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REVIEW

The IL-12 family of cytokines: pathogenetic role in diabetic retinopathy and therapeutic approaches to correction

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Abstract

One vision-threatening side effect of systematic diabetes mellitus is diabetic retinopathy (DR). Recent studies have revealed that the development and progression of DR depend critically on inflammation resulting from diabetes. By attracting leukocytes to endothelium, the higher production of the inflammatory mediators induces degeneration of retinal capillaries, hence increasing vascular permeability and thrombosis probability. The leukocytes that are recruited eventually generate additional proinflammatory and proangiogenic substances, resulting in the increased infiltration of leukocytes in the retina. This process also leads to changes in the blood retinal barrier and the formation of new blood vessels, which helps to counteract the damage caused by the blockage of blood flow. IL-12 family members, IL-12, IL-23, IL-27, and IL-35, play a crucial role in regulating the responses of T helper (Th)1 and Th17 cell populations. The collected data from studies investigating the levels of IL-12 family members in the blood and eye tissues suggest that IL-12 is linked to DR, indicating that it may have a role in the development of DR as a sequential component of the immune response. This review specifically examines the possibility of using IL-12 family cytokines as a therapeutic approach for diabetes, taking into consideration their involvement in the development of DR.

Keywords Diabetes · Retinopathy · Diabetic retinopathy · Cytokine · IL-12 family

Introduction

Diabetic retinopathy (DR) is the predominant and primary cause of blindness globally, as stated by the World Health Organization (WHO) (Raghav et al. 2017). Approximately 33% of individuals with diabetes experience the development of DR (Ting et al. 2016). This public health issue emphasizes the necessity for timely identification, treatment, and predictive indicators, aiding ophthalmologists in determining the most appropriate therapy for patients with DR and reducing the severity of this consequence. The underlying mechanism of DR involves damage to the small blood vessels in the retina, resulting in leakage and reduced blood flow. This leads to the growth of new blood vessels in the retina, following a well-known pathway involving increased levels of advanced glycation end products, activation of protein kinase C, and involvement of the superoxide pathway (Yang et al. 2019). These atypical metabolic pathways result in the secretion of proangiogenic, immunological, and inflammatory substances. The glycated hemoglobin A1c (HbA1c) is the biomarker in blood serum that has been extensively researched. This clinical biomarker is the only one that has been confirmed to be valid for assessing the occurrence and advancement of type 2 diabetes (T2DM) and DR (Adki and Kulkarni 2020). Numerous research has investigated the function of vascular endothelial growth factor (VEGF) in the development of DR. While anti-VEGF medication has been utilized as a treatment in clinical practice for a considerable period, it is crucial to note that the pathophysiology of DR is multifaceted. Additionally, other possible inflammatory factors also have significant roles (Wang and Lo 2018). Several cytokines are involved in DR and have several interactions that affect the development of this condition in T2DM. Hence, it is crucial to examine the cytokine profile during every stage of DR. The interleukin (IL)-12 family of cytokines consists of four members: IL-12, IL-23, IL-27, and IL-35. IL-12, IL-23, and IL-27 are released by activated antigen presenting cells (APC) during

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the process of presenting antigens to naïve T cells. On the other hand, IL-35 is produced by regulatory T and B cells (Shen et al. 2014). Their role is to facilitate the connection between the innate and adaptive immune systems by preparing immature $CD4^+$ T cells to develop into T helper (Th) subsets that produce cytokines, as well as memory T cells (Steinman 2006). IL-12 cytokines not only affect the cell-fate decisions of differentiating lymphocytes, but also control the cellular pathways necessary for the immune system to function properly. Some members of these cytokines activate pro-inflammatory responses, which help protect against infections. On the other hand, other members of these cytokines limit excessive immune responses that can lead to autoimmune diseases (Hunter 2005). This review aims to investigate the notable link between IL-12 family cytokines and DR. Furthermore, we offer a thorough analysis of the existing and possible treatment methods that focus on IL-12 family cytokines in the context of diabetes.

