Müller Glial Cells in Retinal Disease

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Key Words

Müller cell · Gliosis · Glutamate toxicity · Antioxidants · Adenosine · Edema

Abstract

Virtually all pathogenic stimuli activate Müller cells. Reactive Müller cells exert protective and toxic effects on photoreceptors and neurons. They contribute to oxidative stress and glutamate toxicity due to malfunctions of glutamate uptake and glutathione synthesis. Downregulation of potassium conductance disrupts transcellular potassium and water transport, resulting in neuronal hyperexcitability and edema. Protective effects of reactive Müller cells include upregulation of adenosine 5'-triphosphate (ATP)-degrading ectoenzymes, which enhances the extracellular availability of the neuroprotectant adenosine, abrogation of the osmotic release of ATP, which might protect retinal ganglion cells from apoptosis, and the release of antioxidants and neurotrophic factors. The dedifferentiation of reactive Müller cells to progenitor-like cells might have an impact on future therapeutic approaches. A better understanding of the gliotic mechanisms will be helpful in developing efficient therapeutic strategies aiming at increased protective and regenerative properties and decreased toxicity of reactive Müller cells.

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Introduction

In addition to microglial cells, the resident immune cells of the retina, the retina contains two types of macroglial cells: astrocytes and Müller cells [1]. Astrocytes play a crucial role in retinal vascularization [2, 3]; in the mature retina, they are restricted to the nerve fiber and ganglion cell layers [4, 5].

The human retina contains 8–10 million Müller cells. Each Müller cell constitutes the core of a column of retinal neurons, which represents the smallest functional unit for 'forward information processing' [6]. Müller cells interact with the neurons of their columns in a kind of symbiotic relationship and are responsible for the functional and metabolic support of their associated neurons [1, 7]. Müller cells provide neurons with trophic substances and remove metabolic waste. They play a critical role in regulating the extracellular space volume, ion and water homeostasis, and in maintaining the inner blood-retinal barrier. They release gliotransmitters and other neuroactive substances, and have an impact on synaptic activity by neurotransmitter recycling, which involves the supply of neurons with precursors of neurotransmitters [8]. All these functions directly or indirectly modify neuronal activity. Müller cells support the survival of photoreceptors and neurons, are responsible for the structural stabilization of the retina, and modulate immune and inflammatory responses [7, 8]. They guide the light to the

photoreceptors [9] and buffer mechanical deformations of the retinal tissue [10]. Müller cells become activated by virtually all pathogenic stimuli [7, 11]. Reactive Müller cells are neuroprotective but may also stop supporting the neurons and, instead, contribute to neuronal degeneration. This article provides a short overview of the involvement of Müller cells in pathological processes of the retina. Currently, the numerous roles of Müller cells in retinal disease are not fully understood, and are the subject of ongoing research. Much of the current knowledge about Müller cell functions and dysfunctions was derived from animal models and cultured Müller cells, and thus awaits confirmation in human cells in situ.

Müller Cell Gliosis

Reactive gliosis is thought to represent a cellular attempt to protect retinal tissue from further damage, to promote retinal tissue repair, and to limit tissue remodeling [7, 8]. It includes morphological, biochemical, and physiological changes; these responses vary with the type and severity of the insult. Upregulation of the glial intermediate filaments vimentin and glial fibrillary acidic protein (GFAP) (fig. 1b) is a very sensitive early indicator of 'retinal stress' [7, 12, 13]. Other gliotic alterations in-

clude Müller cell hypertrophy and proliferation, and de-differentiation to progenitor-like cells (see below) [8].

Müller cell gliosis has both protective and toxic effects on retinal neurons [7, 8]. Particularly under conditions of massive (proliferative) gliosis, the regular glial-neuronal interactions are disrupted and the retina degenerates. An inverse relation between Müller cell proliferation and the expression of neuron-glia symbiosis-mediating proteins has been observed [14–21]. However, dysfunction of Müller cells may also contribute to neurodegeneration in the case of 'conservative' gliosis (associated with short-term or low-level Müller cell proliferation). After retinal detachment, for example, downregulation of cellular retinaldehyde-binding protein (usually involved in cone photopigment recycling [22]) and glutamine synthetase [14, 15] disrupts the glial-neuronal interactions involved in photopigment and neurotransmitter recycling. Downregulation of carbonic anhydrase [14, 15] and inwardly rectifying potassium (Kir) channels (fig. 1d, 2, 3a, b, d) [23–38] results in disturbances of retinal acid-base, ion and water homeostasis (see below) [7, 39].

