CYTOKINES: THEIR ROLE IN UVEAL DISEASE

AIZE KIJLSTRA

Amsterdam, The Netherlands

Cytokines are small proteins (10–45 kilodaltons), that play a major role in the communication between cells throughout the body.¹ Their concentration in body fluids is mainly in the picogram range, although their concentration at the site of action may be much higher since most cytokines display their activity in the direct vicinity of their cellular source. Cytokines are generally secreted immediately after their production and exert their action after binding to specific membrane-bound receptors on the same cell (autocrine), a neighbouring cell (paracrine) or after transport via the lymphatic system or blood to a distant site (hormonal).

The cytokine network is characterised by the fact that it is pleiotropic as well as redundant. The pleiotropic aspect of the network is exemplified by the observation that one cytokine may have many different functions and the redundancy is due to the fact that many cytokines have overlapping activities.

Cytokines have been grouped into different families and include the interleukins, the interferons, the colony stimulating factors, the chemokines and the growth factors. Cytokines have also been subdivided into those involved in immunoregulation, inflammation, haematopoiesis, anti-viral activity, wound healing and angiogenesis. Many cytokines are not constitutively produced by a cell and need a stimulus to induce their synthesis. Stimuli include bacterial endotoxin (monocytes, antigen (lymphocytes), Fc and complement receptors and various cytokines within the network, whereby some stimuli act synergistically on cytokine production.

THE ROLE OF CYTOKINES IN THE REGULATION OF THE IMMUNE RESPONSE

A large number of cytokines play an essential role in dictating which types of lymphocytes or antibody

classes will be involved in the immune defence.² The cytokines interferon gamma (IFN- γ) and interleukin (IL)-12 are involved in the generation of a delayed-type hypersensitivity response (type 1 response), whereas IL-4 and IL-13 are involved in the immediate-type hypersensitivity responses by stimulating lymphocytes that regulate IgE production by B cells (type 2 response). The balance between these two types of response is critical in determining the outcome of the immune defence mechanisms employed to combat infectious disease and is also considered to be involved in the pathogenesis of autoimmune and allergic disease.

A classical example showing the balance between the type 1 and type 2 response comes from a mouse model of leishmaniasis. Mouse strains that respond to this parasitic infection with a Th2 type response die, whereas animals showing a Th1 immune response survive. Modulation of the Th2 response in these strains to a Th1 response results in protection and survival of the mice.

Th1 responses are thought to be primarily responsible for the delayed-type hypersensitivity response and are characterised by high interferon gamma and IL-2 production and a low or absent release of IL-4. The Th1 response is considered to be beneficial in the immune response against intracellular micro-organisms whereas a Th2 response is implicated in the defence against extracellular parasites. Th2 cells produce large amounts of IL-4 and IL-5 and play a key role in the IgE response. The cytokines derived from the Th2 cells deactivate macrophages and thus prevent the tissue destruction so characteristic of the Th1 response. An exaggerated Th2 response may be responsible for allergic disease and immunoglobulin-mediated autoimmunity, whereas a Th1 response causes contact hypersensitivity and autoimmune diseases such as rheumatoid arthritis and autoimmune uveitis. Several organ-specific autoimmune diseases are caused by interferon gamma producing Th1 cell and this has led to new approaches for the immunotherapy of inflammatory autoimmune diseases that are based on

From: Department Ophthalmology of the Netherlands Ophthalmic Research Institute and the Department of Ophthalmology of the Academic Medical Centre of the University of Amsterdam, The Netherlands.

Correspondence to: Professor Dr A. Kijlstra, The Netherlands Ophthalmic Research Institute, PO Box 12141, 1100 AC Amsterdam, The Netherlands. Fax: +31-206913401; e-mail: a.kijlstra@amc.uva.nl.

a deviation of the harmful Th1 response towards an immunosuppressive, more benign Th2 response.³

Although experimental evidence points to an important role of a Th1 type response in the pathogenesis of autoimmune uveitis,⁴ the evidence for such a mechanism in the pathogenesis of clinical uveitis is not very strong at present due to the lack of available ocular material from these patients. Evidence for a Th2 response in conjunctival allergic disorders is supported by the observation of a Th2 type of infiltrate in biopsy samples.⁵

Cytokines play an important role in maintaining the immunosuppressive environment of the anterior chamber. Streilein and coworkers⁶ have shown that aqueous-humour-derived factors modify professional antigen presenting cells in such a way that they are unable to generate a delayed-type hypersensitivity response against certain antigens, and have evidence that the responsible factors in aqueous include transforming growth factor beta (TGF- β). Extracts from the cornea, iris and ciliary body also exhibit as yet poorly characterised immunosuppressive activity.⁷