IL-12 family of cytokines

The IL-12 family of cytokines consists of IL-12 (IL-12p35/IL-12p40), IL-23 (IL-23p19/IL-12p40), IL-27 (IL-27p28/Ebi3), and IL-35 (IL-12p35/Ebi3). These cytokines play a crucial role in regulating the immune response of the host. Every member consists of an α-subunit that has a helical shape like type 1 cytokines such as IL-6, and a β-subunit that is structurally comparable to the extracellular sections of Type 1 cytokine receptors, such as the soluble IL-6 receptor (Vignali and Kuchroo 2012). The α subunits consist of IL-12p35, IL-23p19, and IL-27p28, while the β subunits consist of IL-12p40 and Ebi3. The secretion of the bioactive cytokine necessitates the co-expression of both chains (Wolf et al. 1991). There is a suggestion that the synthesis of each of the four heterodimeric cytokines may be restricted by the presence of the α chain. For example, the secretion of IL-12 or IL-35 is limited by the availability of IL12p35, whereas the secretion of IL-23 is primarily observed in tissues or cell types that have a high level of IL23p19 expression (Collison and Vignali 2008). One unique quality that explains in part IL-12 cytokine participation in several facets of host immunity is chain-pairing promiscuity. The dimerization of an alpha chain with IL-12p40 (such as IL-12 or IL-23) produces IL-12 cytokines that stimulate inflammation and the progression of chronic inflammatory diseases. On the other hand, when the alpha chain dimerizes with Ebi3, it produces members such as IL-27 or IL-35 that suppress inflammation and alleviate autoimmune diseases (Fig. 1). Another significant characteristic of IL-12 cytokines is their ability to exert

