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Homeostasis and dyshomeostasis of the retina

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Abstract

Retinal homeostasis is maintained through a network of the nervous, circulatory, endocrine and immune systems. The integrity of the blood-retinal barrier, immune-inflammatory responses, and metabolic changes all significantly affect the maintenance of normal visual function. Retinal degenerative diseases, which include age-related macular degeneration, retinitis pigmentosa, diabetic retinopathy, and other disorders, are a group of heterogeneous and multi-etiological diseases resulting in an irreversible visual impairment. Whether these disorders are inherited, acquired, or from systemic origins, the gradual loss of the retinal pigment epithelium (RPE) and/or retinal neurons is a common feat. This process often begins with compromised retinal integrity, followed by a disruption in the equilibrium of inflammation, immune response, metabolism, and other aspects, resulting in retinal dyshomeostasis that affects not only disease progression but also the effect of therapeutic intervention. Therefore, a comprehensive understanding of the retinal homeostasis and dyshomeostasis will assist the development of treatment strategies for retinal degenerative diseases and open new avenues for clinical translation.

Keywords Retinal disease, Homeostasis, Dyshomeostasis, Degeneration, Photoreceptor, Microglia, Vessel

1 Introduction

Under physiological conditions, the various components and physicochemical properties of the internal environment in the body fluctuate within a narrow range. This delicate control system, known as homeostasis, is a dynamic process rather than a fixed state (Khonsary 2017; Rheinberger and Ernst 2020; The Wisdom of the Body 1934). In healthy individuals, organs and systems collaborate to keep an internal balance. The greatly interacted effectors in this system consist of central and peripheral nervous systems, hormone axes, and the circulatory, metabolic and immune systems. Dyshomeostasis occurs when the system is challenged by internal or external adverse forces, usually due to the malfunction of one or more cell types or tissues (Fig. 1).

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Vision is the primary function of retina, largely dependent on the integrity of retinal neurons. In the meanwhile, Müller glial cells (MGs), astrocytes, endothelial cells (ECs), pericytes, and retinal pigment epithelium cells (RPEs) act as supporting cells to optimize the function of retinal neurons (Subirada et al. 2018; Sorrentino et al. 2016). Visual ability is guaranteed by metabolic networks, immune-inflammatory responses, and the integrity of the blood-retinal barrier (BRB). The term "retinal homeostasis" refers to the state in which various mediators maintain the normal range.

Retinal degenerative diseases (RDDs) are a diverse set of multi-etiological illnesses that may cause a progressive vision loss, including the age-related macular degeneration (AMD), retinitis pigmentosa (RP), diabetic retinopathy (DR), glaucoma, and many others (Shaw et al. 2017; Narayan et al. 2016; Hernández et al. 2016). RDDs are the primary cause of blindness, affecting more than 300 million people globally, and resulting in a considerable decrease in quality of life and a substantial increase of socioeconomic burden

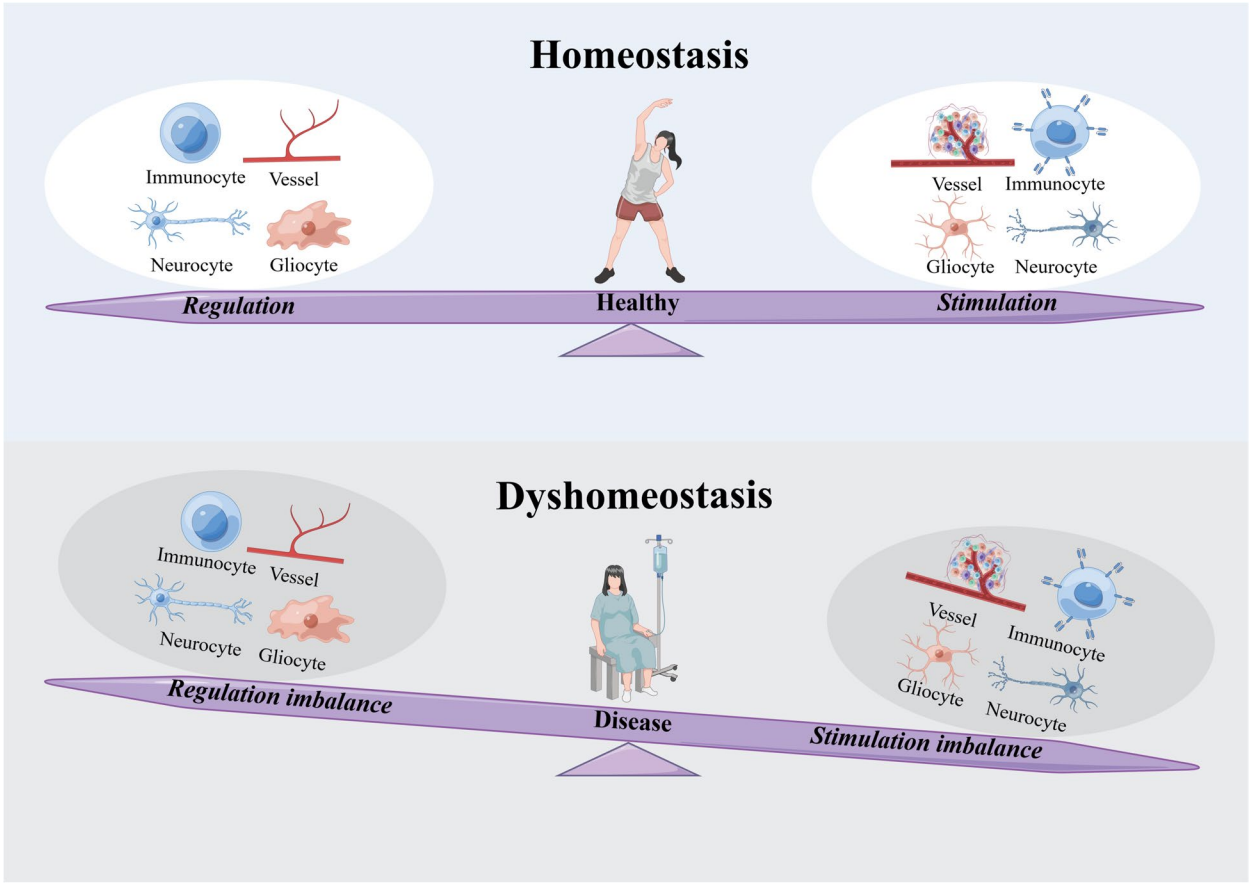

Fig. 1 Schematic overview of homeostasis and dyshomeostasis

(Schwartz et al. 2014). All these diseases have diverse etiologies and could be hereditary, acquired, or systemic. However, all these degenerative retinal illnesses feature a gradual loss of RPEs and/or retinal neurons. The process often starts with compromised retinal integrity, followed by a disturbance in the inflammatory and immune response systems, activation and infiltration of inflammatory cells, and eventual death of RPE and/or photoreceptor cells, resulting in the development of retinal disorders (Iwai-Takekoshi et al. 2016). RDDs have comparable pathophysiological microenvironment, including reactive gliosis, immune abnormalities and metabolic disorders.

Long-term dyshomeostasis may compromise retinal health, resulting in vision-threatening diseases. It promotes the onset and development of retinal illnesses such as AMD, DR, and RP, posing additional hazards to vision. In this study, we present evidence for dyshomeostasis in various retinal disorders and propose therapeutic strategies based on retinal homeostasis.

2 Retinal homeostasis in the conventional sense

Homeostasis exists when the biological system's internal chemical and physical circumstances are stable. The homeostasis theory was initially proposed by the French physiologist Claude Bernard in 1865, and the term was first used by Walter Bradford Cannon in 1926. Bradford coined the term homeostasis from ancient Greek phrases. Homeostasis is essential for the survival of organisms. It is usually regarded as resistance to adverse changes in the external environment. In addition, homeostasis is a self-regulating mechanism that controls the essential internal factors for living. In other words, homeostasis is a process that can preserve the stability of the internal environment regardless of changes in the external environment. The human body maintains homeostasis by regulating many factors, such as body temperature, blood pH, blood glucose levels, fluid balance, and sodium, potassium, and calcium ion concentrations.

However, the homeostasis of tissue remains undefined. The primary function of the retina, which is part of the

central nervous system (CNS), is to capture incoming light and transmit the signal to brain for vision formation. Retinal neurons are the primary cells responsible for vision generation and processing. RPEs, MGs, microglia, retinal vascular endothelial cells, and pericytes are synergistic cells that support and enhance the functioning of retinal neurons (Subirada et al. 2018; Sorrentino et al. 2016). Although the eye is a relatively independent organ in the body, which is protected by BRB and immune suppressive microenvironment, the retinal homeostasis is inseparable from the systemic homeostasis of the whole body. We propose that retina homeostasis comprises intact spatial organization of retinal cells, proper immune-inflammatory responses, and balanced metabolism.

2.1 The homeostasis in the blood-retinal barrier

The BRB is an integral part of retinal anatomy, which consists of retinal blood vessels and RPE (Cunha-Vaz and Maurice 1967; Cunha-Vaz 1979). The vascular endothelium and RPE have a well-developed junctional complex composed of adhesive and tight junctions, thereby highly controlling solute and fluid permeability (Runkle and Antonetti 2011). The permeability of the BRB is divided into inward and outward BRB (Fig. 2) (Campbell and Humphries 2012). Outer blood-retina barrier (oBRB) is the barrier through which compounds enter the retina, while inner blood-retina barrier (iBRB) is the barrier through which substances in the retina reach the capillary lumen or choroidal tissue. In most cases, the inner permeability is much lower than the outer permeability, which is necessary for maintaining retinal homeostasis. The existence of the BRB protects the neuronal retina from circulation, and the content of the extracellular fluid is tightly held. Once this barrier is breached, cytokines and leukocytes will infiltrate into retina, resulting in the pathological changes seen in many retinal disorders. Understanding the formation and maintenance of the BRB is vital to develop treatments to restore damaged BRB or transmit target therapeutic drugs through the barrier when necessary.

Due to its unique physiological structure, BRB has important clinical significance. oBRB is established when monolayer RPEs contact the porous choroidal capillary layer and Bruch's membrane (BM) (Fig. 2C). RPE is firmly interconnected with adjacent cells to prevent fluid from

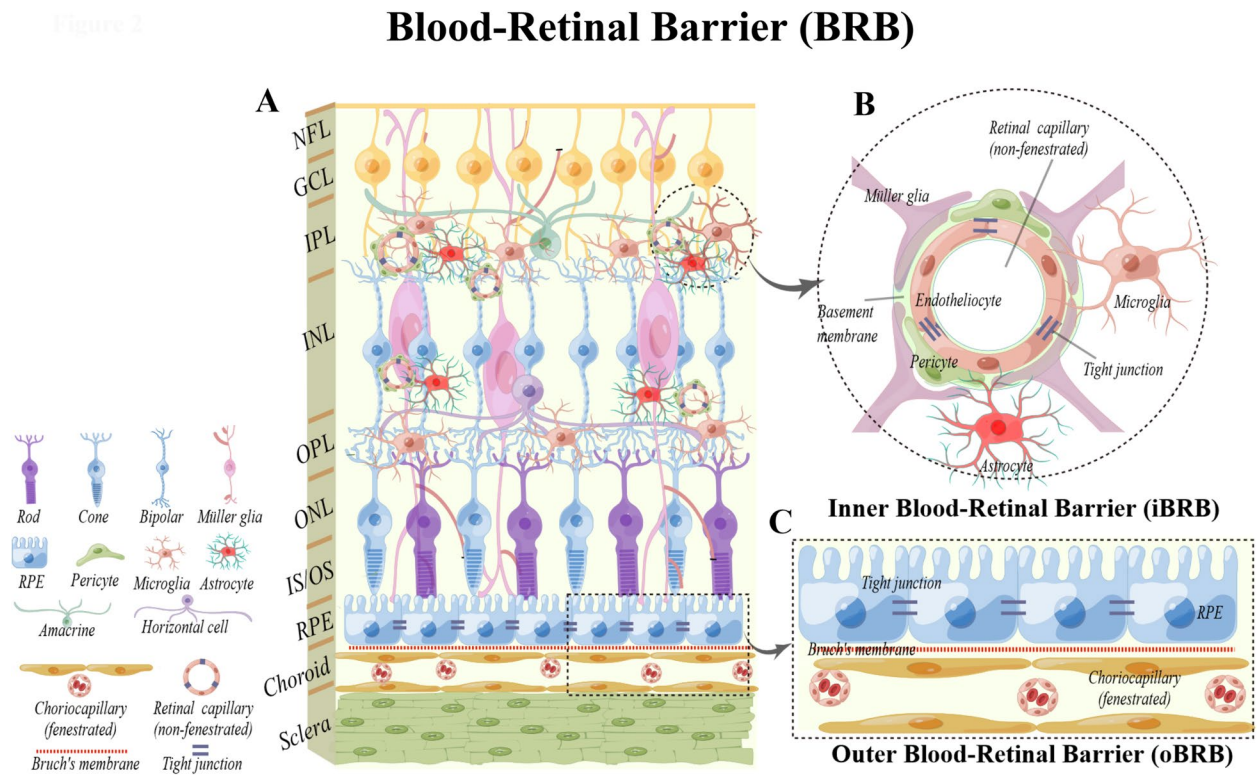

Fig. 2 The structure of the blood-retinal barrier (BRB). **A** Schematic representation of the whole retina. **B** The iBRB comprises vascular endothelial cells, pericytes, glial cells and neurons. **C** The oBRB is formed by interactions of the choroid, Bruch's membrane, and retinal pigment epithelium (RPE). oBRB, outer blood retinal barrier; iBRB, inner blood retinal barrier; NFL, nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, plexiform layer; IS/OS, inner or outer segment

