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An ocular view of the IGF-IGFBP system

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Abstract

IGFs and their binding proteins have been shown to exhibit both protective and deleterious effects in ocular disease. Recent studies have characterized the expression patterns of different IGFBPs in retinal layers and within the vitreous. IGFBP-3 has roles in vascular protection stimulating proliferation, migration, and differentiation of vascular progenitor cells to sites of injury. IGFBP-3 increases pericyte ensheathment and shows anti-inflammatory effects by reducing microglia activation in diabetes. IGFBP-5 has recently been linked to mediating fibrosis in proliferative vitreoretinopathy but also reduces neovascularization. Thus, the regulatory balance between IGF and IGFBPs can have profound impact on target tissues. This review discusses recent findings of IGF and IGFBP expression in the eye with relevance to different retinopathies.

Keywords

IGF; IGF binding protein; retinopathy; hypoxia; blood retinal barrier; vascular protection

Introduction

Insulin-like growth factors (IGFs) are peptides produced in the liver and throughout most tissues that stimulate mitogenic activity through their interaction with IGF receptors (IGFRs) [1]. Two forms have been identified: IGF-I and IGF-II; they are regulated by insulin-like growth factor binding proteins (IGFBPs) and IGFBP proteases to collectively form the IGF system. IGFBPs interact with a glycoprotein, the acid-labile subunit (ALS), and binds free IGF in serum to form a ternary complex and modulate IGF binding to IGFRs on endothelium [2]. Of the IGFBPs, IGFBP-3 is most abundant in postnatal serum and carries more than 75% of serum IGF-I and IGF-II in complexes [1,3]. Other IGFBPs bind a small proportion of IGF and less than 1% of IGFs are circulating freely [2]. The existence of IGFBPs was postulated in the 1960s but the definitive studies were carried in the mid 1980s until successful cloning and sequencing of six IGFBPs (IGFBP-1 to IGFBP-6) in the early 1990s [2,4–9]. Since then, nine IGFBP related proteins (IGFBP-rPs) sharing some homology have been identified. All bind to IGF although with lower affinity than IGFBPs [10–12].

Serum IGF-I is synthesized and released from the liver following activation of hepatic receptors via binding of growth hormone (GH), so IGF-I may be important for regulating

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growth [13,14]. A dual effector theory has been proposed suggesting that GH causes cell differentiation while IGF-I promotes cell proliferation [15]. Early studies in GH deficient children showed that IGF-I has a major role in regulating fetal growth, especially during the third trimester [16]. Recent pharmacokinetic studies have determined dosing parameters of IGF-I/IGFBP-3 to maintain IGF-I levels at normal physiologic range in preterm infants without significant changes to blood pressure, heart rate, or blood glucose levels [17]. Premature infants with insufficient IGF-I can be given exogenous IGF-I to promote normal vessel development and to prevent retinopathy of prematurity (ROP) [17,18].

Modulating IGFBP expression may have inhibitory or stimulatory effects depending on the microenvironment and cellular context [19–21]. IGF-I and IGF-II have been linked to atherosclerosis to stimulate vascular smooth muscle cell proliferation (VSMC) and maintain plaque stability [22,23]. Although VSMC proliferation may contribute to the development of plaques, it has also been suggested that reducing IGF-I levels below physiologic levels may lead to loss of VSMC, destabilize plaques, and thus increase in risk of thrombosis [24]. A reduction in circulating IGF-I levels has been shown to promote atherosclerosis in Apolipoprotein E-deficient mice [25]. Increased IGFBP-1 levels reduced plaque burden, lowers blood pressure, and confers protection from atherosclerosis in mice overexpressing IGFBP-1 [26]. Upon plaque inflammation, IGFBP-1 is activated to control SMC proliferation which may regulate fibroproliferative processes and subsequently plaque stability [27].

