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Toll-Like Receptor 4 Signaling in the Trabecular Meshwork

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Primary open-angle glaucoma is one of the leading causes of blindness worldwide. With limited therapeutics targeting the pathogenesis at the trabecular meshwork (TM), there is a great need for identifying potential new targets. Recent evidence has implicated Toll-like receptor 4 (TLR4) and it is signaling pathway in augmenting the effects of transforming growth factor beta-2 (TGFβ2) and downstream extracellular matrix production. In this review, we examine the role of TLR4 signaling in the trabecular meshwork and the interplay between endogenous activators of TLR4 (damage-associated molecular patterns (DAMPs)), extracellular matrix (ECM), and the effect on intraocular pressure

Keywords: trabecular meshwork, TLR4, ECM, intraocular pressure, glaucoma

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INTRODUCTION

Glaucoma is a progressive neurodegenerative disease and is the second leading cause of blindness worldwide, affecting over sixty million people (Kingman, 2004; Quigley and Broman, 2006). Primary open-angle glaucoma (POAG) is the most common form of the glaucoma's and affects approximately fifty-two million people worldwide and more than 2.5 million in the United States (Friedman et al., 2004; Weinreb and Khaw, 2004; Weinreb et al., 2014; Lu et al., 2017; Zhang et al., 2021). Current therapies are supportive, with the aim to reduce intraocular pressure (IOP), a primary risk factor for glaucoma progression. IOP homeostasis is maintained by the rate at which aqueous humor (AH) is secreted by the ciliary epithelium, and how efficiently it is drained through the outflow pathways in the iridocorneal angle of the eye. Most of the outflow of AH drains through the conventional route of drainage, which is made up of the trabecular meshwork (TM) and Schlemm's canal (Tamm, 2009). The TM is well known to be a critical tissue in AH drainage and imparts a normal resistance to AH outflow that becomes abnormally increased in glaucoma. The TM is a porous structure consisting of a series of fenestrated beams and sheets of extracellular matrix (ECM) covered with endothelial-like TM cells (Hogan et al., 1971; Vranka et al., 2015). The ECM of the TM is important in forming a fluid flow pathway for AH drainage (Gong et al., 1996; Morrison and Acott, 2003). Genes that are broadly categorized as regulating cell signaling comprise the highest percentage of genes that are upregulated in the TM when their homeostatic state is altered, such as during changes in IOP (Vittitow and Borrás, 2004). The ability of the TM to respond to the dynamic changes in IOP in a homeostatic state relies on the ECM remodeling capabilities of the TM (Keller et al., 2009). When this ability becomes impaired, IOP rises and can eventually lead to vision loss. While current drug and surgical interventions are in use, their efficacy is not always guaranteed or long lasting. Additionally, many of the current therapeutics aim to decrease the production of aqueous humor and are not able to target the key site of drainage impairment in glaucoma, which is the TM. While progress has been made in increasing the efficiency of humor drainage through the outflow pathway, such as with prostaglandins and Rho-kinase inhibitors, these therapies address only a small fraction of the mechanisms used by the TM to exert its

function and thus more treatment options are needed. Therefore, much effort is being conducted into understanding the molecular pathways of the TM and how they are altered during glaucoma.

Increases in outflow resistance through the TM can be contributed to multiple factors, such as actin cytoskeletal rearrangement in the TM and changes to the inner wall endothelium of Schlemm's canal (Stamer and Acott, 2012; Vahabikashi et al., 2019). Additionally, the ECM composition of the outer most layer of the TM, the juxtacanalicular tissue (JCT), as well as the inner layers of the TM plays a key role in the regulation of IOP and there is also a great deal of evidence that there are changes to the ECM of the TM in glaucoma. Increased deposition of ECM proteins in the TM, increased AH outflow resistance, and increased IOP are all associated with POAG (Rohen and Witmer, 1972; Lütjen-Drecoll, 1999). Matrix stiffness is a critical component to a tissue's function as it can be perceived by cells and cause intracellular responses such as intracellular signals to control gene transcription, protein expression, and cell behavior. The matrix stiffness is also dependent on the type of ECM proteins present as well as the morphology and organization of the ECM itself. The glaucomatous TM has increased deposition of fibronectin and fine fibrillar material (Lütjen-Drecoll et al., 1986; Babizhayev and Brodskaya, 1993; Rohen et al., 1993). This demonstrates that the ECM architecture of the TM is important in regulating aqueous humor outflow and IOP.

