Chapter 4

Reactive Muller Glia as Potential Retinal Progenitors

Teri L. Belecky-Adams, Ellen C. Chernoff,
Jonathan M. Wilson and Subramanian Dharmarajan

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/55150

1. Introduction

Regenerative medicine has become a driving force in the treatment of disease and injury over the last decade [1]. This is due to the accumulation of knowledge in several key areas; 1) the mechanisms of disease processes, 2) creation of stem cells/induced pluripotent stem cells that might be used for therapeutic purposes, and 3) factors that are necessary for the proper differentiation of specific cell types. In any tissue, it might be possible to regenerate lost cells from exogenous stem cells, endogenous stem or progenitor cells, or endogenous cells that can dedifferentiate, proliferate and re-differentiate. Several endogenous populations of cells localized to the eye have been shown to be capable of replacing some or all retinal cell types in various species; 1) an endogenous population of progenitor cells in the periphery of the eye referred to as the ciliary marginal zone (CMZ), 2) the retinal pigmented epithelium, 3) non-pigmented cells adjacent to peripheral retina, 4) $NG2^+$ glial progenitors of the optic nerve, and finally 5) Müller glia of the retina [2]. This chapter will focus specifically on the responsiveness of Müller glia to disease or injury to the retina with a special emphasis on signals that have been shown to lead to the injury response and changes to the extracellular matrix that play a role in dedifferentiation and proliferation.

2. Müller Glial cell basics

Müller Glia, named after their discoverer Heinrich Müller, were first described in 1851 [3]. Müller Glia are a unique blend of radial glia, astrocytes, and oligodendrocytes that span the width of the mature retina from the outer limiting memberane in the outer nuclear layer to the inner limiting membrane at the edge of the retina and vitreous humor [4]. Müller cells are one of three possible macroglial cells that can be found in the retina. Astrocytes also migrate into

the retina from the optic nerve and some species also contain oligodendrocytes in the nerve fiber layer [5]. However, Müller glia are the only glial cells that are derived from retinal progenitors. Müller cells play a wide variety of roles in both the developing and mature retina. In order to consider the full effect of gliosis in the diseased or injured retina, we must first understand their function in the normal retina.

2.1. Retinal histogenesis

Lineage analysis of retinal progenitors using various techniques have shown that many retinal progenitors have the capacity to produce all retinal cell types [6-10]. Retinal cells undergo a stereotypical pattern of differentiation in which some cells leave the cell cycle (are born) very early in retinal histogenesis, such as cone photoreceptors, ganglion cells, and horizontal cells, while other cells are generated at later timepoints [6, 7, 9-12]. Müller glia are born in the group of cells that are generated late in the ontogenic period.

Vertebrate retinal cells are arranged in a specific fashion in both layers and in columns [6-8, 13-17]. Figure 1 shows the arrangement of mature retinal cells in the outer, inner and ganglion cell layers. However, some of the cells are also arranged in a columnar fashion. The later-born cells, which include the rods, bipolar, and subpopulation of the amacrine cells, all migrate along the radially arranged Müller glial cells. These cells remain in close contact with the Müller glia even as differentiation continues and are thought to comprise a metabolic and/or processing circuit within the retina [17]. The early-born cells are not a part of this columnar unit. Rather than relying on the Müller glia to migrate to the correct layer of the retina, these cells undergo nuclear translocation in the relatively thinner early retina [18, 19].

Müller glia also share properties that allow them to organize the laminar structure of the retina. Cultured Müller glia or Müller glial conditioned-medium are capable of organizing the retinal neurospheres into a layered pattern which closely resembles that seen in the mature retina [20, 21]. While these experiments suggest that there may be a secreted factor which may mediate the organizational properties of Müller glia, recent experiments done in zebrafish suggest that the apico-basal polarity that is inherent in the development of Müller glia is also a critical part of its organizational capacity [22]. A disrupted apical Müller glial cell process in zebrafish mutated in the P50 subunit of dynactin leads to a disruption in the normal laminar development of the retina [22]. In mice, disruption of the outer limiting membrane that is comprised of the apical Müller glial endfeet disrupts the placement of photoreceptors such that misplaced photoreceptor nuclei are found adjacent to the retinal pigmented epithelium, in a region where photoreceptor outer segments would normally be located [23].

2.2. Synapse formation

The role of astrocytes in synaptogenesis in the CNS has been established by many investigators [24-26]. Müller glial cells have been considered by many to be astrocyte-related cells (See Table 1), hence Müller glia may play some role in synapse formation and/or maintenance in the retina. This idea has been tested in zebrafish retina with somewhat contradictory results [27, 28]. While it appears that the Müller glial cell processes do not invade the outer plexiform later

http://dx.doi.org/10.5772/55150

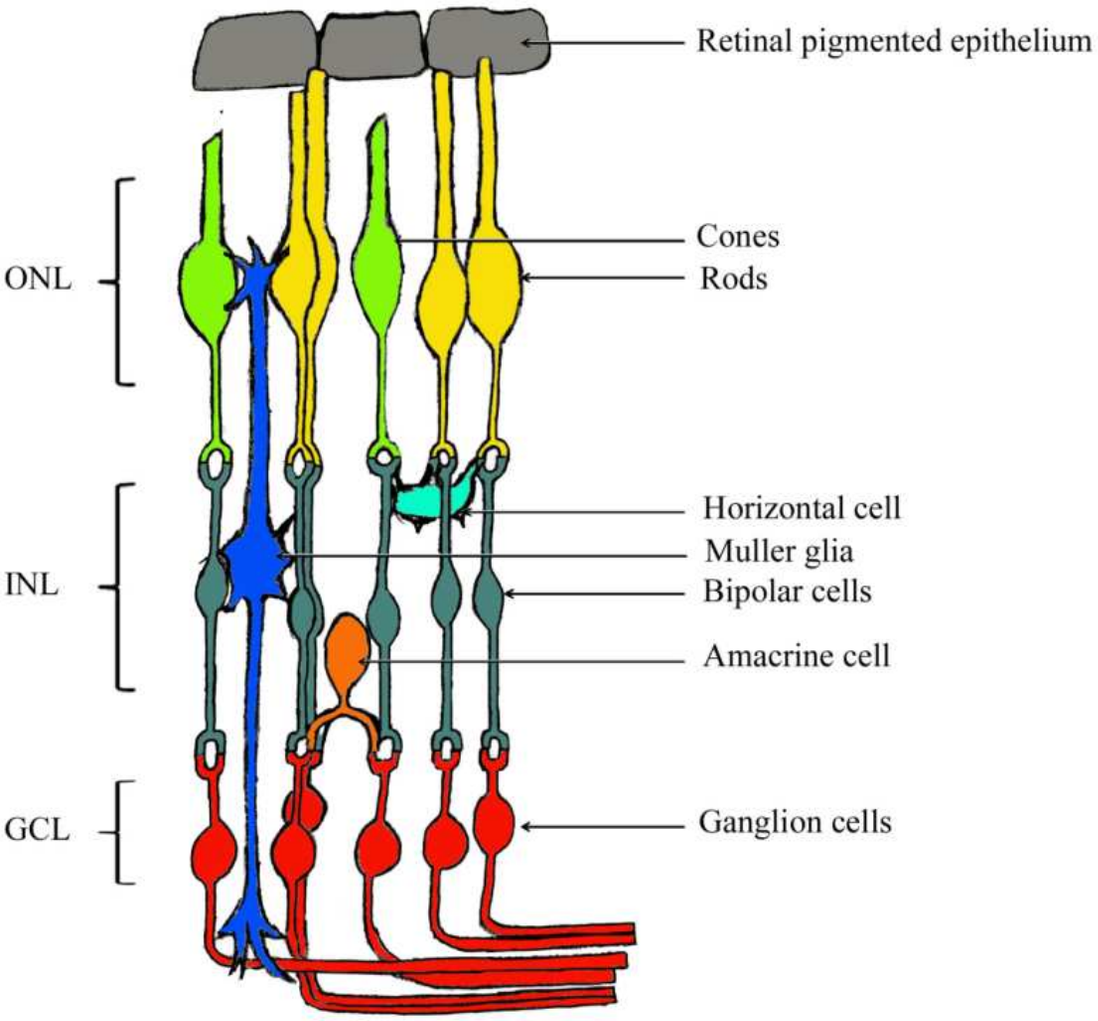

Figure 1. Organization of the mature retina: The retinal cells, which consist of neurons and glia, are organized into the outer nuclear layer (ONL), inner nuclear layer (INL) and the ganglion cell layer (GCL). The ONL consists of the rod and cone photoreceptor cells. The INL is made up of the horizontal cells, amacrine cells as well as the bipolar cells. The Müller glial cell bodies are also present in this layer. However, the processes of the Müller glial cells extend outward into the adjacent layers, extending throughout the thickness of the retina. The GCL is primarily consists of the ganglion cells which send out their axons out of the eye through the optic disc.

until after synapses have already formed and deletion of Müller glia during early retinal development does not affect cone synaptogenesis, a separate study examining the role of harmonin (USH1C) in zebrafish which is found in the retinal Müller glia, have disrupted ribbon synapses [27, 28]. Until this conflict can be resolved and the role of these cells have been investigated in other species, the role of Müller glia remains open.

	Astrocytes	Müller glia
Location	• Throughout the nervous system, including the retina and optic nerve [226]	• Found exclusively in the inner nuclear layer of the retina with the process spanning the entire width of the retina [227, 228]
Origin	• Originate from the glial restricted neural stem cells or the bipotent O2A progenitor cell type [229]	• Originate from the neural retinal progenitor cells [227, 228]
Morphology	• Have a stellate or star like morphology [226]	• Have a radial morphology [227]
Functions	• Scaffolding for migration of developing neurons [230] • Aid in the formation of synapses [231-233] • Aid in the formation of the blood brain barrier [234] • Serve as a source of nourishment and energy reserve for the neurons by providing glucose and storing excess glucose in the form of glycogen [235, 236] • Possess various channels and transporter (Na^+/K^+ channels, aquaporins etc.) which aid in the maintenance of homeostasis, pH levels and removal of toxic metabolites [237, 238] • Possess transporters for neurotransmitters (such as GABA, glycine, glutamate)which aid in clearance and release of these molecules into the synaptic space which can affect synaptic transmission[232, 239]	• Serve as a scaffolding for retinal organizations [227] • Help direct light through the retinal layers to the photoreceptor cells [240] • Help in recycling photopigments [241] • Aid in the formation of the blood retinal barrier [242] • Similar to astrocytes serve as a source of nourishment and energy reserve in the form of glucose and lactate respectively [227] • Help in maintenance of homeostasis and removal of toxic metabolites in a manner similar to astrocytes [115] • Neurotransmitter receptors (AMPA, GluR4, NMDA, GABA-A etc.), transporters and modulators (GLAST, GS, GAT etc.) help in neutransmitter recycling and also aid in glia-neuron communication [115]
Changes during reactive gliosis	• Changes in gliosis based on extent of injury which ranges from mild to moderate to severe [243] • Cells hypertrophy (particularly by increasing the expression of GFAP), change in morphology and upregulate various markers [244] • Increase proliferation and in severe cases form the “glial scar” [245]	• Similar to astrocytes following retinal damage, cells hypertrophy, change morphology and upregulate various markers [246] • Based on the ability or the lack of cells to proliferate, Müller cell gliosis is referred to as non conservative or conservative gliosis, respectively [115] • Glial scar is not a prominent feature of gliosis of the Müller glia [114, 115]

	Astrocytes	Müller glia
Stem cell potential	Following injury – • Cells dedifferentiate and have the potential to re-enter cell cycle [111] • Begin to express proteins associated to neural stem cells or radial glia (NG2, BLBP, nestin, DSD1, CD15) [99]	Following retinal injury – • Müller glial cells re-enter cell cycle and can proliferate [111, 114] • Following targeted ablation of photoreceptor and ganglion cells, regeneration of the respective cell types was observed from the Müller glia [111, 247]

Table 1. Comparison of Astrocyte and Müller glial Characteristics

2.3. Blood retinal barrier development and maintenance

The blood-brain barrier refers to the separation between the circulating blood and extracellular fluid found within the central nervous system. In the brain, this barrier is formed through the interactions between astrocytes and endothelial cells that form the vasculature [29]. In the eye, the blood-retinal barrier is maintained at two junctures; 1) an „outer barrier" in the form of the retinal pigmented epithelium (RPE), and 2) the „inner barrier" that is comprised of the endothelial cells of the retinal vasculature [30]. The endothelial cells of the retinal vasculature form tight junctions that are selectively permeable to hydrophobic molecules such as O_2, CO_2, and hormones, while restricting the entrance of bacteria and large or hydrophilic molecules (See Fig 2). Endothelial cells and pericytes that adhere to the outside of the endothelial cells are both encompassed by a basal lamina as well as the astrocytic endfeet. There is evidence that inner barrier is induced and maintained by both Müller glial and retinal astrocytic endfeet that ensheath retinal blood vessels [31]. The processes of retinal astrocytes, however, are limited to the never fiber and ganglion cell layer and can only interact with superficial vasculature near the inner surface of the retina [32]

Müller glia (as well as retinal astrocytes and retinal pigment epithelium) express factors that are critical to the formation of the deep plexus vasculature in the retina [33]. Angiogenesis is the result of a balance between the pro-angiogenic factor vascular endothelial growth factor (VEGF) and anti-angiogenic factor pigment-epithelium derived factor (PEDF) [33, 34]. The ratio of these factors carefully controls the growth of the deep plexus retinal vasculature. Not surprisingly, misregulation of these factors can lead to pathological neovascularization, a topic which will be covered later in this chaper. Many other interactions between Müller glia/astrocytes and the vasculature have been proposed and/or documented. For instance, Paulson and Newman simulated a process whereby the activity of neurons indirectly regulated blood vessel dilation [35]. In a process referred to as siphoning, the Müller glia are proposed to take up K^+ released by active neurons and then release the K^+ at the endfeet that are in close proximity to the vasculature [35]. Thus the astrocyte can effectively redistribute the K^+ from the neuron, which may be some distance away from the nearest blood vessel, to a region immediately adjacent to the arteriole in a manner that is faster than would otherwise take place

if the K^+ was undergoing simple diffusion. Further, this could also concentrate K^+ released over a wider area to the smaller area of the endfeet.

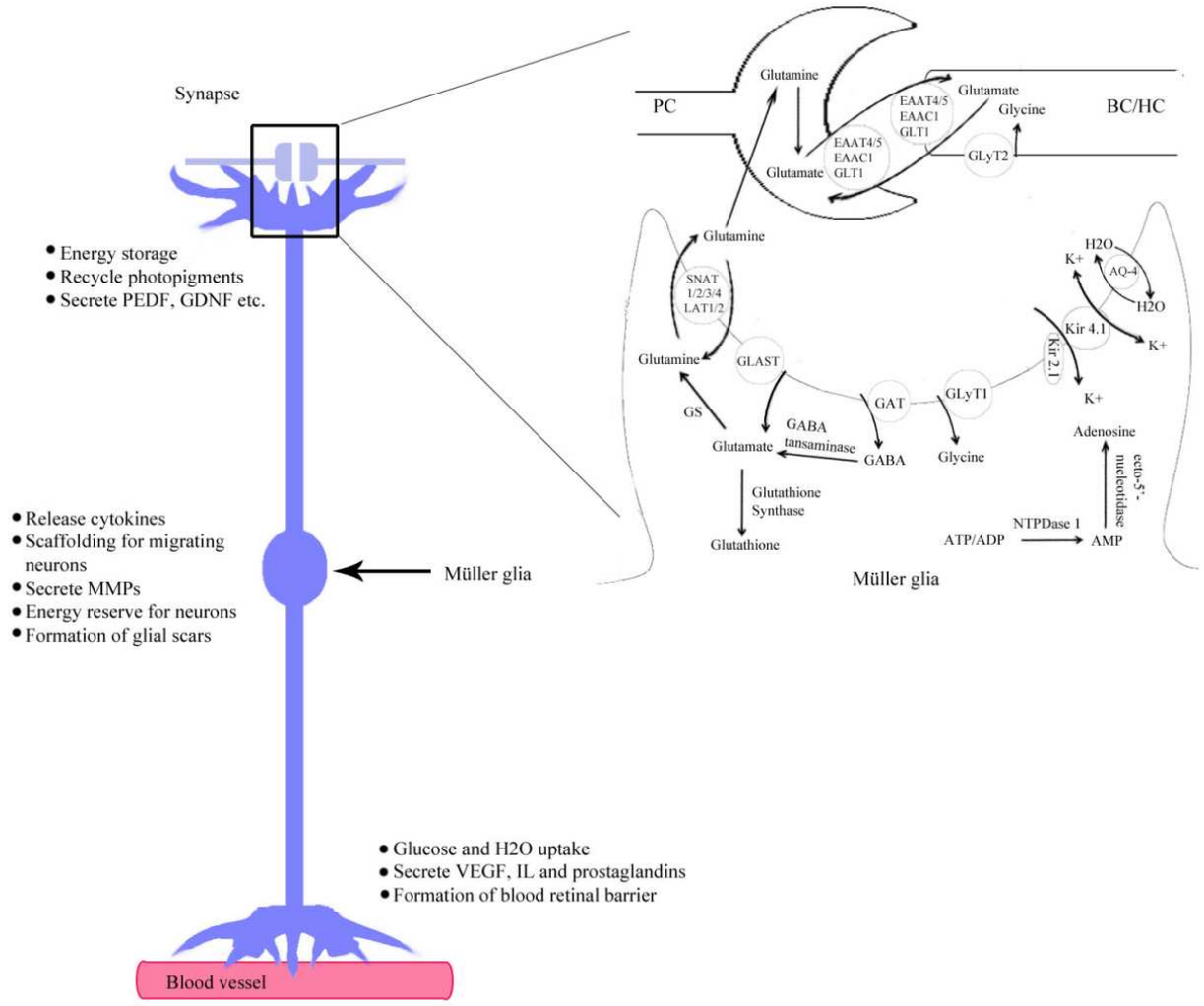

Figure 2. Aquaporin-4 (AQ-4), bipolar cell/ horizontal cell (BC/HC), excitatory amino acid transporter (EAAT), excitatory amino acid carrier (EAAC), glial cell derived neurotrophic factor (GDNF), glutamate transporter (GLT), glycine transporter(GlyT), glutamine synthetase (GS), interleukins (IL), L-type amino acid transporter (LAT), matrix metalloproteinases (MMP), photoreceptor cell (PC), pigment epithelium derived factor (PEDF), Na+ coupled neutral amino acid transporter (SNAT), glutamate aspartate transporter (GLAST), vascular endothelial growth factor (VEGF).

