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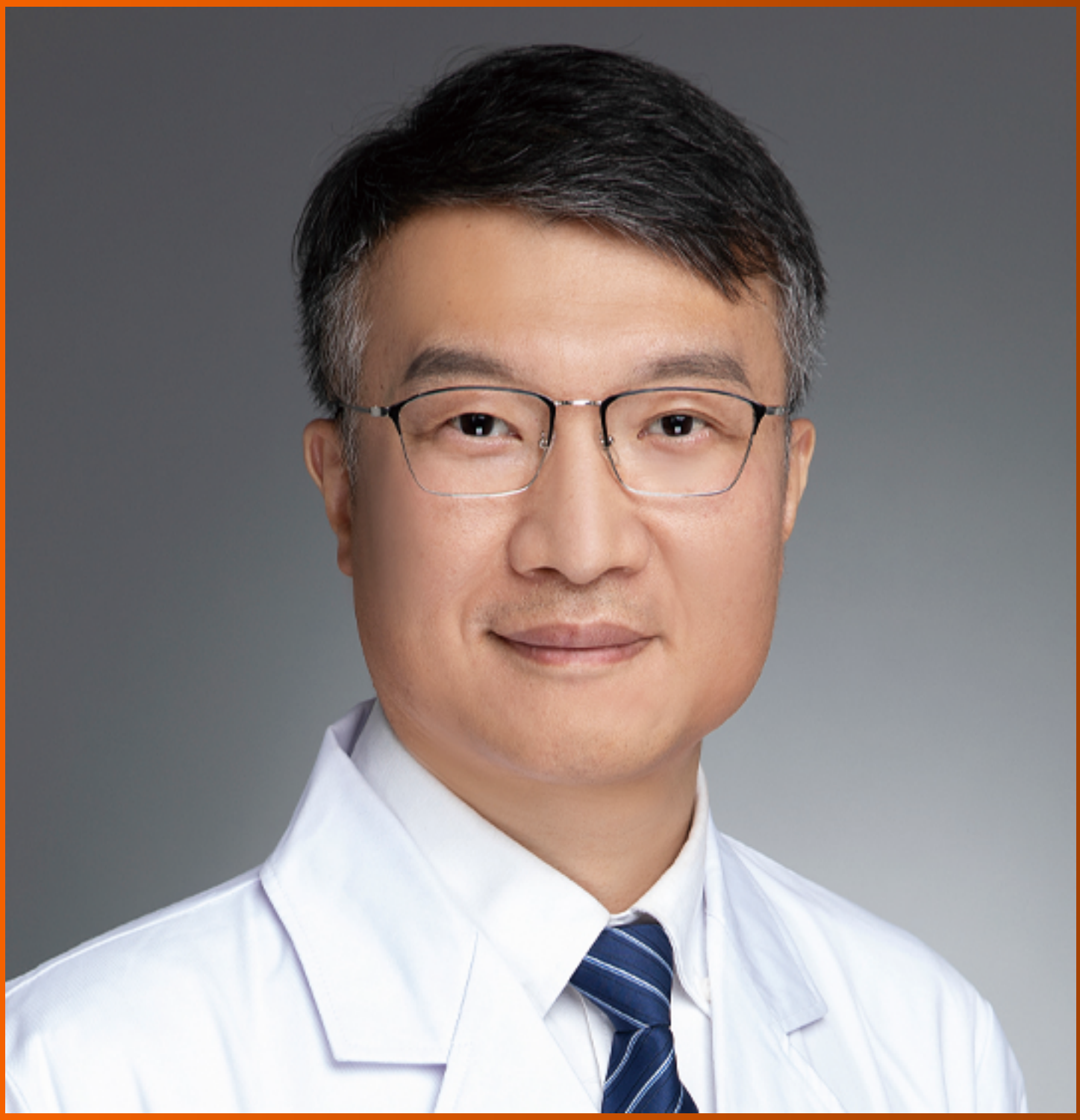

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## ABOUT COVER

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## AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJD* mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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REVIEW