ASSOCIATION OF TOLL-LIKE RECEPTOR 4 WITH GLAUCOMA

Glaucoma is a complex disease and is well known to have genetic heterogeneity with multiple chromosomal loci linked to the disease. However, the complex molecular mechanisms leading to disease pathology are not fully understood. Here we review the role of toll-like receptor 4 (TLR4) in the development of glaucomatous trabecular meshwork damage. In human glaucomatous donor eyes several toll-like receptors, including TLR4, have been shown to have upregulated expression in the retina after IOP elevation (Luo et al., 2010; Rieck, 2013). Additionally, *TLR4* polymorphisms are indicated to be involved with slower responses to infection, reduced autoimmunity, and glaucoma (Arbour et al., 2000; Radstake et al., 2004). Specifically, association of *TLR4* gene polymorphisms have been identified in Chinese and Japanese cohorts with POAG, normal-tension, and exfoliation glaucoma (Shibuya et al., 2008; Chen et al., 2012; Takano et al., 2012). These data suggest that TLR4 may have a significant role in the cellular pathogenesis of multiple types of glaucoma.

TOLL-LIKE RECEPTOR 4 SIGNALING

Toll-like receptors (TLRs) play a significant role in the detection of pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) (Miller et al., 2015). Functional TLRs 1-10 have been identified in humans and TLRs 1-13 in murine species (Szabo et al., 2006; Yarovinsky, 2014; Nie et al., 2018). Humans have a nonfunctional TLR11 and do not express TLR12 and 13. Unlike TLR3, 7, 8, and 9 which are found in endosomes, TLR4, like TLR1, 2, 5, 6, and 10 are found in the cell membrane. Like most receptors, TLRs require homodimerization or heterodimerization of receptors to activate transcription factors that ultimately lead to the production of chemokines and cytokines. Ultimately, all mammalian TLRs have an extracellular domain that contains leucine-rich domains and an intracellular domain that activates a signaling cascade leading to nuclear factor-kappa beta (NF-κB) activation and translocation to the nucleus (Medzhitov et al., 1997; Chaudhary et al., 1998; Medzhitov et al., 1998; Rock et al., 1998; Chow et al., 1999; Janeway and Medzhitov, 1999; Yang et al., 2000).

TLR4 was first identified as the receptor for lipopolysaccharide (LPS) and was shown to play a vital role in innate immunity (Poltorak et al., 1998). Activation of TLR4 by LPS occurs when the ligand LPS binds to circulating LPS-binding protein (LBP). The LPS bound to LBP binds to TLR4, forming the LPS-TLR4 receptor complex. Once TLR4 is activated, downstream adaptor molecules bind to the Toll/Interleukin-1 receptor (TIR) domain of TLR4. TLR4 requires four adaptor molecules to transduce signals from its TIR domain, with a key adapter being myeloid differentiation factor 88 (MyD88). Signal transduction initiation leads to the activation of NF-κB (Kawai and Akira, 2010). Once activated, NF-κB moves into the nucleus where it initiates both pro-fibrotic and pro-inflammatory gene transcription, such as fibronectin (FN1), interleukin 1 (IL-1), and tumor necrosis factor alpha (TNF-α). TLR4 can also activate the MyD88-independent signaling pathway following endocytosis. This mechanism of endocytosis of LPS bound TLR4 and its degradation through the ubiquitin pathway is one of the negative regulatory mechanisms in the LPS induced TLR4 pathway, and the purpose of this internalization is to limit the receptor expression and the signaling of the pro-inflammatory MyD88 dependent pathway.