Müller glia are also known for releasing many growth factors, and many of these factors effect the endothelial cells. Transforming growth factor β1 (TGFβ1) is released by Müller glia and can increase the expression of tissue plasminogen activator inhibitor-1, which could potentially have the protective effect of reducing hemorhaging in the brain [36-38]. TGF-β1 also has been shown to have a morphological effect on cultured endothelial cells, inducing them to form capillary-like structures [39]. Mice with a loss of the integrin $\alpha V\beta 8$ that is necesary for TGF-β activation within the retina also have abnormal superficial as well as deep plexus formation

[40]. Glial-derived neurotrophic factor (GDNF) and neurturin are also released by Müller glia and appear to enhance barrier function as measured by transendothelial resistance [41].

Communication between Müller glia and endothelial cells is not a one-way street. There also appear to be inductive signals released from the endothelial cells that effect Müller glial differentiation/function. It is well established that leukemia inhibitory factor (LIF) is secreted from endothelial cells and that it helps to induce astrocyte differentiation in optic nerve astrocytes [42, 43]. LIF and ciliary neurotrophic factor (CNTF) share a part of their receptor complex and intracellular signaling pathway; therefore it is not surprising to find that CNTF has also been shown to have effects on astrocyte development [44, 45]. Both CNTF and LIF are present in the developing retina and CNTF does increase the production of Müller glia [46]. However, an increase in the expression of LIF from the lens during retinogenesis inhibited the development of retinal vasculature and increased the expression of VEGF in retinal astrocytes and Müller glia [47]. Hence it is unclear whether LIF plays a role in Müller glial cell differentiation.

2.4. Metabolic coupling with neurons

The brain is a high energy consuming organ, using approximately 25% of the glucose present in the human body [48]. There is very tight coupling between the demand and supply in the central nervous system (CNS), and most of this expenditure is due to neuronal activity [48, 49]. However, neurons do not store much glycogen and therefore are reliant upon external sources to fuel their oxidative metabolism. In the retina, this need is met by both the Müller glia and retinal astrocytes. Glucose enters Müller glia via glucose transporter-1 (GLUT-1) and is phosporylated by hexokinase to produce glucose-6-phosphate (Fig 2). From here, part of the glucose-6-phosphate is stored with the Müller glial cell body as glycogen and the rest is metabolized to various carbohydrate intermediates [50-52]. Neurons can use a variety of substrates to fuel their oxidative metabolism, including lactate, pyruvate, alanine, glutamine, and glutamate [53, 54]. Müller glia metabolize glucose and glycogen deposits predominantly to pyruvate and lactate which is released to the extracellular milieu by the monocarboxylate transporter MCT2 [55, 56]. Neurons can then take up pyruvate and use it directly in the Krebs cycle to compensate during times of low glucose [50, 57]. Lactate generated by Müller glia is converted by lactate dehydorgenase and pyruvate kinase to pyruvate to power the Krebs cycle [55].

Active neurons, in turn, release glutamate, NH_4^+, K^+, and CO_2, all of which are taken up by the Müller glial cells and are either disposed of or recycled [4]. Glutamate is an excitatory neurotoxin, even at low extracellular concentrations, and is tightly regulated by Müller glia in the retina [58]. Müller cells take up glutamate via the glutamate/aspartate transporter, GLAST, and NH_4^+ via an ammonia transporter (AMT) [59, 60]. In addition to transporting glutamate into Müller glial cells, the GLAST protein co-transports $3Na^+$ ions and one H^+ and counter-transports one K^+ [61]. The influx of Na^+ into the Müller cell activates the Na^+/K^+ ATPase which further stimulates glycolysis [4, 62]. Both the NH4+ and glutamate are use to create L-glutamine by glutamine synthetase [60, 63-65]. The glutamine produced by Müller glia is then transported back to neuronal cells to aid in the synthesis of neurotransmitters glutamate and GABA [54]. The presence of glutamate and NH_4^+ have a combined action of increasing glycolysis by the Müller glia, in part by increasing the expression levels of glutamine synthetase [54, 66, 67].

Müller glia also act as a sink for excess extracellular K^+ in the retina, which is taken up by the inwardly rectifying K^+ (Kir) channels and the Na^+/K^+ ATPase of the Müller cells [62]. This elevation of K^+ concentration increases the glycogenolysis in cultured Müller glia, tightly coupling the breakdown of glycogen to neuronal activity [17]. The K^+ is then disposed of by passing K^+ into the subretinal space, the vitreous body, or the blood. [68, 69]. Finally, carbonic anhydrase converts CO_2 to bicarbonate which is then released by way of the H^+/HCO_3^- exchanger into the vitreous or blood (Fig 2) [70-73].

2.5. Regulation of neurotransmission

In the retina, glutamate is the primary excitatory neurotransmitter [74]. Müller glia have transporters for a wide variety of transmitters, including glutamate, GABA, Glycine, D-serine, dopamine, and ATP [75, 76]. The Müller glia take up neurotransmitters and other neuroactive substances and convert them to substances that can be supplied to retinal neurons as neurotransmitters or neurotransmitter precursors (Fig 2). The modulation of neuronal excitability through regulation of neurotransmitter availability is thought to serve three functions; 1) termination of neuronal signaling, 2) prevention of neurotransmitter spread to adjacent synapses, and 3) prevention of neurotoxicity resulting from prolonged presence of a transmitter at a synapse [4, 75]. In this section, we will briefly cover transport of the major retinal neurotransmitters into Müller glia, processing of the transmitter by the Müller glia and transport of products back to retinal neurons.

Müller glia express several glutamate transporters, depending upon the species, including the previously mentioned GLAST protein (also known as excitatory amino acid transporter 1 or EAAT1). In humans for instance, the dominant transporter is EAAT1, but EAAT2 and 3 can also be found [77]. Glutamate is the most widely used neurotransmitter used by retinal neurons, including photoreceptors, bipolar and ganglion cells. Both the photoreceptors and the bipolar cells have graded potentials, hence the amount of neurotransmitter released is directly correlated to the amount of stimulus. In addition, photoreceptors are wired a little differently than other neurons that transduce sensory information; they release glutamate in the dark and less glutamate upon transduction of light signals. Hence, removal of glutamate from the synaptic region is critical for normal tranmission of light signals to take place. Knockdown and knockout studies in the retina have indicated that a loss of GLAST leads to a loss of the electroretinogram b-wave, primarily because it aids in signal processing between photoreceptors and bipolar cells, rather than any neurotoxicity associated with high levels of glutamate [78, 79]. Consistent with the idea that Müller glia are critical for clearing away glutamate released at synapses are studies in which clearance of D-aspartate was tracked first to Müller glia followed by a redistribution into other neuronal cell types of the retina [80]. Glutamate can be converted to glutamine by glutamine synthetase, and is then transported back to neurons as a precursor to glutamate [63, 81]. Loss of glutamine synthetase activity leads to a loss of glutamate content in retinal neurons which leads to functional blindness within 2 minutes [82, 83].

There are several other neurotransmitters used in the retina, such as GABA, glycine, and dopamine. Since the interactions of these neurotransmitters are not as heavily studied as

glutamate, only their uptake mechanism and potential processing within Müller glia will be discussed here. GABA is used by horizontal and amacrine cells within the retina and termination of GABA activity is brought about through the uptake of GABA by Na^+/Cl^--dependent GABA transporters (GATs) found in presynaptic neurons, Müller glia, and retinal astrocytes [76, 84, 85]. After uptake into Müller glia, GABA can be converted to glutamine via glutamine synthetase and, as specified above, is returned to neurons to act as substrates for neurotransmitters [86]. Müller glia also express glutamate decarboxylase which catalyzes the decarboxylation of glutamate to GABA. It is unclear, however, whether GABA can be released by Müller glia [76].

Dopamine performs a large number of functions in the developing and mature retina that are well out of the scope of this chapter. A full discussion of this topic can be found elsewhere [87]. Both the transporter and enzymes necessary for converting tyrosine to dopamine are expressed in Müller glia [88]. Likewise, ATP also performs a large number of functions in the developing and mature retina [89-91]. Müller glia express a subset of the P2X and P2Y ATP receptors and they also have the ability to convert ATP to adenosine and release both ATP and adenosine into the intracellular space [91, 92].

Müller glia also carry glutamate, GABA, purinergic, glycine, dopaminergic, noradrenergic and cholinergic receptors [76]. In some instances these receptors have been shown to coordinate release of neurotransmitters by neurons with enzymatic activity and or gene regulation in the Müller glial cells. An excellent example of this coordination is the regulation of glutamate receptors on GLAST activity and expression of GLAST. When glutamate receptors are activated on Müller glial membranes it leads to an increase in intracellular Ca^{2+} and protein kinase C (PKC). The activation of metabotropic glutamate receptors in Müller cells leads to an increase in Ca^{2+} and protein kinase C, and phosphorylation of GLAST by PKC leads to an increase in transport of glutamate [82, 93]. The increased transport of glutamate through GLAST appears to regulate activation of mammalian target of rapamycin (mTOR), which activates DNA binding of the transcription factor activator protein-1 (AP-1) and an increase in GLAST mRNA [94].

2.6. Other

Müller glia perform a variety of other functions beyond those already mentioned. For instance, in addition to siphoning K^+ released by retinal neurons, the Müller glia are also responsible for the transport of water that accumulates in the tissue as the end product of ATP synthesis [95]. The movement of water is specifically coupled to the movement of Na^+ and K^+ and, like K^+, is released into the bloodstream. Müller cells are also involved in phagocytosis of debris in the retina and in the release of antioxidant glutathione [96, 97]

3. Properties that are similar to stem cells/astrocytes

Studies using reactive astrocytes have shown the potential to dedifferentiate into cells having neural progenitor or stem cell like properties (Table 1) [98, 99]. Following stimulation, these cells show activation of signaling pathways such as EGF, FGF, SHH and Wnts, previously

shown to be associated with the neural stem cells [98, 100-102]. Similarly, activated Müller glial cells following retinal injury have also shown the capacity to dedifferentiate into retinal progenitor cells [103]. Studies in lower vertebrates such as fish, amphibians and birds have shown the presence of a stem cell niche in the ciliary marginal zone (CMZ) of the retina [104-107]. Mammals, however, do not have a CMZ [108]. In mammals, a small group of cells in the non-pigmented portion adjacent to the retina can proliferate up to postnatal day 21, but these cells are low in abundance and are not thought to generate many cells [103, 109]. It may be more feasible to generate many retinal progenitor cells from activated Müller glia. Expression profiling of proliferating Müller cells suggests a stem cell like role for these cells [110, 111]. Culture of the Müller cells in an enriched medium generated "multipotent neurospheres", elucidating the stem cell role of Müller cells *in vitro*. Further transplantation of enriched Müller glial cells into injured retina generated cells with neuron like characteristics [112]. Müller cells have been shown to dedifferentiate, proliferate and give rise to amacrine cells, bipolar cells, retinal ganglion neurons as well as the photoreceptor cells. [110, 111, 113]. One important factor aiding the transformation of the Müller glial cells is the membrane depolarization due to a reduction of potassium ion conductance, primarily due to downregulation of the Kir channels in the Müller cell [114]. The dowregulation of the Kir channels leads to a decrease in the p27kip1 cyclin kinase inhibitor, which is then succeeded by re-entry into cell cycle. The downregulation of the Kir channels pushes these cells towards the proliferative stage [115].

4. Response of Müller Glia to injury or disease states

When there is injury or disease within the CNS, astrocytes respond by entering a state referred to as reactive gliosis. Reactive gliosis is an ill-defined set of molecular changes that alters the homeostatic role of the cells and their interactions with neurons, vasculature, and the immune system. Reactive gliosis is thought to be the result of signals received from the injured or diseased tissue that begins a molecular cascade within the glial cells resulting in a change of state [103]. There are a mulitude of questions that have arisen as a result of our limited understanding of gliois, and investigators are currently working to answer these questions. Among them:

- Is reactive gliosis one condition, or a host of related conditions?
- What are the molecular triggers of gliosis?
- Do all the triggers that appear to be involved in gliosis converge on one or two pathways that mediate the changes in Müller glial state, or, are their multiple pathways that can mediate multiple changes?
- Do different signals mitigate mild, moderate or severe reactive gliosis? How are these forms of gliosis related?
- Can severe reactive gliosis be attenuated, even when triggers are chronically present?

- Can the reactive gliosis be used to „supply" multipotent stem cells to the retina to replace dead or dying neurons?
- Can the multipotent stem cells that arise from Müller glial cells be directed in their differentiation in vivo and can the number of progenitor cells differentiating into cell types other than Müller glia be increased substantially?

There appears to be a continuum in the states of reactive gliosis, from mild to severe. In the mild to moderate forms of gliosis, the cells may hypertrophy and show some changes to their functionality, but, if the trigger is removed, the cells may revert back to their former condition without altering the tissue [116]. In the more severe forms of reactive gliosis, cells hypertrophy, lose functionality, form glial scars that are inhibitory to axonal regeneration and neuronal surivival, and may also proliferate [116, 117]. The severe state is marked by the persistance of these characteristics. Within the mammalian retina, both the Müller glia and retinal astrocytes display reactivity to injury and disease. In this section we will talk about triggers of Müller glia, evidence that BMP7 may also be a trigger, and the changes in retinal homeostasis that result from reactive gliosis in the retina.

5. Triggers of reactive gliosis

5.1. Known triggers

Müller glial reactivity can be found in every identified disease and injury that plagues the eye, including diabetic retinopathy, glaucoma, age-related macular degeneration, retinitis pigmentosa, and many many others [118-122]. In considering reactive gliosis, there appears to multiple levels of complexity. For instance, there are a wide range of factors which have been shown to trigger reactive gliosis in Müller glia (Figure 3 and Table 2). Some of these triggers can have concentration-dependent effects upon astrocytes [116]. Further, different triggers can lead to specific molecular and functional changes in the Müller glia that may correspond to the various aspects of reactive gliosis [123]. Not only are there multiple triggers, but there is heterogeneity in the response of Müller glia to the same factor [118].

5.2. Bone morphogenetic proteins in Müller cell gliosis

Studies in the injured spinal cord have indicated a role for another family of growth factors; the bone morphogenetic proteins (BMPs). The BMPs are members of the TGF-β superfamily of growth factors. The receptors include two basic types, Type I and Type II, both of which are serine-threonine kinases. Receptors from each type must form heterodimers in order for signaling to occur, although the Type I receptors are downstream of the Type II. There are two non-canonical signaling pathways, BMP-MAPK and FRAP-STAT, that have more recently been identified in addition to the canonical SMAD-related pathway [45, 124-129]. Three type I receptors have been associated with the BMPs, activin-like kinase 2 (ALK2), ALK 3 and ALK6. Accumulated evidence has shown that in regards to the Type I receptor, BMP 6 and 7 activate the ALK2 receptor preferentially, whereas BMPs 2 and 4

Growth Factors and Cytokines
Ciliary Neurotrophic Factor/Leukemia Inhibitory Factor [86, 248-251]
Epidermal growth factor/HB-EGF [84, 87, 180]
Fibroblast growth factor 2 [250, 252]
Brain-derived neurotrophic factor [250]
Transduction Pathways and Transcription Factors
STAT3 [248, 253, 254]
NF-κB [255, 256]
Toll-like receptor 2 [257]
TRPV1 (Vanilloid Receptor) [85]
Gp130 [249]
Epidermal growth factor receptor [87]
Fibroblast growth factor receptor [179]
MEK [179, 258]
Other
Oxidative Stress/Ischemia [38, 254, 255]
ATP
Glucose [88, 259]
Amyloid Beta [260]
Endothelins [261]
Nitric Oxide

Table 2. Triggers of Müller Glia Cell Activation

activate either ALK3 or ALK6 [130]. In addition to the canonical SMAD pathway, ALK3 and 6 also activate the BMP-MAPK and FRAP-STAT pathways [45, 124, 129]. The BMPs have been shown to act as a gliosis trigger in penetrating spinal cord injuries, and a differential role for ALK3 and 6 receptors has been ascribed to various aspects of gliosis, including hypertrophy, inflammation, and tissue loss [131, 132]. While BMPs have been studied in retinal injury, primarily as a survival factor for retinal neurons, it has not been studied as a potential trigger for reactive gliosis in Müller glia [133].

