The molecular mechanisms of action of PPAR-γ agonists in the treatment of corneal alkali burns (Review)

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Abstract. Corneal alkali burns (CAB) are characterized by injury-induced inflammation, fibrosis and neovascularization (NV), and may lead to blindness. This review evaluates the current knowledge of the molecular mechanisms responsible for CAB. The processes of cytokine production, chemotaxis, inflammatory responses, immune response, cell signal transduction, matrix metalloproteinase production and vascular factors in CAB are discussed. Previous evidence indicates that peroxisome proliferator-activated receptor γ (PPAR-γ) agonists suppress immune responses, inflammation, corneal fibrosis and NV. This review also discusses the role of PPAR-γ as an anti-inflammatory, anti-fibrotic and anti-angiogenic agent in the treatment of CAB, as well as the potential role of PPAR-γ in the pathological process of CAB. There have been numerous studies evaluating the clinical profiles of CAB, and the aim of this systematic review was to summarize the evidence regarding the treatment of CAB with PPAR-γ agonists.

Contents

1. Introduction

The cornea is the protective ocular surface, and is transparent to enable the transmission of light. Chemical burns can damage this barrier (1), and in addition to corneal injury and eyelid burns, are risk factors for ocular complications, including ulcers, scars and neovascularization (NV) (2,3). Several potential interventional strategies, including limbal stem cells, amniotic membranes and corneal transplantations have been demonstrated to have some success in clinical outcomes. There are numerous risk factors and molecular markers for the progression of ocular chemical burns. Improvements in the knowledge of the novel biomarkers associated with the inflammation, angiogenesis and fibrosis of ocular chemical injuries have contributed to the development of novel therapeutics. Chemical burns can be divided into alkali and acid burns, with corneal alkali burns (CAB) frequently resulting in a greater severity of injury (4). Peroxisome proliferator-activated receptor (PPAR) controls the regulation of genes through the activation of nuclear receptors, and plays a role in the control of a variety of inflammatory, angiogenic and fibrotic physiological processes (5). This reviews covers the key aspects associated with biomarker research into the pathological process of CAB, and analyzes the potential therapeutic role of PPAR agonists in the treatment of CAB. The processes of cytokine production, chemotaxis, inflammatory and immune responses, signal transduction, matrix metalloproteinase (MMP) production and vascular factors in CAB are summarized, and the potential application of PPAR agonists as treatments to control lesion severity in CAB are also discussed.

2. Conventional CAB treatment

Stem cells potentiate regeneration due to their ability to differentiate into multiple cell lineages. The most common sources of stem cells for clinical use are embryonic, adult and induced (6). Surface transplantation and subsequent keratoplasty can result in good visual function following ocular injury (7). Limbal stem cell grafts with amniotic membrane transplantation or simple limbal epithelial transplantation may additionally be used to restore vision and reduce symptoms in cases with limbal stem cell deficiency following chemical burns (8-12). Cultivated oral mucosal epithelial transplantation has been indicated to enable the complete epithelialization of persistent corneal epithelial defects, and stabilize the ocular surface in patients with severe ocular surface disease (13). The Boston keratoprosthesis type I is an effective artificial cornea and aids in the recovery from advanced ocular surface disease, and has

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been shown to result in a significant increase in eyesight (14). Additionally, Boston keratoprosthesis implantation may reduce the risk of post-keratoplasty complications by the wearing of contact lenses (15). Alternatively, a large tectonic corneoscleral lamellar graft represents a good treatment method (16). These methods can treat a selection of clinical applications and present some benefits; however, they require further study.

3. Limitations of traditional therapeutic strategies

Scarring has been attributed to the proliferation of inflammatory cells and fibroblasts during burn wound healing. The irregular remodeling of matrix structures may lead to scar formation. Stem cell immunomodulation has been indicated to address pathological scarring (17-19). Limbal transplantation is a standard procedure to restore ocular surface disorders and, considering the shortage of corneal donors, is a viable alternative treatment strategy; however, the success rate remains low (20). Additionally, the separation and purification rates of limbal cells and the efficiency of migration require further investigation, and the therapeutic efficacy and safety of limbal transplantation should be clarified (21). Furthermore, the rejection rate of keratoplasty is high in cases of CAB, and the number of suitable donor corneas available is not sufficient to meet the demands (22,23). Corticosteriods are the predominant current treatment, and treat the inflammation associated with corneal NV (CNV); however, they can result in side-effects, such as cataracts and increased intraocular pressure (24). Further studies are required to understand stem cell applications targeting NV and the inflammatory and fibrotic processes associated with CAB (Fig. 1).