The involvement of reactive Müller cells in immune and inflammatory responses may also exert detrimental effects. After retinal injury, such as retinal detachment, Müller cells upregulate inflammatory factors, including monocyte chemoattractant protein-1, which recruit

Fig. 1. Müller cell reactivity in a blue light-injured rat neuroretina. **a** Focal illumination of the rat retina with excessive blue light results in apoptotic degeneration of photoreceptor cells as indicated by the disappearance of aquaporin-1 immunoreactivity in the photoreceptor segment (PRS) layer and outer nuclear layer (ONL; right). Slices of a control retina (left) and a retina obtained 3 days after light treatment (right) were immunostained against aquaporin-1 (red) and the Müller cell marker glutamine synthetase (blue). Blood vessels and activated immune cells were labeled with isolectin (green). Usually, aquaporin-1 is localized to photoreceptor cells, a class of glycinergic amacrine cells (white arrow), and erythrocytes within the vessels (white arrowheads). Yellow arrowhead: isolectin-stained invading macrophage. **b** Localization of GFAP (green) and aquaporin-4 (red) immunoreactivities in slices of a control retina and a retina 2 days after light treatment. Note that both immunoreactivities are largely absent from the ONL under control conditions, and present after light treatment. Also note the disappearance of aquaporin-4 immunoreactivity in the outer plexiform layer (OPL), indicating early loss of ribbon synapses after light treatment. Blue stain: cell nuclei. **c** Blue-light injury is associated with disruption of the outer blood-retinal barrier, resulting in extravasation of blood proteins such as IgG and invasion of macrophages into the outer nuclear layer, which phagocytize the debris of degenerated photoreceptors. Slices of a

control retina (left) and a retina 3 days after blue-light treatment were stained against IgG (green) and with isolectin (blue) which labels blood vessels and activated immune cells including macrophages (arrows). The presence of IgG-labeled Müller cell fibers (arrowhead) indicates that Müller cells phagocytize blood-derived proteins. The left sides show differential interference contrast (DIC) images of the slices. **d** Potassium currents of 2 Müller cells isolated from a control retina and a retina 3 days after light treatment (left). Note the decreased Kir currents after light treatment. The bar diagram on the right displays the time-dependent decrease in the mean Kir currents of Müller cells after blue-light treatment of the retina. **e** Blue-light injury alters the osmotic swelling properties of Müller cells. The cross-sectional area of Müller cell somata was measured in slices of untreated (control) retinas and of retinas isolated 3 days after light exposure. Acute exposure of the slices to a hypoosmolar solution (60% of normal osmolarity) induced time-dependent swelling of Müller cell bodies in light-injured retinas, and had no effect on the size of Müller cell bodies in control retinas. The **insets** display original records of a dye-filled Müller cell soma in a slice of a light-injured retina, obtained before (left) and during (right) hypoosmotic exposure. Scale bar: 5 μ m. GCL = Ganglion cell layer; INL = inner nuclear layer; IPL = inner plexiform layer. Scale bars, 20 μ m and 5 μ m (**insets**).

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phagocytotic monocytes/macrophages and microglial cells to the injured area [40, 41]. Invading macrophages and neutrophils release oxygen free radicals and cytotoxic cytokines, which play critical roles in photoreceptor apoptosis after retinal detachment [42] and in neuronal degeneration after ischemia-reperfusion [43]. Vimentin- and GFAP-deficient mice display an attenuation of distinct detachment-induced glial responses [activation of extracellular signal-regulated kinases (ERK1/2) and c-Fos, induction of monocyte chemoattractant protein-1] and, as a consequence, decreased monocyte infiltration and photoreceptor apoptosis [44]. A similar recruitment of blood-derived macrophages into the retinal tissue was observed after experimental blue-light retinal injury (fig. 1a, c) [34].

On the other hand, reactive Müller cells might also protect photoreceptors and neurons from cell death by various mechanisms, including the secretion of neurotrophic and growth factors, in particular basic fibroblast growth factor (bFGF, FGF-2) [45–47]. The glial cell line-derived neurotrophic factor (GDNF) induces phosphorylation of ERK1/2 in Müller cells, resulting in transcriptional upregulation of bFGF that in turn supports photoreceptor survival [47, 48]. GDNF also protects photoreceptors and ganglion cells from apoptosis through upregulation of the glial glutamate-aspartate transporter (GLAST) [49, 50]. Retinal preconditioning with bright light or mechanical stress protects photoreceptors from apoptosis because these stimuli induce upregulation of bFGF and ciliary neurotrophic factor in Müller cells [45, 51]. Likewise, argon laser photocoagulation slows photoreceptor degeneration by induction of bFGF in Müller cells [52]. Other neuroprotective effects of gliosis include the production and release of antioxidants, such as glutathione (see below), pyruvate, α -ketoglutarate, metallothionein, lysozyme, ceruloplasmin, heme oxygenase and reduced ascorbate [41, 53–58]. Müller cells phagocytize cellular debris [59] and blood-derived proteins (fig. 1c).