My lab has investigated the role of BMP7 as a potential trigger for reactive gliosis in Müller glia and retinal astrocytes. We and others have documented changes in BMP expression and signaling following injury or disease in the retina and optic nerve [134]. We have determined expression levels of BMPs and BMP intracellular signaling pathway members in a diabetic mouse model, the Akita mouse model (Ins^{AKITA}). These mice contain a naturally occurring missense mutation in

http://dx.doi.org/10.5772/55150

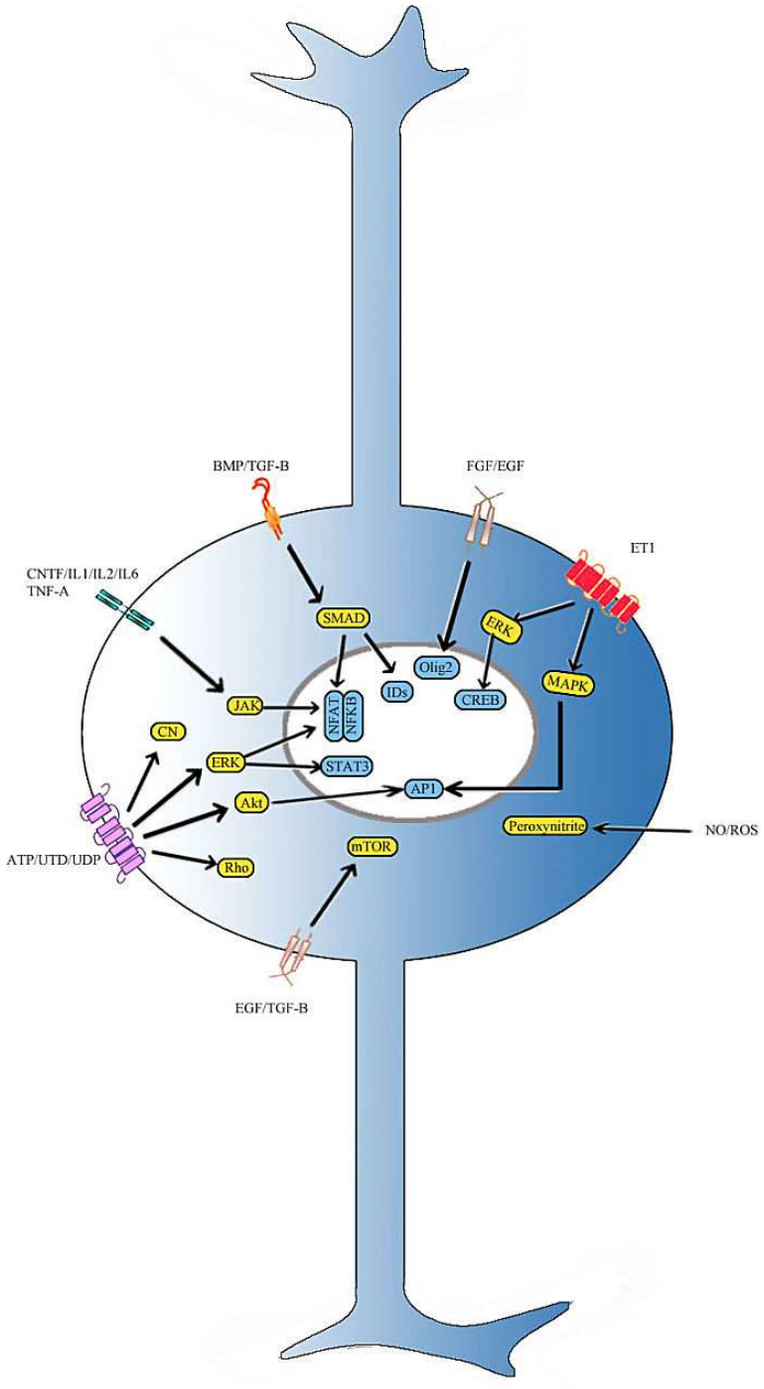

Figure 3. Schematic representation of various signaling mechanisms which trigger and regulate reactive gliosis in Müller glia. Growth factors such as TGF-β, BMP, EGF and CNTF; interleukins; as well as reactive oxygen species and free radicals are known factors to trigger gliosis in Müller glial cells. Activator protein-1 (AP1), adenosine triphosphate (ATP), bone morphogenetic protein (BMP), ciliary neurotrophic factor (CNTF), calcineurin (CN), cAMP response element binding protein (CREB), epidermal growth factor (EGF), endothelin 1 (ET1), extracellular-signal-regulated kinase (ERK), fibroblast growth factor (FGF), interleukin (IL), inhibitor of differentiation (ID), janus kinase (JAK), mitogen activated protein kinase (MAPK), mammalian target of rapamycin (mTOR), nuclear factor of activated T-cells (NFAT), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), nitric oxide (NO), reactive oxygen species (ROS), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), uridine triphosphate (UTP), uridine diphosphate (UDP).

the insulin 2 gene that causes a switch from a cysteine to a tyrosine residue at amino acid 96, removing one of the cysteines necessary for an intramolecular disulfide bond [135]. Heterozygous mice are severely insulin deficient and become diabetic at about 6 weeks of age [135]. For these studies we used two stages; mice that are 3 weeks of age have mild to no reactive gliosis, while 6 weeks of age has moderate gliosis. Levels of BMP expression were determined by reverse transcription – quantitative polymerase chain reaction (RT-qPCR) of RNA samples from 3 and 6 week old wild type and heterozygous mice. The graphs show changes in mRNA levels in the 3 and 6 week Ins^{AKITA} mice relative to levels of mRNA in wild type samples (Fig 4A, B). Further, genes that are known downstream targets of the BMP pathway, such as inhibitor of differentiation (ID) 1, 3, and MSX2 are also increased, consistent with an increase in BMP signaling (Fig 4A, B). To verify there was an increase in canonical BMP signaling, an increase in nuclear localization of phospho-SMAD1 (p-SMAD1,5,8) sections through wild-type and 6 week Ins^{AKITA} retina were immunolabeled for p-SMAD1,5,8 and glutamine synthetase (Fig 4C-N). The Ins^{AKITA} retina showed a clear increase in p-SMAD1,5,8 expression in the inner nuclear layer at 6 weeks of age, some of which was coincident with cells glutamine synthetase-expressing Müller glia (Fig 4L-N). There was also clear increase in p-SMAD1, 5, 8 in other cells of the inner nuclear layer and cells of the ganglion cell layer.

To test the role of BMPs in reactive gliosis in vivo, adult murine eyes were injected intravitreally with vehicle or BMP7 and analyzed 3 or 7 days post injection. At both 3 and 7 days post vehicle injection, there were the normal low levels of GFAP expression and moderate levels of glutamine synthetase in Müller glia (Fig 5A, B, G, H). A low level of the chondroitin sulfate proteoglycan, neurocan, is present throughout the retina (Fig 5C, I). Three days post BMP7 injection, no increase in GFAP was detected, but an increase in both glutamine synthetase and neurocan levels were detected (Fig 5D-F). Immunolabel of BMP7-injected eyes showed an increase of GFAP, glutamine synthetase and neurocan in comparson to vehicle-injected eyes (Fig 5J-L).

6. Characteristics of reactive gliosis in Müller Glial cells

Müller glia display many changes during reactive gliosis (Fig 6). We have grouped these changes into 6 broad categories; 1) hypertrophy, 2) loss of functionality, 3) neuroprotection, 4) inflammation, 5) proliferation, 6) remodeling.

6.1. Hypertrophy

Hypertrophy refers to the swelling of the Müller glial cell body and processes. The swelling is, in part, brought about by an increase in the expression of two type III intermediate filament genes, GFAP and vimentin. As with many changes that occur with reactive gliosis, upregulation of intermediate filaments and the ensuing hypertrophy has both good and bad characteristics associated with it. Hypertrophic glia help to form and maintain a barrier around injured tissue which helps to protect surrounding tissues from inflammatory signals [136, 137]. On one hand, there is evidence that the increased production of GFAP does not lead to diminished neuronal metabolism, eletrophysiology or visual function [138]. However,

evidence from injured spinal cord indicates axonal regeneration and functional recovery was increased in GFAP/vimentin double-knockouts in comparison to wild type controls [139]. Further, the retinas of GFAP/vimentin double knockouts were also protected from retinal degeneration following retinal detachment, and integration and neurite extension from transplanted cells is also enhanced [140].

In addition to increased intermediate filament expression, hypertrophy is also the product of a loss of K^+ conductance into the blood stream as already covered in section 1.3, Müller glia take up K^+ released by retinal neurons and release it into the bloodstream. Water in the tissue, created through the process of oxidative synthesis of ATP, is removed through the pigmented epithelium and Müller glia. The movement of water is coupled to the movement of osmolytes, including Na^+ and K^+ ions, and are subsequently removed from the Müller cell bodies via release into the bloodstream [4]. Müller glia undergoing gliosis downregulate the K^+ channel, Kir4.1, that delivers K^+ to the vasculature, which uncouples the movement of K^+ and water into the blood. The end result is swelling of the Müller cell body.

6.2. Loss of functionality

Loss of functionality is a part of the general response of the cells to undergo dedifferentiation. However, the response of the Müller cells can vary depending upon the disease or injury present. A good example of this is the regulation of the glutamate transporter in disease and following mechanical injury. Downregulation of glutamate transporters is observed in glaucoma, ischemia and diabetic retinopathy, due to a decrease in the activity of the glutamate transporter GLAST. This in turn downregulates the activity of glutamine synthetase, an enzyme involved in glutamate recycling [141]. However, following mechanical nerve injury, as seen with the optic nerve crush model, glutamine synthetase was found to localize to the ganglion cell layer, aiding in the recycling of the excess glutamate released due to neuronal injury. [142].

The Kir channels (potassium channels) in the Müller glial cell membrane play an important role in the gliosis response as well. Decrease in conductance of the potassium ions due to down regulation of Kir 4.1 leads to an increase in potassium ions outside the membrane. This, in turn, decreases the transport of glutamate, glucose and water across the Müller glial cell surface. Consequently, an increase in the glutamate toxicity, decrease in glutathione synthase activity and osmotic swelling were observed in the retina, which contribute to the loss of glia/neuron interactions [97, 114, 120, 143-146].

There is also a reduction in the blood-retinal barrier function under hypoxic conditions. This appears to be driven by changes Müller cell expression of growth factors that regulate endothelial cell tight junctions. The balance between factors that increase endothelial cell tight junctions (PEDF, glial derived neurotrophic factor (GDNF), transforming growth factor Beta (TGFβ), thrombospondin, etc) and factors that decrease barrier function (VEGF, TNFα, FGF2, etc) is disrupted by reactive gliosis [34, 41, 147-153]. VEGF appears to be the dominant factor released from Müller glial cells in decrease of barrier function and angiogenesis that occurs in many forms of retinal injury and disease [153].

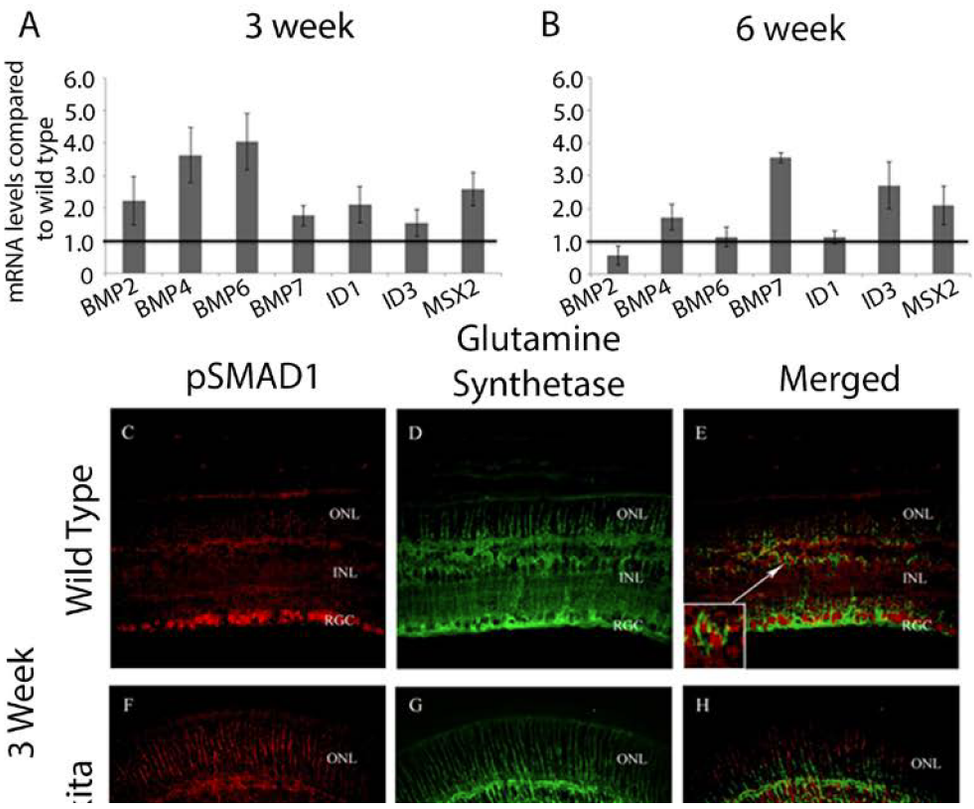

Figure 4. Analysis of retinas of the Ins2^{Akita} diabetic mouse shows increase in BMP signaling in the diseased eye when compared to the wild type eye. **A** and **B**: qPCR results analyzing the levels of various BMP molecules shown to be regulated during reactive gliosis and some of the targets of the canonical BMP signaling pathway, using RNA obtained from whole retinas in 3 week and 6 week diseased eye, respectively, normalized to their respective wild types. At the 3 week stage (**A**), when little or no gliosis is observed (data not shown) levels of BMP 2, 4 and 6 appear to be high. At the 6 week stage (**B**) when we do seen an increase in expression of GFAP, GS and neurocan (data not shown), there is

http://dx.doi.org/10.5772/55150

an increase in levels of BMP7 with a subsequent decrease in the levels of other BMP molecules, indicating a role for BMP7 in reactive gliosis in the diseased state. Immunohistochemistry was performed to determine the localization of phospho SMAD with glutamine synthetase in the retinas (**C – N**). The 3 week retinas show similar nuclear phospho SMAD levels in both the wild type and the $Ins2^{Akita}$ (**C, E, F and H**). In the 6 week $Ins2^{Akita}$, there is a clear increase in the phospho SMAD levels in the inner nuclear layer nuclei (**L and N**) when compared to the wild type (**I and K**), possibly due to the increase in BMP7 shown previously (**B**).

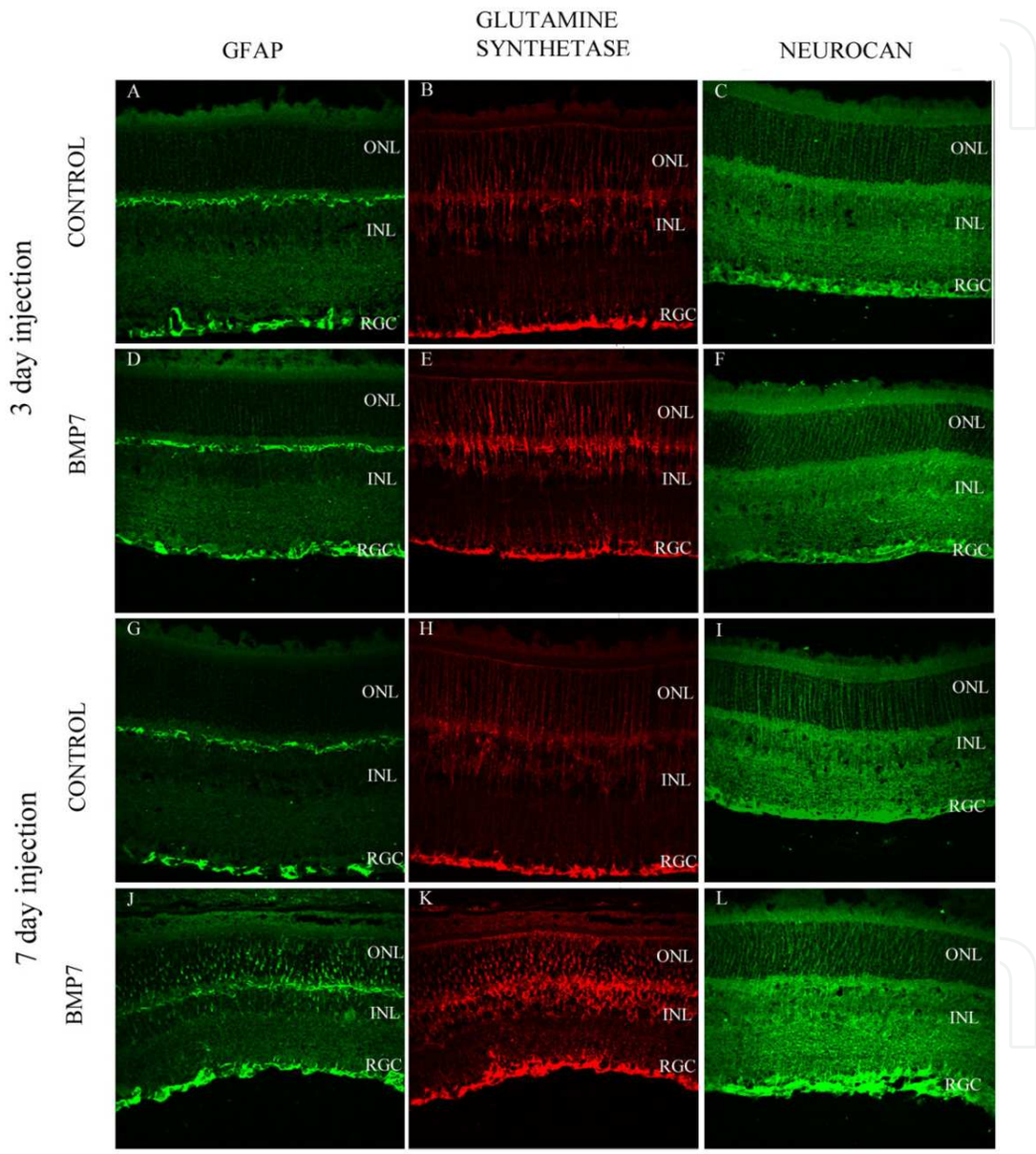

Figure 5. Effect of intra vitreal injections of BMP7 into normal mouse eyes – Retinal sections of eyes injected with either vehicle or BMP7 were analyzed 3 days (**A – F**) and 7 days (**G – L**) post injection via immunohistochemistry for the localization of glial fibrillary acidic protein (GFAP), glutamine synthetase (GS) and neurocan. Retinas isolated 3 days post injections do not show an increase in GFAP (**A and D**) or neurocan (**C and F**), although GS does seem to show an increase when compared to the vehicle injected eyes (**B and E**). Retinas isolated 7 days post injection did show a clear increase in GFAP (**G and J**), GS (**H and K**) and neurocan (**I and L**) in the BMP7 injected eyes compared to the control eyes, suggesting the BMP7 was able to trigger gliosis in these retinas.

