Pharmacological Targeting of Müller Cell Reactive Gliosis to Enhance Visual Acuity Following Retinal Reattachment

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Abstract

Retinal detachment is a severe ophthalmological emergency when by the retina separates from the underlying retinal pigment epithelium (RPE). Although current surgical interventions achieve anatomical reattachment, in the majority of cases, functional visual recovery often remains compromised by biological remodeling of the retina. This discrepancy is primarily driven by reactive gliosis of Müller cells, a defensive but ultimately pathological wound-healing response which disrupts the metabolic homeostatic balance of the retina. This article evaluates the intracellular signaling pathways that are involved in reactive gliosis, with the objective of identifying pharmacological targets that can prevent cellular remodeling post retinal detachment. Here we show that the Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) and Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase (MAPK/ERK) pathways function as convergent signaling bottlenecks for retinal injury. The analysis of immunohistochemical studies demonstrates the activation of these pathways directly drives the upregulation of intermediate filaments, specifically Glial Fibrillary Acid Protein (GFAP) and Vimentin, while simultaneously suppressing the transcription of the essential Kir4.1 potassium channel. The primary findings indicate that pharmacological inhibition of the JAK/STAT and MAPK/ERK pathways is effective in reducing reactive gliosis, preventing physical stiffening of the retina as a result of Müller cell hypertrophy and providing potentially improved visual acuity post retinal reattachment. These insights advocate for a shift in the clinical setting to a traditional mechanical reattachment paired with a targeted biochemical intervention during the post-detachment window. By incorporating signaling inhibitors into the standard of care, it may be possible to bridge the current “functional gap.” Significantly improving visual acuity and long-term quality of life for patients following retinal surgery.

Introduction

Retinal detachment is one of the most significant ophthalmological emergencies, occurring in around 10 cases per 100,000 individuals annually.[8] During a retinal detachment event, the neurosensory retina is fully separated from the retinal pigment epithelium (RPE). Generally, the clinical solution to this problem is to anatomically reattach the retina and ensure that the retina lays flat against the RPE. But despite a retinal reattachment success rate of 90%, it has been observed that a significant discrepancy still remains in the restoration of patients functional vision post-surgery. [8,11] Even patients that experience early intervention to repair the detachments suffer from, often, profound vision loss with extremely low best-corrected visual acuity (BCVA). This gap suggest that the physical reattachment of the retina is only the first step in ensuring that patients can regain retinal functionality following retinal reattachment. [11]

The greatest functional obstacle that patients tend to face following surgery is the onset of Proliferative Vitreoretinopathy (PVR). This clinical diagnosis defines a retinal wound-healing failure, in which the healing response is exaggerated, creating an excess of fibrous membranes within the eye. [7] As these fibers mature, they contract and become tense and fragile, leaving them more susceptible to breaking which promotes the recurrent detachment of the retina. However, even if patients can avoid recurrent detachment, the reactive gliosis that occurs during the detachment and subsequent reattachment significantly alters the structure of the retina at the cellular level. Specifically, the Müller cells in the eye change from the primary support structure to thick, structural barriers that prevent the proper functioning of the retina and photoreceptors. [2]

Thus, in order to understand why the retina fails to recover functionally, the changes that take place in the Müller cell must be studied. Müller cells in a healthy retina are transparent and flexible, but following mechanical strain of retinal detachment and the presence of inflammatory

cytokines, the Müller cells undergo reactive gliosis. [3] Reactive gliosis was evolutionarily evolved to seal wounds in the eye and protect the neural tissues from any more damage. [11] However, this function can change from a protective mechanism to that of a neurodegenerative mechanism. The hypertrophy that occurs in the retina as a result creates both a physical and biochemical barrier to visual restoration in the patient.

This article explores the idea that to achieve optimal visual acuity in patients following retinal reattachment, both the mechanical and pharmacological aspects need to be considered, the latter of which remains largely under researched. This review proposes that the targeting of intracellular signaling pathways such as, JAK/STAT and MAPK/ERK, can provide a route to mitigate the detrimental scarring process of the retina. The article evaluates the current pharmacological interventions that have been designed to inhibit either signaling pathway in order to promote both anatomical and functional success. By stabilizing the reactive Müller cells through signaling inhibition, it is possible to maintain the homeostasis and architecture of the eye following retinal detachment. This shift toward a surgical and biochemical approach provides a promising strategy for overcoming limitations with visual acuity, and promoting functional restoration for patients.