the choroid from spreading to the retina (Shechter et al. 2013). At the initial stage of development, RPE cell junctions are leaky, but RPE gradually form tight cell junctions (Rizzolo 1997). GTP enzyme Rap1 regulates the formation and maintenance of RPE cell connection; it is a vital regulator of RPE cell junctions and is necessary to maintain barrier function (Wittchen and Hartnett 2011). RPEs produce a variety of immunomodulatory mediators, including proinflammatory and inhibitory factors (Fields et al. 2020). The resident RPEs on the inner surface of the BRB have unique ability to transform T cells into regulatory T (Treg) cells and inhibit the activation of bystander $CD4^+$ T cells (Horie et al. 2010; Sugita et al. 2011; Sugita et al. 2009). Therefore, the balance between activated $CD4^+$ T cells and resident RPEs in the retina maintains retinal homeostasis. These properties of the oBRB are analogous to those of the endothelium of the blood–brain barrier (BBB), resulting in significant transendothelial electrical resistance (TEER) and restricted paracellular permeability (Butt et al. 1990). The resistor of BRB is unknown. However, it may be comparable to that of BBB (Butt et al. 1990). These traits make oBRB the dominant immune surveillance site in the retina.

The iBRB comprises complicated tight cell junctions of retinal capillary endothelial cells (Fig. 2B). Retinal astrocytes, MGs, and pericytes may affect intercellular junction development and maturation and are also implicated in the proper function of iBRB (Cunha-Vaz 1997; Small et al. 1993). Retinal glial cells include astrocytes, microglia and MGs which serve as a crucial connection between retinal neurons and blood vessels. They are essential for maintaining the stability of retinal homeostasis and preventing and repairing retinal injury. Astrocytes extend their terminals to the retinal blood vessel wall and wrap around the vessel wall to affect the barrier function (Cunha-Vaz 1997; Small et al. 1993). They can also partially improve the properties of BRB through increasing the expression of tight junction proteins. MGs expand the terminal feet and cover the retinal blood vessels, demonstrating a solid spatial connection between MGs and blood vessels (Small et al. 1993), which may stimulate vascular endothelial cells to establish barrier properties (Tout et al. 1993). In addition, MGs-derived factors can also regulate endothelial cell function (Abukawa et al. 2009). Pericytes have contractile proteins, especially smooth muscle actin, desmin and non-muscle myosin (Bandopadhyay et al. 2001; Allt and Lawrenson 2001; Tomasek et al. 2006). Pericytes and smooth muscle cells modulate capillary diameter by myogenic contraction and relaxation, hence cooperatively regulating blood flow (Yamanishi et al. 2006; Peppiatt et al. 2006). In conclusion, the tight junction of endothelial cells in iBRB can be formed by cell–cell interactions involving MGs, pericytes, astrocytes, and endothelial cells (Kim et al. 2009). The BRB is compromised in a variety of retinal disorders, including AMD, DR, retinal vein occlusion and other inflammatory illnesses.

2.2 Immune homeostasis in the retina

The retina has traditionally been recognized as an immunologically privileged tissue, with its BRB and immunosuppressive microenvironment shielding it from internal and external injury (Fig. 3) (Avichezer et al. 2003). The mechanisms that maintain retinal immune privilege involve two sets of defense systems. The BRB provides the first physical protective barrier for the retina (Soubrane and Coscas 2013). When the barrier is broken, retinal cells suppress the local inflammatory response by secreting anti-inflammatory factors, initiating a second defense mechanism. At the same time, the systemic immune system is also subjected to subretinal exposure to antigens, which induces antigen-specific tolerance or inhibitory immune responses (Streilein 1995; Ferguson and Griffith 1997). Immunity and defense systems collaborate to preserve retinal homeostasis. In supporting this balance, innate immune cells such as neutrophils, monocytes-macrophages and microglia are crucial to the health and diseases of the retina (Riera Romo et al. 2016). These cells and immunosuppressive molecules in the retina actively control the inflammation, minimize subsequent tissue damage to ensure retinal homeostasis (Riera Romo et al. 2016).

Retinal immune privilege emerges as an active process, and the systemic inflammatory response is largely limited in retina. To eliminate threats from pathogenic microorganisms and minimize tissue damage at the same time, the body needs to properly regulate the immune responses (Murakami et al. 2020). The retinal homeostasis is related with antigen tolerances, selected entry of immune cells, and in situ modulation of immunosuppressive cells. This balance is disrupted when uncontrolled inflammation causes cellular injury and the organism is unable to create a stable and appropriate immune response to threats (Taylor and Kaplan 2010; Streilein 2003; Benhar et al. 2012). In other words, through inhibiting the related inflammation, the retinal degeneration may be postponed and the retinal integrity can be preserved (Yao et al. 2018). A number of soluble and cell-bound inhibitors contribute to retinal immune privilege, including the transforming growth factor-β (TGF-β) (Taylor and Ng 2018), retinoic acid (RA) (Zhou et al. 2011) and various immunosuppressive factors (Taylor 2016), as well as the constitutive expression of Fas ligand (Griffith et al. 1995), galectin (Toscano et al. 2006), and membrane glycoprotein CD200 receptor 1 (Zamiri

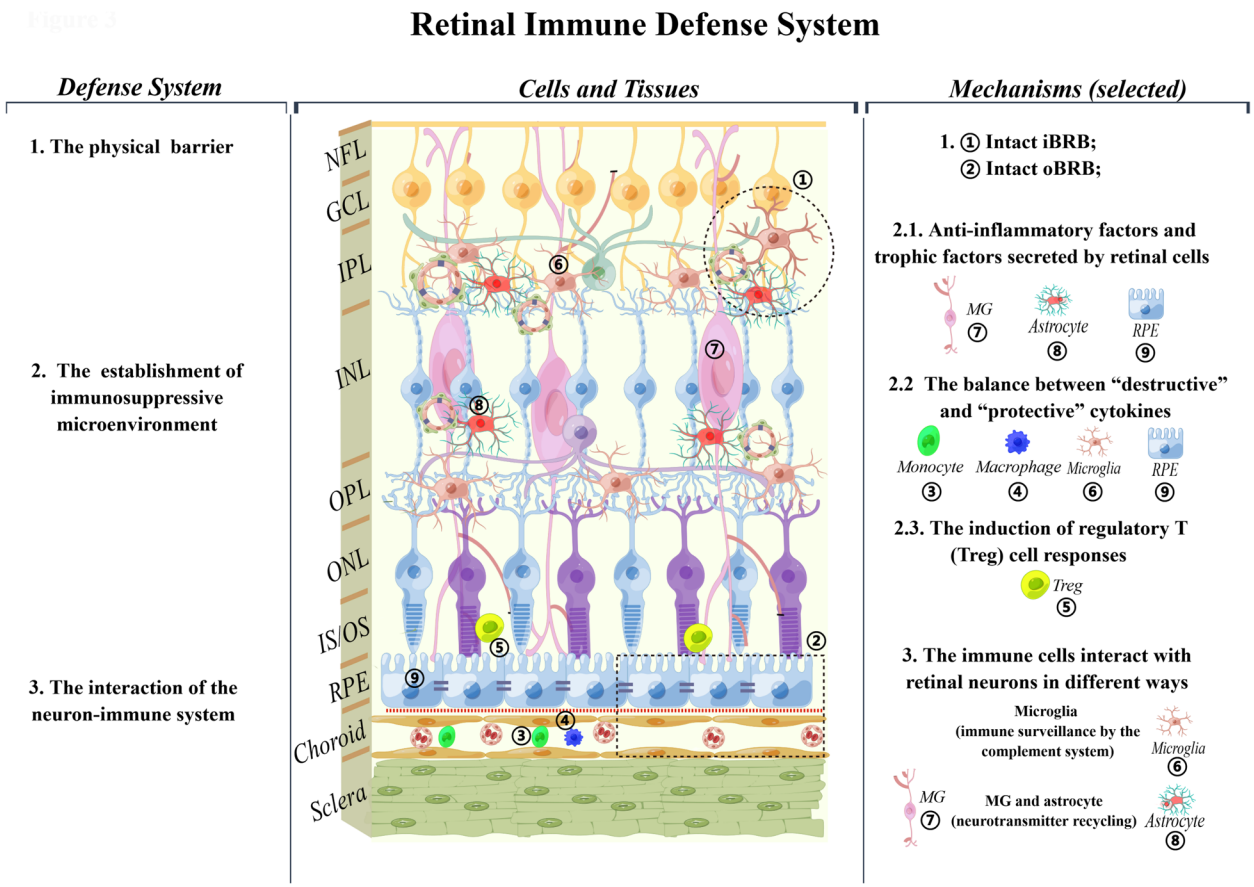

Fig. 3 Retinal immune defense system. In normal immunological conditions, multiple mechanisms contributed to retinal immune defense system. (1) The first physical barrier includes iBRB and oBRB, which blocks the entry of circulating immune cells inside the retina and prevents antigens from escaping the retina. (2) The retinal microenvironment is established by the anti-inflammatory factors and trophic factors secreted by numerous retinal cells, the balance of protective and destructive cytokines, and the induction of regulatory T (Treg) cell responses. (3) The interaction of the neuron-immune system controls the activation of retinal microglia and the complement system. MGs and astrocytes also play an essential role in the regulation of the retinal neuron-immune system

et al. 2005). Meanwhile, the Treg cells naturally contained in retina actively induce suppression of the systemic immune response. However, hyalocytes scattered on the surface of the vitreous have considerable scavenging activity, which may capture antigens on the retinal cell surface and transport antigen presentation to the spleen through blood, eliciting Treg cell responses (Sakamoto and Ishibashi 2011).

As the first physical barrier to keep the independence of ocular immune system, BRB can prevent retinal antigens from being accessed by the systemic immune system, and blood-borne infections from invading the retina (Fig. 3) (Cunningham et al. 2013). When BRB is intact, the interaction of the neuron-immune system controls the activation of retinal microglia and the complement system. In the normal retina, microglia located in the plexiform layer exhibit complex branching processes responsible for retinal immune surveillance (Karlstetter et al. 2015). The activation of microglia or macrophages is modulated by CX3CL1, CD200, CD47 and endocannabinoid pathway in the retina. The activation of T cells is inhibited by thrombin-sensitive protein-1 (TSP-1), TGF-β, CTLA4 and CTLA2, (Horie et al. 2010; Sugita et al. 2009; Sugita et al. 2008; Zamiri et al. 2005; Mochizuki et al. 2013; Kawazoe et al. 2012) while inhibition of complement activation is achieved by the expression of several complement regulatory factors (such as CFH, CD46, CD55, and CD59). When BRB is destroyed, the balance of neuron-immune system interaction is broken, resulting in retinal dysfunctions. This CNS neuron-immune system interaction has been extensively studied and is critical for maintaining CNS homeostasis (Veiga-Fernandes and Artis 2018). Studies have shown that retinal neurons can also express a variety of complement inhibitors, including C1-inhibitor (Serping1), H factor

(CFH) and CD59 which can strictly control the activation of complement (Liu et al. 2020). However, once the BRB is disrupted, the disorders in the retinal immune-inflammatory response will cause retinal dyshomeostasis. Retinal neurons and RPEs can reduce the damage caused by immune-inflammatory imbalance through programmed death or conversion of infiltrated immune cells through Fas/FasL, TRAIL/TRAIL-rs or CTLA-2α/PDL-1 pathway. To sum up, microglia are crucial in the neuron-immune system of the retina and play a role in homeostasis, damage healing, and the development of disease (Chen and Xu 2015; Langmann 2007).