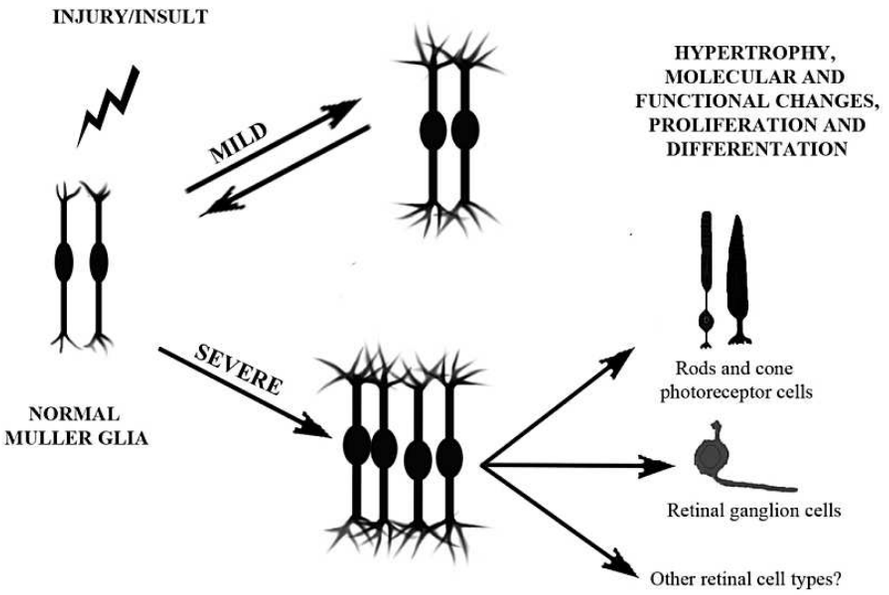

Figure 6. Schematic representation of reactive gliosis response in Müller glia depending on the extent of the injury. Mild changes in reactive gliosis comprises of hypertrophy of the cells due to an increase in glial fibrillary acidic protein and changes to the function and morphology of the cell, with little or no proliferation which has the potential to re-solve once the stimulus subdues. Severe reactive gliosis occurs following tissue damage and induces Müller glial cell proliferation, overlapping of cell processes, hypertrophy, functional and morphological changes. Under severe gliosis conditions reactive Müller cells have shown the ability to dedifferentiate and give rise to some of the retinal cells types.

6.3. Neuroprotection

Reactive gliosis in Müller cells is a complex response dependent on the injury or disease. Diseases which lead to retinal degeneration such as retinal detachment, retinitis pigmentosa or physical damage to the retina elucidate such a response from the Müller cells to aid in neuoprotection and prevent apoptosis [114, 141]. A wide range of growth factors secreted by the reactive Müller cells, including bFGF, GDNF, CNTF, and VEGF [114, 141, 150, 154, 155]. Upregulation of CNTF and bFGF have been observed following mechanical injury, ischemia and NMDA mediated neuronal death [156-158]. These growth factors help to increase neuron survival and inhibit apoptosis, either directly as is the case for bFGF, or indirectly in the case of CNTF and GDNF [159, 160]. GDNF also upregulates GLAST, thereby, protecting neurons from excessive glutamate excitotoxicity [160]. VEGF is another factor which is upregulated following gliosis. Hypoxia as well as diabetes has shown to increase the VEGF secretion by Müller glial cells [161, 162]. VEGF may act directly by increasing the permeability of the endothelial cells [163]. VEGF may also be regulated by TGF-β released during hypoxia, which, along with other cytokines such as TNF-α, increase the expression of matrix metalloproteinases which can clear the basement membranes of these cells generating leaky vessels [38, 164].

http://dx.doi.org/10.5772/55150

Müller cells also protect retinal neurons from oxidative stress, excitotoxicity and from damaging reactive oxygen species via conversion of glutamate to glutamine as well as synthesis and release of antioxidants such as glutathione [165, 166]. However, concomitant with an increase in the antioxidant glutathione, during hypoxia, diabetic retinopathy, hyperglycemia and ischemia there is also an increase in the expression of inducible nitric oxide synthase and cyclooxygenase-2 [167, 168]. These enzymes can lead to production of nitric oxide, prostaglandins and superoxides which are detrimental to retinal neurons and may induce apoptosis in neural cells [169]. Nitric oxide also has a beneficial role as it increases blood flow by dilating blood vessels and prevents glutamate toxicity by closing *N*-methyl –D-aspartate (NMDA) receptors [170].

6.4. Inflammation

Müller cells also play a role in the inflammatory response observed in the retina, primarily seen in the diabetic retina. Under these conditions, the activated Müller cells begin expressing pro inflammatory cytokine interleukin-6 (IL-6) and IL-1B [171, 172]. They also increase expression of TNF-α which increases the expression of the chemokine IL-8 and MCP-8, and promotes infiltration of inflammatory cells [173]. The inflammatory response is further supported by the decrease in glutamate uptake in diabetic retinas. This increases the expression of glutaredoxin, which translocates NF-κB to the nucleus and increases the expression of pro-inflammatory proteins [141].

6.5. Proliferation

Dedifferentiation and proliferation of Müller glia is known to occur in many different species, including chick, fish, and even mammalians [108, 110, 174-177]. Several aspects of Müller cell proliferation are of interest here; 1) the molecular pathways that result in the release of the cells from their normally quiescent state, 2) extrinsic signals that are necessary for the proliferative reponse, and 3) directing progenitor cells to differentiation and integration into retinal tissue.

Several intracellular signaling pathways have been investigated to determine those that may be important for the proliferative response in dedifferentiating Müller glia. The FGF-MAPK pathway appears to be indespensible for the proliferative activity seen during reactive gliosis [178, 179]. The heparin binding epidermal growth factor (HBEGF)-MAPK pathway is be also induced in the Müller glia found in injured areas and appears to be associated with regeneration-associated genes [180]. Further, the HB-EGF pathway appears to be upstream of the WNT-β-catenin pathway, which has been very clearly associated wth re-entrance of Müller glia into the cell cycle [181]. More specifically, Müller glia that are poised to re-enter the cell cycle accumulate β-catenin in injured zebrafish retina, whereas those Müller cells that remain quiescent do not accumulate β-catenin [181]. Further, activation of the WNT/β-catenin pathway stimulates a loss of Müller glia and a concomitant increase in newly generated photoreceptors [181].

In order for Müller glia to re-enter and progress in the cell cycle, the cells would also have to suppress some of the cell cycle check-points that are responsible for the quiescent state of the cells. Inhibition of the cyclin kinase inhibitor p27 has been shown to play a pivitol role in the ability of Müller glia to re-enter the cell cycle. P27 regulates the cell cycle by blocking cell cycle progression into the S-phase, and hence is necessary for maintainance of the quiescent state [182]. Knock-out mice for p27 show many of the characteristics of reactive gliosis, including an increase in GFAP expression and proliferation and migration of cells into the subretinal space [138, 182-184].

6.6. Remodeling

There appears to be three elements of the retina which can undergo remodeling as a result of gliosis; 1) vasculature, 2) the Müller glia themselves, and 3) the extracellular matrix. The neovascularization is, for the most part, due to an imbalance between the antiangiogenic factor PEDF and and the angiogenic factor VEGF [162, 185-190]. Under hypoxic conditions, transcriptional activation of VEGF occurs by translocation of the newly stabilized hypoxia inducible factor-1α (HIF-1α) and it's partner HIF-1β to the nucleus where they bind to the hypoxia responsive element (HRE) in the 5' flanking regions of the VEGF gene [191, 192]. VEGF is released into the extracellular mileu, where it penetrates the basal laminae and interacts with retinal endothelial cells. This interaction results in an increase in the release of a family of zinc-dependent endopeptidases called the matrix metalleoproteinases (MMPs), plasminogen activators, and other proteinases which degrade proteins, such as occludens, which necessary for the tight junction formation between endothelial cells [192-196]. The VEGF activates the MAPK pathway via phospholipase C-γ, which mediates proliferation of the endolthelial cells [197]. The MMPs also degrade the basal laminae, removing contact inhibition of the endothelial cells and permitting proliferation [38].

The Müller glia participate in remodeling themselves by extending hypertrophied processes into areas they are not typically found. For instance, processes can protrude into the subretinal space, plexiform layers, the vitreous, into occluded blood vessels, and even into the choroid [122, 198-203]. In some respects, the Müller glia are expanding into areas where degenerating neurons and/or axonal processes are found, such as the subretinal space or plexiform layers [204]. If these new processes persist, the end result is the formation of scar tissue, which can permanently block the reattachment of the retina, regeneration of outer segments or regeneration of synaptic contacts in the plexiform layers [118, 122, 205-209]. The extension of processes onto the vitreal surface of the retina results in the formation of periretinal membranes that may under epithelial to mesenchymal transformation into myofibrocytes that spread and become contractile [210]. The contractility leads to folds and/or deformations in the retina, causing visual distortions at the very least, and, at worst, can cause retinal detachments [211, 212]. Glial membranes/scars are a significant issue in the treatment of visual disorders in humans, occuring in appoximately 15% of retinal detachments [213].

The last element of the retina that undergoes remodeling during reactive gliosis is the extracellular matrix (ECM). During reactive gliosis, Müller glia upregulate expression of MMPs and the gene products are secreted and activated [196, 214-218]. Each MMP specifically targets and

proteolytically cleaves one or more ECM molecules. The activity of MMPs is regulated by activators as well as inhibitors; the precursor molecules must be processed, either by already activated MMPs or by one of a variety of serine proteases and the MMPs can be inhibited by the tissue inhibitors of metalloproteinases (TIMPs) [219]. When activated, the MMPs degrade the existing ECM in preparation for replacement with an ECM that partially inhibits neurite outgrowth or supports abnormal neurite outgrowth [141]. In the normal adult retina heparin sulfate proeoglycans (HSPGs) are typically found on Müller glial endfeet and in retinal basal lamina, serving as a substrate for axonal outgrowth. The HSPG, via the HS chains, is also a ligand for the protein tyrosine phosphatase-sigma (PTP-σ), used in signaling in axons and growth cones in response to matrix cues. The HSPGs involved are agrin and collagen XVIII [220]. The HSPGs are lost in favor of the axonal outgrowth inhibitory molecules known as the chondroitan sulfate proteoglycans (CSPGs). The CSPGs include phosphacan, aggrecan, NG2, brevican, versican, and neurocan [221]. In addition to turning over the ECM, the degradation of the ECM also releases growth factors that are bound to the ECM, such as EGF, FGFs, BMPs, insulin, and VEGFs [219].

Müller glia can form new neurons in a process said to involve dedifferentiation of the Müller glia. Tenascin C (TNC), a matricellular protein, influences the dedifferentiation behavior of Müller glia in response to FGF2 in vitro, affecting the composition of the ECM. Sulfated chondroitin glycosaminoglycan chains in CSPG are the main target. Chondroitin sulfate increases in TNC-deficient mouse ECM [222]. The proteoglycan most affected by TNC is the CSPG Phosphacan/RPTPβ/ζ which bind to TNC [223]. TNC shows overlapping expression with phosphacan [224]. In a TNC knock out mouse TNC level rise. Studies using immunocytochemistry for phosphacan, Western Blots and PCR for mRNA levels show that it is the chondroitin sulfate chains that increase, not the amount of mRNA for CSPG core protein. Proliferation rates also increase in the TNC-deficient mice, but it is not clear if this affects exit from the cell cycle and differentiation [222].

SPARC (secreted protein, acidic and rich in cysteine)/osteonectin is also a matricellular. It interacts with growth factors and ECM forming a link that modulates the cell cycle and other cell behavior. SPARC remains expressed at significant levels in the adult CNS, more so than in most normal adult tissues. SPARC is widely expressed in remodeling injured tissue and in morphogenesis in development [225]. In normal newborn and adult bovine retinas SPARC is found in ganglion cell soma and in ganglion cell axons, with higher expression in the adult tissue. SPARC is thought to have a function in maintaining healthy retinas and is localized to the ganglion cell layer (GCL), nerve fiber layer (NFL) and some retinal capillaries. Müller glia showed no immunoreactivity, but the GFAP-positive retinal astrocytes were SPARC-positive [225].

7. Conclusion

The evidence to date has shown that Müller glia undergo dedifferentiation and generate retinal progenitors that may be capable of differentiating into retinal neurons. Several potential problems have arisen that impact on the ability of those progentiors to effectively be used to

regenerate large numbers of neurons following injury or during disease. Of the proliferating population that arise from dedifferentiated Müller glia, a very small percentage go on to become retinal neurons [4, 141]. The inability of the cells to differentiate into retinal neurons implies that either the signals and/or competence necessary for differentiation have been lost or there are signals present that direct progenitor cells away from differentiation into retinal neurons. Further, if the progenitor cells can be induced to differentiate, they will have to functionally integrate into the diseased or injured retina. This, in and of itself, will be a challenge if glial scars are present in the tissue as the glial scars will prevent ntegration by inhibiting migration, placement, and/or synapse formation. Clearly, investigators have been untangling which signaling pathways are critical for various aspects of reactive gliosis to occur. If signals that are necessary for proliferation can be separated from those necessary for glial scars to form, there is the possibility that therapeutic approaches could be engineered that will block scar formation while allowing proliferation to occur. There are many challenges ahead before the potential of Müller glia as a source for retinal regeneration can be realized.

Acknowledgements

This work was supported by grant 1R01EY019525 (TBA) and 1R15EY020816 (TBA) from the National Eye Institute and the American Health Assistance Foundation (TBA).

Author details

Teri L. Belecky-Adams[1,2], Ellen C. Chernoff[1,2], Jonathan M. Wilson[1,2] and Subramanian Dharmarajan[1,2]

*Address all correspondence to: tbadams@iupui.edu

1 Department of Biology, Indiana University-Purdue University Indianapolis, Indianapolis, IN, USA

2 Center for Regenerative Biology and Medicine, Indiana University- Purdue University Indianapolis, IN, USA

References

[1] Daadi MM. Novel paths towards neural cellular products for neurological disorders. Regenerative medicine. 2011 Nov;6(6 Suppl):25-30. PubMed PMID: 21999259. Epub 2011/10/26. eng.

[2] Wohl SG, Schmeer CW, Isenmann S. Neurogenic potential of stem/progenitor-like cells in the adult mammalian eye. Prog Retin Eye Res. 2012 May;31(3):213-42. PubMed PMID: 22353284. Epub 2012/02/23. eng.

[3] Sarthy VaR, Harris. The Retinal Muller Cell Structure and Function. Blakemore C, editor: Kluwer Academic Publishers; 2002.

[4] Bringmann A, Pannicke T, Grosche J, Francke M, Wiedemann P, Skatchkov SN, et al. Muller cells in the healthy and diseased retina. Prog Retin Eye Res. 2006 Jul;25(4): 397-424. PubMed PMID: 16839797. Epub 2006/07/15. eng.

[5] Miller RH. Regulation of oligodendrocyte development in the vertebrate CNS. Prog Neurobiol. 2002 Aug;67(6):451-67. PubMed PMID: 12385864.

[6] Wetts R, Fraser SE. Multipotent precursors can give rise to all major cell types of the frog retina. Science. 1988;239(4844):1142-5.

[7] Turner DL, Cepko CL. A common progenitor for neurons and glia persists in rat retina late in development. Nature. 1987 Jul 9-15;328(6126):131-6. PubMed PMID: 3600789. Epub 1987/07/09. eng.

[8] Holt CE, Bertsch TW, Ellis HM, Harris WA. Cellular determination in the Xenopus retina is independent of lineage and birth date. Neuron. 1988;1(1):15-26.

[9] Turner DL, Snyder EY, Cepko CL. Lineage-independent determination of cell type in the embryonic mouse retina. Neuron. 1990 Jun;4(6):833-45. PubMed PMID: 2163263. Epub 1990/06/01. eng.

[10] Young RW. Cell differentiation in the retina of the mouse. Anat Rec. 1985 Jun;212(2): 199-205. PubMed PMID: 3842042. Epub 1985/06/01. eng.

[11] Belecky-Adams T, Cook B, Adler R. Correlations between terminal mitosis and differentiated fate of retinal precursor cells in vivo and in vitro: analysis with the "window-labeling" technique. Dev Biol. 1996 Sep 15;178(2):304-15. PubMed PMID: 8812131. Epub 1996/09/15. eng.