# Role of interferons in diabetic retinopathy

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## Abstract

Diabetic retinopathy (DR) is one of the major causes of visual impairment and irreversible blindness in developed regions. Aside from abnormal angiogenesis, inflammation is the most specific and might be the initiating factor of DR. As a key participant in inflammation, interferon-gamma (IFN-γ) can be detected in different parts of the eye and is responsible for the breakdown of the blood-retina barrier and activation of inflammatory cells and other cytokines, which accelerate neovascularization and neuroglial degeneration. In addition, IFN-γ is involved in other vascular complications of diabetes mellitus and angiogenesis-dependent diseases, such as diabetic nephropathy, cerebral microbleeds, and age-related macular degeneration. Traditional treatments, such as anti-vascular endothelial growth factor agents, vitrectomy, and laser photocoagulation therapy, are more effective for angiogenesis and not tolerable for every patient. Many ongoing clinical trials are exploring effective drugs that target inflammation. For instance, IFN-α acts against viruses and angiogenesis and is commonly used to treat malignant tumors. Moreover, IFN-α has been shown to contribute to alleviating the progression of DR and other ocular diseases. In this review, we emphasize the roles that IFNs play in the pathogenesis of DR and discuss potential clinical applications of IFNs in DR, such as diagnosis, prognosis, and therapeutic treatment.

**Key Words:** Interferons; Cytokines; Diabetic retinopathy; Interferon-alpha; Interferon-gamma; Inflammation

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**Core Tip:** Diabetic retinopathy (DR) is one of the microvascular complications of diabetes mellitus and seriously threatens the eyesight of the working-age population. Inflammation and inflammatory cytokines are closely related with its pathological mechanisms. Here we discuss the roles of interferons in DR, mainly from the pathogenesis and clinical applications.

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## INTRODUCTION

Diabetes mellitus has reached epidemic proportions globally and affects the health of populations in both developing and developed countries[1]. Diabetic retinopathy (DR) has been recognized as a neurovasculopathy of diabetes and is a leading cause of blindness in populations of 20-74 years old in many developed countries[2-4], accounting for 2.6% of blinding cases around the world[5]. Nearly 30% of diabetic patients develop into DR[6], and once the course of diabetes extends beyond 15 years, DR can occur in almost 98% of patients with type 1 diabetes (T1D) and more than 80% of patients with type 2 diabetes (T2D)[7]. Similarly, the chance of developing sight-threatening DR is higher in T1D patients (11%) than in T2D patients (3%)[8].

Clinically, DR is classified into two stages based on microvascular changes: Non-proliferative (also known as simple or background) DR (NPDR) and end-stage proliferative DR (PDR)[9]. The former is characterized by vascular tortuosity, retinal hemorrhages, microaneurysms, yellow-white hard exudations, and white cotton spots [10]. As the final phase of DR, PDR leads to severe and quick vision impairment, which is featured by aberrant neovascularization, preretinal or vitreous hemorrhages, epiretinal membrane, and tractional detachment of the retina[11,12]. To diagnose DR, fundus photography, optical coherence tomography (OCT), and fundus fluorescein angiography (FFA) are often used to measure vascular abnormalities in the retina, such as retinal blood vessel permeability and thickness[13].

Intensive control of related risk factors, such as blood glucose, blood pressure, smoking, and pregnancy, is the typical method to minimize the progression of lesions, especially in the early stage[14,15]. Anti-vascular endothelial growth factor (anti-VEGF) medications, laser photocoagulation therapy, intravitreal injections of corticosteroids, and vitreoretinal surgery are mainly used to treat DR, especially in the advanced stage[16-18]. These methods are effective in inhibiting pathological vascular proliferation, reducing diabetic macular edema (DME), and saving eyesight[19-21]. However, these methods are restricted by a short therapeutic half-life and the risk of attendant adverse reactions, such as injection site bleeding, increased intraocular pressure, endophthalmitis, loss of peripheral vision, accelerated cataract formation, and retinal detachment[22]. Consequently, detection during the early stage of DR (NPDR) is the most effective way to prevent further worsening of DR and improve treatment and prognosis.

It is well known that inflammation participates in the early phase of DR and plays an important role in DR pathogenesis. Thus, exploring the associated mechanisms of inflammation is essential to many aspects of DR, such as diagnosis, prognosis, and therapeutic treatment. In this review, we mainly summarize the crucial roles of interferons (such as IFN-γ and IFN-α) in DR pathogenesis and discuss the potential clinical applications for patients with DR.

## INFLAMMATION IN DR PATHOGENESIS

To date, the mechanisms and pathogenesis of DR remain unclear. There is a consensus that DR is the result of the interactions of multiple pathways. Hyperglycemia, ischemia- and hypoxia-induced retinal microangiopathy, inflammation and leukocyte stasis, and retinal neurodegeneration are the main causes of DR[23-25], as well as oxidative stress, mitochondrial dysfunction, microRNAs, and other molecular mecha-

nisms[26-28]. Microvascular changes, such as the loss of pericytes, increased permeability, and vasoregression, lead to retinal ischemia/hypoxia through the upregulation of biological factors, such as hypoxia-inducible factor 1 (HIF-1), VEGF, and inducible nitric oxide synthase, which play crucial roles in aberrant neovascularization[29,30].