Glial Scars

Retinal gliosis might result in the formation of glial scars, which inhibit retinal remodeling and regular regeneration of the injured retinal tissue [8]. Usually, Müller cells are softer than neurons [10]. As growing neurites prefer soft substrates [60], soft glial processes may support the growth of neuronal processes implicated in synaptic plasticity [10]. However, gliotic Müller cells display

increased stiffness due to upregulation of intermediate filaments, in particular of GFAP (fig. 1b); this will inhibit neurite growth and might be one reason for aberrant retinal tissue repair after retinal injury [61]. The increased stiffness of gliotic Müller cells might also be responsible for the fact that, in retinal neovascularization, new blood vessels grow towards the vitreous rather than within retinal tissue [62]. In addition, gliotic Müller cells increase the expression of extracellular matrix and cell adhesion molecules [63–70]; these molecules function as chemical inhibitors of axonal growth and neuronal regeneration [71–74]. However, glial inhibition of retinal tissue remodeling is incomplete [75]. Aberrant neurite sprouting and neuronal migration to ectopic sites along the surface of hypertrophied Müller cells were observed in age-related macular degeneration, retinal detachment and proliferative vitreoretinopathy [76–81]. The formation of glial scars may also be a reason for the failure of visual recovery after subretinal implantation of microphotodiode arrays [82]. Scar tissue may function as an electrical barrier between the implant and retinal neurons.

Epiretinal Membrane Formation

Epiretinal membranes are a distinct type of scars that are connected to the retinal tissue by hypertrophied Müller cell fibers [70, 76, 83]. These membranes were suggested to protect retinal tissue from the effects of pathogenic factors present in the vitreous [84]. After partial detachment of the vitreous from the retina, vitreous fibers adhering to Müller cells at sites of vitreoretinal attachment exert tractional forces onto the cells; this activates the cells and results in cellular hypertrophy and proliferation as well as vascular leakage [85]. Mechanical stress induces calcium responses (likely induced by stretch-activated calcium-permeable cation channels [86]), activation of ERK1/2, and upregulation of the transcription factor c-Fos and of bFGF in Müller cells [87]. Mechanically stressed Müller cells release growth factors (e.g. bFGF) and adenosine 5'-triphosphate (ATP) [87–89]. Calcium influx [through stretch-activated and voltage-gated calcium channels, and ionotropic purinergic (P2X₇) receptor channels] and subsequent activation of calcium-activated big-conductance potassium (BK) channels are required for growth factor- and ATP-induced proliferation of Müller cells [90–94].

Fig. 2. Putative involvement of Müller cell dysfunction in the degeneration of the inner retina after exposure to blue light. Excess illumination with blue light causes degeneration of the photoreceptors and the pigment epithelium, resulting in local inflammation which induces Müller cell gliosis. Gliosis is associated with redistribution of the Kir4.1 protein (red) from the prominent expression sites around the vessels (white arrow) and at the limiting membranes of the retina (white arrowheads). Redistribution and

functional inactivation of Kir4.1 disrupt the transglial potassium and water flux (middle), resulting in dysfunctional potassium and water homeostasis within the retinal tissue. This contributes to edema development and neuronal degeneration in the inner retina as indicated by the decrease in the thickness of the inner retina, especially of the inner plexiform layer (IPL; right). Cell nuclei are stained blue. GCL = Ganglion cell layer; INL = inner nuclear layer. Scale bar: 20 μm .

Malfunction of Glutamate Uptake

Glutamate toxicity is a major cause of neuronal loss in many retinal disorders, including glaucoma, ischemia, diabetes, and inherited photoreceptor degeneration [95–102]. Malfunction and/or downregulation of glial glutamate transporters contribute to the rise in extracellular glutamate towards excitotoxic levels [103–105]. Usually, Müller cells remove the bulk of extracellular glutamate from inner retinal tissue [106–112]. In the outer plexiform layer, Müller cells prevent the lateral spread of glutamate beyond the synapses, thus ensuring visual resolution [8].

GLAST is the major glutamate uptake carrier of Müller cells [108, 113–118]. As the amplitude of glutamate transport is voltage dependent (fig. 4a), a very negative membrane potential is essential for an efficient glutamate uptake [119–123].

