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Müller cells in the healthy and diseased retina

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Abstract

Müller glial cells span the entire thickness of the tissue, and ensheath all retinal neurons, in vertebrate retinae of all species. This morphological relationship is reflected by a multitude of functional interactions between neurons and Müller cells, including a 'metabolic symbiosis' and the processing of visual information. Müller cells are also responsible for the maintenance of the homeostasis of the retinal extracellular milieu (ions, water, neurotransmitter molecules, and pH). In vascularized retinae, Müller cells may also be involved in the control of angiogenesis, and the regulation of retinal blood flow. Virtually every disease of the retina is associated with a reactive Müller cell gliosis which, on the one hand, supports the survival of retinal neurons but, on the other hand, may accelerate the progress of neuronal degeneration: Müller cells protect neurons via a release of neurotrophic factors, the uptake and degradation of the excitotoxin, glutamate, and the secretion of the antioxidant, glutathione. However, gliotic Müller cells display a dysregulation of various neuron-supportive functions. This contributes to a disturbance of retinal glutamate metabolism and ion homeostasis, and causes the development of retinal edema and neuronal cell death. Moreover, there are diseases evoking a primary Müller cell insufficiency, such as hepatic retinopathy and certain forms of glaucoma. Any impairment of supportive functions of Müller cells, primary or secondary, must cause and/or aggravate a dysfunction and loss of neurons, by increasing the susceptibility of neurons to stressful stimuli in the diseased retina. On the contrary, Müller cells may be used in the future for novel therapeutic strategies to protect neurons against apoptosis (somatic gene therapy), or to differentiate retinal neurons from Müller/stem cells. Meanwhile, a proper understanding of the gliotic responses of Müller cells in the diseased retina, and of their protective vs. detrimental effects, is essential for the development of efficient therapeutic strategies that use and stimulate the neuron-supportive/protective—and prevent the destructive—mechanisms of gliosis.

Contents

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1. Introduction

Generally, the mammalian retina contains three types of glial cells. In addition to microglial cells, there are two forms of neuron-supporting macroglial cells, astrocytes and Müller (radial glial) cells. As an exception, oligodendrocytes can be found in the myelinated nerve fiber bundles ('medullary rays') of rabbits and hares, as a fourth type of glia. Microglial cells are the blood-derived resident immune cells within the retina that have an important role in host defense against invading microorganisms, initiation of inflammatory processes, and tissue repair. They are normally located in the innermost retinal layers (nerve fiber, ganglion cell, and inner plexiform layers). In species with completely or locally vascularized retinae, astrocytes are also located in these innermost retinal layers (in avascular retinae/retinal areas, they are absent). Retinal astrocytes are in contact with the superficial vascular plexus via processes which wrap around the vessels, and with the vitreo–retinal border (inner limiting membrane = ILM) to which they also extend processes. These latter processes form endfeet at the ILM, intermingled with the many endfeet of the Müller cells.

1.1. Basic properties of Müller cells

The Müller cell is the principal glial cell of the vetebrate retina; in the avascular retinae of many vertebrates (including mammals) it constitutes the only type of macroglial cells. Müller cells are specialized radial glial cells which span the entire thickness of the retina (Fig. 1A, B) and contact/ensheath all retinal neuronal somata and processes (Fig. 1D). The Müller cell population forms a dense, regular pattern (Fig. 1C, bottom); each of these cells can be considered as the core of a columnar 'micro-unit' of retinal neurons (Fig. 1D; Reichenbach and Robinson, 1995a, b). Thus, Müller cells constitute an anatomical link between the retinal neurons and the compartments with

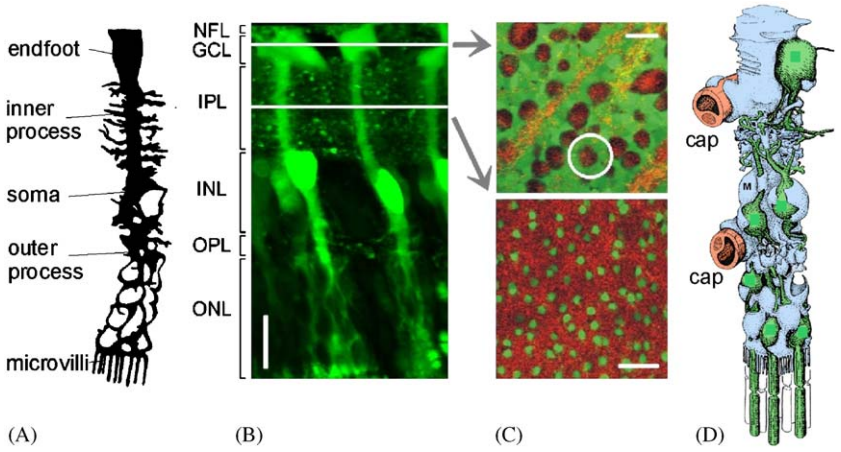

Fig. 1. Morphology of Müller glial cells. (A) Drawing of a Golgi-labeled rabbit Müller cell. (B, C) Living Müller cells in a slice (B) and flat-mount (C), respectively, of a guinea-pig retina selectively stained with Mitotracker Orange (green). (A, B) Müller cells pass through the entire retinal tissue, with somata in the INL from which two main trunks pass toward both surfaces of the retina. In the NFL/GCL, the trunks are enlarged to endfeet that abut the vitreous body. The trunks in the ONL show honeycomb-like shapes that ensheath photoreceptor cell bodies. In both plexiform layers, many side processes cover the synapses. (C) The view onto the flat-mount with the focal plane at the GCL displays neuronal cell bodies that reflect red light (circle), green-stained sections through Müller cell endfeet, and yellow-appearing nerve fiber bundles (top); the view onto the IPL shows green-stained Müller cell profiles and synaptic structures that reflect red light (bottom). (D) Artist's view of a human Müller cell (blue), enveloping various types of retinal neurons (green) and establishing contacts to retinal blood vessels (red). Scale bars, 20 μm. Cap, capillaries; GCL, ganglion cell layer; INL, inner nuclear layer; IPL, inner plexiform layer; NFL, nerve fiber layer; ONL, outer nuclear layer; OPL, outer plexiform layer. Modified after Uckermann et al., 2004 (B, C) and Reichenbach et al., 1993 (D).

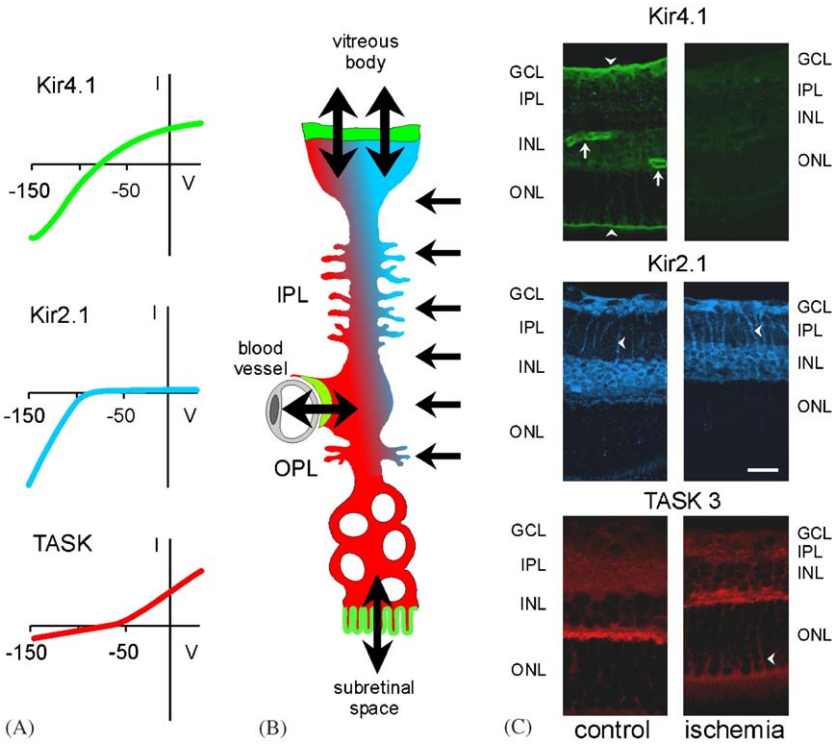

Fig. 2. Müller cells of the rat retina express different subtypes of inwardly rectifying K^+ (Kir) channels in different membrane domains. (A) Current–voltage (*I–V*) curves of three different K^+ channels. The weakly rectifying Kir4.1 channel mediates outward (upwardly) and inward currents (downwardly) of similar amplitudes. The strongly rectifying Kir2.1 channels mediates inward currents but almost no outward currents. The tandem-pore channel TASK3 mediates rather weak inward currents but large outward currents at membrane potentials close to the resting conditions. (B) The Kir4.1 channel is expressed in membranes that have contact to the vitreous body, to the vessels, and the subretinal space. This channel mediates bidirectional K^+ currents between Müller cells and extraretinal fluid-filled spaces. The Kir2.1 channel is expressed in membranes that have contact to neurons and synapses (with exception of the photoreceptor cell bodies). Thus, the transglial K^+ currents are directed from the neuropil through the cells, and into the extraretinal spaces. The TASK channel is expressed along most of the Müller cell membrane; it may contribute to the maintenance of an 'auxiliary' resting membrane potential, and may even play a minor role in K^+ buffering. (C) Immunoreactivities for Kir4.1 (top), Kir2.1 (middle), and TASK3 (bottom) in slices of the rat retina. In control tissues, the Kir4.1 is predominantly expressed at both limiting membranes (arrowheads) and around the vessels (arrows), while the Kir2.1 protein is expressed by Müller cell membranes from the outer plexiform layer up to the ganglion cell layer (the arrowhead marks a Müller cell fiber passing through the IPL). At seven days of reperfusion after transient pressure-induced retinal ischemia for 60 minutes, the expression of the Kir4.1 protein is strongly downregulated, while the expression pattern of Kir2.1 protein is unchanged (and the expression of TASK channels may even be upregulated, arrowhead). This altered K^+ channel expression may cause an accumulation of K^+ ions within the Müller cells that results in an increased osmotic pressure of the cell interior (Pannicke et al., 2004). Note the decreased thickness of the inner ischemic retina compared to the control retina. Scale bar, 20 μm. GCL, ganglion cell layer; INL, inner nuclear layer; IPL, inner plexiform layer; ONL, outer nuclear layer. Modified after Kofuji et al. (2002), Skatchkov et al. (2006), and Iandiev et al. (2006b).

which these need to exchange molecules, i. e., the retinal blood vessels, the vitreous body, and the subretinal space (which, together with the retinal pigment epithelium = RPE, constitutes the pathway to the choroidal blood vessels).

This link is not merely anatomical but also functional. For this purpose, Müller cells are endowed with a wealth of different ion channels, ligand receptors, transmembraneous transporter molecules, and enzymes (Newman and Reichenbach, 1996; Sarthy and Ripps, 2001). Many of these molecules are specifically expressed by Müller cells (i.e., they are not found in retinal neurons or other retinal cell types) or, at least, are most abundant in Müller cells (→2.2.–2.6.). A key feature of normal mature Müller cells is the high K^+ conductance of their plasma membrane. It is provided by a high density of specialized K^+ channels (Fig. 2); several types of these channels have been characterized in mammalian Müller cells. They comprise

- inwardly rectifying channels of the Kir family, mainly Kir4.1 (weakly rectifying at resting membrane potential; mainly located at the vitread endfoot and perivascular membrane areas, and in the microvilli) and Kir2.1 (strongly rectifying, rather evenly distributed in the membrane between endfoot and soma) (Kofuji et al., 2002);
- tandem-pore (TASK) channels which allow for outward currents at depolarized membrane potentials and show a subcellular distribution similar to that of the Kir2.1 channels, plus a prominent expression in the microvilli (Skatchkov et al., 2006), and
- Ca^{2+}-dependent K^+ channels of big conductance (BK channels), requiring intracellular Ca^{2+} rises and/or

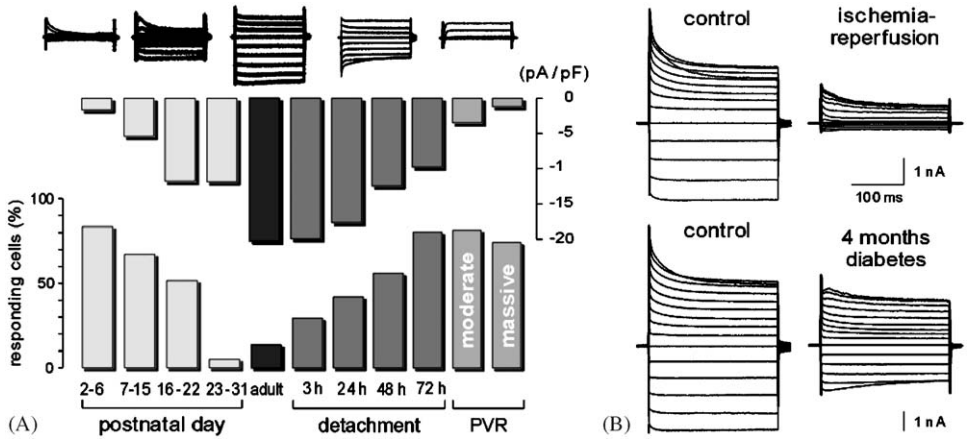

Fig. 3. The expression levels of K^+ inward currents and ATP responsiveness of Müller cells are inversely correlated during development and retinal disease. (A) Above: the amplitude of the inward K^+ currents in Müller cells of the rabbit is dependent on the differentiation degree of rabbit Müller cells. The amplitude increases during the postnatal development, indicating that the K^+ channel expression is one marker for the differentiation degree of Müller cells. After experimental retinal detachment or during moderate and massive proliferative vitreoretinopathy (PVR), the amplitude of the inward K^+ currents is significantly reduced. Below: the percentage of Müller cells that show Ca^{2+} responses upon application of ATP decreases during the postnatal development, and increases after retinal detachment and during PVR. (B) Representative traces of the K^+ currents of rat Müller cells. The cells were derived from control retinas (left) and from retinas at three days of reperfusion after transient pressure-induced retinal ischemia for 60 minutes (right above), and of a retina derived from a diabetic animal at four months after intravenous injection of streptozotocin (right below), respectively. After ischemia and during diabetes, Müller cells downregulate the expression of K^+ channels. The K^+ currents were evoked by depolarizing (upwardly) and hyperpolarizing voltage steps (downwardly) from a holding potential of −80 mV.

membrane depolarizations to enter the open state (Bringmann et al., 1997).