Importantly, the retinal MGs and astrocytes also play an essential role in the regulation of the retinal neuron-immune system (Fig. 3). By releasing trophic factors, circulating glutamate neurotransmitter, and regulating extracellular ion homeostasis, (Reichenbach and Bringmann 2013) MGs across the whole retina (Goldman 2014; Vecino et al. 2016) support the function and metabolism of retinal neurons while retinal astrocytes (Fernández-Sánchez et al. 2015a; Ramírez et al. 1998) confined to the inner axon layer are involved in regulating retinal water homeostasis and neurotransmitter recycling (BRINGMANN, A., et al. 2006; Nagelhus and Ottersen 2013; Papadopoulos and Verkman 2012). In summary, retinal neuron-immune system interaction is important when evaluating the retina's immune-inflammatory homeostasis.

2.3 Metabolic homeostasis in the retina

The retina has various adaptive properties allowing it to regulate energy production and anabolic activities in response to specific demands. It consists of two circulatory systems (retinal capillaries and choroidal arteries) and exhibits the same hypermetabolism features as the brain (Zhu et al. 2012; Daruich et al. 2018; Country 2017). Energy metabolism is required to maintain resting photoreceptor membrane potential, replace photoreceptor outer segments (OSs), and combat retinal oxidative stress (Viegas and Neuhauss 2021; Ozawa 2020; Okawa et al. 2008). The homeostasis of energy metabolism is crucial for maintaining normal retinal function through necessitating several compounds' effective metabolism, including glucose, lipids, and amino acids (Fig. 4). When the retinal metabolism is out of balance, it destroys the local energy supply and redox balance, leading to the risk of death of excitotoxic cells in retinal and onset of various retinal diseases, including AMD, DR, inherited retinal degenerations (IRDs) and macular telangiectasia. Understanding the metabolic homeostasis in the retina is crucial for identifying the pathology and finding therapeutic targets for retinal diseases.

2.3.1 Glucose metabolism in the retina

Major glucose metabolic pathways include glycolysis and mitochondrial oxidative phosphorylation. Under aerobic circumstances, glycolysis is suppressed in normal mammalian cells (Pasteur effect). However, Warburg found that the glycolysis activity of liver cancer cells is more active than that of normal liver cells. Therefore, he proposed that malignant tumor cells also undergo glycolysis in the presence of adequate oxygen. This aerobic glycolysis is characterized by a high glucose absorption rate, active glycolysis, and a high metabolite lactic acid level, known as the Warburg effect (Hurley 2017). In recent years, people have confirmed the existence of the Warburg effect in almost all tumors, and the Warburg effect has been widely recognized as a typical sign of tumors. Intriguingly, glucose metabolism in vertebrate retinas feature aerobic glycolysis (Warburg effect), similar to cancer cells. Rod and cone photoreceptor cells metabolize glucose, which allows only a tiny portion of glucose-derived pyruvate to enter mitochondria. Instead of entirely oxidizing glucose into carbon dioxide in mitochondria, the retina turns 80–96% of glucose into lactic acid under aerobic circumstances, and subsequently lactic acid is delivered to RPEs to provide energy (Viegas and Neuhauss 2021; Grenell et al. 2019; Kanow 2017). There is a growing consensus that retinal and RPE cells perform biological functions and survive as a whole. If the RPEs are deprived of lactic acid, for instance, they begin to utilize glucose as an energy source instead of transporting it to cone and rod cells, which lead to interrupted glucose transfer and the death of cone and rod cells (Hurley 2017; Kanow 2017).

2.3.2 Lipids metabolism in the retina

The important role of lipids in retinal health and disease. Lipids are general terms for fats (triglyceride, fatty acids, phospholipids, sterols, and their derivatives). The retina generally obtains essential lipids through endogenous biosynthesis and systemic circulation. Lipids (phospholipids) in the retina are early discovered in the disc of the outer segment of rod cells (Molday and Molday 1987; Boesze-Battaglia and Albert 1992). The human neural retina is mainly composed of phospholipids (PL), free cholesterol, and a low proportion of cholesteryl esters (CE). The RPE and choroid were composed of 58% PL, 4% triglyceride (TG), 19% CE, 15% free cholesterol and 4% free fatty acids (FAs). Different phospholipids have different FA groups, and the retina has a unique FA structure. The retina has the highest content of long-chain polyunsaturated fatty acids (LCPUFAs), including docosahexaenoic acid (DHA), stearic acid (SA) and palmitic acid (FA) (Acar et al. 2012; Fliesler and Anderson

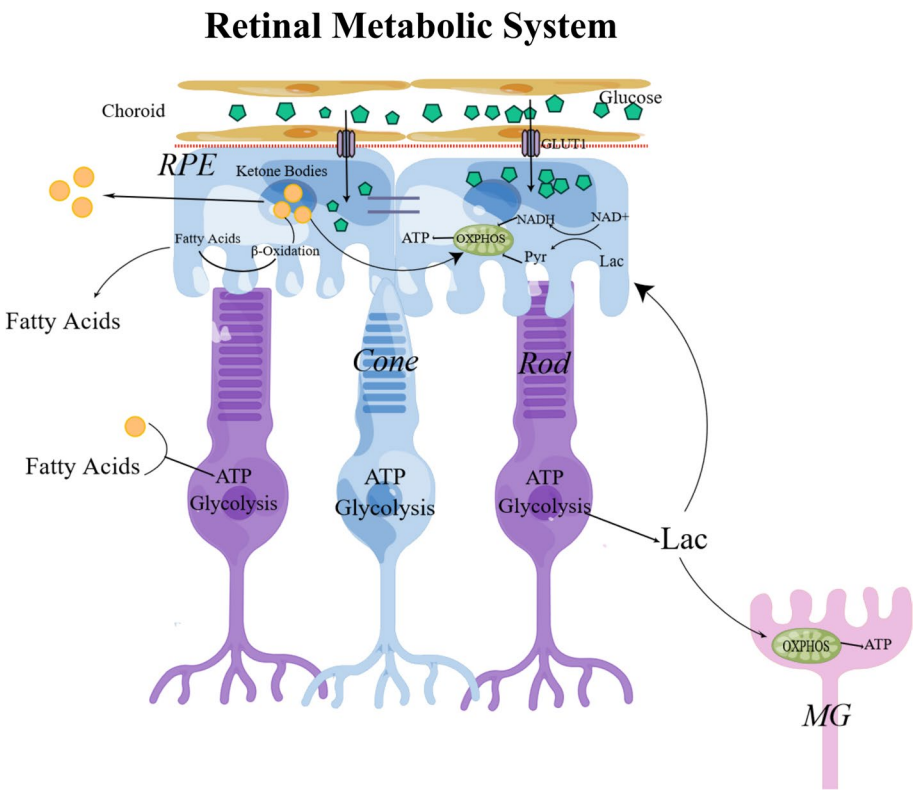

Fig. 4 Metabolic flow of the outer retina. Glucose supplied by the choroid crosses the endothelium and enters the RPE via GLUT1. Photoreceptors convert glucose to Lac and release Lac into the interphotoreceptor matrix. Lac inhibits glycolysis in RPE cells. Similar to cancer cells, glucose metabolism in photoreceptor cells is characterized by aerobic glycolysis (Warburg effect). Rods and cones metabolize glucose, which allows glucose-derived pyruvate to enter mitochondria only. Lactate can also promote the metabolic activity of Muller cells. These fatty acids in the RPE undergo β-oxidation to produce ketone bodies in the form of β-hydroxybutyrate, which can be further metabolized and used in the TCA cycle to supplement RPE mitochondrial activity. Both fatty acids and ketone bodies are transported to the photoreceptor layer, where they are taken up and used to replenish the tricarboxylic acid cycle and OXPHOS. GLUT, glucose transporter; Lac, lactate; OXPHOS, oxidative phosphorylation

1983; Bretillon et al. 2008). Lipids in retinal cells function as substrates for metabolism and components of cell membrane and nerve structure. Firstly, lipids engage in synthesizing liposoluble pigments required for photoreceptor cells. Secondly, lipids emerge in retinal nerve fibers and synaptic connections (Prakash et al. 2017). Their physiological function is not only to provide energy for oxidation, but also to constitute the main components of biofilms (Prakash et al. 2017). Among them, free fatty acids and cholesterol circulate through the retina and choroid blood vessels, and reach the retina through pinocytosis (Delaey and Voorde 2000). The main function of triglycerides (TG) is energy supply. High levels of lipids in nerve tissue are the main components of biofilm, such as cell membrane, endoplasmic reticulum membrane, mitochondrial membrane, and nuclear membrane (Meer et al. 2008). For example, the cell membranes of rods and cones are lipid bilayers. DHA accounts for about 50% of the FAs in photoreceptors, and the outer segment (OS) membrane discs of photoreceptor cells are mainly composed of high levels of LCPUFAs, especially DHA (Gorusupudi et al. 2016; Andrews and Cohen 1983). Large amounts of DHA are beneficial tcell membranes' fluidity, allowing efficient conformational changes of rhodopsin and its associated G protein during phototransduction (Jastrzebska et al. 2011; Fahy et al. 2005). The saturated fatty acids are beneficial to the toughness of cell membranes. Meanwhile, cholesterol plays a vital role in the formation and support of cell membranes, including those of the photoreceptors and RPE (Albert and Boeszebattaglia 2005).

Retinal lipid metabolism is an essential component of retinal cells. It is involved in the growth, development and maintenance of retinal cell function. The maintenance of retinal lipid homeostasis is an important feature of retinal cells, which can be achieved by regulating the synthesis, breakdown and transport of retinal lipids. The input of retinal lipids comes mainly from lipids in the blood, including TGs, cholesterol, PLs, and other lipids. Lipids in the blood are taken up by retinal cells and are converted into lipids within retinal cells, such as TGs,

cholesterol, PLs, and other lipids. In addition, retinal cells can also take up precursors of lipids, such as acylcholine and sodium cholate, from the blood and convert them into lipids within retinal cells. The homeostasis of retinal lipid metabolism is also fine-tuned by several mechanisms regulating retinal lipid transport and clearance between retinal cells and blood circulation.

This section uses retinal cholesterol as an example to elucidate the metabolic cycle of retinal lipids (Fig. 5). The retina generally has an enormous lipid demand which requires either cholesterol synthesis (auto-synthesis) or importing cholesterol from external sources (such as lipoproteins) (Fliesler and Bretillon 2010). Since FAs such as cholesterol and TGs are insoluble in water (Fahy et al. 2005), they rely on carrier lipoprotein to transport between the bloodstream and tissue cells (Hegele 2009). Studies have shown that exogenous cholesterol can pass through the oBRB, with the help of ApoE/A-I, ABCA1/