[12] Zhang X, Serb JM, Greenlee MH. Mouse retinal development: a dark horse model for systems biology research. Bioinformatics and biology insights. 2011;5:99-113. PubMed PMID: 21698072. Pubmed Central PMCID: 3118678. Epub 2011/06/24. eng.

[13] Meller K, Tetzlaff W. Scanning electron microscopic studies on the development of the chick retina. Cell Tissue Res. 1976;170(2):145-59.

[14] Layer PG, Alber R, Mansky P, Vollmer G, Willbold E. Regeneration of a chimeric retina from single cells in vitro: cell-lineage-dependent formation of radial cell columns by segregated chick and quail cells. Cell Tissue Res. 1990 Feb;259(2):187-98. PubMed PMID: 2337919. Epub 1990/02/01. eng.

[15] Williams RW, Goldowitz D. Structure of clonal and polyclonal cell arrays in chimeric mouse retina. Proc Natl Acad Sci U S A. 1992 Feb 15;89(4):1184-8. PubMed PMID: 1741373. Pubmed Central PMCID: 48413. Epub 1992/02/15. eng.

[16] Fields-Berry SC, Halliday AL, Cepko CL. A recombinant retrovirus encoding alkaline phosphatase confirms clonal boundary assignment in lineage analysis of murine retina. Proc Natl Acad Sci U S A. 1992 Jan 15;89(2):693-7. PubMed PMID: 1731342. Pubmed Central PMCID: 48305. Epub 1992/01/15. eng.

[17] Reichenbach A, Stolzenburg JU, Eberhardt W, Chao TI, Dettmer D, Hertz L. What do retinal muller (glial) cells do for their neuronal 'small siblings'? Journal of chemical neuroanatomy. 1993 Jul-Aug;6(4):201-13. PubMed PMID: 8104418. Epub 1993/07/01. eng.

[18] Prada C, Puelles L, Genis-Galvez JM. A golgi study on the early sequence of differentiation of ganglion cells in the chick embryo retina. Anatomy and embryology. 1981;161(3):305-17. PubMed PMID: 7187824. Epub 1981/01/01. eng.

[19] Maslim J, Webster M, Stone J. Stages in the structural differentiation of retinal ganglion cells. J Comp Neurol. 1986 Dec 15;254(3):382-402. PubMed PMID: 3794013. Epub 1986/12/15. eng.

[20] Willbold E, Berger J, Reinicke M, Wolburg H. On the role of Muller glia cells in histogenesis: only retinal spheroids, but not tectal, telencephalic and cerebellar spheroids develop histotypical patterns. J Hirnforsch. 1997;38(3):383-96. PubMed PMID: 0009350510.

[21] Willbold E, Rothermel A, Tomlinson S, Layer PG. Muller glia cells reorganize reaggregating chicken retinal cells into correctly laminated in vitro retinae. Glia. 2000;29(1):45-57. PubMed PMID: 0010594922.

[22] Jing X, Malicki J. Zebrafish ale oko, an essential determinant of sensory neuron survival and the polarity of retinal radial glia, encodes the p50 subunit of dynactin. Development. 2009 Sep;136(17):2955-64. PubMed PMID: 19666822. Pubmed Central PMCID: 2723067. Epub 2009/08/12. eng.

[23] Rich KA, Figueroa SL, Zhan Y, Blanks JC. Effects of Muller cell disruption on mouse photoreceptor cell development. Exp Eye Res. 1995 Aug;61(2):235-48. PubMed PMID: 7556487. Epub 1995/08/01. eng.

[24] Ullian EM, Christopherson KS, Barres BA. Role for glia in synaptogenesis. Glia. 2004 Aug 15;47(3):209-16. PubMed PMID: 15252809. Epub 2004/07/15. eng.

[25] Ransom B, Behar T, Nedergaard M. New roles for astrocytes (stars at last). Trends Neurosci. 2003 Oct;26(10):520-2. PubMed PMID: 14522143. Epub 2003/10/03. eng.

[26] Risher WC, Eroglu C. Thrombospondins as key regulators of synaptogenesis in the central nervous system. Matrix Biol. 2012 Apr;31(3):170-7. PubMed PMID: 22285841. Epub 2012/01/31. eng.

[27] Phillips JB, Blanco-Sanchez B, Lentz JJ, Tallafuss A, Khanobdee K, Sampath S, et al. Harmonin (Ush1c) is required in zebrafish Muller glial cells for photoreceptor synaptic development and function. Disease models & mechanisms. 2011 Nov;4(6):786-800. PubMed PMID: 21757509. Pubmed Central PMCID: 3209648. Epub 2011/07/16. eng.

[28] Williams PR, Suzuki SC, Yoshimatsu T, Lawrence OT, Waldron SJ, Parsons MJ, et al. In vivo development of outer retinal synapses in the absence of glial contact. J Neurosci. 2010 Sep 8;30(36):11951-61. PubMed PMID: 20826659. Pubmed Central PMCID: 2946228. Epub 2010/09/10. eng.

[29] Abbott NJ. Astrocyte-endothelial interactions and blood-brain barrier permeability. J Anat. 2002 Jun;200(6):629-38. PubMed PMID: 12162730. Pubmed Central PMCID: 1570746.

[30] Cunha-Vaz J. The blood-ocular barriers. Surv Ophthalmol. 1979 Mar-Apr;23(5): 279-96. PubMed PMID: 380030. Epub 1979/03/01. eng.

[31] Tout S, Chan-Ling T, Hollander H, Stone J. The role of Muller cells in the formation of the blood-retinal barrier. Neuroscience. 1993 Jul;55(1):291-301. PubMed PMID: 8350991. Epub 1993/07/01. eng.

[32] Bussow H. The astrocytes in the retina and optic nerve head of mammals: a special glia for the ganglion cell axons. Cell Tissue Res. 1980;206(3):367-78. PubMed PMID: 6771013.

[33] Stone J, Itin A, Alon T, Pe'er J, Gnessin H, Chan-Ling T, et al. Development of retinal vasculature is mediated by hypoxia-induced vascular endothelial growth factor (VEGF) expression by neuroglia. J Neurosci. 1995 Jul;15(7 Pt 1):4738-47. PubMed PMID: 7623107. Epub 1995/07/01. eng.

[34] Eichler W, Yafai Y, Keller T, Wiedemann P, Reichenbach A. PEDF derived from glial Muller cells: a possible regulator of retinal angiogenesis. Exp Cell Res. 2004 Sep 10;299(1):68-78. PubMed PMID: 15302574. Epub 2004/08/11. eng.

[35] Paulson OB, Newman EA. Does the release of potassium from astrocyte endfeet regulate cerebral blood flow? Science. 1987 Aug 21;237(4817):896-8. PubMed PMID: 3616619. Pubmed Central PMCID: 2505270. Epub 1987/08/21. eng.

[36] Abukawa H, Tomi M, Kiyokawa J, Hori S, Kondo T, Terasaki T, et al. Modulation of retinal capillary endothelial cells by Muller glial cell-derived factors. Mol Vis. 2009;15:451-7. PubMed PMID: 19247458. Pubmed Central PMCID: 2647974. Epub 2009/02/28. eng.

[37] Ikeda T, Homma Y, Nisida K, Hirase K, Sotozono C, Kinoshita S, et al. Expression of transforming growth factor-beta s and their receptors by human retinal glial cells. Curr Eye Res. 1998 May;17(5):546-50. PubMed PMID: 9617551. Epub 1998/06/09. eng.

[38] Behzadian MA, Wang XL, Al-Shabrawey M, Caldwell RB. Effects of hypoxia on glial cell expression of angiogenesis-regulating factors VEGF and TGF-beta. Glia. 1998 Oct;24(2):216-25. PubMed PMID: 9728767. Epub 1998/09/05. eng.

[39] Ramsauer M, D'Amore PA. Contextual role for angiopoietins and TGFbeta1 in blood vessel stabilization. J Cell Sci. 2007 May 15;120(Pt 10):1810-7. PubMed PMID: 17502485. Epub 2007/05/16. eng.

[40] Arnold TD, Ferrero GM, Qiu H, Phan IT, Akhurst RJ, Huang EJ, et al. Defective retinal vascular endothelial cell development as a consequence of impaired integrin alphaVbeta8-mediated activation of transforming growth factor-beta. J Neurosci. 2012 Jan 25;32(4):1197-206. PubMed PMID: 22279205. Epub 2012/01/27. eng.

[41] Igarashi Y, Chiba H, Utsumi H, Miyajima H, Ishizaki T, Gotoh T, et al. Expression of receptors for glial cell line-derived neurotrophic factor (GDNF) and neurturin in the inner blood-retinal barrier of rats. Cell Struct Funct. 2000 Aug;25(4):237-41. PubMed PMID: 11129793. Epub 2000/12/29. eng.

[42] Mi H, Haeberle H, Barres BA. Induction of astrocyte differentiation by endothelial cells. J Neurosci. 2001 Mar 1;21(5):1538-47. PubMed PMID: 11222644. Epub 2001/02/27. eng.

[43] Sakimoto S, Kidoya H, Naito H, Kamei M, Sakaguchi H, Goda N, et al. A role for endothelial cells in promoting the maturation of astrocytes through the apelin/APJ system in mice. Development. 2012 Apr;139(7):1327-35. PubMed PMID: 22357924. Epub 2012/02/24. eng.

[44] Bonni A, Frank DA, Schindler C, Greenberg ME. Characterization of a pathway for ciliary neurotrophic factor signaling to the nucleus. Science. 1993 Dec 3;262(5139): 1575-9. PubMed PMID: 7504325. Epub 1993/12/03. eng.

[45] Rajan P, McKay RD. Multiple routes to astrocytic differentiation in the CNS. J Neurosci. 1998 May 15;18(10):3620-9. PubMed PMID: 9570793. Epub 1998/06/06. eng.

[46] Goureau O, Rhee KD, Yang XJ. Ciliary neurotrophic factor promotes muller glia differentiation from the postnatal retinal progenitor pool. Dev Neurosci. 2004;26(5-6): 359-70. PubMed PMID: 15855765. Epub 2005/04/28. eng.

[47] Ash J, McLeod DS, Lutty GA. Transgenic expression of leukemia inhibitory factor (LIF) blocks normal vascular development but not pathological neovascularization in the eye. Mol Vis. 2005;11:298-308. PubMed PMID: 15889014. Epub 2005/05/13. eng.

[48] Belanger M, Allaman I, Magistretti PJ. Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell metabolism. 2011 Dec 7;14(6):724-38. PubMed PMID: 22152301. Epub 2011/12/14. eng.

[49] Sokoloff L. Relation between physiological function and energy metabolism in the central nervous system. J Neurochem. 1977 Jul;29(1):13-26. PubMed PMID: 407330. Epub 1977/07/01. eng.

[50] Kuwabara T, Cogan DG. Retinal glycogen. Arch Ophthalmol. 1961 Nov;66:680-8. PubMed PMID: 14460992. Epub 1961/11/01. eng.

[51] Poitry-Yamate C, Tsacopoulos M. Glial (Muller) cells take up and phosphorylate [3H]2-deoxy-D-glucose in mammalian retina. Neurosci Lett. 1991 Jan 28;122(2):241-4. PubMed PMID: 2027525. Epub 1991/01/28. eng.

[52] Poitry-Yamate CL, Poitry S, Tsacopoulos M. Lactate released by Muller glial cells is metabolized by photoreceptors from mammalian retina. J Neurosci. 1995 Jul;15(7 Pt 2):5179-91. PubMed PMID: 7623144. Epub 1995/07/01. eng.

[53] Zielke HR, Zielke CL, Baab PJ. Direct measurement of oxidative metabolism in the living brain by microdialysis: a review. J Neurochem. 2009 May;109 Suppl 1:24-9. PubMed PMID: 19393005. Pubmed Central PMCID: 2792919. Epub 2009/05/07. eng.

[54] Poitry S, Poitry-Yamate C, Ueberfeld J, MacLeish PR, Tsacopoulos M. Mechanisms of glutamate metabolic signaling in retinal glial (Muller) cells. J Neurosci. 2000 Mar 1;20(5):1809-21. PubMed PMID: 10684882. Epub 2000/02/24. eng.

[55] Tsacopoulos M, Poitry-Yamate CL, MacLeish PR, Poitry S. Trafficking of molecules and metabolic signals in the retina. Prog Retin Eye Res. 1998 Jul;17(3):429-42. PubMed PMID: 9695799. Epub 1998/08/08. eng.

[56] Lin RY, Vera JC, Chaganti RS, Golde DW. Human monocarboxylate transporter 2 (MCT2) is a high affinity pyruvate transporter. J Biol Chem. 1998 Oct 30;273(44): 28959-65. PubMed PMID: 9786900. Epub 1998/10/24. eng.

[57] Gohdo T, Ueda H, Ohno S, Iijima H, Tsukahara S. Heat shock protein 70 expression increased in rabbit muller cells in the ischemia-reperfusion model. Ophthalmic Res. 2001 Sep-Oct;33(5):298-302. PubMed PMID: 11586064. Epub 2001/10/05. eng.

[58] Izumi Y, Kirby CO, Benz AM, Olney JW, Zorumski CF. Muller cell swelling, glutamate uptake, and excitotoxic neurodegeneration in the isolated rat retina. Glia. 1999 Feb 15;25(4):379-89. PubMed PMID: 10028920. Epub 1999/02/24. eng.

[59] Otori Y, Shimada S, Tanaka K, Ishimoto I, Tano Y, Tohyama M. Marked increase in glutamate-aspartate transporter (GLAST/GluT-1) mRNA following transient retinal ischemia. Brain Res Mol Brain Res. 1994 Dec;27(2):310-4. PubMed PMID: 7898315. Epub 1994/12/01. eng.

[60] Derouiche A, Rauen T. Coincidence of L-glutamate/L-aspartate transporter (GLAST) and glutamine synthetase (GS) immunoreactions in retinal glia: evidence for coupling of GLAST and GS in transmitter clearance. J Neurosci Res. 1995 Sep 1;42(1): 131-43. PubMed PMID: 8531222. Epub 1995/09/01. eng.

[61] Kanai Y, Hediger MA. The glutamate/neutral amino acid transporter family SLC1: molecular, physiological and pharmacological aspects. Pflugers Arch. 2004 Feb; 447(5):469-79. PubMed PMID: 14530974. Epub 2003/10/08. eng.

[62] Tsacopoulos M, Magistretti PJ. Metabolic coupling between glia and neurons. J Neurosci. 1996 Feb 1;16(3):877-85. PubMed PMID: 8558256. Epub 1996/02/01. eng.

[63] Linser P, Moscona AA. Induction of glutamine synthetase in embryonic neural retina: localization in Muller fibers and dependence on cell interactions. Proc Natl Acad Sci U S A. 1979 Dec;76(12):6476-80. PubMed PMID: 42916. Pubmed Central PMCID: 411888. Epub 1979/12/01. eng.

[64] Tsacopoulos M, Poitry-Yamate CL, Poitry S. Ammonium and glutamate released by neurons are signals regulating the nutritive function of a glial cell. J Neurosci. 1997 Apr 1;17(7):2383-90. PubMed PMID: 9065499. Epub 1997/04/01. eng.

[65] Brew H, Attwell D. Electrogenic glutamate uptake is a major current carrier in the membrane of axolotl retinal glial cells. Nature. 1987 Jun 25-Jul 1;327(6124):707-9. PubMed PMID: 2885752. Epub 1987/06/01. eng.

[66] Bringmann A, Kuhrt H, Germer A, Biedermann B, Reichenbach A. Muller (glial) cell development in vivo and in retinal explant cultures: morphology and electrophysiology, and the effects of elevated ammonia. J Hirnforsch. 1998;39(2):193-206. PubMed PMID: 10022343. Epub 1999/02/18. eng.

[67] Germer A, Jahnke C, Mack A, Enzmann V, Reichenbach A. Modification of glutamine synthetase expression by mammalian Muller (glial) cells in retinal organ cultures. Neuroreport. 1997 Sep 29;8(14):3067-72. PubMed PMID: 9331915. Epub 1997/10/23. eng.

[68] Newman EA, Frambach DA, Odette LL. Control of extracellular potassium levels by retinal glial cell K+ siphoning. Science. 1984 Sep 14;225(4667):1174-5. PubMed PMID: 6474173. Pubmed Central PMCID: 2693189. Epub 1984/09/14. eng.

[69] Karwoski CJ, Lu HK, Newman EA. Spatial buffering of light-evoked potassium increases by retinal Muller (glial) cells. Science. 1989 May 5;244(4904):578-80. PubMed PMID: 2785716. Pubmed Central PMCID: 2562506. Epub 1989/05/05. eng.

[70] Newman EA. Acid efflux from retinal glial cells generated by sodium bicarbonate cotransport. J Neurosci. 1996 Jan;16(1):159-68. PubMed PMID: 8613782. Epub 1996/01/01. eng.

[71] Linser P, Moscona AA. Carbonic anhydrase C in the neural retina: transition from generalized to glia-specific cell localization during embryonic development. Proc Natl Acad Sci U S A. 1981 Nov;78(11):7190-4. PubMed PMID: 6118868. Pubmed Central PMCID: 349222. Epub 1981/11/01. eng.

[72] Sarthy PV, Bunt AH. The ultrastructure of isolated glial (Muller) cells from the turtle retina. Anat Rec. 1982 Feb;202(2):275-83. PubMed PMID: 7065426. Epub 1982/02/01. eng.

