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Editorials

The role of cytokines in ocular inflammation

Cytokines are low molecular weight proteins involved in the communication between cells.[1] Sometimes this involves the communication at larger distances (endocrine), the interaction with neighbouring cells (paracrine), or signalling with the same cell (autocrine). The above statement implies the interaction between a secreted protein and its receptor on the same or another cell type. Advances in the field of molecular biology and the availability of immunochemical assays with a sensitivity at the picogram level have led to a rapid growth in the understanding of cytokine function. The actions of cytokines are numerous and involve almost every biological process ranging from the induction of differentiation, activation, or proliferation of target cells.

Cytokines involved in the immune response play an essential role in dictating which types of cells or antibody classes will be involved in host defence mechanisms.[2] Cytokines such as interferon gamma and interleukin 2 (IL-2) induce the formation of cellular immunity mediated by T helper cells of the Th1 class, whereas the cytokine IL-4 is involved in the immediate type hypersensitivity responses by stimulating Th2 lymphocytes that regulate IgE production by B cells. Balance between the cytokines mentioned above is crucial in determining the outcome of the immune defence mechanisms employed to combat infectious disease. Since intraocular structures may suffer from bystander damage of the inflammatory response, it has been hypothesised that the immune defence within the eye should be deviated to a benign Th2 type response. Evidence for this hypothesis stems from experimental animal models and has implicated the cytokine transforming growth factor beta (TGF-ß) as an important regulator of the immune response of antigens presented from within the eye.[3] In line with these ideas are the experimental data showing that the autoimmune attack occurring in experimental uveitis is mediated by a Th1 type response. Deviation of the autoimmune reaction to a Th2 type response is capable of preventing uveitis in these experimental animals.[4] Current studies are now under way to apply these deviation protocols in clinical uveitis.[5]

Most attention concerning the role of cytokines in ocular disease has been directed to the role of inflammatory cytokines during uveal inflammation.[6] Various cytokines have been detected in the eyes of patients with intraocular inflammation and experimental animal studies have shown that injection of recombinant cytokines into eyes can cause uveitis. The general mode of action appears to involve the initial triggering of IL-1 and tumour necrosis factor alpha (TNF-α) and subsequent amplification of the inflammatory response through stimulation of prostaglandin production and induction of chemokines (IL-8 and MCP) which attract and activate inflammatory cells such as macrophages and granulocytes. Resident ocular cells that have been shown to produce cytokines include the retinal pigment epithelium, Müller cells, lens epithelial cells, corneal stromal and epithelial cells, and ciliary body epithelial cells.

All layers of the human cornea have been shown to express IL-1[7,8] and in vitro studies have shown that addition of exogenous IL-1 to corneal cell cultures stimulates the synthesis of IL-6 and IL-8.[9,10,11] Recent observations showing that cytokines such as Il-1 and Il-8 can induce corneal neovascularisation underline the importance of these mediators.[12,13] In view of the potent proinflammatory activities of IL-1 it is evident that regulatory mechanisms should be present to control IL-1 initiated corneal inflammatory sequelae. The finding of a high expression of the natural antagonist of IL-1, the IL-1 receptor antagonist (IL-1ra) in both human and rat corneas was therefore not completely surprising.[14,15] IL-1ra shares amino acid sequences with both IL-1 α and ß and competes for the binding to the type I and type II IL-1 receptors.[16,17] Whether corneal inflammation is associated with a disrupted balance between IL-1 and IL-1ra needs further investigation before topical application of IL-1ra can be considered as an anti-inflammatory treatment.

Evidence that cytokines might also play a role in the inflammatory response seen after cataract extraction came from the observation of Malecaze *et al* who observed that levels of IL-6 in aqueous humour of patients with moderate uveitis after cataract surgery were dramatically increased when compared with preoperative values.[18] Post-surgical inflammation after cataract surgery may be caused by the surgical trauma and at later stages by activation of residual lens epithelial cells. Nishi *et al* obtained evidence for the hypothesis that residual lens epithelial cells might be involved in pseudophakic inflammation by demonstrating that cultured human lens epithelial cells released IL-1 α and prostaglandins.[19]

In line with the discussion raised above concerning the control of IL-1 mediated responses in the cornea it may be envisaged that IL-1ra might also play a role in the control of post-surgical inflammation after cataract surgery. In this issue of the journal, Nishi *et al* are the first to report an experiment in which they investigated the effect of intraocularly administered IL-1ra after cataract extraction in a rabbit model.

