

# The two sides of cytokine signaling and glaucomatous optic neuropathy

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**Abstract** The mechanistic study of glaucoma pathogenesis has shifted to seeking to understand the effects of immune responses on retinal ganglion cell damage and protection. Cytokines are the hormonal factors that mediate most of the biological effects in both the immune and nonimmune systems. CD4-expressing T helper cells are a major source of cytokine production and regulation. Type 1 helper T (Th1) cells are characterized by the production of proinflammatory cytokines such as interferon-gamma, interleukin (IL)-2, IL-12, IL-23, and tumor necrosis factor-alpha while type 2 helper T (Th2) cells are characterized by the production of IL-4, IL-5, IL-6, and IL-10. The balance of Th1/Th2 cytokine production influences many pathological processes and plays both causative and protective roles in neuron damages. Growing evidence indicates that imbalances of Th1/Th2 cytokine production are involved in neural damage or protection in many neurological diseases. In this review, we discuss the possible roles of Th1/Th2 cytokine production and imbalance of Th1/Th2 cytokines in retina, especially glaucomatous optic neuropathy.

**Keywords** Glaucoma · Cytokines · Neuropathy · Neuroprotection

## Introduction

Glaucoma is one of the leading causes of vision loss as a result of impairment of retina ganglion cells (RGCs). Although lowering of intraocular pressure (IOP) is currently the method of choice for the treatment of glaucoma, glaucomatous neuropathy may still develop and lead to loss of vision [1]. There are no other effective therapeutic and/or preventive interventions. Other risk factors, besides the increase in IOP, have also been closely associated with degeneration of RGCs. These include ischemia, glutamate excitotoxic stress, high reactive oxygen species production, and the loss of mitochondrial function. Recent mechanistic studies have focused on immunological changes during glaucomatous pathogenesis and possible preventive therapies [2]. The major targets of interest are cytokines and their functions in damage or protection of retinal ganglion cells. Recent advances in the studies of glaucoma or RGCs reveal that cytokines are a possible factor in the pathogenesis of glaucoma and may regulate RGCs survival or death. Here, we will review the roles of both type 1 helper T (Th1)-derived and type 2 helper T (Th2)-derived cytokines such as interferon-gamma (IFN- $\gamma$ ), interleukin (IL)-2, IL-12, IL-23, tumor necrosis factor (TNF)-alpha, IL-4, IL-6, and IL-10 in damage or protection of RGCs and the possible relationship of these cytokines with human glaucoma.

## Cytokines from T helper cells and neuronal diseases

CD4-expressing T helper cells develop into two major subtypes of cells known as Th1 and Th2 cells [3, 4]. The two subtypes produce different sets of cytokines, which are involved in many physiological and pathological processes

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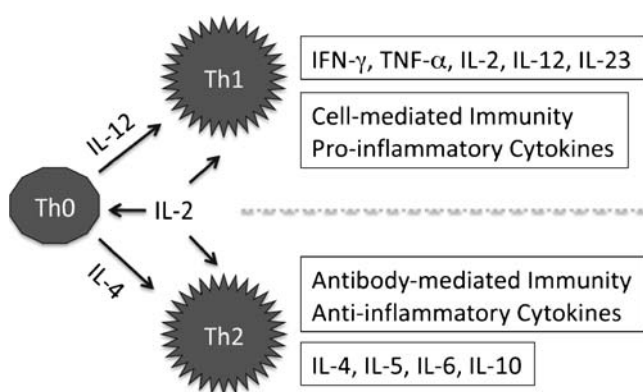
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in human. It has been considered that Th1 cells are characterized by the production of proinflammatory cytokines such as IFN- $\gamma$ , IL-2, IL-12, IL-23, and TNF-alpha while Th2 cells are characterized by the production of IL-4, IL-5, IL-6, and IL-10 (Fig. 1). We now know that this classification is an oversimplification and that the effects of cytokines are far more complicated in the tissue and cells in response to stresses.

The functions of T helper cytokines have been extensively studied in a number of different conditions [5, 6], including neural damage and protection. In the autoimmune central nervous system disease multiple sclerosis and its animal model experimental autoimmune encephalomyelitis (EAE), T helper lymphocytes play a crucial role in inflammatory tissue damage to the neurons [7]. Cytokines, such as interferon-gamma, are also involved in neuron damage resulting from nonautoimmune conditions such as ischemia [8] and a number of neurodegenerative diseases [9]. In contrast, T helper cytokines can also play significant roles in protection against neural cell death [10], indicating the two sides of cytokines functions in neural damage and protection.

