Human Müller Glial Cells: Altered Potassium Channel Activity in Proliferative Vitreoretinopathy

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PURPOSE. To determine differences of K⁺ channel activity between Müller glial cells obtained from retinas of healthy human donors and of patients with retinal detachment and proliferative vitreoretinopathy.

METHODS. Müller cells were enzymatically isolated from retinas of healthy donors and from excised retinal pieces of patients. The whole-cell and the cell-attached configurations of the patch-clamp technique were used to characterize the current densities of different K⁺ channel types and the activity of single Ca²⁺-activated K⁺ channels of big conductance (BK).

RESULTS. Cells from patients displayed a less negative mean membrane potential (−52.8 mV) than cells from healthy donors (−80.6 mV). However, the membrane potentials in cells from patients scattered largely between −6 and −99 mV. The inwardly rectifying K⁺ permeability in cells from patients was strongly reduced (0.3 pA/pF) when compared with cells from healthy donors (6.0 pA/pF). At the resting membrane potential, single BK channels displayed a higher mean activity (open probability, Pₒ, and channel current amplitude) in cells from patients (Pₒ: 0.30) than in cells from healthy donors (Pₒ: 0.03). The variations of BK current amplitudes were correlated with the variations of the membrane potential.

CONCLUSIONS. The dominant expression of inwardly rectifying channels in cells from healthy donors is thought to support important glial cell functions such as the spatial buffering of extracellular K⁺. The downregulation of these channels and the less negative mean membrane potential in cells from patients should impair spatial buffering currents and neurotransmitter clearance. The increased activity of BK channels may support the proliferative activity of gliotic cells via feedback regulation of Ca²⁺ entry and membrane potential. (Invest Ophthalmol Vis Sci. 1999;40:3316–3325)

One of the main functions of Müller cells is the spatial buffering of the extracellular K⁺ concentration in response to rises of neuronal activity. The removal of excess K⁺ from areas of high neuronal activity must be mainly mediated by inwardly rectifying K⁺ (KᵢR) channels because these channels are the only K⁺ channels with a high open-state probability at the hyperpolarized resting membrane potential characteristic for Müller cells. Therefore, a high expression level of KᵢR channels is one of the main indicators of the differentiated state of Müller cells. In addition to KᵢR channels, however, Müller cells express various depolarization-activated K⁺ channels including fast-inactivating (A-type; KₒA), delayed rectifying (KₒDR) and large-conductance Ca²⁺-activated (BK) K⁺ channels. The functional role of the depolarization-activated K⁺ channels in Müller cells is presently unclear.

The expression of ion channels by Müller cells may change in response to various conditions. Human Müller cells derived from patients with different eye diseases lack KᵢR currents, or express this current type at greatly reduced densities. The lack of KᵢR channels is accompanied by a shift of Müller cell’s membrane potential toward more depolarized potentials. During postnatal development of radial glial (Müller) cells of the rabbit retina, the expression of KᵢR channels increases strongly during the second postnatal week. In the first postnatal week, the amplitude of KᵢR currents is very small, whereas depolarization-activated outwardly rectifying K⁺ currents (particularly KₒA and BK currents) predominate the K⁺ permeability of the membrane. The resting membrane potential increases from low neonatal values (−40 mV) to high values negative to −80 mV at day 9. This shift of the membrane potential is accompanied by a correlated strong developmental decrease in the activity of BK channels as recorded in on-cell patches at the resting membrane potential.

The aim of the present study was to evaluate whether the BK channel activity differs among human Müller cells freshly isolated from retinas of healthy donors and of patients with proliferative vitreoretinopathy (PVR). Because cells from patients display a less negative mean membrane potential than
cells from healthy donors,8 and because BK channels are depolarization-activated,7 one should assume that the mean “native” (i.e., measured at the resting potential) open probability of BK channels is elevated under pathologic conditions. In addition, pathologic alterations in the activity of the other K+ channels were investigated to establish a “map” of the K+ current pattern characteristic for “reactive” human Müller cells in PVR.