In retinal ischemia and diabetes, the efficiency of glutamate transport into Müller cells is reduced [104, 124]. In experimental glaucoma, reduced GLAST activity coincides with excitotoxic damage to the retina [105]. The decreased glial glutamate uptake is mainly caused by cellular depolarization. Depolarization of Müller cells occurs as a result of pathological rises in extracellular potassium (as observed in ischemia and glaucoma), malfunction of the Na^+, K^+ -ATPase induced, for example, by inflammatory

lipids such as arachidonic acid and prostaglandins, opening of cation channels in the Müller cell membrane (fig. 4b), and a decrease in the potassium permeability of Müller cell membranes after inactivation and/or downregulation of Kir channels [1, 20, 23, 125–130]. Inactivation of Kir channels was observed in animal models of various retinopathies and in Müller cells from patients with proliferative retinopathies (fig. 1d, 3a, b, d, 5a) (see below).

Depolarization of Müller cells may even cause a reversal of glutamate transport [131–133]. Glutamate and aspartate released through glial glutamate transporters are implicated in excitotoxic damage to retinal ganglion cells [133, 134]. Release of glutamate from Müller cells might also be mediated by the cystine-glutamate antiporter (which is activated when increased production of the antioxidant glutathione requires increased uptake of cystine; see below) and by exocytosis of glutamate-containing secretory vesicles [135–138].

Hypoxia increases mitochondrial peroxide production; the resulting lipid peroxidation disrupts glutamate transport into Müller cells [139]. This mechanism is probably implicated in the neuronal dysfunction in diabetic retinopathy [124] and ganglion cell death in Leber hereditary optic neuropathy [140]. Inflammatory lipids, such as arachidonic acid, and a reduction in extracellular pH as it occurs in ischemia also directly inhibit glial glutamate uptake [132, 141].

Various diseases are associated with a breakdown of the blood-retinal barrier, resulting in extravasation of blood constituents (fig. 1c). Blood plasma and other blood constituents, like thrombin, inhibit the Kir channels and induce Müller cell depolarization [142, 143]. The reduced efficiency of glial glutamate transport may partly explain the clinical observation that the presence of hemorrhages at sites of vascular leakage is associated with a greater reduction in retinal function [144].

Malfuction of Glutathione Synthesis

The retina has a high need for antioxidant protection; this results from light exposure together with the high oxygen consumption of photoreceptors, the weak autoregulation of choroidal blood flow in response to the oxygen requirements of photoreceptors [145, 146], and the high levels of polyunsaturated fatty acids in photoreceptors. In addition, the outer retina underlies circadian periods of hypoxia (dark) and hyperoxia (light) [147, 148]; both increase the oxidative stress in the retinal tissue. Müller cells produce the antioxidant glutathione, a tripeptide synthesized from glutamate, cysteine and glycine [149–152]. In response to hypoxia, hypoglycemia and oxidative stress, glutathione is rapidly released from Müller cells and made available to the neurons [58, 151, 153]. The glial release of antioxidants like

glutathione and of neuroprotective factors like bFGF and adenosine participates in the protection of photoreceptors from the harmful effects of circadian light exposure [154–156].

Glutathione synthesis is dependent on the availability of extracellular glutamate and cystine [150, 157]. The decreased glutamate uptake by Müller cells in diabetic retinopathy reduces glutathione synthesis [150, 158] and results in upregulation of glutaredoxin which induces nuclear translocation of NF- κ B and expression of proinflammatory factors [159]. Müller cells from aged animals contain reduced levels of glutathione; this is associated with mitochondrial damage, membrane depolarization and reduced cell viability [160, 161]. The age-dependent decrease in retinal glutathione may accelerate the pathogenesis of retinopathies in the elderly. Externally administered radical scavengers like *Ginkgo biloba* extract enhance the intrinsic glutathione content of aged Müller cells and protect the mitochondria from the damaging action of free radicals [160, 161].

Extracellular Formation of Adenosine

Adenosine is a major neuroprotectant involved in the retinal response to ischemia-hypoxia and hypoxic states of photoreceptors in the dark [156, 162–166]. Adenosine has anti-inflammatory effects, induces retinal hyperemia

Fig. 3. In the course of retinal ischemia-reperfusion, rat Müller cells alter their membrane conductance, osmotic swelling properties and Kir channel expression. Transient retinal ischemia was induced by elevation of the intraocular pressure above the systolic blood pressure for 1 h. **a** Examples of the whole-cell potassium currents of Müller cells isolated from a control retina, and from retinas 3 and 7 days after transient retinal ischemia. **b** The amplitude of the Kir currents decreases time dependently after transient retinal ischemia. Simultaneously, the resting membrane potential (RMP) of the cells decreases and the whole-cell capacitance (that is proportional to the cell membrane area) increases, indicating cellular hypertrophy. The parameters were measured at different periods (3 h to 3 days) after transient ischemia. **c** Under hypoosmotic stress, Müller cells in slices of retinas 3 days after ischemia display cellular swelling, which is not observed in Müller cells in slices of control retinas. The time-dependent alteration in the cross-sectional area of Müller cell somata is shown. The images display Müller cell somata in a postischemic retina, before (above) and after (below) hypotonic challenge. Scale bar: 5 μ m. **d** Immunolocalization of glial Kir channel proteins in normal and postischemic rat retina. The Kir4.1 protein is predominantly localized at the limiting membranes of the retina (arrow-