Structural and Biochemical Organization of Müller Cells in the Retina

The Müller cell is the only type of cell in the eye that spans the entire thickness of the retina, working as a bridge between the vitreous humor and the subretinal space of the eye. As indicated in **Figure 1**, Müller cells' larger base begins at the Inner Limiting Membrane of the eye and separates the retina from the vitreous body of the eye. [3] A much thinner stalk of the cell

extends through the rest of the retina and connects to the majority of the neuronal synapses that are present in the retina. In this role the Müller cell serves as a structural stability feature.[8] The end of the Müller cell attaches to the Outer Limiting Membrane, which connects the rods and cones to the retina. Additionally, due to their highly organized structure and aided by their trans-retinal span, the Müller cells are able to guide scattered light to the photoreceptors that are at the back of the eye.

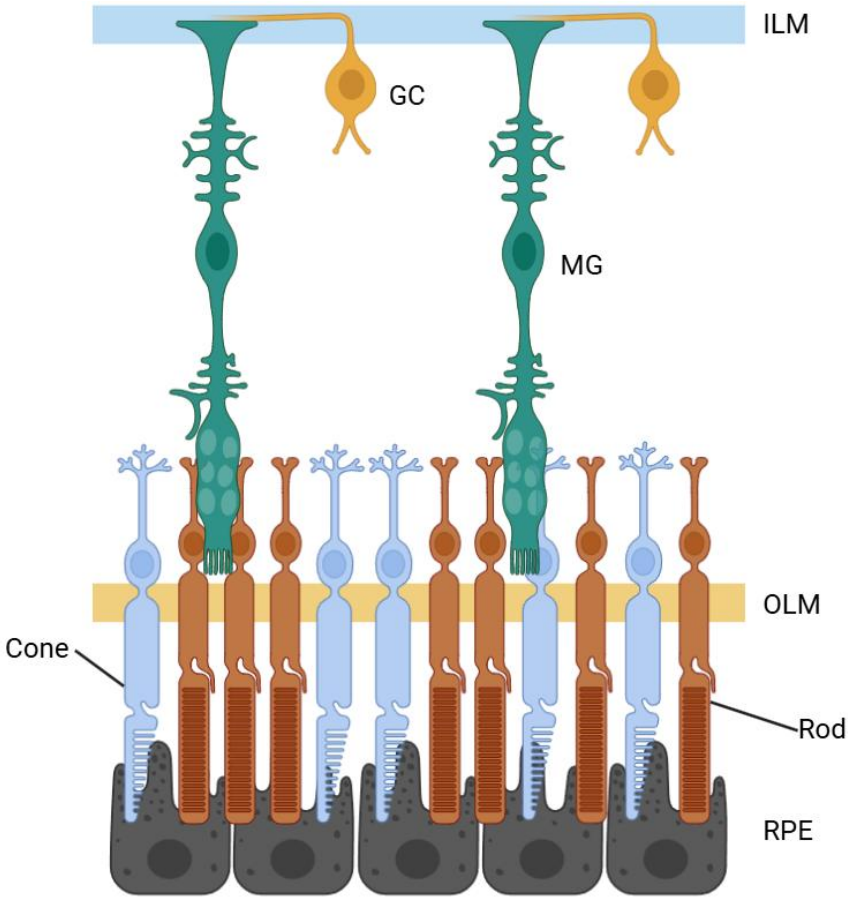

Figure 1. A simplified depiction of the mammalian retinal anatomy. Müller glia (MG) span from the Outer Limiting Membrane (OLM) to the Inner Limiting Membrane (ILM), traversing the entire mammalian retina. Müller glia connect to the rod and cone photoreceptors as well as the neuronal ganglion cells (GC) in the eye, making them uniquely suited to provide structural scaffolding and ensure retinal homeostasis. Adapted from Salman et al., 2021.[9]

The Müller cell's connection to the rods and cones of the eye is crucial for visual success. The two systems work together to ensure that the eye remains in good condition to receive and process light signals. Müller cells work to eliminate waste, such as carbon dioxide and ammonia, build up that is a by-product of the photoreceptors and provides them with lactate and pyruvate to promote their ability to detect incoming light signals. [9]

Additionally, Müller cells are responsible for the repair of the cones in the eye, called the visual cycle. As a photon of light is received by a cone, its visible pigments become bleached and non-functional. [3] This non-functional visible pigment is called an all-trans retinal, which is converted to all-trans retinol before being exported to the Müller cell. Müller cells have an enzyme, DES1, that is essential in the regeneration of pigment in cones, allowing for the ability to see color, even in environments that have changing light. *Dihydroceramide desaturase-1 (DES1) converts the all-trans retinol into 11-cis retinol, which is then transported back to the cone of the eye by Cellular Retinaldehyde-Binding Protein (CRALBP). [9] Once it arrives at the cone, 11-cis retinol is converted to 11-cis retinal and binds to the cone, prepared to receive a photon of light. However, when the retina detaches, the physical separation that occurs destroys the sharing of biochemical resources that the Müller cells house. Even if not fully severed from the retina, the longer distance that the resources may have to travel can lead to slow repair/reset of cone pigments. Thus, in an environment with increasing waste products, and no way to get rid of them, the rods and cones begin to decline leading to rapid vision and color loss.