In addition to the classical activation by exogenous LPS, TLR4 can also be activated by endogenous ligands known as damage-associated molecular patterns (DAMPs) (**Figure 1**). DAMPs are formed *in situ* because of cell damage, cell injury, and remolding of the ECM (Miyake, 2007; Piccinini and Midwood, 2010). DAMPs can upregulate as well as amplify fibrotic responses in diseases such as renal and hepatic fibrosis, lesional skin and lung in scleroderma patients, as well as in *Tlr4* mutant mice, and augment TGFβ-1 signaling (Poltorak et al., 1998; Seki et al., 2007; Pulskens et al., 2010; Campbell et al., 2011; Bhattacharyya et al., 2013). Endogenous DAMP ligands in the TM can include cellular fibronectin containing the EDA isoform (FN-EDA), high-mobility group box (HMGB)-1, low molecular weight hyaluronic acid (LMWHA), and others (Piccinini and Midwood, 2010; Bhattacharyya et al., 2013). The specific interaction between TLR4 and each of these DAMPs is not completely understood. It is known that HMGB1 binds TLR4 and then signals through adaptor molecules via the Toll/IL-1 receptor-domain to MyD88, IRAK, TRAF and finally to NF-κB (Yang et al., 2010). Specifically, how

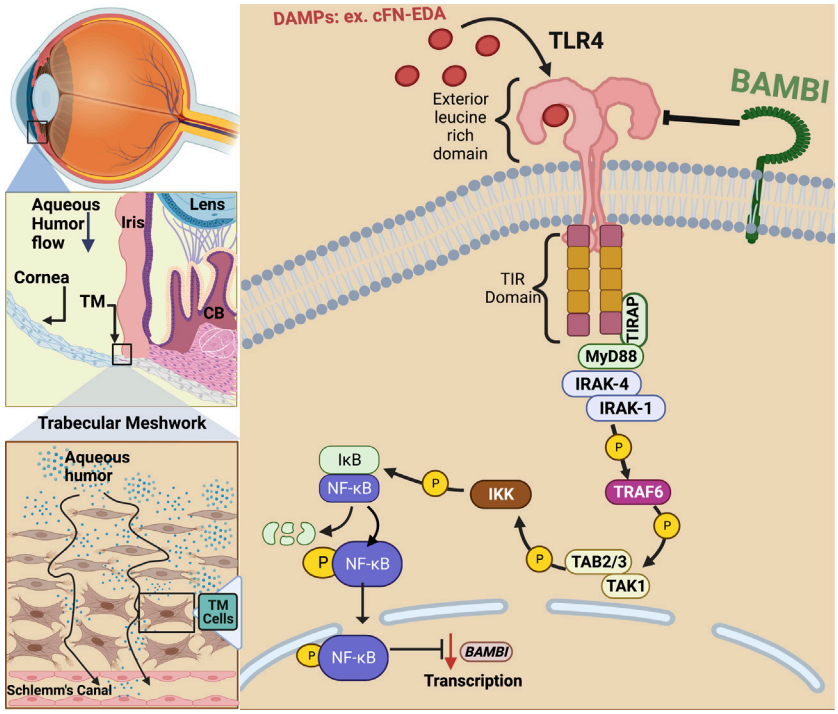

FIGURE 1 | TLR4 activation in the trabecular meshwork. In primary open-angle glaucoma, damage to the TM and inner wall of Schlemm's canal (SC) endothelium prevents sufficient aqueous humor outflow leading to elevated IOP. Damage associated molecular patterns (DAMPs) such as cellular fibronectin containing EDA isoform (cFN-EDA) are produced from TM tissue damage and excess TGFβ2 signaling and can activate TLR4 leading to Nuclear Factor-Kappa Beta (NF-κB) activation and downregulation of BMP and Activin Membrane Bound Inhibitor (BAMBI) expression.