In prostate cancer, IGFBP-3 has been shown to mediate anti-growth signals, induce apoptosis in prostate cancer cells, and display antiangiogenic properties [28–32]. In breast cancer cells, IGFBP-3 appears to maintain cell survival under adverse microenvironments by binding to glucose-regulated protein 78 and stimulating autophagy [33]. IGFBP-3 can also bind to a cell death receptor, IGFBP-3R, that is expressed in M12 human prostate cancer cells and MDA231 breast cancer cells [34]. IGFBP-3/IGFBP-3R mRNA expression is reduced in invasive tissues compared to benign tissues [34]. Restoring the expression of IGFBP-3/IGFBP-3R enhanced tumor suppressive activity by activating Caspase-8 signaling [34].

Most tissues can synthesize IGF-I, therefore locally derived IGF-I may have more dominant roles in regulating the tissue microenvironment than serum IGF-I [15,35]. Within the eye, IGF-I receptors (IGF-IR) are present on retinal microvascular cells and their activation increases both DNA synthesis and promotes migration [15,36,37]. Vitreal IGF-I levels were found to be increased in diabetic patients [14,15,38]. Thus, IGF-I may be involved in retinal neovascularization, which is a primary determinant for retinopathy of prematurity (ROP) or proliferative diabetic retinopathy (PDR) [15]. Numerous studies have identified expression patterns of IGFBPs in the retina and vitreous humor when exposed to certain microenvironments. The focus of this review will examine recent findings of the IGF-IGFBP system and its role in retinopathy.

IGF/IGFBP expression in the eye

IGF-I and IGF-IR have been detected in retinal endothelial cells, lens epithelial cells, retinal pigment epithelium, cone photoreceptor cells, and Müller cells [39–43]. Using models of oxygen-induced retinopathy (OIR), microarrays determined differential global expression profiles between hypoxic and hyperoxic retinas. Retinas removed from hyperoxic chambers showed upregulation of genes associated with vasculogenesis, neurogenesis, and inflammation and included IGFBP-3 [44]. Alternatively, IGFBP-7, or IGFBP-rP1, was downregulated when compared to normoxic retinas [44].

Closer examination using laser capture microdissection identified localization and abundance of IGFs and IGFBPs [45]. IGF-IR expression was predominantly found in photoreceptor cells, which may be important for retinal vascular development since IGF-IR null mice showed decreased retinal vasculature [45,46]. IGFBP-2, IGFBP-4, and IGFBP-5 are expressed similarly between normoxic and hypoxic conditions. IGFBP-3 basal expression was lower, but was significantly induced to similar levels of other IGFBPs under hypoxia [45]. There were increased mRNA levels of IGFBP-3 and IGFBP-5 within neovascular tufts, however no functional protein levels were measured [45].

IGFBP levels in vitreous of the eye have been reported. Western blot analyses using biotinylated IGF-II revealed that IGFBP-2 and IGFBP-3 were predominant in the vitreous, but a small ~29kDa band confirmed by in vitro studies with IGFBP-3 protease indicated that IGFBP-3 existed in a cleaved form [47]. Schoen et al. found the cleaved form of IGFBP-3 to be more prominent in diabetic vitreous humor, suggesting a role of IGFBP-3 protease in regulating IGFBP-3 in the vitreous [48]. The functionality of the fragmented IGFBP-3 and significance of IGFBP-3 proteases in the vitreous has not been determined.

(mRen-2)27, a hypertensive rat model with elevated serum and ocular renin levels, was treated with streptozotocin to induce diabetes to evaluate expression of the IGF system [49]. In the diabetic state, overall abundance of IGFBP-5 was increased in the cornea and iris while IGFBP-6 was reduced [49]. IGFBP-1 was present in retinal layers with no change with diabetes whereas IGFBP-2, IGFBP-3, and IGFBP-4 were not detected by in situ hybridization [49]. Differences in consensus of mRNA expression of IGF system may be due to assay conditions and the particular animal model [49,50].

