL-1β, IL-6, IL-17, RANTES) and chemokines (CCL2) (73).

Infliximab and adalimumab are biological TNFα inhibitors approved for treating inflammatory disorders such as Crohn’s disease, ulcerative colitis, rheumatoid arthritis, plaque psoriasis, and uveitis (125, 135). By lowering the expression of TNFR1 and caspase-3 activity, infliximab alleviated retinal degeneration induced by PDE6 inhibition in cultured porcine retina (74, 127). Adalimumab administered intraperitoneally or topically improved PR survival while decreasing microglial activation and reactive gliosis in the rd10 retina. Inhibition of PARP and RIPK signaling, as well as NLRP3 inflammasome assembly, are mechanisms involved in this protective response (25, 75).

2.1.3 Protective effects of TNF signaling

Notably, TNFα KO retinas tend to express both pro- and anti-inflammatory factors at reduced levels when compared with controls (73), implying that removing TNFα would also damage the immune system’s defenses. Recent work by Kuhn et al. established that TNFα, in collaboration with TNFR1, TNFR2, and p75NTR, induces signals that are indispensable for neural development and that disturbances to TNFR family signaling result in unhealthy axonal development (136).

ADAM17 regulates the expression of TNFα as well as the receptor TNFR (124). Muliyil et al. reported that ADAM17 and soluble TNF mediate a novel cytoprotective pathway in
**Drosophila.** Loss of ADAM17 or TNF/TNFR signaling drives the accumulation of lipid droplets and degeneration in the *Drosophila* retina, whereas restoration of ADAM17 or TNF/TNFR in glia is sufficient to rescue the degeneration phenotype. TNF and TNFR are explicitly needed in glia; loss of either in glia, but not neurons, leads to the accumulation of lipid droplets. Furthermore, inactivation of ADAM17 in human iPSC-derived microglia similarly induces aberrant lipid droplet accumulation and mitochondrial reactive oxygen species generation (137), indicating that comparable processes in which TNF works not as an inflammatory trigger but as a trophic survival factor (137) may also be involved in the mammalian retina.

Benoot et al. evaluated the numerous contradictory findings of TNFα application in lung cancer (138), bringing to our awareness the varied functions of various TNF family members and the positive impacts of TNF signaling. Modern genomic, transcriptomic, and proteomic techniques are useful for identifying signaling events and molecules in signal transduction (139, 140). Tanzer et al. (141) discussed in detail for identifying signaling events and molecules in signal transduction (139, 140). Tanzer et al. (141) discussed in detail how modern proteomic approaches offer a novel perspective on TNF signaling.

Currently, the precise mechanisms of TNFα synthesis remain obscure. Future investigation of TNFα signaling requires the power of new technology, and the potential protective function of TNFα merits greater consideration.

### 2.1.4 TNFα and microglia-Müller glia interaction

Müller glia exposed to activated microglia modify the expression of a variety of signaling molecules, including (1) elevation of growth factors such as GDNF and leukemia inhibitory factor (LIF), (2) enhanced proinflammatory factor production, and (3) overexpression of chemokines and adhesion proteins (142). TNFα is the most prevalent cytokine produced by reactive microglia, and it stimulates LIF expression in Müller glia in a p38MAPK-dependent manner. Inhibition of p38 MAPK activity lowered LIF expression and accelerated PR mortality in light-damaged retinas (143), similar to previous reports that TNFα prevents cell death by activating the JAK/STAT3 pathway through the IL-6 receptor (144). When TNFα stimuli engage previously activated Müller glia, however, inducible cytokines consisting of more proinflammatory cytokines (TNFα, iNOS, IL-6) and less LIF are produced (145). In other words, depending on the type and degree of stimuli, Müller glia activation generates both neuroprotective and proinflammatory responses, and Müller glia under continuous stimulation are likely to exhibit a detrimental phenotype.

### 2.2 TLR signaling

Toll-like receptors (TLRs) are a class of pattern recognition receptors (PRRs) responsible for identifying pathogen-associated molecular patterns (PAMPs) and DAMPs and mediating immune responses; the generation of PAMPs or DAMPs prompts pathogen invasion or tissue injury. TLR expression is conserved among species, and to date, 10 TLRs (TLR1–10) in humans and 12 TLRs (TLR1–9 and TLR11–13) in mice have been described. TLRs are predominantly but not exclusively expressed on immune cells (146–148).

TLRs serve as the first line of defense for the innate immune system. Upon recognition of DAMPs or PAMPs, TLRs dimerize and initiate recruitment of Toll/IL-1 receptor (TIR) domain-containing adaptor molecules, including myeloid differentiation primary response 88 (MyD88), TIR-domain-containing adaptor-inducing interferon-β (TRIF), MyD88 adaptor-like protein (Mal), and TRIF-related adaptor molecule (TRAM), thereby initiating intracellular signaling cascades: the MyD88- or TRIF-dependent pathways (146). TLR activation facilitates the transduction of NF-kB and MAPK (149–151), as well as the release of proinflammatory cytokines (TNFα, IL-6, IL-1β, and IFNβ), chemokines, and cluster of differentiation 80 (CD80), CD86, CD40, and major histocompatibility complex class II (146).

Activation of TLR signaling has been shown to worsen inflammation and accelerate the course of RP (77, 152, 153). Microglia highly express TLRs (154), and TLR activation in the retina facilitates microglial activation and infiltration (77, 155). Moreover, microglia in the rd1 retina undergo RIP1/RIP3-dependent necroptosis mediated by TLR4 activation, which amplifies retinal inflammation and destruction with large amounts of proinflammatory cytokines (TNFα and CCL2) (152).

#### 2.2.1 DAMPs activate TLRs in RP

High-mobility group box-1 (HMGBl) is a proinflammatory factor and DAMP released by dying cells or activated macrophages that mediates the immune response via PRRs (156–158). HMGBl stimulates an inflammatory response in diabetic retinopathy through TLR4/NF-kB signaling (159).

Increased levels of HMGBl were detected in the vitreous of patients with RP, along with the presence of necrotic enlarged cone cells (53). In cultured cone-like 661W cells, recombinant HMGBl treatment induces apoptosis and upregulates the expression of IL-6 and TNFα (160), and external HMGBl induces retinal ganglion cell death via TLR2/4 signaling (161), whereas HMGBl inhibition or neutralization augments the inflammatory response and promotes retinal neuron survival (162, 163).

#### 2.2.2 TLR blockade

Upregulation of Tlr2, Il1b, Myd88 and Tirap was found in RP model rd10 and P23H mice, demonstrating TLR activation involvement in RP-associated retinal degeneration. Genetic deletion of TLR2 alleviated PR loss and vision impairment in...
both models (76). Similarly, in a light-induced retinal degeneration model, genetic TLR4 deletion reduced retinal inflammation and degeneration (77). Minocycline is an effective microglial inhibitor. In inherited and induced RP models, minocycline administration decreased microglial infiltration and proinflammatory molecule expression and promoted PR survival and functional retention (78–82). Minocycline treatment suppresses MAPK and NF-κB signaling in LPS-stimulated microglia (164), and it has been ascertained that minocycline prevents microglial activation by inhibiting TLR2 (165, 166) and TLR4 (167) signaling.

2.2.3 MyD88

Most TLRs (except for TLR3) use MyD88 as a downstream adaptor protein; moreover, MyD88 is a component of the IL-1R signaling cascade (168, 169). MyD88 features a death domain and a TIR domain. Upon TLR/IL-1R ligation, MyD88 is recruited to the receptor and interacts with IRAK2/4 through their death domains, which activates NF-κB, activator protein-1, and interferon regulatory factors (169).

MyD88 KO mice display attenuated immune responses and are unable to produce normal levels of inflammatory cytokines (170). This diminished immune response preserved PR survival and retinal function during degeneration in rd1 mice lacking MyD88 (83). Similarly, pharmacologic inhibition of MyD88 in rd10 mice with MyD88 inhibitor peptide reduced PR apoptosis and improved rod-related function; treatment also lowered the number of microglia in the PR layer and increased microglia/macrophage expression of the neuroprotective marker Argl (84). Further proteomic analysis demonstrated that treatment with such MyD88 inhibitor peptides boosted crystalline expression, suggesting that MyD88 inhibition may also enhance intrinsic tissue-protective mechanisms (85).

2.2.4 AMWAP

Activated microglia/macrophage WAP domain protein (AMWAP), secreted by reactive microglia, is a hallmark of microglial activation. While AMWAP overexpression in microglia lowers the production of proinflammatory factors such as IL-6, iNOS, CCL2, CASP11, and TNFα, extracellular AMWAP endocytosed by microglia inhibits TLR2- and TLR4-induced NF-κB translocation by preventing IRAK-1 and 1x8to proteolysis (86). AMWAP administration lowers the apoptosis of 661w cone-like cells treated with microglia-conditioned medium (86), indicating that AMWAP is a potential self-modulator of TLR signaling in microglia.

