

## Neuroinflammation and Neurodegenerative Disorders of the Retina

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### Abstract

The retina is composed of neural networks that are responsible for visual function, and vascular networks that support the tissue. Although vascular targeting therapies for retinal diseases have recently been developed, therapies directly targeting the neuronal component of these diseases have yet to be developed. Here, we review recent studies describing the pathological signaling that occurs within the neuronal cells of retinal disease models. The molecular changes caused by endogenous or exogenous factors in the retinal neural cells and the molecular events involved in neuroinflammation are illustrated. These underlying molecular mechanisms reveal promising targets for new therapeutic approaches for retinal neural disorders.

**Keywords:** Neuron; Retina; Inflammation; Oxidative stress; iPS cells

### Background

The retina is composed of neural networks that are responsible for visual function, and vascular networks that support the tissue. One type of neuron, the photoreceptor cell, receives light and converts it to electric signals, which are subsequently transferred to secondary and tertiary neurons. During signal transfer, interneurons process the visual information, and then the integrated information is transmitted to the brain through the retinal ganglion cells, whose axons form the optic nerve. Retinal neural tissue also contains Müller glial cells, which develop from retinal progenitor cells; The retinal progenitor cells also generate retinal neuronal cells, i.e. photoreceptor cells and retinal ganglion cells. The Müller glial cells support the neuronal cells, both through direct cellular interactions and by maintaining the microenvironment of the retinal tissue. The neural retina, a neural network composed of glia and 6 kinds of neurons, originates from the neural tube. Like the rest of the central nervous system, the retina cannot be regenerated once it is destroyed.

Thus, the impairment of visual function due to retinal diseases is often irreversible. It is sometimes accompanied by retinal neuronal death resulting from cellular dysfunction due to changes in the microenvironment (Figure 1). These changes can result from the altered production of endogenous factors, originating within the neurons themselves, or from exogenous factors secreted by the surrounding vascular cells or invading inflammatory cells, as well as surrounding neural cells. One such disease that is believed to represent the latter scenario is age-related macular degeneration (AMD) [1], a leading cause of blindness. This disease is categorized as either wet or dry AMD. The majority of patients suffer from wet AMD, characterized by choroidal neovascularization, which proliferates under the macula, the central area of the retina, resulting in exudative changes. Neurons, particularly the photoreceptor cells, are influenced by the extracellular changes, leading to visual dysfunction.

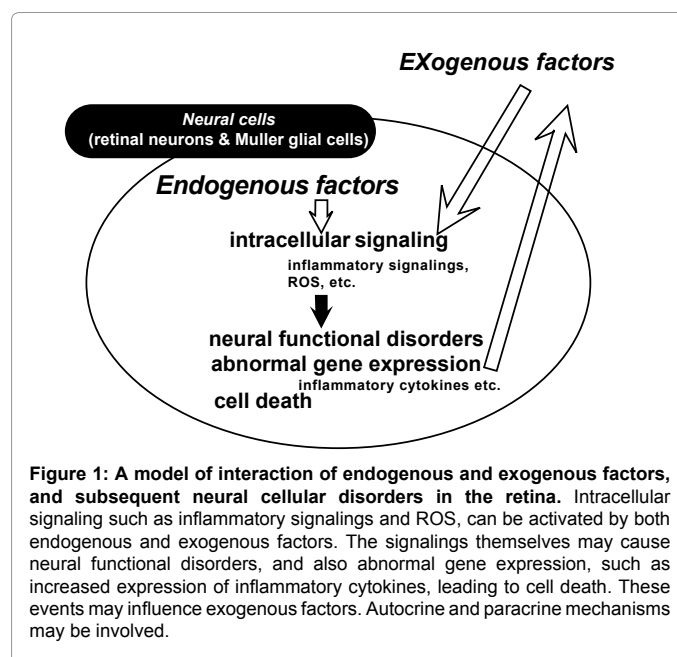
AMD has long been thought to be incurable; however, the application of anti-vascular endothelial growth factor (anti-VEGF) to suppress the vascular proliferation and exudation, has largely improved the prognosis. Under this therapy, the reduced progression of the vascular lesion enables the recovery of dying neurons by removing the source of the exogenous stimuli [2].