[73] Newman EA, Astion ML. Localization and stoichiometry of electrogenic sodium bicarbonate cotransport in retinal glial cells. Glia. 1991;4(4):424-8. PubMed PMID: 1657777. Epub 1991/01/01. eng.

[74] Wu SM, Maple BR. Amino acid neurotransmitters in the retina: a functional overview. Vision Res. 1998 May;38(10):1371-84. PubMed PMID: 9667005.

[75] Bringmann A, Pannicke T, Biedermann B, Francke M, Iandiev I, Grosche J, et al. Role of retinal glial cells in neurotransmitter uptake and metabolism. Neurochem Int. 2009 Mar-Apr;54(3-4):143-60. PubMed PMID: 19114072. Epub 2008/12/31. eng.

[76] de Melo Reis RA, Ventura AL, Schitine CS, de Mello MC, de Mello FG. Muller glia as an active compartment modulating nervous activity in the vertebrate retina: neurotransmitters and trophic factors. Neurochem Res. 2008 Aug;33(8):1466-74. PubMed PMID: 18273703. Epub 2008/02/15. eng.

[77] Kugler P, Beyer A. Expression of glutamate transporters in human and rat retina and rat optic nerve. Histochem Cell Biol. 2003 Sep;120(3):199-212. PubMed PMID: 12898275. Epub 2003/08/05. eng.

[78] Barnett NL, Pow DV. Antisense knockdown of GLAST, a glial glutamate transporter, compromises retinal function. Invest Ophthalmol Vis Sci. 2000 Feb;41(2):585-91. PubMed PMID: 10670492. Epub 2000/02/12. eng.

[79] Harada T, Harada C, Watanabe M, Inoue Y, Sakagawa T, Nakayama N, et al. Functions of the two glutamate transporters GLAST and GLT-1 in the retina. Proc Natl Acad Sci U S A. 1998 Apr 14;95(8):4663-6. PubMed PMID: 9539795. Pubmed Central PMCID: 22547. Epub 1998/05/16. eng.

[80] Pow DV, Barnett NL, Penfold P. Are neuronal transporters relevant in retinal glutamate homeostasis? Neurochem Int. 2000 Aug-Sep;37(2-3):191-8. PubMed PMID: 10812204. Epub 2000/05/17. eng.

[81] De Bock M, Culot M, Wang N, da Costa A, Decrock E, Bol M, et al. Low extracellular Ca(2+) conditions induce an increase in brain endothelial permeability that involves intercellular Ca(2+) waves. Brain Res. 2012 Jul 10. PubMed PMID: 22789903.

[82] Gonzalez MI, Lopez-Colom AM, Ortega A. Sodium-dependent glutamate transport in Muller glial cells: regulation by phorbol esters. Brain Res. 1999 Jun 12;831(1-2):140-5. PubMed PMID: 10411993.

[83] Barnett NL, Pow DV, Robinson SR. Inhibition of Muller cell glutamine synthetase rapidly impairs the retinal response to light. Glia. 2000 Mar;30(1):64-73. PubMed PMID: 10696145. Epub 2000/03/01. eng.

[84] Nickerson PE, McLeod MC, Myers T, Clarke DB. Effects of epidermal growth factor and erythropoietin on Muller glial activation and phenotypic plasticity in the adult mammalian retina. J Neurosci Res. 2011 Jul;89(7):1018-30. PubMed PMID: 21484851.

[85] Leonelli M, Martins DO, Britto LR. TRPV1 receptors are involved in protein nitration and Muller cell reaction in the acutely axotomized rat retina. Exp Eye Res. 2010 Nov; 91(5):755-68. PubMed PMID: 20826152.

[86] Xue W, Cojocaru RI, Dudley VJ, Brooks M, Swaroop A, Sarthy VP. Ciliary neurotrophic factor induces genes associated with inflammation and gliosis in the retina: a gene profiling study of flow-sorted, Muller cells. PLoS One. 2011;6(5):e20326. PubMed PMID: 21637858. Pubmed Central PMCID: 3102695.

[87] Douglas MR, Morrison KC, Jacques SJ, Leadbeater WE, Gonzalez AM, Berry M, et al. Off-target effects of epidermal growth factor receptor antagonists mediate retinal ganglion cell disinhibited axon growth. Brain. 2009 Nov;132(Pt 11):3102-21. PubMed PMID: 19783665.

[88] Layton CJ, Becker S, Osborne NN. The effect of insulin and glucose levels on retinal glial cell activation and pigment epithelium-derived fibroblast growth factor-2. Mol Vis. 2006;12:43-54. PubMed PMID: 16446701.

[89] Dale N. Dynamic ATP signalling and neural development. J Physiol. 2008 May 15;586(10):2429-36. PubMed PMID: 18356200. Pubmed Central PMCID: 2464351.

[90] Leybaert L, Sanderson MJ. Intercellular Ca(2+) waves: mechanisms and function. Physiological reviews. 2012 Jul;92(3):1359-92. PubMed PMID: 22811430.

[91] Wurm A, Pannicke T, Iandiev I, Francke M, Hollborn M, Wiedemann P, et al. Purinergic signaling involved in Muller cell function in the mammalian retina. Prog Retin Eye Res. 2011 Sep;30(5):324-42. PubMed PMID: 21689780.

[92] Newman EA. Propagation of intercellular calcium waves in retinal astrocytes and Muller cells. J Neurosci. 2001 Apr 1;21(7):2215-23. PubMed PMID: 11264297. Pubmed Central PMCID: 2409971.

[93] Lopez-Colome AM, Salceda R, Fragoso G. Specific interaction of glutamate with membranes from cultured retinal pigment epithelium. J Neurosci Res. 1993 Mar 1;34(4):454-61. PubMed PMID: 8097266.

[94] Lopez-Colome AM, Martinez-Lozada Z, Guillem AM, Lopez E, Ortega A. Glutamate transporter-dependent mTOR phosphorylation in Muller glia cells. ASN neuro. 2012 Jul 23. PubMed PMID: 22817638. Pubmed Central PMCID: 3420017.

[95] Nagelhus EA, Horio Y, Inanobe A, Fujita A, Haug FM, Nielsen S, et al. Immunogold evidence suggests that coupling of K+ siphoning and water transport in rat retinal Muller cells is mediated by a coenrichment of Kir4.1 and AQP4 in specific membrane domains. Glia. 1999 Mar;26(1):47-54. PubMed PMID: 10088671.

[96] Francke M, Makarov F, Kacza J, Seeger J, Wendt S, Gartner U, et al. Retinal pigment epithelium melanin granules are phagocytozed by Muller glial cells in experimental retinal detachment. J Neurocytol. 2001 Feb;30(2):131-6. PubMed PMID: 11577251.

[97] Reichelt W, Stabel-Burow J, Pannicke T, Weichert H, Heinemann U. The glutathione level of retinal Muller glial cells is dependent on the high-affinity sodium-dependent uptake of glutamate. Neuroscience. 1997 Apr;77(4):1213-24. PubMed PMID: 9130799.

[98] Buffo A, Rite I, Tripathi P, Lepier A, Colak D, Horn AP, et al. Origin and progeny of reactive gliosis: A source of multipotent cells in the injured brain. P Natl Acad Sci USA. 2008 Mar 4;105(9):3581-6. PubMed PMID: ISI:000253846500072. English.

[99] Robel S, Berninger B, Gotz M. The stem cell potential of glia: lessons from reactive gliosis. Nat Rev Neurosci. 2011 Feb;12(2):88-104. PubMed PMID: ISI: 000286420100003. English.

[100] White BD, Nathe RJ, Maris DO, Nguyen NK, Goodson JM, Moon RT, et al. beta-Catenin Signaling Increases in Proliferating NG2+Progenitors and Astrocytes during Post-Traumatic Gliogenesis in the Adult Brain. Stem Cells. 2010 Feb;28(2):297-307. PubMed PMID: ISI:000275058400014. English.

[101] Liu B, Neufeld AH. Activation of epidermal growth factor receptors in astrocytes: From development to neural injury. J Neurosci Res. 2007 Dec;85(16):3523-9. PubMed PMID: ISI:000251778200003. English.

[102] Amankulor NM, Hambardzumyan D, Pyonteck SM, Becher OJ, Joyce JA, Holland EC. Sonic Hedgehog Pathway Activation Is Induced by Acute Brain Injury and Regulated by Injury-Related Inflammation. J Neurosci. 2009 Aug 19;29(33):10299-308. PubMed PMID: ISI:000269087300013. English.

[103] Fischer AJ, Bongini R. Turning Muller glia into neural progenitors in the retina. Mol Neurobiol. 2010 Dec;42(3):199-209. PubMed PMID: 21088932. Epub 2010/11/23. eng.

[104] Perron M, Kanekar S, Vetter ML, Harris WA. The genetic sequence of retinal development in the ciliary margin of the Xenopus eye. Dev Biol. 1998 Jul 15;199(2):185-200. PubMed PMID: ISI:000075365200002. English.

[105] Fischer AJ, Reh TA. Identification of a proliferating marginal zone of retinal progenitors in postnatal chickens. Developmental Biology. 2000;220(2):197-210.

[106] Fischer AJ, Bongini R. Turning Muller Glia into Neural Progenitors in the Retina. Mol Neurobiol. 2010 Dec;42(3):199-209. PubMed PMID: ISI:000284654000004. English.

[107] Otteson DC, Hitchcock PF. Stem cells in the teleost retina: persistent neurogenesis and injury-induced regeneration. Vision Res. 2003 Apr;43(8):927-36. PubMed PMID: ISI:000182254200009. English.

[108] Fischer AJ, Reh TA. Potential of Muller glia to become neurogenic retinal progenitor cells. Glia. 2003 Jul;43(1):70-6. PubMed PMID: 12761869. Epub 2003/05/23. eng.

[109] Kubota R, Hokoc JN, Moshiri A, McGuire C, Reh TA. A comparative study of neurogenesis in the retinal ciliary marginal zone of homeothermic vertebrates. Brain Res Dev Brain Res. 2002 Mar 31;134(1-2):31-41. PubMed PMID: 11947935.

[110] Fischer AJ, Reh TA. Muller glia are a potential source of neural regeneration in the postnatal chicken retina. Nature Neuroscience. 2001;4(3):247-52.

[111] Ooto S, Akagi T, Kageyama R, Akita J, Mandai M, Honda Y, et al. Potential for neural regeneration after neurotoxic injury in the adult mammalian retina. P Natl Acad Sci USA. 2004 Sep 14;101(37):13654-9. PubMed PMID: ISI:000223917900047. English.

[112] Das AV, Mallya KB, Zhao X, Ahmad F, Bhattacharya S, Thoreson WB, et al. Neural stem cell properties of Muller glia in the mammalian retina: regulation by Notch and Wnt signaling. Dev Biol. 2006 Nov 1;299(1):283-302. PubMed PMID: 16949068. Epub 2006/09/05. eng.

[113] Fischer AJ, Reh TA. Exogenous growth factors stimulate the regeneration of ganglion cells in the chicken retina. Dev Biol. 2002 Nov 15;251(2):367-79. PubMed PMID: 12435364. Epub 2002/11/19. eng.

[114] Bringmann A, Pannicke T, Grosche J, Francke M, Wiedemann P, Skatchkov SN, et al. Muller cells in the healthy and diseased retina. Prog Retin Eye Res. 2006 Jul;25(4): 397-424. PubMed PMID: ISI:000239884500003. English.

[115] Jadhav AP, Roesch K, Cepko CL. Development and neurogenic potential of Muller glial cells in the vertebrate retina. Prog Retin Eye Res. 2009 Jul;28(4):249-62. PubMed PMID: ISI:000269296600002. English.

[116] Sofroniew MV. Molecular dissection of reactive astrogliosis and glial scar formation. Trends Neurosci. 2009 Dec;32(12):638-47. PubMed PMID: 19782411. Pubmed Central PMCID: 2787735.

[117] Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. Acta neuropathologica. 2010 Jan;119(1):7-35. PubMed PMID: 20012068. Pubmed Central PMCID: 2799634. Epub 2009/12/17. eng.

[118] Roesch K, Stadler MB, Cepko CL. Gene expression changes within Muller glial cells in retinitis pigmentosa. Mol Vis. 2012;18:1197-214. PubMed PMID: 22665967. Pubmed Central PMCID: 3365136.

[119] Robaszkiewicz J, Chmielewska K, Figurska M, Wierzbowska J, Stankiewicz A. Muller glial cells--the mediators of vascular disorders with vitreomacular interface pathology in diabetic maculopathy. Klinika oczna. 2010;112(10-12):328-32. PubMed PMID: 21469528.

[120] Lieth E, Barber AJ, Xu B, Dice C, Ratz MJ, Tanase D, et al. Glial reactivity and impaired glutamate metabolism in short-term experimental diabetic retinopathy. Penn State Retina Research Group. Diabetes. 1998 May;47(5):815-20. PubMed PMID: 9588455. Epub 1998/05/20. eng.

[121] Ganesh BS, Chintala SK. Inhibition of reactive gliosis attenuates excitotoxicity-mediated death of retinal ganglion cells. PLoS One. 2011;6(3):e18305. PubMed PMID: 21483783. Pubmed Central PMCID: 3069086.

[122] Sullivan R, Penfold P, Pow DV. Neuronal migration and glial remodeling in degenerating retinas of aged rats and in nonneovascular AMD. Invest Ophthalmol Vis Sci. 2003 Feb;44(2):856-65. PubMed PMID: 12556422.

[123] Fischer AJ, Omar G, Eubanks J, McGuire CR, Dierks BD, Reh TA. Different aspects of gliosis in retinal Muller glia can be induced by CNTF, insulin, and FGF2 in the absence of damage. Mol Vis. 2004 Dec 22;10:973-86. PubMed PMID: 15623987. Epub 2004/12/30. eng.

[124] Yamaguchi K, Nagai S, Ninomiya-Tsuji J, Nishita M, Tamai K, Irie K, et al. XIAP, a cellular member of the inhibitor of apoptosis protein family, links the receptors to TAB1-TAK1 in the BMP signaling pathway. EMBO J. 1999 Jan 4;18(1):179-87. PubMed PMID: 9878061. Pubmed Central PMCID: 1171113. Epub 1999/01/07. eng.

[125] Ishitani T, Ninomiya-Tsuji J, Nagai S, Nishita M, Meneghini M, Barker N, et al. The TAK1-NLK-MAPK-related pathway antagonizes signalling between beta-catenin and transcription factor TCF. Nature. 1999 Jun 24;399(6738):798-802. PubMed PMID: 10391247. Epub 1999/07/03. eng.

[126] Meneghini MD, Ishitani T, Carter JC, Hisamoto N, Ninomiya-Tsuji J, Thorpe CJ, et al. MAP kinase and Wnt pathways converge to downregulate an HMG-domain repressor in Caenorhabditis elegans. Nature. 1999 Jun 24;399(6738):793-7. PubMed PMID: 10391246. Epub 1999/07/03. eng.

[127] Kimura N, Matsuo R, Shibuya H, Nakashima K, Taga T. BMP2-induced apoptosis is mediated by activation of the TAK1-p38 kinase pathway that is negatively regulated by Smad6. J Biol Chem. 2000 Jun 9;275(23):17647-52. PubMed PMID: 10748100. Epub 2000/04/05. eng.

[128] Zhang D, Gaussin V, Taffet GE, Belaguli NS, Yamada M, Schwartz RJ, et al. TAK1 is activated in the myocardium after pressure overload and is sufficient to provoke heart failure in transgenic mice. Nat Med. 2000 May;6(5):556-63. PubMed PMID: 10802712. Epub 2000/05/10. eng.

[129] Rajan P, Panchision DM, Newell LF, McKay RD. BMPs signal alternately through a SMAD or FRAP-STAT pathway to regulate fate choice in CNS stem cells. J Cell Biol. 2003 Jun 9;161(5):911-21. PubMed PMID: 12796477. Pubmed Central PMCID: 2172962. Epub 2003/06/11. eng.

[130] Aoki H, Fujii M, Imamura T, Yagi K, Takehara K, Kato M, et al. Synergistic effects of different bone morphogenetic protein type I receptors on alkaline phosphatase induction. J Cell Sci. 2001 Apr;114(Pt 8):1483-9. PubMed PMID: 11282024. Epub 2001/04/03. eng.

[131] Sahni V, Mukhopadhyay A, Tysseling V, Hebert A, Birch D, McGuire TL, et al. BMPR1a and BMPR1b signaling exert opposing effects on gliosis after spinal cord injury. J Neurosci. 2010 Feb 3;30(5):1839-55. PubMed PMID: 20130193. Pubmed Central PMCID: 3093918. Epub 2010/02/05. eng.

[132] Fuller ML, DeChant AK, Rothstein B, Caprariello A, Wang R, Hall AK, et al. Bone morphogenetic proteins promote gliosis in demyelinating spinal cord lesions. Ann Neurol. 2007 Sep;62(3):288-300. PubMed PMID: 17696121. Epub 2007/08/19. eng.

[133] Ueki Y, Reh TA. Activation of BMP-Smad1/5/8 signaling promotes survival of retinal ganglion cells after damage in vivo. PLoS One. 2012;7(6):e38690. PubMed PMID: 22701694. Pubmed Central PMCID: 3368846.

[134] Zode GS, Clark AF, Wordinger RJ. Bone morphogenetic protein 4 inhibits TGF-beta2 stimulation of extracellular matrix proteins in optic nerve head cells: role of gremlin in ECM modulation. Glia. 2009 May;57(7):755-66. PubMed PMID: 19031438. Epub 2008/11/26. eng.