hyaluronic acid and TLR4 interact is still not known, but it is known that this interaction requires the co-receptors MD2 and CD14 (Jiang et al., 2011). In patients with POAG, high molecular weight hyaluronic acid has been shown to be depleted in the TM; however, the amount of low molecular weight hyaluronic acid in the TM of POAG patients remains to be elucidated (Knepper et al., 1996). An extracellular matrix protein responsible for persistence organ fibrosis known as Tenascin-C directly works with TLR4 and this interaction leads to the activation of NF-κB (Bhattacharyya et al., 2016; Zuliani-Alvarez et al., 2017). Like HMGB-1, FN-EDA also activates TLR4 leading to NF-κB activation. However, whether the signaling pathway is exclusively through the MyD88-dependent pathway is still not known.

Evidence continues to surface that links DAMP activated TLR4 signaling to the regulation and production of ECM proteins in hepatic fibrosis and to TM damage and ocular hypertension (Seki et al., 2007; Bhattacharyya et al., 2013; Hernandez et al., 2017). Regarding fibrosis, specific SNP alleles in TLR4 have been shown to have an overall protective effect and be associated with a delayed progression of fibrosis in liver disease (Huang et al., 2007; Li et al., 2009). As mentioned, DAMPs can activate TLR4 and in doing so, they augment TGFβ signaling and downstream fibrotic responses (Bhattacharyya et al., 2013; Hernandez et al., 2017). DAMPs have also been shown to control the inflammatory and downstream fibrotic response in ischemic wounds when they bind TLR4 (Brancato et al., 2013). TLR4 activation also downregulates the TGFβ pseudoreceptor known as BMP and the activin membrane-bound inhibitor (BAMBI). Bone morphogenic proteins (BMPs) are a group of growth factors that are involved in regulating the ECM and importantly, BMPs can lower ECM deposition caused by TGFβ2 activation (Fuchshofer et al., 2007). BAMBI functions to inhibit TGFβ as well as BMP and activin signaling (Seki et al., 2007; Yan et al., 2009; Bhattacharyya et al., 2013). It is known that BAMBI functions to inhibit TGFβ signaling by cooperating with SMAD7 and impairing SMAD3 activation, while knockdown of *Bambi* expression enhances TGFβ signaling (Yan et al., 2009). In addition, BAMBI can interact directly with either BMP receptors or TGFβ receptors to antagonize downstream signaling (Lin et al., 2006). We have shown that when *Bambi* is conditionally knocked down in the TM, IOP becomes elevated in mice (Hernandez et al., 2018). Downregulation of *Bambi* by TLR4 is controlled by the NFκB-dependent signaling pathway (Seki et al., 2007; Guo and Friedman, 2010; Yang and Seki, 2012). Activation of TLR4 therefore downregulates *Bambi* resulting in unopposed TGFβ signaling and fibrogenesis. This leads to an upregulation and subsequent accumulation of DAMPs, creating a feed-forward loop and further amplification and continuation of the fibrotic response via TGFβ signaling.

