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Reactive Muller Glia as Potential Retinal Progenitors

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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 membrane 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 layer

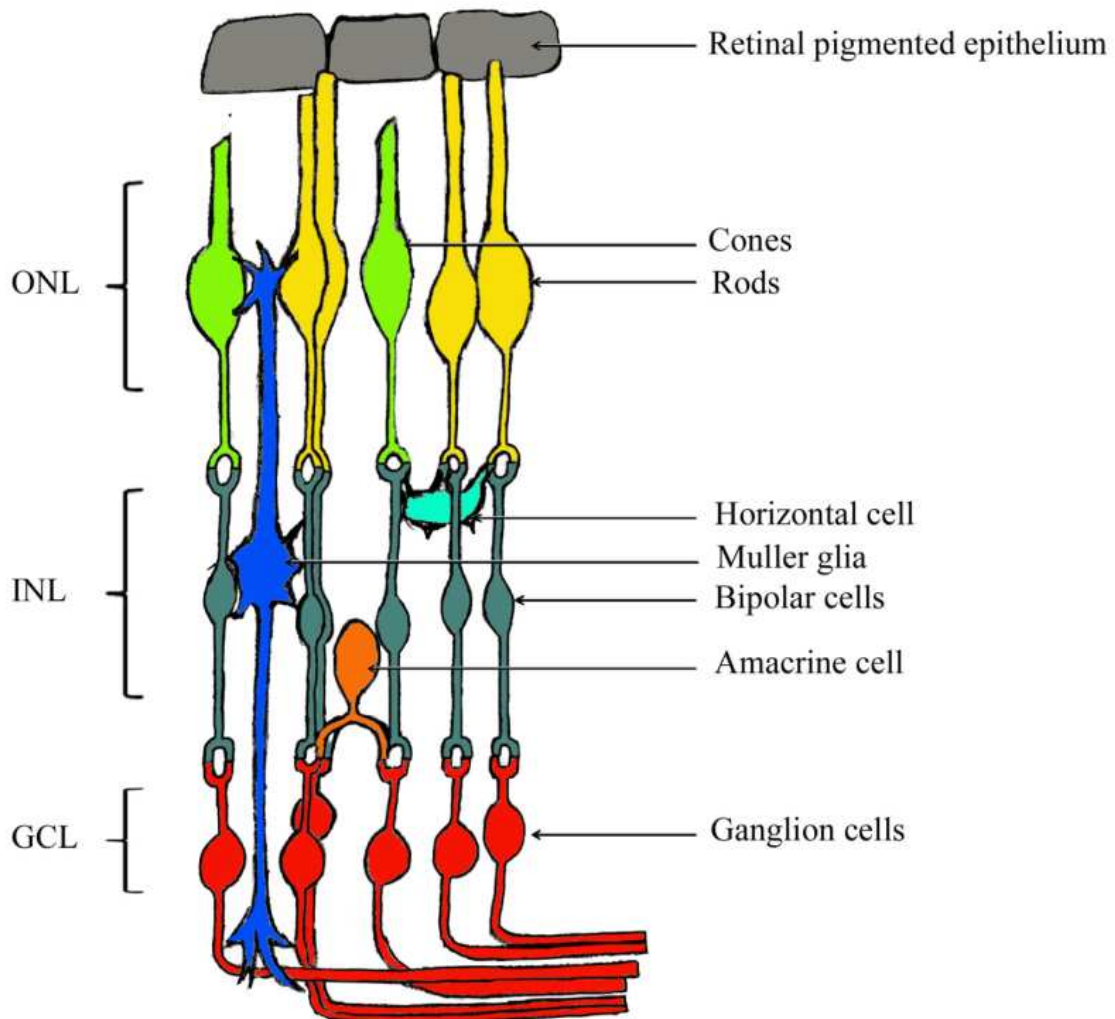


Figure 1. Organization of the mature retina: The retinal cells, which consist of neurons and glia, are organized into the outer nuclear layer (ONL), inner nuclear layer (INL) and the ganglion cell layer (GCL). The ONL consists of the rod and cone photoreceptor cells. The INL is made up of the horizontal 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	<ul style="list-style-type: none"> • Throughout the nervous system, including the retina and optic nerve [226] 	<ul style="list-style-type: none"> • Found exclusively in the inner nuclear layer of the retina with the process spanning the entire width of the retina [227, 228]
Origin	<ul style="list-style-type: none"> • Originate from the glial restricted neural stem cells or the bipotent O2A progenitor cell type [229] 	<ul style="list-style-type: none"> • Originate from the neural retinal progenitor cells [227, 228]
Morphology	<ul style="list-style-type: none"> • Have a stellate or star like morphology [226] 	<ul style="list-style-type: none"> • Have a radial morphology [227]
Functions	<ul style="list-style-type: none"> • 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] 	<ul style="list-style-type: none"> • 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 neurotransmitter recycling and also aid in glia-neuron communication [115]
Changes during reactive gliosis	<ul style="list-style-type: none"> • 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] 	<ul style="list-style-type: none"> • 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	<p>Following injury –</p> <ul style="list-style-type: none"> • 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] 	<p>Following retinal injury –</p> <ul style="list-style-type: none"> • 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 O₂, CO₂, 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 nerve 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 chapter. 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.