Methods

All human tissue was used in accordance with applicable laws and with the Declaration of Helsinki. The use of human retinas/retinal pieces was approved by the ethics committee of the Leipzig University Medical School. Eyecups of postmortem eyes (serving as sources for corneal transplantations) were obtained from healthy organ donors and were supplied within 12 to 24 hours after death. Eyecups from 15 organ donors were obtained (1 woman, 12 men; age, 31.8 ± 17.4 years; range, 16–58 years). Retinal tissue from patients was obtained by vitreoretinal surgery, between 2 and 6 hours after the tissue was excised. Such retinal pieces were removed from eyes with detached retinas (and, in one case, with trauma) when partial retinectomies were necessary to relieve traction due to PVR. Retinal pieces were obtained from 27 patients (12 women, 16 men; age, 60.1 ± 16.5 years; range, 16–80 years). Müller cells were isolated using papan and DNase-containing solutions as previously described.8

Electrophysiological Recordings

The whole-cell and the cell-attached configurations of the patch-clamp technique were used.10 The recordings were made at room temperature. The bath solution contained (in millimoles) 110 NaCl, 5 KCl, 2 CaCl2, 1 MgCl2, 10 HEPES, and 11 glucose (pH 7.4 adjusted with Tris-base). The pipette solution was made of (in millimoles) 10 NaCl, 130 KCl, 1 CaCl2, 2 MgCl2, 10 EGTA, and 10 HEPES (pH 7.2), resulting in a free [Ca2+] of 26 nM. Gigaseals (5–10 GΩ) were formed with borosilicate pipettes (GB150F8P, Biological, Science Products, Frankfurt/Main, Germany) that displayed resistances between 5 and 10 MΩ. Recordings were made using an EPC 7 amplifier (List Electronics, Darmstadt, Germany) and the TIDA 5.72 computer program (HEKA elektronik, Lambrecht, Germany). High frequencies >1 kHz were cut off. The series resistance was compensated by 30% to 60%.

Cell-attached patches were voltage-clamped at a pipette potential of 0 mV (i.e., at the native resting membrane potential), and de- and hyperpolarizing voltage steps of 1-seconds’ duration were applied. The pipette tips were placed onto the soma or the lateral face of the end foot. No significant differences in the single-channel activity were found between patches at the two different locations. Only those patches were used for evaluation of channel activity that contained active BK channels when the patch potential was stepped up to ±80 mV away from the resting potential.

During whole-cell recordings, the cells were voltage-clamped at −80 mV, and voltage steps from −160 to +200 mV were applied with an increment of 20 mV. The K+ amplitude was determined as the peak current evoked by a voltage step to +10 mV after a 500-msec pre-pulse to −120 mV, subtracted from the current evoked after a 500-msec pre-pulse to −40 mV.

The recordings of K+ currents were performed in control solution as well as in extracellular solution containing 5 mM 4-aminopyridine (4AP); the two recordings were then subtracted to obtain the 4AP-sensitive transient currents. The whole-cell BK currents were measured between voltage steps to +160 and +200 mV, when the KIR currents were blocked by Ba2+ (1 mM). The membrane capacitance of the cells was measured in whole-cell recordings at the uncompensated capacitive artifact evoked by a hyperpolarizing voltage step from −80 to −90 mV, when the K+ currents were blocked by Ba2+ (1 mM).

Data Analysis

For whole-cell data, the membrane (holding) potentials are given with respect to the intracellular side of the membrane. In cell-attached data, the pipette potential means the voltage applied to the pipette (extracellular side of the patch). Amplitude histograms of the single-channel currents were used to calculate the open probability (Po) as described earlier.11 Po means the open probability of a single K+ channel. Whole-cell BK channel-mediated and KIR-mediated currents were measured as steady-state currents in voltage-step traces that were obtained during external application of Ba2+ (1 mM) to block KIR currents. KIR currents were measured at steps between −20 and +20 mV. The currents and membrane potentials of the whole-cell recordings were corrected both for the shunt through the seal and for the junction potential. Statistical analysis (unpaired Student’s t-test, Mann–Whitney U test, regression analysis) and curve fits were made using the Graphpad Prism program (Graphpad Software, San Diego, CA). Data are expressed as mean ± SD.