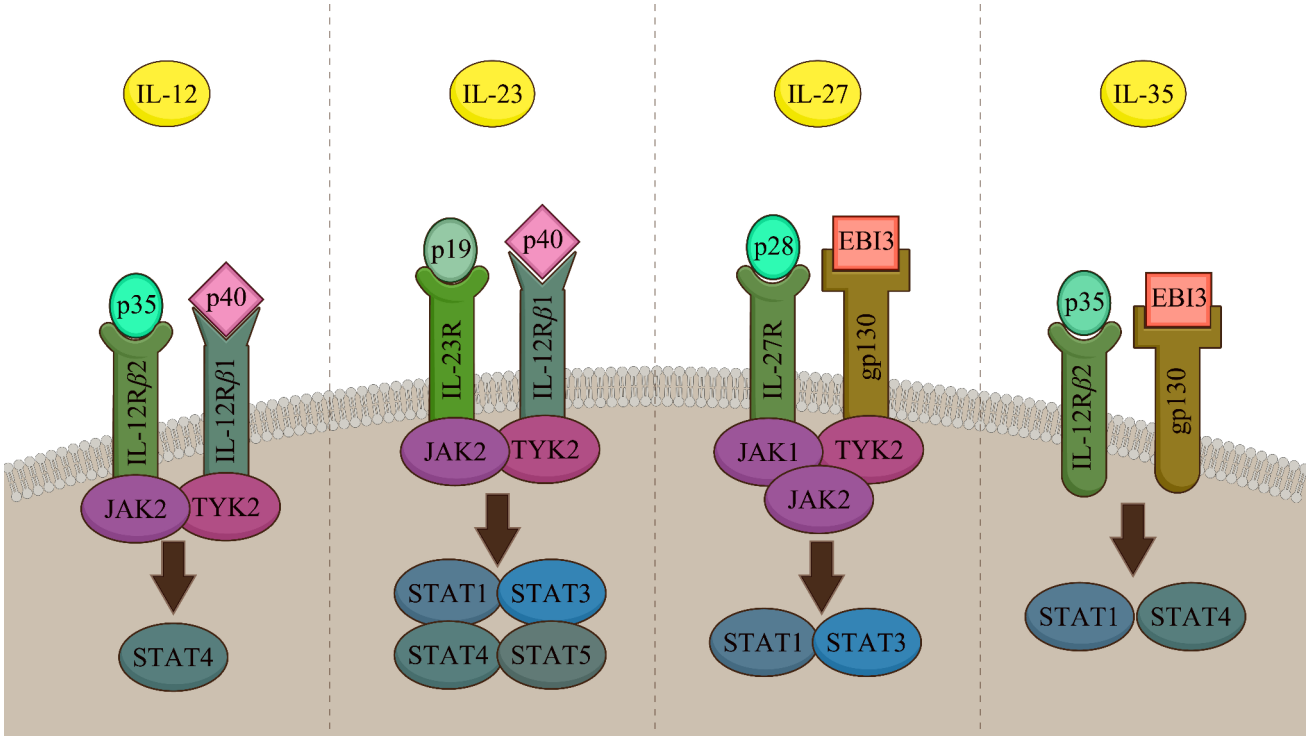

Fig. 1 The structure and design of the IL-12 cytokine family. The IL-12 family of cytokines, together with their receptors and Jak-STAT signaling partners, are provided. The functional range of these cytokines is indicated, ranging from the most proinflammatory (IL-23) to the most inhibitory (IL-35)

their biological effects by binding to heterodimeric receptors associated with Janus kinases (JAKs) and activating JAK-signal transducer and activator of transcription (STAT) signaling pathways (Trinchieri et al. 2003). Every IL-12 cytokine causes the recruitment and activation of particular STAT family members of transcription factors, which explains the distinct, as well as overlapping patterns of gene transcription produced by different IL-12 cytokines (Levy and Darnell Jr 2002). Very little is known about IL-27 or IL-35, despite much is known about the molecular and functional properties of IL-12 and to a lesser extent IL-23. Technical problems that have hampered the synthesis of biologically active, native heterodimeric IL-27 or IL-35 explain this.

IL-12 family of cytokines in DR

The diagnostic potential of IL-12 family cytokines in T1DM and T2DM is reflected by their circulating levels, which indicate the risk and severity of the diseases. They manipulate islet β cells and immune cells to worsen inflammation, while simultaneously decreasing inflammation by blocking nearly every stage of the immunological response. These cytokines also contribute to the development of diabetes complications, such as retinopathy, impaired wound healing, neuropathy, and atherosclerosis (Luo et al. 2024). In the following, we will discuss the IL-12 family cytokines in DR.

IL-12 in DR

IL-12 is a cytokine consisting of two different subunits, p40 and p35, and is mostly known for its pro-inflammatory properties. Antigen-presenting cells, such as dendritic cells (DC) and macrophages, produce it. It plays a vital role in attracting and activating $CD8^+$ T and natural killer (NK) cells (Zundler and Neurath 2015). The presence of pro-inflammatory mediators suggests that certain individuals with DR experience a hidden inflammation within the eye. Diabetic patients who receive phacoemulsification cataract surgery appear to experience a twofold increase in the progression rates of DR 12 months following the surgery (Funatsu et al. 2009). Several research has indicated potential links between the amounts of IL-12, IFN-γ –inducible protein 10 (IP-10), or tumor necrosis factor-alpha (TNF-α) in aqueous fluid and DR (Gverović Antunica et al. 2012; Wu et al. 2017). Furthermore, the study conducted by *Cvitkovic* et al. found that the serum concentration of IL-12 was notably elevated in the DR group compared to the control group (Cvitkovic et al. 2020). IL-12, a chemokine family cytokine, can decrease the levels of matrix metalloproteinase (MMP)-9 and VEGF-A and inhibit tumor angiogenesis. Therefore, IL-12 may offer improved therapeutic effectiveness against DR. *Zeng* et al. conducted a study where they created IL-12-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles (IL-12-PNP) using a double emulsion technique. They stated that IL-12-PNP serves as a highly efficient medication delivery system for DR treatment (Zeng et al. 2019). Neoangiogenesis is an intricate process, in which the VEGF, TNF-α, and IL-12, appear to play a significant part (Geindreau et al. 2022). According to a study by *Zorena* et al., the group with retinopathy had statistically significantly higher levels of VEGF, TNF-α, and IL-12 than the groups without retinopathy and the healthy control group (Zorena et al. 2007). Additionally, proinflammatory and angiogenic factor levels in the aqueous humor of diabetic individuals with and without retinopathy were compared by *Cheung* et al. Researchers discovered that the aqueous humor cytokine profile of patients with diabetes without retinopathy was comparable to that of patients with DR and that there was a negative correlation between the levels of VEGF, IL-12, and TNF-α (Cheung et al. 2012). Notably, the IL-12 concentration was considerably lower in diabetic patients compared to the nondiabetic controls. Furthermore. There was a strong negative association between the severity of DR and the amounts of IL-12 in the aqueous humor, with IL-12 levels decreasing as the severity of DR rose (Dong et al. 2013). The impact of administering bevacizumab (IVB) through an intravitreal injection before surgery on the levels of IL-12 was investigated. The study revealed that preoperative intravitreal bevacizumab (IVB) not only decreased the level of intravitreal VEGF, but also reduced the levels of various other inflammatory cytokines, such as IL-1RA, IL-5, IL-10, IL-12, IL-13, and IFN-γ. These findings point to the interaction of a few cytokines in the vitreous fluid of patients with proliferative DR and raise the prospect that preoperative IVB could influence the inflammatory response through putative cytokine networks in addition to directly reducing vascular proliferation through its antivascular endothelial growth factor effect (Suzuki et al. 2014).