Although abnormal neovascularization is the most characteristic change in lesions, altered inflammation occurs before the development of microvascular lesions[31,32]. Leukocyte stasis, neutrophil and macrophage infiltration, complement and microglial activation, cytokine upregulation, and increased chemokine synthesis occur in the retina[11,33]. Studies have shown a reciprocal relationship between inflammation and angiogenesis[34]. To a certain extent, the onset of DR relies on the release of proinflammatory cytokines and the adhesion of leukocytes to retinal capillaries[35]. Moreover, accumulating evidence has shown that treatments to inhibit the inflammatory reaction, such as intravitreal steroids, interleukin-6 (IL-6) inhibitors, IL-6 receptor inhibitors, and integrin inhibitors, are effective in preventing the development and worsening of DR[6,23].

The upregulation of inflammatory cytokines, such as IFN-γ, IL-1β, IL-6, and IL-10, is the primary contributor to persistent low-grade inflammation[36], which can increase vascular permeability, accelerate the progression of DME, and increase angiogenic responses of endothelial cells (ECs)[37,38]. As a proinflammatory cytokine, IFN-γ can be found in different parts of the eye in DR, such as tears[39], aqueous humor[40,41], vitreous fluids[42-45], and serum[46-48], even during the early stage of DR. Moreover, clinically significant differences exist between DR and diabetes without retinopathy (DNR), or between PDR and NPDR, suggesting that IFN-γ is closely related to the occurrence and development of DR. Therefore, similar to other substances, such as hemoglobin A1c (HbA1c), VEGF, complement component C3, intercellular adhesion molecule 1, and IL-6[49-51], IFN-γ may be a potential candidate biomarker of DR and greatly contribute to diagnosis, treatment, and prognosis.

According to existing studies, IFN-γ and IFN-α are involved in DR. IFN-α induces a marked effect on not only DR, but also the pathological processes of other ocular and systematic diseases, such as conjunctival papilloma, uveitis, HIV infection, central nervous system diseases, and malignant tumors, due to its important role in innate and adaptive immunity[52-56]. Moreover, IFN-α can cause associated ocular pathophy -siological changes, such as endophthalmitis and neovascularization of the retina, when used to treat diseases of the eye or other systematic dysfunctions, such as serpiginous choroidopathy and hepatitis C[57,58].

## IMMUNOLOGICAL REGULATION OF IFNS

As discussed above, IFNs might be involved in the inflammation and pathogenesis of DR. The activity of IFNs was first discovered in 1957 by Isaacs and Lindenmann[59]. IFNs are a group of glycoproteins that are synthesized and secreted by almost all cells in mammals and after stimulation by specific antigens[60]. IFNs are an endogenous family of cytokines with pleiotropic antiviral, antiproliferative, and immunomodulatory properties that play important roles in host defense mechanisms and maintaining homeostasis[54,61]. According to the cell surface receptors to which they bind, IFNs can be classified into three main families: Types I, II, and III[62]. There are various kinds of type I IFN, IFN-γ is the only type II IFN, and type III IFN consists of four molecules[63,64]. Clinically, IFNs are widely used, and each type has specific indications, such as the use of IFN-α for leukemia and melanoma and IFN-β for multiple sclerosis[65-67].

Regarding the molecular mechanisms, highly coordinated signaling events composed of viral sensors, adaptor proteins, kinases, and transcription factors can activate IFN transcription[61]. Currently, the mechanisms by which IFNs affect viruses, tumors, or other diseases are not completely understood. The Janus kinase signal transducer and activator of transcription (JAK/STAT) pathway is strongly associated with IFN signaling in viral infections[68]. Meantime, Gysemans *et al*[69] found that STAT-1 is a pivotal factor that controls the death of beta-cells and the accompanying immune-mediated diabetes. Once viral sensors such as pattern recognition receptors recognize viral proteins and nucleic acids and detect viral genes, adaptor proteins initiate a signal transduction cascade that leads to the formation of transcription factors and IFN I/III. The secreted IFNs act in an autocrine and paracrine manner. Then, the infected cells activate the JAK/STAT pathway and accelerate the expression of IFN-stimulated genes (ISGs)[70,71]. ISGs encode antiviral effectors or

