

Original Article

Interleukin-33 and interleukin-10 expression in proliferative diabetic retinopathy

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Abstract

Diabetic retinopathy is associated with immune dysregulation driven by chronic hyperglycemia. The role of cytokine balance in its progression remains incompletely understood. To evaluate IL-33 and IL-10 levels and their ratios in patients with diabetic retinopathy depending on disease stage and metabolic control. Patients with proliferative and non-proliferative diabetic retinopathy were stratified by compensated and decompensated diabetes. IL-33 and IL-10 concentrations were measured by ELISA, and IL-33/IL-10 and IL-10/IL-33 ratios were calculated. IL-33 levels did not differ significantly between groups ($p > 0.05$), although a decreasing trend was observed in non-proliferative diabetic retinopathy with compensated diabetes. IL-10 levels were significantly higher in non-proliferative diabetic retinopathy compared with proliferative ($p < 0.05$). The IL-33/IL-10 ratio was increased in proliferative, indicating higher pro-inflammatory potential, while it was reduced in non-proliferative diabetic retinopathy with decompensated diabetes. Conversely, the IL-10/IL-33 ratio was elevated in decompensated diabetes regardless of retinopathy stage ($p < 0.05$). Cytokine balance between IL-33 and IL-10 depends on both disease stage and metabolic control. IL-10 may exhibit context-dependent pro-inflammatory effects in decompensated diabetes. Cytokine ratios may serve as potential biomarkers of immune dysregulation in diabetic retinopathy.

Keywords: diabetic retinopathy, IL-33, IL-10, cytokines, inflammation

Introduction

One of the most serious complications of diabetes mellitus is diabetic retinopathy, which ranks among the leading causes of visual impairment and blindness worldwide [1, 2]. The pathogenesis of diabetic retinopathy is associated with the toxic effects of hyperglycemia [3–5]. In the early stages, patients may have no complaints, symptoms, or clinical signs; however, focal retinal abnormalities, vitreous and retinal detachment, and partial or complete loss of vision can develop rapidly [6–8].

Proliferative diabetic retinopathy (PDR) is the most severe and advanced stage of diabetic retinal disease.

It is characterized by retinal ischemia-induced pathological growth of new, fragile blood vessels into the retina and vitreous body. This process leads to vitreous hemorrhage and retinal detachment and may ultimately result in complete blindness. PDR is a serious complication of diabetes mellitus that requires prompt treatment [9, 10].

Diabetes mellitus induces vascular dysfunction and pathological alterations within the retinal layers. In diabetic retinopathy, reduced ocular blood flow leads to tissue hypoxia. This oxygen deficiency stimulates pathological neovascularization, resulting in the growth of new vessels that are abnormally thin and fragile. Consequently, these vessels are prone to recurrent



intraocular hemorrhages. Collectively, these processes compromise retinal integrity and drive the progressive deterioration of visual function [11].

Diabetic retinopathy develops gradually. Depending on the extent of pathological changes in the retinal vasculature, several stages of the disease are distinguished [12, 13].

Non-proliferative diabetic retinopathy is the initial stage. At this stage, retinal blood vessels become thinned, dilated (with the formation of microaneurysms), and fragile, resulting in frequent hemorrhages. The development of retinal edema is also characteristic of this stage.

As diabetic retinopathy advances, it enters the pre-proliferative stage, characterized by more pronounced ocular changes. Retinal hemorrhages become increasingly frequent, and in certain regions, blood flow may be completely obstructed. The resulting ischemia deprives retinal cells of adequate oxygen and nutrients, causing functional impairment and accelerating the deterioration of visual acuity.

At the third stage, proliferative diabetic retinopathy, insufficient retinal perfusion triggers the growth of very thin, fragile new blood vessels. These newly formed vessels give rise to fibrous (scar) tissue, which can cause retinal detachment and subsequent vision loss.

Importantly, both metabolic and immunological factors play significant roles in the onset and progression of diabetic retinopathy and its advanced stages [14].

Purpose of the study was to elucidate the pathogenetic roles of interleukin-33 (IL-33) and interleukin-10 (IL-10) in the development of diabetic retinopathy. By clarifying their contributions to disease mechanisms, the research seeks to improve diagnostic strategies, support the prevention of complications, and reduce the risk of disease progression.