4. Topical CAB therapies from bench to clinic

A number of topical therapeutics against NV or inflammation associated with CAB are under investigation (25). Some of these potential topical therapeutics under investigation are aloe vera, prospero homeobox 1 short interfering RNA, Rho-associated protein kinase inhibitors (AMA0526), 0.5% ketorolac tromethamine, keratinocyte growth factor-2, omentum, protein phosphatase magnesium dependent-1 and melatonin, and may potentially be used for the treatment of CAB in clinical practice (26-33). Subconjunctival bevacizumab injection may be considered as a secondary treatment for CNV caused by chemical injuries that are not responsive to conventional steroid therapy (34,35). These topical therapies may be effective treatments for severe cases of CAB, although further studies may be required to fully determine this.

5. PPAR-γ and the healing process of CAB

PPARs belong to a nuclear receptor superfamily that includes steroid, thyroid hormone, vitamin D and retinoid receptors. PPAR-γ is activated by transcription factors and plays an important role in the regulation of cell proliferation and inflammation (36,37). PPAR suppresses inflammatory cytokines, proteolytic enzymes, adhesion molecules, chemotactic and atherogenic factors (38-40). Transforming growth factor (TGF) β1 has been shown to transdifferentiate keratocytes to myofibroblasts involved in the repair of the corneal epithelium, and stromal and corneal scar formation in CAB, by regulating monocytes, macrophages, vascular endothelial growth factor (VEGF), neutrophils and monocyte/macrophage chemotactic protein-1 (32,41). In a previous study, the expression of the PPAR-γ gene was shown to induce anti-inflammatory and anti-fibrogenic responses in an alkali-burned mouse cornea. Additionally, PPAR-γ gene expression suppressed TGFβ1 and MMP expression in macrophages, indicating a potentially effective strategy for the treatment of CAB (3). PPAR-γ expression has been reported to increase with the infiltration of numerous inflammatory cells in the pathological process of CAB. As previously demonstrated, treatment with an ophthalmic solution of a PPAR-γ agonist suppressed the expression levels of interleukin (IL)-1β, IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNF-α), TGFβ1 and VEGF-A in corneal inflammation induced by an alkali burn. An ophthalmic solution of the PPAR-γ agonist may provide a novel treatment strategy with useful clinical applications for corneal inflammation and wound healing (42). Burns induce the activation of an inflammatory cascade and wound progression. The PPAR-γ agonsist, rosiglitazone, reduces the percentage of unburned skin interspaces that progress to full necrosis in a rat model and prevent burn-induced organ damage. Therefore, the PPAR-γ agonists hold potential for clinical application (36,43). In this review, the potential role of PPAR-γ agonists in the treatment of CAB and the underlying molecular mechanisms are discussed.

6. Potential role of PPAR agonists in the treatment of CAB

PPAR-γ ligands are divided into endogenous (9, 13 and 15-hydroxyoctadecadienoic acid) and synthetic (pioglitazone, troglitazone, rosiglitazone, liglitazone and TZD18) compounds (44). PPAR isoforms (PPAR-γ, PPAR-α and PPAR-β/δ) have been shown to exhibit anti-inflammatory and immunomodulatory properties. PPARs may represent a novel target in the treatment of inflammatory and vascular diseases (45). Pioglitazone may inhibit corneal fibroblast migration and reduce corneal fibroblast-induced collagen contraction in the corneal wound healing process (46). Previous studies have supported the anti-inflammtory, anti-angiogenic and anti-fibrotic functions of PPAR-γ.