heads) and around the blood vessels (arrows). Kir2.1 protein is localized in the inner retina in membrane domains of Müller cells that abut on neuron compartments, e.g. processes that cross the inner plexiform layer (IPL) (arrowheads). Seven days after transient retinal ischemia, Kir4.1 protein expression is largely down-regulated, whereas the localization of Kir2.1 protein is unaltered. Note the decrease in the thickness of the inner retina, which is a characteristic of retinal ischemia-reperfusion injury. Scale bars: 20 μ m. **e** Scheme of the potassium-buffering currents flowing through Müller cells during neuronal activation. Activated neurons release potassium which is absorbed by Müller cells through Kir2.1 and Kir5.1/4.1 channels, and distributed into the blood vessels, the vitreous and the subretinal space through Kir4.1 channels. Kir4.1 channels mediate in- and outward currents and thus contribute to the osmohomeostasis between the neuroretina and extraretinal fluid-filled spaces. The diagrams display the current-voltage (I-V) relations of Kir4.1 and Kir2.1 channels. Kir4.1 channels mediate inward and outward potassium currents with similar amplitudes, whereas Kir2.1 channels mediate inward currents and almost no outward currents. GCL = Ganglion cell layer; INL = inner nuclear layer; IPL = inner plexiform layer; ONL = outer nuclear layer.

after ischemia and protects neurons from glutamate toxicity by suppressing excitatory neurotransmission [162, 164, 166, 167]. Adenosine also inhibits osmotic swelling of Müller cells (see below); this prevents detrimental reductions in extracellular space volume which otherwise would result in neuronal hyperexcitation [168, 169].

Usually, Müller cells release adenosine through nucleoside transporters; this release is implicated in Müller cell volume regulation (fig. 6b) [35, 138, 170–174]. Adenosine cannot be extracellularly generated from ATP because the retinal parenchyma lacks the nucleoside triphosphate diphosphohydrolase (NTPDase) 1 (fig. 6a) [175–177]. NTPDase1 catalyzes the degradation of ATP and adenosine 5'-diphosphate (ADP) to adenosine 5'-monophosphate (AMP) [178]. AMP is the substrate of the ecto-5'-nucleotidase (fig. 6a) which catalyzes the hydrolyzation of AMP to adenosine. NTPDase1 is exclusively localized to the retinal vasculature, while the retinal parenchyma contains NTPDase2 (fig. 6a) [175–177]. NTPDase2 preferentially catalyzes the degradation of ATP to ADP [179].

In experimental diabetic retinopathy, Müller cells upregulate NTPDase1 expression (fig. 6a) [171]. This enables extracellular adenosine formation by the consecutive action of NTPDase1 and ecto-5'-nucleotidase (fig. 6b). NTPDase1 upregulation increases the availability of extracellular adenosine and results in a more effective clearance of ATP from the extracellular space. In experimental glaucoma, extracellular ATP (acting at P2X₇ receptors) mediates the apoptotic death of retinal ganglion cells [180, 181]. Retinal glial cells are a major source of extracellular ATP [88, 89]. As Müller cells release ATP in response to mechanical stimuli [88, 89], ATP is increasingly liberated from Müller cells in the presence of mechanical perturbations like retinal detachment and elevated intraocular pressure [181–183]. As adenosine inhibits the ATP-induced retinal ganglion cell apoptosis, the balance between extracellular ATP and adenosine levels determines the level of ganglion cell death [184]. The upregulation of NTPDase1 in the diseased retinal parenchyma (fig. 6a) [171] may decrease the extracellular ATP levels and, thus, prevent retinal ganglion cell death.

Dysfunctional Retinal Potassium Homeostasis

Light onset causes increases in extracellular potassium in the plexiform layers [185, 186]. If not corrected, increased potassium will cause neuronal hyperexcitation.

Müller cells buffer imbalances in the extracellular potassium concentration via permission of transcellular potassium currents [187–189]. They take up excess potassium from the extracellular space, and release equal amounts of potassium into fluid-filled spaces outside the neuroretina (blood vessels, vitreous and subretinal space; fig. 3e) [187–189].