The presence of IGFBPs both in the retina and in the vitreous to varying levels depending on the model suggest that they may have functional roles in regulating ocular physiology. Current evidence shows that IGFBPs play a key role in limiting free IGFs in circulation which can inhibit retinal angiogenesis growth and development. Since IGFBP-3 is the major protein that binds to free IGF, the predominantly cleaved form in the vitreous of diabetic eyes may lead to altered regulation of IGFs [47,48,51–53]. Further studies are necessary to understand the regulation of IGF axis expression and function as a protective or pathophysiological process.

Role of IGFBP-3 under hypoxia

Retinopathy is associated with both dysfunctional repair and maintenance of the retinal vasculature. In diabetes associated retinal complications, endothelial progenitor cells (EPCs) displaying the $CD34^+$ surface marker have reduced migratory, proliferative, and differentiation potential. $CD34^+$ cells exposed with exogenous IGFBP-3 were able to migrate in a dose-dependent manner and increase endothelial nitric oxide synthase (eNOS) activity, a prominent factor in vasodilation, suggesting that IGFBP-3 can stimulate recruitment of precursor cells [3,54]. In vivo studies support this finding through increased bone marrow derived GFP^+ cells in the retina in response to endothelial cell overexpression of IGFBP-3 (Figure 1).

Migration of $CD34^+$ progenitors represents a critical process for routine vascular maintenance as well as repair of injuries. We have previously shown that IGFBP-3 promotes retinal repair by stimulating bone marrow-derived cell homing following injury; many of these migrating cells are vascular progenitors [53]. Vasodilator-stimulated phosphoprotein (VASP) plays a pivotal role in cell migration and its activation is nitric oxide (NO)-dependent [55,56]. IGFBP-3 also induces eNOS activation and subsequent NO generation. We, therefore, investigated whether IGFBP-3 treatment affected VASP redistribution in human microvascular endothelial cells. Treatment with IGFBP-3 caused a rapid

redistribution of VASP to the tip of lamellipodia promoting cell motility (Figure 2). IGFBP-3-mediated VASP redistribution was blocked by preincubation with by an NO scavenger [54].

EPC numbers were also lower in the retina in IGFBP-3 knockout mice [57]. In vivo studies showed that overexpression of IGFBP-3, using a proliferating endothelial cell specific promoter, protected against vaso-obliteration in an OIR model and also reduced preretinal neovascularization in a model of branch vein occlusion (BVO) [3,58]. The laboratory of Lois Smith found similar results where low IGFBP-3 was correlated with vaso-obliteration [57]. The study implicates a role of IGFBP-3 in recruiting vascular progenitor cells to sites of injury following hypoxia and administration of IGFBP-3 may be a treatment strategy for revascularization and repair.

IGFBP-3 has additional roles aside from recruiting hematopoietic stem cells (HSCs) and progenitor cells to sites of retinal injury. While IGFBP-3 can promote HSC differentiation to endothelial cells, it can also regulate differentiation into pericytes and astrocytes to stabilize the vasculature [58]. Additionally, upon induction of retinal injury using laser photocoagulation injury, injection of an endothelial specific IGFBP-3 expressing plasmid showed increased pericyte ensheathment based on an observed increased in $NG2^+$ immunoreactivity [58]. There was also a reduction in pericyte apoptosis based on less $NG2^+/TUNEL^+$ labeling compared to contralateral uninjected and control-vector injected eyes [58].

In hypoxic environments, inflammatory responses are recapitulated in the OIR model through the activation of resident microglia [58,59]. IGFBP-3 attenuates inflammatory responses by increasing microglia apoptosis and reducing the numbers of activated microglia [58]. The anti-inflammatory roles of IGFBP-3 have been observed in tissues other than the retina. IGFBP-3 has been shown to activate caspase activity in lungs of an asthma mouse model to degrade inhibitor of kappa B alpha and nuclear factor kappa B [60]. Similarly, administration of both IGF-I and IGFBP-3 in children with burn injuries reduced interleukin (IL)-6, IL-1β and tumor necrosis factor-alpha inflammatory markers [61,62].