A block or down-regulation of the K^+ channels depolarizes the cell membrane (Newman, 1989; Pannicke et al., 2000b). The high K^+ conductance of the Müller cell membrane, accompanied by a very negative resting membrane potential of about -80 mV, is characteristic for normal mature Müller cells (Fig. 3; →2.1.), and is the essential precondition for virtually all neuron-supportive functions of the cells (→2.3.–2.6.).

As the Müller cells are the dominant (or even the only) type of macroglial cells in the retina, they play a wealth of crucial roles in supporting the neurons and their functions that are carried out by the concerted action of astrocytes, oligodendrocytes, and ependymal cells in other regions of the central nervous system (Fig. 5, Table 1). From early stages of retinal development, they are essential in creating and maintaining the neuroretinal architecture (Willbold et al., 1997), and support neuronal survival and regular information processing (Reichenbach et al., 1993; Newman and Reichenbach, 1996). The importance of Müller cells for the maintenance of retinal structure and function is elucidated by the observation that selective Müller cell destruction causes retinal dysplasia, photoreceptor apoptosis and, at a final state, retinal degeneration and proliferation of the RPE (Dubois-Dauphin et al., 2000). Specifically, in the healthy retina Müller cells

- are involved in retinal glucose metabolism, providing retinal neurons with nutrients such as lactate/pyruvate for their oxidative metabolism (Poitry-Yamate et al., 1995; Tsacopoulos and Magistretti, 1996) and removing metabolic waste products;
- regulate the retinal blood flow (Paulson and Newman, 1987) and contribute to the formation and maintenance of the blood-retinal barrier (Tout et al., 1993) (→2.2.);
- contribute to the neuronal signaling processes, particularly by rapid uptake and recycling of neurotransmitters (Matsui et al., 1999) and by providing precursors of neurotransmitters to neurons (→2.3.);
- maintain the ion and water homeostasis of the retinal tissue including the pH (Newman, 1996; Newman and Reichenbach, 1996; Bringmann et al., 2004) (→2.4., 2.5.); and
- release factors (e.g., D-serine and glutamate) which control the excitability of neurons (Newman and Zahs, 1998; Stevens et al., 2003), and are likely to be involved in the recycling of photopigments, as they express cellular retinaldehyde-binding protein (CRALBP) (Bunt-Milam and Saari, 1983), bind all-*trans*-retinal, convert it into 11-*cis*-retinol, and release it into the extracellular space for uptake by cone photoreceptors (Das et al., 1992) (→2.6.).

It has been known for many years that retinal neurons (particularly, photoreceptor cells) are highly susceptible to various forms of injury including insufficient blood supply. By contrast, Müller glial cells are strikingly resistant to ischemia, anoxia, or hypoglycemia (Silver et al., 1997; Stone et al., 1999); this can be attributed to their peculiar energy metabolism (→2.2.). Thus, Müller cells survive most retinal injuries, and remain available as players in the pathogenic events.

For instance, under pathological conditions Müller cells may act as modulators of immune and inflammatory responses, by producing proinflammatory cytokines in response to infection, for example (Caspi and Roberge, 1989; Roberge et al., 1991; Drescher and Whittum-Hudson, 1996). Furthermore, Müller cells are capable of phagocytosing fragments of retinal cells and foreign substances (Mano and Puro, 1990; Stolzenburg et al., 1992; Francke et al., 2001a) (Fig. 7D–F). Most noteworthy, Müller cells become 'activated' or 'reactive' in response to virtually every pathological alteration of the retina. This reaction is called Müller cell gliosis; it is one component of a complex retinal response to pathogenic stimuli which also includes microglial activation, alterations of the vasculature, and immigration of blood-derived leukocytes into the retinal tissue. Very probably, the initiation of (at least, certain steps or forms of) Müller cell gliosis requires an interaction between microglia and Müller cells, such as shown in the case of retinal light damage (Harada et al., 2002). In particular, micoglial cells modulate the production of a variety of trophic factors by Müller cells, including some that promote survival and some that promote death of photoreceptor cells (Harada et al., 2002).

1.2. Müller cell gliosis

Müller cell gliosis is characterized by both non-specific responses, i. e., stereotypic alterations independent of the causal stimulus, and specific responses which depend on the given pathogenic factor or mechanism. The most sensitive non-specific response to retinal diseases and injuries, which can be used as a universal early cellular marker for retinal injury, is the upregulation of the intermediate filament protein, glial fibrillary acidic protein (GFAP) (Bignami and Dahl, 1979; Eisenfeld et al., 1984; Bringmann and Reichenbach, 2001). Another non-specific Müller cell response is an activation of the extracellular signal-regulated kinases (ERKs) which was observed early during experimental retinal detachment, retinal ischemia-reperfusion, and endotoxin-induced uveitis, respectively (Geller et al., 2001; Akiyama et al., 2002; Takeda et al., 2002), as well as in the glaucomatous eye (Tezel et al., 2003) (Table 2).

A prominent example of the specific gliotic responses of Müller cells is an altered expression of glutamine synthetase (GS), a Müller cell-specific enzyme normally involved in neurotransmitter recycling (→2.3.) and ammonia detoxification (→2.2.). After a loss of major

Table 1
Selective functions of Müller cells

Physiological process	Müller cell function	Glia-specific protein/peptide	Reference
Metabolic support and nutrition of neurons	• Delivery of lactate/pyruvate • Storing of glycogen and glycogenolysis	(Lactate dehydrogenase) Glycogen phosphorylase	Poitry-Yamate et al. (1995) Kuwabara and Cogan (1961) Pfeiffer-Guglielmi et al. (2005)
K^+ and water homeostasis	• CO_2-buffering • Removal of external K^+ ions (spatial buffering) • Dehydration of inner retina	Carboanhydrase Kir4.1 channel AQP4 water channel	Newman (1994) Newman et al. (1984), Kofuji et al. (2002) Nagelhus et al. (1998)
Protection against oxidative stress	• Scavenging free radicals	Glutathion	Schütte and Werner (1998), Pow and Crook (1995), Reichelt et al. (1997b)
Contribution to neuronal signalling	• Transmitter uptake • Transmitter recycling	Glutamate transporter GABA transporter Glutamine synthetase	Brew and Attwell (1987), Rauen et al. (1998) Qian et al. (1993), Biedermann et al. (2002) Linser and Moscona (1979), Pow and Robinson (1994)
Recycling of photopigments	• Transport and conversion of bleached photopigments	CRALBP	Das et al. (1992)
Release of neuroactive substances	Storage and release of • D-serine • Glutamate • ATP		 Stevens et al. (2003) Newman and Zahs (1998) Newman (2003)
Release of vasoactive substances	Synthesis and release of • VEGF • PEDF • TGF-β		 Eichler et al. (2000) Eichler et al. (2004a) Ikeda et al. (1998)
Retinal development	• Scaffold for orientation (immature radial glia cells)		Willbold et al. (1997)

Table 2
Characteristics of reactive Müller cells in various diseases

	Retinal detachment	Proliferative retinopathies	Diabetic retinopathy	Ischemia-reperfusion	Inflammation	Glaucoma
Expression of:						
• GFAP	↑	↑	↑	↑	↑	↑
• Glutamine synthetase	↓					
• Transcription factors	↑					
• ERK phosphorylation	X			X	X	X
K^+ conductance	↓	↓	↓	↓	↓	↓
Membrane potential	↓	↓	—	↓	↓	↓
P2Y-mediated Ca^{2+} responses	↑	↑				
Mislocation of Kir4.1 channels			X	X	X	
Release of angiogenic factors			X	X		
Apoptosis			X			
References	Erickson et al. (1987), Francke et al. (2001b), Geller et al. (2001), Lewis et al. (1999), Uhlmann et al. (2003)	Francke et al. (1997), Francke et al. (2002)	Amin et al. (1997), Hammes et al. (1995), Hirata et al. (1997), Pannicke et al. (2006), Rungger-Brändle et al. (2000)	Akiyama et al. (2002), Eichler et al. (2004b), Pannicke et al. (2004)	Pannicke et al. (2005)	Francke et al. (1997), Tezel et al. (2003)

glutamate-releasing neurons such as occurs after photoreceptor degeneration evoked by light or retinal detachment (Grosche et al., 1995; Lewis et al., 1989), the expression of GS in Müller cells is reduced whereas an enhanced expression is observed during hepatic retinopathy when GS activity is necessary to detoxify the tissue from elevated levels of ammonia (Reichenbach et al., 1995b). On the other hand, no alteration of the GS expression by Müller cells is observed in diabetic retinopathy and after optic nerve crush (Mizutani et al., 1998; Chen and Weber, 2002). However, after optic nerve crush a translocation of the GS protein within the Müller cells is observed towards their endfeet in the ganglion cell layer, where injury of ganglion cells might result in the release of excess glutamate (Chen and Weber, 2002).

To understand the clinical consequences of Müller cell gliosis it is essential to note that it may include a de-differentiation of the cells. As a most important step of this de-differentiation, the cells reduce the K^+-conductance of their membrane (particularly, the Kir4.1-mediated currents; this is generally associated with a mislocation of the Kir4.1 channels in the Müller cell membrane) (Figs. 2C, 3; Bringmann et al., 2000). This will cause a severe loss of the functions involved in normal neuron-glia interaction, most of which require a hyperpolarized membrane potential. A similar mislocation of the Kir4.1 protein has been described in retinas of mice carrying a genetic inactivation of the dystrophin gene product, Dp71, which is proposed to be involved in the clustering of Kir4.1 channels in the plasma membrane (Connors and Kofuji, 2002). This mislocation of Kir4.1 protein was associated with an enhanced vulnerability of retinal ganglion cells to ischemic stress (Dalloz et al., 2003). Thus, as in the brain, gliosis in the retina is Janus-faced, contributing to both damage and protection of neurons (Bringmann and Reichenbach, 2001).

Early after injury, gliosis is neuroprotective, and is thought to represent a cellular attempt to protect the tissue from further damage, e.g., by release of neurotrophic factors and antioxidants (Schütte and Werner, 1998; Frasson et al., 1999; Honjo et al., 2000; Oku et al., 2002). Some of the factors released by activated Müller cells such as the vascular endothelial growth factor (VEGF), however, may have both neuroprotective (Yasuhara et al., 2004) and detrimental effects, as VEGF may exacerbate disease progression by inducing vascular leakage and neovascularization (→3.2., 3.4., 3.5.). Likewise, in response to ischemia and early in diabetic retinopathy Müller cells increase the expression of the inducible form of nitric oxide synthase (Goureau et al., 1994; Abu-El-Asrar et al., 2001). Enzymatically formed nitric oxide exerts beneficial effects by counteracting ischemia through dilating retinal vessels, and low nitric oxide protects neurons from glutamate toxicity via closing of

N-methyl-*D*-aspartate (NMDA) receptor channels (Kashii et al., 1996). However, higher concentrations of nitric oxide and subsequent formation of free nitrogen radicals are cytotoxic for neurons, and are involved in the development of diabetic retinopathy, for example (Roth, 1997; Goureau et al., 1999; Koeberle and Ball, 1999) (→3.2.).

At later stages and/or in more severe cases of gliosis the de-differentiation of the cells contributes to neuronal cell death, e.g., via impairment of neurotransmitter removal (i.e., excitotoxicity) and dysregulation of the ion and water homeostasis after down-regulation of K^+ channels (e.g., formation of edema) (→3.1., 3.5.). Generally, an impairment of supportive functions of Müller cells may have an additive effect on dysfunction and loss of neurons, by increasing the susceptibility of neurons to stressful stimuli in the diseased retina.

Finally, Müller cells may re-enter the proliferation cycle (→3.4., 3.5.) to establish a glial scar (Burke and Smith, 1981). Glial scars are one reason for the failure of the central nervous system to regenerate. During retinal detachment, for example, Müller cell processes grow through the outer limiting membrane and fill the spaces left by dying photoreceptors (Lewis and Fisher, 2000). Within the subretinal space, the Müller cell processes then form a fibrotic layer that completely inhibits the regeneration of outer photoreceptor segments (Anderson et al., 1986). Glial scars involve the expression of inhibitory molecules on the surface of reactive glial cells which additionally inhibit regular tissue repair and neuroregeneration (Fawcett and Asher, 1999).