Because Müller cell membranes are highly permeable to potassium [190, 191], Müller cells usually have a very negative resting membrane potential, around –80 mV [190, 192, 193]. Potassium permeability is mainly mediated by potassium channels belonging to the Kir subfamily [194]. In particular, Kir4.1 (which mediates bidirectional potassium currents; fig. 3e) and Kir2.1 channels (which mediate inward potassium currents) are implicated in potassium buffering [195, 196]. The channel proteins are localized in a polarized fashion in the Müller cell membrane. Homomeric Kir4.1 channels are mainly localized in membrane domains across which the cells extrude potassium into spaces outside the neuroretina (perivascular membranes and at both limiting membranes of the retina; fig. 2, 3d) [195, 197]. Membranes which abut neuronal cell structures contain Kir channels that mediate inward potassium currents, i.e. Kir2.1 (fig. 3d) and heterotetrameric Kir4.1/Kir5.1 channels [32, 196, 198].

Many of the homeostatic functions of Müller cells, including potassium buffering and neurotransmitter uptake, depend on the very negative membrane potential constituted by Kir4.1 channels [195]. Kir4.1 channels of Müller cells are dislocated and/or downregulated under various pathological conditions (fig. 2, 3d, 5); this results in a decrease in the potassium currents across Müller cell membranes (fig. 1d, 3a, b). Such alterations have been observed in animal models of various retinal diseases, including ischemia-reperfusion, inflammation, diabetic retinopathy, blue-light injury, detachment, vein occlusion and proliferative vitreoretinopathy, as well as in Müller cells from patients with proliferative retinopathies (fig. 5a) [17–20, 23–38, 199]. Ischemia causes a decrease in Kir4.1 (but not Kir2.1) expression (fig. 3d) [32]. Inactivation of Kir4.1 impairs potassium transport through Müller cells and causes cell depolarization which impairs the glutamate uptake (see above). Human Müller cells display an age-dependent decrease in Kir currents (fig. 5b) [200]. This decrease enhances susceptibility to age-dependent retinopathies when additional pathological complications like diabetic alterations of the blood vessels are present.

Fig. 4. The glutamate transport into Müller cells is voltage dependent. **a** Administration of glutamate (1 mM) to a rabbit Müller cell generates an inward current at negative membrane potentials (left). The current-voltage relation of the glutamate transporter currents in guinea pig Müller cells (right) shows that the efficiency of glutamate transport increases with increasing (i.e. more negative) membrane potentials. **b** Activation of the cation conductance of purinergic P2X₇ receptors in human Müller cells by 2'-/3'-O-(4-benzoylbenzoyl)-ATP (BzATP) impairs glutamate uptake by Müller cells. The uptake currents evoked by glutamate (Glu; 100 μ M; arrows) are abrogated in the presence of BzATP (10 μ M). Inhibition of P2X₇ receptor activation by KN-62 (1 μ M) suppressed the BzATP-evoked current, resulting in glutamate uptake currents similar in amplitude to those under control conditions.

Fig. 5. Age- and disease-related alterations in the membrane conductance of human Müller cells. **a** Four different types of potassium currents can be recorded in Müller cells from postmortem donors without apparent eye diseases (left): BK, currents mediated by BK channels; fast transient (A-type) potassium currents (K_A); delayed rectifying potassium currents (K_{DR}) and Kir currents. Müller cells obtained from patients with proliferative vitreoretinopathy (PVR) display an almost complete absence of Kir currents. The inward potassium currents (evoked by membrane

hyperpolarization from a holding potential of -80 mV) are depicted downwardly. The outward potassium currents (evoked by membrane depolarization) are depicted upwardly. The white arrow indicates transient inward currents through voltage-gated sodium channels. **b** Age-dependent alterations in the densities of Kir and L-type voltage-gated calcium channel (VGCC) currents in human Müller cells. While Kir currents display an age-dependent decrease, currents through L-type calcium channels increase in the course of aging.

Fig. 6. The source of extracellular adenosine alters in experimental diabetic retinopathy. **a** Immunolocalization of nucleotide-degrading ectoenzymes in retinal slices from control (above) and diabetic rats (below). The slices were stained against NTPDase1, NTPDase2 and ecto-5'-nucleotidase, respectively (red). The slices were counterstained against the glial proteins vimentin and cellular retinaldehyde-binding protein (CRALBP), respectively (green). Arrows: Müller cell fibers crossing the inner plexiform layer (IPL). Arrowheads: blood vessels. Note that the immunolabeling of NTPDase1 is restricted to the blood vessels in the control retina, while in the retina of the diabetic animal, NTPDase1 immunoreactivity is also localized to Müller cell fibers. GCL = Ganglion cell layer; INL = inner nuclear layer; ONL = outer nuclear layer; PRS = photoreceptor segments. Scale bars: 20 μm. **b** Scheme of the autocrine glutamatergic-purinergic signaling cascade involved in the VEGF-induced inhibition of Müller cell swelling.

