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Review

Interleukin-17: The Role for Pathological Angiogenesis in Ocular Neovascular Diseases

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Ocular neovascular diseases are featured by abnormal angiogenesis in the eye, and they seriously threaten the human visual health. These diseases include proliferative diabetic retinopathy (PDR), age-related macular degeneration (AMD), retinopathy of prematurity (ROP), and retinal vein occlusion (RVO). In fact, ocular neovascular diseases represent the leading causes of vision impairment and blindness worldwide. Ocular neovascularization, the process of pathological vessel formation in eye, underlies ocular neovascular diseases. Cytokines have important regulatory roles in neovascularization through immunological networks. Interleukin (IL)-17, the signature cytokine produced by T helper 17 (Th17) cells, has proven to be involved in ocular neovascularization. However, roles of IL-17 in ocular neovascular diseases still remain controversial. This review provides an overview of the functional roles of IL-17 in ocular neovascular diseases from basic research to clinical evidence by focusing on PDR, AMD, ROP, and RVO. The possible roles of IL-17 in neovascularization are achieved through a regulatory network of cytoskeleton remodeling, vascular endothelial growth factor (VEGF), VEGF-related cytokines, and complement components. Current applications as well as potential therapies targeting IL-17 with genome editing systems are also outlined and discussed. Targeting IL-17 might be a promising therapeutic strategy against ocular neovascular diseases.

Keywords: cytokine; interleukin-17; ocular neovascular disease; T helper 17 cell; vascular endothelial growth factor
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Introduction

Ocular neovascular diseases, such as proliferative diabetic retinopathy (PDR), age-related macular degeneration (AMD), retinopathy of prematurity (ROP) and retinal vein occlusion (RVO), seriously threaten the human visual health worldwide (Yoshida et al. 1999; Gariano and Gardner 2005; Campochiaro 2013). Ocular neovascularization is the newly formation of vessels from existing capillaries in eyes, which results in ocular neovascular diseases. Neovascularization normally occurs during the process of development and repair. However, numerous pathological conditions, such as inflammation, tumorigenesis, aberrant development and hypoxia, may lead to growth of abnormal new blood vessels. Vascular endothelial growth factor (VEGF) has been proved to be a leading factor that leads to intraocular neovascularization, and anti-VEGF agents are widely used in clinical therapeutic applications (Rizzo et al. 2008; Hosseini et al. 2009; Osaadon et al. 2014; Xu et al. 2014; Amadio et al. 2016). However, the short efficacy exists in conducting intraocular injection of anti-VEGF agents (Salam et al. 2011; Osaadon et al. 2014) in addition to the high expense of the therapy, the poor response to the treatment in some of the patients, and a gradual decrease in drug sensitivity with long-term drug use. Moreover, the anti-VEGF therapy is not only target pathological neovascularization in the eye, but also in normal blood vessels and tissues, which may cause severe systemic cardiovascular and cerebrovascular complications, such as hypertension and cerebral vascular myocardial infarction (Wu et al. 2008; Jardeleza and Miller 2009).

In recent years, immunotherapy based on cytokines such as interleukin (IL)s has become a research hotspot in a series of refractory diseases (Klatzmann and Abbas 2015; Drutskaya et al. 2016). Leukocytes such as macrophages, dendritic cells, and lymphocytes, produce a group of cytokines and factors in participating pathogenesis of intraocular neovascular diseases (Ishida et al. 2003; Zhou et al.

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2015, 2017).

T helper (Th) cells are considered to play an important role in adaptive immune response, by helping the activation of other immune cells to release T cell cytokines (Nakayama et al. 2017). Th cells are traditionally classified into two subtypes: Th1 and Th2. Cytokines induce macrophage polarizations to pro-inflammatory M1 or anti-inflammatory M2, which show different functions in a group of pathogenesis (Mantovani et al. 2004; Martinez et al. 2008; Murdoch et al. 2008; Jetten et al. 2014; Sica et al. 2015; Zandi et al. 2015), from Th1 and Th2 activation (Mantovani et al. 2013). Traditionally, M1 phenotype is thought to be anti-angiogenesis, while M2 cells play opposite roles in pro-angiogenesis, which has also been demonstrated in ocular diseases (Zandi et al. 2015; Zhou et al. 2015, 2017).

As a novel recognized phenotype of Th cells, Th17 cells are involved in a pathway that is different from Th1 and Th2 cells (Duechting et al. 2017; Song and Yang 2017). Th17 cells play important roles in the mucosal barriers, but they are also related to the pathogenesis of autoimmune and inflammatory diseases.

IL-17 (also known as IL-17A), a signature cytokine belongs to IL-17 family, is originally regarded to be produced by Th17 cells, a T helper subset developed from activated CD4+ cells (Korn et al. 2009). Although as a signature cytokine of Th17 cells, IL-17 is also expressed by other adaptive and immune cell types, including CD8+ T cells, $\gamma\delta$ T cells, natural killer (NK) cells, invariant natural killer T (iNKT) cells, lymphoid-tissue inducer (LTi)-like cells, and Group 3 innate lymphoid cells (ILC3) (Zenobia and Hajishengallis 2015; Song and Yang 2017). Actions of other cytokines such as IL-1β and IL-23 can trigger $\gamma\delta$ T cells at mucosal sites into IL-17-producing cells (Sutton et al. 2012). RORγt-producing neutrophils were recently identified as IL-17-producing and responding cells (Tan et al. 2013). Furthermore, naïve T cells, memory T cells, and CD4+ Foxp3+ regulatory T cells (Tregs) have all been identified to have the ability to differentiate into an IL-17-producing phenotype (Zenobia and Hajishengallis 2015).