Reactive Gliosis Pathway & Mechanism

When the retina detaches from the retinal epithelium (RPE at the back of the eye, it creates a physical trauma that triggers a cellular response, starting with Müller cells. This detachment creates a strain on the Müller cells which span the entire retinal thickness by stretching them. [10] During the stretching, two channels, the transient receptor potential cation channel (TRPV4) and Piezo1 channels are physically pulled open, allowing a rush of calcium ions (Ca^{2+}) into the Müller cell. This sudden spike in calcium ions, along with the mechanical strain, is the first signal that informs the Müller cells that an injury to the eye has occurred and to begin reactive gliosis. [7]

The Müller cells, influenced by the stretching factor and the stress on surrounding neurons, begin to release cytokines, specifically Interleukin-6 (IL-6). IL-6, an important trigger for the JAK/STAT pathway, binds to specific receptors on the surface of the Müller cells. With the receptors now clustered together by cytokines, the Janus Kinase 2 (JAK2) enzyme, attached to the side of the receptor that is inside of the cell, is activated. These JAK2 enzymes auto-phosphorylate each other and then phosphorylates the receptor. When Signal Transducer and Activator of Transcription 3 (STAT3) inside of the cell's cytoplasm recognizes the phosphorylated receptor and attaches to it, STAT3 changes its shape and creates a dimer. Once dimerized the STAT3 can pass through the nuclear membrane and binds directly to the promoter regions of genes for the Glial Fibrillary Acid Protein (GFAP) and Vimentin, which are typically dormant in healthy Müller cells. [9]

Glial fibrillary acid protein (GFAP) and Vimentin are important intermediate filament proteins found in Müller cells and astrocytes in the mammalian retina. During retinal injury

GFAP and Vimentin increase in abundance, marking a correlation to retinal gliosis. As GFAP and Vimentin accumulate within the cell they form dense stress fibers that promote hypertrophy in the Müller cells. As the hypertrophy increases, the retina begins to expand past its usual physical volume, becoming thicker. In some cases, the glial outgrowth that occurs in this phase can push past the Outer Limiting Membrane and create a barrier that prevents any light from reaching the photoreceptors and creates difficulty in reattachment of the retina. [1] Thus, the scars that form on both the inner and outer surface of the retina create thick, opaque, membranes that negatively impact visual acuity.

While the JAK/STAT pathway provides the change in structure necessary to create scarring, the MAPK/ERK provides a driving factor for cell division. This pathway drives the cells to rapidly generate, creating more scarring, thickening the retina. As the Müller cell utilizes all of its energy to continually proliferate, its normal functions begin to suffer. [3] In a healthy Müller cell, Kir4.1 potassium channels are used to remove extra K^+ that is released by neurons during signaling and redistribute it to the vitreous fluid or surrounding blood vessels. This serves to prevent the neurons from depolarizing and losing function. But, as Müller cells upregulate the production of GFAP through the JAK/STAT pathway, the Kir4.1 channels are downregulated, which leads to a buildup of potassium. This downregulation occurs because when Extracellular Signal-Regulated Kinase (ERK1/2) is phosphorylated following retinal detachment, it begins a signaling cascade that ultimately inhibits the transcription of the Kir4.1 channel. [14] Loss of these channels and the resulting high concentration of potassium in the cell, encourages swelling of the cell due to increased osmotic pressure, preventing the neurons from firing correctly and promoting increased hypertrophy. Symptomatically, this swelling presents itself as persistent blurry vision despite surgical reattachment of the retina. [13]

Additionally, the Müller cells exhibiting reactive gliosis lose their ability to clear glutamate, the primary excitatory neurotransmitter in the retina. In a healthy Müller cell, Excitatory Amino Acid Transporter 1 and 2 (EAAT1 and EAAT2) are used to quickly and efficiently create the glutamate from the retina and convert it to the significantly less toxic, glutamine. During retinal detachment, the quantity of EAAT1 and EAAT2 are decreased in the cell due to the volume lost to thickened scar tissue. Without the ability to be removed from the cell, the glutamate becomes toxic, causing rapid cell death of the photoreceptors needed for vision because it overstimulates them for too long. [6]

Thus, the combination of the scarring from hypertrophy and the build up of glutamate and potassium in the cell creates a functional failure of the retina. With both of these biochemical elements the brain becomes unable to distinguish a clear visual signal from the rods and cones of the eye due to the blocked or distorted signals that it is receiving.