Hypoxia and ischemic injury can be attenuated with vasodilatory responses. We showed that IGFBP-3 can affect vasodilation in rat posterior cerebral arteries. IGFBP-3 administration displayed a dose-dependent decrease in artery constriction placed under intraluminal pressure [54]. The vasodilatory effect was lost in the presence of inhibitors to eNOS [54,63]. IGFBP-3 stimulated NO release in intact arteries that is independent of calcium mediated NO release [54]. IGFBP-3 by promoting NO generation and vasodilation may be important for ROP and for counteracting the progression of non-proliferative diabetic retinopathy (NPDR) to proliferative diabetic retinopathy (PDR). Further studies to determine reperfusion capability by IGFBP-3 through NO production in the retina should be examined.

IGFBP-3 and blood retinal barrier integrity

Blood retinal barrier (BRB) breakdown is strongly associated with the development of ocular disease [64–66]. Emerging evidence indicates that IGFBP-3 may have roles that maintain and restore the integrity of the BRB following injury. We isolated a mutant IGFBP-3 that does not bind to IGF-I (IGFBP-3NB) and found it improved vascular barrier protection and maintained claudin-5 and vascular endothelial-cadherin expression upon exposure to vascular endothelial growth factor (VEGF) [63,65]. Under normal physiological conditions, IGFBP-3 can counteract the activation of VEGF by binding IGF-I, however these results show an IGF-I independent role of IGFBP-3 in protecting the BRB [63,65]. Additionally, IGFBP-3 may protect the BRB by modulating inflammation. IGFBP-3NB was shown to reduce proinflammatory sphingomyelinase levels in the retina [65].

Vascular protective signaling mechanism of IGFBP-3

The induction of recruitment of $CD34^+$ cells to sites of vascular injury involves a cascade of signaling mechanisms. IGFBP-3 binds to scavenger receptor class B, type1 (SR-B1), a receptor for high-density lipoprotein (HDL) [67,68]. NO is generated upon activation of SR-B1 by IGFBP-3 and subsequently by stimulation of eNOS activity [63,69]. A later study found IGFBP-3 activates PI3K/Akt pathway through SR-B1 [69]. IGFBP-3 also can stimulate sphingosine kinase (SphK)-1 activity which phosphorylates sphingosine to generate sphingosine-1-phosphate (S1P), a proangiogenic factor [63,69]. Mechanisms are summarized in Figure 3.

IGF axis in diabetes-induced retinopathy

Chronic hyperglycemia can influence cellular responses in the presence of IGF-I. Bovine retinal endothelial cells (RECs) exposed to low and high levels of glucose showed enhanced proliferation in the presence of IGF-I [66,70]. Integrins may have roles in PDR progression [71]. IGF-I can activate $\alpha V\beta 3$ integrin activation and maintain the signaling pathways that stimulate cell proliferation [66]. IGF-I protected human RECs (HRECs) from apoptosis when exposed to high glucose and serum starvation [72]. Exogenous IGFBP-3 induced a dose-dependent inhibition of HREC proliferation and at very high doses (1 mg/mL) increased apoptosis [72]. Alternatively, high glucose has also been shown to increase expression of IGFBP-3 in proximal tubular epithelial cells and induce apoptosis [73]. In prostate cancer, tumor cell proliferation was increased by over 3-fold in IGFBP-3 knockout lines [31].

VEGF-A is a major growth factor involved in ocular angiogenesis in retinopathy and its levels are correlated with neovascularization [74]. IGFBP-4 and IGFBP-5 have been found to counteract neovascularization in response to pro-angiogenic growth factors. Overexpression of IGFBP-5 inhibited VEGF-induced angiogenesis and inhibited both cell proliferation in human umbilical vein endothelial cells (HUVECs) and endothelial tube formation [75]. IGFBP-5 also suppressed phosphorylation of eNOS, thereby inhibiting endothelial vasodilation suggesting an antagonistic effect when compared with IGFBP-3 [75]. IGFBP-4 on the other hand inhibited fibroblast growth factor-2 and IGF-I induced angiogenesis in endothelial cells but had no effect in response to VEGF [76].