IL-23 in DR

IL-23, which shares the component IL-12p40 with IL-12, has been demonstrated to hinder the process of wound healing by encouraging the differentiation of macrophages into the M1 phenotype (Lee et al. 2018). *Peng* et al. conducted a study to examine the levels of systemic inflammatory mediators in patients with non-proliferative DR (NPDR) and diabetic macular edema (DME). The aim was to investigate the relationship between systemic inflammatory mediators and DME. They discovered that the levels of IL-23 were noticeably higher in both the DME group and the Non-DR(NDR) group compared to the Non-DME group. This indicates that IL-23 has a role in the development of DME in NPDR patients (Peng et al. 2024). *Zhang* et al. conducted a study to investigate the variations in IL-23 levels in the aqueous humor of patients at different stages of proliferative DR. It was discovered that the level of

IL-23 was initially elevated in the NDR group and increased more as DR progressed. Furthermore, the IL-17 level exhibited a substantial increase in both the NPDR and PDR groups when compared to the NDR and control groups. Additionally, there was a positive correlation between higher IL-17 levels and the presence of more severe DR (Zhang et al. 2020). They determined that the excessive production of IL-23 and IL-17 in aqueous humor might have a combined impact on the development of the disease well before the stage of cell growth, and was consistently associated with the severity of DR. *Xu* et al. (Xu et al. 2015) conducted a study to examine the impact of the IL-23-Th17-IL-17A pathway on streptozotocin (STZ)-induced DR in rats. The study focused on the involvement of Th17 cells in the chronic inflammatory and immunological response, specifically their effect on the blood-retinal barrier. It was discovered that the levels of IL-17A protein in the peripheral blood and retinas of rats treated with STZ were dramatically increased. The researchers showed that injecting an anti-IL23Rp19 antibody directly into the vitreous cavity of rats treated with STZ resulted in enhanced integrity of the blood-retinal barriers (Xu et al. 2015). Hence, directing therapeutic efforts towards anti-IL-23p19 or its receptor shows potential for the treatment of DR. In the following, *sui* et al. (Sui et al. 2021) examined the mechanism via which the IL-23/IL-17 axis controls retinal neovascularization (RNV), which is a degenerative process observed in both mice with oxygen-induced retinopathy (OIR) and in vitro cell experiments. They demonstrated that the activation of the IL-23/IL-17 axis in the retinas of OIR mice led to an increase in regulated RNV formation. This effect was accompanied by an increase in macrophage recruitment and the activation of the nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor 3 (NLRP3) inflammasome. Furthermore, suppressing the IL-23/IL-17 pathway decreased the quantity of macrophages and the levels of expression and activation of NLRP3 inflammasome. Conversely, the recombinant forms of IL-23p19 and IL-17A stimulated the production and activation of the NLRP3 inflammasome, as well as the proliferation and migration of macrophages. Eliminating macrophages reduced the expression and activity of NLRP3 inflammasome as well as the activation of IL-23/IL-17 axis (Sui et al. 2021).