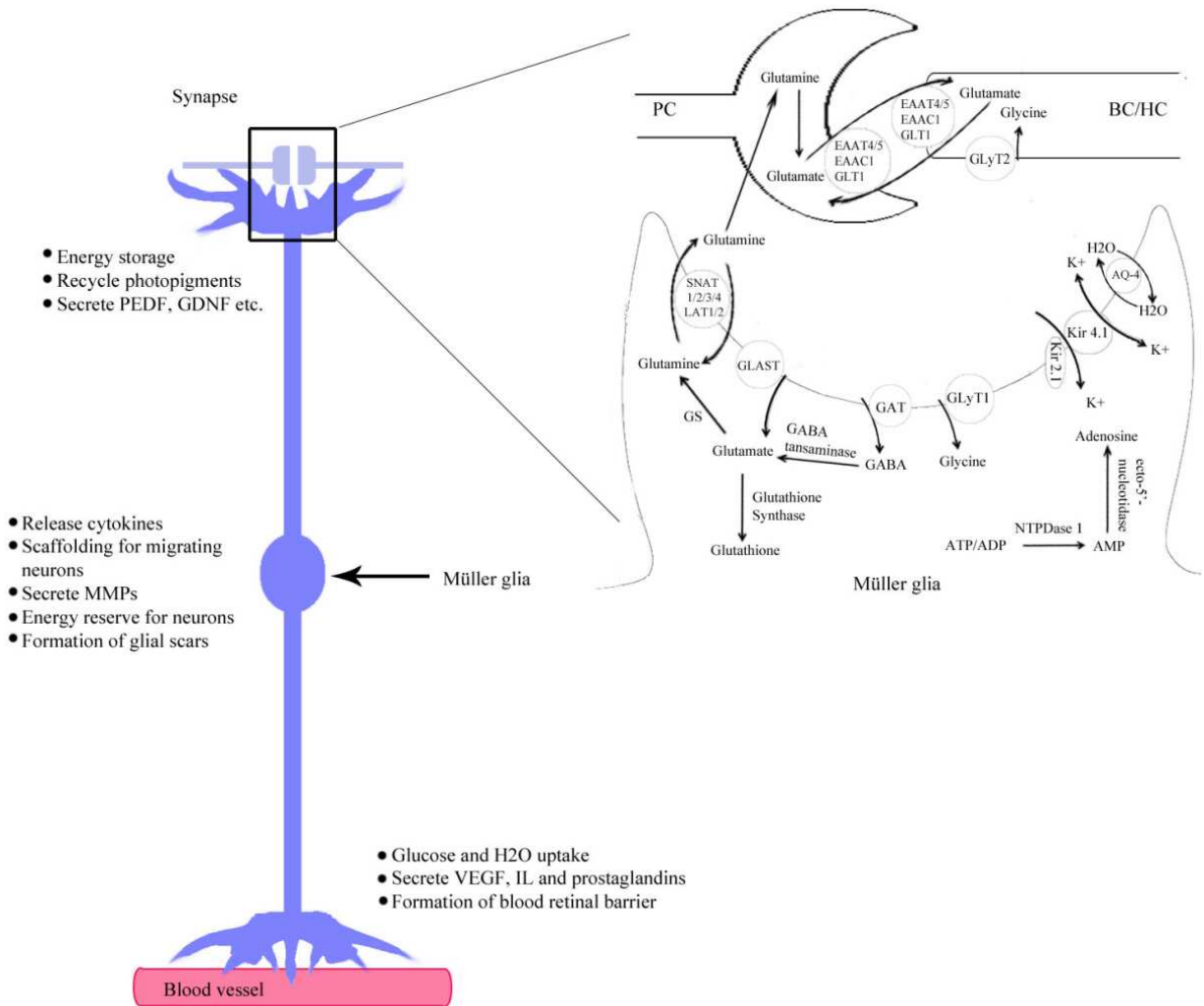


Figure 2. Aquaporin-4 (AQ-4), bipolar cell/ horizontal cell (BC/HC), excitatory amino acid transporter (EAAT), excitatory amino acid carrier (EAAC), glial cell derived neurotrophic factor (GDNF), glutamate transporter (GLT), glycine transporter (GlyT), glutamine synthetase (GS), interleukins (IL), L-type 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 $\beta 1$ (TGF $\beta 1$) 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 hemorrhaging in the brain [36-38]. TGF- $\beta 1$ 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 necessary 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 phosphorylated 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 dehydrogenase 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-transporters 3Na^+ ions and one H^+ and counter-transporters one K^+ [61]. The influx of Na^+ into the Müller cell activates the Na^+/K^+ ATPase which further stimulates glycolysis [4, 62]. Both the NH_4^+ and glutamate are used 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^+ (K_{ir}) 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 transmission 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 downregulation 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 multitude of questions that have arisen as a result of our limited understanding of gliosis, 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 survival, and may also proliferate [116, 117]. The severe state is marked by the persistence 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