In summary, a proper understanding of the gliotic responses of Müller cells in the diseased retina, and of their protective and detrimental effects, is essential for the development of efficient therapeutic strategies that increase the supportive/protective and/or decrease the destructive roles of gliosis. Therefore, this article summarizes the present knowledge about some of the key functions of Müller cells in the healthy retina, and of the involvement of Müller cells in various retinopathies.

2. Müller cells in the healthy retina

2.1. Retinal development

From early embryonic stages, the immature Müller cells are important for the histotypic organization of the developing retina, and for the proper wiring of its neuronal circuits. They provide an orientation scaffold and migration substrate for postmitotic young neurons (Willbold et al., 1997) as well as for their growing neurites (Stier and Schlosshauer, 1998). It is noteworthy that after de-differentiation, reactive Müller cells appear to recover this capability; in degenerated retinas of aged rats, or in retinas from human subjects with age-dependent macular degeneration, retinal neurons migrate out of the retina into the choroid along remodeled processes of Müller cells that extend through gaps in Bruch's membrane (Sullivan et al., 2003).

Another property of (immature) Müller cells might become important in future clinical applications. In some (sub-)mammalian vertebrates, the transition from the radially aligned, bipolar-shaped late progenitor cells to the radial glial (Müller) cells is not abrupt, and partially reversible. Thus, under certain conditions young Müller cells may re-enter the mitotic cycle, and generate new neurons and Müller cells (Fischer and Reh, 2001). Generally in the vertebrate retina, there are no glia- or neuron-specific progenitor cells; even the final division of a late progenitor cell typically generates one rod photoreceptor or bipolar cell and one Müller cell (Turner and Cepko, 1987; for review see Reichenbach and Robinson, 1995b). Before this last division, each of the late progenitor cells undergoes a species-specific varying number of cell divisions, eventually generating a columnar aligned group of neurons together with one Müller cell in its core (Reichenbach and Robinson, 1995b). Thus, most of the cells in a given columnar 'micro-unit' (Fig. 1D) are clonally as well as functionally related.

To take on the multitude of supportive functions for its 'small neuronal siblings' (Reichenbach et al., 1993), the young Müller cell must undergo a radical differentiation. In laboratory rodents, this differentiation occurs during the first 2–3 postnatal weeks. This period includes the cessation of cell proliferation (during the first days) and the establishment of the mature synaptic wiring of retinal neurons (end of first week) as well as the full development of photoreceptor outer segments (second week). Accordingly, the retinal glia differentiates from a progenitor-like state, via a stage of immature radial glia, to mature Müller cells. This differentiation involves morphological, biochemical, and (electro-) physiological changes; the cells extend side branches between the neuronal somata and synaptic processes (Reichenbach and Reichelt, 1986), accumulate glia-specific enzymes such as GS (Germer et al., 1997), and dramatically change the expression pattern of membrane proteins (Bringmann et al., 1999b; Felmy et al., 2001; Pannicke et al., 2002). As these latter changes are very important for many Müller cell functions (→1.1.) and are largely reversible in cases of gliotic de-differentiation (→1.2.; Fig. 3) they will be considered in more detail.

During the first postnatal days, the immature radial glial cells display a characteristic pattern of membrane-physiological features, suitable to support a mitotic activity of the cells (Bringmann et al., 2000): there are virtually no inward currents (Fig. 3A); the resting membrane potential is very 'low', i.e., depolarized (about −20 mV: Bringmann et al., 1999b; Felmy et al., 2001; Pannicke et al., 2002); the open probability of BK channels is very high, at least in some species (Bringmann et al., 1999b), and virtually all cells respond to stimulation of purinergic receptors by elevating intracellular free Ca^{2+} (Fig. 3A). This ATP-evoked Ca^{2+} responsiveness decreases rapidly during Müller cell differentiation (Fig. 3A), as well as the open probability of BK

channels (Bringmann et al., 1999b). By contrast, in the differentiating Müller cells there occurs a dramatic increase of the inward K^+ current density (Fig. 3A), accompanied by a hyperpolarization of the membrane potential towards the adult levels of about −80 mV (Bringmann et al., 1999b; Felmy et al., 2001; Pannicke et al., 2002). This is apparently due to the insertion of Kir4.1-type K^+ channels into the Müller cell membrane during the second week of life (Kofuji et al., 2002) and provides the essential precondition for most of the neuron-supportive functions of mature Müller cells (→1.1., 2.3.–2.6.) as well as for the cessation of proliferative activity (Bringmann et al., 2000).

Taken together, several features of the Müller cells mature in concert to fit the requirements of the maturing neuronal network. For example, in neurotransmitter recycling (→2.3.), after neural synapses are established at the early second week of life, the Müller cells then (i) send side branches towards the synapses, and ensheath them, (ii) express glutamate uptake transporter molecules in the membrane of these perisynaptic sheaths, (iii) hyperpolarize their resting membrane potential to provide the necessary driving force for the transporters, and (iv) express the enzyme, GS, to convert the internalized glutamate molecules into glutamine. In parallel, the young Müller cells are involved in the control of retinal vascularization (Wolburg et al., 1999) including the induction of the blood–retina barrier (Tout et al., 1993).

2.2. *'Metabolic symbiosis'*

It has already been mentioned that Müller cells, in contrast to retinal neurons, are strikingly resistant to a wide variety of pathogenic factors, including ischemia, hypoxia, and hypoglycemia. One reason for this relative insusceptibility to injury is their specialized energy metabolism. As in many types of glial cells, it relies mainly upon anaerobic glycolysis, even in the presence of sufficient oxygen supply. Therefore, Müller cells display a low rate of oxygen consumption and may withstand even long-lasting anoxia (Poitry-Yamate et al., 1995; Winkler et al., 2000). As long as oxygen is available, Müller cells are also resistant to the absence of glucose since other substrates such as lactate, pyruvate, glutamate, or glutamine can be metabolized to generate energy substrates by the Krebs cycle, a pathway that is normally non-dominant (Tsacopoulos et al., 1998; Winkler et al., 2000). Short periods of glucose deficiency and even ischemia may be compensated by the glycogen deposits in Müller cells (Kuwabara and Cogan, 1961; Reichenbach et al., 1999; Gohdo et al., 2001). Müller cells are abundantly endowed with the brain-specific glycogenolytic isoenzyme, BB glycogen phosphorylase (Pfeiffer-Guglielmi et al., 2005). Elevation of the extracellular K^+ concentration causes rapid glycogenolysis in cultured Müller cells (Reichenbach et al., 1993), indicating that the amount of glycogenolysis depends on the momentary neuronal activity in the retina (and may be increased under pathological conditions, as well).

As a *caveat* to this scenery of Müller cells as 'oxygen-independent survivors', it must be said that most of the above-mentioned data were obtained on Müller cells from the rabbit and guinea-pig retina which both are avascular and display extremely low oxygen partial pressures proximal to the outer limiting membrane (Yu and Cringle, 2001). Such Müller cells contain only a few mitochondria at their distal-most end, directed towards the choroid as the only oxygen source (Germer et al., 1998a, b). Indeed, the mitochondrial energy production of these cells may be blocked over hours without measurable effects on energy-consuming functions such as the maintenance of the hyperpolarized resting membrane potential (whereas it rapidly depolarizes in the presence of iodoacetate, a blocker of anaerobic glycolysis) (Reichenbach et al., 1999). However, Müller cells from vascularized retinae contain many mitochondria, distributed along the entire length of the cells (Germer et al., 1998a) probably due to a sufficient oxygen availability throughout the tissue (Germer et al., 1998b). When the mitochondrial energy production of such Müller cells (from rat retina) is blocked, their membrane potential slowly depolarizes suggesting that these cells cannot be completely resistant to anoxia (AR and coworkers, unpublished results). The membrane potential of these cells also depolarize more rapidly in the presence of iodoacetate, which inhibits a predominant anaerobic component of their energy metabolism.

What does this mean for the interaction between Müller cells and retinal neurons? The glycolytic metabolism of glial cells results in the generation of lactate, which is converted into pyruvate by the glial enzymes, lactate dehydrogenase and pyruvate kinase (Tsacopoulos et al., 1998). Pyruvate is then released from the cells likely via their monocarboxylate transporter, MCT2 (Lin et al., 1998), and taken up by the neurons which then use it as a substrate for their own Krebs cycle (Poitry-Yamate et al., 1995) (Fig. 5C). This interaction has beneficial consequences for both neurons (which are being 'fed' by the substrate of their metabolism, without the necessity of an own unefficient but 'costly' glycolytic pathway) and glial cells (which are getting rid of the 'unwarranted' acidic end product of their metabolism). A 'mirror image' of this mutual benefit arises at the end of the aerobic pathway when CO_2 and water are generated by the neurons. By means of the glia-specific enzyme, carbonic anhydrase (Sarthy and Lam, 1978; Deitmer, 2002), the glial cells transfer CO_2 to HCO_3^-, which is either transported via a H^+/HCO_3^--exchanger into the vitreous body (Newman, 1996) or into the blood vessels, or used to synthesize lipids (Cammer, 1991) (Fig. 5C). Thus, one type of retinal cell (Müller cells) is responsible for inactivating a potentially dangerous end product (neurons are unable to inactivate CO_2 on their own) and the other type of cells receive a substrate for their metabolism (the glial cells, which do not generate enough CO_2 in their own gycolytic metabolism). This type of interaction can be called a 'metabolic symbiosis' between retinal neurons and glial cells.

2.3. Neurotransmitter recycling

Müller cells play a major part in the recycling of neurotransmitters in glio–neuronal interaction. For the fast clearance of transmitters in synaptic spaces, Müller cell membranes express uptake systems for amino acid transmitters (Ehinger, 1977) such as glutamate (Brew and Attwell, 1987; Derouiche and Rauen, 1995; Sarthy et al., 2005), γ-aminobutyric acid (GABA) (Sarthy, 1982; Qian et al., 1993; Biedermann et al., 2002), and glycine (Gadea et al., 2002). The clearance of synaptic glutamate by Müller cells is required for the normal functioning of excitatory synapses and for the prevention of neurotoxicity (Barnett and Pow, 2000). Müller cells express the glutamate/aspartate transporter, GLAST (Otori et al., 1994; Derouiche and Rauen, 1995), which is the predominant transporter for the removal of glutamate within the retina (Fig. 4; Harada et al., 1998; Rauen et al., 1998); it mediates the rapid termination of the postsynaptic action of glutamate (Matsui et al., 1999). The Na^+-dependent glutamate uptake of Müller cells is electrogenic (Brew and Attwell, 1987) and, therefore, energy-dependent; a very negative membrane potential is necessary for efficient uptake. Cell depolarization, e.g., by activation of glial ionotropic receptors (Pannicke et al., 2000a) or by elevated extracellular K^+, decreases the uptake rate substantially. Malfunction of the glutamate transport into Müller cells results in an increased extracellular level of glutamate

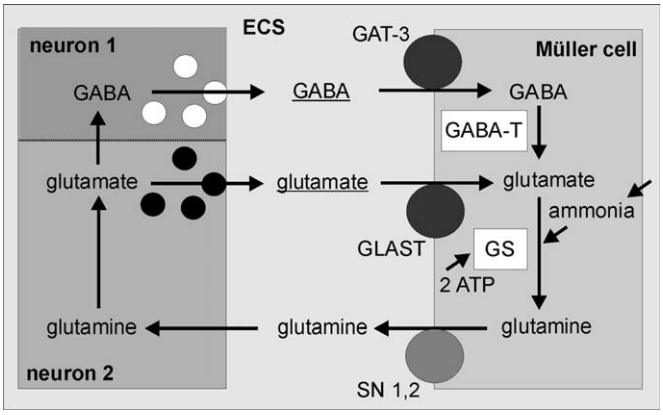

Fig. 4. Schematic diagram of neurotransmitter recycling in the retina. A GABAergic (neuron 1) and a glutamatergic neuron (neuron 2) are drawn together for simplicity. They release the neuroactive (underlined) substances, GABA and glutamate, respectively, into the extracellular space (ECS) from where they rapidly are taken up by the Müller glial cell. For this purpose, the Müller cell is endowed with high-affine uptake transporters for GABA (dominantly, GAT-3; Johnson et al., 1996) and glutamate (as the most important, GLAST). Once GABA has entered the cytoplasm, it is converted into glutamate by means of the GABA transaminase (GABA-T). Then, glutamate (either converted from GABA or directly taken up) is transformed into the non-neuroactive substance, glutamine. This transformation requires the glia-specific enzyme, glutamine synthetase (GS), and energy (in the form of ATP). The GS reaction is the only pathway of ammonia detoxification in the retina. Glutamine is then exported by the glutamine transporters, SN 1 and SN 2 (Umapathy et al., 2005), into the ECS from where the neurons may take it up, and use it for the re-synthesis of glutamate and GABA.

which may contribute to neuronal dysfunction and apoptosis in the diseased retina (Barnett and Pow, 2000). After experimental inhibition of glutamate uptake by Müller cells, even low concentrations of extracellular glutamate become neurotoxic, via activation of ionotropic glutamate receptors on neurons (Kashii et al., 1996; Izumi et al., 1999).