Material and methods

The study included 70 patients who received treatment at the Medical Center LLC "Eye Health Center". Patients were selected based on clinical data and were aged 35–65 years (mean age 46.0 ± 2.0 years), with a male-to-female ratio of 1:1. Patients were stratified into groups according to the level of diabetes mellitus compensation and the presence of retinal proliferation in diabetic retinopathy. Group 1 consisted of 20 patients with verified proliferative diabetic retinopathy and decompensated diabetes mellitus. Group 2 included 17 patients with verified proliferative diabetic retinopathy

and compensated diabetes mellitus. Group 3 comprised 16 patients with non-proliferative diabetic retinopathy and decompensated diabetes mellitus. Group 4 included 17 patients with non-proliferative diabetic retinopathy and compensated diabetes mellitus. During scheduled surgical procedures, samples of aqueous humor from the anterior chamber were collected by passive outflow. Concentrations of IL-33 and IL-10 in the aqueous humor were measured using a commercially available *in vitro* enzyme-linked immunosorbent assay (ELISA) kit (BioSource) [15].

Statistical analysis was performed using STATISTICA software, version 8.0 (StatSoft, USA). Data are presented as mean $\pm$ standard deviation. Statistical significance was defined as $p < 0.05$ [16].

Results

Examination of patients with diabetic retinopathy revealed complex alterations in the concentrations of interleukin-33 (IL-33) and interleukin-10 (IL-10) within the aqueous humor. These changes varied according to the degree of diabetes mellitus compensation and the presence of retinal proliferation. The detailed results of the observed interleukin alterations are summarized in Table 1.

IL-33 concentrations did not differ significantly among the study groups ($p > 0.05$), although a trend toward reduction was noted in Group 4 compared with the others. This finding suggests that in non-proliferative diabetic retinopathy (NPDR) with compensated diabetes mellitus, there is a tendency toward diminished pro-inflammatory activity.

IL-10 levels in patients with NPDR and decompensated diabetes mellitus were 28% higher than in patients with proliferative diabetic retinopathy (PDR) and decompensated diabetes, and 36% higher than in patients with PDR and compensated diabetes ($p < 0.05$). In addition, IL-10 levels in patients with NPDR and compensated diabetes were 23% higher than in patients with PDR and compensated diabetes ($p < 0.05$). These findings indicate activation of anti-inflammatory mechanisms in NPDR compared with PDR.

The IL-33/IL-10 ratio in patients with PDR and decompensated diabetes was 35% higher than in patients without retinal proliferation and decompensated diabetes ($p < 0.05$). In patients with PDR and compensated diabetes, the ratio was 52% higher than in patients without proliferation and decompensated diabetes ($p < 0.05$). Among NPDR patients, the ratio in the compensated

Table 1: Changes in IL-33 and IL-10 levels in the aqueous humor depending on the presence of retinal proliferation in diabetic retinopathy, stratified by diabetes mellitus compensation status (n=70).

Patient groups/ parameters	Group 1	Group 2	Group 3	Group 4
IL 33 (pg/ml)	8.69±0.70	8.64±0.70	8.16±0.70	7.48±0.70
IL 10 (pg/ml)	20.43±0.10	19.17±0.20 *	26.11±0.90 *, #	23.56±0.80 *, #, &
IL 33/IL 10	0.42±0.01	0.47±0.01	0.31±0.04 *, #	0.49±0.05 &
IL 10/IL 33	3.02±0.20	2.21±0.20 *	3.2±0.20 #	2.08±0.09 *, &

Note: * – the probability of differences compared with the control group 1 ($p < 0.05$); # – the probability of differences compared with the control group 2 ($p < 0.05$); & – the probability of differences compared with the control group 3 ($p < 0.05$).

diabetes subgroup exceeded that of the decompensated diabetes subgroup by 58%. The ratio was significantly reduced in NPDR patients with decompensated diabetes, reflecting a decrease in pro-inflammatory potential in this group.

The IL-10/IL-33 ratio in patients with proliferative diabetic retinopathy (PDR) and decompensated diabetes mellitus was 37% higher than in patients with compensated diabetes. In patients with non-proliferative diabetic retinopathy (NPDR) and decompensated diabetes, the ratio was 54% higher than in patients with compensated diabetes ($p < 0.05$). This parameter was significantly elevated in patients with decompensated diabetes regardless of the presence of retinal proliferation. These findings suggest that the pleiotropic properties of IL-10 may manifest in this context, with an associated increase in pro-inflammatory potential in decompensated diabetes mellitus.

