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Crystal ball

Will it be steroids for ever?

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Corticosteroids are by far the most effective therapy currently available for the treatment of asthma and other allergic diseases and work in almost every patient [1]. Allergic diseases involve complex inflammatory mechanisms, with the participation of many interacting inflammatory and structural cells, the release of multiple mediators and complex inflammatory effects in the respiratory tract or skin. There is increased expression of multiple inflammatory proteins, including cytokines, chemokines, adhesion molecules, inflammatory enzymes and inflammatory mediator receptors. Many of these proteins are regulated at a transcriptional level by pro-inflammatory transcription factors, such as nuclear factor-κB and activator protein-1 that are activated by inflammatory signals. The activation of inflammatory genes involves opening up of the chromatin structure as a result of acetylation of core histones in response to coactivator molecules that have intrinsic histone acetyltransferase activity [2]. It is likely that corticosteroids control inflammation mainly by inhibiting the expression of these activated inflammatory genes and the molecular mechanisms whereby corticosteroids suppress inflammation are now much better understood [3].

How do corticosteroids switch off inflammatory genes?

Corticosteroids bind to cytoplasmic glucocorticoid receptors (GR) that translocate to the nucleus and bind to recognition sites (glucocorticoid response elements) in the promoter region of steroid-sensitive genes to switch on the transcription of genes that encode anti-inflammatory proteins, such as mitogen-active protein (MAP) kinase phosphatase-1, which inhibits MAP kinase pathways activated by inflammation. However, it seems unlikely that this mechanism can entirely account for the extraordinary efficiency of corticosteroids in suppressing inflammation at rather low concentrations, as there are relatively few anti-inflammatory genes that are steroid sensitive and high concentrations of corticosteroid are usually needed to activate these genes. It is more likely that the major mechanism for the anti-inflammatory effect of corticosteroids is suppression of the multiple inflammatory genes that have been activated in allergic diseases. An important mechanism for switching off inflammatory genes is the recruitment of histone deacetylase-2 (HDAC2) by activated GR to the activated inflammatory gene complex, thus reversing the acetylation of core histones and suppressing gene activation [4]. This provides a mechanism whereby corticosteroids can switch off all inflammatory genes that have been activated during the inflammatory process. Moreover, this effect of corticosteroids occurs at low concentrations that are likely to be relevant in therapeutic practice. This mechanism also explains why corticosteroids are largely free of side-effects when given topically, as they predominantly switch off activated inflammatory genes and do not affect genes regulating other cell functions or metabolism. Systemic side-effects of corticosteroids are largely mediated through DNA binding and may be because of interaction with negative recognition sites that suppress genes involved in the hypothalamic–pituitary axis and bone metabolism, for example. Corticosteroids also have post-transcriptional effects and destabilize the messenger RNA of some inflammatory proteins, preventing their synthesis.

How can corticosteroids be improved?

Corticosteroids work by virtue of the fact that they bind to and activate GR. It is the interaction between activated GR and genes, coactivators and other nuclear proteins that accounts for all of the anti-inflammatory effects of corticosteroids. This makes it difficult to envisage the design of non-steroidal molecules that could achieve the same effects. There have been many attempts to improve the safety of topical corticosteroids, but these have relied on pharmacodynamic improvements, with reduced oral bioavailability. However, there is increasing interest in the possibility of designing novel ''dissociated'' steroids which separate the actions of steroids that involve DNA binding (*trans*-activation, side-effects) from the actions that involve gene suppression (*trans*-repression, anti-inflammatory effects). This is possible because DNA binding requires a GR dimmer, whereas *trans*-repression and interaction with coactivator proteins requires only GR monomers. Several dissociated corticosteroids are now being investigated with a view to improving the safety profile and even allowing safe oral administration [5]. The design of novel corticosteroids is likely to be aided by the resolution of the crystal structure of the ligand binding site of GR [6].

Are there alternative strategies?

There has been a long search for alternative anti-inflammatory treatments that are as effective and safe as corticosteroids, but this has so far led to no new classes of therapy for allergic diseases [7]. New drugs for asthma and other allergies are either less effective or have greater problems with side-

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effects. The Holy Grail is to find an oral drug that matches the efficacy of corticosteroids, but without significant side-effects. It is very unlikely that this will be possible since drugs that have the broad spectrum of anti-inflammatory treatment that is necessary for efficacy inevitably inhibit cellular mechanisms that result in side-effects.

Is it possible to reverse corticosteroid resistance?

There are some patients with asthma who fail to respond to corticosteroids, although they are extremely rare [8]. Other patients (approximately 1% of all asthmatic patients) are relatively resistant to corticosteroids and require high doses, usually via oral administration, for adequate control. Although these patients constitute only a small minority they are responsible for a disproportionate amount of health care spending. There is a pressing need to find new classes of treatment that benefit these patients as an add-on therapy to corticosteroids. Several new classes of therapy are currently under investigation, including anti-IgE antibodies, tumour necrosis factor inhibitors and phosphodiesterase-4 inhibitors [7].

An alternative approach that is currently under consideration is to reverse the molecular mechanisms contributing to corticosteroid resistance. There are several molecular mechanisms that may contribute to corticosteroid resistance in asthma, including defects in GR nuclear translocation, phosphorylation of GR by p38 MAP kinase and abnormal histone acetylation patterns [9, 10]. Another cause of corticosteroid resistance is oxidative stress that results in a reduction in HDAC2 activity and expression, thus disabling the mechanism whereby corticosteroids switch off inflammatory genes. This mechanism is likely to account for corticosteroid resistance in chronic obstructive pulmonary disease (COPD), but it may also be an important mechanism in patients with severe asthma and in asthmatic patients who smoke, who also show a degree of corticosteroid resistance [11]. Oxidative stress appears to impair HDAC2 function through nitration of the enzyme by peroxynitrite formed from an interaction between superoxide anions and nitric oxide (NO) [12]. This implies that antioxidants or inhibitors of NO formation might therefore reverse corticosteroid resistance in these patients. While effective antioxidants have proved difficult to develop, selective inhibitors of inducible NO synthase are now in clinical development [13]. A completely different approach is the use of theophylline to activate HDAC to overcome the reduced HDAC activity found in oxidative stress [14]. Low concentrations of theophylline have already been shown to restore HDAC activity to normal in macrophages from COPD patients and to restore the responsiveness of these cells to corticosteroids [15]. A similar approach might be effective in patients with severe asthma and asthmatic patients who smoke.

Will corticosteroids be replaced in the future?

Current evidence suggests that it is highly unlikely that corticosteroids will be replaced by novel anti-inflammatory treatments in the future management of allergic diseases. This is largely because the molecular mechanism of action of corticosteroids is difficult to mimic by any single drug, so that alternative treatments are likely to be less effective. There is certainly a need for new anti-inflammatory treatments in COPD, where corticosteroids are ineffective and such therapies may also have a use in patients with severe asthma [16]. The combination of corticosteroids with long-acting β_2-agonists has proved to be particularly efficacious in the treatment of asthma and has allowed the use of lower doses of corticosteroids to control asthma with a minimal risk of systemic adverse events [17]. Perhaps the most promising approach for the future is to reverse the molecular mechanisms involved in steroid resistance so that corticosteroids are universally effective. So, although it may not be corticosteroids for forever, it seems virtually certain that it will be corticosteroids for the forseeable future.

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