After being taken up by Müller cells, glutamate is intracellularly converted into glutamine by the enzyme, GS which is only expressed in Müller cells (Linser and Moscona, 1979) and which operates in concert with GLAST (Derouiche and Rauen, 1995) (Fig. 4). Likewise, after the uptake of GABA into Müller cells, it is converted to glutamate (Biedermann et al., 2002) which then is fed into the GS pathway. Glutamine is transported back to neurons as precursor for their synthesis of glutamate and GABA (glutamate–glutamine cycle of the retina) (Pow and Crook, 1996) (Figs. 4, 5B). Due to the efficiency of the GS, demonstrable levels of glutamate are only present in Müller cells when the GS is experimentally inhibited (Pow and Robinson, 1994) or down-regulated under pathological conditions (Erickson et al., 1987). When the GS is experimentally blocked in Müller cells, retinal neurons lose their glutamate content, and the animals become rapidly (within 2 min) functionally blind (Pow and Robinson, 1994; Barnett et al., 2000).

The expression and activity of GLAST in Müller cells is regulated by the availability of the substrate, mediated by intracellular signaling pathways. Glutamate receptor activation in Müller cells results in an increase in the intracellular free calcium and in activation of protein kinase C (Lopez-Colome et al., 1993). Activation of protein kinase C increases the glutamate uptake by phosphorylation and increased expression of transporter protein (González et al., 1999), suggesting that the enhanced expression of GLAST by activated Müller cells observed under certain pathological conditions (Otori et al., 1994; Reichelt et al., 1997a) may be caused by this mechanism. In a similar manner, the expression level of GS appears to be regulated by the availability of its two substrates, glutamate and ammonia. Young Müller cells express the enzyme shortly after the glutamatergic synapses mature; when the major glutamate-releasing neuronal population, the photoreceptors, degenerate, the expression of the enzyme decreases in Müller cells (Germer et al., 1997; Reichenbach et al., 1999). In chicken retinal Müller cells, the expression of GS is also regulated by steroid hormones (Linser and Moscona, 1979, 1983); this is probably not a prominent regulatory mechanism in mammalian Müller cells (Germer et al., 1997). It has also been shown that exposure to elevated levels of ammonia (such as occurring in cases of liver failure) causes an up-regulation of GS expression in Müller cells (Germer et al., 1997; Bringmann et al., 1998). As the GS of Müller cells is the only enzyme available for ammonia detoxification in the retina, this is an important 'sideway function' of neurotransmitter recycling (→2.6.) (Fig. 5B). Furthermore, as the GS

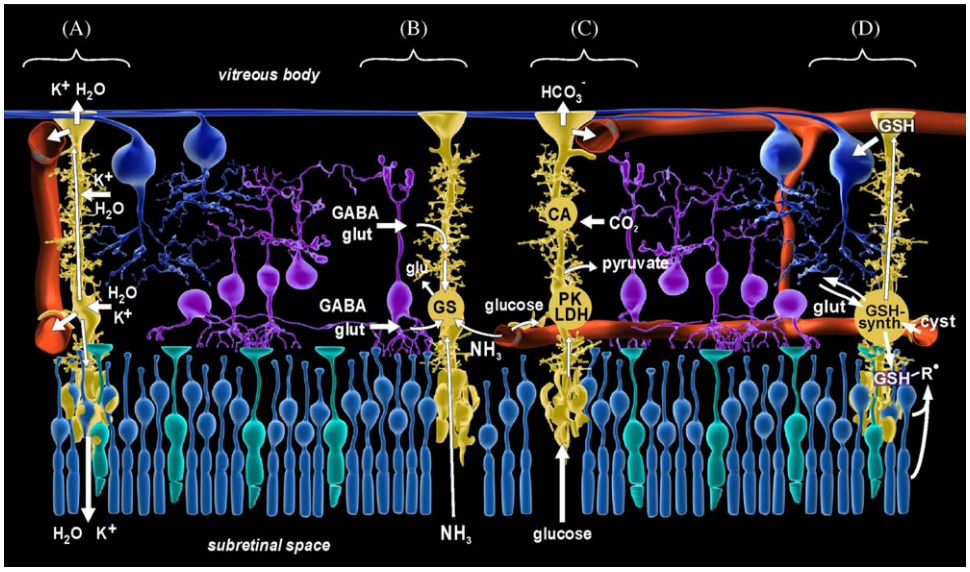

Fig. 5. Important Müller cell–neuron interactions in the normal mature retina. (A) Spatial buffering of K^+ ions and water (→2.4., 2.5.). (B) Transmitter recycling (→2.3.). (C) 'Metabolic symbiosis' (→2.2.). (D) Free radical scavenging/GSH metabolism (→2.6.). CA, carbonic anhydrase; cyst., cysteine; GABA, gamma-aminobutyric acid; glut, glutamate; GS, glutamine synthetase; GSH, glutathion; LDH, lactate dehydrogenase; PK, pyruvate kinase; $R^•$, free radical molecule. For details, see text. Original.

reaction requires energy, a chronical exposure to high ammonia concentrations may cause a metabolic overload of Müller cells, and finally retinal damage by hepatic retinopathy (→3.6.).

Finally, it should be pointed out that the uptake of glutamate is also important for other metabolic pathways and functions of Müller cells; one example is the retinal defense against free radicals (→2.6.) (Fig. 5D).

2.4. Retinal K^+ homeostasis

Müller cells are crucially involved in retinal K^+ homeostasis, by mediating transcellular spatial buffering K^+ currents which counteract local changes in extracellular K^+ concentration associated with neuronal activity (Newman et al., 1984; Reichenbach et al., 1992; Newman and Reichenbach, 1996). A dysregulation of the K^+ homeostasis causes K^+-evoked neuronal hyper-excitation and glutamate toxicity. As mentioned above (→1.1.) the plasma membranes of Müller cells are highly permeable to K^+ (Newman, 1985) as a consequence of the strong expression of special K^+ channels (Fig. 3; Newman, 1993); this high K^+ permeability causes a very negative membrane potential of the cells close to the equilibrium potential of K^+ ions (Witkovsky et al., 1985). Active neurons release K^+ ions especially within the plexiform (synaptic) layers (Steinberg et al., 1980). This causes a local driving force for K^+ inward currents into the Müller cells; thus, Müller cells take up the neuron-derived excess K^+ from the plexiform layers, and release a similar amount of K^+ into fluid-filled spaces outside of the neural retina (blood, vitreous, and subretinal space) (Fig. 2, 5A) (Newman et al., 1984; Karwoski et al., 1989; Reichenbach et al., 1992). Though the Na,K-ATPase and transporter molecules contribute to Müller cell-mediated K^+ homeostasis (Reichenbach et al., 1992), these passive K^+ currents through inwardly rectifying K^+ channels (called 'spatial buffering': Orkand, 1986; or 'potassium siphoning': Newman et al., 1984) play a major role in counteracting fast extracellular K^+ increases. Among the various subtypes of K^+ channels expressed by Müller cells (Bringmann et al., 1997; Raap et al., 2002; Kofuji et al., 2002; Skatchkov et al., 2006), especially the inwardly rectifying K^+ channel of the Kir4.1 subtype has been implicated in mediating the K^+ buffering currents (Ishii et al., 1997; Kofuji et al., 2000). The Kir4.1 channel protein is expressed in a polarized fashion in the plasma membrane of Müller cells, with strong enrichment in such membrane domains across which the cells release excess K^+ into 'sinks', i.e., in perivascular membrane sheets, and at the inner and outer limiting membranes (Fig. 2) (Nagelhus et al., 1999; Kofuji et al., 2000, 2002). Kir4.1 channels are weakly rectifying channels, i.e., they mediate outward and inward K^+ currents with similar amplitudes (Fig. 2) (Takumi et al., 1995). Other types of inwardly rectifying K^+ channels, e.g., the Kir2.1 channel, are strongly rectifying channels and mediate predominantly inward K^+ currents and almost no outward currents (Kubo et al., 1993). Kir2.1 channels are expressed by Müller cells in such membrane domains which abut retinal neurons (Fig. 2) (Kofuji et al., 2002). Thus, the polarized expression of different subtypes of K^+ channels (together with the local transmembraneous K^+ gradients) determines the direction of the transglial K^+ currents: excess K^+ is absorbed by Müller cells from the space around neurons, and is distributed into the blood, the vitreous, and the subretinal space (Fig. 5A). In reactive gliosis when the currents through Kir4.1 channels are reduced or even missing, other

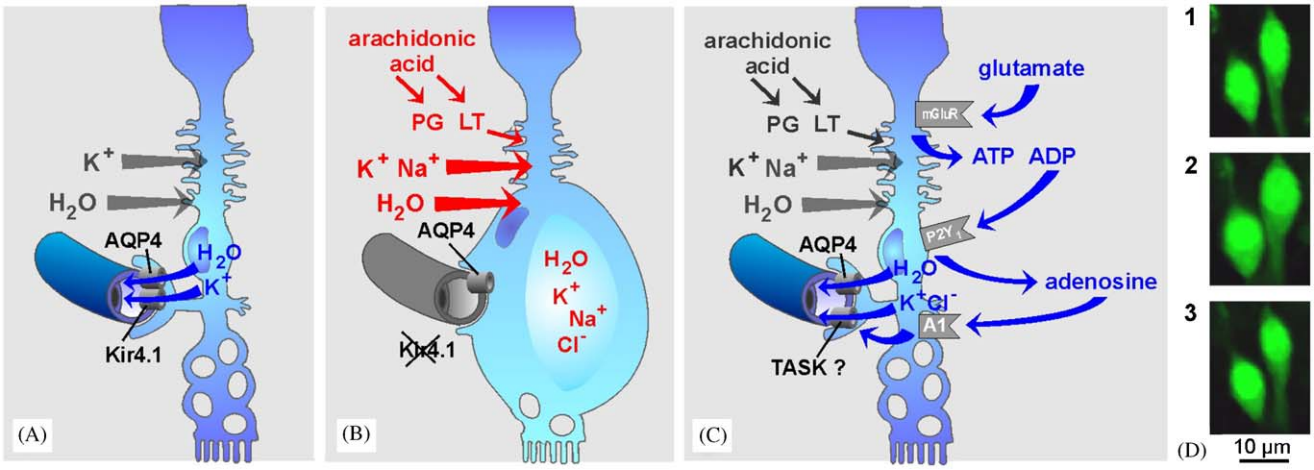

Fig. 6. Müller cell swelling in the diseased retina. (A) In the healthy retina, Müller cells dehydrate the retinal tissue in dependence on the neuronal activity. Activated neurons release K^+ into the extracellular space which is taken up by Müller cells via K^+ channels expressed in their plasma membranes, and which is released into the blood through Kir4.1 channels expressed in the perivascular processes of Müller cells. Osmotically coupled to the transglial K^+ currents, water flows through the Müller cell bodies from the retinal parenchyma into the blood. The transglial water transport is facilitated by aquaporin-4 water channels expressed in the plasma membranes of Müller cells. (B) Müller cells in ischemic, inflamed, or diabetic retinas downregulate the expression of their Kir4.1 channels which are normally expressed in their perivascular membrane sheets, resulting in inhibition of K^+ release into the blood and interruption of the dehydrating K^+ currents through Müller cells, while the cells still take up K^+ via K^+ channels (e.g., Kir2.1) expressed in membrane domains that abut retinal neurons. This mechanism increases the osmotical pressure within the cells, and results in an osmotic difference at the gliovascular interface which favors water inflow into the cells via the still expressed aquaporin-4 water channels. In addition, the osmotic stress in perivascular membrane domains activates the phospholipase A_2, and the production of arachidonic acid (and derivatives like prostaglandins [PG] and perhaps also leukotriens [LT]) causes influx of Na^+ ions and intracellular Na^+ overload which further increases the osmotical driving force for water inflow into the cells, resulting in Müller cell swelling. Since the dehydration of the retina by Müller cells is dysregulated in the diseased retina, this should also exacerbate the extracellular accumulation of fluid derived from leaky vessels. (C) Glutamate release by retinal neurons evokes a purinergic signaling cascade that inhibits osmotic swelling of Müller cells. This purinergic signaling cascade involves the release of endogenous ATP and adenosine, and the consecutive activation of $P2Y_1$ and A1 adenosine receptors. A1 receptor activation results in opening of K^+ channels (likely, TASK channels (Skatchkov et al., 2006)) in the perivascular membrane processes of Müller cells which allows the release of K^+ ions into the blood and dehydration of the retina, resulting in inhibition of cell swelling. (D) Example of osmotic swelling of Müller cell bodies in a slice of an ischemic rat retina. The somata were recorded before (1), during (2), and after (3) application of a hypotonic solution which contained 60% of control osmolarity. Modified after Pannicke et al. (2004) and Uckermann et al. (2006).

types of K^+ channels such as the TASK channels (Fig. 2) may maintain an 'auxiliary', depolarized membrane potential (Pannicke et al., 2000b; Skatchkov et al., 2006) but potassium siphoning must be dramatically impaired or even extinguished.

Since the vitreous is (in addition to the blood) a main sink for the K^+ redistribution, exchanging the vitreous body by media without the capability to dissolve K^+ ions (e.g., by perfluorocarbon liquid or silicone oil) should disturb the K^+ buffering function of Müller cells and may favor neuronal degeneration (Winter et al., 2000, and references therein).