IGF-I has been shown to protect HRECs from apoptosis and enhance proliferation, therefore abnormally high levels observed in the vitreous humor may drive the progression of PDR [70]. Overexpression of IGF-I impaired functional recovery of acute ex vivo ischemic insult [77]. Our previous study disrupted IGF-IR and IGF-I binding using an IGF-IR ribozyme to investigate the interaction of IGF-I and retinopathy [43]. This ribozyme, driven by a proliferating endothelial cell specific promoter, reduced pre-retinal neovascularization in both OIR and BVO models [43]. Widespread IGF-IR disruption through loss of norepinephrine, however, reduced IGF-IR phosphorylation and signaling which led to increased apoptosis in the inner nuclear layers of the retina [78]. Similarly, long term diabetes have revealed increased IGFBP-3 expression in human tears which can reduce IGF-IR phosphorylation and may be implicated in the pathogenesis of ocular surface complications of the cornea [79].

Studies have established that PDR and accelerated neovascularization is preceded by elevated IGF levels, however serum levels correlating to the pathogenesis of PDR remain controversial [38,80–83]. Serum levels of IGF-I was found to be decreased in retinopathy, nephropathy, and neuropathy [84–91]. However, another study examining patients with either NPDR or PDR found no association of serum IGF-I in either insulin-dependent or insulin-independent diabetes [92]. The differences in these results may be due to sample size

or patient characteristics and the methodology used to detect IGF-I [92]. Furthermore serum levels may not be as relevant as localized increases in IGFs and IGFBPs due to increased BRB permeability may be more relevant in PDR [52].

IGFBPs and proliferative vitreoretinopathy

Vascular injury or inflammation can lead to retinal detachment from the basement membranes of the eye. Proliferative vitreoretinopathy (PVR) is a fibrous scarring complication that is the leading cause in failing to treat rhegmatogenous retinal detachment [93–95]. Retinal tearing leads to fibrocellular scar formation at the vitreoretinal surface which contracts, pulling the retina away from the retinal pigment epithelium (RPE) [96]. Numerous studies have attributed RPE-derived cells in the role of retinal detachment as they are exposed to cytokines localized to the vitreous [97–99]. Human RPE cells exhibited increased proliferation when exposed to basic fibroblast growth factor or epidermal growth factor, and the effect is enhanced under hypoxic conditions [100]. One study examined whether IGFBP-5 could inhibit *N*-(4-hydroxyphenyl)retinamide (4HPR) induced neuronal differentiation of human retinal pigment epithelial cells (ARPE-19). IGFBP-5 did not inhibit transdifferentiation of ARPE-19, however, exogenous addition of recombinant IGFBP-5 showed increased proliferation of RPE cells [21]. Thus, the expression of IGFBP-5 may stimulate proliferation and migration of RPE cells that can be fibrotic, leading to progression of PVR [101].

Mukherjee et al. recently reported IGFBP expression patterns present in several RPE progressive phenotypes: normal, early reactive, and myofibroblastic [102]. IGFBP-1 was not detected, IGFBP-2 and IGFBP-4 were expressed only in normal RPE, while IGFBP-3, IGFBP-5, and IGFBP-6 were found in all three phenotypes, with IGFBP-5 being predominant in the myofibroblastic phenotype [102]. IGFBP-2 has been shown to inhibit IGF-induced responses, therefore the loss of IGFBP-2 in the early reactive phenotype may lead to increased growth factor activity and IGF mediated tractional force generation [99,103]. IGFBP-5 has also been shown to induce migration of human lung fibroblasts and induction of skin fibrosis, where migration of lung fibroblasts was via IGF independent mechanisms [104,105]. Similarly, inflammation has been linked to the pathogenesis of PVR, and IGFBP-5 has been shown to induce migration of mononuclear cells [104,106]. The presence of IGFBP-5 in a fibrotic state in different cell types may suggest a function of IGFBP-5 in mediating ocular fibrosis.

