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Invited Review

Importance of Müller Cells

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Abstract

Müller cells (MCs) are the most common glial cell found in the human retina. MCs have an important role in architectural and metabolic functions in the retina. Additionally, there has been consideration that MC dysfunction might contribute to the pathogenesis of some retinal diseases, such as proliferative vitreoretinopathy, diabetic retinopathy, macular edema, retinal vein occlusion, macular telangiectasia type 2, age-related macular degeneration, retinal degeneration, hepatic and methanol-induced retinopathy, and glaucoma. This review is a summary of the functions of MCs and a discussion of the importance of these glial cells.

Keywords: Architectural and metabolic support, functions, Müller cell.

Introduction

Müller cells (MCs) (retinal gliocytes, Müller glia) are the most common of the 3 glial cells found in the human retina, followed by astroglia and microglia. Retinal gliocytes were first described by Heinrich Müller (1). The MC is the only retinal glial cell sharing a common cell line with retinal neurons. MCs have been shown to originate from neural crest cells (2).

A single progenitor cell forms both MCs and retinal neurons. The early phase of neurons born at the apical border of neuroepithelium adjacent to the pigment epithelium produces cone cells, horizontal cells, and ganglion cells, while the second phase of cells produces MCs, rod photoreceptors, bipolar cells, and amacrine cells (2–3).

MCs cover the entire thickness of the retina and have interactions with every type of neuronal cell body. MCs are aligned radially in the retina. The uppermost portion of the MCs creates the internal limiting membrane, which separates the retina from the vitreous. The cell bodies sit on the inner nuclear layer. The apical portion extends to the rear to form the outer limiting membrane and separates the internal and external parts of the photoreceptors. MCs contain blood vessels in the plexiform and nerve fiber layers (Fig. 1). MCs fill gaps in the retina that the neuron cells do not fill. As all glial cells do, they serve as support cells for neurons. MCs contribute to the internal blood-retinal barrier formed by endothelial cells by inducing the synthesis of tight junction and tight junction proteins (4).

MCs contribute important structural and metabolic functions to ensure the viability and stability of retinal cells. They work in a symbiotic relationship with neurons. MCs interconnect the neural elements of the retina with synapses and dendrites. MCs serve as a soft substrate for neurons to protect them in case of mechanical trauma and also for neuronal development and neuronal plasticity. Furthermore, MCs may differentiate into neural progenitors or stem cells that reproduce lost photoreceptors and neurons under pathological conditions (5, 6). Research continues to examine their role in neural regeneration in humans (7, 8). Studies in human models have shown that MCs have the potential to serve as stem cells in the adult retina and are rod pho-

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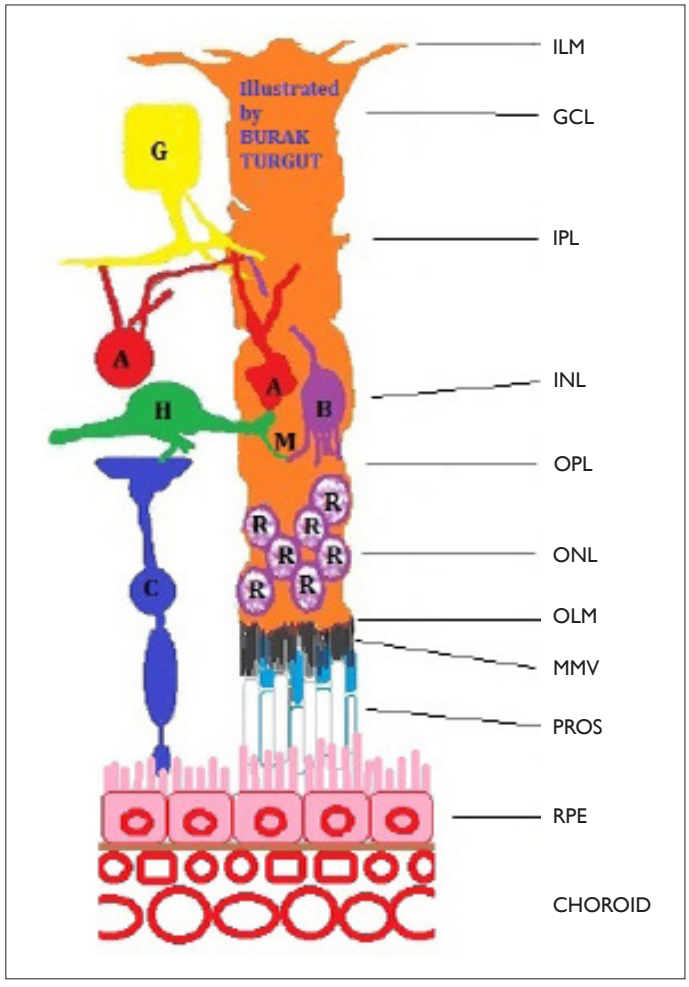