IL-27 in DR

IL-27 is a pleiotropic that has been recognized as an immunoregulatory cytokine implicated in inflammatory diseases (Jones et al. 2015). IL27 has been reported to have an anti-inflammatory function in ocular inflammation (Lee et al. 2011). VEGF A is a highly effective agent in promoting the growth of blood vessels, and it can also attract macrophages and granulocytes or cause vasodilation (Bardach 1990). It has been discovered that IL-27 has a regulatory function in suppressing VEGF A secretion by human macrophages. Through the intricate interplay of various biological mechanisms, the production of VEGF A is stimulated in a positive feedback loop. This is achieved through the combined effects of purinergic signaling and the activation of hypoxia-inducible factor 1 alpha (HIF-1α). Signaling of IL-27 in human macrophages interrupts this beneficial cycle, hence inhibiting the synthesis of VEGF A. The downregulatory effect on HIF-1α is reversed and the inhibitory effect on VEGFA production is partially blocked by blocking IL-27 signaling with a JAK2 antagonist. Finally, macrophages from patients with DR show a greater tendency to generate VEGF A, and this tendency is increased when they are exposed to the pro-inflammatory cytokine IL-1β in a laboratory setting. IL-27 inhibits the production of VEGF A by macrophages from patients with DR, even when exposed to IL-1β. This suggests that IL-27 could be used as a viable therapy for DR in a clinical setting (Zhang et al. 2019).

Houssen et al. discovered that individuals with DR exhibit elevated concentrations of IL-27 in the fluid within their eyes, known as aqueous humor. This rise in IL-27 is a compensatory reaction to inflammation. Furthermore, the concentration of IL-27 in the aqueous humor was found to be associated with certain risk variables for DR, such as the concentrations of serum glucose and HbA1C (Houssen et al. 2018). These findings indicate that IL-27 may have the ability to prevent DR by inhibiting the activity of Th17 cells. Consistent with this research, *Batsos* et al. discovered that the median level of IL-27 was elevated in patients with PDR compared to the control group. Similarly, the DME patients had a greater median concentration of IL-27 compared to the control group (Batsos et al. 2022). Conversely, the concentration of IL-27 in the serum was considerably lower in patients with PDR compared to the control group (Yan et al. 2018).

Il-35 in DR

Th17 cells play a role in controlling inflammatory processes and are involved in the development of DR by influencing the activity of IL-17. IL-35, an anti-inflammatory substance, has a detrimental effect on the expression of IL-17 and the development of Th17 cells (Li et al. 2012). *Yan* et al. (Yan et al. 2022) demonstrated that IL-35 was decreased, whereas IL-17 was increased, in peripheral blood mononuclear cells (PBMCs) of individuals with PDR. Furthermore, immunofluorescence investigation revealed an increased occurrence of Th17 cells in the PBMCs of individuals with PDR. Th17 differentiation is heavily influenced by the regulators ROR γt and ROR α. These regulators have garnered attention as possible targets for diseases associated with Th17 cells (Castro et al. 2017). The absence of ROR γt and ROR α led to the elimination of Th17 cell development (Yang et al. 2008). IL-35 has been documented to decrease the expression of ROR γt and ROR α and suppress the frequency of

Th 17 cells (Okada et al. 2017). Thus, IL-35 inhibited the development of Th17 cells and decreased the production of IL-17 by suppressing the expression of ROR γt and ROR α, thereby contributing to the reduction of PDR. Furthermore, the process of angiogenesis, which involves the breakdown of the basement membrane and the production of capillary tubes, has a role in inflammatory reactions and facilitates the progression of PDR (Rübsam et al. 2018).

IL-12 family targeting in diabetes

The IL-12 family cytokines, which are crucial cytokines for immune regulation, have demonstrated significant potential in controlling inflammation.