PPAR-γ, cytokines and cellular immunity. Toll-like receptors (TLRs) play key roles in innate immune responses. PPAR-γ gene silencing affects genes involved in the innate immune process (47). Injury primes the innate immune system for enhanced TLR-2- and TLR-4-mediated responses, and suggests that increasing TLR activity may contribute to the progression of systemic inflammation following severe injury (48). Previously, Th1-activated macrophages were considered a key cellular defense against intracellular pathogens. However, more recently, Th2-activated macrophages have been indicated to be involved in repair and tissue regeneration via the modulation of PPARs in immunological inflammation, and this may lead to new therapeutic approaches (49-51). Dendritic cells (DCs) from burned skin notably express low levels of human leukocyte antigen-antigen D related and TLR-4 immediately following cell isolation. In the post-burn period, the ability of skin DCs to respond to bacterial stimuli is impaired. These

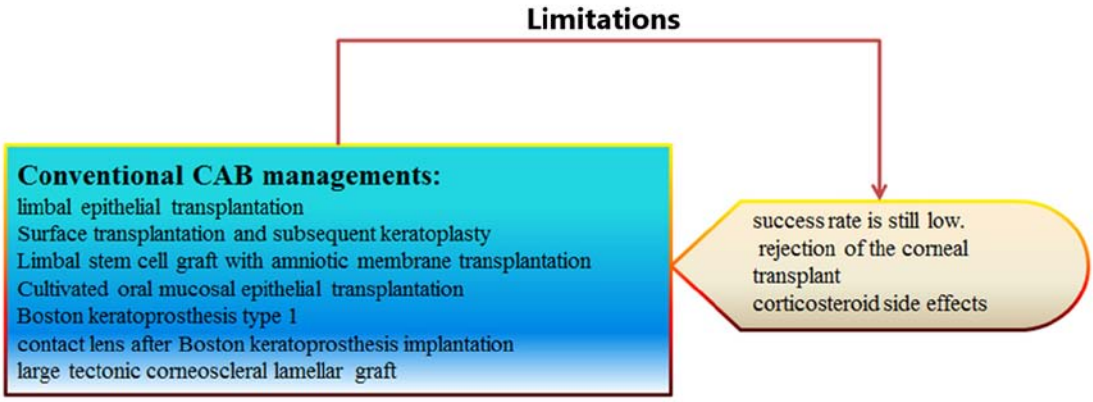

Figure 1. Conventional corneal alkali burns (CAB) managements and their limitations.

alterations in DCs may contribute to impaired host defenses against bacteria, leading to post-burn infection (52). Burns are associated with γδ T-cell activation at the injury site, which initiates the infiltration of the wound with large numbers of αβ T-cells that may facilitate the transition from the inflammatory to the proliferative phase of healing (53). Burns and TLRs are associated with the induction of the innate immune system, with a greater number of TLR-2-induced Kupffer cells (KCs) and macrophage inflammatory protein (MIP)-1β production post-injury, whereas the levels of IL-6, IL-10 and MIP-1β and the number of KCs are greater following TLR-4-induced activation following burns. TLR-mediated inflammatory responses have been reported to be augmented post-burn by the induction of inflammatory mediators (54). TLR-5 is normally present on the superficial cells of the conjunctival epithelium, and may be upregulated following chemical burns (55). TLR activates the innate immune system to recognize antigens and induce the production of inflammatory cytokines and chemokines (56,57). The TLR-related genes, heat-shock 70kDa protein (HSP)A1A, Harvey rat sarcoma viral oncogene homolog, mitogen-activated protein kinase (MAPK) kinase 3, Toll interacting protein, v-rel avian reticuloendotheliosis viral oncogene homolog A, FBJ murine osteosarcoma viral oncogene homolog and TLR-1 have been observed to be reduced in the primary epidermal keratinocytes of patients with severe burns, and restoring the expression of these genes may improve clinical outcomes (58). High levels of cytokines promote collagen degradation, the apoptosis of keratinocytes and vascular compromise. Local inflammation induced by severe burns can clear cellular debris, protect against microbial agents and induce cell growth and proliferation (58,59). The reduction of the activation and recruitment of macrophages may be a potential therapeutic strategy for the corneal scarring of alkali-burned ocular surfaces (60). Agonists of TLR-4, 1/2 and -5 suppress the activity of PPAR-α and PPAR-γ in astrocytes (61). PPAR-β/δ expression is regulated in TLR agonist-stimulated astrocytes via the regulation of the pro-inflammatory genes. p38, MAP2K1/2, MAPK2/3 and c-Jun N-terminal kinase (JNK) (62). The PPAR-α agonist, WY14643, has been shown to significantly reduce amylase, lipase and myeloperoxidase activity, and IL-6, intercellular adhesion molecule-1, and TLR-2 and 4 levels (63). PPAR-γ inhibits interferon (IFN)-β production in TLR3- and 4-stimulated macrophages by preventing interferon regulatory factor 3 binding to the IFN-β promoter (64). Treatment with rosiglitazone was previously shown to result in higher levels of PPARγ and a reduction in serum inflammatory cytokine levels, and the levels of TLR2/4 and nuclear factor-κB (NF-κB) activity in aortic tissues. These biological functions of rosiglitazone in *P. gingivalis*-accelerated atherosclerosis were shown to be dependent upon the inhibition of the inflammatory response and the TLR/NF-κB signaling pathway (65). PPAR-γ and TGF-β can enhance regulatory T cell (Treg) generation, providing a potential therapeutic strategy for the treatment of inflammatory and autoimmune diseases (66). PPAR-γ restores the abnormal immune gene expression of p38MAPK, activating transcription factor-2, MAPK-activated protein kinase 2 and HSP27 in T-cell mediated immune responses *in vivo* (67). Cell types in the innate and adaptive immune system, including neutrophils, macrophages, mast cells, B cells and T cells, have all been implicated to play a role in burn-induced immunology (68). Burn injury disrupts the immune system, resulting in the marked suppression of the immune response. The mononuclear phagocyte system (MPS) is a critical component of the innate immune response, and is able to initiate an adaptive immune response. Severe burns inhibits the functions of DCs, monocytes and macrophages. The MPS in the pathophysiology of severe burns will guarantee a more rational immunotherapy for patients with severe burns (69). These results collectively suggest that PPAR-α, -γ and -β/δ are likely mediators of TLR activation in transducing inflammation in CAB pathologies; however, the relative immune mechanisms require clarification. The molecular mechanisms of CAB are summarized in Fig. 2.