[135] Izumi T, Yokota-Hashimoto H, Zhao S, Wang J, Halban PA, Takeuchi T. Dominant negative pathogenesis by mutant proinsulin in the Akita diabetic mouse. Diabetes. 2003 Feb;52(2):409-16. PubMed PMID: 12540615. Epub 2003/01/24. eng.

[136] Lewis GP, Fisher SK. Up-regulation of glial fibrillary acidic protein in response to retinal injury: its potential role in glial remodeling and a comparison to vimentin expression. Int Rev Cytol. 2003;230:263-90. PubMed PMID: 14692684.

[137] Pekny M, Nilsson M. Astrocyte activation and reactive gliosis. Glia. 2005 Jun;50(4): 427-34. PubMed PMID: 15846805. Epub 2005/04/23. eng.

[138] Vazquez-Chona FR, Swan A, Ferrell WD, Jiang L, Baehr W, Chien WM, et al. Proliferative reactive gliosis is compatible with glial metabolic support and neuronal function. BMC Neurosci. 2011;12:98. PubMed PMID: 21985191. Pubmed Central PMCID: 3203081. Epub 2011/10/12. eng.

[139] Menet V, Prieto M, Privat A, Gimenez y Ribotta M. Axonal plasticity and functional recovery after spinal cord injury in mice deficient in both glial fibrillary acidic protein and vimentin genes. Proc Natl Acad Sci U S A. 2003 Jul 22;100(15):8999-9004. PubMed PMID: 12861073. Pubmed Central PMCID: 166427.

[140] Nakazawa T, Takeda M, Lewis GP, Cho KS, Jiao J, Wilhelmsson U, et al. Attenuated glial reactions and photoreceptor degeneration after retinal detachment in mice deficient in glial fibrillary acidic protein and vimentin. Invest Ophthalmol Vis Sci. 2007 Jun;48(6):2760-8. PubMed PMID: 17525210. Epub 2007/05/26. eng.

[141] Bringmann A, Wiedemann P. Muller glial cells in retinal disease. Ophthalmologica Journal international d'ophtalmologie International journal of ophthalmology Zeitschrift fur Augenheilkunde. 2012;227(1):1-19. PubMed PMID: 21921569.

[142] Chen H, Weber AJ. Expression of glial fibrillary acidic protein and glutamine synthetase by Muller cells after optic nerve damage and intravitreal application of brain-de-

rived neurotrophic factor. Glia. 2002 Apr 15;38(2):115-25. PubMed PMID: 11948805. Epub 2002/04/12. eng.

[143] Francke M, Faude F, Pannicke T, Bringmann A, Eckstein P, Reichelt W, et al. Electrophysiology of rabbit Muller (glial) cells in experimental retinal detachment and PVR. Invest Ophthalmol Vis Sci. 2001 Apr;42(5):1072-9. PubMed PMID: 11274088.

[144] Francke M, Faude F, Pannicke T, Uckermann O, Weick M, Wolburg H, et al. Glial cell-mediated spread of retinal degeneration during detachment: a hypothesis based upon studies in rabbits. Vision Res. 2005 Aug;45(17):2256-67. PubMed PMID: 15924940.

[145] Marc RE, Murry RF, Fisher SK, Linberg KA, Lewis GP. Amino acid signatures in the detached cat retina. Invest Ophthalmol Vis Sci. 1998 Aug;39(9):1694-702. PubMed PMID: 9699559.

[146] Sherry DM, Townes-Anderson E. Rapid glutamatergic alterations in the neural retina induced by retinal detachment. Invest Ophthalmol Vis Sci. 2000 Aug;41(9):2779-90. PubMed PMID: 10937598.

[147] Drescher KM, Whittum-Hudson JA. Herpes simplex virus type 1 alters transcript levels of tumor necrosis factor-alpha and interleukin-6 in retinal glial cells. Invest Ophthalmol Vis Sci. 1996 Oct;37(11):2302-12. PubMed PMID: 8843914.

[148] Aiello LP, Pierce EA, Foley ED, Takagi H, Chen H, Riddle L, et al. Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor chimeric proteins. Proc Natl Acad Sci U S A. 1995 Nov 7;92(23):10457-61. PubMed PMID: 7479819. Epub 1995/11/07. eng.

[149] Roque RS, Rosales AA, Jingjing L, Agarwal N, Al-Ubaidi MR. Retina-derived microglial cells induce photoreceptor cell death in vitro. Brain Res. 1999;836(1-2):110-9. PubMed PMID: 0010415410.

[150] Yafai Y, Iandiev I, Wiedemann P, Reichenbach A, Eichler W. Retinal endothelial angiogenic activity: effects of hypoxia and glial (Muller) cells. Microcirculation. 2004 Oct-Nov;11(7):577-86. PubMed PMID: 15513867.

[151] Walshe TE, Saint-Geniez M, Maharaj AS, Sekiyama E, Maldonado AE, D'Amore PA. TGF-beta is required for vascular barrier function, endothelial survival and homeostasis of the adult microvasculature. PLoS One. 2009;4(4):e5149. PubMed PMID: 19340291. Pubmed Central PMCID: 2659748.

[152] Howe KL, Reardon C, Wang A, Nazli A, McKay DM. Transforming growth factor-beta regulation of epithelial tight junction proteins enhances barrier function and blocks enterohemorrhagic Escherichia coli O157:H7-induced increased permeability. Am J Pathol. 2005 Dec;167(6):1587-97. PubMed PMID: 16314472. Pubmed Central PMCID: 1613202.

[153] Simo R, Carrasco E, Garcia-Ramirez M, Hernandez C. Angiogenic and antiangiogenic factors in proliferative diabetic retinopathy. Current diabetes reviews. 2006 Feb; 2(1):71-98. PubMed PMID: 18220619.

[154] Bringmann A, Reichenbach A. Role of Muller cells in retinal degenerations. Frontiers in bioscience : a journal and virtual library. 2001 Oct 1;6:E72-92. PubMed PMID: 11578954. Epub 2001/10/02. eng.

[155] Eichler W, Yafai Y, Wiedemann P, Reichenbach A. Angiogenesis-related factors derived from retinal glial (Muller) cells in hypoxia. Neuroreport. 2004 Jul 19;15(10): 1633-7. PubMed PMID: 15232297.

[156] Honjo M, Tanihara H, Kido N, Inatani M, Okazaki K, Honda Y. Expression of ciliary neurotrophic factor activated by retinal Muller cells in eyes with NMDA- and kainic acid-induced neuronal death. Invest Ophthalmol Vis Sci. 2000 Feb;41(2):552-60. PubMed PMID: 10670488. Epub 2000/02/12. eng.

[157] Mervin K, Valter K, Maslim J, Lewis G, Fisher S, Stone J. Limiting photoreceptor death and deconstruction during experimental retinal detachment: the value of oxygen supplementation. American journal of ophthalmology. 1999 Aug;128(2):155-64. PubMed PMID: 10458170. Epub 1999/08/24. eng.

[158] Akiyama H, Nakazawa T, Shimura M, Tomita H, Tamai M. Presence of mitogen-activated protein kinase in retinal Muller cells and its neuroprotective effect ischemia-reperfusion injury. Neuroreport. 2002 Nov 15;13(16):2103-7. PubMed PMID: 12438934. Epub 2002/11/20. eng.

[159] Wahlin KJ, Adler R, Zack DJ, Campochiaro PA. Neurotrophic signaling in normal and degenerating rodent retinas. Exp Eye Res. 2001 Nov;73(5):693-701. PubMed PMID: 11747369. Epub 2001/12/19. eng.

[160] Koeberle PD, Baehr M. The upregulation of GLAST-1 is an indirect antiapoptotic mechanism of GDNF and neurturin in the adult CNS. Cell Death Differ. 2008 Mar; 15(3):471-83. PubMed PMID: ISI:000253239900006. English.

[161] Amin RH, Frank RN, Kennedy A, Eliott D, Puklin JE, Abrams GW. Vascular endothelial growth factor is present in glial cells of the retina and optic nerve of human subjects with nonproliferative diabetic retinopathy. Invest Ophthalmol Vis Sci. 1997 Jan;38(1):36-47. PubMed PMID: ISI:A1997WC89700005. English.

[162] Eichler W, Kuhrt H, Hoffmann S, Wiedemann P, Reichenbach A. VEGF release by retinal glia depends on both oxygen and glucose supply. Neuroreport. 2000 Nov 9;11(16):3533-7. PubMed PMID: 11095513.

[163] Murohara T, Horowitz JR, Silver M, Tsurumi Y, Chen D, Sullivan A, et al. Vascular endothelial growth factor/vascular permeability factor enhances vascular permeability via nitric oxide and prostacyclin. Circulation. 1998 Jan 6-13;97(1):99-107. PubMed PMID: 9443437.

[164] Majka S, McGuire PG, Das A. Regulation of matrix metalloproteinase expression by tumor necrosis factor in a murine model of retinal neovascularization. Invest Ophthalmol Vis Sci. 2002 Jan;43(1):260-6. PubMed PMID: 11773040. Epub 2002/01/05. eng.

[165] Kawasaki A, Otori Y, Barnstable CJ. Muller cell protection of rat retinal ganglion cells from glutamate and nitric oxide neurotoxicity. Invest Ophthalmol Vis Sci. 2000 Oct; 41(11):3444-50. PubMed PMID: 11006237. Epub 2000/09/28. eng.

[166] Huster D, Reichenbach A, Reichelt W. The glutathione content of retinal Muller (glial) cells: effect of pathological conditions. Neurochemistry international. 2000 Apr;36(4-5):461-9. PubMed PMID: 10733014. Epub 2000/03/25. eng.

[167] Du YP, Sarthy VP, Kern TS. Interaction between NO and COX pathways in retinal cells exposed to elevated glucose and retina of diabetic rats. Am J Physiol-Reg I. 2004 Oct;287(4):R735-R41. PubMed PMID: ISI:000223884500006. English.

[168] Goureau O, Regnier-Ricard F, Courtois Y. Requirement for nitric oxide in retinal neuronal cell death induced by activated Muller glial cells. J Neurochem. 1999 Jun;72(6): 2506-15. PubMed PMID: ISI:000080434800032. English.

[169] Brune B, von Knethen A. The role of nitric oxide and cyclooxygenase-2 in attenuating apoptosis. Journal of environmental pathology, toxicology and oncology : official organ of the International Society for Environmental Toxicology and Cancer. 2002;21(2):103-12. PubMed PMID: 12086396. Epub 2002/06/28. eng.

[170] Goldstein IM, Ostwald P, Roth S. Nitric oxide: a review of its role in retinal function and disease. Vision Res. 1996 Sep;36(18):2979-94. PubMed PMID: 8917798. Epub 1996/09/01. eng.

[171] Nakamura N, Hasegawa G, Obayashi H, Yamazaki M, Ogata M, Nakano K, et al. Increased concentration of pentosidine, an advanced glycation end product, and interleukin-6 in the vitreous of patients with proliferative diabetic retinopathy. Diabetes research and clinical practice. 2003 Aug;61(2):93-101. PubMed PMID: 12951277. Epub 2003/09/03. eng.

[172] Tezel G, Wax MB. Increased production of tumor necrosis factor-alpha by glial cells exposed to simulated ischemia or elevated hydrostatic pressure induces apoptosis in cocultured retinal ganglion cells. J Neurosci. 2000 Dec 1;20(23):8693-700. PubMed PMID: 11102475. Epub 2000/01/11. eng.

[173] Yoshida S, Yoshida A, Ishibashi T. Induction of IL-8, MCP-1, and bFGF by TNF-alpha in retinal glial cells: implications for retinal neovascularization during post-ischemic inflammation. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2004 May;242(5):409-13. PubMed PMID: 15029502. Epub 2004/03/19. eng.

[174] Bernardos RL, Barthel LK, Meyers JR, Raymond PA. Late-stage neuronal progenitors in the retina are radial Muller glia that function as retinal stem cells. J Neurosci. 2007 Jun 27;27(26):7028-40. PubMed PMID: 17596452.

[175] Fausett BV, Goldman D. A role for alpha1 tubulin-expressing Muller glia in regeneration of the injured zebrafish retina. J Neurosci. 2006 Jun 7;26(23):6303-13. PubMed PMID: 16763038.

[176] Karl MO, Hayes S, Nelson BR, Tan K, Buckingham B, Reh TA. Stimulation of neural regeneration in the mouse retina. Proc Natl Acad Sci U S A. 2008 Dec 9;105(49): 19508-13. PubMed PMID: 19033471. Pubmed Central PMCID: 2614791.

[177] Ooto S, Akagi T, Kageyama R, Akita J, Mandai M, Honda Y, et al. Potential for neural regeneration after neurotoxic injury in the adult mammalian retina. Proc Natl Acad Sci U S A. 2004 Sep 14;101(37):13654-9. PubMed PMID: 15353594. Pubmed Central PMCID: 518808.

[178] Fischer AJ, Scott MA, Ritchey ER, Sherwood P. Mitogen-activated protein kinase-signaling regulates the ability of Muller glia to proliferate and protect retinal neurons against excitotoxicity. Glia. 2009 Nov 1;57(14):1538-52. PubMed PMID: 19306360. Pubmed Central PMCID: 2775435. Epub 2009/03/24. eng.

[179] Fischer AJ, Scott MA, Tuten W. Mitogen-activated protein kinase-signaling stimulates Muller glia to proliferate in acutely damaged chicken retina. Glia. 2009 Jan 15;57(2):166-81. PubMed PMID: 18709648. Pubmed Central PMCID: 2774719. Epub 2008/08/19. eng.

[180] Wan J, Ramachandran R, Goldman D. HB-EGF is necessary and sufficient for Muller glia dedifferentiation and retina regeneration. Developmental cell. 2012 Feb 14;22(2): 334-47. PubMed PMID: 22340497. Pubmed Central PMCID: 3285435.

[181] Meyers JR, Hu L, Moses A, Kaboli K, Papandrea A, Raymond PA. ss-catenin/Wnt signaling controls progenitor fate in the developing and regenerating zebrafish retina. Neural development. 2012 Aug 24;7(1):30. PubMed PMID: 22920725.

[182] Dyer MA, Cepko CL. Control of Muller glial cell proliferation and activation following retinal injury. Nat Neurosci. 2000 Sep;3(9):873-80. PubMed PMID: 10966617.

[183] Koguchi K, Nakatsuji Y, Nakayama K, Sakoda S. Modulation of astrocyte proliferation by cyclin-dependent kinase inhibitor p27(Kip1). Glia. 2002 Feb;37(2):93-104. PubMed PMID: 11754208.

[184] Levine EM, Close J, Fero M, Ostrovsky A, Reh TA. p27(Kip1) regulates cell cycle withdrawal of late multipotent progenitor cells in the mammalian retina. Dev Biol. 2000;219(2):299-314. PubMed PMID: 0010694424.

[185] Ohno-Matsui K, Morita I, Tombran-Tink J, Mrazek D, Onodera M, Uetama T, et al. Novel mechanism for age-related macular degeneration: an equilibrium shift be-

tween the angiogenesis factors VEGF and PEDF. J Cell Physiol. 2001 Dec;189(3): 323-33. PubMed PMID: 11748590.

[186] Ogata N, Nishikawa M, Nishimura T, Mitsuma Y, Matsumura M. Unbalanced vitreous levels of pigment epithelium-derived factor and vascular endothelial growth factor in diabetic retinopathy. Am J Ophthalmol. 2002 Sep;134(3):348-53. PubMed PMID: 12208245.

[187] Duh EJ, Yang HS, Suzuma I, Miyagi M, Youngman E, Mori K, et al. Pigment epithelium-derived factor suppresses ischemia-induced retinal neovascularization and VEGF-induced migration and growth. Invest Ophthalmol Vis Sci. 2002 Mar;43(3): 821-9. PubMed PMID: 11867604.

[188] Miller JW, Adamis AP, Shima DT, D'Amore PA, Moulton RS, O'Reilly MS, et al. Vascular endothelial growth factor/vascular permeability factor is temporally and spatially correlated with ocular angiogenesis in a primate model. Am J Pathol. 1994 Sep; 145(3):574-84. PubMed PMID: 7521577. Epub 1994/09/01. eng.

[189] Boehm BO, Lang G, Feldmann B, Kurkhaus A, Rosinger S, Volpert O, et al. Proliferative diabetic retinopathy is associated with a low level of the natural ocular anti-angiogenic agent pigment epithelium-derived factor (PEDF) in aqueous humor. a pilot study. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 2003 Jun;35(6):382-6. PubMed PMID: 12920663.

[190] Boehm BO, Lang G, Volpert O, Jehle PM, Kurkhaus A, Rosinger S, et al. Low content of the natural ocular anti-angiogenic agent pigment epithelium-derived factor (PEDF) in aqueous humor predicts progression of diabetic retinopathy. Diabetologia. 2003 Mar;46(3):394-400. PubMed PMID: 12687338.

[191] Schofield CJ, Ratcliffe PJ. Oxygen sensing by HIF hydroxylases. Nat Rev Mol Cell Biol. 2004 May;5(5):343-54. PubMed PMID: 15122348.

[192] Penn JS, Madan A, Caldwell RB, Bartoli M, Caldwell RW, Hartnett ME. Vascular endothelial growth factor in eye disease. Prog Retin Eye Res. 2008 Jul;27(4):331-71. PubMed PMID: 18653375.

[193] Mignatti P, Tsuboi R, Robbins E, Rifkin DB. In vitro angiogenesis on the human amniotic membrane: requirement for basic fibroblast growth factor-induced proteinases. J Cell Biol. 1989 Feb;108(2):671-82. PubMed PMID: 2465298. Pubmed Central PMCID: 2115414.