Results

Cell Membrane Capacitance and “Resting” Membrane Potential

Müller cells isolated from patients displayed a higher mean membrane capacitance (81.5 ± 27.4 pF, n = 227) than cells from healthy donors (56.3 ± 16.2 pF, n = 153, P < 0.0001). Because the membrane capacitance is proportional to the cell membrane area, these data may indicate a hypertrophy of Müller cells in diseased retinas. The membrane potentials were measured as zero current potentials in I-V curves of the whole-cell currents. Examples of whole-cell recordings are shown in Fig. 1A. In Figure 1B, the density of the inwardly directed whole-cell conductance is plotted against the membrane potential for two populations of Müller cells: cells obtained from healthy donors and from patients, respectively. Although the membrane potentials of cells from patients were scattered over a wide range between −99 and −6 mV (mean = −52.8 ± 20.8 mV, n = 158), the potentials of most cells from healthy donors were found within a relatively small range close to −80 mV (mean = −80.6 ± 9.0 mV, n = 134). Exposure to extracellular Ba2+ ions depolarizes Müller cells, by blocking their KIR channels.5,12 As shown in Figure 1C, the extracellular application of Ba2+ (1 mM) decreased the mean membrane potential in cells from healthy donors and patients to similar “minimum” values of −38.7 ± 19.4 mV (n = 79) and −34.4 ± 20.9 mV (n = 45), respectively.
Examples of whole-cell recordings of three cells from one healthy and two patients, respectively, are shown in Figure 1A. Although the membrane conductance of the normal cell was dominated by large inwardly (downward) directed currents, these inwardly directed currents were strongly downregulated in cells from diseased retinas. The membrane conductance of cells from diseased retinas was mainly constituted by voltage-gated outwardly rectifying K\textsubscript{IR} currents (KA and KDR currents), by BK channel–mediated K\textsuperscript{+} currents (uppermost two noisy traces in the recordings of Fig. 1A), and by inwardly directed fast transient currents probably mediated by Na\textsubscript{1} channels (arrow in Fig. 1A).

Current density values from all cells tested are shown in Figure 1B. Although the inwardly directed currents in cells from healthy donors generally exceeded 1.5 pA/pF (mean 6.3 ± 2.8 pA/pF, n = 115, measured at voltage steps from −80 to −120 mV) they were mostly decreased below this “limit” in Müller cells from patients (mean 0.5 ± 0.6 pA/pF, n = 158, P < 0.0001). Extracellular application of Ba\textsuperscript{2+} (1 mM) strongly reduced the amplitude of the inwardly directed currents in cells from healthy donors to 0.3 ± 0.2 pA/pF (n = 76; Figs. 1D and 2A, 2B). Because these currents were very small in cells from patients already in control solutions, their Ba\textsuperscript{2+}-induced reduction was less dramatic, although the Ba\textsuperscript{2+}-insensitive “remnant currents” were similar (0.2 ± 0.2 pA/pF, n = 43; Figs. 1D and 2C). Because the Ba\textsuperscript{2+}-sensitive currents are mainly mediated by K\textsubscript{IR} channels, these results indicate that the mean K\textsubscript{IR} current density in cells from patients was only approximately 5% of that in cells from healthy donors.

The downregulation of K\textsubscript{IR} channels in cells from diseased donors was accompanied by a strong increase of the mem-
brane resistance (measured around the zero current potential). Although cells from healthy donors displayed a mean membrane resistance of $189 \text{ M} \Omega (n = 115)$, the membrane resistance of cells from diseased donors was $3.2 \text{ G} \Omega (n = 161, P < 0.0001)$. The latter value was not significantly different from the values found in another series of experiments, involving a block of the KIR currents by extracellular application of 1 mM Ba$^{2+}$, in cells from both healthy ($3.6 \text{ G} \Omega, n = 77$) and diseased ($3.6 \text{ G} \Omega, n = 45$) donors.

**KIR Channels**

In on-cell recordings using 130 mM KCl in the pipette solution and 3 mM KCl in the bathing solution, inwardly directed currents through single K$^+$ channels of different types were recordable at a pipette potential of 0 mV (i.e., the native resting membrane potential). The most abundant channel type in membranes of Müller cells from healthy donors was the inwardly rectifying K$^+$ (KIR) channel (Fig. 3). The KIR channels exerted a high open probability ($P_o > 0.8$ at the resting potential (Fig. 3A). The $P_o$ of KIR channels was barely voltage-dependent, with high values recorded over a relatively wide voltage range around the resting potential, and with slight $P_o$ reductions when the membrane was strongly hyperpolarized. The open channel $I-V$ relationship of KIR Channels was linear, with a mean slope conductance of $21.7 \pm 2.9 \text{ pS}$ (Fig. 3B).