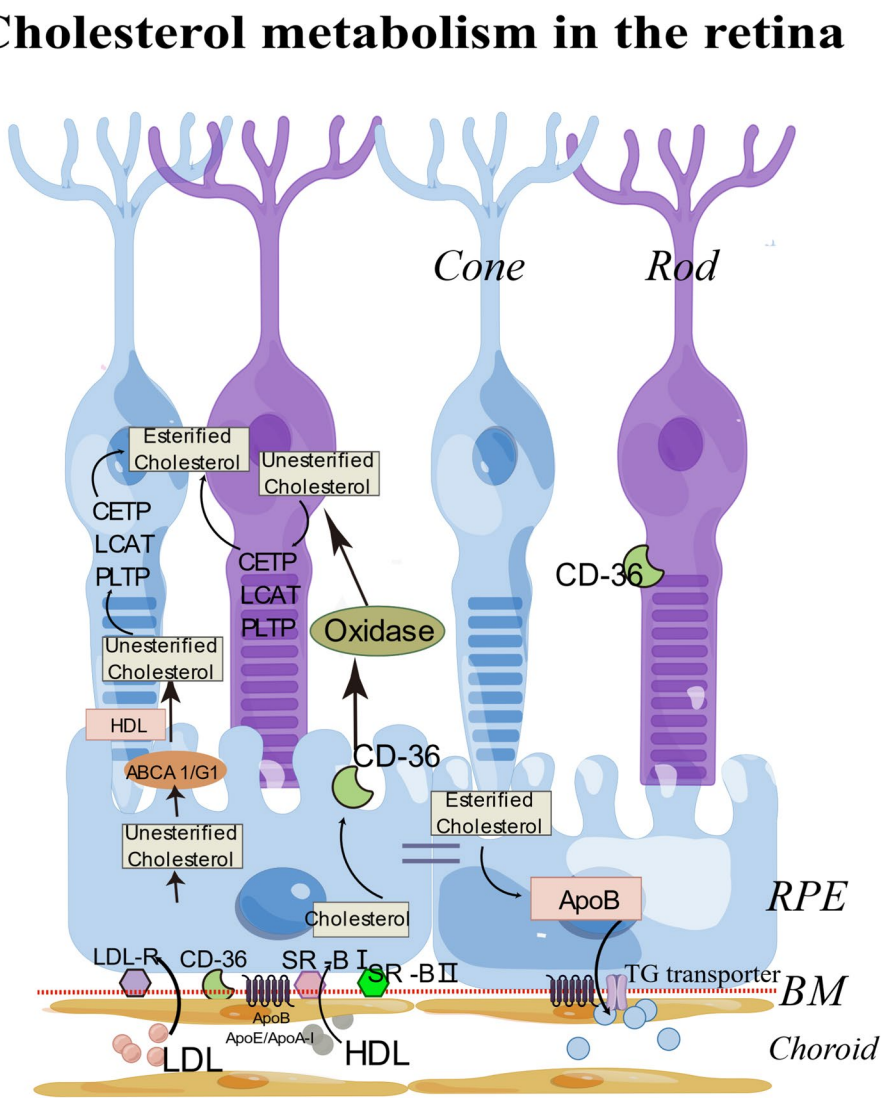

Fig. 5 Cholesterol metabolism in the retina. The transmembrane uptake of retinal cholesterol is mediated by receptors such as lipoprotein (LDL-R), ApoE/A-I, ABCA1/G1 and SR-B I-II in the BMs of the RPE. Lipid transport in the retina involves HDL-like particles that are rich in ApoE or ApoA-I. Exogenous cholesterol can be transported as HDL-like particles by the ABCA1/G1 transporter expressed in RPEs. Lipoprotein particles bound to receptors such as SR-BI, SR-BII, CD-36, or LDL-R are oxidized and cleared in photoreceptors. Esterified cholesterol lipoprotein particles can be released into the BMs via ApoB and microsomal TG transporters produced by the RPEs to be maintained and cleared in the choroidal circulation. Lipoprotein particles of unesterified cholesterol are matured in the IPM and retaken for recycling with the help of LCAT, PLTP, and CETP. HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; LCAT, lecithin cholesterol acyltransferase; PLTP, phospholipid transfer protein; CETP, cholesteryl ester transfer protein; BM, basement membrane

G1 and SR-B I-II receptors on the basement membranes (BMs) of the RPE (Tserentsoodol et al. 2006a; Tserentsoodol et al. 2006b; Ananth et al. 2014), or penetrate the neuro-retinal cells through lipoproteins (especially LDL) (Fliesler and Bretillon 2010; Tserentsoodol et al. 2006a; Tserentsoodol et al. 2006b; Elner 2002; Leeuwen et al. 2018). The transport process of lipoprotein-carrying cholesterol into RPEs requires the coordination of specific lipoprotein receptors LDL-R and SR-B I-II and CD-36 on the RPE BMs (Fliesler and Bretillon 2010; Tserentsoodol et al. 2006a, 2006b; Duncan et al. 2002). However, the permeability of iBRB for circulating lipoproteins is still unclear. Except for exogenous source, retinal cholesterol can also be biosynthesized by retinas in vivo (Fliesler and Anderson 1983*).* However, it remains unclear which type of retinal cells are responsible for cholesterol biosynthesis (Fliesler and Bretillon 2010). MGs contain ApoE and ABCA1/G1 transporters (Amaratunga et al. 1996), indicating that they may play a role in the lipoprotein transport of neuroretina. Moreover, ApoE can be secreted by RPEs, which can also synthesize ApoA-I (Tserentsoodol et al. 2006a, b). In rodent models, it has been demonstrated that retinal biosynthesis accounts for the bulk of total cholesterol (Lin et al. 2016).

Lipid transport in the retina involves high-density lipoprotein (HDL)-like particles rich in ApoE or ApoA-I (Tserentsoodol et al. 2006a, b). Exogenous cholesterol can be exported to the subretinal space in the form of HDL-like particles by ABCA1/G1 transporter expressed in RPEs (Ananth et al. 2014). Then lipoprotein binds to receptors such as SR-BI, SR-B II, CD-36 or LDL-R into photoreceptors, which are converted into oxysterols catalyzed by cholesterol oxidases CYP46A1, CYP27A1 and CYP11A1 (Pikuleva and Curcio 2014), and are cleared by lipoprotein particles in the retina (Fourgeux et al. 2009). Furthermore, esterified cholesterol-rich lipids can be released to the BMs through apolipoprotein b (ApoB) and the microsomal TG transporter generated by RPEs, as well as maintained and cleared in the choroidal blood circulation via the choroidal capillary endothelium (Curcio et al. 2011, 2010; Curcio 2018a, b). The difference is that lipoprotein particles carrying unesterified cholesterol are mature in the photoreceptor matrix (IPM) with the help of lecithin-cholesterol acyltransferase (LCAT), phospholipid transfer protein (PLTP), and cholesterol ester transfer protein (CETP), and then reuptake by the photoreceptors via the scavenger receptor (Leeuwen et al. 2018). The metabolic process of lipids mentioned above can maintain metabolic homeostasis in the retina.

2.3.3 Other metabolism in the retina

In healthy and diseased retinas, the metabolic disturbance of iron and calcium ions has been reported (Shinde et al. 2016; Song and Dunaief 2013), indicating that ion metabolic homeostasis also plays an essential role in the integrity of retinal function and structure. However, due to space limitation, it will not be discussed in this review.

3 The dyshomeostasis in the retinal diseases

The common pathological basis of RDDs is the injury and death of RPEs and/or retinal neurons, which leads to the loss of visual function and the disorders of light signal transduction. The pathology and repair of RDDs involve complex cellular and molecular mechanisms. The disruption of the visual pathway with retinal cell death is the core of retinal disorders. The molecular mechanism of retinal cell injury in diverse diseases is vital to visual research. The survival and function of retinal neurons are highly dependent on the homeostasis of the microenvironment composed of RPEs, glial cells and retinal vasculature. It is anticipated that uncovering the interaction and response mechanism of retinal cells and microenvironment homeostasis would provide new ways for the early diagnosis and treatment of RDDs. In the context of diseases, these regulatory mechanisms are controlled by genetic and/or environmental stimuli, and chronic innate immune responses that regulate or contribute to a variety of retinal dyshomeostasis, resulting in the onset of retinal degenerative diseases, retinal vascular diseases, and retinal fibrosis.

3.1 The dyshomeostasis in retinal degenerative diseases (RDDs)

RDDs are a group of heterogeneous diseases characterized by progressive degeneration or death of retinal neurons. RDDs are the leading cause of blindness while there is no effective cure strategy. Currently, the main challenge is to clarify the biological mechanism of retinal degeneration. RDDs can be caused by protein defects involved in light transduction, synaptic transmission, RPE integrity or function, intracellular transport and ciliary function or accumulation of retinoid toxicity. These defects can lead to retinal dyshomeostasis, resulting in destructive changes in retinal function and structure.

3.1.1 The dyshomeostasis in age-related macular degeneration (AMD)

AMD is a multifactorial disease involving a complex interplay between aging, environmental risk factors and genetic susceptibility, characterized by the dysfunction and injury of the RPE (Flaxman et al. 2017). According to different fundus presentations, it can be divided into dry and wet AMD (Ferris et al. 2013). Dry AMD is characterized by a slow decline in visual acuity, drusen of various sizes in the posterior pole, hyperplasia of pigment epithelium in the macular region, and geographic atrophy

(GA) (Bressler et al. 1994; Bird et al. 1995; Age-Related Macular Degeneration 2002). Wet AMD, also known as neovascular AMD, is characterized by rapid vision loss, neovascularization in the macular region, or hemorrhage and exudation in the lesion area, and the formation of gray-white scar lesions in the later stage (Tan and Sadda 2017). Although numerous factors and processes leading to RPE dysfunction and degeneration have been identified, the pathogenesis is not fully understood. The current study suggests that AMD involves a series of retinal dyshomeostasis, including the imbalance of oxidative stress, the changes in protein homeostasis, the dysfunction of inflammation and immune system, and the defects in lipid and glucose metabolism. This dyshomeostasis form an internal vicious feedback loop that leads to RPE dysfunction, resulting in misfolded protein formation and abnormal lipid accumulation that gradually develops drusen. However, the exact interaction between the pathophysiological events leading to drusen formation and the associated degenerative processes remains to be elucidated. The above reactions run through the progression of AMD. Multi-pathway dyshomeostasis is an essential factor in the pathophysiology of AMD, and the following pathways do not occur separately in the process of AMD, but rather interact with one another.

The pathogenesis of AMD can be divided into genetic and non-genetic related factors. In recent years, genetic factors of AMD have been gradually discovered. The Y402H allele (CFH^{Y402H}) of complement factor H (CFH) is the first gene mutation proved to be directly related to the occurrence of AMD (Toomey et al. 2018a). The CFH^{Y402H} mutation impairs the regulatory function of CFH to inhibit the activation of C3b by complement component 3 (Cc3) and degrade C3b, which leads to the overactivation of complement system and an increased risk of AMD (Goverdhan, et al. 2008). In addition, Cc3 is the convergence of all complement pathways, and the mutation R102G of the C3 gene is also involved in the process of AMD from the early stage to the late stage (Despriet et al. 2009). The C3a can enhance the expression of vascular endothelial growth factor (VEGF) and promote the formation of choroidal neovascularization (CNV) (Nozaki et al. 2006).

Non-genetic factors are the main factors involved in the pathogenesis of AMD, including functional or structural imbalances in lipid metabolism, inflammation and immune responses, neovascularization, RPE senescence, oxidative stress, hemodynamics, autophagy and circadian rhythm. Studies have found that high levels of high-density lipoprotein and cholesterol are associated with higher risk of AMD (Hwang et al. 2022). Lipid peroxides also exist in lipofuscin, drusen and BMs in patients with AMD (Kaemmerer et al. 2007; Kopitz et al. 2004), in which the accumulation of lipid peroxidation end products (LPEP) disrupts protein stability, leading to apoptosis of photoreceptors and RPEs. Vitreous drusen contain a variety of pro-inflammatory factors, which indicates that local inflammatory response is a predictor of the early onset AMD (Abdelsalam et al. 1999; Anderson et al. 2002; Lookeren Campagne et al. 2014). Studies have found that C-reactive protein (CRP) levels are higher in AMD patients (Seddon 2004). CRP can recruit CFH to eliminate necrotic tissue and prevent the release of pro-inflammatory cytokines. When CFH mutation Y402H binds to CRP, which shows lower binding ability, complements are activated and inflammation was induced (Lauer et al. 2011). While most complement proteins cannot penetrate through the BMs, C5a passes through the BMs to cause the destruction of BRB, leading to inflammation and neovascularization (Clark et al. 2017). In addition, the oxidative damage of RPE induced by the emergence of a significant number of reactive oxygen species (ROS) causes AMD's dyshomeostasis. The retina is one of the tissues with the highest oxygen consumption in the human body (Eshaq et al. 2014), and intense oxygen metabolism will promote ROS in the retina. Lipofuscin is regarded as the primary ROS source (Boulton et al. 2004; Rózanowska et al. 1995). Lipofuscin accumulates in RPEs with age, which enhances oxidative stress in the retina. Studies have shown that excessive lipofuscin is associated with AMD (Wihlmark et al. 1997). With aging, human retinal pigment epithelial cells (HRPECs) become senescent, and the activity of lysosomal enzymes gradually decreases. This diminishes the capacity to clear degenerative cells and protein aggregations dependent on autophagy, and increases the accumulation of lipofuscin, which ultimately leads to AMD.