The TLR signaling pathway plays a fundamental role in inflammatory and immune responses. Molecules released from injured neurons induce an intracellular signaling cascade through TLR/MyD88, contributing to further retinal damage. Blockage of TLR/MyD88 alleviates RP by reducing inflammatory responses and enhancing protective effects.

2.3 NLRP3 inflammasome activation

Inflammasomes are cytosolic multiprotein complexes that facilitate the release of mature IL-1β, IL-18, and cleaved caspase-1. The intracellular PRRs, NOD-like receptors (NLRs), are important components of the inflammasome complex. Some NLRs oligomerize upon activation to form multiprotein complexes that function as caspase-1-activating scaffolds (171). NLRP3 is the most well-studied NLR; NLRP3 inflammasome assembly requires two signals: a priming signal that activates NF-κB, followed by transcription of NLRP3, pro-IL-1β, and pro-IL-18. A second activation signal facilitates the recruitment and oligomerization of NLRP3, adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD), and pro-caspase-1. Once the inflammasome is assembled, it stimulates pro-caspase-1 self-cleavage and activation, and cleaved caspase-1 catalyzes pro-IL-1β and pro-IL-18 maturation and induces the release of their mature forms. The recognition of DAMPs or PAMPs that act through PRRs such as TLRs or cytokines that act through particular receptors (TNFR, IL-1R) exemplifies the priming signal. The activation signal encompasses a wide range of stimuli, including ion flux (K+, Cl−, Ca2+), lysosomal instability, mitochondrial dysfunction, reactive oxygen species generation, and trans-Golgi disassembly, with K+ efflux being the upstream event in almost all NLRP3 activations (172, 173).

Inflammasome activation initiates the host’s defense response to endogenous or external damaging stimuli and aids in homeostasis maintenance. Nevertheless, chronic inflammasome activation and the subsequent overproduction of caspase-1, IL-1β, and IL-18 can be detrimental.

Canine models of RP upregulate NLRP3 inflammasome-related genes (26). NLRP3 was detected in cone PRs and one-third of reactive microglia in P23H rhodopsin mutant retinas, which also upregulates the expression of mature IL-1β and IL-18, as well as cleaved caspase-1, indicating inflammasome activation during retinal degeneration. In rd10 mice, administration of the antioxidant N-acetylcysteine prevented PR loss and suppressed inflammasome activation (24). Studies conducted on P23H mice demonstrated that N-acetylcysteine lowered NLRP3 expression by 50% and decreased microglial infiltration, hence improving cone survival and retinal function (87).

2.3.1 P2X7R

The purinergic receptor P2X7R is an adenosine triphosphate (ATP)-gated ion channel and a well-known inflammasome activator that can enhance the expression of the NLRP3 inflammasome in microglia (174). By inducing K+ efflux, ATP-mediated P2X7R activation promotes NLRP3 inflammasome activation (173).

ATP is abundant in PRs as an energy source and neurotransmitter. During retinal degeneration, ATP leaches
from dying PRs and activates P2X7R (175). Intravitreal injection of PPADS (pyridoxal-phosphate-6-azophenyl-2′,4′-disulfonic acid), a purinergic antagonist, lowers PR loss in rd1 mice (88). In contrast, intravitreal administration of ATP to WT (wild-type) retinas induces PR degeneration similar to that in the P2H5 RP model (176), whereas treatment with the selective P2X7R inhibitor BBG (Brilliant Blue G) protects against this ATP-mediated PR apoptosis (177). BBG therapy also reduced inflammasome components (NLPR3, cleaved caspase-1 and mature IL-1β proteins) in P23H retinas (87).

In the absence of extracellular ATP, P2X7R functions as a scavenger receptor that governs microglial clearance of extracellular debris, whereas P2X7R overactivation triggers NLPR3 inflammasome activation by provoking lysosomal instability. Lowering extracellular ATP levels may have the dual benefit of enhancing phagocytosis while decreasing inflammation (178).

### 2.3.2 IL-1β

IL-1β is a key product of NLPR3 inflammasome activation and a potent immunomodulation factor that orchestrates inflammatory and host defense responses (172, 179). IL-1β signals through IL-1R1. IL-1β binding to IL-1R1 stimulates pathways such as NF-κB, p38, JNKs, ERKs, and MAPKs, facilitating inflammatory cell recruitment and local/systemic inflammatory responses (180). Appropriate IL-1β/IL-1R1 signaling is required for a host’s defensive response to infections, whereas excessive IL-1β signaling is seen in a variety of hereditary and nonhereditary autoinflammatory disorders. IL-1β activity is endogenously regulated by IL-1R2 and IL-1Ra; IL-1R2 is a decoy receptor that sequesters the IL-1β signal, while IL-1Ra blocks IL-1β by competitively binding to IL-1R1 (180).

Intravitreal delivery of exogenous IL-1β triggered an immediate inflammatory response in the retina, including leukocyte recruitment and BRB destruction (181). However, IL-1β does not trigger PR death directly, as IL-1R1 expression is low in PRs. Through IL-1R1 expressed on Müller glia, IL-1β drives glutamate excitotoxicity-induced rod PR loss. The IL-1β/IL-1R1 signal disrupts the process of glutamate conversion into glutamine in Müller glia, resulting in an increased intracellular glutamate concentration, and upregulates xCT (the core subunit of the cystine/glutamate transporter system xc-) expression, which facilitates glutamate release into the extracellular space. Furthermore, IL-1β upregulates the expression of the ionotropic glutamate receptor in retinal neurons, which may increase neuronal vulnerability to glutamate excitotoxicity (182). Infiltrating microglia in the rd10 retina upregulate the expression of IL-1β (19) and block IL-1β signaling using anakinra, a commercially available recombinant IL-1Ra that is fully active in blocking IL-1RI (183), which reduces PR apoptosis and preserves outer nuclear layer thickness in rd10 animals (19). In contrast, Todd et al. (184) demonstrated that IL-1β expressed by reactive microglia provides neuroprotection via IL-1R1 expressed on astrocytes in another mouse model of NMDA-induced retinal degeneration. Despite the use of different models, we were able to determine that IL-1β acts on the surface receptors of distinct glial cells and has varying effects on PR survival.

### 2.4 Chemokine signaling

#### 2.4.1 CX3CL1/CX3CR1

CX3CR1 expression in the central nervous system (CNS) is considered to be restricted to microglia, and the expression of its sole ligand, CX3CL1 (also known as fractalkine), is confined to certain neurons (185). CX3CL1/CX3CR1 signaling facilitates the interaction between neurons and glia and plays a vital role in CNS neuroinflammation (186, 187).

CX3CL1/CX3CR1 signaling contributes to normal microglial and PR function. CX3CR1 signaling governs the dynamic activity of retinal microglia (188). Microglial ablation and repopulation in the mouse retina have shown that microglial recruitment is regulated by CX3CL1/CX3CR1 signaling (40), and Müller glia augment microglial migration and infiltration by increasing CX3CL1 secretion and microglial CX3CR1 expression (68). In addition, CX3CR1 signaling is required for retinal neuron growth, as CX3CR1-deficient retinas have shorter outer segments and diminished cone-related retinal function (189).

CX3CL1/CX3CR1 signaling affects microglial homeostasis by modulating the inflammatory response and phagocytosis. Increasing CX3CL1/CX3CR1 signaling in RP retinas could be beneficial. CX3CR1 deficiency impairs microglial phagocytic clearance of neurotoxic species. Reportedly, CX3CL1 signaling enhances microglial erythrophagocytosis through the CD163/HO-1 axis (190), whereas CX3CR1 KO weakens microglial phagocytosis to β-amyloid and mediates lysosomal dysfunction, resulting in an escalation of neuroinflammation due to β-amyloid accumulation (191).

CX3CR1 deficiency enhances the inflammatory response of microglia. CX3CR1-deficient microglia exhibit greater neurotoxicity (192), and CX3CR1-deficient microglia have an elevated amount of surface P2X7R, which increases IL-1β maturation and release (193). CX3CR1 deletion in microglia-like cells generated from human iPSCs induced enhanced inflammatory responses to LPS stimuli and phagocytic activity to fluorescent beads (194). Loss of CX3CR1 signaling in young animals resulted in a microglial transcriptome similar to that of aged mice, with dysregulated expression of genes related to immune function (195).