Activation of KDR/flk-1 by VEGF evokes exocytotic release of glutamate from Müller cells. Glutamate activates metabotropic glutamate receptors (mGluRs), which results in ATP release from Müller cells. ATP is extracellularly converted to ADP by NTPDase2 that activates P2Y₁, resulting in nucleoside transporter-mediated release of adenosine. Activation of A₁ adenosine receptors opens potassium and chloride channels. Neuron-derived glutamate may activate the volume-regulatory signaling cascade in dependence on neuronal activity. Müller cell-derived glutamate and adenosine may also activate neuronal α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate (AMPA/KA) and A₁ receptors, resulting in stimulation and inhibition, respectively, of neuronal activity. In the retinal parenchyma of diabetic rats, NTPDase1 (which hydrolyses ATP and ADP about equally well) is upregulated, and extracellular formation of adenosine contributes to the inhibitory effect of glutamate and ATP on swelling.

Contribution to Vascular Edema

Vascular leakage caused by opening of the tight junctions between vascular endothelial cells and increased vesicular transport of serum proteins across the vascular endothelia is an important pathogenic mechanism of retinal edema [201]. Retinal capillaries are closely ensheathed by glial processes [7]. Usually, Müller cells enhance the barrier function of vascular endothelia [202–204] by the secretion of factors such as pigment epithelium-derived factor (PEDF), thrombospondin-1, neurturin, and GDNF [205–208]. PEDF expression in Müller cells is regulated by soluble factors released from vascular endothelial cells [209].

Vascular endothelial growth factor (VEGF) is the major hypoxia-induced vessel-permeabilizing factor [210–213]. In addition, inflammatory factors such as tumor necrosis factor, interleukin-1β, and prostaglandins enhance the permeability of retinal vessels [212, 214, 215]. In response to hypoxia, inflammation and glucose deprivation, Müller cells produce vessel-permeabilizing factors such as VEGF and tumor necrosis factor [204, 206, 216–221]. Posterior vitreous detachment from the retina is associated with mechanical stress on Müller cells, which results in the release of vessel-permeabilizing factors including bFGF [85, 87]. Müller cells are also a source of matrix metalloproteinases [94, 221, 222], which (among others) degrade occludin, a tight-junction protein [223]. High glucose stimulates the production of proteinases [223].

Dysfunctional Fluid Clearance and Cytotoxic Edema

Edema is caused by an imbalance between fluid influx from the blood into retinal tissue and fluid clearance from the tissue [39, 224]. Edema develops by vascular leakage and/or neuronal and glial cell swellings (cytotoxic edema) [39, 224]. Fluid clearance is usually mediated by osmotic water transport through glial and pigment epithelial cells which is coupled to the transport of osmolytes, in particular potassium and chloride ions [39, 197, 225, 226]. The coupled potassium and water transport through Müller cells is facilitated by Kir channels and water channels, in particular aquaporin-4 (fig. 1b) [34, 197, 227–229].

Because water transport through Müller cells is coupled to potassium currents [197], dysfunction of Kir4.1 channels as observed under pathological conditions (fig. 1d, 2, 3a, b, d, 5) should also disturb transcellular water transport [39, 224]. Indeed, Müller cell bodies in slices of diseased retinas swell upon hypoosmotic challenge which is not observed in control retinal tissues (fig. 1e, 3c) [27, 29, 30, 34–36, 38, 138, 170, 171, 174, 177, 230–237]. Because Müller cells lack functional Kir4.1 channels, they are not capable of rapidly releasing potassium which otherwise would compensate the osmotic gradient between the Müller cell interior and the hypoosmotic environment [27, 39, 224]. This results in water influx and cellular swelling. However, Müller cells are still capable to take up potassium through Kir2.1 channels, which are not altered in their expression after ischemia (fig. 3d) [32]. This may result in a potassium accumulation within the cells and, thus, in increased intracellular osmotic pressure [27, 39] which (in situ) draws water from fluid-filled spaces outside the neuroretina (blood, vitreous) into the perivascular and endfoot regions of Müller cells, resulting in Müller cell swelling. Thus, dysfunctional water clearance and possibly Müller cell swelling contribute to the development of edema. The age-dependent decrease in potassium conductance of human Müller cells (fig. 5b) [200] may contribute to the higher incidence of retinal edema in the elderly. Triamcinolone acetonide inhibits Müller cell swelling by inducing endogenous adenosine signaling and opening of ion channels in the Müller cell membrane [230]; the latter might re-establish the fluid clearance function of Müller cells when the Kir4.1 channels are dysfunctional [224].