The target cells of IL-17 include primarily epithelial, endothelial, and stromal cells (such as fibroblasts and osteoblasts) (Chabaud et al. 2001; Shen et al. 2005; Honorati et al. 2006; Lubberts 2008). Other IL-17-targeting cell types consist of synoviocyte and chondrocytes in arthritis, keratinocytes in psoriasis, neutrophils in fungus/virus infections, macrophages, dendrite cells, T cells, B cells and lung/gut epithelial cells (Onishi and Gaffen 2010). Due to its ubiquitously expressing receptor, IL-17 could exert either adverse or beneficial effects in different pathological and physiological scenarios.

IL-17 plays diverse roles in a variety of pathological processes (Fig. 1). The major function of IL-17 in humans is pro-inflammatory and anti-microbial pathogens (Matsuzaki and Umemura 2018), including extracellular bacterial and fungal infections. In host-pathogen defense, the release of IL-17 stimulates a massive inflammatory response, contributing to neutrophil activation and accumulation (Ouyang et al. 2008; Yang et al. 2014). The IL-17-associated inflammatory response depends on a cooperation or synergism with other immune mediators, as well as the regulation of its target genes, and the following activation of inflammatory cascade/networks (Ouyang et al. 2008).

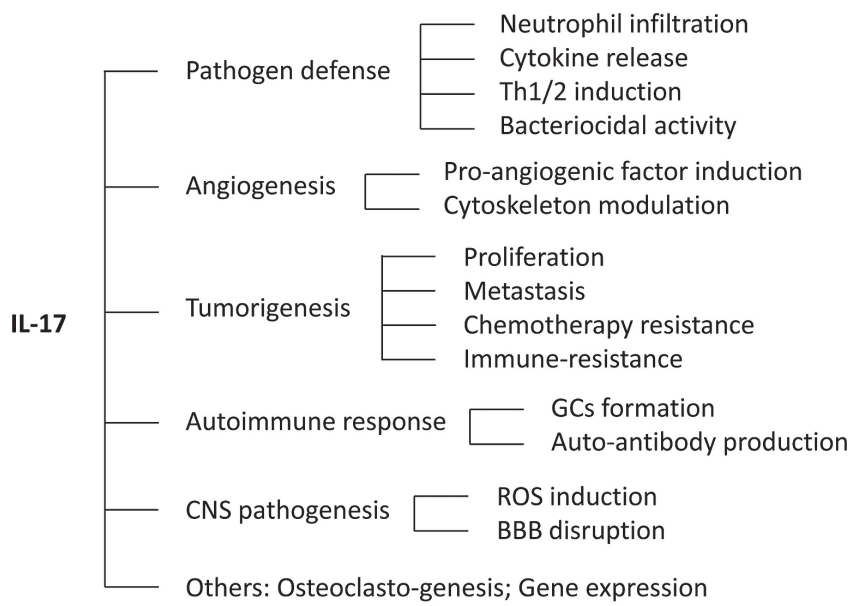

Fig. 1. The biological functions and roles of IL-17.
IL-17 targets IL-17R-expressing cells including epithelial cells and fibroblasts, and plays different roles in the inflammation, autoimmune process, tumorigenesis, angiogenesis, *etc*. The IL-17 pro-/anti-angiogenic roles in the tumor microenvironment are controversial and possibly context-dependent.
BBB, blood-brain barrier; CNS, central nervous system; GCs, germinal centers; ROS, reactive oxygen species; Th, T helper cell.

IL-17 could induce blood-brain barrier disruption, thereby participating in the development of inflammation of the central nervous system (Kebir et al. 2007; Huppert et al. 2010).

Furthermore, it has been shown that IL-17 is involved in the pathogenesis of a wide range of diseases from autoimmune diseases to allograft transplantation (Song and Yang 2017). Researchers also suggest that the variation of IL-17 level is linked with various diseases, including multiple sclerosis (Li et al. 2017), depression (Beurel et al. 2013; Beurel and Lowell 2018), pulmonary fibrosis (Cipolla et al. 2017), bronchial asthma (Herjan et al. 2018), ischemic brain injury (Shichita et al. 2009), psoriasis (Croxford et al. 2014; Hohenberger et al. 2018), rheumatoid arthritis (Li et al. 2012), inflammatory bowel diseases (Zhang et al. 2006; Hohenberger et al. 2018), ischemic heart failure (Chang et al. 2018), ocular surface and corneal diseases (Garbutcheon-Singh et al. 2018), and innate and acquired immunity (Matsuzaki and Umemura 2007). In particular, IL-17 has been proved to enhance angiogenesis in tumor and rheumatoid arthritis (Numasaki et al. 2003; Pickens et al. 2010).

