

## Cytokines in Uveitis

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**U**veitis represents the 5<sup>th</sup> leading cause of visual loss in Europe with a prevalence of approximately 35-80 per 100,000<sup>1</sup> causing approximately 5%-20% of blindness. Extrapolated to the current British population (59 million), uveitis accounts for >40,000 patients with visual impairment and costs British society an estimated EUR 114.6 million (approximately US \$152 million) for uveitis-induced blindness.<sup>1</sup> Thus uveitis constitutes a serious problem for the patient, treating physician and community. The costs and the severe morbidity of the disease provide a stimulus for both mechanistic and clinical research for the development of effective therapy.

Non-infectious uveitis is initiated by an inflammatory stimulus in which cytokines play a central role. In the normal eye, cytokines are part of the immunological response that protects the eye from potential harmful microbes and non-infectious triggers from the environment. Proinflammatory cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$  (IFN- $\gamma$ ) and interleukin-1 (IL-1), regulate the immune system to maintain a balanced inflammatory response. The monocyte-macrophage system and uveitogenic CD4<sup>+</sup> Th1 cells produce most of the cytokines. However, retinal cells, such as retinal pigment epithelium, are also an important source of cytokines.

In the immunoprivileged eye, autoimmunity can develop when natural mechanisms of tolerance fail. Local immunosuppressive molecules including overexpression of transforming growth factor- $\beta$  (TGF- $\beta$ ), migration inhibitory factor, and  $\alpha$ -melanocyte-stimulating hormone together with a constitutive expression of the cytoprotective Fas ligand in cornea, uvea and retina are protective factors for the eye. A failure in regulation can be a result of internal or environmental triggers combined with genetic factors. Various systemic diseases with ocular involvement are thought to have an imbalance in their cytokine expression, for example overexpression of TNF- $\alpha$  in rheumatoid arthritis and Crohn's disease.

Although the etiology of a dysregulated immune system is unknown, uveitis has been characterized by a Th1-directed inflammation with elevations in IL-2, IFN- $\gamma$  and lymphotoxin. Those cytokines are produced after peripheral clonal expansion of Th1 cells. In addition, increased  $\gamma\delta$ -T-cells, proinflammatory cytokine production (TNF- $\alpha$ )

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and a shortage of T-regulatory cells are found to contribute to overall tissue damaging effects. Hence, therapy is most often T-cell directed with nonspecific immunosuppressive agents.

The authors of the extensive review in this issue of *Clinical Medicine & Research* attempt to correlate the pattern of what is known about (pro)inflammatory cytokines in experimental uveitis with specific uveitis-causing molecules in order to gain knowledge about the immunoetiological mechanisms involved in uveitis.<sup>2</sup> Experimental autoimmune uveitis is an *in vivo* model that can be used for ocular inflammation studies, but caution should be exercised when extrapolating experimental autoimmune uveitis results because, although elevated intrauveal IFN- $\gamma$  is associated with protection in mice, it exacerbates the development of uveitis in rats and humans.

Research on cytokine expression has been limited by the small volume of target tissue (e.g., aqueous humor) available for study. Most research has utilized techniques such as enzyme-linked immunosorbent assays or polymerase chain reaction to measure plasma or intrauveal cytokine levels, and has stimulated numerous clinical and preclinical studies, with which it has been demonstrated that cytokines can be used as therapeutic targets (e.g., TNF- $\alpha$  blocking therapy). Recently, some very promising new techniques, such as multiplexed bead immunoassays, gene microarrays and two-dimensional gel electrophoresis, have been developed to overcome the limitation of inadequate volumes of aqueous humor. These new techniques will help to provide a substantial amount of new and important data on a large profile of cytokines, growth factors and chemokines in aqueous humor, thus providing significantly more insight into the complex pathophysiology of uveitis. For example, cluster analyses in idiopathic anterior uveitis already has revealed a distinctive cytokine pattern of IL-6, IL-8, CCL2, IL-13, TNF- $\alpha$  and IL-2 in aqueous humour.<sup>3</sup> It will only be a matter of time before data from larger numbers of tissue analyses will be available to provide new insight into the complex etiology of non-infectious uveitis.

Whether cytokines are the primary cause of the various intraocular inflammatory diseases, or whether the diseases are a result of the derangement of processes upstream remains to be determined. Additional research is necessary to understand this complex disease.

## References

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