ROLE OF CYTOKINES DURING INTRACULAR INFLAMMATION: EXPERIMENTAL MODELS

Research concerning the role of cytokines in eye disease⁸ can be divided into five major areas. Early work concerned the injection of purified or recombinant cytokines into the eyes of experimental animals followed by an examination of the inflammatory response.^{9,10} A second area deals with the detection of cytokines in ocular fluids and tissues during various experimental and clinical ocular disorders. A further area of research for investigating the role of cytokines in ocular inflammation is to alter the course of the disease by interfering in the cytokine network. A novel approach concerns the investigation of transgenic animals which express cytokine genes under the control of eye-specific proteins or the use of knockout mice that are deficient in certain cytokines. A large area of research deals with the analysis of the *in vitro* production of various cytokines and their antagonists by isolated ocular cells. At present the retinal pigment epithelium (RPE) cell is considered to play a key role in the regulation of the ocular inflammatory response in the posterior segment of the eye. *In vitro* studies have shown that this cell is capable of producing a number of inflammatory cytokines as well as the natural antagonist IL-1-RA.¹¹⁻¹⁶

Numerous cytokines, including tumour necrosis factor (TNF), IL-1, IL-6, IL-8, IFN- γ and granulocyte macrophage colony stimulating factor (GM-CSF), have been shown to induce ocular inflammation after intraocular administration; IL-1 appears to

cause the most serious disease.¹⁷⁻²¹ In most cases, the inflammation resembles that induced by endotoxin injection and is characterised by heavy infiltration with leucocytes and a breakdown of the blood-aqueous barrier. Cytokines appear to induce ocular inflammation only when injected directly into the eye; their systemic administration has not been described to be associated with ocular inflammation and nor have patients with high circulating cytokine levels been reported to develop ocular complications.

A classical model to study the role of cytokines in ocular disease is the so-called endotoxin-induced uveitis model. In this model a systemic (footpad, intravenous or intraperitoneal) injection of bacterial lipopolysaccharide leads to an acute ocular inflammation. The disease is characterised by a marked upregulation of various inflammatory cytokines within the uveal tissue and release of cytokines into the aqueous humour.^{8,22,23}

A novel approach to understanding the role of cytokines in uveal disease involves examination of eyes from transgenic animals excessively expressing a cytokine gene, or studying models of ocular inflammation in cytokine-deficient animals. An unusual syndrome of blindness has been described in transgenic mice aberrantly expressing GM-CSF.²⁴ The increased expression of GM-CSF is associated with high expression of TNF and IL-1 by macrophages which may be held responsible for the ocular syndrome seen in these animals. Transgenic mice aberrantly expressing IL-4 have been observed to have ocular inflammation characterised by a conjunctivitis associated with heavy infiltration with eosinophils, mast cells and macrophages.²⁵

Aberrant expression of IFN- γ using the rhodopsin promoter to direct expression of IFN- γ in the retina²⁶ results in a mouse strain that develops intraocular inflammation characterised by cell infiltration, cell proliferation, loss of photoreceptors, cataract, corneal clouding and an increased expression of MHC antigens in the retina. Intraocular injection of herpes simplex virus into the eyes of these transgenic animals showed that an increased presence of IFN- γ induced a more vigorous immune response against the virus and protected the untreated eye from disease, whereas control animals developed bilateral retinitis.²⁷ Targeting an increased expression of IFN- γ in the lens also induces severe ocular abnormalities, including effects on the growth of the eye as well as an increased expression of MHC antigens in various tissues of the eye.²⁸

Targeted mutagenesis of cytokine genes has resulted in the generation of a number of mouse strains deficient in the following cytokines: IL-1, IL-2, IL-4, IL-6, IFN- γ , TNF receptor and IFN- γ receptor. These mice are particularly valuable in the unravelling of the role of various cytokines in

immunoregulation and inflammation. To date, cytokine knockout animals have scarcely been employed as tools to investigate the role of cytokines in ocular inflammation. Experiments in IFN- γ deficient mice showed that interphotoreceptor retinoid binding protein (IRBP)-induced autoimmune uveitis was not dependent on the presence of IFN- γ .²⁹ Intravitreal injection of endotoxin into the vitreous of IFN- γ knockout mice did result in a significantly lower influx of inflammatory cells compared with controls, implicating this cytokine as an important mediator in this experimental uveitis model. Future studies using the various knockout and transgenic mice in experimental models of eye disease will provide valuable information concerning the role of the cytokine network in ocular inflammation.

