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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16 Eisenberg SP, Brewer MT, Verderber E, Heimdal P, Brandhuber BJ, Thompson RC. Interleukin-1 receptor antagonist is a member of the interleukin 1 gene family: evolution of a cytokine control mechanism. Proc Natl Acad Sci USA 1991; 88: 5232-6.

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 A2 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 A2 (TXA2) 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 TXA2 has been identified as a metabolite of other tissues including ocular tissues where its function was postulated primarily in a proinflammatory role.12 Chen et al. have taken these findings to the next level by identifying the TXA2 effector cells, those that express the TXA2 receptor using contemporary autoradiographic binding assays and in situ hybridisation techniques. Their findings indicate that TXA2 receptors are specifically concentrated in the corneal epithelium, the ciliary processes, retina, and the posterior ciliary arteries. From this it seems clear that TXA2 is more than just a vasoactive lipid.

The significance of TXA2 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 TXA2, synthesize 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.1

The presence of TXA2 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 inflammatory occurs in rats with widespread destruction of retinal photoreceptor cells 2 weeks after immunisation with bovine S-antigen, a protein derived from photoreceptor cells.12 Li et al. recently reported that oral feeding of a TXA2 synthase inhibitor, CGS-13080, postoperatively 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 TXA2 in EAU. Li et al., in an earlier report, studied the role of mast cells, presumably, as a source of TXA2 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 TXA2 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 TXA2, resulting in cell death.

Auto-regulation 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.16 Thus, the observation that TXA2 receptors are concentrated

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in the posterior ciliary in the human eye is highly significant since these vessels are thought to supply the anterior surface of the optic nerve as well as the choroid. TxA₂ must be considered to be an important mediator in maintaining the fine balance between vasodilatation and vasoconstriction in the maintenance of autoregulation of choroidal blood flow; Chen et al speculate as to the importance of their findings in the pathogenesis of glaucomatous and ischaemic optic atrophy.

One has to keep in mind that the so-called TxA₂ receptor has another equally potent endogenous agonist, the prosta-glandin endoperoxide (PGH₂) which is the final unstable metabolite of the cyclo-oxygenase activity on arachidonic acid and the substrate for the TxA₁, synthase. PGH₂ is also a potent vasoconstrictor and a platelet aggregator. The emerging information regarding different cyclo-oxygenase (COX) genes, in particular the existence of the inducible form, opens a new front in the role of prostanoids in inflammatory and immune related disorders. To date no information is available regarding COX-2 inducibility in ocular inflammation. However, since COX-2 has been shown to be induced in response to inflammatory and immune cytokines in many tissues, it is possible that such activity could exist in inflamed ocular tissues and therefore could increase the amount of TxA₂, receptor agonists, PGH₂ and TxA₁, to significant levels.

Localisation of receptors is a very important step in understanding the pathophysiological impact of any modulator, either endogenously formed or exogenously added as a foreign compound. Localisation should be followed by identification of those receptors as functional receptors—that is, the receptors bind their ligand and this binding provokes a receptor mediated signal transduction ending with the final effect. Chen et al provide us with evidence of functional receptors by presenting a correlation between receptor mRNA and ligand binding. This should follow with functional studies which in all together will bring a promise of new therapeutic opportunities.

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