As mentioned above, the density of KIR channels was strongly decreased in cells from patients. However, as indicated in Figure 1D, the loss of KIR channels seemed often not to be complete. Indeed, the activity of a single KIR channel could often be recorded in cell-attached patches on cells from patients, even if only a very small density of the inwardly directed whole-cell currents was recorded after breaking into the cell's interior. An example of such a pair of on-cell and whole-cell recordings in one cell from a patient is shown in Figures 3C and 3D. In patches on Müller cells of healthy retinas, on the other hand, the activity of several KIR channels in one patch was regularly recorded (Fig. 6A) due to the higher KIR channel density in these cells.

**KA and KDR Currents**

Human Müller cells display voltage-gated fast transient K$^+$ (K$A$) currents. In 77% of the investigated cells from healthy donors ($n = 73$) and in 100% of the cells from patients ($n = 107$), K$A$ currents could be evoked. The K$A$ currents in cells from patients were found to be slightly enhanced in their amplitudes (Fig. 4C, right). The K$DR$ currents displayed similar amplitudes in cells from healthy donors and patients (Fig. 4C, right).

**BK Channel Activity**

The densities of the BK channel-mediated whole-cell currents were not different in cells from healthy donors ($11.4 \pm 7.5$ M$\Omega$, $n = 13$).
FIGURE 4. 4AP blocks a fast transient K+ current in human Müller cells. (A) Whole-cell currents evoked in a Müller cell isolated from a diseased retina, recorded in control solution (top) and during extracellular exposure of 5 mM 4AP (middle); the 4AP-sensitive currents were obtained by subtraction (bottom). (B) I–V curves of the peak and steady-state amplitudes of the 4AP-blocked currents; mean values of 7 cells obtained from patients. (C) Mean current density of the peak KDR current and of the steady-state K\textsubscript{DR} current, respectively, obtained from cells of healthy donors and patients (cell numbers in parentheses). The data used for estimation of the KDR currents represent the amplitudes of the KDR currents plus the (small) steady-state component of the Kc currents. The point indicates a significant difference of P = 0.033. A pA/pF, n = 69) and from patients (10.8 ± 7.4 pA/pF, n = 139), indicating that the expression level of this channel type does not differ between the two cell populations. Because the whole-cell currents mediated by BK channels were found to be activated at very strongly (i.e., “unphysiologically”) depolarized voltages positive to +100 mV,\textsuperscript{11} the currents through BK channels were further investigated in on-cell membrane patches.

Examples of single-channel recordings are shown in Figure 5a. The recordings were made at a pipette potential of 0 mV (i.e., at the resting membrane potential). Downward deflections indicate cation fluxes from the extra- to the intracellular side of the membrane through single K+ channels. In the records on cells from healthy donors, small deflections represent the activity of several K\textsubscript{on} channels, which caused the noisy baselines of the records. Large deflections represent the activity of BK channels. At the resting potential, BK channels in cells from healthy donors were evoked by a voltage step to +40 mV. Mean P\textsubscript{o} was 0.30 ± 0.26 for cells from diseased retinas (n = 58) and 0.03 ± 0.05 for cells from healthy retinas (n = 21; P < 0.0001). The mean amplitude of currents through single BK channels was \(-5.82 ± 2.30\) pA for cells from diseased retinas (n = 59) and \(-9.06 ± 1.90\) pA for cells from healthy donors (n = 21; P < 0.0001).

It should be kept in mind that for technical reasons, the BK channel currents were recorded using a high-K+ solution within the pipette, enforcing the measured K+ “inward” currents at 0 mV pipette potential. Under physiological conditions (low extracellular K+), however, the K+ currents flow “outward” and are larger in cells from patients than in cells from healthy donors (cf. arrows in Fig. 6C, for a crude estimate of the physiological relationships). This means that under physiological conditions, both the P\textsubscript{o} and the current amplitude of BK channels were significantly larger in cells from patients than in cells from healthy donors.

Figures 5B and 5C illustrate the relationships between BK current amplitude and P\textsubscript{o}, respectively (both measured in on-cell patches at the resting membrane potential), and the entry potentials of the cells. The entry potential was measured in the current-clamp mode immediately after establishing the whole-cell configuration, when the single-channel recordings were finished. The entry potentials differed considerably among the individual cells. However, the mean entry potential of cells from healthy donors was found to be higher (\(-52.1 ± 15.0\) mV, n = 13) than that of cells from patients (\(-25.4 ± 16.9\) mV, n = 29; P < 0.0001). Significant correlations existed between the BK channel current amplitude and the entry potential, in cells from healthy donors and patients alike (Fig. 5B). No correlations were found between the entry potentials and P\textsubscript{o} (Fig. 5C).