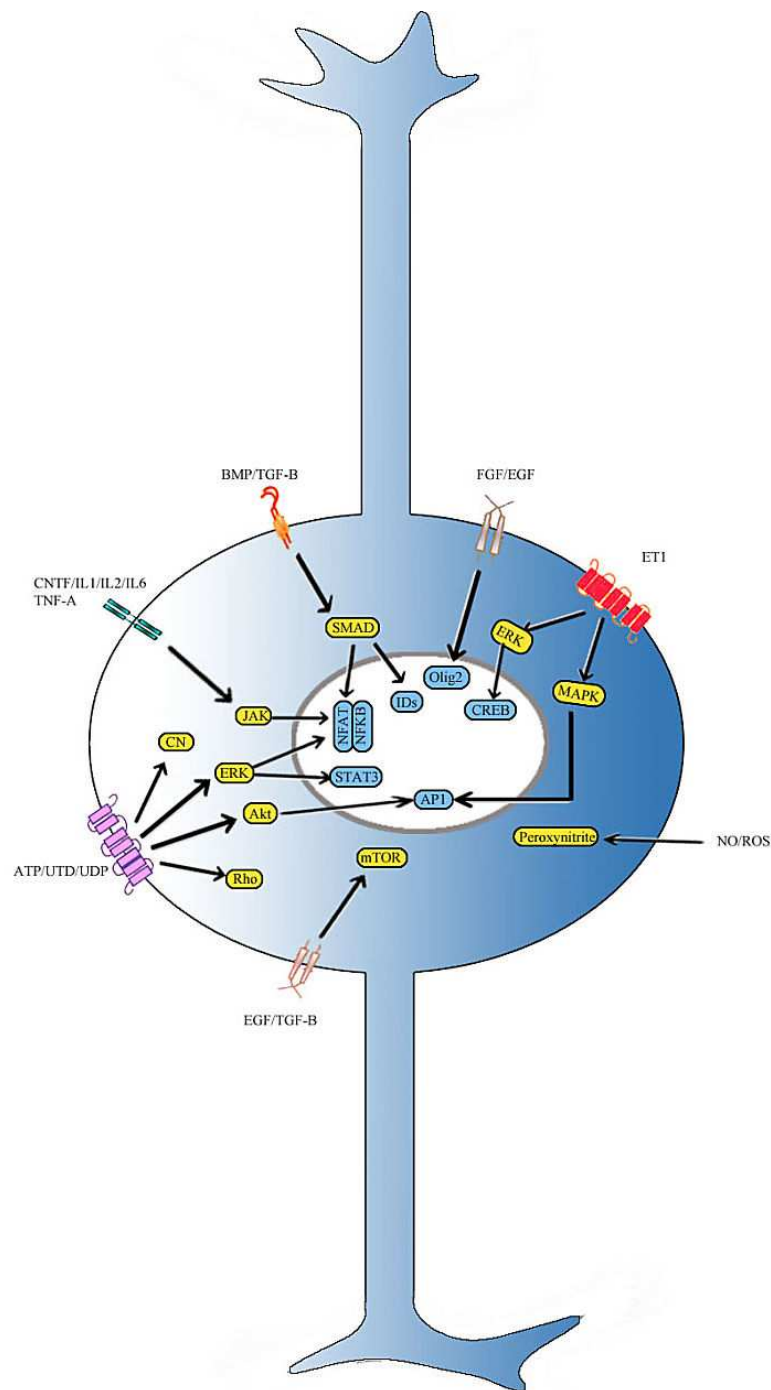


Figure 3. Schematic representation of various signaling mechanisms which trigger and regulate reactive gliosis in Müller glia. Growth factors such as TGF- β , BMP, EGF and CNTF; interleukins; as well as reactive oxygen species and free radicals are known factors to trigger gliosis in Müller glial cells. 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- κ B), 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 comparison 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, electrophysiology 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 ($TGF\beta$), thrombospondin, etc) and factors that decrease barrier function (VEGF, $TNF\alpha$, 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].

