THERAPEUTIC MANIPULATION OF INFLAMMATORY MEDIATORS

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by

David R. Haynes, B.Sc.(Hons)

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Abstract

Inflammation normally fulfils an important protective role for the host. However, under certain conditions, such as rheumatoid arthritis, the chronic inflammatory responses can be detrimental. Central to the process of inflammation is the complex interaction of different inflammatory cells. They communicate by releasing mediators that target appropriate cells to induce changes in their function. The manipulation of these mediators may provide a way of controlling the progression and tissue damage of chronic inflammation.

The drugs most commonly used in the treatment of both chronic and acute inflammation are the 'Aspirin like' nonsteroidal antiinflammatory drugs (NSAIDs). It is generally accepted their mode of action is the inhibition of prostaglandin (PG) production by inhibiting the enzyme arachidonate cyclooxygenase. This thesis shows that the production and action of inflammatory cytokines, such as interleukin (IL)-1, IL-2 and tumour necrosis factor (TNF), are enhanced with NSAID treatment in vivo and in vitro by reducing PG's which normally suppress IL-1, IL-2, interferon (IFN)γ and TNF. Conversely, IL-6 production is enhanced by PG's.

Like PGE_2, the PGE's $_1$ and $_3$ regulate cytokines and other cell functions. In addition, PGE analogues, such as Misoprostol, have similar effects. All these PG's seem to bind to the same cell surface receptor(s) and effectively raise levels of intracellular cyclic AMP. PGE's enhance IL-6 production by stimulating gene transcription.

Cyclosporin A (CsA) is very effective in preventing the development of adjuvant induced arthritis in rats. CsA inhibits production of the inflammatory cytokines IL-1, IL-2, IFNγ and TNF. IL-6 production is not affected in vitro but enhanced ex

vivo. Assays with monoclonal antibodies indicate that these effects may be mediated by selectively targeting T-helper type 1 lymphocytes.

Overall, this study indicates that PGE's and CsA may have similar modes of action. The findings suggest that therapies that selectively target subpopulations of leucocytes, and manipulate the inflammatory mediators they produce, may be effective in the treatment of chronic immuno-inflammatory diseases similar to rheumatoid arthritis.