2.5. Retinal water homeostasis

Under normal conditions, water accumulates within the retinal tissue due to (i) the ongoing endogenous production of water associated with oxidative synthesis of adenosine 5′-triphosphate (ATP), (ii) an influx of water from the blood coupled to the uptake of metabolic substrates such as glucose, and (iii) forcing of water into the retina by the intraocular pressure (Marmor, 1999). This water is continuously redistributed out of the neural retina by the pigment epithelium which dehydrates the subretinal space (Pederson, 1994), and by Müller cells which dehydrate the inner retinal tissue (Bringmann et al., 2004). Both pigment epithelium and Müller cells mediate transcellular water fluxes that are coupled to fluxes of osmolytes, particularly ions, and which are facilitated by the polarized plasma membrane expression of water transporting proteins, the aquaporins. Müller cells mediate a transcellular water transport from the retinal interstitium through the cell bodies into the blood. The co-expression of K^+ (Kir4.1) and aquaporin-4 water channels in distinct membrane domains of Müller cells has led to the suggestion that the water transport through Müller cells is tightly coupled to the spatial buffering K^+ currents mediated by the cells (Nagelhus et al., 1999) (Figs. 5A, 6). In addition, aquaporin-4 water channels are also expressed in the plexiform layers (Nagelhus et al., 1998); thus, aquaporin-4 is expressed in all membrane domains through which Müller cells take up and release excess K^+. The coexpression of aquaporin-4 and Kir4.1 (which mediates bidirectional K^+ currents) may suggest that osmotical differences between the retinal tissue and the blood and vitreous are compensated by K^+ and water in- and effluxes from Müller cells, in dependence on the momentary neuronal activity (Fig. 6A).

Since K^+ and water transport through Müller cells are coupled, any inhibition of the rapid water transport should delay the K^+ currents through the cells; vice versa, an impairment of transglial K^+ currents (e.g., after the downregulation of K^+ channels in reactive Müller cell gliosis) should disturb the rapid transglial water transport (Fig. 6B). What may be the consequences of such alterations? A (direct or indirect) dysregulation of the K^+ homeostasis should impair synaptic activity. In the brain, an association between aquaporin-4-mediated water shifts through glial cells and synaptic activity is suggested by the observation that mice lacking aquaporin-4 display elevated electrographic seizure thresholds and prolonged seizure durations (Binder et al., 2004; Manley et al., 2004). In aquaporin-4 knockout mice, the b-wave potential of the electroretinogram is reduced (Li et al., 2002), suggesting a reduced or disturbed excitability of second-order neurons after inhibition of the rapid transglial water (and, thus, K^+) transport. The transglial water transport may be also involved in mediating neuronal hyper-excitation as occurring during ischemia-reperfusion. This suggestion is based on the observation that aquaporin-4 gene disruption protects against retinal cell death after ischemia (Da and Verkman, 2004). An implication of the aquaporin-4 water channels on Müller cells in ischemia-evoked neuronal apoptosis may be explained by the necessity of rapid water fluxes to accompany the strong ion movements through ionotropic glutamate receptors which mediate excitotoxicity (Bringmann et al., 2005). Thus, the aquaporin-4 water channels expressed by Müller cells may facilitate the constitutive water redistribution out of the retinal parenchyma into the blood as well as the activity-dependent rapid water fluxes necessary for regular neuronal activation and synaptic transmission.

2.6. Other interactions

It has already been mentioned that there are many other functions of Müller cells (some of which remain to be elucidated in detail). In order to understand the pathological conditions described below (→3.), several of these functions are briefly summarized in the following.

An important neuroprotective effect may be exerted by Müller cells because of their involvement in the retinal defense against free radicals. Müller cells synthesize the tripeptide glutathione from glutamate, cysteine, and glycine (Pow and Crook, 1995; Reichelt et al., 1997b; Schütte and Werner, 1998). Reduced glutathione is provided to neurons (Schütte and Werner, 1998; Francke et al., 2003) and acts as a scavenger of free radicals and reactive oxygen compounds (Fig. 5D). During hypoxia and hypoglycemia, the glutathione levels in Müller cells decrease dramatically (Huster et al., 2000); an ischemia-induced lack of glutathione may increase the intraretinal level of oxygen-derived free radicals. Müller cells from aged animals contain a reduced amount of glutathione as compared to cells from young animals (Paasche et al., 1998). Thus, an age-dependent decrease of the Müller cell-mediated defense against free radicals may accelerate the pathogenesis of retinopathies in elderly patients.

Another way of neuroprotection is the uptake and/or detoxification of potentially harmful substances and even particles (either intrinsic or foreign) by Müller cells. This involves

- the phagocytosis of debris from dead neurons or pigment epithelial cells (Francke et al., 2001a) and of foreign bodies such as copper particles (Rosenthal and Appleton, 1975) or latex beads (Stolzenburg et al., 1992);
- the expression of multidrug-resistance transporters in the Müller cell membrane (Francke et al., 2003); these are thought to remove large molecules from extracellular space, and probably mediate the rapid uptake of vital dyes into the Müller cells (→Fig. 1B, C); and
- the GS of Müller cells which has been already mentioned as the only enzyme available for ammonia detoxification in the retina.

Finally, Müller cells may not only participate in the extracellular homeostasis and transport of neuronal 'waste products' and metabolites, but also contribute more directly to information processing in the retina. They may generate and/or store and release neuroactive substances, most likely in dependence on the momentary neuronal activity and/or metabolic state. Such substances might include ATP, glutamate, and D-serine (Newman and Zahs, 1998; Stevens et al., 2003; Newman, 2004).

3. Müller cells in the diseased retina

3.1. Retinal detachment

The neural retina may become separated from the pigment epithelium during trauma or inflammatory eye diseases, or in the presence of retinal holes and tears. Detachment increases the distance between the choriocapillaris and the neural retina, and results in a decreased oxygen and nutrient supply of the photoreceptor cells (Stone et al., 1999; Linsenmeier and Padnick-Silver, 2000). The decreased energy supply was suggested to cause photoreceptor cell death and subsequent retinal degeneration (Mervin et al., 1999). In addition to the initial damage to the outer segments, and subsequent photoreceptor cell deconstruction and apoptotic death (Machemer, 1968; Erickson et al., 1983; Anderson et al., 1983; Cook et al., 1995), there are morphological and biochemical alterations of the inner retinal neurons (Lewis et al., 1998; Faude et al., 2001; Coblentz et al., 2003), as well as a fast activation of pigment epithelial cells and macro- and microglial cells (Lewis et al., 1999; Geller et al., 2001; Francke et al., 2001b; Jackson et al., 2003; Uhlmann et al., 2003). The activation of glial cells in the experimentally detached retina begins immediately after creation of detachment and proceeds during the first hours and days of detachment (Geller et al.,

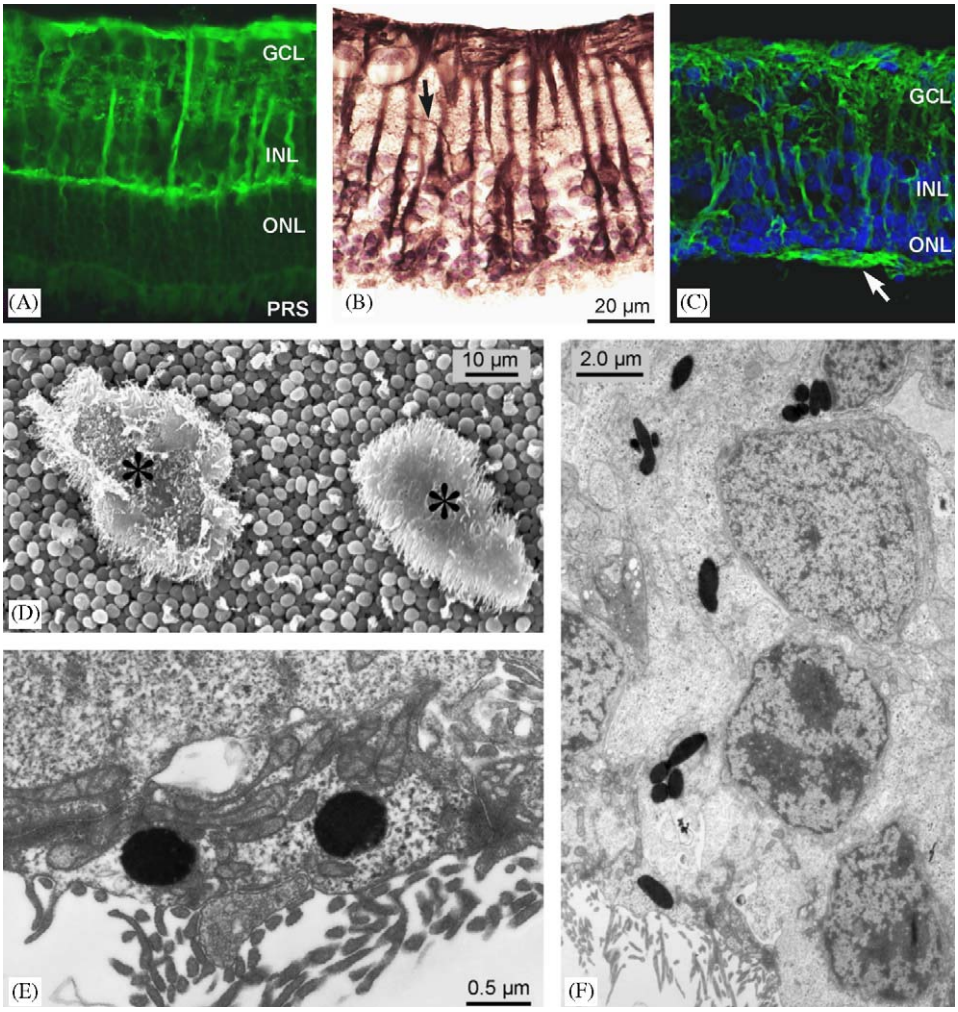

Fig. 7. Reactive gliosis after experimental detachment of the rabbit retina. GFAP immunoreactivity (green fluorescence in A and C; brown DAB-nickel reaction product in B) after 2 days (A) and one week (B) of detachment. (C) Proliferative vitreoretinopathy (PVR; cell nuclei were counter-stained with Hoechst 33258 dye = blue). (A) At 2 days after detachment, no morphological indications of neurodegeneration are obvious. The Müller cells are immunopositive for GFAP within their inner processes (up to the INL). (B) After one week, many photoreceptor cells are already degenerated as indicated by the thin ONL; the Müller cells display GFAP immunoreactivity throughout their length, and some cells extend additional side branches (arrow). (C) When a PVR develops, some Müller cells grow out of the retina (arrow). The scale bar in B is valid for A–C. (D) Rabbit retina, immediately after experimental detachment; some pigment epithelial cells are adhering (asterisks); raster electron micrograph. (E) Transmission electron micrograph of the sclerad retinal surface after three weeks of detachment. The Müller cell cytoplasm contains many mitochondria and two typical melanin granules. (F) Outer retina after six weeks of detachment. A Müller cell contains melanin granules scattered throughout the sclerad stem process up to the level of the inner nuclear layer (top). GCL, ganglion cell layer; INL, inner nuclear layer; ONL, outer nuclear layer; PRS, photoreceptor segments. Modified after Francke et al. (2001a, b).

2001; Francke et al., 2001b; Uhlmann et al., 2003). Within minutes of detachment, Müller cells show an increased protein phosphorylation (e.g. of the fibroblast growth factor receptor 1 and of the ERKs) and increased production of transcription factors (Geller et al., 2001). Within three hours of detachment, neuronal cell bodies are depleted of glutamate while Müller cells show an increased content of glutamine (Sherry and Townes-Anderson, 2000). Within one day of detachment, Müller cells begin to proliferate, and an increased expression of the intermediate filaments, GFAP and vimentin, is evident (Fisher et al., 1991; Lewis et al., 1994, 1995) (Fig. 7B). At three days of detachment, GFAP labeling of Müller cells extends throughout the retina (Lewis et al., 2005), and Müller cell hypertrophy is obvious in the retina and in the subretinal space; subretinal fibrosis is caused by outgrowing Müller cell processes (Anderson et al., 1986; Fisher et al., 1991; Lewis et al., 1994; Francke et al., 2001b) (Fig. 7C). The detachment-induced proliferation of Müller cells peaks at three to four days of detachment, and may continue at a slower rate for weeks to months (Fisher et al., 1991; Geller et al., 1995). Finally, Müller cells migrate onto the surfaces of the detached retina and proliferate there (Laqua and Machemer, 1975; Erickson et al., 1990) (Fig. 9A, B).

The Müller cell reactivity may be caused (directly or indirectly) by the detachment-induced hypoxia since ischemia has been shown to induce Müller cell proliferation

(Stefansson et al., 1988), and since Müller cell proliferation and hypertrophy has been shown to be reduced by oxygen supplementation during experimental detachment (Lewis et al., 1999). The hypertrophy and proliferation of Müller cells in detached retinas may be induced by the basic fibroblast growth factor or endothelin-2 released by photoreceptor cells (Lewis et al., 1992; Rattner and Nathans, 2005), or by direct cone-Müller cell contacts (Lewis and Fisher, 2000). Photoreceptor-derived endothelin-2 may activate Müller cells via their endothelin B receptors (Rattner and Nathans, 2005; Iandiev et al., 2005).