Improved, neuro-protective therapies that directly target neuronal tissue to prevent cell death in AMD and other retinal diseases are now being investigated. To establish neuron-targeting therapies, it will be necessary to gain an understanding of the molecular changes occurring

within the affected neurons. The diseases of interest for this approach involve both the common diseases, such as diabetes and inflammatory diseases, and also, the hereditary genetic diseases, such as retinitis pigmentosa.

### Neuroinflammatory Signaling and Cellular Disorders in the Retina

Microangiopathy is a common characteristic of diabetic



**Figure 1: A model of interaction of endogenous and exogenous factors, and subsequent neural cellular disorders in the retina.** Intracellular signaling such as inflammatory signalings and ROS, can be activated by both endogenous and exogenous factors. The signalings themselves may cause neural functional disorders, and also abnormal gene expression, such as increased expression of inflammatory cytokines, leading to cell death. These events may influence exogenous factors. Autocrine and paracrine mechanisms may be involved.

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retinopathy; however, impaired vision begins prior to the appearance of an obvious vascular lesion in this disease [3,4]. At the early stage of this disease, impaired inner retinal function was detected by observing the oscillatory potentials (OPs) recorded by electroretinogram (ERG) [3,4]. In parallel, atrophy or thinning of the inner retinal layer was also reported, based on optical Coherent Tomography (OCT) observations, in diabetes patients with no detectable clinical diabetic retinopathy [5]. Taken together, the appearance of retinal neural changes prior to a detectable vascular lesion suggests the involvement of pathological signaling within the retinal neurons that may induce vascular lesion. Our understanding of the underlying pathogenesis of diabetic retinopathy is becoming increasingly clear, largely due to experiments using animal disease models. Results of these studies have indicated that oxidative stress [6-8] and inflammatory signaling [7-11] in the retinal neural tissue are deeply involved in the disease-related mechanisms.

A systemic increase in the level of oxidative stress is one of the characteristics of diabetes [12-18]. In fact, Reactive Oxygen Species (ROS) were found to accumulate in the retinal neurons of a mouse diabetes model, using dihydroethidium (DHE), which reacts with superoxide to generate a fluorescent signal [7]. ROS are usually generated physiologically; however, when their levels exceed the capacity of anti-oxidative enzymes, such as the Superoxide Dismutases (SODs) and catalase, their accumulation leads to dysregulated cellular function. SOD-1-deficient mice show a specific reduction in the number of retinal ganglion cells as they age [19]. The increased accumulation of ROS in the diabetic retina probably results from both an increase in ROS generation, at least in part due to high glucose level, and a decrease in the expression of anti-oxidative enzymes as previously shown in the animal model [6], even when there is no genetic defect.

ROS play a role in mediating various intracellular signaling pathways, including the pro-inflammatory MAPK, STAT, and NF- $\kappa$ B pathways [7,20-22]. Thus, via ROS, proinflammatory signaling can be activated endogenously, even without exogenous cytokine stimuli, and cause neuroinflammation in a cell-autonomous fashion. Moreover, ROS can also induce production of inflammatory soluble factors including cytokines [22-24]. In studies using selective retinal ganglion cell culture, ROS accumulation was induced by deleting antioxidants from the culture medium. The elevated ROS levels were found to induce angiotensin II expression, resulting in an autocrine/paracrine-induced activation of the angiotensin II type 1 receptor (AT1R) [24].

Retinal neural cells produce abundant levels of inflammatory cytokines [22]. Interleukin-6 (IL-6) mRNA is expressed in the retinal ganglion cells and inner nuclear layer cells, including the Müller glial cells [25]. Retinal ganglion cells express additional cytokines such as vascular endothelial growth factor (VEGF) [26], which contributes to the pathogenesis of diabetic retinopathy. Mice with streptozotocin (STZ)-induced diabetes show elevated VEGF levels in the retina; however, this increase was not seen in mice with a conditional knockout of hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) in the Müller glial cells. Moreover, when the same mice were tested in the oxygen-induced retinopathy model, in which retinal neovascularization occurs in response to excessive VEGF expression, the HIF-1 $\alpha$  deficiency decreased the pathological neovascularization in the retina [26]. Other group also reported that Müller glial cell-derived VEGF is essential for diabetes-induced retinal inflammation and vascular leakage [27]. Data of leukostasis in the retinal vessels and vascular leakage assessed by measuring the retinal albumin, as well as molecular expression of inflammatory molecules such as TNF- $\alpha$ , ICAM-1, and NF- $\kappa$ B in the retina, are all suppressed in the diabetic model mice derived from the VEGF conditional knockout mice generated using Cre-loxP system, in which Cre-recombinase is

selectively expressed in the Müller glial cells. Taken together, VEGF, previously characterized as a vascular modifier and pro-inflammatory factor, was found to originate in the neural tissue of diabetic mice and to be required for the disease pathogenicity.