molecules that are engaged in a wide array of cellular functions[72]. Additionally, ISGs regulate IFN signaling both positively and negatively[61]. For example, ISGs modulate viral replication (OAS/RNase L, ADAR, CD74, and GBP family members), viral entry (IFITM1/2/3, MOV10, and ZAP), protein translation (MB21D1, DDIT4, PKR, and MAP3K14), and viral egress (BST2/tetherin and RSAD2)[73]. Moreover, IFN-α can upregulate the expression of major histocompatibility complex (MHC) class I molecules as well as inflammation and endoplasmic reticulum stress markers in β cells and induce β cell apoptosis with IL-1β[74]. IFN-γ upregulates MHC class I and MHC class II molecules, which can increase the susceptibility of infected cells to lysis by cytotoxic T lymphocytes[75,76].

In this review, we highlight the relationship between DR and IFN-α or IFN-γ, elaborating on their key roles in DR.

## IFN-γ IN DR

IFN-γ is the only type II IFN and is released by T helper 1 lymphocytes, natural killer cells, natural killer T lymphocytes, and CD8+ T cells[77]. IFN-γ can inhibit cell proliferation, modulate the activity of cytotoxic T cells, stimulate the biosynthesis of other cytokines, and is closely associated with innate and adaptive immunity[78-80]. In addition, IFN-γ and IFN-α can upregulate the expression of programmed death-ligand 1 in pancreatic β cells in the context of T1D, which may exert protective effects to resist T cell-mediated β cell apoptosis[81].

It is well documented that inflammation is a central driver of capillary occlusion and hypoxia, which can maximize the expression of VEGF[82]. IFN-γ plays a role in the etiology of DR due to its inflammatory functions. Numerous studies have improved the understanding of the relationship between IFN-γ and DR: (1) The concentration of IFN-γ is increased in tears in DR compared with those in DNR and the ratios of anti-angiogenic and angiogenic cytokines, such as IFN-γ/MCP and IFN-γ/IL-8 are decreased[39], suggesting the formation of an angiogenic environment; (2) The level of IFN-γ is higher in the aqueous humor in DR than in DNR[40,41]; and (3) The concentrations of IFN-γ in serum and vitreous fluids in DR are significantly higher than those in DNR or DM[42,45-47] (Tables 1 and 2). These studies all provide evidence that IFN-γ promotes and sustains chronic inflammation in the diabetic retina, which can result in neuro-glial degeneration, activation of inflammatory cells, vascular dysfunction, and breakdown of the blood-retina barrier (BRB)[50,83]. In addition, IFN-γ seems to be correlated with blood glucose. It has been found that IFN-γ was significantly increased in uncontrolled T2D or patients diagnosed with T2D recently but without treatment compared with patients who received effective glucose-lowering treatment[84,85]. IFN-γ is closely correlated with systolic blood pressure, platelets, mean platelet volume (MPV), and platelet distribution width (PDW)[85], which can be used to predict microvascular complications in diabetes[85,86]. The pathological changes mediated by IFN-γ not only exist in the retina, but also occur in the cornea and vitreous.

As essential parts of innate immunity, macrophages have two primary phenotypes: M1 and M2. The balance between these two phenotypes is controlled by macrophage phenotypic plasticity, inflammatory modulators, and the activity of intracellular signaling mediators and transcription factors[87]. M1 macrophages release inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), IL-1, IL-6, IL-12, type I IFN, and proteases and perform phagocytosis, while M2 macrophages perform phagocytosis and tissue repair and remodeling, and generate chemokines and anti-inflammatory cytokines such as transforming growth factor-β (TGF-β) and IL-10[76,88,89]. In DR, M1 macrophages inhibit angiogenesis and mediate inflammation, while M2 macrophages are involved in abnormal neovascularization. M1 polarization can be induced by IFN-γ[90]. Hence, IFN-γ may mediate the pathogenesis of DR by modulating the polarization of macrophages. Moreover, we know that IL-12 participates in the process of anti-angiogenesis in many diseases, such as corneal neovascularization and tumors[91,92]. Zhou *et al*[93] showed that IL-12 could mediate and inhibit pathological neovascularization in a mouse model of oxygen-induced retinopathy through the downstream molecules IP-10 (CXCL10) and MIG (CXCL9), which are mainly induced by IFN-γ. Importantly, the study demonstrated that the intravitreal injection of recombinant IL-12 did not significantly decrease the expression of VEGFA or fibroblast growth factor-2 (FGF2), which suggests that the mechanisms of IL-12 are independent of VEGFA and FGF2[93].