The morphological markers of Müller cell gliosis (Fig. 7C) are associated with distinct physiological alterations. Among others, the Müller cells down-regulate the expression of proteins that are involved in homeostatic functions and in glio-neuronal interactions, such as GS, CRALBP, and carbonic anhydrase (Marc et al., 1998; Lewis et al., 1999). Müller cells also down-regulate the K^+ conductance of their plasma membranes (Müller cells show a decrease in their K^+ currents after two days of detachment; Fig. 3 (Francke et al., 2001b)), and upregulate their intracellular Ca^{2+} responsiveness upon stimulation of distinct receptors such as purinergic P2Y receptors (Fig. 3) (Francke et al., 2001b; Uhlmann et al., 2003; Iandiev et al., 2006a). Both the down-regulation of the K^+ conductance and the enhanced P2 receptor-mediated signaling may be involved in Müller cell proliferation, and are indicators of cellular de-differentiation, reflecting similar features of the immature Müller cells at the early postnatal stage (Fig. 3) (Bringmann et al., 2000, 2001; Moll et al., 2002; Milenkovic et al., 2003; Uhlmann et al., 2003). It has been suggested that the down-regulation of functional K^+ channels in gliotic Müller cells contributes to the neuronal degeneration after detachment, since an impairment of the retinal K^+ homeostasis favors neuronal hyper-excitation and glutamate toxicity (Francke et al., 2001b, 2005). The degeneration of the detached retina is suggested to be mediated, at least in part, by an impairment of glutamate recycling by Müller cells (Marc et al., 1998; Sherry and Townes-Anderson, 2000). A reduction of GS activity in Müller cells of detached retinas (Erickson et al., 1987; Lewis et al., 1999) may underlie the accumulation of glutamate in these cells (Marc et al., 1998; Lewis et al., 1999) which reflects a disruption of glutamate recycling.

Gliotic Müller cell changes, e.g., the down-regulation of the K^+ conductance, the up-regulation of the Ca^{2+} responsiveness, and the increased expression of GFAP, are not restricted to the focally detached retina but are also present in the surrounding non-detached retinal areas (Francke et al., 2001b; Uhlmann et al., 2003; Iandiev et al., 2006a) which may be correlated with distinct neuronal alterations within the non-detached areas (Francke et al., 2005). Disturbed supportive functions of gliotic Müller cells in non-detached retinal areas, e.g., an impaired K^+ buffering due to the down-regulation of K^+ channels, may explain observations in human patients with local detachments who show functional defects also in such areas of their visual field that correspond to retinal regions which are not detached (Sasoh et al., 1997). This finding is supported by observations of a depressed macular function in cases with purely peripheral detachment (Chisholm et al., 1975), and of a decreased retinal blood flow rate in both detached and non-detached retinal areas (Satoh, 1989).

Reactive gliosis upon detachment may be a clinically significant limiting factor in the recovery of vision after reattachment (Anderson et al., 1986; Fisher and Lewis, 2003; Francke et al., 2005). The hypertrophied and proliferating glial cells fill the spaces left by dying neurons and degenerated axons, synapses, and photoreceptor segments. The subretinal fibrosis (Fig. 7C) reduces the number and integrity of adjacent photoreceptors, and inhibits the regeneration of outer segments (Anderson et al., 1986; Sethi et al., 2005). The outgrowth of Müller cell processes onto the vitreal surface of the retina after reattachment (Fisher and Lewis, 2003) contributes to or even initiates the development of epiretinal membranes, and the hypertrophied side branches of Müller cells that grow into the plexiform layers may limit the reformation of disconnected synaptic contacts (Erickson et al., 1983). It has been proposed that attempts to reduce Müller cell gliosis may inhibit retinal degeneration and support neuroregeneration after reattachment (Fisher and Lewis, 2003; Francke et al., 2005).

3.2. Diabetic retinopathy

Decreases in certain components of the electroretinogram (Sakai et al., 1995) and increased apoptosis of retinal neurons (Barber et al., 1998) indicate an early neuronal degeneration in the diabetic retina. It has been suggested that the functional loss and the death of neurons in the diabetic retina can be attributed to reactive changes in Müller cells (Fletcher et al., 2005). Although diabetic retinopathy is a primary microangiopathy, reactive changes in Müller cells such as an up-regulation of GFAP (Lieth et al., 1998; Barber et al., 2000; Rungger-Brändle et al., 2000) occur early in the course of the disease and precede the onset of overt vascular changes. The up-regulation of GFAP in Müller cells in the retina of diabetic rats is inhibited by the aldose reductase inhibitor, sorbinil, as well as by melatonin, suggesting that an hyperactive polyol pathway and oxidative stress contribute to the progression of Müller cell gliosis (Asnaghi et al., 2003; Baydas et al., 2004). In addition, the Müller cell gliosis is characterized by responses to the inflammatory milieu present in the diabetic retina (Gerhardinger et al., 2005).

Diabetic retinopathy is one of the rare pathological conditions in which not all Müller cells survive; in the diabetic retina the cells display both proliferation and apoptosis. As the density of Müller cells is increased in experimental diabetes (Rungger-Brändle et al., 2000), the rate of proliferation appears to exceed that of apoptosis. Apoptosis in the diabetic rat retina occurs primarily in ganglion and Müller cells which is associated with an

increased expression of the p75 receptor on both cell types (Hammes et al., 1995; Mizutani et al., 1998). Treatment of diabetic rats with nerve growth factor prevents the apoptosis in both cell types, as well as the development of pericyte loss and acellular occluded capillaries (Hammes et al., 1995). Hyperglycemia induces Müller cell apoptosis in vitro, by inactivation of the Akt survival pathway (Xi et al., 2005). A similar inactivation of Akt may contribute to the Müller cell apoptosis in the diabetic retina (Xi et al., 2005).

Retinal capillaries consist of endothelial cells and pericytes which are covered by a basement membrane, and are ensheathed by membranes of astrocytes and Müller cells. Müller cells participate in the establishment of the blood–retinal barrier (Tout et al., 1993) which is constituted by the tight junctions between the vascular endothelial cells (Wolburg et al., 1999). A disturbance of this function is assumed to contribute to vessel leakage in the diabetic retina. In vitro, Müller cells enhance the endothelial cell barrier function under normoxic conditions, and impair the barrier function under hypoxic conditions (Tretiach et al., 2005). Müller cells produce factors that increase (glial cell line-derived neurotrophic factor [GDNF], neurturin, pigment epithelium-derived growth factor [PEDF]) and others that decrease the tightness of the endothelial barrier (tumor necrosis factor, VEGF, etc.) (Aiello et al., 1995; Drescher and Whittum-Hudson, 1996; Jingjing et al., 1999; Igarashi et al., 2000; Eichler et al., 2004a; Yafai et al., 2004). After breakdown of the blood–retinal barrier, the extravasated plasma protein, immunoglobulin G, may further trigger the reactive gliosis of Müller cells (Chu et al., 1999), and serum components leaking into the perivascular environment may stimulate Müller cell proliferation (Kodal et al., 2000).

VEGF (the "vascular permeability factor") is the major angiogenic factor in the retina to promote pathological neovascularization and vascular leakage (D'Amore, 1994; Miller et al., 1994). In the healthy retina, Müller cells provide a permanent anti-proliferative condition for vascular endothelial cells, by release of anti-angiogenic factors such as PEDF and thrombospondin-1 (Eichler et al., 2004b). Hypoxia and glucose deprivation induce VEGF expression in Müller cells (Aiello et al., 1995; Satake et al., 1998; Eichler et al., 2000). The production of VEGF by Müller cells is increased in diabetes. In fact, VEGF expression in Müller cells precedes neovascularization in the diabetic human retina, at times when there is no anatomical evidence of retinal malperfusion (Amin et al., 1997). The hyperglycemia-induced formation of advanced glycation end products (AGEs) in diabetic retinas may contribute to the induction of VEGF production (Hirata et al., 1997), via an activation of the AGE receptors on Müller cells (Hammes et al., 1999). PEDF, which is expressed in the neural retina by neurons and glial cells (Aymerich et al., 2001; Ogata et al., 2002; Eichler et al., 2004a), acts as an anti-angiogenic factor and an opponent of VEGF. PEDF expression is reduced under hypoxic conditions in the retina and Müller cells (Duh et al., 2002; Eichler et al., 2004a); a low PEDF level is a strong predictor of progression of diabetic retinopathy (Boehm et al., 2003).

VEGF and other angiogenic cytokines released by reactive Müller cells, such as basic fibroblast growth factor (FGF-2) and tumor necrosis factor (TNF-α), increase the release of matrix metalloproteinases by endothelial cells (Mignatti et al., 1989; Unemori et al., 1992; Lamoreaux et al., 1998; Behzadian et al., 2001; Majka et al., 2002). Moreover, the Müller cells themselves secrete matrix metalloproteinases, e.g., upon stimulation of purinergic receptors (Milenkovic et al., 2003). High glucose levels stimulate the production of matrix metalloproteinases (Giebel et al., 2005). Matrix metalloproteinases impair the tight junction function in retinal endothelial and pigment epithelial cells, by proteolytic degradation of the tight junction protein, occludin (Giebel et al., 2005), and thus may facilitate vascular leakage. Moreover, the secretion of metalloproteinases allows endothelial cells to penetrate their underlying basement membrane, and eliminates the contact inhibition which normally blocks endothelial cell proliferation (Behzadian et al., 2001). A further way for Müller cells to stimulate vasculogenesis may involve the renin–angiotensin system which has been implicated in diabetes. Müller cells express angiotensin II and renin, with the expression being most obvious in the endfeet closely apposed to retinal blood vessels, while the angiotensin receptors are expressed by neurons and vascular cells (Berka et al., 1995; Fletcher et al., 2005).

Diabetic retinopathy is associated with an increased production of nitric oxide and with glucose-mediated oxidative stress (Trotti et al., 1996; Kowluru and Kennedy, 2001; van Dam, 2002). The expression of the inducible nitric oxide synthase and of the cyclooxygenase-2 increases in the diabetic retina (Du et al., 2004); both enzymes are assumed to be involved in the retinal cell death observed under hyperglycemic conditions. It has been shown that hyperglycemic conditions stimulate the expression of both enzymes in Müller cells in vitro; the hyperglycemia-induced increase of nitric oxide in Müller cells stimulates the production of cytotoxic prostaglandins by cyclooxygenase-2 (Du et al., 2004). Müller cells express the inducible nitric oxide synthase in diabetic retinas (Abu-El-Asrar et al., 2001); the Müller cell-derived nitric oxide may induce neuronal cell death (Goureau et al., 1999). Furthermore, Müller cells respond to the inflammatory milieu of the diabetic retina by an upregulation of gene transcripts for inflammation-related proteins, e.g., for acute phase and antioxidant proteins (Gerhardinger et al., 2005). It has been suggested that the strong enhancement of the proinflammatory cytokine, interleukin-1β in the diabetic retina (Carmo et al., 1999) may be a primary cause of altered gene expression in Müller cells (Gerhardinger et al., 2005).

It has been mentioned above that reactive Müller cells may contribute to retinal damage not only directly (e. g., by

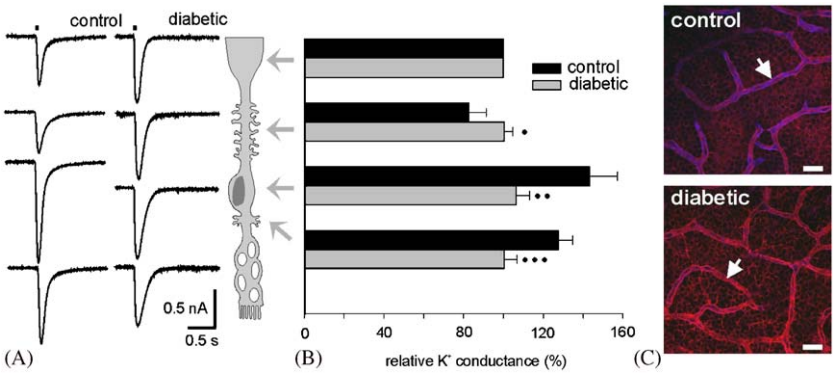

Fig. 8. Experimental diabetes changes the subcellular distribution of the plasma membrane K^+ conductance of isolated retinal glial cells. The distribution of the inward K^+ currents was determined by focal ejection of a high-K^+ (50 mM) solution onto four different membrane domains of acutely isolated cells. The control K^+ concentration was 3 mM. (A) Representative traces of inward currents in cells from a control (left) and a 6-months diabetic animal (right). Thick bars indicate the ejection time (50 ms). (B) Subcellular distribution of the inward K^+ conductance in cells from control and diabetic animals at 6 months after induction of diabetes. The K^+ conductance is normalized to the values obtained at the endfeet membranes (100%). (C) Immunocytochemical double-labeling of Kir4.1 protein (blue) and aquaporin-4 protein (red). The perivascular Kir4.1 expression almost completely disappears in the diabetic retina. Modified from Pannicke et al. (2006).

the release of toxic molecules) but also indirectly, by an impairment of neuron-supportive functions (→1.2.). It is noteworthy in this context that normal Müller cells are the 'communicators' between vessels and neurons, responsible for the uptake of glucose from the circulation, the glycolytic metabolism of glucose, and the transfer of substrates such as lactate and pyruvate to neurons (→2.2.). Generally, the uptake and metabolization of glucose in glial cells are closely linked to the release of glutamate from neurons and its uptake by glia (Westergaard et al., 1995; Sonnewald et al., 1997; Poitry et al., 2000). The limiting factor in both glutamate and glucose uptake by glial cells is the activity of the Na,K-ATPase which decreases very rapidly in hyperglycemic tissues (MacGregor and Matschinsky, 1986; Ottlecz et al., 1993). An impairment of the glial sodium pump causes a depolarization of the plasma membrane that lowers the efficiency of the electrogenic glutamate uptake (→2.3.). Insufficient glutamate uptake was shown to cause a decrease of the glutathione synthesis in Müller cells (Reichelt et al., 1997b) which must enhance oxidative stress in the retina. Likewise, the conversion of glutamate into glutamine is reduced in the diabetic retina, resulting in an increased retinal glutamate content (Lieth et al., 1998). Whether a dysfunction of the glutamate uptake of diabetic Müller cells (Li and Puro, 2002) contributes to the reduced formation of glutamine remains to be clarified (Ward et al., 2005). Finally, an impairment of Na,K-ATPase activity should disturb retinal K^+ homeostasis since a very negative membrane potential is a prerequisite for effective K^+ distribution by Müller cells (Newman, 1985; Chao et al., 1994; Bringmann et al., 1999a) (→2.4.).