Hypertensive retinopathy

Long-term hypertension can potentially have similar retinal vascular pathology as observed in diabetic retinopathy. Association studies have found that uncontrolled hypertensive patients with no diabetic complications to be at higher risk of developing retinopathy [107]. 50–70% of hypertensive patients were more likely to have retinal hemorrhages [107,108]. Plasma levels of IGF-I were found to be inversely associated with hypertension and both in vitro and in vivo experiments showed that IGF-I decreases vascular resistance [109–111]. Groups have proposed a correlation of blood pressure to retinal microvascular changes, however the correlation decreases with age [107,109,112,113].

The regulation of IGFBP-3 levels may be influenced by standard treatments for hypertension. Basic and clinical studies to date suggest IGFBP-3 to be vascular protective, however its effect on hypertensive retinopathy is unclear. The ilSIRENTE study showed that older adults on angiotensin converting enzyme (ACE) inhibitors were found to have significantly increased IGFBP-3 levels in serum, however there was no significant association of ACE inhibitors with free IGF-I levels [114,115]. It may be that ACE inhibitor

mechanism of action does not directly stimulate IGF-I activity to reduce vascular resistance, but rather works via increases in IGFBP-3 levels.

Retinal macroaneurysms can develop with complications of atherosclerosis and hypertension in up to 75% patients and manifests generally in elderly [116,117]. IGFBP-7 has recently been linked to familial retinal arterial macroaneurysm (FRAM) [118]. FRAM may be due to reduced mechanical integrity of the arterial wall and individuals with FRAM were found to have homozygous mutations in IGFBP-7 [118]. In situ hybridization of retinal whole-mounts indicated that IGFBP-7 expression was specific to the lens and retina in mouse embryos, however the expression of IGFBP-7 has not been carried out in human eyes [118]. Additionally, hypertension has not yet been associated with influencing expression of IGFBP-7, however IGFBP-7 has been linked to vascular function and endothelial-dependent vasodilation in high-ferritin insulin-dependent diabetes [119]. These findings reveal previously unknown roles of the low affinity binding proteins to IGFs and in disease. One can speculate that IGFBP-7 may have other potential functions in the pathogenesis of other retinopathies.

Conclusion

Efforts in studying IGFBPs in recent years have identified an increasing role of IGFs and IGFBPs in ocular complications. IGFBP-3 appears to have protective functions in the retina and BRB through stimulation and recruitment of $CD34^+$ cells, pericyte stability, and reducing inflammation. However, the tissue microenvironment influences whether IGFBPs have stimulatory or inhibitory properties. The roles of IGFBP-5 in the RPE in PVR and IGFBP-7 in FRAM have opened up the field to further investigation. Future work should ascertain other regulatory mechanisms of the IGF system in ocular physiology and pathology.

