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Müller cells and diabetic retinopathy

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A B S T R A C T

Müller cells are one of the primary glial cell types found in the retina and play a significant role in maintaining retinal function and health. Since Müller cells are the only cell type to span the entire width of the retina and have contact to almost every cell type in the retina they are uniquely positioned to perform a wide variety of functions necessary to maintaining retinal homeostasis. In the healthy retina, Müller cells recycle neurotransmitters, prevent glutamate toxicity, redistribute ions by spatial buffering, participate in the retinoid cycle, and regulate nutrient supplies by multiple mechanisms. Any disturbance to the retinal environment is going to influence proper Müller cell function and well being which in turn will affect the entire retina. This is evident in a disease like diabetic retinopathy where Müller cells contribute to neuronal dysfunction, the production of pro-angiogenic factors leading to neovascularization, the set up of a chronic inflammatory retinal environment, and eventual cell death. In this review, we highlight the importance of Müller cells in maintaining a healthy and functioning retina and discuss various pathological events of diabetic retinopathy in which Müller cells seem to play a crucial role. The beneficial and detrimental effects of cytokine and growth factor production by Müller cells on the microvasculature and retinal neuronal tissue will be outlined. Understanding Müller cell functions within the retina and restoring such function in diabetic retinopathy should become a cornerstone for developing effective therapies to treat diabetic retinopathy.

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1. Introduction

Müller cells are the principle glia of the retina. They are the only cells to span the entire width of the retina and have intimate contact with both the retinal blood vessels and retinal neurons. Because of this arrangement, Müller cells have a variety of important functions in the healthy retina. Functions of Müller cells can be divided into 3 major categories: (1) Uptake and recycling of neurotransmitters, retinoic acid compounds, and ions (such as potassium K^+), (2) control of metabolism and supply of nutrients for the retina, and (3) regulation of blood flow and maintenance of the blood retinal barrier.

The extensive contact of Müller cells with retinal neurons allows Müller cells to actively participate in proper neurotransmission. They rapidly take up and clear glutamate and γ-aminobutryic acid (GABA) in the inner plexiform layer (Barbour, Brew, & Attwell, 1988; Biedermann, Bringmann, & Reichenbach, 2002; Derouiche & Rauen, 1995; Matsui, Hosoi, & Tachibana, 1999). Studies have shown that Müller cells take up extracellular glutamate through the Glutamate Aspartate Transporter (GLAST) and indicate that glutamate removal and prevention of neurotoxicity in the retina is achieved primarily by this mechanism (Harada et al., 1998; Rauen, Taylor, Kuhlbrodt, & Wiessner, 1998). Once taken up, glutamate is converted to glutamine by glutamine synthetase and released back to neurons for re-synthesis of glutamate and GABA (Poitry, Poitry-Yamate, Ueberfeld, MacLeish, & Tsacopoulos, 2000). This process provides substrate for neurotransmitter synthesis and also prevents glutamate toxicity. Müller cells further maintain proper retinal function by participating in a process known as "potassium spatial buffering", a process that redistributes and normalizes K^+ in the surrounding microenvironment to avoid prolonged accumulation of K^+ (Orkand, Nicholls, and Kuffler, 1966). It has been shown that Müller cells can take up K^+ from the inner and outer plexiform layers where neuronal synapses occur and release the K^+ into the vitreous humor in an effort to redistribute K^+ ions (Karwoski, Lu, & Newman, 1989). This process is also involved in retinal fluid removal. Müller cells act as potassium shuttle by taking up potassium from the extracellular fluid through Kir2.1 potassium channels and depositing the potassium into the vasculature using Kir4.1 channels that are found on the Müller cell processes that encompass the blood vessels (Bringmann, Reichenbach, & Wiedemann, 2004; Nagelhus et al.,

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1999). This leads to osmotic fluid removal through aquaporin-4 (Iandiev et al., 2005; Nagelhus et al., 1998 1999; Patil, Saito, Yang, & Wax, 1997).

In addition to regulating neurotransmitters and ion levels within the retina, Müller cells also participate in the retinoid cycle with cone photoreceptors by taking up all-*trans* retinol from the subretinal space (Edwards, Adler, Dev, & Claycomb, 1992; Kanan et al., 2008; Mata, Radu, Clemmons, & Travis, 2002; Trevino, Villazana-Espinoza, Muniz, & Tsin, 2005). During the visual cycle, photons of light lead to isomerization of 11-*cis* retinal to all-*trans* retinal in the rod and cone photoreceptors. Once isomerized, all-*trans* retinal is expelled from the opsin protein to be reduced by retinol dehydrogenases to all-*trans* retinol (Palczewski et al., 1994). The all-*trans* retinol from the cones is then released into the extracellular space where it is taken up by Müller cells, isomerized back to 11-*cis* retinol by all-*trans* retinol isomerase, and released back to the extracellular space to be taken up by the cone photoreceptors where it can finally be oxidized from 11-*cis* retinol back to original 11-*cis* retinal to restart the visual cycle (Kanan et al., 2008; Mata, Ruiz, Radu, Bui, & Travis, 2005; Mata et al., 2002; Trevino et al., 2005).