CX3CL1 expression is downregulated in rd10 retina before the onset of primary rod degeneration (196), and CX3CR1 KO

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in rd10 mice increases microglial infiltration and phagocytosis, as well as the generation of pro-inflammatory cytokines, which accelerates PR loss (82, 89), whereas exogenous CX3CL1 supplementation preserves morphology and function (89). CX3CL1 has been shown to deactivate microglia by blocking the NF-κB pathway and activating the Nrf2 pathway (197). A norgestrel-supplemented diet protected rd10 retinas from PR degeneration, and this protection was achieved by the upregulation of CX3CL1/CX3CR1 signaling and the reduction of proinflammatory cytokine production (91, 92).

Recent work by Wang et al. demonstrated that overexpression of soluble CX3CL1 via AAV8 prolongs cone survival and improves cone-related visual function in RP model rd1 and rd10 mice. This therapeutic effect is restricted to cone PRs, has no effect on microglial activity or inflammatory factor levels and is not even dependent on the presence of a normal number of microglia (90). In light of this, further research is needed to determine whether CX3CL1 action in the retina is limited to microglia or whether other pathways exist.

### 2.4.2 CCL2/CCR2

Part of the evidence suggests that CCL2/CCR2 signaling is detrimental, as inhibition of CCL2/CCR2 signaling attenuates microglial activity and degeneration in RP (95–97). CCL2 is highly expressed by stressed PRs, activated microglia, and Müller glia in degenerating retina (95, 198, 199). By binding to its receptor, CCR2, which is expressed on peripheral mononuclear phagocytes, mediates the influx of circulating monocytes into inflamed retinas (200). Using fluorescent protein-labeled Mertk (-/-) Cx3cr1 (GFP+/-) Ccr2 (RFP+/-) mice, Kohno H and colleagues demonstrated that both minocycline and lecithin-bound iodine (LBI) ameliorate PR death by inhibiting CCL2/CCR2 signaling (93, 94). Meanwhile, constitutive expression of CX3CR1 in the retina represses CCL2 expression and the recruitment of neurotoxic inflammatory CCR2+ monocytes (201).

However, there is evidence that CCL2 signaling may have a protective role in the degradation of RP. In a light-induced mouse model of degeneration, blocking CCL2/CCR2 signaling decreased infiltrating monocytes but had no effect on the rate of retinal thinning (198). Alde-Low EPCs (low aldehyde dehydrogenase activity endothelial progenitor cells) transplantation therapy rescued vasculature and PRs in rd1 mice, and CCL2 secreted by Alde-Low EPCs recruited a subpopulation of monocyte-derived macrophages that highly expressed CCR2 and the neuroprotective factors TGF-β, IGF-1 and IL-10 (202). In brief, induction of CCL2 expression by Alde-Low EPCs in rd1 retinas resulted in the recruitment of neuroprotective macrophages.

It is apparent that CCL2/CCR2 signaling mediates the recruitment of monocyte-derived macrophages in the degenerating retina, but it remains to be determined whether these recruited cells are beneficial or detrimental.

### 2.5 JAK/STAT signaling

The JAK/STAT signaling pathway is a ubiquitously expressed intracellular signal transduction system implicated in a wide range of biological functions. Various ligands, including cytokines, growth hormones, growth factors, and their receptors, can activate the JAK/STAT pathway (203). Briefly, ligand binding to specific receptors induces receptor multimerization and JAK activation, activated JAKs phosphorylate the receptors, activate and phosphorylate their primary substrate STAT, and phosphorylated STAT dimerizes and translocates into the nucleus, where it binds to particular regions to either activate or inhibit the transcription of target genes. Suppressor of cytokine signaling (SOCS) is a negative modulator of JAK/STAT signaling, and its expression is promoted by stimulation of JAK/STAT signaling (203, 204).

Numerous studies on the JAK/STAT pathway have revealed its significance in neoplastic and inflammatory disorders (203, 205).

#### 2.5.1 JAK/STAT and microglia-associated inflammation

Expression and activation of STAT proteins are implicated in the plasticity of the retina during embryonic and postnatal stages (206), and mice deficient in SOCS1/STAT1 develop severe ocular illnesses with massive inflammatory cell infiltration (207). STAT signaling plays a central role in the degeneration of the rd10 retina, as evidenced by proteomic profiling (208). Furthermore, activation of JAK/STAT signaling was also observed in the retinas of light-induced and inherited (rd1 and VPP mouse) RP animal models (98, 209).

AG490 is a JAK2-specific inhibitor that suppresses microglial activation and the production of inflammatory factors such as TNFα and IL-6 by reducing STAT3 phosphorylation (210). AG490 induces M2-type microglial polarization by blocking JAK2/STAT3 signaling in acute paraquat exposure-induced microglial activation (211). In light-damaged retinas, AG490 treatment decreased JAK and STAT phosphorylation as well as PR apoptosis (98).

Olfactory ensheathing cell (OEC) transplantation improved retinal function in RCS rats. OEC treatment dramatically reduced active resident microglia/infiltrated macrophages and the release of proinflammatory cytokines while increasing anti-inflammatory cytokines in the transplantation area. This neuroprotection appears to be mediated in part by increased SOCS3 expression and decreased JAK2/STAT3 activity. Coculture of OECs with the BV2 microglial cell line revealed a shift in microglial cytokine release toward an anti-inflammatory pattern (99). According to the literature, SOCS3-deficient microglia display increased phagocytic activity (212), whereas elevated SOCS3 expression in microglia decreases GM-CSF/IFN-γ-driven inflammatory responses by blocking the activities of JAK1 and JAK2 through its KIR domain (213). In addition,
increasing SOCS1 signaling with SOCS1-KIR, a SOCS1 mimetic peptide, suppressed the recruitment of inflammatory cells into the retina and stimulated IL-10 production (214).

Multiple jakinibs (JAK inhibitors) are approved for the clinical management of malignancy, rheumatic, lymphoproliferative, and inflammatory diseases, and most recently, coronavirus disease 2019 (205), but their efficacy in the treatment of RP has not been evaluated.

2.5.2 JAK/STAT and Müller glial neuroprotection

Activation of JAK/STAT signaling has a protective effect on the RP retina. pMSC-derived retinal progenitor cell transplantation increased PR preservation in rd12 mice, and this protection was partially mediated by activation of the JAK/STAT pathway (100).

Application of ciliary neurotrophic factor (CNTF) in RP preclinical research has gained significant neuroprotection and has been employed in clinical trials (101, 215, 216). CNTF therapy enhances the protective properties of Müller glia through LIF/gp130/STAT3 signaling, thereby preventing retinal degeneration. CNTF treatment elevates the expression of LIF and endothelin 2 (Edn2) (102), and LIF is essential for CNTF-elicited STAT3 activation (217). LIF belongs to the IL-6 cytokine family and signals through the gp130 receptor. In a mouse model of light-induced retinal degeneration, intravitreal delivery of LIF improved PR survival and retinal function by activating STAT3 in Müller glia and PR (103). Stressed PRs secrete signal molecules such as Edn2 and H2O2 that facilitate LIF induction in Müller glia; Edn2 triggers LIF transduction by binding to endothelin receptor B (Ednrb) localized to Müller glia; and H2O2 increases LIF transcript levels by stabilizing LIF mRNA via ILF3 (interleukin enhancer binding factor 3) (98, 218–220). LIF deficiency or Ednrb antagonism diminishes JAK/STAT activation and the amount of reactive Müller glia, resulting in accelerated degeneration; in contrast, LIF supplementation or Ednrb agonism improves PR survival in degenerating retina (218, 221).

Deletion of gp130 in either Müller glia or rod PRs severely dampened the activation of CNTF-triggered signaling as well as PR rescue (102), and when Müller glia were ablated, LIF no longer provided protection (222). However, other research suggests that gp130 deficiency in Müller glia decreases STAT3 phosphorylation but does not weaken the neuroprotection of exogenous LIF (223) because gp130 activation in PR presumably mediates a cell-autonomous protective mechanism with a general protective role independent of pathological stimulus (223, 224).

Modulation of JAK/STAT signaling results in contrary immunomodulatory effects in different retinal components. On the one hand, inhibition of JAK2/STAT3 in microglia contributes to inflammation mitigation. On the other hand, LIF-induced STAT3 signaling in Müller glia favors neuroprotection, which seems to be an endogenous protective mechanism. We speculate that this paradoxical outcome involves crosstalk between retinal microglia and Müller glia, which is not yet fully understood. Phosphorylated JAK also activates PI3K, so there may be synergy between JAK/STAT signaling and other pathways.

3 Epigenetic modulation in inflammation suppression

Epigenetic modifications, which include DNA methylation, histone modification, and noncoding RNAs, refer to changes in gene expression patterns without altering the genomic DNA sequence (225). Epigenetic modifications are implicated in aspects of individual growth and disease development, including gene expression, cell proliferation and differentiation, misfolded protein response, and cytoskeletal dynamics (226). Although the concept of curing diseases through epigenetic regulation is relatively new, it has demonstrated considerable therapeutic potential in research on cancer, autoimmune diseases, endocrine diseases, congenital disease and many others (227, 228). Epigenetic changes contribute to the development of RP, and remarkable progress has been made in the treatment of RP with epigenetic modification therapies.