Figure 1. Schematic drawing of the relationship between a Müller cell and other retinal neurons.
A: Amacrine cell; B: Bipolar cell; C: Cone cell; G: Ganglion cell; GCL: Ganglion cell layer; H: Horizontal cell; ILM: Inner limiting membrane; INL: Inner nuclear layer; IPL: Inner plexiform layer; M: Müller cell; MMV: Müller micro-villi; OLM: Outer limiting membrane; ONL: Outer nuclear layer; OPL: Outer plexiform layer; PROS: Photoreceptor outer segments; R: Rod cell; RPE: Retinal pigmented epithelium.

toreceptor progenitors. Damage to retinal cells causes MCs to undergo gliosis. It is known that the destruction of MCs can lead to the development of a macular hole or pseudohole. The result of the response depends on the damage and the organism in which damage occurs. In the zebrafish genus, MCs have been shown to differentiate into multipotent progenitor cells. The progenitor cell may be divided and differentiated into a number of retinal cell types, including photoreceptor cells that may have been damaged during injury (9–11).

The unique funnel shape of MCs, the radial alignment in the retina, and more suitable physical properties allow light to be transmitted from the vitreous to the photoreceptors behind the retina (3, 4). The cytoplasm of MCs contains several mitochondria that help to reduce light scattering and are enriched with long, thin filaments that form the dielectric anisotropy. The characteristics of MCs contrast with the rest of the retina, which has a surprisingly high light scattering effect. Other research has shown that MCs have acted as a funnel to provide light to rod and cone photoreceptors in the mammalian eye, similar to fiber optic plates (12).

MCs are thought to synthesize retinoic acid from retinol and to recycle the photopigments via the transport and conversion of bleached photopigments. Additionally, they contribute to the generation of the electroretinogram (ERG) b-wave, the slow P3 component of the ERG, and the scotopic threshold response (13, 14).

MCs have effects on voltage-gated ion channels, neurotransmitter receptors, and various carrier systems (15). These properties allow MCs to control the activity of retinal neurons by regulating the extracellular concentration of neuroactive substances such as potassium (K+), gamma-aminobutyric acid (GABA), and glutamate. They protect neurons from harmful changes in the ionic environment. Furthermore, they control the composition of extracellular fluid by mediating intracellular ion, water, and bicarbonate transport. In rats, aquaporin-4 in the MCs was reported to transfer water to the vitreous (14). These cells also synthesize and store glucose, and provide glucose to neighboring cells. MCs contain glycogen, mitochondria, and intermediate filaments. They are immunoreactive for vimentin, and for glial fibrillary acidic protein (GFAP), to some extent. These second filaments are normally found in the inner half and the ends of MCs. However, following trauma to the retina, in cases such as retinal detachment, both vimentin and GFAP are massively up-regulated and present throughout the cell (17, 18). MCs remove neural waste, such as carbon dioxide and ammonia and recycle used amino acid transmitters. It has been shown that MCs in chicken embryos were important in inducing glutamine synthetase, an actor in the regulation of glutamine and ammonia concentrations in the central nervous system (19).

MCs not only participate in extracellular homeostasis, neuronal waste removal, and transport of metabolites, but also directly contribute to the processing of information in the retina. They may produce, store, or release neuroactive substances, most likely in immediate reaction to neuronal activity or metabolic condition. Such materials may include adenosine 5'-triphosphate (ATP), glutamate, and D-serine. The protective effects of reactive MCs include the regulation of ATP-degrading ectoenzymes. This effect is achieved by increasing the extracellular presence of adenosine, a neuroprotectant, by preventing the osmotic release of ATP, which can protect retinal ganglion cells from apoptosis, and by increasing the release of antioxidants and neurotrophic factors (4, 20).

Since they defend the retina against free radicals, MCs may have a significant neuroprotective effect. MCs protect neurons through the secretion of neurotrophic factors, intake and degradation of glutamate and excitotoxins, and antioxidant and glutathione secretion (17). MCs synthesize glutathione from glutamate, cysteine, and glycine. Reduced glutathione is delivered to neurons and acts as a cleanser for free radicals and reactive oxygen compounds. In the event of hypoxia or hypoglycemia, the glutathione level in MCs is dramatically reduced. A lack of glutathione due to ischemia may increase the intraretinal level of oxygen-derived free radicals. MCs obtained from older animals contained a smaller quantity of glutathione compared to the cells seen in young animals. Therefore, the decrease in the MC-mediated defense against free radicals due to age may accelerate the pathogenesis of retinopathy in elderly patients (16, 20).