In respect to impaired retinal K^+ homeostasis it is aggravating that the K^+ conductance of Müller cells is significantly reduced in experimental diabetes, as documented after retinal detachment (Fig. 3B). This decrease of K^+ conductance is associated with a mislocation of the Kir4.1 protein in the diabetic retina (Pannicke et al., 2006). Though the Kir4.1 protein is still expressed within the retinal tissue, the prominent expression at both limiting membranes and, particularly, around the vessels is absent (Fig. 8C). This suggests that the decrease of the K^+ currents in cells from diabetic retinas is caused by an alteration in the expression pattern of Kir4.1 channels. The downregulation of Kir4.1 channel-mediated currents should cause an impairment of the transglial K^+ currents and, therefore, a disturbance of the retinal K^+ homeostasis which may contribute to neuronal cell death in the diabetic retina (→2.4.). A strong reduction of the K^+ conductance was also found in Müller cells of human patients with proliferative diabetic retinopathy (Bringmann et al., 2002). Müller cells of the human retina display an age-dependent decrease of their K^+ conductance (Bringmann et al., 2003); this age-related down-regulation should contribute to retinal complications of diabetes in elderly patients.

Glial cells are crucially implicated in activity-dependent regulation of the local blood flow, and it has been suggested that the release of K^+ ions from perivascular endfeet plays a role in local dilation of arterioles (Paulson and Newman, 1987). A decrease of the activity-dependent K^+ efflux in the diabetic tissue may result in a decrease of the local blood flow, thus exacerbating hypoxic insults. Since the gating of Kir4.1 channels is dependent on intracellular ATP (Takumi et al., 1995; Kusaka and Puro, 1997), a functional inactivation of these channels may thus further aggravate the impairment of retinal K^+ homeostasis in ischemic tissue areas.

3.3. Macular edema

Most frequently, the presence of a macular edema is responsible for the decreased vision in patients with diabetic retinopathy (Bresnick, 1983; Larsen et al., 2005).

By compression of retinal neurons, nerve fibers, and capillaries, edema contributes to photoreceptor degeneration and neuronal cell death, and exacerbates the ischemic conditions. The development of chronic edema depends on two parameters: the rate of fluid entry into the retinal parenchyma through leaky vessel walls, and the rate of fluid reabsorption from the retinal tissue back into the blood. The fluid absorption is carried out by the pigment epithelium (which absorbs the fluid from the subretinal space) and by Müller cells (which absorb the fluid from the inner retinal tissue by transcellular water transport) (Bringmann et al., 2004) (→2.5.). Retinal edema may be caused by an opening of the blood–retinal barrier (vascular leakage causing extracellular edema) or by swelling of retinal cells (intracellular, cytotoxic edema). The development of macular edema is thought to be primarily caused by vascular leakage (Marmor, 1999; Antcliff and Marshall, 1999). However, it has been shown that clinically significant diabetic macular edema occurs only when (in addition to vascular leakage) the active transport mechanisms of the blood–retinal barriers are dysfunctional (Mori et al., 2002), suggesting that a disturbance of fluid absorption from retinal tissue is a necessary step in edema formation. In the preclinical stage of diabetic retinopathy, there are two types of increased retinal thickness that may or may not be associated with angiographic vascular leakage (Lobo et al., 2000). Also, the presence of fluid-filled cysts is not necessarily associated with vascular leakage, suggesting that both vasogenic edema and cell swelling may contribute to cystoid macular edema. It has been suggested that swelling of glial cells is involved in the development of cystoid edema, with the cysts being formed by swollen and dying Müller cells (Fine and Brucker, 1981; Yanoff et al., 1984).

Since the water transport through Müller cells is coupled to K^+ currents (→2.5.), a down-regulation of K^+ channels by Müller cells should impair the transglial water transport out of the retinal tissue. Müller cells in diabetic retinas of the rat display a down-regulation of K^+ currents (→3.2.) associated with a mislocation of the major K^+ channel of Müller cells (Kir4.1) normally present in perivascular and endfeet membranes of the cells (Pannicke et al., 2006) (Fig. 8). The decrease of K^+ currents may result in an accumulation of K^+ ions and, therefore, in an accumulation of fluid in the retinal tissue (Pannicke et al., 2004; Bringmann et al., 2004). Müller cells in slices of diabetic rat retinas swell under hypotonic conditions; this swelling is not observed in cells from control tissues. (The hypotonic conditions mimicks the osmotic gradient between the hyperosmolar retinal tissue [accumulation of K^+] and extraretinal fluid-filled spaces such as blood and vitreous.) The osmotic swelling of Müller cells in diabetic retinas is inhibited by blocking of phospholipase A_2 or cyclooxygenase, and in the presence of a reducing agent, suggesting that inflammatory conditions and oxidative stress play important roles in Müller cell swelling (Pannicke et al., 2006, Fig. 6B). The swelling of Müller cells under anisoosmotic conditions may suggest that Müller cells have lost their capability to rapidly extrude osmolytes (in particular, K^+ ions) and, therefore, water into the blood and vitreous. A similar osmotic swelling and down-regulation of K^+ channels in Müller cells of the rat retina was observed during retinal ischemia-reperfusion and during endotoxin-induced uveoretinitis (Pannicke et al., 2004, 2005).

The anti-inflammatory glucocorticoid, triamcinolone acetonide, is commonly used clinically for the rapid resolution of diabetic macular edema (Martidis et al., 2002; Jonas et al., 2003). Triamcinolone inhibits vascular leakage and inflammation, by reduction of the secretion of VEGF (Ando et al., 1994; Matsuda et al., 2005). However, triamcinolone also inhibits the osmotic Müller cell swelling in the postischemic, inflamed, and diabetic retina (Uckermann et al., 2005; Pannicke et al., 2006). The effect of triamcinolone is mediated by stimulation of the release of endogenous adenosine; activation of adenosine A1 receptors leads to an opening of K^+ and Cl^- channels in the plasma membrane of Müller cells (Uckermann et al., 2005; Fig. 6C). An efficient therapy of the macular edema is thought to involve both inhibition of vascular leakage and stimulation of the coupled osmolyte and water transport through Müller cells.

3.4. Proliferative retinopathies

Proliferative vitreoretinopathy (PVR) is a frequent complication of retinal detachment (and, unfortunately, of retina surgery) (Fisher and Anderson, 1994). PVR is suggested to represent a maladapted, over-stimulated wound healing process, and is a disease characterized by strong proliferation of retinal cells including Müller cells, and the formation of fibrocellular membranes on both surfaces of the retina (Fig. 9). Müller cells are an important constituent of the fibroproliferative scar tissue formed during PVR or during proliferative diabetic retinopathy (PDR) (Nork et al., 1987). The periretinal membranes are connected with the sensory retina via hypertrophied Müller cell fibers (Fig. 7C). Müller cells in fibroproliferative membranes may transdifferentiate into myofibroblasts that generate tractional forces in response to growth factors of the vitreous, thus causing traction retinal detachment (Guidry, 2005). During diabetes, Müller cell processes grow into the lumen of occluded vessels where they form a glial scar; the glial scars within vessels may cause vessel occlusion (Bek, 1997).

Müller cells from surgically excised retinal tissue of patients with PVR or PDR display strong alterations of their plasma membrane characteristics: the cells show hypertrophy, an almost complete absence of currents through inwardly rectifying K^+ channels, and a decrease of the membrane potential (Francke et al., 1997; Bringmann et al., 1999a, 2002). On the other hand, the activity of Ca^{2+}-dependent K^+ channels, necessary for the proliferation of Müller cells (Puro et al., 1989; Kodal et al., 2000; Bringmann et al., 2001), is increased in Müller cells from

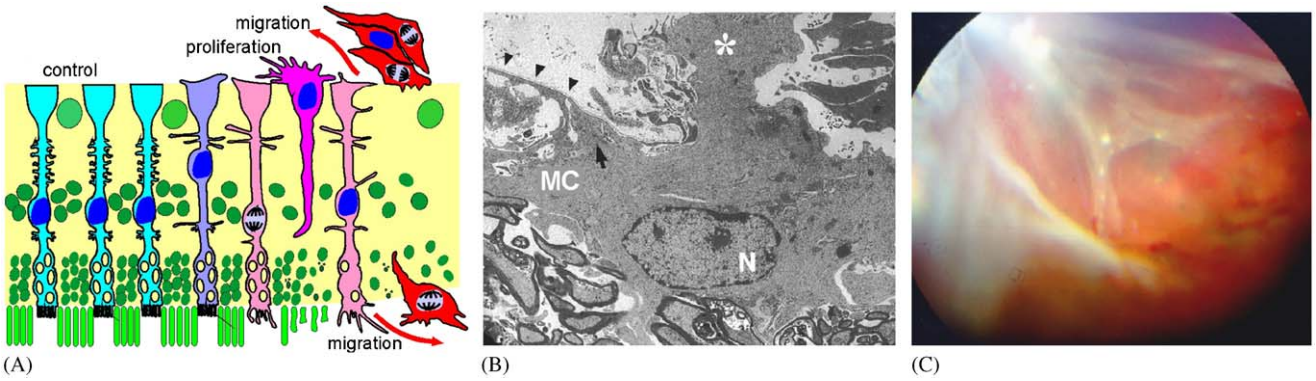

Fig. 9. Proliferative Vitreoretinopathy. (A) Schematic drawing of increasing degrees of Müller cell reactivity (from left to right). (B) Transmission electron micrograph of a reactive Müller cell (MC) migrating through a hole in the inner limiting membrane (arrowheads) into the vitreous body (asterisk); the nucleus (N) of the Müller cell is already translocated into the innermost retinal layer. (C) Ophthalmoscopic image of an experimentally induced PVR in the rabbit eye; note the large, folded cellular masses on the vitread surface of the retina.

PVR retinas (Bringmann et al., 1999a). This current pattern suggests a de-differentiation of the cells, reminiscent of the pattern characteristic of non-differentiated glial cells early in ontogenesis (Fig. 3) (Bringmann et al., 1999b). Retinas of patients with proliferative vitreoretinopathy display a strong downregulation of the gene expression of Kir4.1 and aquaporin-4 proteins (Tenckhoff et al., 2005). It has been proposed that the downregulation of the K^+ channels is a prerequisite for the re-entry of gliotic Müller cells into the proliferation cycle (Bringmann et al., 2000). The strong downregulation of K^+ and water channels in Müller cells also suggests that retinal K^+ and water homeostasis are largely disturbed during proliferative retinopathies, while the cell depolarization impairs the electrogenic neurotransmitter uptake. Indeed, PVR and PDR are accompanied by a massive loss of retinal neurons, and finally end up in blindness. An increase of fast transient Na^+ currents in Müller cells from patients with PVR (Francke et al., 1996) may indicate a transdifferentiation towards neuron-like cells.

Another feature of gliotic Müller cells which is associated with their proliferation is an upregulation of their responsiveness to extracellular ATP mediated by activation of purinergic P2 receptors. Human Müller cells from PVR retinas display an increase of ionotropic $P2X_7$ receptor-mediated cation currents (Bringmann et al., 2001) while rabbit Müller cells from PVR retinas show an upregulation of their responses to activation of metabotropic P2Y receptors (Fig. 3) (Francke et al., 2002). The increased responsiveness of Müller cells to extracellular ATP may support their mitotic activity in proliferative retinopathies (Moll et al., 2002) and may stimulate the release of different growth factors, e.g., of heparin-binding epidermal and platelet-derived growth factors (Milenkovic et al., 2003). Since the platelet-derived growth factor is one of the crucial factors involved in the development of PVR (Andrews et al., 1999), the release of ATP and of growth factors by Müller cells may be involved in the development of proliferative retinopathies.