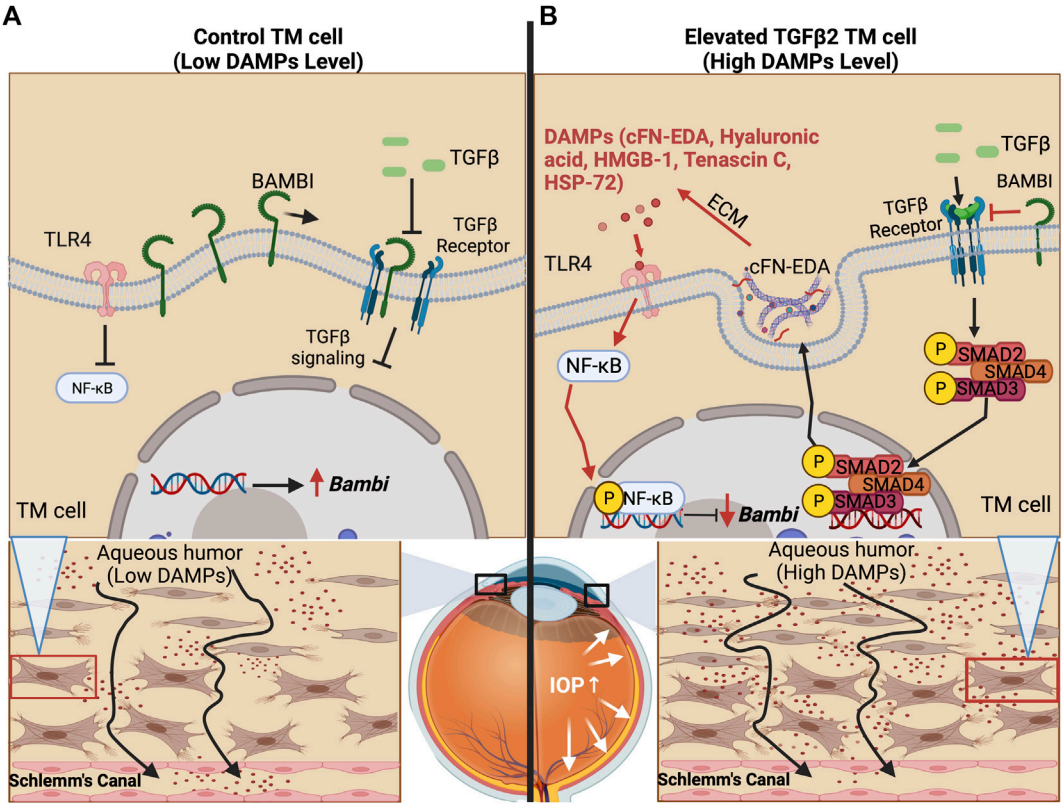

FIGURE 2 | TLR4 and TGFβ2 signaling crosstalk. **(A)** The trabecular meshwork under homeostasis expresses basal levels of extracellular matrix proteins and BMP and Activin Membrane Bound Inhibitor (BAMBI), which inhibits endogenous TGFβ2 signaling. **(B)** Bioactivated TGFβ2 leads to the expression of DAMPs, including cFN-EDA and LMW Hyaluronic acid, which activate TLR4 and lead to subsequent NF-κB activation. Phosphorylated NF-κB lowers the expression of BAMBI, which in turn, leads to uninhibited TGFβ2 signaling.

CROSSTALK OF TGFβ2–TLR4 SIGNALING

TGFβ2 is a profibrotic cytokine that when in its bioactivated form upregulates ECM proteins, some of which are FN, elastin, and several forms of collagens. In a healthy eye, TGFβ2 is the predominant isoform of TGFβ. TGFβ is known to induce various growth factors, such as connective tissue growth factor (CTGF) and fibroblast growth factors (FGFs) (Saika, 2006) and helps maintain tissue homeostasis in the TM regulating ECM synthesis, deposition, and degradation (Sethi et al., 2011b). Importantly, these factors have roles in restoration of normal tissue following injury. In addition to its ability to influence ECM remodeling, TGFβ is also known to affect multiple cellular processes, from cell growth to apoptosis (Chen and Ten Dijke, 2016). However, uninhibited and increased TGFβ2 signaling can lead to deleterious effects. Elevated TGFβ2 signaling results in damage to the ECM of the TM and increased stiffness of the TM (Russell and Johnson, 2012; Vranka et al., 2018). TGFβ2 is highly elevated in the aqueous humor of glaucoma patients and plays a vital role in the development of POAG (Tripathi et al., 1994; Inatani et al., 2001; Ochiai and Ochiai, 2002; Ozcan et al., 2004). We and others have shown that treatment of TM cells with TGFβ2 induces cross-linking of the ECM as well as alteration in the composition of the ECM (Welge-Lüssen et al., 1999; Fleenor et al., 2006; Fuchshofer et al., 2007; Wordinger et al., 2007; Sethi et al., 2011a; Tovar-Vidales et al., 2011; Hernandez et al., 2017). In anterior segment perfusion organ culture models the addition of TGFβ2 elevates IOP and overexpression of TGFβ2 in mouse eyes causes ocular hypertension (Gottanka et al., 2004; Shepard et al., 2010; Hernandez et al., 2017). In human TM cells, TGFβ2 signals through the canonical SMAD and non-SMAD pathways and also alters the ECM (Sethi et al., 2011a; Tovar-Vidales et al., 2011; Zode et al., 2011). Specifically, TGFβ2 causes phosphorylation of a SMAD signaling complex. This complex then moves into the nucleus, leading to the induction of pro-fibrotic gene transcription, which causes an increase in the production of fibrotic factors, such as the various ECM components in the TM. For ocular hypertension to occur in mice, TGFβ2 signaling through the canonical SMAD pathway is essential (McDowell et al., 2013). Taken together, this indicates that the effects of TGFβ2 signaling are a major component in the development of ocular hypertension and that TGFβ2 regulates the expression of ECM proteins in the TM. Our group has shown that there is crosstalk between the TGFβ2 and TLR4 signaling pathways in the TM and that this crosstalk is contributing to glaucomatous ocular hypertension (**Figure 2**) (Hernandez et al., 2017). Although studies in the TM have focused primarily on the canonical SMAD-dependent TGFβ2 signaling pathway in the context of