Cytokines and cellular immunity. As an anti-TNF-α monoclonal antibody, topical infliximab has been reported to significantly reduce corneal perforation, leukocyte infiltration, cluster of differentiation (CD)45$^+$ cell infiltration and fibrosis in the eyelids. The topical application of infliximab may be useful in the treatment of ocular diseases (70). Topically applied IL-1 receptor antagonist (IL-1ra) may suppress corneal inflammation and promote recovery following CAB. All cytokine/chemokine levels, in particular IL-6 and IL-10, have been shown to be significantly reduced in IL-1ra-treated eyes, with the opposite effect observed in IL-1ra knockout mice (71-74). The treatment

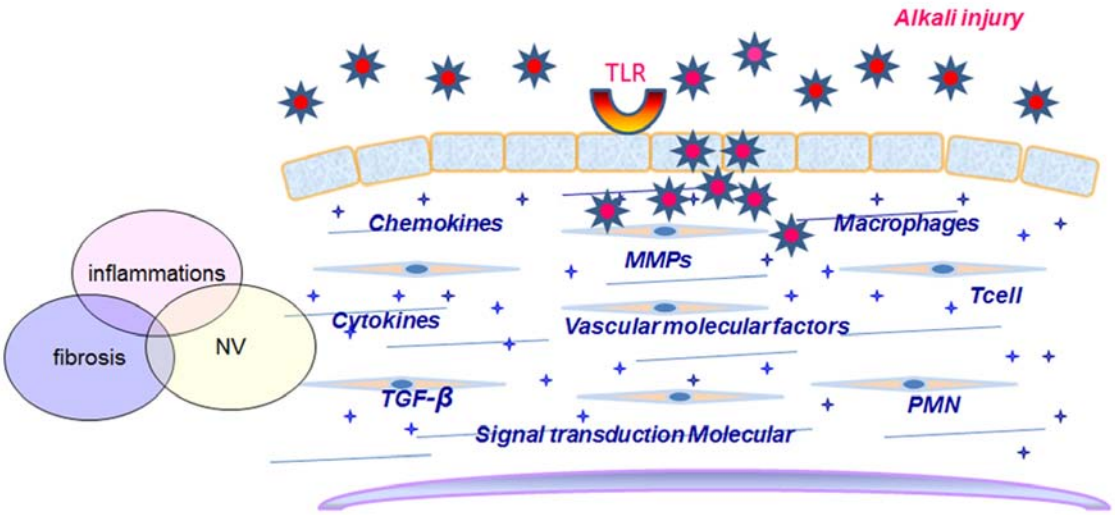

Figure 2. The molecular mechanisms associated with corneal alkali burns (CAB).