Confirmatory Immunohistochemistry Analysis

A study using a porcine model, chosen for the fact that pigs have vascularized eyes just like humans, established that Müller cell reactivity is rapid and extensive, impacting all of the eye even if it is not the site of detachment. Fourteen young adult domestic white pigs (n=14) utilized, and ten were given a subretinal injection of saline followed by 0.25% sodium hyaluronate to induce a retinal detachment ventral to the optic nerve. The remaining four pigs had the vitreous fluid of the eye removed, to serve as a surgical control group. Immunohistochemical staining, as shown in **Figure 2**, revealed that Vimentin was immensely upregulated during a 7 day window following retinal detachment, extending past its typical

localization at the Müller cell end feet. Imaging at sites detachment, peri detachment, and attachment within the affected retina showed this upregulation was ubiquitous throughout the eye. Similar results were observed in GFAP expression in the retina, and this expansive Müller cell hypertrophy can explain the impaired visual recovery that is observed in parts of the eye that were not detached.[2] It can be determined that increased abundance of Vimentin and GFAP provides mechanical scaffolding for hypertrophy and remodeling of the eye following retinal detachment.

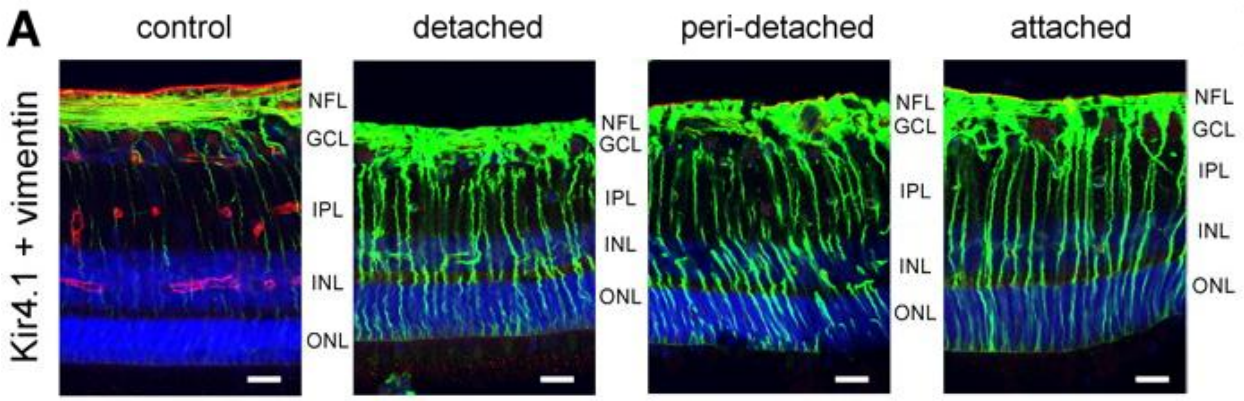

Figure 2. Experimental detachment in porcine eyes changed the expression of intermediate filament proteins by Müller cells in both detached and nondetached retinal areas. The slices were derived from nonsurgical and virectomized control retinas and from detached and attached areas of porcine retinas at 7 days following surgery. The attached tissues were derived from an area located in situ near the detachment (peridetached) or from areas more distant (10–15 mm) from the detachment (attached). Immunoreactivities for vimentin are shown in green. Adapted from Iandiev et al., 2006.[2]

Pharmacological Targeting of Müller Cell Signaling

The JAK/STAT and MAPK/ERK pathways are effective pharmacological targets for inhibiting Müller cell hypertrophy following retinal detachment because they serve as molecular signaling bottlenecks. Upon retinal detachment Müller cells receive a variety of stimuli including: mechanical displacement, an increase in inflammatory cytokines, and the release of

growth factors. Instead of attempting to block each of the individual ligands, the JAK/STAT or MAPK/ERK pathways can instead be inhibited to suppress the multiple converging signals that are a result of the vastly different stimuli. The signaling outcomes of the JAK/STAT and MAPK/ERK pathway work to drive hypertrophy and cell proliferation respectively. [5, 9] By inhibiting these specific pathways, the downstream expression of GFAP and Vimentin can be turned off before they can form thick, irreversible, physical scars.