TGFβ2-TLR4 signaling crosstalk, work in other tissues has indicated that TLR4 activation can also effect non-canonical TGFβ pathways as well (McKeown-Longo and Higgins, 2017). However, whether changes in the TGFβ2 pathway occur first to induce crosstalk or if TLR4 induction first occurs to facilitate crosstalk between the pathways, is still not completely clear. It is known that increased TGFβ2 levels in glaucoma may be due to epigenetics (Bermudez et al., 2016), suggesting that it is the increased TGFβ signaling that occurs first leading to production of excess ECM and DAMPs, which would then activate TLR4 leading to a feedforward signaling loop.

As mentioned, TGFβ2 signaling increases the production of ECM proteins, including FN. We and others have identified FN, a dimeric multidomain ECM glycoprotein, to be elevated in glaucomatous TM tissues and aqueous humor (Faralli et al., 2009; Hernandez et al., 2017). Fibronectin functions as a regulator of cellular processes, directs and maintains tissue organization and ECM composition, directs ECM-ECM and ECM-cell interactions, and regulates activity of growth factors and proteins associated with ECM remodeling. The multi-domain dimer is composed of type I, type II, and type III domains with over twenty alternatively spliced isoforms. FN is composed of either cellular FN or plasma FN isoforms. Cellular FN has multiple isoforms generated by alternative processing of a single primary transcript at three domains: extra domain A (EDA), extra domain B (EDB), and the type III homologies connecting segment (White et al., 2008). The expression of FN-EDA is upregulated as a response to tissue injury, repair, or remodeling, and during disease states (Kuhn et al., 1989; Muro et al., 2003). The FN-EDA isoform is elevated in glaucomatous TM tissue compared to normal TM tissue and amplifies the response of TGFβ2 in primary TM cells in culture (Medina-Ortiz et al., 2013; Hernandez et al., 2017). Importantly, FN-EDA acts as an endogenous ligand (DAMP) for TLR4 (Okamura et al., 2001). We have identified FN-EDA as an important regulator of pathogenic TLR4 and TGFβ2 signaling in the TM (Hernandez et al., 2017; Roberts et al., 2020). Importantly, the consequence of the continuous activation of TLR4 due to this endogenous ligand is the subsequent uninhibited TGFβ2 signaling and an amplification of the fibrotic response in the TM. The activation of TLR4 is known to be dependent on the expression of MD-2 and other TLR4 accessory proteins (Yang et al., 2000; Okamura et al., 2001). The α4β1 integrin has been identified to function as a TLR4-coreceptor to initiate a FN-EDA dependent response in fibroblasts and it is known that FN-EDA contains integrin α4β1 binding sites (Liao et al., 2002; Kelsh-Lasher et al., 2017). Studies on pathogen-initiated TLR4 signaling suggest that adhesion receptors may play important roles in the regulation of the TLR4-mediated fibrotic response to tissue damage, so this may be a route that FN-EDA utilizes to elicit a TLR4 mediated response in TM cells (Gianni et al., 2012; Ling et al., 2014; Casiraghi et al., 2016).