IL-12 and IL-23 targeting

Exciting findings have been achieved in animal studies exploring the therapeutic possibilities of Synthekines for managing diabetes. More precisely, the combination of two components, IL-12p40 and IL-12p28, from the IL-12 family of cytokines, known as scIL-Y, showed efficacy in preventing the development of diabetes in non-obese diabetic (NOD) mice (Flores et al. 2015). Drugs that bind to the subunits shared by IL-12 family cytokines can impede the activation of their corresponding receptors on immune cells. The IL-12 family cytokines share the common feature of stimulating the JAK-STAT pathways. Baricitinib, a JAK2 inhibitor, has demonstrated the ability to hinder the process of Th1 differentiation by blocking IL-12 stimulation and Th17 differentiation by blocking IL-23 stimulation (Kubo et al. 2018). Baricitinib is now undergoing clinical trials to evaluate its effectiveness in treating newly diagnosed individuals with T1DM (NCT04774224) (Waibel et al. 2022). One alternative method is to hinder the creation of IL-12 subunits, specifically IL-12p35 and IL-12p40, by utilizing Apilimod (STA-5326). This compound prevents the movement of C-Rel, a protein that plays a role in the NF-κB signaling pathway, from the cytoplasm to the nucleus (Billich 2007). Through

Table 1 Targeting of IL-12 family of cytokines in diabetes

IL-12 family	Platform	Component	Function	Outcome
IL-12 and IL-23	Cytokines engineering	scIL-Y	Fusion of IL-12p40 and IL-12p28	Prevents the onset of diabetes
	Drug therapy	Baricitinib	Inhibit Th1 and Th17 differentiation	It is s being tested in a clinical trial for newly-onset diabetes patients
	Drug therapy	Apilimod	Blocks the production of IL-12 subunits	Anti-inflammatory effects
	Drug therapy	Empagliflozin	Induces autophagy in liver macrophages as IL-23 source	Improves NAFLD associated with T2DM
	Drug therapy	Ustekinumab	Interrupts the signaling pathway of IL-12 and IL-23	Improve inflammation in islets of patients with diabetes
	Drug therapy	Lisofylline	Suppresses the phosphorylation of STAT4	Effective for T1DM patients
	Drug therapy	Sitagliptin	Decreases the circulating Th17 cells	Effective for Newly Diagnosed T2DM patients
	Drug therapy	OLL2712	Enhances the activity of TLR-2 and decreases IL-12 and IL-23 production	Anti-inflammatory effects
IL-27 and IL-35	Cell therapy	Modifying bone marrow-derived DCs	Decreases IL-27 production	Inhibits the secretion of islet-specific antibodies
	Cell therapy	Spleen DC cells transfected with the single-chain IL-35Ig gene	Excessive IL-35	Reduces the pro-inflammatory immune cells around the islet β cells
	Gut microbiota	Clostridium Faecalibacterium prausnitzii	Stimulates IL-27 secretion and promotes IL-10 production	Reduces inflammation in the islets
	Gut microbiota	Intestinal bacteria	Induces intestinal B cells to secrete IL-35	prevents the development of T2DM
	Drug therapy	TLR-2 inhibitors	Inhibits the activation of TLR-2	Alleviates islet inflammation
	Gene therapy	AAV8mIP-IL-35	Reduces the T cells in the islets	Decreases levels of pro-inflammatory factors in the islets

DC dendritic cells; *NAFLD* non-alcoholic fatty liver disease, *TLR-2* toll like receptor 2; *T1DM* Type 1 diabetes; *T2DM* Type 2 diabetes