Another means of neuroprotection is the uptake and/or detoxification of potentially harmful substances or particles by MCs. This includes phagocytosis of dead neurons or pigment epithelial cells and debris from foreign bodies, such as copper particles or latex particles. MCs are thought to remove large molecules from the extracellular matrix and possibly induce glutathione synthetase, the only enzyme present in the retina for ammonia detoxification. They can play a role in both neuronal debris phagocytosis and the release of neuroactive substances such as GABA, taurine, and dopamine. It has been demonstrated that neurotransmitters (GABA as well as acetylcholine) served as important mediators in the deterioration and preservation of a suitable retinal microenvironment in turtles (16, 17, 20).

MCs are important for the preservation of retinal homeostasis and play a role in the regulation of the blood-retinal barrier. Thus, the blood need and angiogenesis of the retina are controlled (21). In general, MCs increase the barrier function of the vascular endothelium through the secretion of factors such as pigment epithelium-derived factor, thrombospondin-1, neurturin, and glial cell-derived neurotrophic factor. In response to hypoxia, a high glucose level, or inflammation conditions, multiple signaling pathways are activated in MCs, followed by an increase in proangiogenic factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), matrix metalloproteinases, netrin-4, and angiopoietin-4. These changes are important features of retinal diseases, including diabetic retinopathy (DR), retinal vein occlusion, macular telangiectasia type 2, and some forms of age-related macular degeneration (ARMD) (22–26). It will be of great interest to learn if including neurotrophins and perhaps other trophic factors with anti-VEGF drugs is beneficial to preserve neuronal viability in patients subjected to long-term anti-VEGF treatment for DR, diabetic macular edema, advanced neovascular ARMD, retinopathy of prematurity, and other hypoxic retinal diseases (27).

Posterior vitreous separation from the retina is associated with mechanical stress in MCs, resulting in the secretion of vascular permeability factors, including bFGF. MCs are also a source of matrix metalloproteinases that break down occludin, a tight binding protein. This stimulates high glucose proteinase production. Epiretinal membranes are a prominent type of scar that connects retinal tissue with hypertrophic MC fibers. These membranes are thought to protect the retina from the effects of pathogenic factors in the vitreous. After partial separation of the vitreous from the retina, vitreous fibers adhering to MCs at the vitreoretinal attachment sites exert traction on the cells. This event activates cells and results in cellular hypertrophy and proliferation as well as vascular leakage. Mechanically stressed MCs secrete growth factors (e.g., bFGF) and ATP. The intracytoplasmic swelling of MC corresponds to retinal swelling and liquefaction necrosis of MCs and leads to cystoid macular edema. MCs have been detected in epiretinal tissues in fibrovascular-contractive retinal disorders, such as proliferative vitreoretinopathy (PVR) and proliferative DR (28–34).

Primary MC failure has been proposed as the cause of different cases of retinal degeneration, including hepatic and methanol-induced retinopathy and glaucoma. Almost all pathogenic stimuli activate MCs. Reactive MCs demonstrate protective and toxic effects on photoreceptors and neurons. They contribute to oxidative stress and glutamate toxicity due to glutamate uptake and glutathione synthesis failures. Reduction of intercellular potassium and water permeability causes neuronal hyperexcitability and edema (35–38).

In a glaucomatous retina, MCs are reactivated (gliosis). Reactive MCs undergo various changes in their cellular physiology, biochemical, and morphological properties. Reactive MCs can also produce cytotoxic factors, including nitric oxide, tumor necrosis factor alpha, reactive oxygen species, and prostaglandin E2, thereby inducing apoptosis of the retinal ganglion cell and causing cell death (25, 39–43).

Conclusion

MCs have an important architectural and metabolic role that affects the retina. MC dysfunction may cause the development of vitreoretinal diseases, such as PVR, DR, macular edema, retinal vein occlusion, macular telangiectasia type 2, ARMD, retinal degeneration, hepatic- and methanol-induced retinopathy, and glaucoma. Greater understanding of the functions of MCs and the results of dysfunctions will be of great importance in the development of new therapeutic approaches for some vitreoretinal diseases.

Disclosures

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