Another inflammatory factor, angiotensin II, is converted from angiotensinogen in a step-wise manner by various converting enzymes. Together with their receptors, the related molecules are known as the Renin-Angiotensin System (RAS). Each of the components is expressed in various cells that comprise the retina, including the retinal ganglion cells, Müller glial cells, and photoreceptor cells [8]. This type of expression is referred to as tissue RAS, and is regulated independently of systemic RAS. [28]. Recent reports show that angiotensins 1 to 7 and aldosterone, one of the mineral corticoids, are also expressed in the retina [28].

The inflammatory effect of angiotensin II on retinal neural tissue has been studied in the STZ-induced diabetes model. In that study, ERK activation downstream of the AT1R resulted in the decreased expression of a synaptic vesicle protein, synaptophysin [10]. The underlying mechanism, revealed by experiments using a neuronal cell line, was found to be an AT1R-dependent and ERK-dependent increase in the Ubiquitin Proteasome System (UPS)-mediated protein degradation [10]. Thus, the tissue RAS, which is activated independently of the systemic RAS, activates ERK, a pro-inflammatory intracellular signaling molecule, resulting in neuroinflammation in the diabetic retina.

The activation of inflammatory signaling pathways in neural cells has been also demonstrated in the LPS-induced retinitis and uveitis model (also known as the Endotoxin-induced uveitis or EIU model) [29]. IL-6 mRNA is upregulated in the retina of these mice, indicating that the inflammatory reaction occurs locally [23]. In addition, STAT3 has been shown to be activated downstream of IL-6 in neural cells, including the photoreceptor cells [19]. Studies in mice with a retina-specific knockout of suppressor of cytokine signaling 3 (SOCS3), a negative feedback intracellular molecule of STAT3, showed that activated STAT3 is elevated in the EIU model; this activated STAT3 accelerates the posttranscriptional decrease in rhodopsin, a visual pigment specifically expressed in the rod photoreceptor cells. This reduction in rhodopsin levels occurs as a result of excessive degradation by the UPS, most probably by upregulating an E3-ligase, ubiquitin-protein ligase E3 component, n-recogin 1 (UBR1) [29]. This rhodopsin loss influences visual function by reducing the visual activity of rod photoreceptor cells. This is a good example of neuroinflammation originating in the retinal neural cells in an autocrine and/or paracrine manner, in contrast to classic neuroinflammation, in which inflammatory cells are the primary effector cells.

In addition to increased pathological signaling, reduced levels of neurotrophic factors may be involved in the pathogenesis of diabetic retinopathy. The levels of brain-derived neurotrophic factor (BDNF) [7] and nerve growth factor (NGF) [30] are both decreased in the diabetic retina. NGF is produced from pro-NGF by the proteolytic activity of matrix metalloproteinase (MMP)-7. In contrast to NGF, pro-NGF increases neuronal cell death signaling through the receptor p75<sup>NTR</sup>. Pro-NGF, which is induced in Müller glial cells in the diabetic retina, causes retinal ganglion cell death at least in part through p38 MAPK signaling [31]. In the disease state, when the NGF levels are low, the phosphorylation and activation of TrkA, the NGF receptor, are reduced, which also contributes to cell death [31]. Thus, the balance of pro-NGF and NGF activities may be one of the key regulators of neuronal dysfunction in the diabetic retina.

The manipulation of these various soluble factors and their downstream intracellular signaling pathways to recover dying neurons in the retina will be a promising therapeutic strategy for retinal diseases. Although which signaling is in the most upstream has not been definitively known and we have to learn more, interrupting the positive feedback loops of the inflammatory signaling may be, at least in part, effective to suppress the pathogenesis.

Interaction between retinal neural cells and the non-neural cells is also investigated [32]. Dysfunction of astrocytes coincidentally observed with the inner retinal hypoxia, was reported to be found in the earlier stage of diabetes rather than the later stage when the obvious changes in Müller glial cells were observed. Involvement of microglia which is also activated in the early phase of diabetes in the retinal pathogenesis is also reported [33]. Activated microglia could release inflammatory cytokines such as IL-1 $\beta$  to induce apoptosis [33], although a recent report showed the possibility that the vascular endothelial cells might be the greater contributor for IL-1 $\beta$  secretion in response to the high glucose [34].