of inflammation with minimal infiltrating cells and normal levels of IL-1α and IL-1β may accelerate the healing of CAB (75). A reduction in IL-6 and TGF-β1 expression has been indicated to protect the cornea from chemical damage (76). In addition, the inhibition of inflammation and NV has been reported to play a significant role in preventing corneal angiogenesis and inflammation in alkali-burned corneal beds, which results in higher allograft survival rates (77). Furthermore, in a CAB model, the infiltrated polymorphonuclear leukocytes and the mRNA expression of VEGF receptor 1 and 2, basic fibroblast growth factor, IL-1β, IL-6, MMP-2, -9 and -13, in addition to the protein expression levels of VEGFR2, IL-1β, IL-6 and MMP-2 and -9, were upregulated in the corneas. The suppression of CNV, inflammatory cytokines and MMPs aids in reducing the damage associated with CAB (78). Human peripheral blood mononuclear cells and inflammatory cytokines can be stimulated by chemically injured keratocytes. MMP-9 and macrophage migration inhibitory factor levels have been reported to be higher in burn injury (79). CD4 and CD44 (memory) CD8 T cells have been found to be significantly increased, in addition to TLR-4, post-burn injury, and functional T cell responses have additionally been demonstrated. Complex adaptive immune responses have been reported in burn injury (80); however, this differs in the process of CAB. IFN-γ and CD4 were not detected in rat corneas following alkali burns, indicating that cytokines were induced in the cornea by burn injury without a specific immunological stimulus (81). To inhibit excessive inflammatory damage, particular anti-inflammatory agents may be applied for the treatment of alkali burns. PPAR-γ agonists are a good candidate for anti-inflammatory activity in preventing TNF-α damage (82). Pioglitazone therapy has been demonstrated to suppress the mRNA levels of the inflammatory cytokines monocyte, MCP-1, IL-1 and IL-6, produced by macrophages in the cerebral arteries (83). PPAR-γ represents an appealing strategy for decreasing inflammation and improving the healing of chronic injuries, and PPAR-γ in inflammatory cells may be a potential therapeutic target (84,85). Pioglitazone has been shown to exert anti-inflammatory effects on acute gouty arthritis by inhibiting the expression of TNF-α and IFN-γ (86). Notably, there is anti-inflammatory therapeutic potential for the treatment of Alzheimer's disease, dental implants and lipid inflammation processes through the PPAR-γ pathway (47,87,88). PPAR-γ modulates macrophage and T cell-mediated inflammation. Reductions in the levels of PPAR-γ in T cells have been shown to result in an increased expression of adhesion molecules and pro-inflammatory cytokines (IL-6 and IL-1β), and to modulate Treg recruitment (89). Thus, PPAR-γ agonists are effective in controlling inflammation-related damage and inhibiting cytokines and chemokines, suggesting their therapeutic potential in the treatment of CAB.

PPAR-γ and NV. Pathological conditions including infection, trauma and loss of the limbal stem cell barrier can lead to CNV formation, from the limbal area to the vascular cornea (90). NV is mediated by cellular and molecular factors, such as VEGF and pigment epithelium-derived factor (PEDF), which play roles in the development of NV (91). Corneal transparency is essential for maintaining good visual acuity, and NV in CAB forms the basis of multiple visual pathologies that may result in blindness. However, CNV formations respond poorly to current therapies. Therefore, potential anti-angiogenic topical treatments against CNV resulting from alkali burns have been investigated in *in vitro* studies and clinical trials (25,92-95). The suppression of VEGF and placental growth factor levels in the cornea in a mouse model of alkali burns was observed to significantly inhibit NV growth and the regression of established vessels (96). PPAR-γ agonists are potent inhibitors of NV and show potential for the treatment of inflammatory vasculoproliferative diseases (97-100). Rosiglitazone has been shown to protect vascular endothelial cells by reducing the expression of the chemerin receptor, ChemR23 (101). Thiazolidinediones (TZDs) inhibit retinal and choroidal NV by suppressing tube formation in human umbilical vein endothelial cells (HUVECs). In addition, TZDs may inhibit VEGF induced non-inflammatory NV *in vivo* (102). PEDF is a potent anti-angiogenic factor and can induce endothelial cell apoptosis, and can inhibit angiogenesis