Recent studies suggest that IL-17 plays important roles in tumor proliferation, angiogenesis or angiostasis, tumor immune resistance, and metastasis (Yang et al. 2014). Evidence included that the IL-17 level was elevated in several human cancers, including cervical, hepatocellular, ovarian, esophageal, breast, gastric, and colorectal cancer (Song and Yang 2017). Regulation of signaling pathways associated with tumorigenesis, such as the Src/PI3K/Akt/NFκB, MAPK, STAT3, and COX-2 pathways, is one of the mechanisms by which IL-17 plays role in tumor biology (Song and Yang 2017). Transforming growth factor-β (TGF-β) is a key factor that stimulates the generation of Th17 cells from naïve T-cells, together with several inflammatory cytokines (IL-21, IL-6 and IL-23), and leads to the induction and activation of transcription factor (retinoic acid-related orphan nuclear receptor gamma, RORγ) (Manel et al. 2008; Yang et al. 2008). Besides, IL-17 associates with several key regulators, including TNFR-associated factors (TRAFs) and myeloid-derived suppressor cells (MDSCs) (Nagashima et al. 2016; Guan et al. 2018).

Although accumulating evidence suggested that IL-17 mediates neovascular progression in ocular diseases, the relevant results still remain conflict and specific mechanism controversial. The present review will illustrate research advances of IL-17, in particular to its possible roles in ocular neovascular diseases (Fig. 2).

Expression of IL-17 from Clinical Evidence

In addition to the important roles in autoimmune and inflammation diseases, IL-17 and Th17-related cytokines have been implicated in the pathological process of various ocular diseases. The relationship between altered levels of IL-17/Th17-related cytokines and ocular diseases remains to be clarified. Elucidation of the disturbances of IL-17/Th17 in the pathogenesis of different ocular neovascular diseases is of significance in tailor treatment. Relevant clinical studies have shown a series of evidence, and more are now in progress.

Diabetic retinopathy

Diabetic retinopathy (DR) is a complication of diabetes and leads to visual impairment over the world (Fong et al. 2004). The pathogenesis of DR includes oxidative stress, advanced glycation end products, and inflammation (Tang and Kern 2011). Dysregulation of inflammatory cytokines including IL-17 has been involved in DR progression (Karbasforooshan and Karimi 2018). Suzuki et al. (2011) reported the significant increase in vitreous fluid concentrations of IL-6, IL-8, IL-10, IL-13, interferon-inducible 10-kDa protein (IP-10), monocyte chemoattrac-

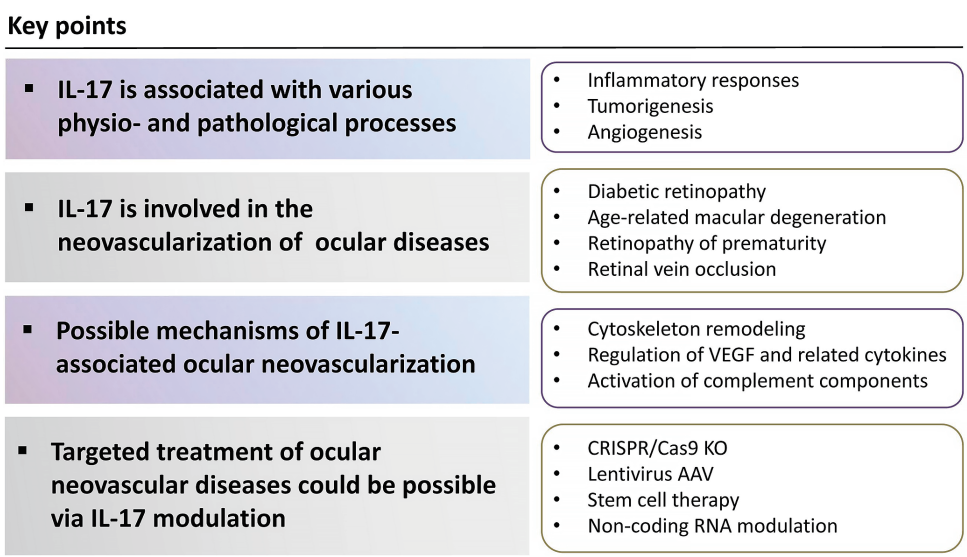

Fig. 2. Summary of the review: IL-17 in ocular neovascular diseases.

tant protein-1 (MCP-1), macrophage inflammatory protein-1 beta (MIP-1β), platelet-derived growth factor (PDGF), and VEGF in DR samples, compared with those of control eyes with epiretinal membrane or macular hole, except for IL-17. However, the level of IL-17 in the vitreous fluid was later determined to be up-regulated in Type 2 Diabetes Mellitus (T2DM) with DR as compared with that of the control (Chen et al. 2016). Besides, Takeuchi et al. (2015) reported that vitreous levels of IL-17A, IL-4, IL-22, IL-31, and TNF-α are higher in PDR as compared with those of other non-inflammatory vitreoretinal diseases or uveitis. Using the beads-array system, the study group measured that Th17 cell-related inflammatory cytokines in aqueous humor and vitreous fluid from PDR eyes. It was found that the level of IL-17A (IL-17) level in the vitreous fluid was correlated significantly with the vitreous levels of cytokines including IL-4, IL-22, IL-31, and TNF-α. A subsequent study from the same research group further showed that the level of vitreous IL-17A was related significantly to IL-10, IL-22, and TNF-α levels in both vitreous and aqueous humor (Takeuchi et al. 2017). One explanation is that the immune response of PDR involves both posterior and the anterior segments (Takeuchi et al. 2017). Further investigation is needed to illustrate the IL-17 receptor distribution, the regulation of IL-17-related signaling pathway, and the relevant cytokines or mediators in the different segments of eyes in PDR.