The existence of BRB plays a vital role in maintaining retinal homeostasis. To prevent potentially harmful blood components such as killer lymphocytes, immune complexes, and complements to the retina, retinal neurons/glial cells are segregated from blood microcirculation and choroidal tissue fluid (Katamay et al. 2013; Cunha-Vaz 1976). BRB injury is an important condition for the migration of immune components into the retina and their involvement in the development of retinal disorders (Crane and Liversidge 2008; Kerr et al. 2008). The destruction of oBRB can be directly related to wet AMD (Shao et al. 2016).

3.1.2 The dyshomeostasis in inherited retinal degenerative diseases (IRDs)

Inherited retinal diseases (IRDs) are relatively rare blindness caused by gene mutation (Schneider et al. 2022), including RP, Leber hereditary optic neuropathy (LHON), choroideremia, Leber congenital amaurosis (LCA),

Stargardt's disease (STGD) and X-linked retinoschisis (XLRS) (Gordon et al. 2019). Although there is no viable therapeutic strategy to delay the progression of most IRDs, the pathogenesis of IRDs has been investigated further with the advancement of molecular biology. IRDs are a group of visual diseases with genetic and phenotypic heterogeneity, which mainly affect the function of photoreceptor cells. A variety of biochemical processes and genetic mechanisms affect photoreceptor cells in IRD patients and are involved in light transduction pathways, protein transport, ciliary connection, lipid metabolism, retinal development and synaptic function. Furthermore, mitochondrial failure, RPE dysfunction, and BRB disruption may all play a role in causing IRDs. Although much progress has been made in understanding the effects of photoreceptors and RPE in different retinal pathologies, the exact mechanism leading to the degeneration and death of retinal neurons remains unclear. At present, different mechanisms of cell death have been proposed, including apoptosis, necrosis, pyroptosis, autophagy, excessive calpain activation, and PARP-1-dependent cell death (parthanatos) (Peng et al. 2020). With the advent of next-generation sequencing technology, significant progress has been made in identifying IRDs' genetic defects.

Take retinitis pigmentosa (RP) as an example, studies have shown that RP is a genetic disease associated with more than 80 disease-causing genes. Genetic or de novo mutation is the primary driver of RP, followed by chronic immune-inflammation and metabolic disorders that result in retinal dyshomeostasis (Newton and Megaw 2020a). It was shown that humoral immunity and cellular immunity are abnormal in RP patients (Yamamoto et al. 1992). The vitreous cavity of RP patients contains activated T cells, B cells, and macrophages, and the RPEs express HLA-DR antigen. Meanwhile, it was discovered that RP patients show autoimmune phenomena (Brinkman et al. 1980; Chant et al. 1985), but there was insufficient evidence whether immunity played pathogenic role. Regarding biochemistry, it was reported that RP individuals had an aberrant lipid metabolism, and lipofuscin particles accumulated in the retina (Newsome et al. 1988). The metabolism of enzymes and other trace elements like zinc and copper was also abnormal (Atmaca et al. 1989). To sum up, the RP is a disease with multifaceted etiology, probably resulted from retinal dyshomeostasis.

Gene mutations and susceptibility factors determine the pathogenesis of different IRDs, but the dominating cause of vision loss is the damage of photoreceptor (Botto et al. 2022). Here, we only discuss the dyshomeostasis of photoreceptor degeneration, in order to arouse the macroscopic thinking of researchers on the dyshomeostasis of IRDs. As the most common IRD, RP is characterized by rhodopsin overexpression, underexpression, or structural abnormalities caused by gene mutations which lead to the progressive degeneration of early rod cells. Rod cell degeneration results in the release of inflammatory molecules (including free radicals), which will lead to retinal dyshomeostasis and ultimately affect the survival of cone cells (Kunte et al. 2012; Campochiaro and Mir 2018).

In terms of immune-inflammation, genetic factors include the expression levels of genes that promote or inhibit inflammation. The equilibrium between inflammatory and anti-inflammatory genes of the retina is vital for homeostasis (Lively and Schlichter 2018). During the progression of RP, multiple inflammation-related genes are activated while the counteracting genes are silenced and hence the immune balance is destroyed. A considerable number of inflammatory genes are related to the programmed cell death. The most common pattern of rod cell death in RP is orderly apoptosis, followed by necrosis, necroptosis, pyroptosis, and parthanatosis (Olivares-González et al. 2021). In the process of rod cell loss, inflammatory factors and free radicals are released, which threaten the survival of cone cells. The activation of the NLRP3 inflammasome involves the overexpression of NLRP3, ASC, and caspase1, followed by secretion of large amounts of inflammatory cytokines such as IL-1beta and IL-18, which in turn leads to pyroptosis (Haines et al. 2005). Retinal microglia usually involve in stabilizing inflammation and suppressing immune responses. In RP, microglia are activated and monocytes are recruited, after that T cells and dendritic cells respond to monocyte chemoattractant protein 1 (MCP-1) and lead to retinal injury. Microglia in these locations have an amoeboid appearance and secrete cytokines that initiate various inflammatory pathways. The IL-6, IL-1α, IL-1β and TNF-α lead to the further deterioration of RP. Complement-related factors such as C3, C9, CFH, and CFI can also aggravate retinal inflammation (Jong et al. 2021). Non-genetic factors, including intense sunlight exposure, smoking, aging, body fat rate, alcohol, diabetes and trama, will also accelerate retinal dyshomeostasis.

Recent studies revealed that retinal metabolic dysfunction is one of the main causes of IRDs. Metabolic changes caused by gene mutations or deletions have been widely reported (Genc et al. 2020a; Genc et al. 2020b; Conley et al. 2014; Ding 2004; Stuck et al. 2016, 2014; Murenu et al. 2021; Sinha, et al. 2021; Kelley et al. 2017). Retinal photoreceptors require more energy than any other type of cell (Hurley 2021), confirmed by the extremely high glucose and oxygen consumption in the retina (Damsgaard and Country 2022; Chertov et al. 2011). Metabolic dyshomeostasis is gradually discovered as a common event in IRDs (Sinha, et al. 2021; Kaplan et al. 2021; Joyal et al. 2016; Punzo et al. 2012; Griciuc et al.

2014; Du et al. 2015). The diseased retina may modify its metabolic pathways in the early stages to respond to changes in the microenvironment and maintain homeostasis. But when the condition worsens, metabolic issues ultimately result in retinal degeneration (Sinha, et al. 2021). Whether metabolic homeostasis fluctuate within indicated range determines the progression and stages of disease.

In addition, cystoid macular edema (CMO) occurs in many cases of RP, and the increased permeability of the inner retina implies that the iBRB has ruptured (Vinores et al. 1995). The tight junction proteins between retinal endothelial cells are essential for the maintenance of iBRB. Therefore, the degradation of tight junction proteins leads to the formation of CMO in RP patients. However, not all retinal degenerative models exhibit BRB abnormalities, and the underlying mechanism needs to be further explored (Falasconi 2019; Campbell et al. 2006).

3.1.3 The retinal dyshomeostasis in pathological myopia

Pathological myopia (PM) is the leading cause of low vision and blindness worldwide (Wong et al. 2014; Ohno-Matsui et al. 2016). Pathological myopia is characterized by various degenerative fundus lesions, including tessellated fundus, diffuse/patchy chorioretinal atrophy, macular atrophy, lacquering cracks, choroidal neovascularization (CNV) and Fuchs spots (Ohno-Matsui et al. 2016). The pathogenesis of PM is very complicated. The development of axial myopia into high myopia, which is the pathological foundation of PM, depends on posterior scleral extension and thinning. In vivo studies have shown that oxidative stress initiated neuroretinal degeneration in PM (Francisco et al. 2015; Ham et al. 1984). However, there are few studies on the pathophysiological mechanism of myopic retinopathy.

Various animal models of myopia have been established over the last few decades, providing great support for investigating myopia pathogenesis. However, there are currently no animal models that can adequately imitate human PM retinopathy. And numerous pathological changes in human retinal tissues are difficult to replicate, which greatly limits the study of the pathogenesis of PM.

3.2 The dyshomeostasis in retinal vascular diseases

The retinal blood vessel system is similar to those of other body parts, and its main function is to maintain the metabolism of supporting tissues. Unlike blood vessels in other tissues, the particular location of retinal blood vessel system determines that it must ensure the transparency of the retina to the greatest extent to facilitate vison. This requirement is mainly guaranteed by the BRB composed by retinal vasculature. Retinal vascular diseases affect visual function in different ways, but they are all associated with restricted blood circulation, characterized by changes in blood flow, vascular structure, or blood consistency. From the standpoint of this physiological function, retinal vascular diseases can be roughly divided into two categories: the first is that diseased retinal vessels cannot ensure the effective metabolism of retinal tissue (Chen et al. 2022); the second is that abnormal BRB causes retinal edema or blood component exudation, which affects the transparency and imaging function of the retina (Hayreh 2010). Common retinal vascular diseases include DR, wet AMD, hypertensive retinopathy, retinal vein occlusion, central retinal artery occlusion and ocular ischemic syndrome. This section will focus on the dyshomeostasis of DR and wet AMD.

3.2.1 The dyshomeostasis in diabetic retinopathy (DR)

DR features leakage, occlusion and proliferative microvascularization in retina (Shukla and Tripathy 2022). Clinically, the disease is divided into two distinct phases based on the existence of retinal neovascularization: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) (Wang and Lo 2018). In the non-proliferative phase, the diseased retina shows changes in retinal blood flow and vascular permeability, thickening of the BMs, loss of pericytes and formation of acellular capillaries, followed by microaneurysms, venous beading, and intraretinal microvascular abnormalities (Roy and Kim 2021). Due to the destruction of the BRB, plasma components leak into the retinal tissue, resulting in retinal edema and ischemia(Romero-Aroca et al. 2016; Kang and Yang 2020). When edema occurs in the macular area, it causes central vision damage. As the ischemia persists, the main fundus changes of PDR is neovascularization, which are primarily manifested by the proliferation of neovascularization or proliferative membrane along the retinal surface (Silva, et al. 2013). When the neovessels break, retinal and vitreous hemorrhage follows, and the contraction of the proliferative membrane leads to tractional retinal detachment (Kang and Yang 2020). The progression of DR is a complex process involving multiple molecular and biochemical pathways, and the interaction of these systems results in dyshomeostasis of retinal blood vessels and their microenvironment.

The metabolic disorder of diabetes is the main cause of DR. Elevated blood glucose triggers a cascade of complicated pathophysiological changes. Continuous hyperglycemia can damage the BRB in the early stage, followed by increased permeability, microvascular leakage, late retinal neovascularization, fiber proliferation, and ultimately structure changes (Curtis et al. 2009). The disruption of the BRB causes an increase in vascular permeability, which results in the exudation of fluid in the macular

region and the formation of diabetic macular edema (DME), which is the leading cause of visual impairment in diabetes patients (Kang and Yang 2020). As the disease worsens, vasoconstriction and capillary occlusion lead to capillary damage and retinal ischemia. Severe hypoxia prompts neovascularization, vitreous hemorrhage (VH) and retinal detachment. Retinal ischemia leads to a non-perfusion state which upregulates the expression of vascular endothelial growth factor (VEGF), the most crucial cytokine causing PDR. Pathological factors such as inflammation and oxidative stress also stimulate the expression of VEGF through transcriptional regulation. The upregulated VEGF drives the pericyte apoptosis and act as a strong pro-angiogenic factor, partly by regulating the expression of angiopoietin-1 (Ang1) and angiopoietin-2 (Ang2) (Maisonpierre et al. 1997). Ang1 activates Tie-2 pathway to maintain vascular stability while its competitive antagonist Ang2 interferes with the Ang1/Tie-2 axis and results in exudation in DR (Stewart et al. 2016). In short, VEGF-induced vascular leakage and neovascularization are vital compensatory responses to hypoxia in the diabetic retina that contributes to diabetic retinopathy (Ferrara and Davis-Smyth 1997).