**Table 1 Expression of interferons in samples**

| Source | Condition of disease | Expression |
|---|---|---|
| Tears | DR | (IFN-γ) ↑↑, (IFN-γ/MCP-1) ↓, (IFN-γ/IL-8) ↓[39] |
| | DNR | (IFN-γ) ↑[39] |
| Aqueous humor | PDR | (IFN-γ) ↑↑[40] |
| | NPDR | (IFN-γ) ↑[40] |
| | DR | (IFN-γ) ↑↑[41], (IFN-α) ↓↓[117,118] |
| | DNR | (IFN-γ) ↑[41], (IFN-α) ↓[117,118] |
| Vitreous fluids | DR | (IFN-γ) ↑[42] |
| | DM | (IFN-γ) ↑[45] |
| Serum | DR | (IFN-γ) ↑↑[46] |
| | DNR | (IFN-γ) ↑[46] |
| | DM | (IFN-γ) ↑[47,48] |
| Plasma | DM | (IFN-α) ↑, (IFN-β) ↑[113] |
| Retina | DR | (IFN-β) ↑[115] |

DR: Diabetic retinopathy; DNR: Diabetes without retinopathy; PDR: Proliferative diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; DM: Diabetes mellitus; IFN: Interferons.

**Table 2 Concentration of interferons in patient samples**

| IIFNs | Source | Condition of disease | Concentration |
|---|---|---|---|
| IFN-γ | Tears (multiplex bead analysis) | Controls | 1463.0 ± 158.8 (pg/mL)[39] |
| | | DNR | 1612.8 ± 228.2 (pg/mL)[39] |
| | | DR | 1957.50 ± 166.1 (pg/mL)[39] |
| | Aqueous humor (CBA) | Controls | 60.29 ± 14.17 (pg/L)[40] |
| | | DNR | 54.96 ± 16.29 (pg/L)[40] |
| | | NPDR | 114.26 ± 50.76 (pg/L)[40] |
| | | PDR | 136.36 ± 35.55 (pg/L)[40] |
| | Vitreous fluids (ELISA) | Controls | 3.83 ± 0.80 (pg/mL)[42] |
| | | DR | 6.25 ± 0.84 (pg/mL)[42] |
| | Serum (ELISA) | Controls | 2.9 (pg/mL)[46] |
| | | DNR | 27.8 (pg/mL)[46] |
| | | DR | 56.8 (pg/mL)[46] |
| IFN-α | Aqueous humor (Bio-Plex pro$^{tm}$ magnetic color-bead-based multiplex assay) | Controls | 26.2 (0-84) (pg/mL)[117] |
| | | DNR | 0 (0-20) (pg/mL)[117] |
| | | DR | 0 (0-18) (pg/mL)[117] |

Data are expressed as the mean ± SEM or median (range). DNR: Diabetes without retinopathy; DR: Diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; CBA: Cytometric bead array technique; ELISA: Enzyme linked immunosorbent assay; IFN: Interferons.

In addition, IFN-γ is involved in other microcirculatory damage in diabetes. Taylor *et al*[94] showed that the proinflammatory cytokine IFN-γ and abnormal IFN-γ signaling were responsible for microglial repair of microvascular injuries and cerebral microbleeds (CMBs) in T1D through the downregulation of *P2ry12* gene expression, which decreased the accumulation and polarization of microglia. In addition, many other studies have shown that overexpressed IFN-γ was blood-derived, and entered

the brain through the injured blood-brain barrier to bind to highly-expressed IFN-γ receptors 1 and 2 on microglia[95,96]. Du *et al*[97,98] reported that IFN-γ played a protective role in the kidney in type II diabetes and could inhibit the excessive accumulation of mesangial matrix by activating the JAK2/STAT pathway, which could suppress the high glucose-induced increase in TGF-β1 and collagen IV. In addition, IFN-γ can impair renal fibrosis by inhibiting fibroblast activation and proliferation and reducing collagen synthesis[99].