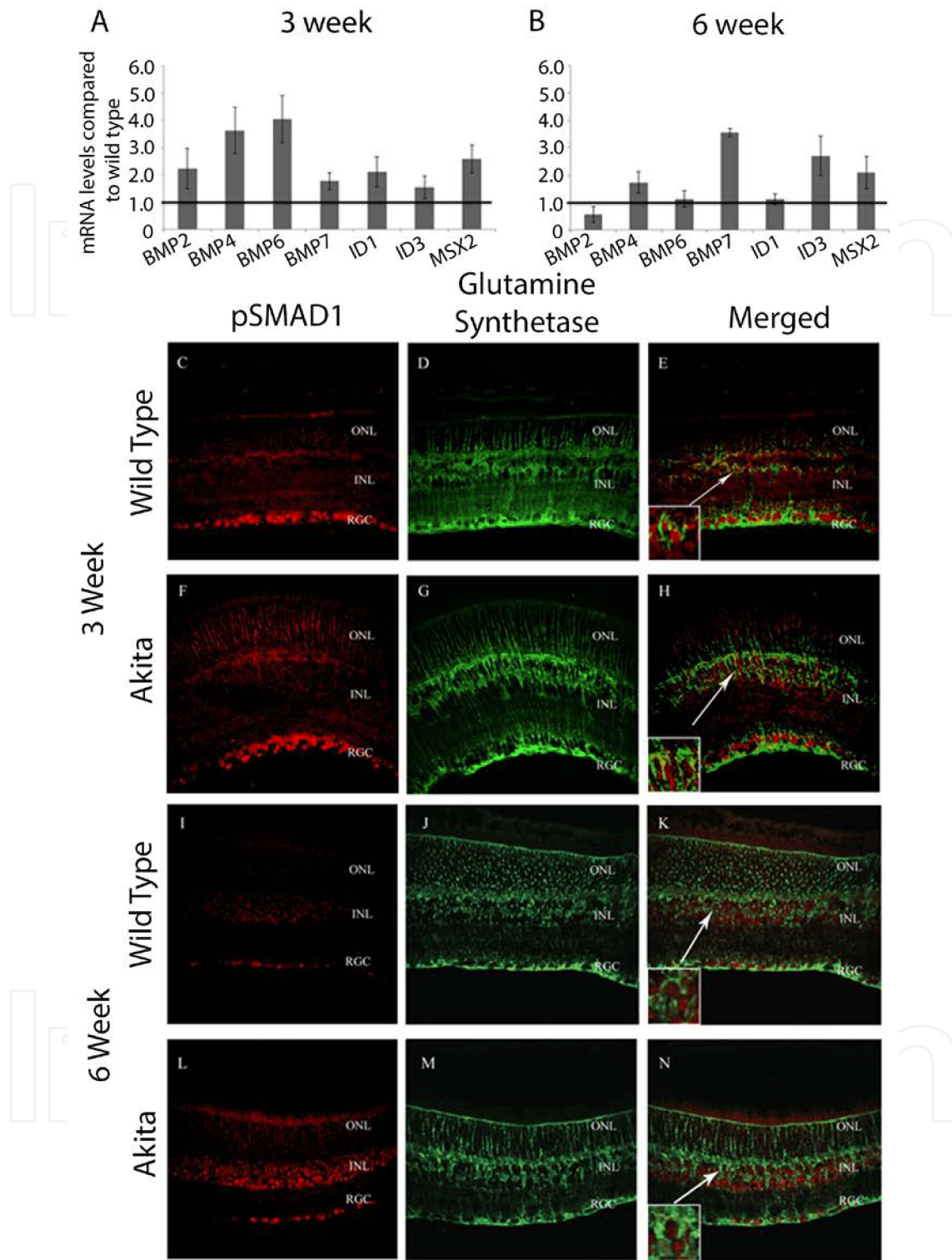


Figure 4. Analysis of retinas of the *Ins2^{Akita}* diabetic mouse shows increase in BMP signaling in the diseased eye when compared to the wild type eye. **A** and **B**: qPCR results analyzing the levels of various BMP molecules shown to be regulated during reactive gliosis and some of the targets 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 see an increase in expression of GFAP, GS and neurocan (data not shown), there is

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).