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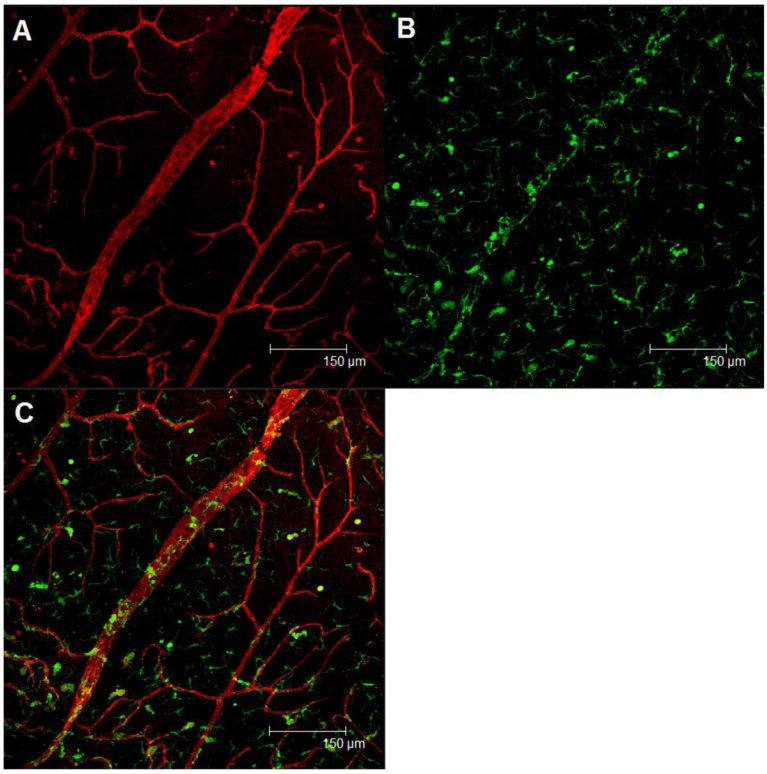

Figure 1. Retinal vasculature in a GFP$^+$ chimeric mouse (WT mouse undergoing bone marrow transplantation) that received within the vitreous liposomes containing a plasmid expressing IGFBP-3 under an endothelial specific promoter

The mouse then was subjected to the retinal branch vein occlusion model. Three weeks after liposome injection, the mouse was sacrificed and a retinal flat mount was prepared. (A) The retinal vessels were labeled with rhodamine agglutinin (red) and imaged using confocal fluorescence microscopy. (B) Enhanced incorporation of GFP$^+$ progenitor cells (green) into the retinal vessels is shown. (C) Merged channel. IGFBP-3's protective and reparative effects on the vasculature may be, in part, the result of its ability to recruit endothelial progenitor cells, to sites of retinal injury.

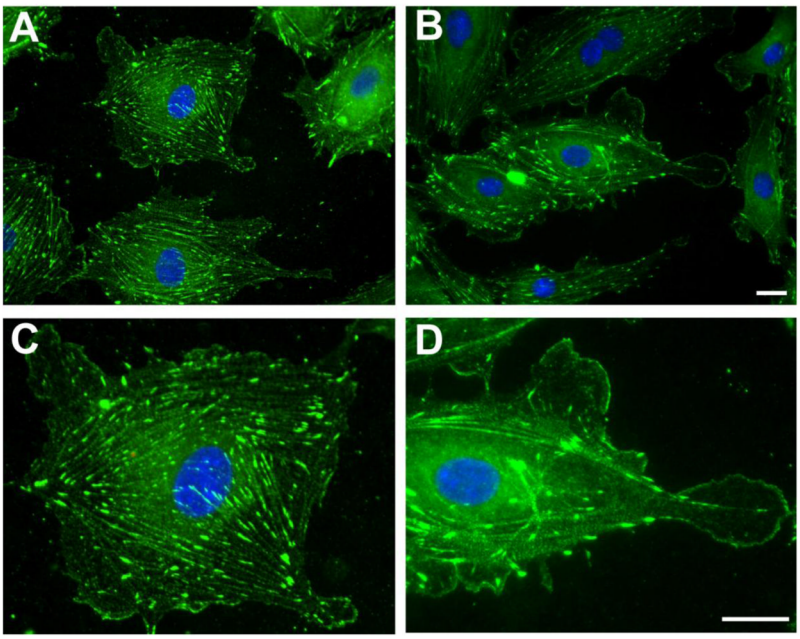

Figure 2. IGFBP-3-mediated VASP redistribution in human microvascular endothelial cells from the lungs (HMVEC-L)