IL-17 level in plasma showed a similar pattern as that in the vitreous fluid, supported by several clinical studies of PDR patients. Hang et al. (2014) examined the plasma levels of inflammatory cytokines in diabetic patients (with or without DR) and revealed that IL-17 was significantly increased in diabetic group and was related to PDR. It was further confirmed that IL-17 concentrations in the serum of DR (both PDR and non-PDR) patients were significantly higher than those in the control, and IL-17 significantly enhanced the risk of non-PDR (Liu et al. 2016; Wang et al. 2016). On the other hand, the expression of IL-17 in peripheral blood mononuclear cells (PBMCs) from DR patients is controversial. Chen et al. (2016) revealed that Th17 cell proportion and IL-17A concentrations in PBMCs were decreased in DR patients and increased in patients without DR. Additionally, IL-17A concentrations and the frequency of Th17 in PBMCs were decreased with the DR severity (Chen et al. 2016). However, other study showed that protein expression levels of IL-17 were increased in PBMCs from PDR patients (Liu et al. 2016).

IL-17 belongs to the downstream pathway of silent information regulator 1 (SIRT1), nicotinamide adenosine dinucleotide (NAD+)-dependent deacetylases, which removes acetyl groups from proteins (Karbasforooshan and Karimi 2018). SIRT1 activation could inhibit the IL-17 production, and the dysregulation of SIRT1/IL-17 might contribute to the DR pathogenesis (Liu et al. 2016). In the PBMCs of PDR patients, the SIRT1 mRNA and protein expression levels were decreased, which might lead to the upregulation of IL-17 and development of inflammation during retinal damage (Liu et al. 2016). Although the mechanisms involved in the IL-17 regulation in DR are not well characterized, it is shown that micro-RNAs are involved in the modulation of IL-17-related ocular inflammation (Wang et al. 2017). They showed that micro-RNA miR-19a, a member of miR-17-92 clusters, mediates the effect of IL-17 on a suppression of IL-10 in peripheral B cells of DR patients (Wang et al. 2017). The authors stated that IL-17 downregulated the IL-10 in B cells via the upregulation of miR-19a, which could be blocked by miR-19a knockdown (Wang et al. 2017). These findings imply that there might be some interactions of immune and inflammatory factors involving IL-17 in the pathogenesis of DR.

Age-related macular degeneration

AMD is a progressive eye disease, the pathogenesis of which involves the degeneration of the retinal pigment epithelium (RPE) cells, the death of photoreceptors, and loss of central vision (Kauppinen et al. 2016). The formation of drusen, pigmentary changes at the macula and mild to moderate vision loss are the hallmark of early AMD (Hernandez-Zimbron et al. 2018). The wet (neovascular) form is less frequent but is responsible for 90% of acute blindness due to AMD, which is characterized by choroidal neovascularization (CNV) with intraretinal or subretinal leakage, hemorrhage, and RPE detachments (Velez-Montoya et al. 2013). Recent studies provided supporting evidence that inflammatory components and pathways might play crucial roles in the etiology of AMD (Ding et al. 2009; Chan and Ardeljan 2014; Chen et al. 2017).

Th17 cell differentiation and IL-17 have recently emerged to be potentially important in adaptive immunity of AMD (Wei et al. 2012). Zhang et al. (2015) reported the correlation of IL-17A polymorphisms with higher risk of AMD, possibly induced by affecting gene expression. Nassar et al. (2015) studied inflammatory cytokines in serum samples from AMD patients and controls by using multiplex ELISA kits. The subjects were divided into 3 subgroups with improvement, no change or deterioration during anti-VEGF therapy which measured by OCT and funduscopy, and the correlations between cytokines and treatments have been established. Although several cytokines in patients' sera (IL-1α, IL-1β, IL-4, IL-5, IL-10, IL-13, and IL-17) were significantly higher than in controls, the only statistically significant difference between the improved, unchanged and deteriorated groups was observed in the levels of IL-1α and IL-17, which suggested that IL-17 could be a significant predictor for unchanged cases under treatment (Nassar et al. 2015). Another recent study illustrated higher frequencies of IFN-γ and Th17 cells from PBMCs in patients with AMD compared to healthy controls. Besides, significantly higher levels of IFN-γ and IL-17 expression by CD4+ T cells were detected in the patients of AMD. A possible mechanism is that the Th17 cells promoted monocytes toward M1 macrophage polar-

ization, which was associated with retinal damage (Chen et al. 2017).

However, with flow cytometry, Singh et al. (2017) investigated the systemic frequency of Th1 and Th17 cells in peripheral blood from AMD age-matched groups, and it was shown that lower frequency of Th1 cells and CXCR3+ CD4+ T-cells, but not the Th17 cells, was found in patients with wet AMD. There was no significant difference in the frequency of Th17 cells among dry AMD, wet AMD, and the controls.