### Cytokines play essential roles in retina neural damage

The causes of RGC death have been studied in many model systems in vitro and in vivo, including glutamate or *N*-methyl-D-aspartate (NMDA) ocular injection and cytotoxicity, increase of intraocular pressure (IOP), ischemia/reperfusion (I/R), axotomy of optic nerves, optic nerve crush, experimental autoimmune uveoretinitis (EAU), EAE, and serum deprivation in cultured neural cells. Evidences in the past decade reveal that cytokines produced from both Th1 and Th2 cells were involved in RGCs death in



**Fig. 1** Th1 and Th2 cytokine signaling and T helper cells. Th1 and Th2 cells can be induced from Th0 cells by IL-12 and IL-4, respectively. IL-2 promotes Th0 cell and also Th1 and Th2 cell proliferation. The major cytokines produced by Th1 or Th2 cells are listed

response to the insults above. The detailed information is listed in Table 1.

Increased levels of Th1 cytokines, such as IFN-gamma [11], IL-1 [12], IL-2 [13], IL-17 [13], and TNF-alpha [11, 13–18] were reported to be significantly associated with retina and RGC damage caused by distinct insults in vivo and in vitro, while IL-6 is the only Th2 cytokine that has been reported to show similar results [11, 19]. Most work has been focused on the actions of TNF-alpha. TNF-alpha was first found elevated in retina following increase of hydrostatic pressure. RGC apoptosis rates were attenuated approximately 66% by neutralizing antibody against TNF-alpha [14]. An increase of TNF-alpha expression has been associated with the most severely damaged optic nerve heads from human glaucomas [15], indicating that TNF-alpha contributes to the progression of optic nerve degeneration in this disease. Later work has confirmed that TNF-alpha is a critical cytokine in RGC damage caused by different insults, such as EAU [13], optic nerve crush [20], and serum withdrawal [11] in vitro. Direct ocular injection of TNF-alpha [16] in vivo also results in RGC death.

The Th2 cytokine IL-6 is a member of a large cytokine family that triggers the gp130 receptor and activates signal transducer and activator of transcription 1 (STAT1) and STAT3 in response to stress [21]. IL-6 has been considered a neurotrophic factor in protection of neurons from damage in many neural degenerative conditions [22, 23]. While IL-6 can play a neuroprotective role in retina, as described below, it has been shown to be involved in retina or RGC damage under a number of different conditions [11, 19]. In a study of Rho-kinase inhibition on retinal cell survival, the reduction of proinflammatory cytokines including TNF-alpha, IFN-gamma, and IL-6 likely contributed to the significantly lower toxicity on retina explants [11]. Other evidence showed that IL-6 deficiency could increase the rate of RGC survival during the first 24 h after optic nerve injury [19], indicating the complexity of IL-6 in both retina damage and protection.

IL-17 is produced by Th17 cells. This cell type can be stimulated to expand by IL-2 and IL-23. Besides IL-17 production, Th17 cells also secrete IL-6 and TNF-alpha and now are recognized as causative agents of several diseases previously attributed to Th1 cells, such as chronic inflammatory bowel disease [24]. IL-17 is an agent that contributes to retina damage in an EAU model [13]. Retinal damage in this model can be reduced by a neutralized by specific anti-IL-17 antibody.

### Cytokines in retina neural protection

A significant number of studies on cytokine protection of neurons have been performed and these numbers are

**Table 1** Cytokines in retina neural damages

Cytokines	Systems	Methods	Cell types	Insults	Results	Author	Year
IFN-g	Animals	In vitro	Retina explants	Serum deprivation	RGC damage	Tura	2009
IL-1b	Animals	In vitro	RGC	Survival	RGC damage	Abcouwer	2008
	Animals	In vivo	RGC	NMDA	RGC damage	Kitaoka	2007
	Animals	In vivo	RGC	I/R	RGC damage	Zhang	2004
	Animals	In vivo	RGC	I/R	RGC damage	Yoneda	2001
	Animals	In vivo	Retina	EAU	Retina damage	Amadi-Obi	2007
IL-6	Animals	In vitro	Retina explants	Serum deprivation	RGC damage	Tura	2009
	Animals	In vivo	RGC	Glutamate toxicity	RGC damage	Fisher	2001
IL-17	Animals	In vivo	Retina	EAU	Retina damage	Amadi-Obi	2007
TNF-a	Animals	In vivo	Retina	EAU	Retina damage	Amadi-Obi	2007
	Animals	In vitro	Retina	Serum deprivation	RGC damage	Tura	2009
	Animals	In vitro	Retina explants	Culture	RGC damage	Hong	2009
	Animals	In vivo	RGC	IOP	RGC damage	Nakazawa	2006
	Animals	In vivo	RGC	TNF-a injection	RGC damage	Kitaoka	2006
	Animals	In vitro	RGC	Survival	RGC damage	Tezel	2000
	Human	In vivo	Optic nerve	Expression	Optic nerve damage	Yuan	2000
	Animals	In vivo	RGC	Optic nerve crush	RGC damage	Tezel	2004