Müller cells might also contribute to the resolution of edema as observed in experimental retinal light injury [34, 238]. Excessive light causes damage to the retinal pigment epithelium and induces apoptotic death of photore-

ceptor cells (fig. 1a) [34, 238–241]. Both result in the development of local edema in the outer retina. Apoptotic cells undergo shrinkage, which is mediated by channel- and transporter-mediated efflux of ions (potassium and chloride) and water [242–245]. Usually, the expression of aquaporin-4 in the outer nuclear layer is faint and strongly increases after light injury (fig. 1b) [34, 238]. The up-regulation of aquaporin-4 may support the resolution of edema in the outer retina. However, downregulation of Kir4.1 (fig. 1d, 2) and dysregulation of transcellular water transport (fig. 1e) may contribute to secondary inner retinal tissue degeneration, which is often observed after light injury (fig. 2) [34, 246, 247].

Dysfunctional Purinergic Regulation of Müller Cell Volume

Müller cells possess an endogenous purinergic signaling cascade that inhibits osmotic swelling [138, 170–174, 230]. This signaling cascade involves the release of ATP and adenosine, and the consecutive activation of purinergic P2Y₁ and A₁ adenosine receptors (fig. 6b) [138, 170, 171]. Activation of A₁ receptors induces the opening of chloride and potassium channels; ion efflux equalizes the osmotic gradient across the plasma membrane and thus prevents cellular swelling.

The release of ATP from Müller cells can be induced either by glutamate (acting at metabotropic glutamate receptors; fig. 6b) or by osmotic stress, which mechanically perturbs the plasma membrane [172–174]. While Müller cells from control retinas do not swell under hypoosmotic conditions, Müller cells in slices of diseased retinas rapidly swell (fig. 1e, 3c). This suggests that the osmotic/mechanical release of ATP is abrogated under pathological conditions. Abrogation of the osmotic ATP release prevents an excess release of ATP from Müller cells which has neuroprotective effects under conditions associated with mechanical stress like retinal detachment and glaucoma (see above). Abrogation of the osmotic/mechanical ATP release also has glioprotective effects. Because P2Y₁ receptors are the major purinergic receptor subtype that induces calcium responses in Müller cells [248–250], abrogation of the ATP release might protect the cells from cytotoxic calcium overload. The probability that Müller cells become dysfunctional and reactive is increased in the course of aging because an increase in the density of voltage-gated calcium channels (fig. 5b) [251] facilitates calcium-dependent mechanisms of gliosis in the elderly.

Systemic Factors That Induce Müller Cell Swelling

Vascular edema is often accompanied by retinal cell swelling, in particular, Müller cells [252–254]. Increased vascular permeability is associated with the extravasation of albumin; in the presence of a hyposmotic environment, albumin induces Müller cell swelling [255]. Thus, extravasated albumin may represent one factor linking vascular leakage, Müller cell swelling and dysregulation of retinal fluid clearance. Other blood-derived factors, like thrombin and glutamate, may be involved (see above). Müller cell swelling might also be induced by systemic osmotic imbalance, e.g. by a decrease in blood osmolarity [256] due to hyponatremia or hypoalbuminemia in cases of renal and hepatic failure. In hepatic retinopathy, which is caused by liver failure resulting in increased levels of blood ammonia [257], the pathological alterations in the retina are primarily found in glial cells (mitochondrial and cellular swelling, vacuolization and necrosis) [258–260]. The swelling-inducing effect of ammonia is accelerated by hyposmolarity [237], suggesting that hyponatremia (predictive of mortality in end-stage liver disease [261, 262]) acts synergistically with hyperammonemia in inducing cytotoxic swelling of glial cells.

Müller Stem Cells

Müller cells of the mature retina were suggested to represent latent neural stem cells [263–267]. After retinal injury, a population of Müller cells dedifferentiates to cells with properties similar to pluripotent retinal progenitor/

stem cells and express neuronal and photoreceptor proteins [268–273]. However, the neuron-regenerating potential of Müller cells in situ is very restricted. Attempts to facilitate the neurogenic program of Müller cells, e.g. by transdifferentiation of cultured Müller cells, are ongoing [265, 270, 273–280].

Due to their potential for generating neural progenitor/stem cells, Müller cells will have a great impact on future cell-based therapeutic approaches. However, the molecular signals that trigger the neurogenic process remain to be explored to guide the direction of differentiation and to increase the number of newly generated neurons. Surgically removed epiretinal membranes represent one putative source of Müller stem cells [281]; the use of such cells will avoid immunological complications after cell transplantation. The slow progress of this approach underlines that a better understanding of the gliotic mechanisms is essential for the development of efficient therapeutic strategies aimed at increasing the protective and regenerative properties of reactive Müller cells and decreasing their toxicity.

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Disclosure Statement

Both authors have no conflicts of interest to declare.

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