Due to their specificity to JAK kinases, Tofacitinib (Xeljanz) and AG490 are the most commonly studied pharmaceuticals that can inhibit glial reactivity. Tofacitinib is an extremely small molecule that competitively binds with ATP to the catalytic domains of JAK1 and JAK3. This creates a physical barrier that blocks the binding of ATP and thus the donation of a phosphate group to the STAT3 protein. [10] Since the STAT3 protein does not become phosphorylated, it remains in an inactive state and cannot dimerize, keeping it trapped in the cytoplasm and unable to transport to the nucleus. In experimental models, such JAK inhibitors have

Pharmacological agents like Tofacitinib (Xeljanz) and AG490 are among the most studied inhibitors for glial reactivity due to their precise biochemical action on the JAK kinase family. Tofacitinib, a broad range small-molecule ATP-competitive inhibitor, binds directly to the catalytic domain of JAK1 and JAK3, physically blocking the site where ATP would normally donate a phosphate group to the STAT3 protein. [10] Without this phosphorylation event, STAT3 remains trapped in the cytoplasm in an inactive state, unable to dimerize or enter the nucleus to turn on the genes for expression of GFAP and Vimentin. Contrastingly, AG490 acts as a competitive inhibitor for the substrate binding site of the JAK 2 protein, blocking the phosphorylation of tyrosine residues on the receptor. So, it can be deduced that the

administration of JAK inhibitors should reduce the production of GFAP and Vimentin in the cell and in turn the onset of proliferative vitreoretinopathy. [2]

Conversely, the MAPK/ERK pathway can be inhibited by non-competitive MEK inhibitors which bind to an allosteric site on the MEK1/2 enzymes. This creates a conformational change of MEK that prevents the phosphorylation of ERK1/2. By leaving ERK1/2 inactivated, imperative in the culminating step of the growth cascade, the cells proliferation cycle is immediately stopped. Lower levels of phosphorylated ERK (p-ERK) have shown correlation to the restoration of Kir4.1 potassium channels and consequently improved neuronal outcomes as the cells are able to balance the ions in retina.

During retinal detachment, the JAK/STAT and MAPK/ERK pathways are generally cross-activated, suggesting that a strategy that inhibits both pathways may be the most effective, with the best visual acuity outcomes. While a JAK inhibitor works to prevent the accumulation of scar tissue, a MEK inhibitor halts cell proliferation and reduces swelling. [5] This double pharmacological targeting paired with the physical reattachment of the retina through surgery could provide patients with a greater likelihood of minimizing scarring side effects post reattachment.

Conclusion

Retinal specialists continue to face surgical challenges that arise due to the structural and biochemical remodeling that the retina undergoes following detachment. As defined in the review, the Müller cell is the primary structural support and regulator of nutrients in the retina.

However, during retinal injury these cells become thickened, rigid, and opaque which significantly impacts the visual outcomes of patients. This change is caused by reactive gliosis, supported and driven by the JAK/STAT and MAPK/ERK pathways, upregulating the production of intermediate filaments such as GFAP and Vimentin.

In the short term, these structural changes provide the eye with a strong mechanical support system that seals the injured retinal wound. But the irreversibility of these changes lead to a lack of Kir4.1 channels that result in unbalanced ions and neurotoxicity in the cell. [6] The hypertrophy of the Müller cells pushes the photoreceptors of the eye into misalignment, further impairing and limiting the potential best-corrected visual acuity (BVCA) of the patient. Together this evidence suggests that anatomical reattachment of the retina is not sufficient in the functional restoration of the eye.

Emerging pharmacological pathways show that the inhibition of the MAPK/ERK and JAK/STAT pathways is essential in the containment of Müller cell hypertrophy to prevent over scarring and loss of vision. However, it is still unknown when the optimal time for pharmacological inhibition of the Müller cells is. Likely there is an acute window for intervention, in which the Müller cell had still retained some of its plasticity. [2, 9]

Though the possibility of kinase inhibition has shown promising results in experimental models, further research must be done to translate these practices to the clinical sector. Studies should also assess if pharmacological inhibition of Müller cell hypertrophy leads to long term improved BCVA or if the reactive gliosis pathway eventually restarts itself in cases of recurring detachment.

As the clinical sector grows, the change in perspective from purely anatomical success to that of functional success must occur. By acknowledging that Müller cells are the main component that determines the functional success of the retina following reattachment, the biochemical signaling pathways and their contributions to the deterrents to visual success that regulate Müller cell hypertrophy can be assessed. By suppressing or slowing the formation of scare tissue during reactive gliosis, the delicate structure of the human eye can be preserved, ensuring that patients receive a new, high-quality, standard of care with improved patient outcomes.

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