increasing year after year. As with the studies on neural damage, many kinds of insults have been used to test the roles of cytokines in protection of retinal neurons both in vivo and in vitro. In an EAU model, IL-27 and IFN-gamma have been shown to inhibit IL-2-induced expansion of IL-17, produced by Th17 cells, and to ameliorate retina damage by EAU [13]. This indicates that Th1 cytokines such as IFN-gamma could have protective roles on neurons under certain circumstances. In a similar case, IL-1, a mediator of neural injury, has a protective role by preventing neuronal cell death from glutamate neurotoxicity [25]. TNF-alpha, a clear mediator for neural damages, also can prevent secondary death of RGCs after axotomy of the optic nerve in vivo [26].

Th2 cytokines such as IL-4, IL-6, and IL-10 show neuroprotective functions in many different types of RGC injury such as optic nerve axotomy [27] and ischemia/reperfusion [28] in vivo and serum deprivation [29] in vitro (Table 2). Intraocular administration of adenoviral vectors encoding IL-10 and IL-4 may help prevent neurodegeneration caused by the activation of glial cells postaxotomy [27]. IL-6 is upregulated after retinal ischemia/reperfusion injury and its expression by microglia/phagocytic cells may protect neurons in the RGC layer from this insult. Exogenously added IL-6 protects the inner retina after ischemia/reperfusion injury [28]. Our studies on STAT3 [30], the downstream effector of IL-6 and IL-10, have shown that STAT3 activation is essential for RGC survival and persistent activation of STAT3 by neurotrophic factors and cytokines provides strong neuroprotection. This suggests that STAT3 activation will be an effective strategy in a number of chronic retinal diseases.

Cell-mediated immunity and inflammatory responses are also thought to be involved in neural damage and protection. There is evidence that inflammatory leukocyte recruitment can play a causative role in RGC cell death in NMDA-induced excitotoxicity. Anti-inflammatory agents improved RGC survival [31], suggesting that increases in inflammatory responses can lead to neural damage. On the other hand, an evoked T cell-dependent response has been shown to help neuron survival [32]. It was reported that using a single low dose of whole-body or lymphoid-organ gamma-irradiation significantly increased T cell-dependent responses, and this improved the spontaneous recovery of neurodegenerative conditions caused by injection of a toxic dose of intraocular glutamate [33]. Animals with severe immune deficiency or deprived of mature T cells were unable to benefit from this treatment [33], suggesting that this neuroprotection is immune mediated.

### Cytokines in glaucomatous optic neuropathy

Alterations of cytokines in human glaucoma have been studied for over three decades. Fibroblasts from Tenon's capsule are cellular components that contribute to unsuccessful glaucoma filtration surgery. Using the materials from Tenon's capsule [34], many studies have been performed with examination of IFN signaling including IFN-alpha, IFN-beta, and IFN-gamma. As shown in Table 3, both IFN-alpha2b [35] and IFN-gamma [36] inhibit the fibroblast proliferation from Tenon's capsule in vitro. More recently, IL-1 has been linked to an increase in extracellular

**Table 2** Cytokines in retina neural protection

Cytokines	Systems	Methods	Cell types	Insults	Results	Author	Year
IFN-b1a	Animals	In vivo	Optic nerve	EAE	Optic nerve protection	Sättler	2006
IFN-b1b	Animals	In vivo	RGC	EAE	RGC protection	Maier	2006
IFN-g	Animals	In vivo/in vitro	Retina	EUA	Retina protection	Amadi-Obi	2007
IL-1	Animals	In vitro	Glail cell	Glutamate toxicity	RGC protection	Namekata	2008
IL-1b	Animals	In vivo	RGC	Axotomy	RGC protection	Diem	2003
IL-2	Animals	In vitro	RGC	Survival	RGC protection	Sholl-Franco	2001
IL-4	Animals	In vivo	RGC	Axotomy	RGC protection	Koeberle	2004
	Animals	In vitro	RGC	Survival	RGC protection	Sholl-Franco	2001
IL-6	Animals	In vivo	RGC	I/R	RGC protection	Sanchez	2003
	Animals	In vitro	RGC	Survival	RGC protection	Mendonça Torres	2001
IL-10	Animals	In vivo	RGC	Axotomy	RGC protection	Koeberle	2004
	Animals	In vitro	RGC	Serum deprivation	RGC protection	Boyd	2003
IL-27	Animals	In vivo	Retina	EAU	Retina protection	Amadi-Obi	2007
STAT3	Animals	In vitro/in vivo	RGC	I/R and Glutamate toxicity	RGC protection	Zhang	2008
TNF-a	Animals	In vivo	RGC	Axotomy	RGC protection	Diem	2001
Leukocyte recruitment	Animals	In vivo	RGC	NMDA	RGC protection	Nakazawa	2007
T autoimmunity	Animals	In vivo	RGC	Optic nerve crush	RGC protection	Kipnis	2004
T autoimmunity	Animals	In vivo	RGC	Optic nerve crush	RGC protection	Yoles	2001