Neurotrophic factors and inflammatory mediators in the retina maintain a physiologically dynamic balance, but diabetes disturbs this balance. Glial cells are activated by changes in biological pathways such as polyols, protein kinase C (PKC), advanced glycation end products and renin-angiotensin system, and hence release various of inflammatory factors and growth factors, causing chronic inflammatory reactions in retinal endothelial and nerve cells (Hove et al. 2020; Rodríguez et al. 2019; Rübsam et al. 2018). Leukocyte integrins (CD11a, CD11b, and CD18) are up-regulated in hyperglycemia, which enriches leukocyte adhesion molecules (intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), platelet endothelial cell adhesion molecule-1 (PECAM-1), E-selectin, and P-selectin), cytoskeleton protein PDZ and LIM domain protein 1 (Wan et al. 2021). In addition, the interaction between abnormal leukocytes and endothelial cells potentially results in retinal vascular injury in an inflammatory environment (Cheung et al. 2010). The levels of inflammatory factors IL-1β, IL-6, IL-8 and TNF-α in aqueous humor and vitreous cavity of DR patients are increased (Feng et al. 2018), and the presence of these factors is closely related to the severity of diabetes (Simó-Servat et al. 2012; Vujosevic et al. 2015; Kinuthia et al. 2020). Furthermore, it is shown that the expression of inflammatory factors increases with VEGF in the vitreous cavity of PDR patients, as does the expression of the soluble receptor sIL-2R2 (Doganay et al. 2002). Inflammatory bodies containing the (NLRP3) is also activated (Loukovaara et al. 2017). At the same time, the occurrence and development of diabetes are also accompanied by increased expression of some chemokines (such as monocyte chemotactic protein-1, macrophage inflammatory protein-1α, macrophage inflammatory protein-1β). The increased expression of monocyte chemotactic protein 1 (MCP-1) can cause retinal vascular leakage (Spencer et al. 2020; Taghavi et al. 2019). Retinal glial cells that maintain retinal structure and homeostasis are also affected by hyperglycemia. Hyperglycemia can activate microglia to secrete inflammatory mediators (TNF-α, IL-6, VEGF, MCP-1) (Altmann and Schmidt 2018). MGs and astrocytes are also involved in the development of inflammatory responses (Wang and Lo 2018). In conclusion, long-term hyperglycemia can lead to increased levels of retinal cytokines such as inflammatory factors and chemokines, followed by endothelial and glial cells dysfunction, finally causing retinal microvascular damage and nerve degeneration, and accelerating the progress of DR.

Hyperglycemia in diabetes disrupts the intracellular antioxidant system. ROS is a group of oxygen-free radicals generated from the highly reactive mitochondrial electron transport chain (Poprac et al. 2017). ROS is a key player in oxidative stress which stimulates cell metabolism, proliferation, differentiation, and immune regulation, as well as vascular remodeling (Sies et al. 2017). The etiology of many illnesses attribute to excessive ROS production and imbalance of the antioxidant defense system. Oxidative stress has been confirmed to be one of the important factors in the pathogenesis of DR. Oxidative stress can lead to nerve, vascular, and tissue damage through pyroptosis, apoptosis, autophagy, inflammation as well as mitochondrial dysfunction. The retina is susceptible to ROS due to high energy demands and light exposure (Boulton et al. 2001). In diabetes, abundant glucose is catabolized by glycolysis, which increases the electron transport chain load and the formation of oxidants in mitochondria, leading to an excessive production of ROS (Brownlee 2005) and a series of retinal cell dysfunction by inducing retinal oxidative stress and mitochondrial impairments. Metabolic disorders caused by diabetes are the fundaments of DR. Multiple pathways are involved, including the activation of protein kinase C (PKC), polyol pathway and hexosamine pathway; intracellular formation of advanced glycation end products (AGEs) and abnormal increase of angiotensin II (Ang II) (Kowluru and Chan 2007; Hammes 2018). These metabolic abnormalities affect the production of retinal ROS. Meanwhile, the excessive production of ROS further increases the disorder of these metabolic pathways, which can also be related to each other through ROS or

other intermediate components (Kang and Yang 2020; Pal et al. 2020).

Autophagy is a process by which eukaryotic cells degrade cytoplasmic proteins and defective organelles via lysosomes under the control of autophagy-related genes. Autophagy is capable of reacting to cytotoxic stimuli, preventing cell damage, and promoting cell survival in the absence of nourishment. Autophagy includes basal autophagy under physiological conditions and induced autophagy under stress conditions. The former is a self-defense system of cells, which is beneficial to cell growth and development, shields cells from metabolic stress and oxidative damage, and plays a crucial role in maintaining cellular homeostasis and the synthesis, degradation, and recycling of cell products. However, excessive autophagy may lead to metabolic stress, degradation of cell components, and even cell death. Therefore, an efficient autophagy system is essential for maintaining homeostasis in the intracellular environment.

Studies have shown that Autophagy is involved in a variety of physiological and pathological processes, including cellular responses, aging, immunity, tumorigenesis, and neurodegenerative disorders (Duraes et al. 2015; Levine and Klionsky 2004; Shintani and Klionsky 2004). There is evidence that autophagy is associated with neurodegeneration, inflammation, oxidative stress, and apoptosis in human diabetic retina. Previous studies have shown that inhibition of autophagy promotes microvascular circulation disorders. It is found that high glucose inhibits the autophagy function of mouse retinal MGs, resulting in VEGF overexpression which may promote retinal neovascularization (Lopes de Faria et al. 2016). However, other studies showed that high glucose could activate the expression of autophagy-related genes in retinal vascular endothelial cells, thereby inhibiting the release of VEGF and ultimately inhibiting retinal neovascularization (Mao et al. 2017). In contrast, in vitro experiments have shown that high glucose can lead to an abnormal increase of autophagy in endothelial cells, and the increased autophagy flux will damage vascular endothelial cells and induce apoptosis of vascular endothelial cells (Du et al. 2017). The above conclusions propose that autophagy has a dual effect on the retina. Moderate autophagy can maintain the stability of the intracellular environment. Excessive or weakened autophagy caused by a high glucose environment will promote the occurrence of diabetic retinal microvascular disease. Autophagy is closely related to diabetic neurodegeneration (Simó and Hernández 2014). Autophagy dysfunction occurs before retinal vascular injury and apoptosis in diabetic mouse models. The activation of autophagy accelerates the death of mouse retinal cells, thereby causing a thinner outer nuclear layer (ONL) (Ren et al. 2018). High glucose may trigger autophagy in rat retinal MGs, but lysosomal failure causes autophagy substrates to accumulate in the cytoplasm, resulting in excessive VEGF release and a higher apoptosis rate (Lopes de Faria et al. 2016). When human MGs were exposed to glycated low-density lipoprotein cholesterol (HOG-LDL), it was found that HOG-LDL showed obvious toxic effects, inducing autophagy and significantly reducing cell viability, leading to increased apoptosis and glial cell activation. Moreover, in the STZ-induced diabetic mouse model, it is found that intracellular autophagy activity is significantly increased, suggested by increased LC3 immunostaining in the outer plexiform layer (OPL), and up-regulated expression of autophagy proteins Beclin-1 and Atg5 (Piano et al. 2016). In conclusion, in the case of diabetes, autophagy has a dual effect on retinal cells. Under mild oxidative stress conditions, autophagy plays a protective role in cells, but when oxidative stress increases to a specific threshold, autophagy will promote the occurrence of DR and neurodegeneration (Fu et al. 2016).

In summary, the pathogenesis of DR is complicated and has not been fully explored. Further studies on the pathophysiological process of DR will provide a potential therapeutic direction for the treatment of DR.

3.2.2 The dyshomeostasis in wet AMD

Choroidal neovascularization (CNV) distinguishes wet AMD from dry AMD. CNV penetrates the BMs and proliferates between the BM and RPE or in the subretinal space (Green and Enger 1993). CNV in wet AMD may be a secondary response to other pathogenic abnormalities in the early stage. The stress or injury of RPE and corresponding immune responses can promote the production of angiogenic factors, thereby driving the occurrence of CNV (Ambati and Fowler 2012). Moreover, degenerative changes in choroidal vessels are another possible cause of pathological angiogenesis. Vascular loss and/or decreased perfusion in the choroidal capillary layer precede pathological angiogenesis and are often accompanied by macrophage aggregation and early indicators of angiogenesis, including endothelial and pericellular activation (Kornzweig 1977; Sarks et al. 1997; Mullins et al. 2011; Killingsworth 1995; McLeod and Lutty 1994). These early vascular changes may lead to choroidal hypoxia and up-regulation of angiogenic factors, thus forming pathological blood vessels. VEGF is regarded as a key pathogenic factor of wet AMD (Lopez et al. 1996; Kvanta et al. 1996; Frank et al. 1996; Bhutto et al. 2006; Campa et al. 2008; Kwak et al. 2000). Oxygen levels, insulin-like growth factor (IGF), glucose, reactive oxygen intermediates and complement influence the generation and release of VEGF by RPE (Nozaki et al. 2006;

Thurman et al. 2009; Pons and Marin-Castaño 2011; Rohrer et al. 2009). However, RPE is not the sole source of angiogenic factors, which may derive from immune cells or other kinds of cells (Higgins et al. 2003; Fukuoka et al. 2003). Furthermore, with aging, the choroidal capillaries become senescent and atrophied, and the supply of blood and oxygen to the neural retina declines, which promotes the overexpression of VEGF and the formation of neovascularization. The expression of anti-angiogenic factor thrombospondin 1 (TSP1) is significantly reduced in AMD patients, especially in choroidal capillaries in the BMs and submacular regions. Similarly, the anti-angiogenic regulator PEDF, whose expression is decreased under disease conditions, can also lead to the formation of CNV. The above indicates that the decreased expression and activity of anti-angiogenic factors can promote the formation of neovascularization. Therefore, the dyshomeostasis between angiogenic and antiangiogenic factors promotes angiogenesis during the development of wet AMD (Hernández-Zimbrón et al. 2018).

In addition to the angiogenic factor pathway, the inflammatory immune response also plays a significant role in the pathogenesis of wet AMD. Inflammation/immune-related factors, such as IL17 receptor C, IL17-F and IL6 are highly expressed in the eyes of AMD patients (Nussenblatt et al. 2013; Xu 2020). The retina and choroid can recruit macrophages and microglia, which are distributed along non-immune cells (RPE and MGs) and participate in the occurrence and development of the disease. In normal-aged RPE cells, the levels of VEGF, IL12 and IL10 are all increased, but IL12 promotes the production of interferon γ, TNF-α and T lymphocytes, while IL10 inhibits inflammatory mediators (Cao et al. 2011). The expression of chemokine receptors CCR1 and CCR2 on $CD14^{+}/CD16^{+}$ monocytes is also considerably elevated in wet AMD patients (Luo et al. 2013). In CNV, the most important immune cells for vascular remodeling are macrophages, which may be subdivided into classically activated macrophages (M1) and alternatively activated macrophages (M2). The ratio of M1/M2 macrophages can regulate the development of CNV (Nussenblatt et al. 2013), and the increase in the number of retinal macrophages is a marker of CNV (Skeie and Mullins 2009; Grossniklaus 2000; Cherepanoff et al. 2010). Enormous evidence from human and rodent studies has shown that macrophages are the main infiltrating inflammatory cells in CNV, indicating the crucial role of macrophages in the development of wet AMD (Yang et al. 2016). The IL-6 produced by macrophages stimulates angiogenesis of CNV by activating IL-6 receptor (IL-6R)-positive macrophages (Droho et al. 2021). In AMD mouse models with CCR2 or its homologous ligand (CCL2) gene deficiency (Ambati et al. 2003), macrophage mobilization is impaired and choroidal neovascularization develops, suggesting that macrophages also defend retina from CNV (Ambati et al. 2003; Molday et al. 2000). Therefore, the role of macrophages in the occurrence or development of CNV still warrants further study.

Microglia are another type of immune cells that involve in the pathogenesis of CNV. Normal retinal microglia are distributed evenly in the inner plexiform layer (IPL) and outer plexiform layer (OPL) (Santos et al. 2008; Provis et al. 1996). When organism experience aging or disorders, the distribution of retinal microglia is disrupted. In the aging retina, an increasing number of activated microglia migrate into the subretinal space (Xu et al. 2008, 2009). Previous studies present that microglia accumulate in the subretinal space of Cx3cr1-deficient mice and exacerbate neovasculature in laser-induced CNV models (Combadière et al. 2007). In AMD-related genetically modified mouse models, the absence of chemokines CX3CR1 and CCL2 leads to the accumulation and activation of microglia in the subretinal space, which is associated with drusen, RPE degeneration, photoreceptor atrophy and CNV (Combadière et al. 2007; Tuo et al. 2007). Moreover, the expression of RPE65 and tight junction proteins (ZO-1 and claudin-1) decreased after cultured RPE cells were exposed to activated microglia, suggesting an impairment of RPE cells caused by microglia (Ma et al. 2009). In contrast, the expression of chemokines (CCL2, CCL5, SDF-1) and adhesion molecules (VCAM-1, ICAM-1) were increased, and the supernatant of RPE culture could induce the migration of microglia (Ma et al. 2009). In vivo, the activation of transplanted microglia in the subretinal space is also related to the displacement of endogenous microglia from the inner retina to the outer retina. This progressive accumulation of subretinal microglia may gradually destroy the immune-privileged environment of the outer retina, evoke the chronic neuroinflammatory process associated with the pathogenesis of AMD, and promote the formation of CNV, leading to retinal dyshomeostasis.