The above-mentioned differences of the BK channel activity at the resting membrane potential (Fig. 5A) were accompanied by different activation and I–V curves. Figure 6A illustrates examples of on-cell channel recordings at different holding potentials. In the recordings from the cell of a healthy donor (left column), two types of channel openings are discernible. At positive pipette potentials, the noisy baselines of the traces reflect the activity of several K\textsubscript{on} channels. At negative pipette potentials (i.e., when the membrane patch was depolarized), the activity of a single BK channel is visible. The currents through this channel reversed at a pipette potential of about \(-65\) mV. In the recordings from the cell of a patient (right column), the activity of a BK channel prevailed at both negative and (although with smaller P\textsubscript{o}) positive pipette potentials. The channel currents reversed at a pipette potential of about \(-40\) mV. Mean P\textsubscript{o}-voltage (i.e., activation) and I–V curves of BK channels in both populations of cells are shown in Figures 6B and 6C, respectively. The mean activation curve of BK channels in cells from patients is shifted by 50.4 mV toward more hyperpolarized membrane potentials (i.e., positive pipette potentials), compared with the cells from healthy donors (P = 0.0069; Fig. 6B). Moreover, also the mean I–V curve was found to be shifted toward more negative membrane voltages in cells from patients (Fig. 6C). The mean reversal potentials of the single channel currents were found at pipette potentials of \(-76.7 ± 15.1\) and \(-48.0 ± 12.7\) mV in cells from healthy donors (n = 6) and patients (n = 21), respectively (P = 0.0002). These values are very similar to the mean native membrane potentials of both cell populations mentioned above (Fig. 1C). The slopes of the I–V curves, however, were not significantly different; the BK channels displayed mean slope conductances of 113.2 ± 18.9 and 120.6 ± 26.4 pS in cells from healthy donors and patients, respectively.
DISCUSSION

Membrane Potential Changes in Reactive Müller Cells: Reasons and Consequences

Our results show that in cases of PVR, human Müller cells undergo reactive alterations that involve dramatic changes of their membrane properties. These changes are certainly not due to age differences between the donors of control and diseased retinas because the same alterations were found when only healthy donors and patients of the same age range (20–50 years) were compared. Although KA- and KDR-mediated K\textsuperscript{+} currents seem to be, at best, slightly changed (Fig. 4C), reactive Müller cells are characterized by a strong reduction of both the density of KIR-mediated currents and the magnitude of the mean resting membrane potential (Figs. 1C, 1D). KIR channels have been implicated in the stabilization of the membrane potential of glial cells close to E_K.\textsuperscript{13} Indeed, blockade of KIR channels by Ba\textsuperscript{2+} causes a depolarization of the Müller cell membrane\textsuperscript{6,12} (Figs. 1C, 2B, 2C). In agreement with this view, the observed downregulation of KIR channels in reactive Müller cells (Fig. 1D\textsuperscript{6}) was accompanied by a shift of the mean membrane potential toward more positive values (Fig. 1C\textsuperscript{6}). However, the membrane potentials of individual cells from diseased donors scattered largely over a wide range (Fig. 1B). Similar extended ranges of membrane potentials, accompanied by relatively small membrane currents and a low whole-cell slope conductance, were previously described in other cell types (e.g., in endothelial cells).\textsuperscript{14} This suggests that generally a low density of KIR channels causes an “instability” or “flexibility” of the membrane potential. Thus, in Müller cells from diseased donors, the opening or closure of only a small number of KIR channels (Fig. 3C) or of cation channels,\textsuperscript{15} respectively, may be sufficient to cause large membrane hyperpolarizations or depolarizations. This may also explain, at least partially, the observed scattering of the membrane potentials in cells from diseased donors.

The membrane potential differences between cells from healthy donors and from patients are assumed to cause much of the differences in the mean BK channel activity of the two populations of cells; BK channels of cells from patients displayed a higher mean \(P_o\) (Fig. 5A) and (at physiological K\textsuperscript{+} gradients, see above and Fig. 6C) also larger mean amplitudes of single channel currents. First, the individually different entry potentials were significantly correlated with the varying BK channel current amplitudes (Fig. 5B). Second, the difference between the BK channel current amplitudes of control and reactive cells (3.2 pA at pipette potentials of 0 mV) can be explained by a difference in the mean membrane potential of approximately 28 mV, according to the slope conductance of the BK channels (Fig. 6C). Indeed, this value is very close to the measured difference (\(\Delta V\) 27.8 mV; Fig. 1C).