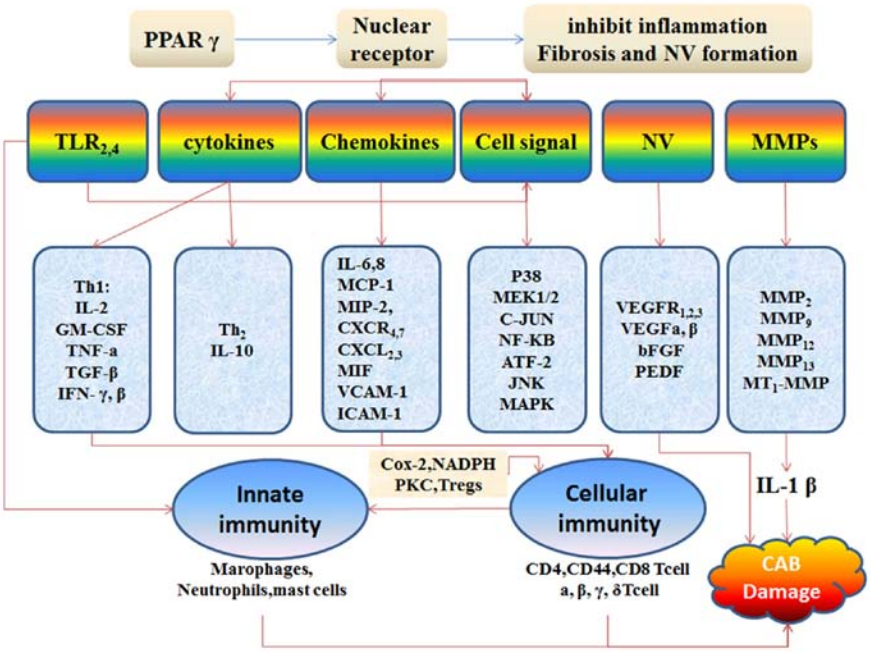

Figure 3. The molecular mechanisms responsible for the inhibitory effects of peroxisome proliferator activated receptor γ (PPAR-γ) agonists on corneal alkali burns (CAB).

by augmenting PPAR-γ expression in ischemic heart tissue (103). Therefore, PPAR-γ may be a useful target in the prevention and treatment of vascular inflammatory diseases.

PPAR-γ and fibrosis. Corneal fibrosis can result in visual impairment and blindness. Alkali burned corneas were observed to exhibit obvious interfibrillar distances with greater levels of the fibrotic marker α-smooth muscle actin (αSMA) (104). The TGFβ-induced differentiation of corneal fibroblasts to myofibroblasts could be prevented (105). The level of inflammation and scarring/fibrosis has been observed to increase during healing in injured tissue in a model of CAB. The prognosis of CAB is dependent upon ocular surface inflammation, and the scarring and fibrosis of the cornea and eyelid (70,106). PPAR-γ possess strong anti-fibrotic properties in the cornea and several other types of tissue, with PPAR-γ ligands blocking αSMA induction (107). A number of studies have demonstrated that treatment with ophthalmic solutions of PPAR-γ agonists reduced the fibrotic reaction in the early phase post-CAB and in additional fibrotic pathologies (106,108,109).

PPAR-γ agonists and cell signal transduction. PPAR-γ is an important modulator of lipid metabolism during inflammation, via the inhibition of the expression of proinflammatory molecules (110). NF-κB is activated and translocates to the nucleus where it controls the expression of a large number of target genes, which are involved in the regulation of inflammation and innate and adaptive immune responses (111). Telomeric repeat binding factor was discovered as a modulator that regulates NF-κB signaling. The inhibition of repeat binding factor may lead to the design of specific inhibitors of NF-κB for the treatment of ocular injuries (112). The effects of SN50, an inhibitor of NF-κB, were reported to be dependent on TNF-α/JNK signaling in a mouse model of CAB, with the topical application of SN50 shown to be effective in treating CAB (113). PPAR-γ has been indicated to be the predominant pathway involved in the inhibition of IL-1β-induced inflammation [nitric oxide and prostaglandin E2 production, in addition to inducible nitric oxide synthase and cyclooxygenase 2 (COX-2) expression, NF-κB and MAPK activation (114).