3.1 Histone acetylation and methylation

Histone acetylation and methylation are the two most well-studied types of histone modification, with acetylation typically resulting in increased gene expression and methylation being related to either increased or decreased gene transcription. Histone acetylation is regulated by histone acetyltransferases and histone deacetylases (HDACs), while histone methylation is regulated by lysine methyltransferases and arginine methyltransferases and histone demethylation by histone demethylases. Enzymes that add or remove epigenetic marks on histones are known as “writers” and “erasers.” In addition, there are “readers” containing bromodomains, chromodomains, or Tudor domains that are able to decipher histone codes (229).

RP retinas exhibit excessive HDAC activity (104, 105, 230), and HDAC inhibition delays retinal degeneration in RP animal models (rd1 and rd10 mice and zebrafish) (104–107). In rd10 mice, the HDAC inhibitor romidepsin prevented rod degeneration and enhanced retinal function. Two molecular mechanisms contribute to this neuroprotective effect. First, by acting on histone targets in PRs, increasing chromatin accessibility and upregulating neuroprotective genes, and second, by acting on nonhistone targets in microglia and
resident and invading immune cells, it suppresses inflammatory gene transcription and inflammation (108).

Microglial activity is related to histone methylation levels. LPS-activated microglia increase HDAC expression, which is accompanied by an increase in inflammatory gene expression (231). HDAC inhibition or knockdown promotes a protective microglial phenotype and reduces neuroinflammation (232–234).

Valproic acid is an HDAC inhibitor that reduces PR degeneration in rd1 and P23H RP models (109, 110). Valproic acid increases the expression of STAT1 by inhibiting HDAC3 expression; subsequently, acetylated STAT1 forms a complex with nuclear NF-kB p65, preventing NF-kB p65 DNA-binding activity (235).

Moreover, suppression of the "read" (bind) behavior to histone acetylation marks of bromodomain and extraterminal domain proteins by JQ1 ameliorated PR degeneration and maintained electoretinographic function in rd10 mice. This protection seems to be partially mediated by the inhibition of retinal microglial proliferation, migration, and cytokine production (111).

Several studies, including our previous report, have reported altered histone methylation in RP retinas (112, 236, 237). Lysine demethylase 1 inhibition attenuated PR degeneration in rd10 mice, in part by inhibiting microglial-related inflammation (108). DZNep (3-deazaneplanocin A) specifically inhibits Ezh2 (H3K27 trimethyltransferase) and mediates neuroprotective effects in rd1 mice by inhibiting H3K27me3 deposition (112). Ezh2 reportedly mediates TLR-induced inflammatory gene expression (238) and activation of multiple types of inflammasomes in microglia (239), hence promoting microglial-related pathologies.

3.2 MicroRNA

MicroRNAs (miRNAs) are small noncoding RNAs that modify gene expression post-transcriptionally by targeting messenger RNAs, long noncoding RNAs, and pseudogenes and circular RNAs. MiRNAs can be packed into exosomes or microvesicles to perform long-distance cell-to-cell communication. MiRNAs play a critical role in gene expression modulation and are therefore interesting candidates for the development of biomarkers and therapeutic targets (240). Throughout development, miRNAs are required for retinal neuron differentiation (241, 242). Dysregulated miRNAs were found in the retinas of mouse and canine models of RP (243, 244), indicating the involvement of miRNAs in the etiology of RP.

MiRNAs regulate microglial phenotypes, as evidenced by various studies on retinal and neurodegenerative disorders (245, 246). Inhibition of miR-6937-5p preserved the outer nuclear layer thickness and promoted the ERG wave response in rd10 mice (113), and AAV-miR-204 attenuated retinal degeneration in two different mouse models. By downregulating microglial activation and PR mortality, miR-204 alters the expression profiles of transgenic retinas toward those of healthy retinas (114). In addition, miR-223 is required for the regulation of microglial inflammation and the maintenance of normal retinal function (247).

3.3 DNA methylation and trained immunity: Epigenetic reprogramming of immunity phenotype

DNA methylation refers to the addition of a methyl group to the 5′-carbon of a cytosine (C) ring, resulting in the formation of 5-methylcytosine (5mC), which mainly occurs in the promoter regions. Typically, methylation modifications result in gene repression, and global genomic hypermethylation relates to heterochromatin formation and inhibits transcription (248). Aberrant regulation of DNA methylation results in PR degeneration and neuronal loss in the retina. In the absence of DNA methyltransferase 1, the initiation of PR differentiation is severely hindered (249). In RP retinas, binding sites of several important transcription factors for retinal physiology were hypermethylated (250). The role of DNA methylation in the development of retinitis pigmentosa has been reviewed in detail elsewhere (251) and will not be repeated here.

We argue that trained immunity regulates the microglial phenotype in RP by plasticizing microglial reactivity via epigenetic modification.

Trained immunity, also known as innate immune memory, refers to the phenomenon in which innate immunity modifies its function after an initial insult and reacts more vigorously to subsequent stimuli. Epigenic reprogramming determines the immune phenotype of immune cells and leads to long-lasting functional alterations (252, 253) (Figure 2). Using macrophages as an illustration, in the resting state, the promoter regions of inflammatory genes are enriched with repressive epigenetic marks, called epigenetic barriers, to prevent activation in the absence of stimuli. Upon stimulus, repressive epigenetic marks are removed, and activating epigenetic marks are introduced to the promoters and enhancers of specific genes in an attempt to encourage inflammatory molecule synthesis and phagocytosis to eliminate the insult. After stimulus elimination, activating epigenetic marks are partly retained (254). The innate immune system may become overly trained in chronic inflammatory diseases as a result of such mechanisms, resulting in pathological tissue damage.
In the context of neurodegenerative disorders of the CNS, the relationship between trained immunity and microglial phenotype has been discussed (255, 256). Low-dose LPS intraperitoneally administered to mice induced long-lasting innate immune memory in brain microglia and exacerbated Alzheimer’s disease pathology. Activated microglia are enriched with the epigenetic marks H3K4me1 and H3K27ac, which define active enhancers (256). In RP model P23H rats, intraperitoneal injection of low-dose LPS increased microglial activation and the number of infiltrating microglia, as well as elevated the expression levels of several inflammation-related genes (257).

In addition to the activation of retinal microglia, elevated levels of serum cytokines show the activation of peripheral immune cells in RP (22, 23). Recent work by Su et al. revealed that monocytes from patients with autosomal recessive RP exhibit a trained-like phenotype. Upon stimulation, these monocytes produce more TNF-α, IL-6, and IL-1β and upregulate inflammatory pathways such as NF-κB (258). Current evidence supports a role for trained immunity in RP pathogenesis by epigenetic reprogramming of microglia and peripheral macrophages to modulate the immune phenotype and trigger an active immune response, although many details remain to be confirmed.

4 Gut microbiome and microglial activity

The gut microbiome, which resides in the intestinal tract and performs nutrition metabolism, has recently been found to influence the maturation of the immune system. Components and metabolites of microbial cells engage in the modulation of immune recognition and immune tolerance through innate immune receptors on intestinal epithelial cells and influence the function of innate myeloid cells and lymphoid cells through diverse mechanisms (Figure 3). In addition, the microbiota’s make-up and function are subject to the innate immune system. Therefore, gut dysbiosis may induce immune system dysregulation and trigger disease emergence (259).

The gut microbiome has been linked to retinal degenerative disorders such as age-related macular degeneration (260) and diabetic retinopathy (261). Using the rd10 RP mouse model, Kutsyr O. et al. (262) related alterations in the composition profiles of the gut microbiome to RP. Compared to healthy mice, the gut microbiome of rd10 mice had reduced ASV richness and diversity. Rd10 mice, in particular, feature a high proportion of B. caecimuris, a species that is uncommon in healthy gut mice, but lack four species (Rikenella spp., Muribaculaceae spp.,...
Prevotellaceae UCG-001 spp., and Bacilli spp.) that are common in the healthy gut microbiome (262). The gut microbiome is susceptible to dietary influences. Further research by the same group demonstrated that a short-term high-fat diet significantly modifies the gut flora, enhances retinal oxidative stress and inflammation, and ultimately accelerates the degeneration of the rd10 retina (263). Thus, dysbiosis in the gut contributes to retinal inflammation and constitutes the pathogenesis of RP.