The underlying mechanism still remained unclear about the IL-17/Th17 variation in AMD patients. It is shown that the anaphylatoxins C3a and C5a, derivations from complement component C5, regulate the IL-1β and IL-6 production, which contributes to the Th17 differentiation and IL-17 production (Liu et al. 2011). Epigenetic regulation such as promoter methylation also affects the expression of IL-17 receptors in AMD patients. Wei et al. (2012) identified that significant hypomethylation of the IL-17 receptor C (IL-17RC) promoter and higher expression of IL-17RC in the macular tissues from the AMD patients as compared with that of the non-AMD controls. Since IL-17RC is the essential component of IL-17 receptor complex triggering the downstream inflammatory reaction of IL-17A and IL-17F, this evidence suggests that the methylation pattern and expression of IL-17RC might serve as a potential biomarker for AMD-related intraocular inflammation (Wei et al. 2012). The relation between CNV and epigenetic modulation of IL-17RC in AMD still remain unexplored; thus, future studies could be conducted to investigate the possible correlations.

Retinopathy of prematurity

ROP affects the immature retinal vascular system in premature infants with an incompletely vascularized retina (Lin et al. 2009). Although the role of inflammation in ROP remains poorly understood, accumulating evidence suggests that prenatal, perinatal, as well as postnatal inflammation, might gradually increase the risk for ROP (Rivera et al. 2017). Several cytokines and chemokines, such as IL-6, IL-7, IL-8, TNF-α, MCP-1, and macrophage inflammatory protein 1 alpha/beta (MIP-1α/β), have been shown to participate in the pathological process of ROP (Silveira et al. 2011; Yu et al. 2014; Veldhoen 2017; Lawrence et al. 2018). An early study into infant eyes of ROP by Sato et al. (2009) reported that vitreous cytokines including IL-17 varied between vascular active ROP, inactive ROP, and congenital cataract eyes. It was later found that shortly after birth (Day 0 to Day 3 of the postnatal period) IL-17A levels reduced significantly in preterm infants, which might lead to an arrest of retinal angiogenesis in ROP (Sood et al. 2010). With a ROP mouse model, Zhu et al. (2016) observed an increase of IL-17A expression at postnatal day 15 and day 18 during retinal NV, while an IL-17A neutralizing antibody treatment could reduce choroidal and retinal NV. Although these observations suggest that targeting IL-17A may serve as a novel route for ROP diagnosis and therapy, via blocking the cytokine-related inflammatory responses, further studies are required to clarify the role of IL-17 in ROP pathogenesis.

Retinal vein occlusion

RVO is another neovascular disease with vision loss, in which including branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) (Iijima 2018). Kaneda et al. (2011) reported that the IL-17 and IL-23 levels were both significantly higher in the aqueous humor from patients with BRVO as compared to that in the control. Sohn et al. (2014) also demonstrated that the aqueous level of IL-17 was significantly higher in BRVO patients than that in the control, which could be reduced significantly by triamcinolone intravitreal injection. On the other hand, the intravitreal IL-17 has also been recognized to express higher in vitreous fluid of CRVO as compared to that in the control (without statistical significance), which suggest that IL-17-related inflammatory reaction may be activated in CRVO (Suzuki et al. 2011).

Possible Mechanisms

Although clinical trials indicate that pathological dysregulation of IL-17 plays a controversial role in ocular neovascularization, the underlying mechanism is presently unknown. In order to investigate the regulation of IL-17 in ocular diseases, a large number of *in vitro* and *in vivo* studies with cell lines and animal models have been performed.

Cytoskeleton remodeling

An *in vitro* study showed that IL-17 receptor A (IL-17RA) and IL-17RC were detected from human choroidal endothelial cells, and IL-17 exerted a pro-angiogenesis effect by promoting cell migration and tube formation via PI3K-Rac1/RhoA-mediated actin cytoskeleton remodeling (Chen et al. 2014). Using human choroidal endothelial cells (HCECs), Chen et al. (2014) found that IL-17 promoted cell migration and tube formation without affecting cell proliferation, possibly through the activation of Rac1 and RhoA. Wortmannin, a PI3K inhibitor, could suppress IL-17-induced Rac1/RhoA activation. The proliferation assay showed that IL-17 revealed no direct promotion of HCECs proliferation, suggesting that IL-17 might be an indirect angiogenic factor which can stimulate angiogenesis *in vivo* (Chen et al. 2014). Thus it was concluded that the pro-angiogenesis effect on HCECs by IL-17 involved the enhancement of cell migration and tube formation, which depended on PI3K-Rac1 and RhoA-mediated cytoskeleton reconstruction (Fig. 3). In addition, a recent *in vitro* study indicated that the expressions of CCL2 and CXCL8 could be mediated by IL-17 in RPE cells, which leads to enhanced migration and tube formation in HCECs (Chen et al. 2018). Similarly, human retinal vascular endothelial cell (HREC) capillary tube formation can be increased by IL-17, through enhancing migration, proliferation, and expression of

VEGF, ICAM-1, IL-6 and IL-8 (Liu et al. 2017a). Besides, Qiu et al. (2017) showed that in DR mice model, intravitreal injection of anti-IL-17A mAb or anti-IL-17RA mAb decreased Müller cell dysfunction, vascular leukostasis, vascular leakage, and tight junction protein downregulation in the retina, in accordance with the Chen study (Chen et al. 2014). Moreover, Sakurai et al. (2016) showed that IL-17A could increase MMP-3 gene expression via inducing the ERK/p38 MAPK/JNK pathway and targeting AP-1 transcription factor. During endometrial degeneration and remodeling, MMPs are closely relevant to degradation, differentiation, proliferation, and migration of endothelial cells, which contributes to the vessel formation favoring tumorigenesis (Mahecha and Wang 2017). Therefore, further studies are required to fully map the linkage of IL-17 and angiogenesis via the regulation of cytoskeleton remodeling.