[194] Unemori EN, Ferrara N, Bauer EA, Amento EP. Vascular endothelial growth factor induces interstitial collagenase expression in human endothelial cells. J Cell Physiol. 1992 Dec;153(3):557-62. PubMed PMID: 1447317.

[195] Lamoreaux WJ, Fitzgerald ME, Reiner A, Hasty KA, Charles ST. Vascular endothelial growth factor increases release of gelatinase A and decreases release of tissue inhibi-

tor of metalloproteinases by microvascular endothelial cells in vitro. Microvascular research. 1998 Jan;55(1):29-42. PubMed PMID: 9473407.

[196] Behzadian MA, Wang XL, Windsor LJ, Ghaly N, Caldwell RB. TGF-beta increases retinal endothelial cell permeability by increasing MMP-9: possible role of glial cells in endothelial barrier function. Invest Ophthalmol Vis Sci. 2001 Mar;42(3):853-9. PubMed PMID: 11222550.

[197] Takahashi T, Yamaguchi S, Chida K, Shibuya M. A single autophosphorylation site on KDR/Flk-1 is essential for VEGF-A-dependent activation of PLC-gamma and DNA synthesis in vascular endothelial cells. EMBO J. 2001 Jun 1;20(11):2768-78. PubMed PMID: 11387210. Pubmed Central PMCID: 125481.

[198] Fisher SK, Lewis GP. Muller cell and neuronal remodeling in retinal detachment and reattachment and their potential consequences for visual recovery: a review and reconsideration of recent data. Vision Res. 2003 Apr;43(8):887-97. PubMed PMID: 12668058.

[199] Wu KH, Madigan MC, Billson FA, Penfold PL. Differential expression of GFAP in early v late AMD: a quantitative analysis. Br J Ophthalmol. 2003 Sep;87(9):1159-66. PubMed PMID: 12928288. Pubmed Central PMCID: 1771844.

[200] Ramirez JM, Ramirez AI, Salazar JJ, de Hoz R, Trivino A. Changes of astrocytes in retinal ageing and age-related macular degeneration. Exp Eye Res. 2001 Nov;73(5): 601-15. PubMed PMID: 11747361. Epub 2001/12/19. eng.

[201] Bek T. Immunohistochemical characterization of retinal glial cell changes in areas of vascular occlusion secondary to diabetic retinopathy. Acta Ophthalmol Scand. 1997 Aug;75(4):388-92. PubMed PMID: 9374245.

[202] Bek T. Glial cell involvement in vascular occlusion of diabetic retinopathy. Acta Ophthalmol Scand. 1997 Jun;75(3):239-43. PubMed PMID: 9253965.

[203] Bek T. Capillary closure secondary to retinal vein occlusion. A morphological, histopathological, and immunohistochemical study. Acta Ophthalmol Scand. 1998 Dec; 76(6):643-8. PubMed PMID: 9881543.

[204] Bringmann A, Wiedemann P. Involvement of Muller glial cells in epiretinal membrane formation. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2009 Jul;247(7):865-83. PubMed PMID: 19415318.

[205] Anderson DH, Guerin CJ, Erickson PA, Stern WH, Fisher SK. Morphological recovery in the reattached retina. Invest Ophthalmol Vis Sci. 1986 Feb;27(2):168-83. PubMed PMID: 3943943.

[206] Fisher SK, Lewis GP, Linberg KA, Verardo MR. Cellular remodeling in mammalian retina: results from studies of experimental retinal detachment. Prog Retin Eye Res. 2005 May;24(3):395-431. PubMed PMID: 15708835.

[207] Zhu CL, Ji Y, Lee EJ, Grzywacz NM. Spatiotemporal pattern of rod degeneration in the S334ter-line-3 rat model of retinitis pigmentosa. Cell Tissue Res. 2012 Nov 10. PubMed PMID: 23143675.

[208] Marc RE, Jones BW. Retinal remodeling in inherited photoreceptor degenerations. Mol Neurobiol. 2003 Oct;28(2):139-47. PubMed PMID: 14576452.

[209] Sethi CS, Lewis GP, Fisher SK, Leitner WP, Mann DL, Luthert PJ, et al. Glial remodeling and neural plasticity in human retinal detachment with proliferative vitreoretinopathy. Invest Ophthalmol Vis Sci. 2005 Jan;46(1):329-42. PubMed PMID: 15623793.

[210] Guidry C. The role of Muller cells in fibrocontractive retinal disorders. Prog Retin Eye Res. 2005 Jan;24(1):75-86. PubMed PMID: 15555527.

[211] Girard P, Mimoun G, Karpouzas I, Montefiore G. Clinical risk factors for proliferative vitreoretinopathy after retinal detachment surgery. Retina. 1994;14(5):417-24. PubMed PMID: 7899716.

[212] Speicher MA, Fu AD, Martin JP, von Fricken MA. Primary vitrectomy alone for repair of retinal detachments following cataract surgery. Retina. 2000;20(5):459-64. PubMed PMID: 11039419.

[213] Miura M, Ideta H. Factors related to subretinal proliferation in patients with primary rhegmatogenous retinal detachment. Retina. 2000;20(5):465-8. PubMed PMID: 11039420.

[214] Hoffmann S, Friedrichs U, Eichler W, Rosenthal A, Wiedemann P. Advanced glycation end products induce choroidal endothelial cell proliferation, matrix metalloproteinase-2 and VEGF upregulation in vitro. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2002 Dec;240(12):996-1002. PubMed PMID: 12483322.

[215] Brown D, Hamdi H, Bahri S, Kenney MC. Characterization of an endogenous metalloproteinase in human vitreous. Curr Eye Res. 1994 Sep;13(9):639-47. PubMed PMID: 7805394.

[216] Grant MB, Caballero S, Tarnuzzer RW, Bass KE, Ljubimov AV, Spoerri PE, et al. Matrix metalloproteinase expression in human retinal microvascular cells. Diabetes. 1998 Aug;47(8):1311-7. PubMed PMID: 9703333.

[217] Steen B, Sejersen S, Berglin L, Seregard S, Kvanta A. Matrix metalloproteinases and metalloproteinase inhibitors in choroidal neovascular membranes. Invest Ophthalmol Vis Sci. 1998 Oct;39(11):2194-200. PubMed PMID: 9761302.

[218] Murphy AN, Unsworth EJ, Stetler-Stevenson WG. Tissue inhibitor of metalloproteinases-2 inhibits bFGF-induced human microvascular endothelial cell proliferation. J Cell Physiol. 1993 Nov;157(2):351-8. PubMed PMID: 7693724.

[219] Page-McCaw A, Ewald AJ, Werb Z. Matrix metalloproteinases and the regulation of tissue remodelling. Nat Rev Mol Cell Biol. 2007 Mar;8(3):221-33. PubMed PMID: 17318226. Pubmed Central PMCID: 2760082.

[220] Aricescu AR, McKinnell IW, Halfter W, Stoker AW. Heparan sulfate proteoglycans are ligands for receptor protein tyrosine phosphatase sigma. Mol Cell Biol. 2002 Mar; 22(6):1881-92. PubMed PMID: 11865065. Pubmed Central PMCID: 135600.

[221] Busch SA, Silver J. The role of extracellular matrix in CNS regeneration. Curr Opin Neurobiol. 2007 Feb;17(1):120-7. PubMed PMID: 17223033.

[222] Besser M, Jagatheaswaran M, Reinhard J, Schaffelke P, Faissner A. Tenascin C regulates proliferation and differentiation processes during embryonic retinogenesis and modulates the de-differentiation capacity of Muller glia by influencing growth factor responsiveness and the extracellular matrix compartment. Dev Biol. 2012 Sep 15;369(2):163-76. PubMed PMID: 22691363.

[223] Adamsky K, Schilling J, Garwood J, Faissner A, Peles E. Glial tumor cell adhesion is mediated by binding of the FNIII domain of receptor protein tyrosine phosphatase beta (RPTPbeta) to tenascin C. Oncogene. 2001 Feb 1;20(5):609-18. PubMed PMID: 11313993.

[224] Faissner A, Heck N, Dobbertin A, Garwood J. DSD-1-Proteoglycan/Phosphacan and receptor protein tyrosine phosphatase-beta isoforms during development and regeneration of neural tissues. Adv Exp Med Biol. 2006;557:25-53. PubMed PMID: 16955703.

[225] Yan Q, Sage EH, Hendrickson AE. SPARC is expressed by ganglion cells and astrocytes in bovine retina. J Histochem Cytochem. 1998 Jan;46(1):3-10. PubMed PMID: 10712100.

[226] Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. Acta Neuropathol. 2010 Jan;119(1):7-35. PubMed PMID: ISI:000273174400003. English.

[227] Newman E, Reichenbach A. The Muller cell: A functional element of the retina. Trends Neurosci. 1996 Aug;19(8):307-12. PubMed PMID: ISI:A1996VA75000002. English.

[228] Reese BE. Development of the retina and optic pathway. Vision Res. 2011 Apr 13;51(7):613-32. PubMed PMID: ISI:000290061300003. English.

[229] Rompani SB, Cepko CL. A Common Progenitor for Retinal Astrocytes and Oligodendrocytes. J Neurosci. 2010 Apr 7;30(14):4970-80. PubMed PMID: ISI:000276414800017. English.

[230] Powell EM, Geller HM. Dissection of astrocyte-mediated cues in neuronal guidance and process extension. Glia. 1999 Mar;26(1):73-83. PubMed PMID: ISI: 000078911800008. English.

[231] Ullian EM, Sapperstein SK, Christopherson KS, Barres BA. Control of synapse number by glia. Science. 2001 Jan 26;291(5504):657-61. PubMed PMID: ISI: 000166616000045. English.

[232] Halassa MM, Fellin T, Haydon PG. The tripartite synapse: roles for gliotransmission in health and disease. Trends Mol Med. 2007 Feb;13(2):54-63. PubMed PMID: ISI: 000244641500002. English.

[233] Barres BA. Thrombospondins are astrocyte-secreted proteins that promote CNS synaptogenesis. Neuropsychopharmacol. 2004 Dec;29:S8-S. PubMed PMID: ISI: 000225588000026. English.

[234] Abbott NJ, Ronnback L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. Nat Rev Neurosci. 2006 Jan;7(1):41-53. PubMed PMID: ISI: 000234139600015. English.

[235] Pellerin L, Bouzier-Sore AK, Aubert A, Serres S, Merle M, Costalat R, et al. Activity-dependent regulation of energy metabolism by astrocytes: An update. Glia. 2007 Sep; 55(12):1251-62. PubMed PMID: ISI:000248678400006. English.

[236] Brown AM, Tekkok SB, Ransom BR. Energy transfer from astrocytes to axons: the role of CNS glycogen. Neurochem Int. 2004 Sep;45(4):529-36. PubMed PMID: ISI: 000222295500010. English.

[237] Obara M, Szeliga M, Albrecht J. Regulation of pH in the mammalian central nervous system under normal and pathological conditions: Facts and hypotheses. Neurochem Int. 2008 May;52(6):905-19. PubMed PMID: ISI:000255431200001. English.

[238] Simard M, Nedergaard M. The neurobiology of glia in the context of water and ion homeostasis. Neuroscience. 2004;129(4):877-96. PubMed PMID: ISI:000225726000004. English.

[239] Tsacopoulos M, Magistretti PJ. Metabolic coupling between glia and neurons. J Neurosci. 1996 Feb 1;16(3):877-85. PubMed PMID: ISI:A1996TQ57300002. English.

[240] Franze K, Grosche J, Skatchkov SN, Schinkinger S, Foja C, Schlid D, et al. Muller cells are living optical fibers in the vertebrate retina. P Natl Acad Sci USA. 2007 May 15;104(20):8287-92. PubMed PMID: ISI:000246599900019. English.

[241] Mata NL, Radu RA, Clemmons RS, Travis GH. Isomerization and oxidation of vitamin a in cone-dominant retinas: A novel pathway for visual-pigment regeneration in daylight. Neuron. 2002 Sep 26;36(1):69-80. PubMed PMID: ISI:000178295100008. English.

[242] Tout S, Chanling T, Hollander H, Stone J. The Role of Muller Cells in the Formation of the Blood-Retinal Barrier. Neuroscience. 1993 Jul;55(1):291-301. PubMed PMID: ISI:A1993LL16300024. English.

[243] Sofroniew MV. Molecular dissection of reactive astrogliosis and glial scar formation. Trends Neurosci. 2009 Dec;32(12):638-47. PubMed PMID: ISI:000272643900005. English.

[244] Ridet JL, Malhotra SK, Privat A, Gage FH. Reactive astrocytes: cellular and molecular cues to biological function. Trends Neurosci. 1997 Dec;20(12):570-7. PubMed PMID: ISI:A1997YJ58000010. English.

[245] Silver J, Miller JH. Regeneration beyond the glial scar. Nat Rev Neurosci. 2004 Feb; 5(2):146-56. PubMed PMID: ISI:000188601400017. English.

[246] Bringmann A, Reichenbach A. Role of Muller cells in retinal degenerations. Front Biosci. 2001 Oct;6:E77-E92. PubMed PMID: ISI:000171372600023. English.

[247] Dubois-Dauphin M, Poitry-Yamate C, de Bilbao F, Julliard AK, Jourdan F, Donati G. Early postnatal Muller cell death leads to retinal but not optic nerve degeneration in NSE-Hu-Bcl-2 transgenic mice. Neuroscience. 2000;95(1):9-21. PubMed PMID: 0010619458.

[248] Peterson WM, Wang Q, Tzekova R, Wiegand SJ. Ciliary neurotrophic factor and stress stimuli activate the jak-STAT pathway in retinal neurons and glia [In Process Citation]. J Neurosci. 2000;20(11):4081-90. PubMed PMID: 0010818143.

[249] Kirsch M, Trautmann N, Ernst M, Hofmann HD. Involvement of gp130-associated cytokine signaling in Muller cell activation following optic nerve lesion. Glia. 2010 May;58(7):768-79. PubMed PMID: 20091786.

[250] Wahlin KJ, Campochiaro PA, Zack DJ, Adler R. Neurotrophic factors cause activation of intracellular signaling pathways in Muller cells and other cells of the inner retina, but not photoreceptors. Invest Ophthalmol Vis Sci. 2000;41(3):927-36.

[251] Ueki Y, Wang J, Chollangi S, Ash JD. STAT3 activation in photoreceptors by leukemia inhibitory factor is associated with protection from light damage. J Neurochem. 2008 May;105(3):784-96. PubMed PMID: 18088375.

[252] Hollborn M, Jahn K, Limb GA, Kohen L, Wiedemann P, Bringmann A. Characterization of the basic fibroblast growth factor-evoked proliferation of the human Muller cell line, MIO-M1. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2004 May;242(5):414-22. PubMed PMID: 14963717.

[253] Nelson CM, Gorsuch RA, Bailey TJ, Ackerman KM, Kassen SC, Hyde DR. Stat3 defines three populations of Muller glia and is required for initiating maximal Muller glia proliferation in the regenerating zebrafish retina. J Comp Neurol. 2012 Aug 8. PubMed PMID: 22886421.

[254] Sasaki M, Ozawa Y, Kurihara T, Noda K, Imamura Y, Kobayashi S, et al. Neuroprotective effect of an antioxidant, lutein, during retinal inflammation. Invest Ophthalmol Vis Sci. 2009 Mar;50(3):1433-9. PubMed PMID: 18997089. Epub 2008/11/11. eng.

[255] Lin ST, Wang Y, Xue Y, Feng DC, Xu Y, Xu LY. Tetrandrine suppresses LPS-induced astrocyte activation via modulating IKKs-IkappaBalpha-NF-kappaB signaling pathway. Mol Cell Biochem. 2008 Aug;315(1-2):41-9. PubMed PMID: 18498042. Epub 2008/05/24. eng.

[256] Dvoriantchikova G, Barakat D, Brambilla R, Agudelo C, Hernandez E, Bethea JR, et al. Inactivation of astroglial NF-kappa B promotes survival of retinal neurons following ischemic injury. Eur J Neurosci. 2009 Jul;30(2):175-85. PubMed PMID: 19614983. Pubmed Central PMCID: 2778328. Epub 2009/07/21. eng.

[257] Shamsuddin N, Kumar A. TLR2 mediates the innate response of retinal Muller glia to Staphylococcus aureus. J Immunol. 2011 Jun 15;186(12):7089-97. PubMed PMID: 21602496. Pubmed Central PMCID: 3110513.

[258] Kinkl N, Sahel J, Hicks D. Alternate FGF2-ERK1/2 signaling pathways in retinal photoreceptor and glial cells in vitro. J Biol Chem. 2001 Nov 23;276(47):43871-8. PubMed PMID: 11571286.

[259] Zong H, Ward M, Madden A, Yong PH, Limb GA, Curtis TM, et al. Hyperglycaemia-induced pro-inflammatory responses by retinal Muller glia are regulated by the receptor for advanced glycation end-products (RAGE). Diabetologia. 2010 Dec;53(12): 2656-66. PubMed PMID: 20835858.

[260] Walsh DT, Bresciani L, Saunders D, Manca MF, Jen A, Gentleman SM, et al. Amyloid beta peptide causes chronic glial cell activation and neuro-degeneration after intravitreal injection. Neuropathol Appl Neurobiol. 2005 Oct;31(5):491-502. PubMed PMID: 16150120.

[261] Rattner A, Nathans J. The genomic response to retinal disease and injury: evidence for endothelin signaling from photoreceptors to glia. J Neurosci. 2005 May 4;25(18): 4540-9. PubMed PMID: 15872101.

IntechOpen