ROLE OF CYTOKINES IN INTRAOCULAR INFLAMMATION: CLINICAL DISEASE

The role of cytokines in the pathogenesis of clinical uveitis has been investigated by analysing aqueous or vitreous samples taken from uveitis patients for diagnostic or therapeutic purposes. Initially the studies concentrated on the detection of the inflammatory cytokines and to date an increased level of the cytokines belonging to this group such as IL-1, TNF, IL-6 and IL-8 have been detected in ocular fluids of uveitis patients and not in cataract or eye bank controls.^{30–35}

IL-1 is one of the key mediators in the cytokine network and is involved in the early steps of the inflammation pathway. IL-1 is not readily detected by enzyme immunoassays and early work showing IL-1 in ocular fluids obtained from inflamed eyes were performed using bioassays.³⁰ Recent findings indicate that IL-1 may be involved in the inflammatory response seen after cataract extraction. Evidence has been obtained that residual lens epithelial cells might play an important role in pseudophakic inflammation due to the fact that they can produce IL-1 *in vitro*.³⁶ The interaction of lens epithelial cells with the plastic intraocular lens is thought to stimulate these cells to produce IL-1, which in turn activates the production of prostaglandins, ultimately causing breakdown of the blood–ocular barrier.

IL-6 has been detected in both aqueous humour and vitreous during clinical uveitis.^{8,32,33,37} Raised IL-6 levels have also been found in aqueous humour following cataract removal, which indicates that IL-6 is also involved in post-cataract inflammation.³⁸ The appearance of IL-6 in the eye is not specific for uveitis and has also been observed in vitreous samples taken from patients with proliferative vitreoretinopathy or retinal detachment.^{33,39} As mentioned above, *in vitro* experiments indicate that the RPE cells are probably the major source of IL-6.^{11,12}

The cytokine IL-8 is an important chemoattractant and activator of neutrophils.⁴⁰ IL-8 levels are increased in approximately 50% of patients with uveitis,³⁴ and confirmation that the immunochemically detected IL-8 in the vitreous was biologically active was obtained by chemotactic assays and blocking experiments with monoclonal anti-human IL-8 antibodies. Further evidence that intraocular IL-8 was responsible for a granulocyte influx was obtained by showing a correlation between intraocular IL-8 levels and the levels of a specific granulocyte enzyme such as elastase. IL-8 is not present in normal vitreous but has also been found in proliferative vitreoretinal disorders.^{34,39,41}

Not many studies have been reported on the analysis of the cytokines belonging to the immunoregulatory group. Early work identified the presence of IL-2 and IFN- γ in uveitic eyes^{31,42} and recently IL-10 has been detected in aqueous or vitreous obtained from uveitis patients (Ongkosuwito *et al.*, in preparation; see also⁴³). The determination of IL-10 has been proposed by Chan *et al.*⁴³ as a tool to diagnose primary intraocular lymphoma.

Whether the inflammatory response in the eye of a uveitis patient is due to a type 1 or a type 2 response has not been reported, and would necessitate the analysis of the characteristic cytokines differentiating these responses, such as IL-4 and IFN- γ . This question is currently being addressed via two different approaches. One approach involves the detection of the soluble cytokines in the intraocular fluid whereas the other involves the investigation of intracellular cytokine profiles of T cells derived from inflamed eyes. Preliminary results from our group revealed a lack of IL-4 activity whereas IFN- γ was readily detected, which is suggestive of a type 1 inflammatory response (Ongkosuwito *et al.*, in preparation).

An intraocular cytokine that has been implicated in the control of unwanted delayed-type hypersensitivity responses in the eye has been identified as TGF- β -2. TGF- β is a multifunctional peptide that is excreted from cells in a latent inactive form. The natural activation involves cleavage of the TGF by proteolytic enzymes, which renders a TGF that can undergo interaction with its receptors. Investigation of ocular fluids from uveitis patients revealed that the total levels of TGF were not altered but that a marked decrease had occurred in the presence of free active TGF.⁴⁴ Whether this was due to a block of proteolytic cleavage or to the binding of α_2 -macroglobulin has not been resolved.⁴⁵

Analysis of cytokine receptors has shown that circulating soluble IL-2 receptor levels are raised in uveitis.^{46,47} Arock-Mettinger *et al.*⁴⁶ reported increased levels of this receptor in patients with Fuchs' cyclitis and in children with juvenile rheuma-

toid arthritis and uveitis, but not in other uveitis entities such as acute anterior uveitis and intermediate uveitis. A twofold increase in IL-2 receptor levels was reported by BenEzra *et al.*⁴⁷ in patients with ocular Behçet's disease.