Additionally, IFN-γ is involved in other neovascularization diseases, such as ischemia, clearance of malignant tumors, and age-related macular degeneration (AMD). IFN-γ plays a central role in the pathogenesis and development of AMD, which is characterized by retinal cell atrophy and choroidal neovascularization in the macula[100]. On the one hand, IFN-γ accelerates pathological progression: (1) IFN-γ selectively promotes M1 macrophage polarization through increased secretion of IFN-regulatory factors (IRFs), such as IRF-1, IRF-5, and IRF-8[101,102], and the activation of nuclear factor-κB and STAT-1[87], which can increase the secretion of inflammatory cytokines, such as IL-1β, IL-6, and TNF-α[89,103]; and (2) IFN-γ independently upregulates VEGF in retinal pigment epithelial cells through the activation of the PI-3K/Akt/mTOR/p70 S6 kinase pathway[104]. On the other hand, IFN-γ mediates protective effects in AMD: It downregulates the functions of VEGF in ECs by inhibiting necessary genes that are indispensable for VEGF bioprocessing and upregulates IL-1 receptor antagonist[105-107].

The role of IFN-γ in angiogenic diseases is inconsistent. One the one hand, IFN-γ can prevent and slow the development of vascular proliferation by increasing the proportion of M1 macrophages, and recombinant IFN-γ can reduce pathological choroidal neovascularization in a dose-dependent manner[108]. On the other hand, IFN-γ accelerates angiogenic process by increasing the expression of VEGF and upregulating other inflammatory cells and cytokines. Further studies are needed to investigate the mechanisms by which IFN-γ affects DR pathogenesis.

## IFN-α IN DR

For many years, approaches to cure DR primarily included anti-VEGF agents, anti-inflammatory therapy, photocoagulation, vitrectomy, and controlling related risk factors[23,109]. With further research on DR, many novel discoveries of new targets and methods are constantly occurring, such as neuroprotective substances (somatostatin and brimonidine), polyphenols, the Tie-2 activator AKB 9778, small interfering RNAs (bevasiranib and PF04523655), encapsulated cell technology, and small intraocular pumps[109,110]. These new interventions can be applied to patients who are resistant to traditional therapies or have severe side effects.

As a type I IFN, IFN-α functions against infection, neoplasms, and immunity[111]. IFN-α is involved in the early stage of β cell death in T1D for its autoimmune ability [112], because IFN-α is markedly increased in the plasma of individuals with T1D, and inhibition of IFN-α/β receptor 1 and antibody against IFN-α can reduce the occurrence of T1D[113,114] (Table 1). Additionally, IFN-β is highly expressed in the retina of DR rats[115] (Table 1). Gerber *et al*[116] showed that IFN-α increased the expression of HIF-1α in a dose- and time-dependent manner by activating JAK1, tyrosine kinase 2, and IFN-stimulated gene factor 3, which inhibit the proliferation of vascular ECs. Priming with IFN-γ followed by IFN-α can enhance the magnitude and duration of HIF-1α. Among 13 human IFN-α subtypes[55], IFN-α 2 has been shown to have a therapeutic effect in a wide range of ophthalmological dysfunctions involving both the anterior and posterior segments of the eye[57] (Table 3). Moreover, it has been reported that IFN-α in the aqueous humor was more unmeasurable in diabetic patients than in non-diabetic patients, and its median level was decreased in turn among nondiabetic patients, DNR patients, and DR patients, suggesting that an imbalance in immune function may be involved in the pathogenesis of DR[117,118] (Table 2).

IFN-α 2a can suppress intraocular inflammation, possibly by helping regulatory T cells restore their inhibitory functions[119]. After subcutaneous injection of 6 million/IU IFN-α 2a 3 times/wk for an average of 10 mo, patients with PDR were found to have obvious improvements in visual acuity, decreased leakage of vessels, and regression of neovascularization after complete laser panretinal photocoagulation (PRP)[120]. Chronic drug use of recombinant IFN-α 2a for PDR presented certain clinical value because regression of capillary tufts and no new hemorrhage or neovascularization were found in patients during treatment[121]. Refractory DME was cured

**Table 3 Applications of interferon-α in ocular disorders**

| IFN | Clinical applications |
|---|---|
| IFN-α-2a | Ocular surface diseases: Tumors (such as limbal conjunctival melanoma, squamous neoplasias, and conjunctival MALT lymphoma)[134, 137]; Mooren's ulcers[138]; herpes simplex keratitis[139] |
| | Uveal disease: Behcet's uveitis[131]; serpiginous choroiditis[140]; choroidal neovascularization[141]; HHV-8-associated uveitis[142]; chronic noninfectious posterior uveitis[143] |
| | Macular and retinal disorders: Uveitic CME; angiogenesis after PRP; refractory non-infectious inflammatory macular edema[144] |
| IFN-α-2b | Ocular surface diseases: Tumors (such as squamous cell carcinoma[145], melanocytic tumors[145], CIN[146], conjunctival papillomatosis [147], and MALT lymphoma[57]); LSCD[135]; vernal keratoconjunctivitis[132] |
| | Uveal disease: Metastatic uveal melanoma[148]; Behcet's uveitis[149] |
| | Macular and retinal disorders: CME caused by intraocular infection[150]; refractory diabetic macular edema[133] |
| IFN-α-2 | Dendritic keratitis[151] |