By exchanging the intestinal microbiota (Fecal microbiota transplant, FMT) of young and aged mice, emerging evidence by Parker et al. (264) suggests that the gut microbiome is a modifier of retinal inflammation. Compared to young mice, aged mice exhibit increased systemic and tissue inflammation, as evidenced by elevated serum proinflammatory cytokines (TNFα, IL-6), microglial overactivation in the brain, and C3 accumulation at the RPE/Brücke’s membrane interface. Transferring aged donor microbiota to young mice disrupts the intestinal epithelial barrier and triggers inflammation in the retina and brain, whereas transfer of aged mice with young donor microbiota could reverse age-related inflammation (264).

The evidence above supports the “diet-gut microbiome-retina axis” hypothesis in the pathogenesis of RP. Despite the fact that this work is still in its early stages, the gut microbiota is a promising therapeutic target for RP.

5 Herbal agents in inflammation suppression

Herbal compounds, or phytochemicals derived from plants, possess a wide range of biological activities and have been explored for the treatment of RP, demonstrating anti-inflammatory properties in RP investigations.

Curcumin is a polyphenolic compound produced from the spice turmeric. Curcumin provided morphological and functional protection in rd1 mice, P23H rats, and an MNU-induced RP model (115, 116, 265, 266). A single vitreous injection of curcumin reduced PR loss in rd1 mice by inhibiting microglial activation and modulating the expression of CCL2, TIMP-1 and VCAM-1 (115).

Lyceum barbarum polysaccharides and zeaxanthin dipalmitate are two main bioactive agents extracted from wolfberry. Lyceum barbarum polysaccharides protects against retinal degeneration by modifying inflammation and apoptosis through the inhibition of NF-κB and HIF-1α expression (117, 118). Zeaxanthin dipalmitate acts through several pathways, including STAT3, CCL2 and MAPK, in parallel to inhibiting inflammation in the rd10 retina (119).

Saffron, widely used in traditional Chinese medicine for its anti-inflammatory and antioxidant properties, protects PRs
exposed to environmental ATP by blocking P2X7R signaling (120). In P23H rats, saffron administration increased PR survival and functional retention while decreasing vascular disruption (121).

Resveratrol (3,40,5-trihydroxystilbene) is found in chocolate, fruits, and vegetables. Resveratrol treatment inhibited microglia-mediated death of 661W cells via downregulation of microglial migratory, phagocytic, and proinflammatory cytokine production (122). Subretinal injection of JC19 (3,4’-diglucosyl resveratrol), a resveratrol prodrug, reduced PR loss and improved functional performance in ERG tests of the rd10 retina. The author speculates that sirtuin1 activation is the underlying mechanism (123).

6 Conclusion and future perspectives

A large body of research conducted on the inflammatory processes during RP tries to discover common mechanisms that target multiple RP genotypes and develop appropriate therapeutic options. However, after reviewing the existing literature, we discovered that no single treatment is appropriate for all types of RP, and the application of valproic acid is a prime example, with treatment effects significantly varying between models with different genetic backgrounds and even exhibiting detrimental effects. This raises the prospect that a link between genetics and RP inflammation needs more investigation. To date, genetic mutations remain the only identified risk factor for RP. Different permutations of inheritance pattern, genotype, and the number of mutations lead to variations in the phenotype and pathological progression of RP. Similarly, we anticipate that the multiple phenotypes of inflammatory activation in RP are closely related to the genetic background. Nevertheless, the relationship between genetic background and inflammation is currently unclear due to the lack of corresponding evidence.

Both RP patients and animal models have a more susceptible immune system and are prone to developing inflammation. This abnormal immune system may depend heavily on the genetic background. The gut microbiota play a critical role in the maturation of the innate immune system after birth, and trained immunity is implicated in this process; however, the influence of genetic background on the maturation of the immune system has not been investigated. Therefore, long-term clinical observation and family tracing of the RP population are necessary. What needs to be documented should include, but is not limited to, macroscopic clinical manifestations, structural and functional measurements, and monitoring of local and peripheral inflammation levels. And appropriate follow-up criteria need to be established to ensure consistency of measurements and to obtain usable information.

Inflammation is an important feature of RP, and the present review highlights the role of immunomodulation in RP treatment. There has been significant interest in modulating the inflammatory response as a strategy to treat RP, and an increasing number of studies have proven the effectiveness of immunomodulation in ameliorating and perhaps reversing retinal degeneration. Therapeutic strategies based on immunomodulation are a potential treatment for RP, and deepening the understanding of immune modulation is helpful in establishing suitable therapies. As with immunotherapies already carried out, artificial regulation of immunity will bring inevitable side effects. It is challenging to regulate immunity accurately and to enhance the beneficial effects and minimize the harmful ones concurrently. Many of these specific mechanisms need to be further studied, especially the interactions between these pathways.

Author contributions

LZ wrote the manuscript and painted the figure. NY and CH reviewed and modified the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Altered cellular immunity and suppressor cell activity in patients with primary retinitis pigmentosa. 

Zhao et al. 10.3389/fimmu.2016.01216

Park UC, Park JH, Ma DJ, Cho IH, Oh BL, Yu HG. A randomized paired-eye trial of intravitreal dexamethasone implant for cystoid macular edema in retinitis pigmentosa. Retina (2020) 40(7):1359–66. doi: 10.1097/IAE.000000000002589

Glibnya IV, Kennedy A, Ashton P, Abrams GW, Iezzi R. Photoreceptor neuroprotection in rcs rats Via low-dose intravitreal sustained-delivery of flustopinol acetate. Invest Ophthalmol Vis Sci (2009) 50(10):4847–57. doi: 10.1167/iovs.08-2831

Glibnya IV, Kennedy A, Ashton P, Abrams GW, Iezzi R. Intravitreal delivery of the corticosteroid flusottonol acetate attenuates retinal degeneration in S334ter-4 rats. Invest Ophthalmol Vis Sci (2010) 51(8):4243–52. doi: 10.1167/iovs.09-4492

Iezzi R, Guru BR, Glibnya IV, Mishra MK, Kennedy A, Kannan RM. Dendrimer-based targeted intravitreal therapy for sustained attenuation of neuroinflammation in retinal degeneration. Biomaterials (2012) 33(9):979–88. doi: 10.1016/j.biomaterials.2011.10.010

Guadagni V, Biagioni M, Novelli E, Aretini P, Mazzanti CM, Stretti E. Rescuing cones and daytime vision in retinitis pigmentosa mice. FASEB J (2019) 33(9):10177–92. doi: 10.1096/fj.20190441R

Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, et al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science (2010) 330(6005):841–5. doi: 10.1126/science.1194637

O’Koren EG, Yu C, Klingeboom M, Wong AYW, Prigge CL, Mathew R, et al. Microglial function is distinct in different anatomical locations during retinal homeostasis and degeneration. Immunity (2019) 50(3):723–37. doi: 10.1016/j.immuni.2019.02.007

Gomez Perdiguero E, Klapproth K, Schulz C, Busch K, Azzone E, Crozet L, et al. Tissue-resident macrophages originate from yolk-Sac-Derived erythroid-myeloid progenitors. Nature (2015) 518(7540):547–51. doi: 10.1038/nature13989

Hume DA, Perry VH, Gordon S. Immunohistochemical localization of a macrophage-specific antigen in developing mouse retina: Phagocytosis of dying neurons and differentiation of microglial cells to form a regular array in the plexiform layers. J Cell Biol (1983) 97(1):253–7. doi: 10.1083/jcb.97.1.253

Silverman SM, Wong WT. Microglia in the retina: Roles in development, maturation, and disease. Annu Rev Vis Sci (2019) 5:659–84. doi: 10.1146/annurev-vision-091517-034425

Dixon MA, Gerefarth U, Fletcher EL, Jobling AL. The contribution of microglia to the development and maturation of the visual system. Front Cell Neurosci (2015) 9:569. doi: 10.3389/fncel.2015.00594

Zhang Y, Zhao L, Wang M, Wu LA, Lao H, Xi NN, et al. Repopulating retinal microglia restore endogenous organization and function under Cxcl11-Cxcr7 regulation. Sci Adv (2018) 4(3):eaaq492. doi: 10.1126/sciadv.aaq492

Ajiabi B, Bennett JL, Kiriger C, Tetzlaff W, Rossii FM. Local self-renewal can sustain cnio microglia maintenance and function throughout adult life. Nat Neurosci (2007) 10(12):1538–43. doi: 10.1038/nn2014

Younger D, Murugan M, Rama Rao KV, Wu LJ, Chandra N. Microglia receptors in animal models of traumatic brain injury. Mol Neurobiol (2019) 56(7):1202–28. doi: 10.1007/s12035-018-1428-7

Butler CA, Popescu AS, Kitchener EJ, Allendorf DH, Puigdegollar M, Brown GC. Microglial phagocytosis of neurons in neurodegeneration, and its regulation. J Neurochem (2021) 158(6):621–39. doi: 10.1111/jnc.15327

Brown GC, Neher JF. Microglial phagocytosis of live neurons. Nat Rev Neurosci (2014) 15(4):209–16. doi: 10.1038/nrn3710

Zhao et al. 10.3389/fimmu.2022.1059947
Intervention of microglial and Müller cells in light-induced retinal degeneration.