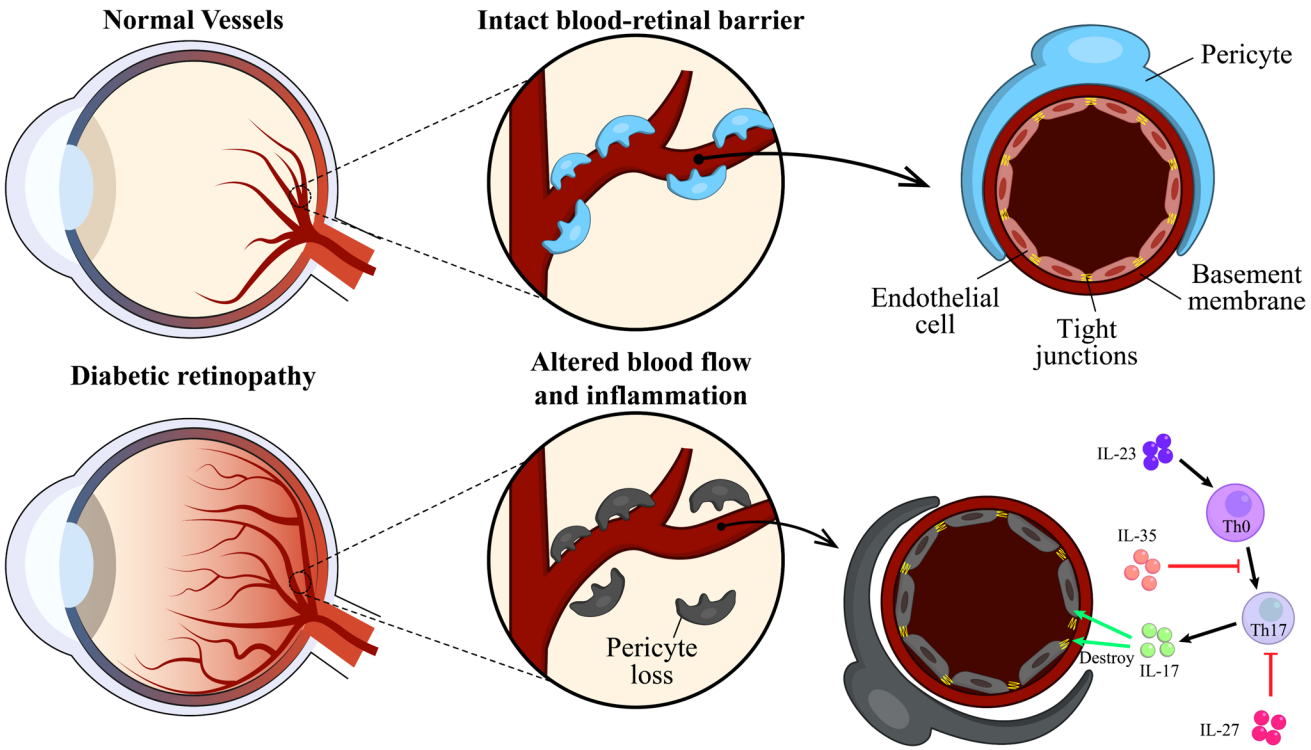

Fig. 2 The role of IL-12 family cytokines in DR. During the development of DR (diabetic retinopathy), IL-23 stimulates the release of IL-17 by Th17 cells in the retina. The interaction between IL-23 and IL-17 leads to the degradation of the internal blood-retinal barrier and the disruption of the tight retinal pigment epithelium. IL-35 suppresses the synthesis of IL-17 by Th17 cells, hence reducing proliferative DR. The precise influence of IL-27 on DR remains uncertain, however certain studies indicate that it could potentially exert a suppressive impact on Th17 function

the stimulation of autophagy in liver macrophages, which play a crucial role in producing IL-23, Empagliflozin has demonstrated its ability to enhance non-alcoholic fatty liver disease (NAFLD) linked to T2DM (Meng et al. 2021). Ustekinumab is an example of one of these drugs. Its mode of action disrupts the downstream signaling pathway of IL-12 and IL-23 when combined with IL-12p40. Through extensive animal experiments, the potential of Ustekinumab as a treatment for diabetes has been shown (Fujihira et al. 2000). In addition, a phase I clinical trial (NCT02117765) discovered that Ustekinumab effectively reduced inflammation in the islets of individuals with T1DM when given through subcutaneous administration (Marwaha et al. 2022). In 2002, the effectiveness of Lisofylline, an anti-inflammatory agent, for T1DM therapy was first reported. In 2002, Lisofylline, an anti-inflammatory agent, was found to be effective in treating T1DM (Yang et al. 2002). Lisofylline functions by decreasing the process of phosphorylation of STAT4, thereby impeding the IL-12 signaling pathway (Yang et al. 2002). Sitagliptin, in contrast, diminishes the generation of IL-23 by reducing the presence of circulating Th17 cells (Rezaeepoor et al. 2020). Lactobacillus plantarum OLL2712 boosts the function of toll like receptor (TLR)-2 and decreases the production of IL-12 and IL-23 from DC generated from bone marrow (Toshimitsu et al. 2017).