The measurement of various cytokines has not been proven to be of diagnostic value in uveitis. Further studies need to be carried out to confirm that the detection of IL-10 is valuable in the differential diagnosis of primary intraocular lymphomas.

Epiretinal membranes removed from patients during vitreoretinal surgery showed staining for TNF- α in 80% of samples investigated.⁴⁸ Analysis of vitreous specimens taken during vitreoretinal surgery for proliferative vitreoretinopathy or diabetic retinopathy have shown that inflammatory cytokines such as IL-6, IL-8 and MCP-1 may be involved in the pathogenesis of these diseases and are instrumental in the infiltration of leucocytes.^{34,39,41}

CYTOKINES AND INTRAOCULAR INFLAMMATION: THERAPEUTIC INTERVENTION

Since cytokines play an essential role in the pathogenesis of intraocular inflammation, new exciting approaches are being developed to control this network. Corticosteroids are the most potent inhibitors of the production of inflammatory cytokines but are frequently associated with serious side-effects such as glaucoma and cataract, which limit their prolonged use.⁴⁹ Strategies are now being developed allowing a more specific action on certain individual members of the cytokine network. The possibility of making peptides or recombinant proteins in large quantities now allows the use of naturally occurring regulatory proteins such as IL-1 receptor antagonist, anti-inflammatory cytokines (IL-4, IL-10, IL-13), anti-viral interferons, soluble cytokine receptors and haematopoietic growth factors to treat various inflammatory eye diseases such as keratitis, scleritis, dry eye disease, corneal allograft rejection, Graves' ophthalmopathy, proliferative vitreoretinal disease, post-surgical inflammation and uveitis.

The paradoxical effects that have been observed in the treatment of various clinical and experimental models of eye disease have been explained by the redundant and pleiotropic nature of the network. IL-1-RA has been used to block IL-1 induced intraocular inflammation in experimental models, but could not influence the uveitis following endotoxin injection. This has been explained by the redundancy of the inflammatory response, involving more than one cytokine initiating the inflammatory response. Of interest is that IL-1-RA was able to inhibit the post-surgical inflammation following cataract surgery in a rabbit model.⁵⁰ IL-10 has been shown to block endotoxin-induced uveitis.⁵¹ Other

anti-inflammatory cytokines such as IL-4 are being used in numerous autoimmune disease models including experimental autoimmune uveitis.⁵²

The background for using IL-4 as immunotherapy for autoimmune diseases stems from the dogma that most autoimmune diseases are considered to be Th1-mediated and are characterised by a delayed-type hypersensitivity response.⁵³ A Th2 response against the same autoantigens responsible for the disease would theoretically result in a production of the anti-inflammatory cytokines IL-4, IL-10 and IL-13 and dampen down the harmful delayed-type hypersensitivity response. Since IL-4 can direct T cell differentiation towards the Th2 arm of the response, experimental immunotherapeutic strategies have been devised using exogenous IL-4 administration. Although encouraging results have been obtained in experimental allergic encephalomyelitis, treatment of Lewis rats with IL-4 paradoxically exacerbated experimental autoimmune uveitis.⁵²

IFN- α has been successfully applied to treat patients with ocular manifestations of Behçet's disease,⁵⁴ but placebo-controlled clinical trials have not yet been published. IFN- γ has been shown to suppress experimental autoimmune uveitis in mice, whereas treatment with anti-IFN- γ antibodies worsens the disease.⁵⁵

Other strategies which are still being studied include the use of monoclonal antibodies against individual cytokines. Anti-TNF therapy has been successfully used to treat rheumatoid arthritis patients.⁵⁶ Blocking of systemic TNF during experimental endotoxin-induced uveitis paradoxically appears to worsen the disease.^{8,57,58} Newer developments include regulation of the cytokine network at the gene level by interfering with the promoter genes, using 'antisense oligonucleotides' to block translation of RNA and inhibiting enzymes (metalloproteinases) involved in secretion of certain cytokines. Alternatively the expression of cytokine genes could transiently be increased introducing these genes into certain tissues by targeted gene therapy. A word of caution is necessary, however, since a number of cytokines may play an important role in homeostasis and disturbances of this complex network may produce paradoxical effects.

Key words: Cytokines, Uveitis.

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