Ramirez AM, Valiente-Soriano FJ, Agudo-Barriuso M, et al. Coordinated microglia activation precedes photoreceptor degeneration in a mouse model of retinal degenerative disease. Front Immunol (2019) 33(3):3680. doi:10.3389/fimmu.2020.01263

Yamasaki R, et al. Microglia sculpt postnatal neural circuits in an activity and inflammation-driven manner. Neuron (2020) 174(4):691–705. doi: 10.1016/j.neuron.2020.03.026

Wang X, Zhao L, Zhang J, Fariss RN, Ma W, Kretschmer F, et al. Requirement for microglia for the maintenance of synaptic function and integrity in the mature retina. J Neurosci (2016) 36(9):2827–42. doi: 10.1523/JNEUROSCI.3575-15-2016

Ramoshoff RM, Perry VH. Microglial physiology: Unique stimuli, specialized responses. Adv Immunol (2009) 27:119–45. doi: 10.1146/annurev.immunol.021208.132528

Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science (2006) 313(5782):1154–8. doi: 10.1126/science.1110647

Neumann H, Korter MR, Franklin RJ. Debris clearance by microglia: An essential link between degeneration and regeneration. Front cellar res (2009) 122(2):288–95. doi: 10.1039/b91097m

Rohrer B, Pinto AM, Hulse KE, Lohr HR, Zhang L, Almeida JS. Multidestructive pathways triggered in photoreceptor cell death of the Rd mouse as determined through gene expression profiling. J Biol Chem (2004) 279(40):41903–10. doi: 10.1074/jbc.M405085200

Murakami Y, Ikeda Y, Nakatake S, Tachibana T, Fujisawa K, Yoshida N, et al. Necrotic enlargement of cone photoreceptor cells and the release of high-mobility group box 1 in retinitis pigmentosa. Cell Death Discovery (2015) 1:15058. doi: 10.1038/cddiscovery.2015.58

Vallariza-Deschamps G, Gia D, Gong J, Jellali A, Drobic P, Forster V, et al. Excessive activation of cyclic nucleotide-gated channels contributes to neuronal degeneration of photoreceptors. Eur J Neurosci (2002) 22(5):913–22. doi: 10.1046/j.1460-9568.2002.02406.x

Wright AF, Chakarova CF, Abd El-Azim MM, Bhattacharyya SS. Photoreceptor degeneration: Genetic and mechanistic dissection of a complex trait. Nat Rev Genet (2010) 11(4):273–84. doi: 10.1038/nrg2717

Mahaling B, Low SWY, Beck M, Kumar D, Ahmed S, Connor TB, et al. Damage-associated molecular patterns (Damps) in retinal disorders. Int J Mol Sci (2022) 23(5):2591. doi: 10.3390/ijms23052591

Blank T, Goldmann T, Koch M, Amann I, Schon C, Bonin M, et al. Early microglia activation precedes photoreceptor degeneration in a mouse model of Cngbl-linked retinitis pigmentosa. Front Immunol (2017) 8:1930. doi: 10.3389/fimmu.2017.01930

Zeiss CJ, Johnson EA. Proliferation of microglia, but not photoreceptors, the outer nuclear layer of the Rd-1 mouse. Invest Ophthal Vis Sci (2004) 45(3):971–9. doi: 10.1167/iovs.03-0301

Zhang L, Cui X, Jauregui R, Park KS, Justus S, Tsai YT, et al. Genetic rescue of cones in the rd1 mouse model of retinal degeneration mediated by all-Trans-Retinal. Cell Death Discovery (2017) 8:1930. doi: 10.3389/fnana.2017.00077

13. Tian L, Zhang Z, Li J, Xu Y, Zhou S, Zhou S, et al. In vivo administration of adalimumab delays retinal degeneration in Rd10 mice. FASEB J (2020) 34(10):13839–61. doi: 10.1096/fj.202000844R

14. Sanchez-Cruz A, Mendez AC, Lizasoain I, de la Villa P, de la Rosa EJ, Hernandez-Sanchez C. Tlr2 gene deletion delays retinal degeneration in two genetically distinct mouse models of retinitis pigmentosa. Int J Mol Sci (2021) 22(15):7815. doi:10.3390/ijms22157815

15. Kohnhe H, Chen Y, Keunen BM, Pearlman E, Miyagi M, Maeda T, et al. Photoreceptor proteins initiate microglial activation Via toll-like receptor 4 in retinal degeneration mediated by all-Trans-Retinal. J Biol Chem (2013) 288(21):15326–41. doi: 10.1074/jbc.M112.448712

16. Di Pierdomenico J, Scholz R, Valiente-Soriano FJ, Sanchez-Migallon MC, Vidal Sanz M, Langmann T, et al. Neuroprotective effects of Fgf2 and minocycline in two animal models of inherited retinal degeneration. Invest Ophthal Vis Sci (2018) 59(11):4392–403. doi: 10.1167/iovs.18-24621

17. Hughes EH, Schlichtenbrede PC, Murphy CC, Broderick C, Van Rooijen N, Ali RR, et al. Minocycline delays photoreceptor death in the rd mouse through a microglia-independent mechanism. Exp Eye Res (2004) 78(6):1077–84. doi: 10.1016/j.exer.2004.02.002

18. Zhang C, Lei B, Zeng Y, Yang F, Sinha D, Tso MO. Neuroprotection of photoreceptors by minocycline in light-induced retinal degeneration. Invest Ophthal Vis Sci (2018) 59(11):4392–403. doi: 10.1167/iovs.18-24621

19. Syeda S, Patel AK, Lee T, Hackam AS. Reduced photoreceptor survival and improved retinal function during retinal degeneration in mice lacking innate immunity adaptor protein Myd88. Exp Eye Res (2015) 24(1):1–10. doi: 10.1016/j.exer.2015.02.027

20. Peng B, Xiao J, Wang K, So KF, Tipple GL, Lin B. Suppression of microglial activation is neuroprotective in a mouse model of human retinitis pigmentosa. J Neurosci (2014) 34(24):8139–50. doi: 10.1523/jneurosci.5200-13.2014

21. Syeda S, Patel AK, Lee T, Hackam AS. Reduced photoreceptor death and improved retinal function during retinal degeneration in mice lacking innate immunity adaptor protein Myd88. Exp Eye Res (2015) 24(1):1–10. doi: 10.1016/j.exer.2015.02.027

22. Garces K, Carney T, Illiano P, Brambilla R, Hackam AS. Reduced photoreceptor death and improved retinal function during retinal degeneration in mice lacking innate immunity adaptor protein Myd88. Exp Eye Res (2015) 24(1):1–10. doi: 10.1016/j.exer.2015.02.027

23. Carney-Bennett T, Myer C, Bhattacharyya SK, Hackam AS. Quantitative proteomic analysis after neuroprotective Myd88 inhibition in the retinal degeneration 10 mouse. J Cell Mol Med (2021) 25(20):9533–42. doi: 10.1111/jcmm.18693

24. Aslanidis A, Karlström T, Scholz R, Fauser S, Neumann H, Fried C, et al. Activated Microglia/Macrophage whereby acidic protein (Ampat) inhibits nkappaB signaling and induces a neuroprotective phenotype in microglia. J Neuroinflamm (2015) 12(77): doi:10.1186/s12974-015-0296-6
87. Viringiparamparaa IE, Metcalfe AL, Bashur AE, Sivak O, Yanai A, Mohammad J. IL-1ß, 2013 inflammation activation drives bystander cone photoreceptor cell death in a P23h rhodopsin model of retinal degeneration. *Hum Mol Genet* (2016) 25(8):1501–16. doi: 10.1093/hmg/ddw029

88. Pathway F, Tucker E. Extracellular ATP induces retinal photoreceptor apoptosis through activation of purinergic receptors in rodents. *J Comp Neurol* (2009) 513(4):430–40. doi: 10.1002/cne.21964

89. Zabel MK, Zhao L, Zhang Y, Gonzalez SR, Ma W, Wang X, et al. Microglial phagocytosis and activation underlying photoreceptor degeneration is regulated by Cx3c17-Cx3cr1 signaling in a mouse model of retinitis pigmentosa. *Glia* (2016) 64(9):1479–91. doi: 10.1002/glia.23016

90. Wang SK, Xue YL, Rana P, Hong CM, Cepko CL. Soluble Cx3cl1 gene therapy improves cone survival and function in mouse models of retinitis pigmentosa. *Proc Natl Acad Sci U.S.A.* (2019) 116(20):10140–9. doi: 10.1073/pnas.1901757116