There is also a link between the activation of the complement system and the pathogenesis of wet AMD. The complement system is part of the innate immune system. Its principal function is to identify and remove foreign pathogens, apoptotic cells and cell debris. The initial pathways of complement activation include the classical complement, alternative and lectin pathway, which all revolve around the cleavage of complement component 3 (C3) (Kato et al. 2020). Complement protein and its activated products exist in retinal drusen of AMD patients. Genetic analysis in a large population has shown that several variants of complement proteins are also associated with an increased risk of AMD (Toomey et al. 2018b; Strittmatter et al. 2016). Early histological studies have

found that the complement component C1q in the classical pathway exists in the choroidal neovascularization membrane (CNVM) of wet AMD patients (Baudouin et al. 1992). Nevertheless, the classical complement pathway currently seems to have no prominent role in the pathogenesis of wet AMD (Rohrer et al. 2007). The C3 component in the alternative pathway may play a critical role in the pathogenesis of wet AMD. The C3 protein and its activation products C3c and C3d are deposited in CNV tissue samples (Baudouin et al. 1992; Lommatzsch et al. 2007; Lommatzsch et al. 2008). In experimental mouse models of wet AMD, local C3a levels also increase during laser-induced CNV (Nozaki et al. 2006). Moreover, the C3 knockout ($C3^{-/-}$) mice can tolerate CNV formation after laser irradiation (Bora et al. 2005). The formation of CNV requires VEGF to stimulate choroidal endothelial cells. The C3a increases VEGF secretion of RPEs in vitro and prompts VEGF secretion of mouse choroid when administered intravenously (Nozaki et al. 2006). However, no C3a receptor is found in human choroidal tissues, suggesting that C3a may recruit monocytes to the choroid via ICAM-1 production (Skeie et al. 2010). Furthermore, complement systems such as C5 and CFH, as well as their related intermediate cascades, can contribute to and influence the incidence and progression of wet AMD via inflammatory immunity, upregulation of VEGF expression and oxidative stress. The regulation of the inflammation-related complement system effectively induces RPE to secrete angiogenic VEGF, and its active complement factors C3a and C5a can also recruit leukocytes to the choroid (Nozaki et al. 2006).

The RPEs can regulate the retinal immune-inflammatory microenvironment in various ways, thus regulating the neovascularization of AMD (Golestaneh et al. 2018). Autophagy dysfunction of RPEs is involved in the pathogenesis of wet AMD. Oxidative stress is also considered an important pathogenesis of wet AMD, which may be achieved by stimulating RPEs to produce VEGF and inducing an inflammatory microenvironment (Abokyi et al. 2020; Kim et al. 2021). In addition, lipid abnormalities and exosomes may also participate in the occurrence and development of wet AMD (Tong et al. 2016; Kishan et al. 2011). The incidence of wet AMD is influenced by various risk factors that trigger neovascularization.

4 The implications of retinal homeostasis for treatment

Homeostasis is required for integrative physiology in cells and the whole body. Enormous parameters are involved in the maintenance of homeostasis. Various mechanisms control the stability of these parameters, and there are complicated relationships among them. The maintenance of homeostasis depends on tissue function, cellular regulatory mechanisms and the stability of blood circulation. Nevertheless, the capacity to preserve homeostasis is limited, and irreversible lesions or injuries will result in dyshomeostasis. Many cellular and molecular pathways are involved in the onset and progression of RDDs, which may result in various dyshomeostasis. Through an in-depth study of retinal homeostasis, the relationship between RDDs and metabolic, neural, immune, inflammatory regulatory pathways and the pathogenesis of RDDs could be revealed, laying the foundation for the retinal homeostasis-oriented treatments to RDDs. Single or multiple molecules or drugs, as well as gene and cell therapies may maintain retinal homeostasis by affecting the interaction of mediators and diverse cellular activities. This section will focus on new strategies for treating dyshomeostasis in retinal degenerative and retinal vascular diseases.

4.1 Progress in new therapies for retinal degenerative diseases

The previous sections have shown that retinal degenerative diseases are associated with multiple pathways, including cellular metabolism, oxidative stress, autophagy and inflammatory responses, imbalance of which leads to the loss of neurons and supporting cells (including RPEs and glial cells) in retinal degeneration. Therefore, strategies targeting retinal neurons warrant more investigation. Although gene and stem cell therapy are transforming from preclinical testing to clinical treatment in some retinal degenerative diseases, challenges still exist, which we have reviewed and discussed in our previous works (Zhang et al. 2021; Jin et al. 2019). Therefore, we will focus on the development of drugs for retinal degenerative diseases in this section. Currently, the main research on medicines for retinal degenerative diseases are of neurotrophic and anti-inflammatory basis. Although current drugs are not able to restore the lost RPE and photoreceptor cells, most drugs can effectively improve the retinal microenvironment and maintain its homeostasis, thereby restoring and delaying the functional damage of RPEs and photoreceptor cells.

Oxidative stress is involved in the neurodegenerative process of almost all retinal degenerative diseases, and antioxidants are considered to have a certain effect on the treatment of retinal degenerative diseases. The application of antioxidants has been shown to preserve residual vision in different retinal degeneration models (Cuenca et al. 2014). Among them, natural antioxidant compounds such as saffron and tauroursodeoxycholic acid (TUDCA) can delay the progression of retinal degeneration in animal models, suggesting potential value in the clinical application (Fernández-Sánchez et al. 2015b). Moreover, a number of substances, including vitamin A

(VA), lutein and docosahexaenoic acid (DHA) and lycium barbarum polysaccharide (LBP), Ginkgo biloba extract (GBE) and astragaloside IV, have been found to have antioxidant effects in animal models of photoreceptor degeneration or damage. Some of these substances have shown promising preliminary results in clinical trials (Zhang et al. 2022; Wang et al. 2022; Li et al. 2022; Newton and Megaw 2020b). However, there is some controversy regarding the effectiveness of dietary antioxidant supplements for slowing down photoreceptor degeneration. There is some evidence that the VA-related supplements may not be suitable for all types of RP, which may be due to different gene mutations with distinct impacts on the pathways of VA involvement. In STGD patients who carried the ABCA4 mutation, excessive VA supplementation promotes the accumulation of A2E which results in RPE cytotoxicity and accelerated RPE cell death. In ABCA4 knockout mice, a high dose of VA leads to lipofuscin accumulation and deposition in the RPE, followed by massive accumulation of all-trans retinoic acid and disruption of visual cycle homeostasis. However, the recently reported chemically modified VA, ALK-001 (C20-D3-VA), can safely delay the progression of STGD while maintains normal visual circulation homeostasis in clinical phase II trials (Holz et al. 2018). In RP patients with the LRAT mutation, the retina is incapable of converting all-trans retinol to all-trans retinaldehyde, resulting in the low storage of all-trans-retinol in RPEs, which directly leads to the failure of 11-cis-retinol recycling and the destruction of visual cycle metabolic homeostasis (Perusek and Maeda 2013). The consumption of VA derivatives has been found to enhance retinal content in individuals with LRAT mutation, compensate for the visual cycle metabolic dyshomeostasis induced by the loss of LRAT function, and postpone photoreceptor cell degeneration (QLT091001, ClinicalTrials). Similar evidence suggests that VA improves retinal function in Rho^{T17M} but not Rho^{P347S} mutant retinal degenerative mice (Li et al. 1998). Overall, there is still a risk for VA intake in individuals with retinal degeneration, and more solid evidence is required to offer reliable support. In addition, dietary supplementation with lipid compounds (ω-3 long-chain polyunsaturated fatty acids, docosahexaenoic acid or eicosapentaenoic acid) are being evaluated in multiple clinical trials for the treatment of RP and AMD due to their antioxidant and anti-inflammatory properties (ClinicalTrials.gov) (Maneu et al. 2022). Supplementation of DHA (a type of ω-3 fatty acids) can slow the progression of visual loss in RP patients (Hoffman et al. 2015), and its combination with VA can also improve the survival rate of photoreceptors in RP patients (Berson 2004). The Age-Related Eye Disease Study (AREDS, AREDS2) is a landmark clinical study conducted by National Eye Institute (NEI) for over two decades. ARED reveals that a specific combination of antioxidants (vitamin C, vitamin E, β-carotene) and zinc could help reduce the risk of disease progression in patients with moderate to advanced dry AMD (Kassoff et al. 1417). The AREDS2 study tested several formulation, such as the addition of omega-3 fatty acids, and the substitution of β-carotene with lutein and zeaxanthin and/or reduced zinc (Lawrenson and Evans 2015; Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration 2013), which can reduce the proportion of moderate dry AMD progression to late atrophic and wet AMD. Moreover, lutein and zeaxanthin have higher benefits than β-carotene and are safer for selected patients. Antioxidant supplements and ROS scavengers have been proposed as potential treatments for various AMD. Supplementation with antioxidants and micronutrients (lutein, zeaxanthin, and polyunsaturated fatty acids) can effectively reduce the development of advanced AMD (Bonds et al. 2014). However, the results of the AREDS trial were based on some relatively well-nourished Americans and may not be generalizable to other populations (Mukhtar and Ambati 2019). Although there is growing evidence that antioxidant treatment has a favorable impact on retinal degeneration, there are still significant variations in the molecules, dosages, and outcomes of antioxidant therapy (Maneu et al. 2022). Therefore, more studies are required to provide authoritative guidance for clinical treatment.

Various immune inflammatory reactions have been gradually discovered in the pathological process of retinal degenerative diseases (Zhao et al. 2015; Kohno et al. 2014). It is a new research hotspot to uncover related inflammatory factors in all stages of retinal degenerative diseases. The strategies to treat RP based on the anti-inflammatory response are independent of its genetic background. Anti-inflammatory therapy does not target molecular mechanism of photoreceptor cell degeneration, but instead seeks to block the signaling pathways that promote photoreceptor degeneration and improve the retinal microenvironment in order to block or slow down the degenerative process in photoreceptors. Inhibition of microglial activation, blockage of chemokine receptors and reduction or suppression of inflammatory mediators are potential therapies for RP. Anti-inflammatory drugs, for example, steroidal anti-inflammatory drugs (SAIDs) and non-steroidal anti-inflammatory drugs (NSAIDs), are often used to relieve pain, photophobia, and edema in ophthalmology. In recent years, studies have found that anti-inflammatory drugs also play a role in the treatment of retinal degenerative diseases. Targeted therapy of *rd10* mice with SAIDs dexamethasone decreased the expression of pro-inflammatory chemokines, reduced the activation of microglia,

inhibited the inflammatory response, and protected the visual function mediated by photoreceptors (Guadagni et al. 2019). The dendrimer-fluocinolone acetate (D-FA) injected into the vitreous cavity of RCS rats also significantly decreased the activation of microglia and reduced retinal neuroinflammation reaction (Iezzi et al. 2012). Currently, the usage of NSAIDs for non-vascular retinal degenerative diseases has not been reported. In addition to classic anti-inflammatory drugs, tetracycline derivative minocycline also inhibited the activation of retinal microglia in *rd10* mice, thereby improving the retinal structure and function, and prolonging the survival of photoreceptor cells (Scholz et al. 2015). Minocycline, a tetracycline derivative, is currently being tested in clinical trials to verify the efficacy and safety of the treatment for RP (NCT04068207, ClinicalTrials).

Polyphenolic monomers and their derivatives with anti-inflammatory and anti-oxidative properties have been extensively studied in preclinical studies and might be employed as prospective drugs to prevent and delay RP (Mandal et al. 2009; Hu et al. 2015). In the Rho^{P23H} transgenic pig (Scott et al. 2015), polyphenolic monomers significantly retained the retinal morphology and revived the localization of rhodopsin. In animal models, it alleviates photoreceptor loss of RP by blocking microglial major proinflammatory cytokines through the vitreous binding protein receptor antagonist cRGD and the TNF-α receptor antagonist (Zhao et al. 2015; Batiha et al. 2020; Martínez-Fernández de la Cámara, et al. 2015). MGs can also act as target cells for polyphenolic monomers. In the mouse model of photooxidative damage, inhibition of the ERK1/2 signaling pathway in MGs could protect retinal function (Zeng et al. 2022). In summary, various strategies against the inflammatory immune response of retinal degenerative diseases delay the progression of retinopathy. However, the specific mechanisms, efficacy and safety of these drugs are yet to be evaluated.