TLR4 SIGNALING IN THE TM

Recently, utilizing a selective inhibitor of TLR4 signaling, TAK-242, we showed TGFβ2 induced ECM production in the TM was inhibited (Hernandez et al., 2017). Notably, FN-EDA amplified TGFβ2 ECM deposition and TAK-242 blocked this effect. To evaluate the role of FN-EDA in the development of ocular hypertension, we utilized an adenovirus vector to overexpress bioactivated TGFβ2 in the TM of mice containing a constitutively active FN-EDA isoform or in FN-EDA null mice, with or without mutation in *Tlr4*. Here we found that TGFβ2-induced ocular hypertension and ECM production is dependent on both EDA and Tlr4, and in mice constitutively expressing FN-EDA the effects of TGFβ2 are amplified (Roberts et al., 2020). To further evaluate the link between the TGFβ2–TLR4 pathway in the TM, we focused our attention on the role of Bambi, which is known to be downregulated via NF-kB signaling after TLR4 activation. We demonstrated that conditional knock-out of *Bambi* in the TM resulted in increased ECM deposition and development of ocular hypertension, likely due to uninhibited TGFβ2 signaling. In addition, we also tested the role of NF-κB, an upstream regulator of *Bambi* expression, in TGFβ2-induced ocular hypertension and found that mutation in the p50 subunit of NF-κB prevented TGFβ2-induced ocular hypertension (Hernandez et al., 2020). These data suggest that TGFβ2-TLR4 signaling crosstalk is important in the development of ocular hypertension and ECM changes in the TM.

We have also examined ways to attenuate the downstream fibrotic signaling initiated by TGFβ2–TLR4 signaling crosstalk. Since NF-κB is necessary for this fibrotic response, we examined how a suppressor of NF-κB signaling, A20, may be able to rescue the effects of TGFβ2 and TLR4 activators, such as FN-EDA, within the TM. Previous work showed that A20 is downregulated in human TM cells that expressed constitutively active α5β3 integrin (Filla et al., 2021). The activation of this integrin is suggested to contribute to the fibrotic-like changes observed in POAG, therefore A20's diminished presence may be contributing to the increased fibrotic response seen in the glaucomatous TM. Expression changes in A20 have also been shown in the retina of glaucomatous human donor eyes (Yang et al., 2011). We showed that TGFβ2 causes a decrease in the expression of A20 in TM cells, while at the same time increasing expression of ECM proteins such as FN (Mzyk et al., 2022). Overexpression of A20 in human TM cells attenuated the amount of FN expressed in TM cells after stimulation with either TGFβ2, LPS, or FN-EDA (Mzyk et al., 2022). These data suggest that A20 is a novel molecular target that inhibits the pathological ECM changes in the glaucomatous TM.

CONCLUSION

This review summarizes the involvement of the TGFβ2-TLR4 signaling pathways in augmenting the pathogenesis of ocular hypertension at the trabecular meshwork. The TLR4 pathway is a fibroinflammatory pathway that can modulate the function of the TM, specifically by altering the TM's rate of deposition of ECM, leading to the impairment of aqueous humor outflow and

the progression of glaucoma. Identification of additional DAMPs and regulators of TLR4 signaling may allow us to identify potential therapeutic targets for POAG. Further investigation of TGFβ2-TLR4 crosstalk in the TM will help to explain the mechanisms involved in the development of glaucomatous TM damage.

AUTHOR CONTRIBUTIONS

PM, HH, and CMM wrote and edited the manuscript. TL and JR made the figures.

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