91. Roche SL, Wyse-Jackson AC, Gomez-Vicente V, Lax P, Ruiz-Lopez AM, Byrne AM, et al. Progerosome attenuates microglial-driven retinal degeneration and stimulates protective fractalkine-Cx3cr1 signaling. *PLoS One* (2016) 11(11):e0165197. doi: 10.1371/journal.pone.0165197

92. Roche SL, Wyse-Jackson AC, Ruiz-Lopez AM, Byrne AM, Cotter TG. Fractalkine-Cx3cr1 signaling is critical for progesterone-mediated neuroprotection in the retina. *Sci Rep* (2017) 7:43067. doi: 10.1038/srep43067

93. Kohn H, Terazuki R, Watanabe S, Ichihara K, Watanabe T, Nishijima E, et al. Effect of lecithin-bound a-iodine treatment on inherited retinal degeneration. *Frontiers in Immunology* (2018) 9:330. doi: 10.3389/fimmu.2018.00330

94. Terauchi R, Kohno H, Watanabe S, Ichihara K, Watanabe T, Nishijima E, et al. Different effects of valproic acid on photoreceptor loss in Rd1 and Rd10 retinal degeneration models of retinitis pigmentosa. *Invest Ophthalmol Vis Sci* (2018) 59(10):4193–9. doi: 10.1167/iovs.18-23313

95. Liu F, Zhang J, Xiang Z, Xu D, So KK, Vardi N, et al. Lycopene suppresses photoreceptor degeneration by curcumin in transgenic rats with P23h rhodopsin mutation. *PLoS One* (2011) 6(6):e21193. doi: 10.1371/journal.pone.0021193

96. Wiedemann J, Rashid K, Langmann T. Resveratrol induces dynamic epigenetic modiﬁcations in neurodegenerative diseases. *Front Cell Neurosci* (2019) 13:298. doi: 10.3389/fncel.2019.00298

97. Hsu T, Wang XD, White WA, Simpson RN, Jablonski MM. Different effects of valproic acid on photoreceptor loss in Rd1 and Rd10 retinal degeneration models of retinitis pigmentosa. *J Neurosci* (2016) 36(6):1753–65. doi: 10.1523/jneurosci.1647-16.2016

98. Sato K, Shi Y, Sanjukta B, Kwon D, Kang H, et al. Zebrafish model of retinitis pigmentosa and a screening platform for potential therapeutic agents. *PLoS One* (2017) 12(1):e0171141. doi: 10.1371/journal.pone.0171141

99. Asanafar K, Aghdassi N, Ghafari K. miR-204 protects from retinal degeneration by attenuation of microglia and photoreceptor cell death. *Mol Ther Nucleic Acids* (2020) 12(10):913. doi: 10.3390/mtNA12100913

100. Zhao L, Li J, Fu YM, Zhang MX, Wang BW, Ouettel E, et al. Photoreceptor protection via blockade of retinal degeneration in a murine model of inherited retinal degeneration. *J Neuroinflammation* (2017) 14(1):14. doi: 10.1186/s12974-016-0775-4

101. Zheng SJ, Xiao LR, Liu Y, Wang YJ, Cheng L, Zhang J, et al. Dnep inhibits H2S2;37me3 deposition and delays retinal degeneration in the Rd1 mouse. *Cell Death Dis* (2018) 9(5):310. doi: 10.1038/s41419-018-0348-9

102. Fraternali FD, Aparicio HD, Saurí L, Vela A, Tobias M, et al. Human primitive mesenchymal stem cell-derived retinal progenitor cells improved neuroprotection, neurogenesis, and vision in Rd12 mouse model of retinitis pigmentosa. *Front Cell Dev Biol* (2021) 9:689. doi: 10.3389/fcdb.2021.689

103. Wiedemann J, Rashid K, Langmann T. Resveratrol induces dynamic epigenetic modiﬁcations in neurodegenerative diseases. *Front Cell Neurosci* (2019) 13:298. doi: 10.3389/fncel.2019.00298

104. Wiedemann J, Rashid K, Langmann T. Resveratrol induces dynamic epigenetic modiﬁcations in neurodegenerative diseases. *Front Cell Neurosci* (2019) 13:298. doi: 10.3389/fncel.2019.00298

105. Wiedemann J, Rashid K, Langmann T. Resveratrol induces dynamic epigenetic modiﬁcations in neurodegenerative diseases. *Front Cell Neurosci* (2019) 13:298. doi: 10.3389/fncel.2019.00298

106. Wiedemann J, Rashid K, Langmann T. Resveratrol induces dynamic epigenetic modiﬁcations in neurodegenerative diseases. *Front Cell Neurosci* (2019) 13:298. doi: 10.3389/fncel.2019.00298

107. Wiedemann J, Rashid K, Langmann T. Resveratrol induces dynamic epigenetic modiﬁcations in neurodegenerative diseases. *Front Cell Neurosci* (2019) 13:298. doi: 10.3389/fncel.2019.00298

108. Wiedemann J, Rashid K, Langmann T. Resveratrol induces dynamic epigenetic modiﬁcations in neurodegenerative diseases. *Front Cell Neurosci* (2019) 13:298. doi: 10.3389/fncel.2019.00298
Microglia-derived pronerve growth factor promotes photoreceptor cell death whereas P75ntr activity is neurotoxic through a paracrine mechanism. Acute models of retinal neurodegeneration trka activity are neuroprotective.

Tlr4-mediated inflammation and cognitive dysfunction in mice. *J Neurochem* (2011) 119(6):2429–39. doi: 10.1111/j.1471-4159.2011.075957

Tumor necrosis factor-α (TNF-α) production by activated retinal Müller cells. *Cell Death Differ* (2013) 20(11):1835–46. doi: 10.1038/cdd.2013.135

Endogenous toll-like receptor ligands induce proinflammatory responses in retinal Müller cells. *Exp Eye Res* (2015) 137:187–203. doi: 10.1016/j.exer.2015.03.015

Microglia contribute to neuroinflammation and cognitive dysfunction in mice. *J Neurochem* (2011) 119(6):2429–39. doi: 10.1111/j.1471-4159.2011.075957

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Upregulation of P2rx7 in Cx3cr1-deficient microglia facilitates a premature aging transcriptome. Life Sci Adv (2019) 26:e20090453. doi: 10.26879/flsia090453

Ziegler M, Ahlert PK, Uhrin P. Cx3cl1 (Fractalkine) protein expression in normal and degenerating mouse retina: In vivo studies. PloS One (2014) 9(9): e106562. doi: 10.1371/journal.pone.0106562

Jiang M, Xie H, Zhang C, Wang T, Tian H, Lu L, et al. Enhancing Fractalkine/Cx3cl1 signaling pathway can reduce neuroinflammation by attenuating microglia activation in experimental diabetic retinopathy. J Cell Mol Med (2022) 26(4):1229–44. doi: 10.1111/jcmm.17179

Karlen SJ, Miller EB, Wang XL, Levine ES, Zawadski RJ, Burns ME. Monocyte infiltration rather than microglia proliferation dominates the early immune response to rapid photoreceptor degeneration. J Neuroinflamm (2018) 15(1):444. doi: 10.1186/s12974-018-1365-4

Feng C, Wang X, Liu T, Zhang M, Xu G, Ni Y. Expression of C2d2 and its receptor in activation and migration of microglia and monocytes induced by photoreceptor apoptosis. Mol Vis (2017) 23:765–77.