Due to the heterogeneity of retinal degenerative diseases, current drugs can only delay the course of the disease within a certain range. Neuroprotective drugs are widely used in nervous system diseases. Clinically, newly developed neuroprotective preparations for retinal degenerative diseases (Dias et al. 2018) include ciliary neurotrophic factor (CNTF), Glial cell line-Derived Neurotrophic Factor (GDNF) and basic fibroblast growth factor (bFGF). GDNF alleviated the death of rod photoreceptors in a model of retinal degeneration (Río et al. 2011). However, the injection of bFGF in the RP rat model showed that a single injection could only delay the degeneration of photoreceptors in a short period (Faktorovich et al. 1990). This may be due to the short half-life of neurotrophic factor, which is challenging to maintain its effectiveness in treatment while frequent injections also increase the risk of injury. Therefore, various novel technologies have been developed for the long-term delivery of neurotrophic factors, such as nanoparticles, viral transduction, and capsule cells that can produce neurotrophic factors. Transplantation of bFGF-producing capsule cells into the vitreous cavity of retinal degeneration rats showed delayed degeneration of photoreceptor cells (Uteza et al. 1999). Similarly, in some RP animal models, CNTF could slow down the degradation of photoreceptors (Maeda et al. 2006; Liang et al. 2001). The implantation of an encapsulated cell device (NT-501) that continuously secrete human CNTF in the intraocular ciliary margin of RP patients showed good tolerance, with no obvious immune response and adverse reactions (Kauper et al. 2012). However, there was no significant change in visual acuity, visual field or electroretinogram (ERG) responses in RP patients (Birch et al. 2013). Therefore, it is necessary to explore the efficacy of different doses of CNTF, and to follow up large samples for a long time. Additionally, nerve growth factor (NGF) (Falsini et al. 2016; Rocco et al. 2015), rod-derived cone viability factor (RdCVF) (Aït-Ali et al. 2015), brain-derived neurotrophic factor (BDNF) (Chen et al. 2012) and pigment epithelium-derived factor (PEDF) (Michelis et al. 2021) may also delay retinal degeneration through retinal neuron protection.

This part summarizes the roles and mechanisms of various drugs targeting different pathways in the treatment of retinal degenerative diseases. Future prospective studies with large populations are needed to confirm these effects in clinical applications.

4.2 Progress of new therapies for retinal vascular diseases

There are several types of retinal vascular disorders with various clinical manifestations, but they are often characterized by the abnormalities of retinal blood vessels. This section will focus on the research progress in treating DR and wet AMD.

Blood glucose control is the primary goal of the treatment of DR. Early detection and laser photocoagulation are the main strategies to improve the prognosis. Diabetes can not only affect retinal vascular endothelial cells, but also activate and damage retinal glial cells. The VEGF signaling pathway is a key factor in the pathogenesis of DR, and its content in the retina is closely related to hypoxia and neovascularization. Anti-VEGF drugs could improve the severity of DR, which is the first-line drug for DR treatment and the standard drug for DME (Chatziralli 2021). In the DR treatment, commonly clinically used anti-VEGF drugs include ranibizumab, bevacizumab, ranibizumab, aflibercept and conbercept (Wang and Lo 2018). However, repeated intravitreal injections

of anti-VEGF drugs may lead to retinal neurodegeneration, choroidal capillary atrophy, macular scar formation and even seriously affect the recovery of vision (Doguizi and Ozdek 2014). In recent years, some new targets have been gradually discovered because anti-VEGF drugs are not effective for all DR patients. Therefore, a new type of intravitreal implant (Ozurdex) came into being, which was effective for macular edema (Corcóstegui et al. 2017). However, how to prolong the half-life of drugs, reduce the number of injections and reduce the economic burden of patients is yet to be explored.

A variety of inflammatory factors are involved in the pathogenesis of DR. Intravitreal corticosteroid injection can be used to treat refractory DME and patients who are unresponsive to anti-VEGF therapy (Wang and Lo 2018; Lattanzio et al. 2017). Moreover, long-term continuous anti-VEGF drug treatment will increase the risk of thrombosis-related diseases (Avery and Gordon 2016). Therefore, the latest guidelines recommend intravitreal hormone therapy as a first-line treatment for DR patients at high risk of cardiovascular events (Schmidt-Erfurth et al. 2017). Since long-term use of intraocular steroids can lead to adverse effects such as ocular hypertension and cataract. Corticosteroids are generally considered second-line options for patients who do not respond to other treatments.

Antioxidants as oxidative stress inhibitors play a role in the prevention and protection of DR. The NADPH oxidase is the main enzyme source of ROS which is directly related to the pathological retinal neovascularization promoted by hyperglycemia (Stitt 2010; Sahajpal et al. 2018). The development of specific NADPH oxidase inhibitors, such as diphenyleneiodonium and apocynin, may improve DR treatment (Peng et al. 2019). The mitochondria of pericytes under high glucose conditions can produce excessive ROS and increase the activity of Caspase-3, suggesting the role of oxidative stress in the process of pericyte apoptosis. The antioxidant ascorbic acid can reduce the apoptosis of microvascular retinal pericytes induced by high glucose. Ascorbic acid and α-tocopherol treatment can inhibit the apoptosis of retinal pericytes in diabetic rats (May 2016). Alpha-lipoic acid (α-la) was also a potent antioxidant to reduce the level of 4-HNE that recognizes ROS-modified proteins and increases GPx levels in the retina of diabetic mice and retinal cells treated with high glucose (Rochette et al. 2015). It was firstly found that treatment targeted the glial cells can improve vascular injury in diabetic animal models. Neurovascular protective agents (erythropoietin) and DPP-4 inhibitors can reduce injury and neurodegeneration. Recent studies have shown that a variety of natural antioxidants (such as resveratrol, crocin and tea polyphenols) are beneficial to DR patients and have become the first choice for preventing and delaying DR (Sepahi et al. 2018). Although the pathogenesis of DR is still unclear, the protection of retinal neurovascular unit, anti-inflammatory and anti-oxidation are still important parts in the treatment of DR. Anti-inflammatory drugs aiming at different targets complement each other in efficacy and are expected to benefit more DR patients.

Wet AMD is also called exudative or neovascular AMD, and the main pathological feature is the abnormal proliferation of CNV passing through the RPE layer. Because the CNV is fragile, it is easy to rupture and leak, which can lead to retinal detachment and macular edema, causing severe and permanent visual impairment (Chakravarthy et al. 2021; Zheng et al. 2020). The treatment of wet AMD has shifted from laser photocoagulation to drug therapy, especially anti-VEGF therapy. The anti-VEGF drugs have become the first-line drugs for treating both occult CNV and typical CNV. At present, ranibizumab, aflibercept and bevacizumab have been approved for the treatment of wet AMD by intravitreal injection. In China, ranibizumab and conbercept which China developed independently, are mainly used. Due to the different mechanisms of different anti-VEGF drugs, patients often need regular and repeated treatment (Ishikawa et al. 2015). In addition, individual differences have different response effects to diseases, which increases the risk of serious complications after intravitreal injection (Miller et al. 2013; Molins et al. 2018; Chen et al. 2010). Among wet AMD patients, patients who received more anti-VEGF injections had a significantly higher risk of developing ischemic retinopathy than patients who received fewer injections (Chen et al. 2019). A better solution to improve the long-term prognosis of wet AMD is to use the same or different anti-angiogenic targets, the use of combination therapy to enhance the consolidation of anti-VEGF function, change the mode of administration to achieve more lasting efficacy, and even more simplified mode of administration to reduce the risk of treatment. A variety of new drugs have quietly entered the stage of clinical trials (Yonekawa and Kim 2015; Tolentino et al. 2015; Mabry et al. 2010). Abicipar pegol (MP0112), an anti-VEGF drug currently in clinical trials, is an ankyrin repeat protein DARPin (designed ankyrin repeat proteins) that mimics the antibody against VEGF-A by genetic engineering (NCT01086761, ClinicalTrials) (Bahadorani and Singer 2017; Al-Zamil and Yassin 2017). Compared with antibody drugs, DARPins protein has the characteristics of small molecular weight, low immunogenicity, high affinity, strong stability and long half-life (Binz et al. 2004), and it has a good prospect in the treatment of wet AMD. Abicipar has stronger VEGF inhibition ability and longer drug maintenance time than other anti-VEGF drugs (Souied et al. 2014), which can

reduce the injection frequency. To further confirm the efficacy and safety of abicipar pegol in patients with wet AMD, two independent phases III studies are ongoing (NCT02462486 and NCT02462928, ClinicalTrials). The single-chain antibody fragment VEGF inhibitor Brolucizumab (RTH 258) is a humanized monoclonal antibody fragment with a small molecular weight (26 kDa), strong penetration, and can bind to all active forms of VEGF-A (Holz et al. 2016). RTH 258 inhibits the activation of the VEGF receptor by preventing ligand-receptor interaction, thereby inhibiting the VEGF conduction pathway, inhibiting the growth of neovascularization, alleviating retinal edema, and improving the vision of patients. RTH 258 has great advantages in drug concentration and dosage. And it is the latest long-acting VEGF inhibitor (Holz et al. 2016; Dugel et al. 2017). A phase III clinical trial is currently underway (Dugel et al. 2017) to compare the efficacy and safety of intravitreal injection of RTH258 or aflibercept in the treatment of wet AMD (NCT02307682 and NCT02434328, ClinicalTrials). To maintain effective drug concentration for a long time, avoid complications and risks of long-term repeated injection, the sustained-release preparations made from biodegradable biomolecular materials are introduced (Medina et al. 2007). At present, there are a variety of sustained-release devices that can achieve intravitreal injection of VEGF inhibitors (Tolentino et al. 2015; Saati et al. 2010; Lai and Landa 2015).

The experimental and clinical results of different anti-VEGF drugs show that they have reached an important milestone in the treatment of wet AMD, which is currently the most important method of inhibiting CNV (McGimpsey and Chakravarthy 2010). Some therapeutic drugs targeting multiple links in the signal transduction process of neovascularization, including VEGF receptor tyrosinase inhibitors (Nagai et al. 2006; Jaffe et al. 2017; Jaffe et al. 2016), vascular disrupting agents (VDAs) (Ibrahim et al. 2013), siRNA (Rittenhouse et al. 2014), angiopoietin-2 inhibitors (Nagai et al. 2006), complement factor [362,363,364] and immunosuppressants (Park et al. 2017; Caballero et al. 2009), can provide multi-target, multi-level and other combinational therapies to reduce the burden of treatment.

5 Summary and future direction

Vision formation depends on the precise structure and function of the retina. Any pressure or injury may damage the retinal structure, resulting in visual impairment, vision loss and blindness. Some genetic, metabolic and environmental factors can change retinal homeostasis, and these factors can initiate various cascades of inflammation and apoptosis. Dyshomeostasis could damage retinal health, leading to a damaged vision. Long-term dyshomeostasis may promote the occurrence and development of retinal diseases such as AMD, DR and RP. In this article, we present evidence for dyshomeostasis in various retinal diseases and propose therapeutic strategies based on retinal homeostasis.

In conclusion, maintaining homeostasis is essential to protect the retina against various injuries. Uninhibited risk factors result in tissue damage, and when the retina is unable to generate an effective defensive response to threats, the "destructive" factors produced by the retina and the system break retinal homeostasis. By elucidating dynamic processes such as the pathogenesis of degenerative retinopathy and changes in the microenvironment, we address dyshomeostasis-related factors of disease occurrence for homeostasis-oriented treatment strategies, which may promote our ability to manage retina disease.

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Authors' contributions
This review article was led and overseen by Z-B.J., who provided guidance and supervision throughout the process. C-J.Z. was responsible for planning and drafting the manuscript, based on the literature review and analysis. Z-B.J. also reviewed and enhanced the manuscript, ensuring its quality and accuracy. The author(s) read and approved the final manuscript.

Declarations

Competing interests
Author Z-B J is a member of the Editorial Board for Current Medicine. The paper was handled by the other Editor and has undergone rigrous peer review process. Author Z-B J was not involved in the journal's review of, or decisions related to, this manuscript.

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