GLUCOCORTICOIDS (GC) have profound effects on the development and homoeostasis of the immune system. Physiological doses of GC modulate the selection of thymocytes [1] and regulate immune responses by influencing the pattern of cytokine secretion [2]. Pharmacological doses of GC prevent or suppress inflammation and other immunologically mediated processes by inhibiting the influx of leucocytes to inflammatory sites; interfering with the function of leucocytes, endothelial cells and fibroblasts; and suppressing the production and effects of humoral factors involved in inflammatory responses [3]. The major mechanism of action of GC responsible for their diverse and multiple biological effects involves the regulation of gene expression. GC may regulate gene expression at the transcriptional or post-transcriptional level. Post-transcriptional regulation may involve alteration in mRNA stability, translational efficiency or the secretion of proteins [3].

The ordered regulation of gene expression underlying cellular responses to physiological stimuli relies on sequence-specific DNA–protein interactions. Gene transcription—the step from DNA to RNA—is the primary level of control in gene expression. Nucleotide sequences that influence transcription are common to many genes and are collectively called ‘the promoter’ of a gene. These sequences lie in regions of DNA upstream of the transcription start site and comprise binding sites for the RNA polymerase and its numerous cofactors. In addition to promoters, other DNA regulatory elements occur in unpredictable locations and like promoters form binding sites for regulatory proteins. These ‘enhancers’ augment transcription from the gene promoter. Nuclear factors (NF) or transcription factors, are proteins which bind to promoters and enhancers, and stimulate (or sometimes inhibit) gene transcription (and thus the formation of mRNA) through direct interactions with DNA [4]. Phosphorylation, triggered by biochemical signals from cell-surface receptors, is a common means of altering the function of transcription factors. Glucocorticoid receptors are ligand-activated transcription factors [5] which activate the transcription of glucocorticoid-responsive genes either directly, i.e. by binding to specific regulatory areas of these genes (so-called glucocorticoid responsive elements, GREs), or indirectly, i.e. by interfering with the binding or function of other transcription factors. Inhibition of gene transcription by GC may result either by the competitive displacement by the activated GR of transcriptional factors which bind to overlapping areas of the DNA [6] or by physical interaction of the activated GR with transcription factors which results in inhibition of their binding [7–12].

Nuclear factors AP-1 and NF-κB are essential regulators of several genes involved in the immune and inflammatory response (cytokines and their receptors, cell adhesion, proteinase, and other genes) whose function is inhibited in the presence of GC receptor due to physical association and functional antagonism between their proteins and the GC receptor [7–12]. In addition to this mechanism, inhibition of NF-κB may occur through a recently described mechanism which involves the transcriptional activation of its cytoplasmic inhibitor, IκBα [14].

NF-κB is an essential transcription factor for the expression of a variety of proinflammatory genes. Interleukin 8 (a chemotactic factor for neutrophils), interleukin 6 (an essential cytokine for the inflammatory response), and interleukin 2 and its receptor (two crucial components of the normal immune response), are some of the best known examples of such genes. In unstimulated cells, NF-κB is held in the cytoplasm. NF-κB, a member of the NF-κB-Rel family of transcription factors, is a heterodimer composed of p50 and p65 subunits. In unstimulated cells, the NF-κB heterodimer is kept as an inactive cytoplasmic complex by inhibitory proteins of the IκB family (IκBα, IκBβ, IκBγ, as well as the NF-κB precursor molecules NF-κB1 and NF-κB2).

Following stimulation of the immune cell through cell-surface receptors (interleukin 1, tumour necrosis factor-α or T-cell antigen receptors), the IκBs are rapidly degraded and free NF-κB dimers translocate to the nucleus where they activate target genes, including their own inhibitor IκBα. Induction of expression of newly synthesized IκBα terminates this process by sequestering NF-κB dimers in the cytoplasm.

Although previous work by several groups has suggested that the GC receptor complex binds to NF-κB and prevents it from binding to DNA and increasing gene transcription [11, 12, 15], two key observations suggest that an additional mechanism may be operant. First, in the presence of GC, the amount of NF-κB that translocates into the nucleus is significantly diminished, suggesting an increased sequestration of the protein in the cytoplasm [13]. Second, whereas GC inhibit the transcription of the IL-2 gene by both nuclear factors AP-1 and NF-κB, only the effect of NF-κB requires new protein synthesis [14]. Both observations suggest that increased transcription and protein levels of IκBα may be the most likely candidate mechanism. Two independent groups have demonstrated that GC increase the rate of IκBα protein synthesis, which in turn traps activated NF-κB in inactive cytoplasmic complexes [13, 14]. This effect has been observed both in cultured cells—Jurkat cells...
GC would result not only in decreased inhibition by (and AP-1) in the regulation of expression of NF-KB suppressive effects of GC? Given the essential role of our understanding of the anti-inflammatory/immunosuppressive effects of low-dose GC, they could be inactivated into the nucleus by associating with the GC receptor. Similar to GC, sodium salicylate and aspirin inhibit the activation of NF-κB by preventing the degradation of IκB, leading to retention of NF-κB in the cytosol [16]. Perturbation of NF-κB may be responsible for the repression of IL-2 production observed in anergic T cells [17]. These studies point to the key role of NF-κB inhibition in suppressing both immune and inflammatory responses. However, similar to aspirin, inhibition of NF-κB (both in vivo and in vitro) requires high concentrations of GC (10^-6-10^-7 M of dexamethasone in vitro or 1 mg/kg in vivo) comparable to those obtained by high-dose daily or pulse GC therapy. The contribution of these mechanisms to the anti-inflammatory/immunosuppressive effects of low-dose GC therapy is therefore not clear at present.

The synthesis of new compounds which selectively inhibit or modulate NF-κB may be a crucial step towards the development of an entire new class of anti-inflammatory and immunosuppressive agents with fewer side-effects. To this end, compounds that inhibit proteasome, a multicatalytic protease required for the activation of NF-κB, have already been synthesized and shown to downregulate the induction of adhesion molecules in response to anti-inflammatory cytokines [18].

Several decades after their introduction into clinical rheumatology, GC continue to be fertile soil for basic and clinical research which helps to elucidate fundamental mechanisms of immunity and inflammation. The future of GC is full of surprises.

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