HMVEC-L, cultured on fibronectin-coated coverslips, were left untreated (A) or were treated with 100ng/ml IGFBP-3 for 15 minutes (B) and Vasodilator-stimulated phosphoprotein (VASP) biodistribution was detected by immunofluorescence. IGFBP-3 treatment caused the rapid redistribution of VASP to the cells' periphery (A and B). C and D show, at higher magnification, a single cell in A and B, respectively. Note the uniform VASP distribution throughout the cytoplasm along the actin filaments in the untreated sample (C) and the presence of VASP-free areas together with increased VASP immunoreactivity along the plasmamembrane in the IGFBP-3- treated cell, (D). Representative results from three independent experiments are shown. Green: VASP; Blue: DAPI (for nuclear staining). (Scale bar = 25μm)

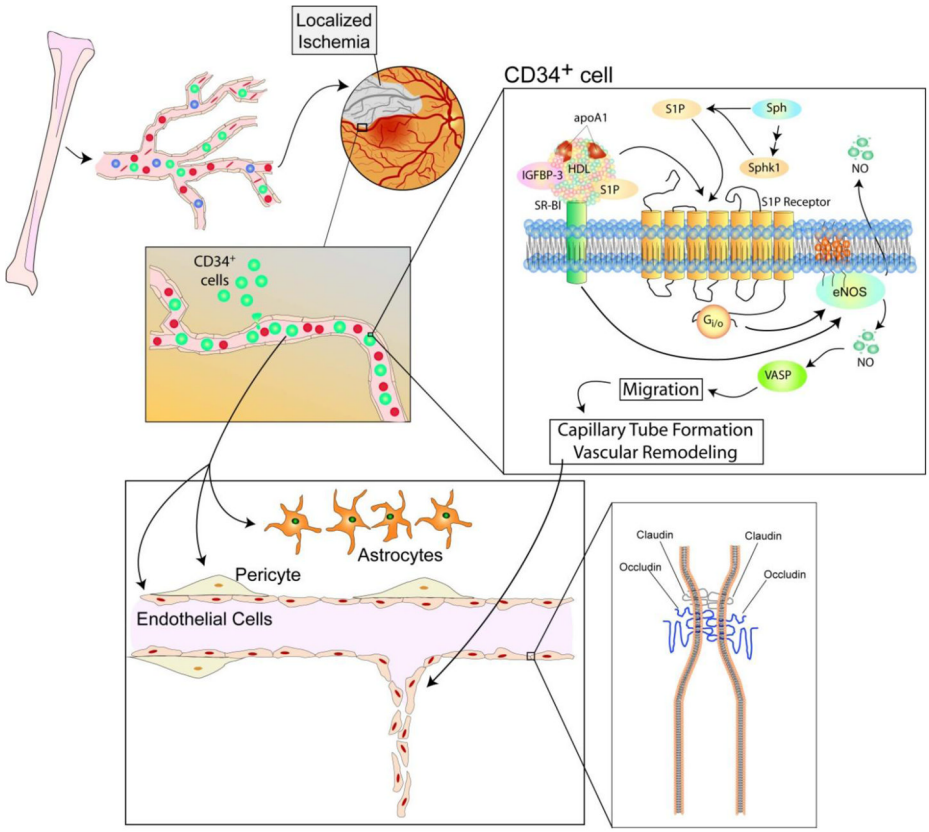

Figure 3. General mechanism of vascular repair by IGFBP-3

$CD34^+$ cells are recruited from the bone marrow by increased IGFBP-3 levels in the vasculature. IGFBP-3 binds to SR-B1, thereby leading to phosphorylation of eNOS and generating NO. IGFBP-3 can also mediate S1P generation by phosphorylating SphK-1, where S1P acts on its receptor to also stimulate phosphorylation of eNOS. NO stimulates a signaling cascade leading to VASP phosphorylation which is redistributed to polar ends of the cell and induces cell migration. Cells migrate to sites of injury to initiate capillary tube formation and vascular remodeling. IGFBP-3 can maintain tight and adherens junctions to maintain endothelium integrity as observed in the BRB.