### Genetic Abnormalities Affecting Neurodegenerative Signaling in the Retina

Retinitis Pigmentosa (RP) is a retinal degenerative disease caused by a genetic abnormality affecting the photoreceptor cells or the retinal pigment epithelial cells which contributes to the maintenance of photoreceptor cells. One of the best characterized mutations of rhodopsin, P23H, occurs with high frequency in RP patients, and has been actively studied using genetically modified animals or cells.

The abnormal structures and misfolding of mutant rhodopsin proteins have been studied using purified proteins expressed in COS-1 cells [35]. The abnormal P23H rhodopsin protein was reported to accumulate in aggregates, and to induce an impairment of the UPS of these cells [36]. Increased levels of the mutant protein were also found in the endoplasmic reticulum (ER), resulting in impaired physiological processing of the normal rhodopsin protein [37]. The visual function of P23H rhodopsin transgenic animals was restored by introducing Grp78/Bip, an ER-localized chaperon that is recruited in response to ER stress [38]. The expression of Grp78/Bip led to a reduction in photoreceptor apoptosis and an increase in photoreceptor function. The involvement of complexes between Bip, caspase-12, and the BH3-only protein BiK was also reported, consistent with the function of BiP in suppressing photoreceptor cell apoptosis [38]. Inadequately glycosylated mutant rhodopsin accumulates in the ER instead of localizing to the rod photoreceptor disks, also leading to photoreceptor degeneration [39]. Thus, the P23H-altered form of rhodopsin associated with RP initiates a series of signaling cascades and molecular events, resulting in neuronal cell dysfunction, and finally neuronal cell death. In addition to this P23H model, there are several gene targeted mice in which molecular mechanisms of the photoreceptor cell death are studied. The involvement of calcium channel in the rod photoreceptor cell death is reported in the mutant mice of rod photoreceptor cGMP phosphodiesterase 6 (rd1 mice) [40]; Ca<sup>2+</sup> channel antagonist D-cis diltiazem delays the kinetics of rd1 rod degeneration, conferring partial rescue of scotopic vision. In the retina of *ATP-binding cassette, sub-family A (ABC1), member 4 (Abca4)*-knock out mice, light-dependent accumulation of retinoids and lipids derivatives are formed [41,42]; *This gene abnormality can be associated with a spectrum of related autosomal recessive retinal degenerative diseases including Stargardt macular degeneration, cone-rod dystrophy and a subset of RP* [41].

Studies using animals expressing various mutants have greatly

increased our understanding of the pathogenic mechanisms underlying RP. However, it is technically difficult to evaluate all of the various mutants in mice. Recent advances in biotechnology have increased our ability to study degenerative diseases caused by gene abnormalities. One new technology is the generation of inducible pluripotent stem cells (iPS cells) [43]. This method enables researchers to generate retinal cells from a patient's somatic cells; these retinal cells contain the patient's genomic abnormality. In fact, in one study, patient-derived iPS cells were used to generate photoreceptor cells, which were examined for their ability to respond to vitamins anticipated to have neuroprotective activities [44]. The results suggested that the vitamins have differential effects, which appear to be specific for individual mutations. Thus, the iPS technology may lead to the identification of new therapeutic targets by facilitating drug screening using *in vitro* cellular systems that represent a multitude of human genetic abnormalities.

### Summary

Most retinal diseases cause neurodegenerative disorders resulting in visual function impairment. Therapies that target the root causes of these disorders, such as the control of blood sugar levels in diabetic retinopathy, and gene therapies for the treatment of genetic diseases, are important approaches. However, we still need to find new therapeutic approaches directed toward resolving the neural cellular dysfunction in the retina. These treatments will focus on controlling the intracellular signaling cascades that fluctuate under pathological conditions. Although the pathological changes in the retinal neural tissue in each condition are becoming well studied, multiple factors could be activated at a given time, and in addition, there would be intercellular associations in the tissue not only between neural cells but also between neural cells and the vascular and/or inflammatory cells. Thus, one therapeutic approach may not resolve all the influences, and moreover, might affect negatively to the other cells. Therefore, further analyses in detail to know the whole underlying molecular mechanisms in the retina are required, before clinical trials are planned.

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