Kuziel WA, Morgan SJ, Dawson TC, Griffin S, Smithies O, Ley K, et al. Severe reduction in leukocyte adhesion and monocyte extravasation in mice deficient in cc chemokine receptor 2. Proc Natl Acad Sci U.S.A. (1997) 94(22):12053–8. doi: 10.1073/pnas.94.22.12053

Sennahsab F, Avunyt C, Calippe B, Lavallette S, Poupld L, Hu SJ, et al. Ccr2 (+) monocytes infiltrate atrophic lesions in age-related macular disease and mediate photoreceptor degeneration in experimental subretinal inflammation in Cx3cl1 deficient mice. EMBO Mol Med (2013) 5(11):1775–93. doi: 10.1002/emmm.201302692

Fukuda S, Nagano M, Yamasita T, Kimura K, Tsudoi I, Salazar G, et al. Functional endothelial progenitor cells selectively recruit neurovascular protective monocyte-derived F4/80(+)Ly6c(-) macrophages in a mouse model of retinal degeneration. Stem Cells (2013) 31(10):2149–61. doi: 10.1002/stem.1469

Xin P, Xu X, Deng C, Liu S, Wang Y, Zhou X, et al. The role of Jak/Stat signaling pathway and its inhibitors in diseases. Int Immunopharmacol (2020) 80.106210. doi: 10.1016/j.intimp.2020.106210

Darnell JE Jr, Kerr KM, Stark GC. Jak-STAT pathways and transcriptional activation in response to IFNs and other cytokines signaling proteins. Science (1994) 264(5164):1451–21. doi: 10.1126/science.8197455

Luo Y, Alexander M, Gadina M, O'Shea JJ, Meylan F, Schwartz DM. Jak-stat signaling in retinal degeneration. J Allergy Clin Immunol (2018) 122(4):911–25. doi: 10.1016/j.jaci.2018.08.084

Zhang SS, Wei JY, Li C, Barnstabile CJ, Fu XY. Expression and activation of stat proteins during mouse retina development. Exp Eye Res (2003) 76(4):421–31. doi: 10.1016/s0014-4835(03)00022-2

Yu CR, Mahdi RM, Liu XB, Zhang A, Naka T, Kishimoto T, et al. Cxcl1 regulates C2d2 expression and migration of Ccr2(+) T cells into peripheral tissues. J Immunol (2008) 181(2):1190–8. doi: 10.4049/jimmunol.181.2.1190

Ly A, Merli-Pham J, Priller M, Gruhn F, Senninger N, Ueffing M, et al. Proteomic profiling suggests central role of stat signaling during retinal degeneration in the rd10 mouse model. J Proteome Res (2016) 15(4):1350–9. doi: 10.1021/acs.jproteome.6b00111

Lange C, Thiersch M, Samardzija M, Grimm C. The differential role of Jak/Stat signaling in retinal degeneration. Adv Exp Med Biol (2010) 664:661–7. doi: 10.1007/978-1-4419-5777-8_69

Chen S, Dong Z, Cheng M, Zhao Y, Wang M, Sai N, et al. Homocysteine exaggerates microglia activation and neuroinflammation through microglia localized Stat3 overactivation following ischemic stroke. J Neuroinflamm (2017) 14(1):187. doi: 10.1186/s12974-017-0963-x

Fan Z, Zhang W, Cao G, Zhou L, Fan X, Qi C, et al. Jak2/Stat3 pathway regulates microglia polarization involved in hippocampal inflammatory damage due to acute paraquat exposure. Ecotoxicol Environ Saf (2022) 234:113372. doi: 10.1016/j.ecoenv.2022.113372

Korovina I, Neworth A, Sprott D, Trouplinski M, Pozit DM, Deussen A, et al. Myeloid Socs3 deficiency regulates angiogenesis Via enhanced apoptotic endothelial cell engulfment. J Innate Immun (2020) 12(3):248–56. doi: 10.1159/000296654

Zhang X, He B, Li H, Wang Y, Zhou Y, Wang W, et al. Socs3 attenuates gm-CSf/Ifn-γ-mediated inflammation during spontaneous spinal cord regeneration. Neurosci Bull (2020) 36(7):778–92. doi: 10.1007/s12264-020-00493-8

He C, Yu CR, Mattappil MJ, Sun L, Larkin J, Egwuagu CE. Socs1 mitc protein peptide suppresses chronic intracranial inflammatory disease (Uveitis). Mediators Inflamm (2016) 2016:293970. doi: 10.1155/2016/293970

Birch DG, Bennett LD, Duncan JL, Weleber RG, Pennessi ME. Long-term follow-up of patients with retinitis pigmentosa receiving intravascular ciliary neurotrophic factor implants. Am J Ophthalmol (2016) 170:10–4. doi: 10.1016/j.ajo.2016.07.013
Gp130 in photoreceptors. Gp130 cytokines, jak-stat signaling and neuroprotection after müller cell ablation protects photoreceptor cells against light-induced degeneration. doi: 10.1038/s41580-2019-0223-5

Expression of leukemia inhibitory factor in müller glia cells is regulated by a redox-dependent mirna stability mechanism. BMC Biol (2015) 13:30. doi: 10.1186/s12915-015-0137-1

Burgi S, Samardzija M, Grimm C. Endogenous leukemia inhibitory factor protects photoreceptor cells against light-induced degeneration. Mol Vis (2009) 15:631-7.

Butyrate-mediated epigenetic regulation enhances neuroprotective function of microglia. Frontiers in Immunology (2016) doi: 10.3389/fimmu.2016.01374.

Microglia during ischemic stroke. J Cereb Blood Flow Metab (2008) 28(6):968-84. doi: 10.1038/sj.jcbfm.9601149.

Histone deacetylase inhibitors suppress immune activation in primary mouse macrophages. BMC Genomics (2016) 17:68. doi: 10.1186/s12864-016-2321-6.

DNA Methylation dynamics in aging: How far are we from understanding the mechanisms? Mech Ageing Dev (2012) 133:17-20. doi: 10.1016/j.mad.2011.12.005.

Histone acetylases in development and physiology: Implications for disease and therapy. Proc Natl Acad Sci U.S.A. (2009) 106(50):21389-94. doi: 10.1073/pnas.0906156106.

Cell Death and Disease: Mech Exp Ther (2015) 13:30. doi: 10.1038/s41418-017-00992-3.

Federico C, et al. Targeting the mirna-155/Tnfsf10 network restrains inflammation through inhibition of Socs3. Cell Death Dis (2014) 5:e427. doi: 10.1038/cddis.2013.416-x.

Frederico C, Tagliatesta S, Caiafa P, Zampieri M. DNA Methylation in aging. Trends Immunol (2019) 40(1):66-80. doi: 10.1016/j.it.2018.11.006.

Front Cell Dev Biol (2020) 8:516. doi: 10.3389/fcell.2020.00516.

Mol Neurobiol (2013) 41:1133-42. doi: 10.1007/s12035-012-8221-6.

Mol Neurobiol (2017) 54(8):6391-411. doi: 10.1007/s12035-016-0259-4.

Mol Neurobiol (2011) 45(3):958-74. doi: 10.1007/s12035-011-0141-4.

Mol Neurobiol (2018) 55(7):332-8. doi: 10.1007/s12035-018-0355-x.

Mol Neurobiol (2019) 56(3):570. doi: 10.1007/s12035-018-0285-6.

Nat Immunol (2020) 21(6):375-88. doi: 10.1038/s41555-020-01106-z.

Nat Immunol (2018) 19(4):321-7. doi: 10.1038/s41555-018-0071-z.

Nat Immunol (2021) 22(17):9331. doi: 10.1038/s41555-021-01256-0.

Nat Neurosci (2006) 9(10):1133-42. doi: 10.1038/nn1820.

Nat Neurosci (2014) 17(3):350. doi: 10.1038/nn.3606.

Nat Immunol (2018) 19(11):1365-82. doi: 10.1038/nait.20171147.

Nat Immunol (2015) 16(9):847-57. doi: 10.1038/ni.3357.

Nat Immunol (2020) 21(5):836-52. doi: 10.1038/s41555-020-01141-0.
261. Khan R, Sharma A, Ravikumar R, Parekh A, Srinivasan R, George RJ, et al. Association between gut microbial abundance and sight-threatening diabetic retinopathy. Invest Ophthalmol Vis Sci (2021) 62(7):19. doi:10.1167/iovs.62.7.19

262. Kutsyr O, Maestre-Carballa L, Lluesma-Gomez M, Martinez-Garcia M, Cuenca N, Lax P. Retinitis pigmentosa is associated with shifts in the gut microbiome. Sci Rep (2021) 11(1):6692. doi:10.1038/s41598-021-86052-1

263. Kutsyr O, Nouilles A, Martinez-Gil N, Maestre-Carballa L, Martinez-Garcia M, Maneu V, et al. Short-term high-fat feeding exacerbates degeneration in retinitis pigmentosa by promoting retinal oxidative stress and inflammation. Proc Natl Acad Sci U.S.A. (2021) 118(43):e2100566118. doi:10.1073/pnas.2100566118

264. Parker A, Romano S, Ansorge R, Aboelnour A, Le Gall G, Savva GM, et al. Fecal microbiota transfer between young and aged mice reverses hallmarks of the aging gut, eye, and brain. Microbiome (2022) 10(1):68. doi:10.1186/s40168-022-01243-w

265. Scott PA, Kaplan HJ, McCall MA. Prenatal exposure to curcumin protects rod photoreceptors in a transgenic Pro23his swine model of retinitis pigmentosa. Transl Vis Sci Technol (2015) 4(5):5. doi:10.1167/tvst.4.5.5

266. Emoto Y, Yoshizawa K, Uehara N, Kinoshita Y, Yuri T, Shikata N, et al. Curcumin suppresses n-Methyl-N-Nitrosourea-induced photoreceptor apoptosis in sprague-dawley rats. In Vivo (2013) 27(5):583–90.