PPAR-γ agonists and chemokines. TC14012 [a chemokine (C-X-C motif) receptor 4 (CXCR4) antagonist and CXCR7 agonist] has been reported to initially enhance alkali burn-induced CNV, then reduce CNV in later stages. In addition to CXCR4, CXCR7 has been implicated in the pathogenesis of CNV (115). Granulocyte-colony stimulating factor (G-CSF) post-traumatic gene expression activates innate immune responses and suppresses adaptive immune responses. The G-CSF signal transducer and activator of transcription axis has been indicated to be a key protective mechanism post-injury in reducing the risk of infection (116). PPAR-γ reduces the expression levels of pro-inflammatory chemokines, including chemokine (C-C motif) ligand 20, CXC ligand (CXCL)2, CXCL3 and chemokine (C-X3-C motif) ligand 1 (CX3CL1) in colon tissues. It has been shown that increasing the transcriptional activity of PPAR-γ can modulate inflammatory signaling pathways, suggesting a novel target for therapeutic agents (117). The investigation of inflammatory markers in vascular disorders reveals augmented levels of circulating cytokines and chemokines among carriers of classic risk factors for atherosclerosis. Dysregulation of the PPAR signaling pathway may explain the association of IL-8/12 and very low density lipoprotein (VLDL)-c in the promotion of dysglycemia (118). The PPAR signaling pathway was shown to be important in the modulation of inflammatory factors, including MCP-1, TNF-α, IL-1 and IL-6, COX-2, nicotinamide adenine dinucleotide phosphate, protein kinase C, vascular cell adhesion molecule-1, NF-κB

and monocyte expressions in HUVECs. The inhibition of the PPAR pathway in endothelial inflammation suggests a potential role of PPAR agonists in the treatment of vascular inflammation (119,120). Rosiglitazone has been shown to suppress angiogenesis by downregulating the expression of CXCR4 in a dose-, time- and PPAR-γ-dependent manner (121). Regulating the expression of MCP-1 and activating the 5' AMP-activated protein kinase-sirtuin 1-PPAR signaling pathway may be a novel therapeutic agent for atherosclerosis (122). PPAR-γ has been indicated to regulate hypoxia/reoxygenation-stimulated IL-8 production in U937 cells (123). PPAR-γ serves an inhibitory role in hepatic injury by downregulating the local expression of proinflammatory cytokines, chemokines and adhesion molecules following reperfusion (124,125).

PPAR-γ agonists and MMPs. Keratocytes are able to directly degrade type I collagen and create stromal spaces, promoting CNV through VEGF induced MMP-13 expression (126). The inhibition of alkali burn-induced CNV in mice may be possible via reductions in the production of the angiogenic factors, inflammatory cytokines and MMPs involved in the angiogenic response (78,127,128). MMP-12 may disintegrate certain components of the extracellular matrix (ECM) released following severe alkali burn, which may be involved in ECM remodeling (129). Inhibiting alkali burn-induced CNV by accelerating corneal wound healing and by reducing the production of angiogenic factors, inflammatory cytokines and MMPs may be a potential therapeutic strategy (29,125,130-133). PPAR-γ agonists are able to affect proliferation, differentiation, apoptosis and inflammation in different cell types. PPAR-γ ligands were able to inhibit K562 and HL-60 cell adhesion to ECM proteins by inhibiting the expression of MMP-2 and -9 (134). PPAR-γ agonists have been shown to inhibit macrophage infiltration, the expression of TNF-α and MMP-9 in aortic tissue, thus may be used as anti-inflammatory agents in cardiovascular fields (135). Degradation of the epithelial basement membrane in burned cornea *in vivo* was reversed by an MMP inhibitor (136), additionally; MMP inhibitors have been shown to block the progression of alkali burns to ulceration (137). These data may indicate that PPAR-γ agonists are a potential strategy for preventing CAB progression.

Taken together, the evidence suggests that PPAR-γ may lessen NV, inflammation and scarring. However, additional studies are necessary to evaluate the potential therapeutic effects of PPAR-γ in ocular NV, tissue inflammation and the resultant fibrosis following burn injury (Fig. 3).

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