VEGF and VEGF-related cytokines

In a corneal NV model, recombinant IL-17A administration promoted alkali-induced corneal neovascularization through increased infiltration of intracorneal progenitor/inflammatory cells, as well as increased expressions of VEGF and IL-6 by fibroblasts and macrophages (Liu et al. 2017b). Corneal neovascularization can be caused by ocular herpes simplex virus (HSV) infection involving IL-17 and VEGF production (Mulik et al. 2012). Evidence has shown that ocular infection by HSV upregulated VEGF-A and IL-17 with increased miR-132 expression, while in IL-17 receptor KO mice with HSK infection the corneal miR-132 was significantly lower (Mulik et al. 2012). This result suggests that miRNA also plays important role in the IL-17-related neovascularization. Another study into "VEGF trap", a strategy of blocking VEGF-A with soluble VEGF receptor 1, revealed that IL-17R KO strategy or IL-17A neutralizing mAb treatment could diminish corneal neovascularization (Suryawanshi et al. 2012). The evidence indicated that the inhibition of IL-17A expression or the application of VEGF trap could serve as new approaches for corneal neovascularization management.

Talia et al. (2016) demonstrated that IL-17A inhibition attenuated pathological neovascular retinopathy in OIR mice model, and RORγ/IL-17A axis decreased VEGF production by reduction of microglia and Müller glia gliosis, but with prevention of ganglion cell loss. Another study showed that IL-17A neutralization significantly reduced laser-induced CNV and oxygen-induced retinal neovascularization, and IL-17A neutralization also decreased subretinal neovascularization in VEGF over-expressed mice (Zhu et al. 2016). However, the study showed that IL-17A promoted M1 polarization of macrophages in OIR mice, and IL-17A-stimulated macrophage supernatant enhanced HUVEC proliferation and tube formation *in vitro*. The author thought the pro-angiogenesis effect of IL-17A might be through promoting M1 macrophage polarization, which is different from the concept that M2 macrophages, rather than M1, enhanced neovascularization. Interestingly, however, Hasegawa et al. (2013) reported that the pro-angiogenic effect of IL-17 in CNV model was independent of VEGF, and the main sources of IL-17 in laser-burned eyes were infiltrated $\gamma\delta$T cells and Thy-1(+) innate lymphoid cells, rather than Th17 cells. It is possible that the production and expression of IL-17 may depend on specific cellular scenarios.

IL-23 is another important cytokine that contributes to Th17 response. Cai et al. (2016) reported IL-23 blockade depressed both retinal and choroidal neovascularization in mice, and IL-23 enhanced the ability of tube formation of endothelial cells in HRECs. However, in a mouse model of CNV, IL-23 was dispensable for the production of IL-17. Instead, IL-1β and high-mobility group box 1 (HMGB1) played pivotal roles in IL-17 induction by $\gamma\delta$T cells in laser-induced CNV eyes (Hasegawa et al. 2013). Besides, Xu et al. (2015) found that the ratio of IL-17A+ CD4+ T cells in PBMCs, the IL-17A protein levels in the peripheral blood and retina, were significantly increased in a streptozotocin-induced DR rat model as compared to the control. However, intravitreal injection of anti-IL-23Rp19 antibody tightened RPE cells significantly, and also reduced the number of microangium and endothelial cells. The expression levels of IL-17A mRNA and protein were decreased significantly in the retina upon anti-IL-23Rp19 antibody injection treatment compared with the placebo-treated group, accompanied by tighter RPE cells and reduced endothelial cells (Xu et al. 2015). The author suggested that an intravitreal application of anti-IL-23Rp19 antibody targeting the IL-23-Th17-IL-17A pathway might serve as potential therapy for DR by improving the structure of the blood-retinal barrier.

The methylation and demethylation of gene promoter regulate expression and production of protein. A recent epigenetic study into the IL-17RC promoter structure revealed that the level of promoter methylation was decreased in RPE cell line under hypoxia condition (Alivand et al. 2016). VEGF and IL-17RC overexpression were both detected in RPE hypoxia group with neovascularization as compared to that under normoxia condition. Thus, IL-17RC might be considered as a significant indicator in the CNV and RPE degeneration in *in vitro* conditions (Alivand et al. 2016).

Activation of complement components

About the origin of IL-17 in ocular NV, evidence has shown that CNV lesions induce local ocular inflammation via C5a-dependent IL-17 recruitment to the AMD eyes (Coughlin et al. 2016). AMD pathogenesis is closely associated with an overactive complement system, and complement component C3a has also been shown to be involved in the IL-17 production in AMD patients (Liu et al. 2011). By laser photocoagulation-induced CNV model, Coughlin et al. (2016) observed that the levels of IL-17 producing $\gamma\delta$T-cells were elevated in the eyes, which could be inhibited by anti-C5-blocking or anti-C5a-blocking antibodies adminis-

tration. Furthermore, the CNV size and ocular γδT-cell infiltration were found to reduce under the antibody's treatment. Using ARPE-19 human RPE cells, Coughlin et al. (2016) also showed that IL-17 led to a pro-inflammatory state, resulting in a 40-fold increase in C3 gene expression without affecting the VEGF mRNA expression. These observations agree with the previous study (Hasegawa et al. 2013), suggesting a VEGF-independent, complement component-related mechanism of the IL-17 pro-angiogenic effect in ocular neovascularization (Fig. 3). Accordingly, the Th17 response might be important, but not be the only pathway of IL-17 functions. Moreover, although VEGF could be a mediator of the pro-angiogenic effect of IL-17, the effect could also be partially independent of VEGF.