Although the data are based on one experiment only, a marked inhibition of aqueous flare and fibrin deposition was seen in IL-1ra treated eyes when compared with controls.

The use of IL-1ra is only one in a series of future options, which also include non-peptidic antagonists, soluble cytokine receptors, and truncated cytokines. It is clear that cytokines undoubtedly play a role in ocular inflammation and it can be envisaged that new drugs that modulate cytokine production and activity will soon be added to the list of anti-inflammatory treatments.

AIZE KIJLSTRA

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Thromboxane in ocular pathophysiology

Thought provoking communications are the lifeblood of the *British Journal of Ophthalmology*. Chen *et al*, in this issue, provide us with such a report, describing the localisation, at the cellular level, of thromboxane A_2 receptors and their corresponding mRNA levels in whole human eyes. The significance of their findings appears to be broad based, touching upon several well known but poorly understood phenomena.

Thromboxane A_2 (TxA_2) is a cell membrane derived lipid, a metabolite of arachidonic acid that exerts four major biological activities: vasoconstriction, platelet aggregation, bronchoconstriction, and membrane destabilisation. It is widely recognised as an important agent in cardiovascular diseases. However, recent evidence suggests a role in the modulation of immunological and inflammatory reactions. Platelets, by far, have the highest synthetic capacity although TxA_2 has been identified as a metabolite of other tissues including ocular tissues where its function was postulated primarily in a proinflammatory role.[1,2] Chen *et al* have taken these findings to the next level by identifying the TxA_2 effector cells, those that express the TxA_2 receptor using contemporary autoradiographic binding assays and in situ hybridisation techniques. Their findings indicate that TxA_2 receptors are specifically concentrated in the corneal epithelium, the ciliary processes, retina, and the posterior ciliary arteries. From this it seems clear that TxA_2 is more than just a vasoactive lipid.

The significance of TxA_2 receptors on the corneal epithelium is a matter of speculation but the abundant presence of mast cells in the adjacent conjunctiva, cells known to be laden with TxA_2 synthase and to participate in the early phase of inflammation, especially of an allergic nature, indicates a role in the effector limb of the response to corneal surface injury.[3] The presence of TxA_2 receptors in the non-pigmented epithelium in the ciliary body and retina might explain some of the pathophysiological changes seen in experimental autoimmune uveoretinitis (EAU), a well established model for human autoimmune conditions. In EAU, a massive inflammation occurs in rats with widespread destruction of retinal photoreceptor cells 2 weeks after immunisation with bovine S-antigen, a protein derived from photoreceptor cells.[4] Li *et al* recently reported that oral feeding of a TxA_2 synthase inhibitor, CGS-13080, postponed the onset of overt EAU, decreased both the incidence and severity of the condition, and inhibited the lymphocytic proliferation response in a dose dependent fashion. This report makes clear the importance of TxA_2 in EAU. Li *et al*, in an earlier report, studied the role of mast cells, presumably, as a source of TxA_2 in the immunogenesis of EAU. The breakdown in the blood-aqueous barrier and the massive destruction of photoreceptor cells may be a consequence of the concentrations of TxA_2 receptors in the retina and the non-pigmented epithelium of the ciliary body. These speculations should be followed by additional experimental evidence that these receptors function in the binding of TxA_2 resulting in cell destruction.

Autoregulation of blood flow, defined as the intrinsic ability of an organ to maintain its blood flow relatively constant despite changes in perfusion pressure, has been described in the choroidal circulation of rabbits and piglets.[5,6] Thus, the observation that TxA_2 receptors are concentrated