Discussion

The present study provides evidence of a complex immunoregulatory balance between IL-33 and IL-10 in diabetic retinopathy, which appears to depend both on the stage of retinal damage and the degree of metabolic compensation.

The observed trend toward reduced IL-33 levels in NPDR with compensated diabetes may indicate decreased pro-inflammatory activity at earlier stages of diabetic retinopathy. Elevated IL-10 levels in NPDR compared with PDR suggest activation of anti-inflammatory mechanisms in non-proliferative stages of the disease. However, the increased IL-10/IL-33 ratio in decompensated diabetes, irrespective of retinal proliferation, may reflect the complex and po-

tentially pro-inflammatory role of IL-10 under certain conditions.

IL-10 is a pleiotropic cytokine known to exhibit both pro- and anti-inflammatory effects. Numerous studies have demonstrated that IL-10 can play a significant role in allergic reactions and exert pro-inflammatory activity on mast cells and other immune cells [17–19]. The pleiotropic nature of IL-10 is reflected not only in its pro-inflammatory action on IgE-mediated mast cell activation but also in its ability to enhance IL-33-induced responses [20].

Interleukin-33 (IL-33), a member of the IL-1 cytokine family, was initially identified as an inducer of type 2 immune responses through activation of T helper 2 (Th2) cells and mast cells. Subsequent studies have demonstrated that IL-33 also stimulates group 2 innate lymphoid cells (ILC2), regulatory T (Treg) cells, Th1 cells, CD8+ T cells, and natural killer (NK) cells. This pleiotropic activity underlies its involvement in tissue and metabolic homeostasis, infection, inflammation, cancer, and central nervous system disorders. Broad expression in stromal and barrier tissues highlights IL-33 as a ubiquitous immune modulator orchestrating type 1, type 2, and regulatory responses. Moreover, IL-33 contributes to cytokine networks that not only facilitate pathogen clearance but also promote tissue repair mediated by ILC2 and Treg cells. Modulation of IL-33 activity, either through activation or inhibition, represents a promising therapeutic strategy for maintaining immune homeostasis and mitigating infectious and inflammatory diseases [21, 22].

Initially, IL-10 was identified as a stimulator of mast cells. IL-10 functions as a potent costimulator of mast cell responses, capable of priming mast cells for IL-33-induced activation, while its effects do not depend on endogenous IL-33 signaling [23, 24]. This

indicates that although IL-10 can promote mast cell degranulation independently of IL-33 signaling, endogenous IL-33 may modulate certain of its effects.

Interleukin-10 (IL-10) not only facilitates IgE-dependent mast cell responses but also co-stimulates IL-33-activated mast cells by enhancing ST2 receptor sensitivity. These findings suggest that the pro-inflammatory effects of IL-10 on mast cells may be broad and not limited to IgE-allergen cross-linking [25, 26].

Recent studies further indicate that IL-10 is essential for the development of allergen-specific Th2 cells and for the activation of T-cell effector functions. In addition, B cell-derived IL-10 has been shown to contribute to allergic sensitization in asthma [27].

Furthermore, IL-10 can enhance cytokine secretion, degranulation, mMCP-1 release, and proliferation in mast cells. Collectively, these data indicate that endogenous IL-33 signaling in mast cells is not necessary for the pro-inflammatory actions of IL-10 on mast cell activation or function [28]. Taken together, these findings support the concept that IL-10 may exert dual effects in diabetic retinopathy, acting as both an anti-inflammatory and a context-dependent pro-inflammatory mediator, particularly in conditions of metabolic decompensation.

Conclusion

As result, in non-proliferative diabetic retinopathy (NPDR) with compensated diabetes mellitus, there is a tendency toward reduced pro-inflammatory potential, as reflected by a trend toward lower IL-33 levels in the aqueous humor. Activation of anti-inflammatory mechanisms is observed in NPDR compared with proliferative diabetic retinopathy (PDR), demonstrated by increased IL-10 levels in the aqueous humor. The IL-33/IL-10 ratio is significantly decreased in NPDR patients with decompensated diabetes, indicating reduced pro-inflammatory potential in this group. Conversely, the IL-10/IL-33 ratio is significantly elevated in patients with decompensated diabetes, independent of the presence of retinal proliferation. These findings suggest that the pleiotropic properties of IL-10 may be manifested, contributing to increased pro-inflammatory potential in decompensated diabetes mellitus.

Conflict of interest

The authors declare no conflict of interest.

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