matrix metalloproteinase-3 (MMP-3). IL-1alpha, and IL-1beta each individually can increase MMP-3 expression in the trabecular meshwork [37], and this affected the aqueous humor outflow facility. TNF-alpha, in combination with IL-1alpha or IL-1beta, produced intense synergistic increases

in MMP-3 and MMP-12 but not in MMP-9. These results suggested a relationship between cytokines and glaucoma pathogenesis.

Recent work has focused on the relationship between cytokine production and glaucomatous optic neuropathy.

**Table 3** Cytokines in human glaucoma studies

Cytokines	Systems	Methods	Cell types	Results	Author	Year
IFN-a2b	Human	In vitro	Tenon’s capsule fibroblasts	Inhibit cell proliferation	Gillies	1993
IFN-g	Human	In vitro	Tenon’s capsule fibroblasts	Inhibit collagen synthesis	Nguyen	1994
IFN-g	Human	In vivo	Blood serum	No change in glaucoma	Huang	unpublished
IL-1	Animals and Human	In vitro	Trabecular meshwork	Increase MMP-3 MMP-12	Kelly	2007
IL-1	Human	In vitro	Trabecular meshwork	ELAM-1	Wang	2001
IL-1	Human	In vitro	Trabecular meshwork	p38 or JNK activation	Zhang	2006
IL-2	Human	In vivo	Blood serum	No change in glaucoma	Yang	2001
IL-2	Human	In vivo	Blood serum	No change in glaucoma	Huang	unpublished
sIL-2R	Human	In vivo	Blood serum	High in glaucoma	Yang	2001
sIL-2R	Human	In vivo	Blood serum	No change in glaucoma	Huang	unpublished
IL-4	Human	In vivo	Blood serum	High in glaucoma	Huang	unpublished
IL-6	Human	In vivo	Blood serum	Low in glaucoma	Huang	unpublished
IL-10	Human	In vivo	Blood serum	High in glaucoma	Yang	2001
IL-12p40	Human	In vivo	Blood serum	High in glaucoma	Huang	unpublished
IL-12p70	Human	In vivo	Blood serum	No change in glaucoma	Huang	unpublished
IL-23	Human	In vivo	Blood serum	Low in glaucoma	Huang	unpublished
TNF-a	Animals and Human	In vivo	Trabecular meshwork	Increase MMP-3 MMP-12	Kelley	2007
TNF-a	Human	In vitro	Optic nerve	High in glaucoma	Yang	2000
TNF-a	Human	In vitro	Blood serum	Low in glaucoma	Huang	unpublished

High levels of sIL-2R and IL-10 have been found in the serum of glaucoma patients compared with their normal controls [38, 39]. An increase in CD3(+)/CD8(+) lymphocytes was also associated with glaucoma, indicating that cellular immunity plays an important role in the initiation and/or sustainment of glaucomatous optic neuropathy. Recently, we compared human serum levels of Th1 and Th2 cytokines among two stages of primary open-angle glaucoma (POAG) and nonglaucomatous controls (Huang et al., unpublished data). The results showed that patients with POAG exhibited a significant elevation of IL-4 and a significant reduction of IL-6 compared to the control group, while no significant differences in IL-4 and IL-6 levels were observed between the patients with severe optic neuropathy and the patients with mild optic neuropathy. The level of IL-12p40 was significantly increased in patients with POAG compared to controls, while the average levels of IL-23 and TNF-alpha were significantly reduced in the POAG patients groups compared with controls. (Huang et al., unpublished data).

### In conclusion

The conflicts of Th1 and Th2 cytokine status in retina neural damage and protection reflect the complexity of immune responses during glaucoma pathogenesis. Cytokines at different circumstances, or actions on different effectors such as RGC, astrocytes, microglial cells, and Müller glial cells, could result in distinct consequences. Although the accumulated evidence has already sketched an outline of the roles of cytokines in glaucoma, adding more details through both experimental and human studies on this topic is essential to help us better understand the ways in which they influence the pathogenesis of glaucoma.

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