Potential Applications and Therapies of IL-17 for Ocular Neovascular Diseases

IL-17 exerts great functions through variable pathways in ocular neovascular diseases, and blockade of IL-17 may be a potential therapeutic avenue in inhibiting retinal and choroidal neovascularization (Hasegawa et al. 2013; Talia et al. 2016) (Fig. 4). As discussed above, the effects of IL-17 on neovascularization are complicated with immune activation through different types of cells, cytokines and factors, and the VEGF pathway may not be the only route of the pro-angiogenesis. Thus, further studies are needed to investigate the synergistic reaction by using anti-IL-17 and anti-VEGF agents.

Several monoclonal antibodies have been used for clinical trials in targeting IL-17 (Spuls and Hooft 2012; Baeten et al. 2013; Papp et al. 2013), but further validation is needed for intraocular effectiveness and toxicity. The strategy to delivery anti-IL-17 agents used in the previous studies was intravitreal injection or systemic administration. Compared with intravitreal injection, subretinal injection, as a novel route of therapeutic delivery, has its advantages in specific targeting, better safety and efficiency (Peng et al. 2017b), which could also be considered as a potential delivery option for personalized medical care of ocular neovascular diseases such as AMD.

Recently, an increasing number of studies used adeno-associated virus (AAV), the lentivirus, by local delivery of drugs for gene therapy, which could be considered to target IL-17 in future studies. The CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR associated protein9) system has been applied to deplete IL-17

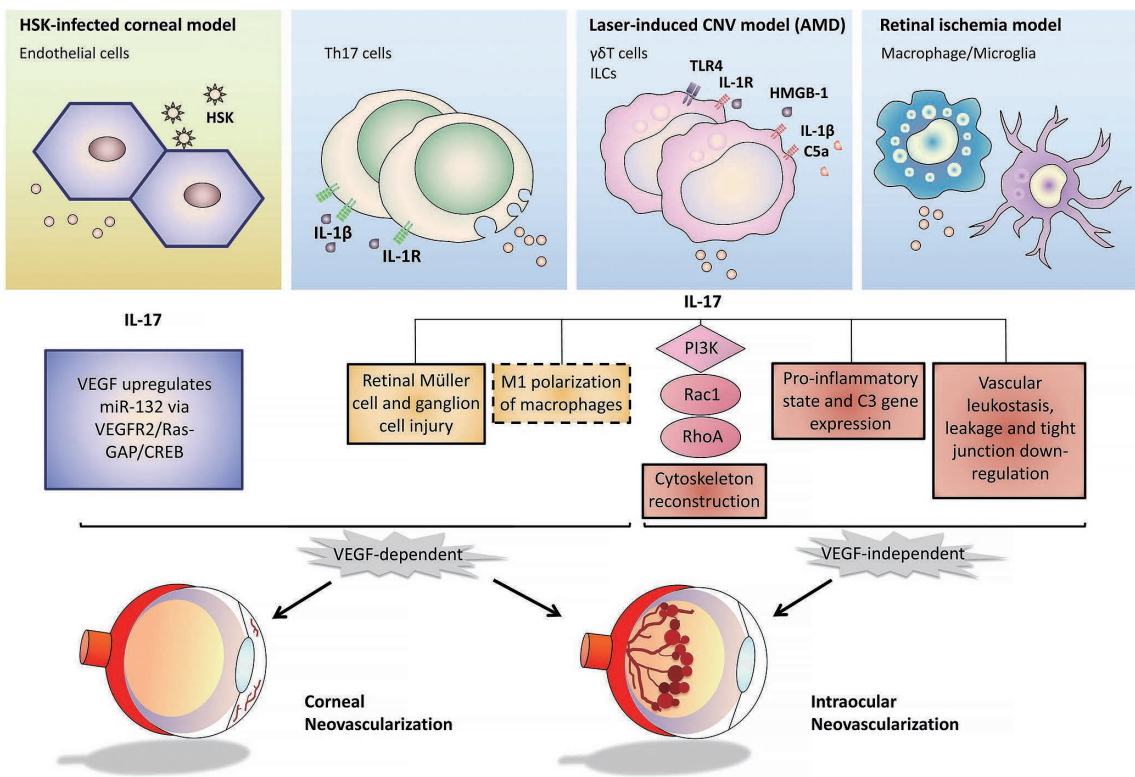

Fig. 3. Possible mechanisms of the IL-17 to ocular neovascular diseases.
Schematic diagram to illustrate the probable pathogenesis of IL-17/Th17 in ocular neovascular events. While IL-17 may promote angiogenesis via VEGF-independent mechanisms involving cytoskeleton reconstruction, the IL-17-induced macrophage polarization and Müller cell injury were considered to be in a VEGF-dependent manner. Dashed lines indicate that there are controversies remained about the study hypothesis, which has been discussed in the text body.
C5a, complement C5a; HMGB-1, high mobility group box 1; HSK, herpes simplex virus; ILCs, innate lymphoid cells; IL-1R, interleukin-1 receptor; PI3K, phosphatidylinositol 3-kinase; RhoA, Ras homolog gene family member A; TLR4, toll like receptor 4.