3.5. Ischemia-reperfusion

Within one hour of ischemia-reperfusion, Müller cells become reactive, as reflected by an enhanced phosphorylation of ERKs (Akiyama et al., 2002). Inhibition of ERK activation results in an elevated degree of ganglion cell death (Akiyama et al., 2002), likely due to inhibition of the release of neurotrophic factors by Müller cells. The neuronal cell loss accompanying ischemia results mainly from an accumulation of excessive amounts of glutamate, and from an over-stimulation of ionotropic glutamate receptors (Osborne et al., 2004). The glutamate transporter GLAST expressed by Müller cells mitigates the ischemic damage to the retina (Harada et al., 1998). During retinal ischemia, glutamate is increasingly released from neurons (Kobayashi et al., 1999) while the glutamate uptake is reduced due to high extracellular K^+ which depolarizes Müller cells and, thus, leads to a saturation of the uptake already at low glutamate concentrations (Napper et al., 1999). In experimental ischemia in the rat retina, the expression of the glutamate transporter GLAST in Müller cells is unaltered but its ability to transport glutamate is greatly reduced (Barnett et al., 2001); this is likely caused by a depolarization of Müller cells due to a down-regulation of their K^+ channels similar as after retinal detachment and in diabetic retinopathy (Fig. 3B) (Pannicke et al., 2004). The strong reduction of Müller cell-mediated glutamate uptake in ischemic insults is accompanied by a significant accumulation of glutamate in retinal neurons which, under normal conditions, is prevented by rapid glutamate uptake into Müller cells (Barnett et al., 2001). Experimental knockout of GLAST leads to an increase of the retinal sensitivity to ischemia and to ganglion cell death (Harada et al., 1998). Likewise, a mislocation of the Kir4.1 protein in Müller cells of mice carrying a genetic inactivation of the dystrophin gene product, Dp71, was associated with an enhanced vulnerability of retinal ganglion cells to ischemic stress (Dalloz et al., 2003), supporting the view that K^+ buffering and glutamate

uptake by Müller cells are crucial in cases of ischemia/reperfusion.

In some respect, glaucoma is related to ischemia/reperfusion. In glaucomatous eyes, Müller cells display hypertrophy and increased expression of GFAP (Tezel et al., 2003). It has been suggested that astrocytes and Müller cells are involved in mediating the early death of retinal ganglion cells upon elevated intraocular pressure (Lam et al., 2003). Functional disorders of the glutamate uptake in Müller cells may be one of the etiologies of glaucoma, especially in patients with satisfactory control of intraocular pressure (Dreyer et al., 1996; Kawasaki et al., 2000).

3.6. Hepatic retinopathy

In contrast to the above-mentioned retinal diseases where retinal neurons or the vasculature are the targets of the pathogenic stimuli, there are retinal diseases involving a primary Müller cell injury. Müller cell dysfunction then causes impaired neuronal function and visual deficits (→1.1., 1.2.). Müller cells were implicated to be primarily affected in hepatic retinopathy (Reichenbach et al., 1995a; Albrecht et al., 1998), methanol-induced retinopathy (Garner et al., 1995), a disease caused by autoantibodies directed to Müller cells (Peek et al., 1998), Müller cell sheen dystrophy (Kellner et al., 1998), and glaucoma (Dreyer et al., 1996; Kawasaki et al., 2000). Moreover, retinoschisis (De Jong et al., 1991), macular hole formation (Gass, 1999), and one type of retinitis pigmentosa (Maw et al., 1997) have been suggested to be caused by Müller cell dysfunction.

Hepatic retinopathy is assumed to be caused by the high level of serum ammonia in patients with liver insufficiency; the primary pathological alterations are found in the Müller cells and retinal astrocytes (Reichenbach et al., 1995a). In the retina, the detoxification of excess ammonia occurs only in the Müller cells by the formation of glutamine from ammonia and glutamate; the high energy consumption of the detoxification is assumed to produce a decreased energy state in Müller cells which damages the cells. The high metabolic activity caused by the necessity to detoxify ammonia is reflected by the enlargement of cell nuclei (Reichenbach et al., 1995a), the glycogen depletion (Ieb, 1971), and the swollen mitochondria (Albrecht et al., 1998). Characteristic Müller cell alterations such as cell swelling, vacuolization, increased GFAP and GS content, down-regulation of K^+ channels, and membrane depolarization are inducible in vitro by enhanced levels of ammonia (Reichenbach et al., 1995b; Germer et al., 1997; Bringmann et al., 1998). By contrast, retinal neurons display no apparent morphological changes. The necessity to detoxify the retina from ammonia results in an enhanced glutamate consumption for glutamine synthesis; the competition with glutathione formation may cause a lack of glutathione, and thus may accelerate pathogenic mechanisms involving free radicals (Reichenbach et al., 1999). A similar pathogenic mechanism (i.e., based on energy depletion in Müller cells caused by the need to detoxify the retina) has been suggested for the methanol-induced retinopathy (Garner et al., 1995).

3.7. Retinoschisis

Retinoschisis is characterized by a cystic degeneration mainly in the deep nerve fiber layer that causes intraretinal splitting. Though the mutation responsible for human X-linked retinoschisis has been localized in the gene coding for the protein, retinoschisin, which is expressed in photoreceptor and bipolar cells and is probably not directly related to Müller cells (Sauer et al., 1997; Grayson et al., 2000; Reid et al., 2003), an involvement of Müller cells in the pathogenic mechanisms of the disease has been proposed (Yanoff et al., 1968). Retinoschisin is selectively taken-up and transported by Müller cells into the inner retina in a direction-specific manner (Reid and Farber, 2005). Deposits of amorphous filamentous material are present within degenerated Müller cells and in adjacent extracellular spaces (Kirsch et al., 1996) which are likely of glial origin. This might be indicative of a degeneration (possibly secondary) of Müller cells. In the course of retinoschisis the inner Müller cell processes become thin and elongated; these 'stretched' fibers run through the widening 'empty' cysts until they become eventually disrupted, and the innermost retinal remnant-layer detaches from the rest of the tissue (Yanoff et al., 1968). It is still a matter of debate whether the mechanical weakness of thin elongated Müller cell processes is a causative factor (Kirsch et al., 1996) or a side-effect of retinoschisis (Mooy et al., 2002). In this respect it is notewothy that in vimentin$^-$/GFAP$^-$ mice lacking intermediate filaments in their Müller cells, retinoschisis does not normally occur; however, in case of ischemia/reperfusion-induced neovascularization or mechanical stress the inner retinal layers appear mechanically weakened (Lundkvist et al., 2004).

Clearly, should the inner Müller cell processes become thin and elongated, or even disrupted, their capability of K^+ syphoning into the vitreous and inner retinal blood vessels must be impaired. An excess of extracellular K^+, due to a decreased K^+ buffering capacity of Müller cells, has been suggested to cause the Mizuo-Nakamura phenomenon in retinoschisis (De Jong et al., 1991). An insufficient clearance of K^+ ions (and, in turn, a depolarization-mediated inhibition of glutamate uptake) should aggravate neurodegeneration within the cystic tissue.

3.8. Retinitis pigmentosa and support of neuronal survival

The loss of photoreceptors in retinitis pigmentosa is usually followed by alterations in the pigment epithelium and in the retinal glia. However, there are also mutations in Müller cell proteins which may cause photoreceptor cell death. In an autosomal recessive retinitis pigmentosa,

a mutation of the gene encoding CRALBP was described (Maw et al., 1997). CRALBP is not expressed in photoreceptors but is abundant in pigment epithelial and Müller cells, where it carries 11-*cis*-retinol and 11-*cis*-retinaldehyde. The mutant protein lacks the ability to bind 11-*cis*-retinaldehyde. The lack of functional CRALBP may lead to a disruption of retinal vitamin-A metabolism (Maw et al., 1997). In Royal College of Surgeons (RCS) rats, the content of glutamine and arginine is elevated in Müller cells prior to the onset of photoreceptor death, due to anomalies in glutamate degradation (Fletcher and Kalloniatis, 1996).

In inherited or injury-induced retinal degeneration, e.g., in retinitis pigmentosa, photoreceptor cells and inner retinal neurons die predominantly by programmed cell death (apoptosis) (Chang et al., 1993; Portera-Cailliau et al., 1994; Cook et al., 1995; Abler et al., 1996). Neurotrophic factors such as basic fibroblast growth factor (bFGF or FGF-2), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), and GDNF, inhibit apoptosis and promote the survival of retinal neurons and photoreceptor cells (Faktorovich et al., 1990; LaVail et al., 1992; Di Polo et al., 1998; Frasson et al., 1999; Chong et al., 1999). Müller cells play an active role in the regulation of the death and survival of retinal neurons and photoreceptor cells, in particular by the release of neurotrophic factors and by mediating the effects of these factors. The protective effects of neurotrophic factors on photoreceptor cells may be induced directly (in the case of bFGF), or—in the case of BDNF and CNTF for which receptors are not present on photoreceptor cells—indirectly, through activation of Müller cells and inner retinal neurons (Kirsch et al., 1997; Wahlin et al., 2000, 2001). Intraocular administration of BDNF or CNTF results in exclusive activation of Müller cells (which is reflected in an increased phosphorylation of ERKs and in an increased c-Fos and GFAP staining), but not photoreceptors (Wahlin et al., 2000). Factors secreted by activated microglial cells, or extracellular glutamate, boost the production of secondary trophic factors by Müller cells, thus increasing the survival of photoreceptor cells (Harada et al., 2002; Taylor et al., 2003). Neurotrophic factors such as CNTF may cause a shift of retinal glial cells toward a more neuroprotective phenotype which is characterized by, for instance, a more efficient buffering of high concentrations of glutamate (van Adel et al., 2005).

Neurotrophins control neuronal survival via two types of receptors: the Trk family of high-affinity tyrosine kinase receptors transmit prosurvival signals, while the low-affinity p75 neurotrophin receptor transmits anti-survival signals (Casaccia-Bonnefil et al., 1999). Müller cells are implicated in either photoreceptor cell death or rescue, in dependence on the receptor activated. Neurotrophin-3 mediates its protective effect on photoreceptor cells by binding on the TrkC receptors of photoreceptors and of Müller cells, which latter event results in an increased release of bFGF from Müller glia (Harada et al., 2000). On the other hand, nerve growth factor reduces the bFGF production in Müller cells via binding on the p75 receptors; the reduced bFGF release by Müller cells may contribute to increased photoreceptor apoptosis (Harada et al., 2000). Additional (previous) retinal injuries like mechanical stress (Faktorovich et al., 1990; Silverman and Hughes, 1990) or preconditioning with bright light (Liu et al., 1998) may protect photoreceptors from degeneration because these stimuli cause an up-regulation of bFGF and CNTF expression in Müller cells (Wen et al., 1995; Liu et al., 1998). Likewise, argon laser photocoagulation slows photoreceptor degeneration in the RCS rat which correlates with an induction of bFGF in retinal blood vessels, Müller cells and astrocytes (Chu et al., 1998).

4. Future directions

Since Müller cells contact all retinal neurons and show a high resistance against various pathogenic stimuli, they are well-situated as targets for therapeutic interventions to inhibit neuronal degeneration. Somatic gene therapy may be carried out via Müller cells. A gene transfer, e.g., of neurotrophic factors, to Müller cells may help to support their protective role in the survival of retinal neurons. Müller cells were found to be primarily transfected when genes, e.g., the gene for BDNF, were delivered by adenoviral vector-injections into the vitreous chamber (Isenmann et al., 1998; Sakamoto et al., 1998; Di Polo et al., 1998). Because Müller cells span the entire thickness of the retina, adenovirus-mediated gene delivery to these cells should be useful to modulate the survival of all neuronal cell types within the retina. Moreover, stimulation of the supportive function of Müller cells has the advantage to stimulate the survival of retinal neurons and photoreceptors independent of the concrete mutation or pathological condition underlying neuronal cell death.

Postmitotic Müller cells retain a remarkable plasticity even in adult retinas; they are capable of de-differentiation and proliferation. Moreover, a subpopulation of Müller cells express markers for neural progenitor (stem) cells even in the adult tissue (“Müller stem cells”) (Limb et al., 2005). Transplantation of Müller stem cells into RCS rats preserved visual function and maintained retinal integrity (Limb et al., 2004). Transient Müller cell proliferation induced by NMDA excitotoxicity in postnatal chicken retinas causes a de-differentiation of Müller cells into retinal progenitor-like cells (Fischer and Reh, 2001). These cells may remain undifferentiated for longer time periods, may generate new Müller cells, or may transdifferentiate into retinal neurons. Similarly, Müller cells may be stimulated to transdifferentiate into neurons and photoreceptor cells in the adult rat retina after toxic injury produced with NMDA (Ooto et al., 2004). These observations suggest that Müller cells are a potential source of neural regeneration within the postnatal retina (Fischer and Reh, 2001). It is conceivable that de-differentiated Müller cells, or “Müller stem cells”, could be used in the future for cell-based therapies to treat or prevent retinal

disease (Limb et al., 2005), with the possibility of simultaneous application of transgenes that guides the direction of the differentiation, thus determining specific neuron types which should develop from Müller stem cells. Moreover, degenerated retinas may be substituted by new retinas generated in culture from Müller stem cells. Perhaps, glial scars, e.g., epiretinal membranes in PVR eyes, may be a source to obtain de-differentiated Müller cells from which new autologous retinas could be formed in vitro. More knowledge is necessary about the pluripotency of Müller cells and the practical ways how these potencies can be used to treat retinopathies.

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