Müller cells seem a primary site of nutrient storage for the retina. It has been shown that ATP production in Müller cells drastically declines when glycolysis is inhibited. However, ATP levels remained equal in aerobic versus anaerobic conditions as long as glucose was provided, indicating that Müller cells live primarily from glycolysis rather than oxidative phosphorylation (Winkler, Arnold, Brassell, & Puro, 2000). This is important as it spares oxygen for retinal neurons and other cell types that use oxidative phosphorylation for ATP production. Furthermore, Müller cells are the primary site of glycogen storage in the retina (Kuwabara & Cogan, 1961; Winkler et al., 2000). When nutrient supplies are low Müller cells can utilize this glycogen storage to provide metabolites for other cell types. Furthermore, the large amounts of lactate they produce via glycolysis and irreversible conversion of pyruvate to lactate due to a specific lactate dehydrogenase isoform can be transported to photoreceptors to be used as a potential alternative source of energy in case of need (Poitry-Yamate, Poitry, & Tsacopoulos, 1995; Poitry-Yamate & Tsacopoulos, 1992; Winkler et al., 2000). Interestingly, studies suggest that the metabolism of glucose and glycogen by Müller cells is regulated by light being absorbed by the photoreceptors (Poitry et al., 2000). This means that as photoreceptors absorb light, the Müller cells respond by metabolizing more glucose in order to provide more lactate for photoreceptors as needed, indicating that Müller cells and photoreceptors are tightly coupled in their respective functions by metabolism. In addition to providing lactate as a fuel source for photoreceptors, Müller cells can also regulate nutrient supplies to the retina via regulation of retinal blood flow. In a healthy retina, increased light stimulation results in increased retinal blood flow, which is required to supply the activated neurons with oxygen and other nutrients, a process termed neurovascular coupling. Müller cells play a crucial role in neurovascular coupling as they release metabolites controlling vasoconstriction and vasodilation of retinal blood vessels (Metea & Newman, 2006; Newman, 2015).

One of the most important functions of Müller cells is their regulation of retinal blood flow and contribution to the blood retinal barrier. The blood retinal barrier is essential for preventing leakage of blood and other potentially harmful stimuli such as pathogens from entering the retinal tissue. It has been shown that Müller cells induce blood-barrier properties in retinal endothelial cells (Abukawa et al., 2009; Tout, Chan-Ling, Holländer, & Stone, 1993). Studies using conditional ablation of Müller cells showed severe blood retinal barrier breakdown (Shen et al., 2012). The exact mechanism of how Müller cells maintain the blood retinal barrier is debated but includes the secretion of factors such as pigment epithelium-derived factor (PEDF) and thrombospondin-1 which are anti-angiogenic and increase the tightness of the endothelial barrier (Bringmann et al., 2006; Eichler, Yafai, Keller, Wiedemann, & Reichenbach, 2004).

It is clear that Müller cells are an integral part of a healthy and well functioning retina. Any disturbance to these cells certainly affects cellular cross-talk within the retina and its proper function. However, despite their importance Müller cells are still an understudied cell type in the context of diseases such as diabetic retinopathy. The following aims to provide an overview about the effects of diabetes on Müller cells and the role Müller cells play in pathological events in the diabetic retina.

2. Influence of diabetes on neurotransmitter and potassium regulation in Müller cells

Functional changes that have been determined in Müller cells begin early in the disease, with significant decreases in glutamate transport via GLAST beginning after just 4 weeks of diabetes in rats (Li & Puro, 2002). This is consistent with reports showing significantly increased glutamate accumulation in the retinas of diabetic rats (Lieth, LaNoue, Antonetti, & Ratz, 2000; Lieth et al., 1998). Furthermore, these studies have shown that there is decreased glutamine synthetase activity and a subsequent decrease in the conversion of glutamate to glutamine necessary for neurotransmitter regeneration (Lieth et al., 1998, 2000). These results are in line with reports demonstrating glutamate increases to a potentially neurotoxic level in the vitreous of diabetic patients (Ambati et al., 1997). However, in neurological diseases such as stroke, therapies targeting glutamate increase have been ineffective indicating that increased glutamate levels might not play a pathophysiological role (O'Collins et al., 2006; Sloan & Barres, 2014). Whether increased glutamate levels actually cause neurotoxicity over time in diabetic retinopathy has yet to be determined.

It seems that Müller cells not only contribute to glutamate toxicity directly by decreased glutamate uptake, but Müller cells also contribute indirectly via decreased K^+ uptake during the progression of diabetic retinopathy. There is decreased K^+ conductance on the plasma membrane of Müller cells isolated from rat retinas after 4 months of experimental diabetes (Pannicke et al., 2006). Redistribution of the Kir4.1 K^+ channel has been identified as the mechanism of decreased K^+ conductance (Pannicke et al., 2006). This decrease in K^+ conductance was also observed in Müller cells of patients with proliferative diabetic retinopathy (Bringmann et al., 2002). Alteration of the Kir4.1 K^+ channel localization in Müller cells in the diabetic retina has been attributed to the accumulation of advanced glycation endproducts (AGEs) (Curtis et al., 2011). Together, this can lead to an imbalance in K^+ concentrations and altered K^+ homeostasis leading to neuronal excitation and subsequent glutamate toxicity.

In diabetes and diabetic macular edema, Müller cells have been shown to downregulate the Kir4.1 channels, but not Kir2.1, leading to continued potassium uptake with no release into the microvasculature (Pannicke et al., 2004, 2006; Reichenbach et al., 2007). This leads to subsequent swelling of Müller cells contributing to Müller cell dysfunction and decreased fluid removal contributing to diabetic macular edema. Diabetic macular edema leads to thickening of the macula due to fluid accumulation and can be observed by optical coherence tomography (OCT). The thickening of the macula due to fluid accumulation typically leads to disruption of the retinal structure and changes in visual acuity.

Release of growth factors and pro-/anti-inflammatory cytokines from Müller cells in response to hyperglycemia – the bad and the potentially good

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