MALT: Mucosa-associated lymphoid tissue; HHV-8: Human herpes virus 8; CME: Cystoid macular edema; PRP: Panretinal photocoagulation; CIN: Conjunctival and corneal intraepithelial neoplasia; LSCD: Limbal stem cell deficiency; IFN: Interferons.

by IFN-α 2a at a dose of 1 million IU/mL 3 times/wk through posterior subtenon injections, and IFN-α 2a could be effective in reducing central macular thickness and improving visual acuity[122]. There are few cases of clinical use of IFN-α 2a in the treatment of DR, thus criterion of when and how to implement and evaluate the therapeutic effect of IFN-α 2a is not unified now, which needs further exploration. Based on clinical experience, clinicians can choose appropriate intervals to review the progression of the disease, such as glucose metabolism index, vision, visual field, neovascularization, and fundus examination. There is hardly any evidence that IFN-α 2b is able to treat DR. Moreover, the susceptibility to and risk for retinopathy are increased after clinicians use IFN-α as a therapeutic method for chronic hepatitis C [123,124], which is known as IFN-associated retinopathy (IAR). Recent guidelines indicate IFN-based therapy (pegylated IFN plus ribavirin) as a first-line method in treating chronic HCV patients[125]. Although this therapeutic plan is effective for most patients, it inevitably has some side effects, including adverse ophthalmological effects. Cotton-wool spots and retinal hemorrhage are the most common symptoms in patients with IAR[126], but these patients rarely exhibit decreased visual acuity and subjective symptoms[58,127]. The potential mechanism of IAR involves IFN-α-induced deposition of immune complexes in the retinal vasculature, which can lead to ischemic changes in the retina, such as occlusion of retinal capillaries, cotton-wool spots, and retinal hemorrhage[128]. Furthermore, another study explained that glucose tolerance was obviously improved by treatment with recombinant IFN-α in both nondiabetic and diabetic HCV patients[129].

IFN-α 2a is a promising treatment for DME and DR, because it can assist in preventing vision deterioration, inhibiting active neovascularization, and promoting the barrier function of ECs in the retina[64]. According to existing clinical records, the clinical effect of IFN-α 2a was only observed in patients after PRP and those with active neovascularization but not meeting the criteria of PRP treatment[120-122]. However, the therapeutic effect of IFN-α is not widely demonstrated by clinical trials and studies, and there are side effects and risks of using IFN-α, such as flu-like symptoms and increased liver enzymes[130]. In addition, the functions of IFN-α in DM and DR seem to be contradictory. On the one hand, the overexpression of IFN-α can result in the onset of T1D; on the other hand, IFN-α has the potential to treat DR and DME and help pancreatic β cells resist T cell-mediated apoptosis. Hence, more studies are needed to estimate the therapeutic effect of IFN-α.

IFN-α is also used in many other ocular disorders, such as uveitis[131], vernal keratoconjunctivitis[132], and refractory DME[133]. In cases of conjunctival melanomas and ocular surface squamous neoplasia (OSSN), intralesional IFN-α 2a injection before surgery exhibited excellent results in reducing size and vascularity, defining tumor margins, and improving prognosis[134]. The combined use of IFN-α 2b and all-trans retinoic acid is effective in patients with partial limbal stem cell deficiency (LSCD)[135]. Topical and subconjunctival administration of IFN-α 2b exhibits good effects in controlling and preventing the recurrence of OSSN, and the adverse effects of IFN-α 2b are less severe than those of 5-fluorouracil and mitomycin C[136]. To date, there have been few reports about the role and expression of other IFNs in DR, which

deserves to be further investigated.

## POTENTIAL APPLICATIONS OF IFNS IN DR

So far, DR diagnosis mainly depends on clinical manifestations. Many types of technologies are utilized to observe specific pathological changes, such as fundoscopy, FFA, and OCT. Besides, some indexes, such as HbA1c and VEGF, have also been suggested for the diagnosis, treatment, or prognosis of DR.