![FIGURE 5](image-url)
On the other hand, there was no significant correlation between the \( P_o \) of BK channels and the entry potentials of individual cells (Fig. 5C), whereas the mean \( P_o \) values showed a clear-cut voltage dependence, different for normal and reactive cells (Fig. 6B). It is also noteworthy that the mean activation \( (P_o–V) \) curve of BK channels in reactive cells was displaced toward positive pipette potentials much more (by 50.4 mV; Fig. 6B) than the mean \( I–V \) curve (by 28.7 mV; Fig. 6C). This suggests the presence of additional factors that increase the \( P_o \) of BK channels in gliotic cells. It is well known that the \( P_o \) of BK channels depends on several factors, including the intracellular [Ca\(^{2+}\)]. It is feasible that in cells from patients the intracellular [Ca\(^{2+}\)] may be elevated (e.g., via voltage-insensitive, nonspecific cation channels\(^{15}\) or Ca\(^{2+}\) channels,\(^{16}\) which both are activated by growth factors such as the basic fibroblast growth factor).\(^{15,16}\) Moreover, a direct modification of channel properties, for example, mediated by channel phosphorylation,\(^{17}\) or channel stimulation via other second messengers like arachidonic acid\(^{18}\) cannot be ruled out. Anyhow, whereas we have presently no indications for any upregulation of BK channel expression in reactive Müller cells, BK channel-mediated currents are dramatically increased in such cells, mainly but not solely due to their decreased transmembrane potential.

**Regulation of K\(^{+}\) Channels in Reactive Müller Cells**

In contrast to the case of BK channels, there is evidence that K\(_{ir}\) channels are indeed downregulated in reactive Müller cells, due to a decreased genetic expression, a decreased insertion into the membrane, or a functional inactivation. For instance, the low K\(_{ir}\) channel-mediated current density (Fig. 1D) is...
certainly not caused by an exhaustion of cellular energy stores. Kir4.1 channels, the predominant Kir channel type of rabbit Müller cells, have a Walker-type A ATP-binding domain in the C terminus, and Kir currents of human and monkey Müller cells were previously found to be decreased by internal ATP depletion. However, when 1 mM Mg-ATP was intracellularly applied with the pipette solution to Müller cells from patients for up to 1 hour (n = 3, data not shown) no increase of the Kir currents was observed.

As of this time, there is poor knowledge about the regulation of K+ channels in Müller cells. It has been speculated that neuronal activity-induced increases of the extracellular [K+] may stimulate the insertion of K+ channels into the Müller cell membrane. In cultured Müller cells, the presence of the extracellular matrix protein laminin and insulin was recently shown to induce the expression and membrane insertion of Kir channels. In the degenerating retina of PVR patients, Müller cells may lose their contacts to "healthy," normally functioning neurons as well as to the laminin-containing basal lamina. This may induce a downregulation of Kir channels. Although this problem is far from being solved, it is noteworthy that similar reductions of the resting membrane permeability for K+ have been observed in astrocytes of epileptic foci and astrocytic tumor cells, and cultured astrocytes from mechanically induced glial scars. Furthermore, the downregulation of Kir channels in proliferating astrocytes suggests that there is a relation between cell proliferation and low K+ permeability of the membrane.

CONCLUSIONS

In PVR, Müller cells proliferate and migrate out of the retina and are involved, among other cell types, in the formation of periretinal membranes. In Müller cells from patients with PVR, we found an enhanced mean BK channel activity (mainly due to the depolarization of a cell membrane with low Kir density). In previous studies, BK channel activity has been implicated in the regulation of proliferative activity of Müller cells. Because a block of voltage-gated Ca2+ channels also decreased the proliferation rate of Müller cells, it might be hypothesized that BK channels modulate the proliferative activity via feedback regulation of the Ca2+ entry. However, further experiments are necessary to examine the functional roles of BK and Kir channels in proliferating and nonproliferating Müller cells. Such experiments may contribute to new therapeutic concepts for the prevention of PVR, one of the most deleterious events in clinical ophthalmology.

References