IL-27 and IL-35 targeting

Enhancing the expression of autoimmune regulators (AIRE) in bone marrow-derived DCs can reduce the production of IL-27, hence inhibiting the release of antibodies specific to the islets (Zou et al. 2021). An important connection between gut microbiota and diabetes is the involvement of IL-12 family cytokines, which play a critical role as intermediates. The probiotic Clostridium Faecalibacterium prausnitzii has been discovered to induce the secretion of IL-27 by DC and facilitate the synthesis of IL-10 by regulatory T cells, so significantly boosting the body's anti-inflammatory response. This discovery has the potential to have an impact on the reduction of inflammation in the islets (Alameddine et al. 2019). It is worth noting that TLR-2 inhibitors have demonstrated the ability to decrease IL-27 production and provide relief from islet inflammation (Zamani et al. 2015). Injecting NOD mice with an adeno-associated virus vector (AAV8mIP-IL-35) that targets islet β cells and contains the

IL-35 transgene leads to a reduction in $CD4^+$ and $CD8^+$ T cells specifically in the islets. This reduction in T cells results in decreased levels of pro-inflammatory molecules such as IFN-γ and TNF-α (Manzoor et al. 2017). Another potential approach being considered is the alteration of DCs to induce tolerant phenotypes. The introduction of the single-chain IL-35Ig fusion gene into spleen DC cells has demonstrated encouraging results in decreasing the presence of pro-inflammatory immune cells in the vicinity of islet β cells (Mondanelli et al. 2015). The gut microbiota generates a metabolite that stimulates the secretion of IL-35 by intestinal B cells, particularly in the presence of a high-fat diet. The release of IL-35 aids in inhibiting inflammation and safeguards against the onset of T2DM (Su et al. 2022). The main findings of the aforementioned investigations have been shown in Table 1.

Conclusion

The dysregulation of IL-12 family cytokines is responsible for the imbalance between pro- and anti-inflammation in islet β cells. Th17 cells contribute to the development of DR. The primary role of IL-12 family cytokines is to regulate the activity of Th17 cells and they also indirectly contribute to the process of immune-mediated tissue damage and repair. Th17 cells in the retina release IL-17 in response to IL-23 when DR develops. The tight retinal pigment epithelium and the internal blood-retinal barrier are being destroyed as a result of this interaction between IL-23 and IL-17. On the other hand, IL-35 reduces proliferative DR by inhibiting Th17 cells' RORα and RPRγt pathways, which prevents the generation of IL-17. The precise influence of IL-27 on DR remains uncertain, but several studies indicate that it may exert a suppressive effect on Th17 function (Fig. 2). Fascinatingly, while IL-23 and IL-12 have the identical component IL-12p40, the amounts of IL-12 in the aqueous humor have no bearing on DR. This suggests that the development of IL-23-mediated drug resistance may mainly rely on the signaling pathway triggered by the IL-23p19 subunit. Targeting IL-12 family cytokines not only provides the benefits of reducing inflammation in the islets but also enhances the treatment of DR. Therefore, directing efforts towards IL-12 family cytokines holds great promise for the treatment of diabetes. Additional research is required to address the current obstacles and further the field of targeting IL-12 family cytokine for DR therapy.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate It is not applicable.

Human ethics It is not applicable.

Consent for publication It is not applicable.

Competing interests The authors declare no competing interests.

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