Inflammation is thought to be an initial event in DR. IFN-γ contributes to inflammation and is involved in the early stage of DR and other microvascular lesions associated with mellitus, such as those in kidney and brain tissues. IFN-γ is tied to indices like MPV, PDW, and blood sugar, which can predict microvascular complications of DM. And a positive correlation exists between IFN-γ and HbA1c%[48,85] and inflammatory cytokines, such as IL-1β and IL-3[47]. Besides, compared with blood glucose and hemoglobin, IFN-γ has the advantage of being less susceptible to dietary changes and better reflecting inflammation of the eye. Hence, we presume that IFN-γ might be a biomarker of DR, indicating the incidence of retinopathy once diabetes has happened, the speed of progression towards PDR, and the possibility of a poor prognosis.

For early-stage patients, the control of relevant risk factors, such as blood pressure, blood sugar, smoking, and blood lipids, is recommended. Anti-VEGF is recommended as the first-line therapy for PDR, but this treatment is restricted by its short half-life, high cost, and adverse effects. Importantly, blocking VEGF is unable to attenuate disease progression completely or reverse damage to the retina, and merely delays the rate of development and alleviates symptoms, but cannot affect a permanent cure. Currently, with the expansion of medications targeting inflammatory pathogenesis, mediators of angiopoietin signaling axes, immunosuppressants, and nonsteroidal anti-inflammatory drugs, such as tocilizumab, EBI-031, and luminate, have been shown to be effective in clinical trials and need to be further verified[23,82]. Therefore, whether there is clinical effectiveness when antibodies against IFN-γ are applied locally or intralesionally is worth being further investigated. However, the findings are controversial because IFN-γ has protective effects against renal fibrosis and inhibits vascular proliferation. Consequently, this therapeutic application for DR requires additional consideration and experimental verification.

IFN-α 2 is effective in multiple ocular diseases, such as uveitis and cystoid macular edema. Clinical effectiveness has only been observed in PDR after PRP, DME, and continued neovascularization in some reports, although this factor is effective on angiogenesis and EC proliferation. And clinicians need to closely observe the progression of patients during the use of IFN-α through a series of physical examination, fundus examination, FFA, *etc*. Moreover, IFN-α enhances glucose tolerance and may improve prognosis. Hence, IFN-α may be a potential therapeutic treatment for DR in the future.

## CONCLUSION

As a retinal neovascularization disease, DR is a frequent and serious microangiopathy associated with diabetes, and is the principal cause of vision loss in the working-age population[5,51]. Inflammation is a major pathological mechanism associated with the occurrence and development of DR, through the effects of many inflammatory cells and cytokines, such as IFN-γ, IL-1β, and IL-6, macrophages, and microglia. IFNs are a group of glycoproteins that are responsible for antiviral activity, inhibiting cell proliferation, and regulating immunity and malignant tumors. Every subset has corresponding functions, and they are broadly applied to malignant tumors and viral infections, such as hepatitis type C, herpes zoster, hairy cell leukemia, T cell lymphoma, and melanoma. IFN-α and IFN-γ are tightly linked with DR in the context of inflammatory pathogenesis and treatment. As a proinflammatory cytokine, IFN-γ can be detected in tears, aqueous humor, the vitreous body, and the retina, indicating that it plays a role in the breakdown of the BRB, inflammatory injuries, abnormal angiogenesis, and other processes. IFN-γ also participates in the pathogenesis of other diabetic vascular complications, such as DN and CMBs. In addition, the presence of IFN-γ results in macrophage polarization to proinflammatory M1 phenotype, which produces inflammatory cytokines, such as TNF-α, IL-8, and IL-12, and exacerbates the inflammation. Meanwhile, IFN-γ is associated with the changes and control of blood

glucose and presents a positive correlation with HbA1c%, IL-1β, and IL-3. Consequently, IFN-γ can be a prospective biomarker of DR. Based on its immunomodulatory effect, IFN-α helps to improve visual acuity, reduce uncommon vascular proliferation, and improve glucose tolerance. However, IFN-α contributes to the occurrence of T1D. IFN-α and IFN-γ also play important roles in other diseases characterized by abnormal angiogenesis, such as AMD, hepatocellular carcinoma, cervical neoplasia, and IAR by proinflammatory and immunoregulatory functions.

Therefore, we believe that IFN-γ has the potential to be a biomarker in the diagnosis and prognosis of DR, as well as to be a key regulator in treating DR. Additionally, the applications of IFN-α still need to be further explored.

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