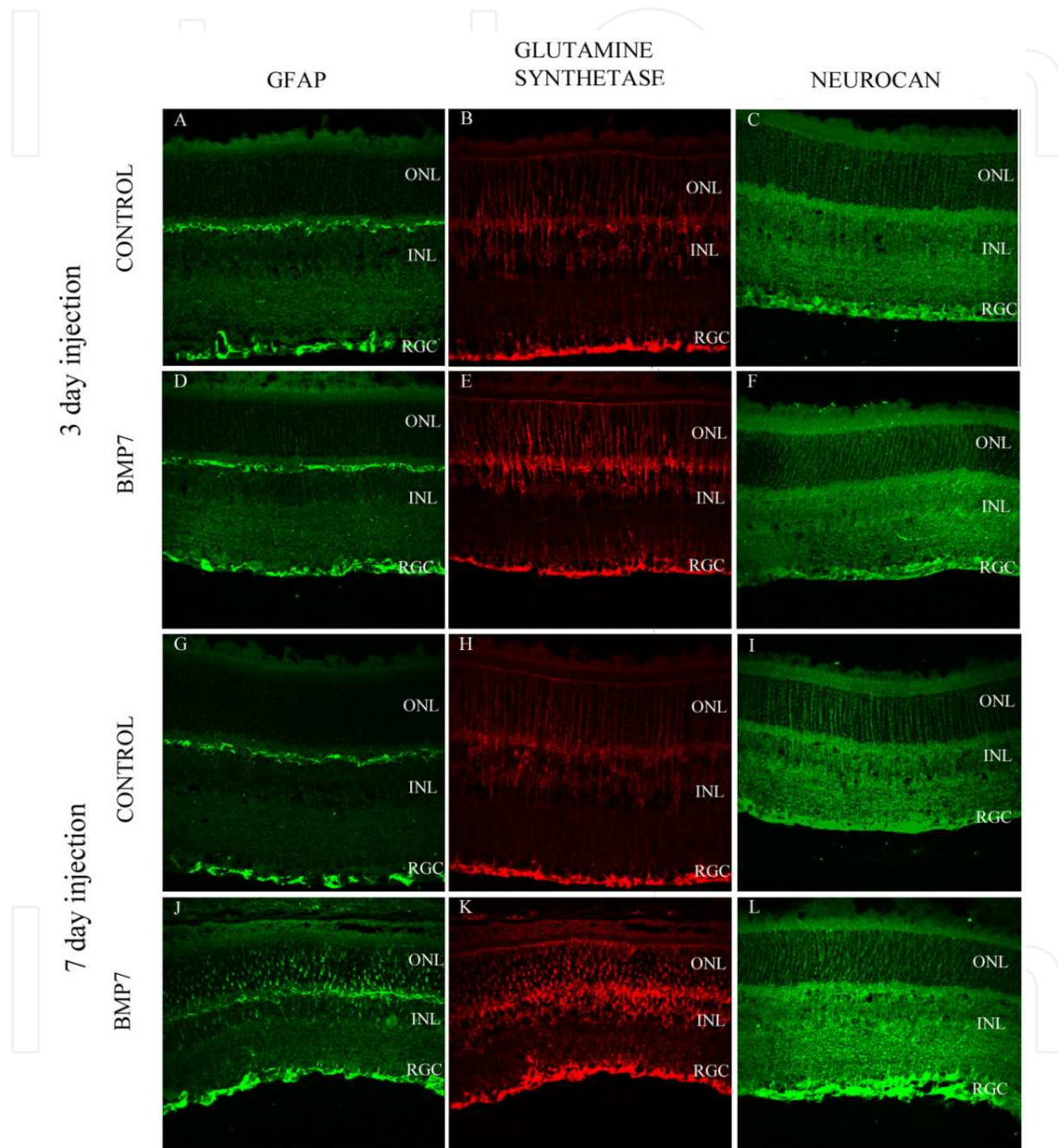


Figure 5. Effect of intra vitreal injections of BMP7 into normal mouse eyes – Retinal sections of eyes injected with either vehicle or BMP7 were analyzed 3 days (A – F) and 7 days (G – L) post injection via immunohistochemistry for the localization of glial fibrillary acidic protein (GFAP), glutamine 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.

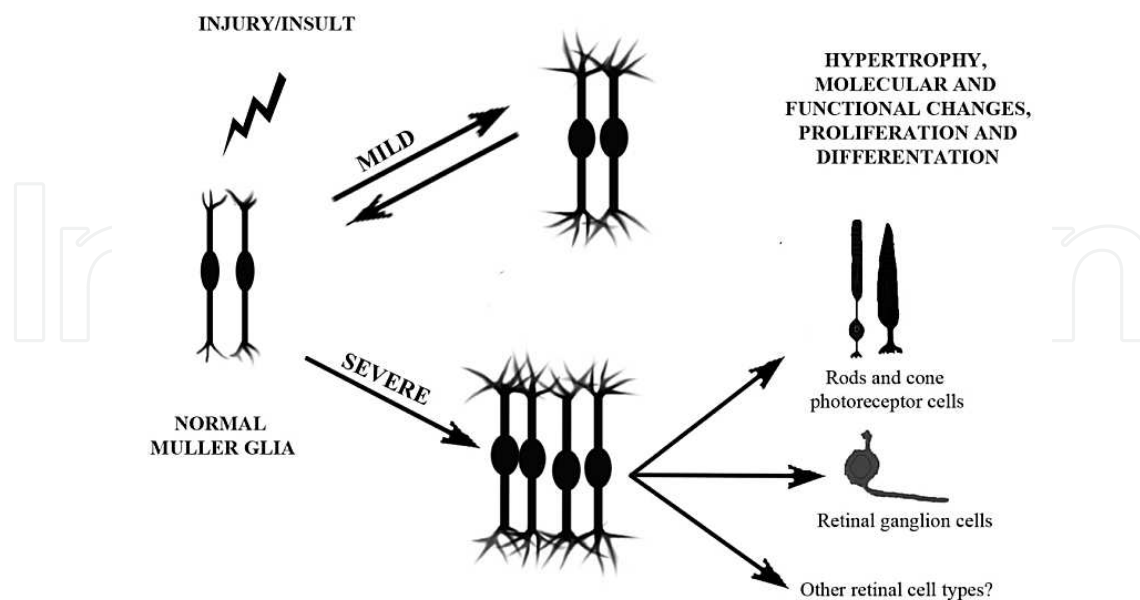


Figure 6. Schematic representation of reactive gliosis response in Müller glia depending on the extent of the injury. Mild changes in reactive gliosis comprises of hypertrophy of the cells due to an increase in glial fibrillary acidic protein and changes to the function and morphology of the cell, with little or no proliferation which has the potential to resolve 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 neuroprotection 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].

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- κ B 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 mammals [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 response, 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 indispensable for the proliferative activity seen during reactive gliosis [178, 179]. The heparin binding epidermal growth factor (HBEGF)-MAPK pathway is 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 with 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 pivotal 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 maintenance 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 the angiogenic factor VEGF [162, 185-190]. Under hypoxic conditions, transcriptional activation of VEGF occurs by translocation of the newly stabilized hypoxia inducible factor-1 α (HIF-1 α) and its partner HIF-1 β 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 milieu, 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 metalloproteinases (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 endothelial 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 undergo 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, occurring in approximately 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 proteoglycans (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 chondroitin 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/RPTP β/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 progenitors 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 integration 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.

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