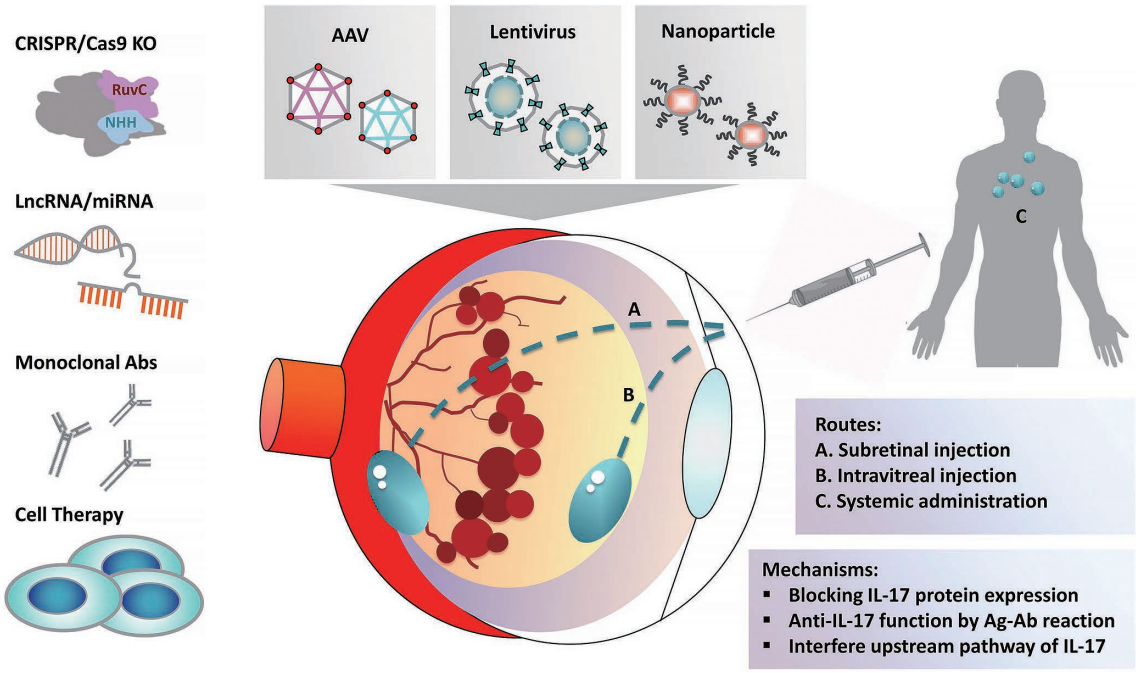

Fig. 4. Potential applications and therapies of IL-17 in ocular neovascular diseases.
Various vectors (plasmid, AAV, lentivirus, and nanoparticles, etc.) could be possibly applied to deliver biotech tools to modulate the level of IL-17 via different routes. CRISPR/Cas9, lncRNA, miRNA could decrease the level of IL-17 by blocking its protein expression, while the monoclonal antibody targets IL-17 by Ag-Ab interactions. Cell therapy with iPSCs is another potential strategy to target the IL-17 response.
AAV, adeno-associated virus; Ag-Ab, antigen-antibody; iPSCs, induced pluripotent stem cells; lncRNA, long noncoding RNA; miRNA, microRNA.

level, downregulate inflammation and protect against sepsis (He et al. 2016). As a novel gene editing technique which has been applied in the eye (Huang et al. 2017), the CRISPR/Cas9 system could also be used to deplete IL-17 in the ocular disease model in both biological study and future clinical applications (Peng et al. 2017a). Besides, as IL-17 is an important cytokine connected with many kinds of cells (such as macrophages, Th cells, and $\gamma\delta$T cells), cell therapy, including stem cells such as induced pluripotent stem cells (iPSCs) (Dabrowska and Skopinski 2017), might also be a promising option combined with targeting IL-17. In a mouse model of non-alcoholic fatty liver disease, it has been demonstrated that the pathogenesis could be regulated by microRNA-26a-IL-6-IL-17 axis (He et al. 2017). Thus, it is worth to further investigate the role of non-coding RNAs (Mercer et al. 2009; Esteller 2011), such as microRNA, long non-coding RNA, circular RNA and small nucleolar RNA, in modulating the pro-angiogenic effect of IL-17.

Conclusion

IL-17 is a cytokine that is involved in the pathogenesis of ocular neovascular diseases. IL-17 is mainly produced by Th17 cells, but also produced by $\gamma\delta$T cells and Thy-1(+) innate lymphoid cells. The functions of IL-17 are achieved with macrophages and lymphocytes. Th17 cells are essential for the IL-17 signal network that is very complicated and still remains unclear. Thus, IL-17 could be a potential target for the treatment of ocular neovascularization. However, until now, researches mainly focused on IL-17, rather than other cytokines of the IL-17 family; thus, more investigations are needed to clarify the functions and mechanisms of other IL-17 family members besides IL-17A. Further studies are necessary to clarify the relevance of IL-17 and VEGF to provide a better therapeutic choice for patients with ocular neovascular diseases.

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Conflict of Interest

The authors declare no conflict of interest.

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