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Molecular Mechanisms of Corticosteroid Resistance*

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Most patients with asthma are successfully treated with conventional therapy. Nevertheless, there is a small proportion of asthmatic patients, including present cigarette smokers and former cigarette smokers, who fail to respond well to therapy with high-dose glucocorticoids (GCs) or with supplementary therapy. In addition, high doses of steroids have a minimal effect on the inexorable decline in lung function in COPD patients and only a small effect on reducing exacerbations. GC insensitivity, therefore, presents a profound management problem in these patients. GCs act by binding to a cytosolic GC receptor (GR), which is subsequently activated and is able to translocate to the nucleus. Once in the nucleus, the GR either binds to DNA and switches on the expression of antiinflammatory genes or acts indirectly to repress the activity of a number of distinct signaling pathways such as nuclear factor (NF)-κB and activator protein (AP)-1. This latter step requires the recruitment of corepressor molecules. Importantly, this latter interaction is mutually repressive in that high levels of NF-κB and AP-1 attenuate GR function. A failure to respond may therefore result from reduced GC binding to GR, reduced GR expression, enhanced activation of inflammatory pathways, or lack of corepressor activity. These events can be modulated by oxidative stress, T-helper type 2 cytokines, or high levels of inflammatory mediators, all of which may lead to a reduced clinical outcome. Understanding the molecular mechanisms of GR action, and inaction, may lead to the development of new antiinflammatory drugs or may reverse the relative steroid insensitivity that is characteristic of patients with these diseases. ***(CHEST 2008; 134:394–401)***

Key words: cigarette smoke; COPD; glucocorticoids; inflammation; severe asthma

Abbreviations: AP = activator protein; CDK = cyclin-dependent kinase; CSR = corticosteroid refractory; CSS = corticosteroid sensitive; GC = glucocorticoid; GR = glucocorticoid receptor; GRE = glucocorticoid response element; HDAC = histone deacetylase; hsp90 = heat shock protein 90; ICS = inhaled glucocorticoid; IL = interleukin; JNK = c-Jun N-terminal kinase; LABA = long-acting β_2-agonist; LXA4 = lipoxin A_4; MAPK = mitogen-activated protein kinase; NF = nuclear factor; NO = nitric oxide; NOS = nitric oxide synthase; PI-3K = phospho-inositol-3 phosphate kinase; TNF = tumor necrosis factor

Asthma currently affects 300 million people worldwide, and it is estimated that by 2025 a further 100 million people will be affected. Glucocorticoids (GCs) are highly effective in treating most inflammatory diseases, and, for example, asthma is controlled, to a greater or lesser extent, in the majority of patients by therapy with inhaled GC (ICS) therapy, either alone or in combination with long-acting β_2-agonists (LABAs), with minimal or no side effects.[1] Nevertheless, there is a small proportion of asthmatic patients, including present cigarette smokers and former cigarette smokers, who fail to respond to GCs even at high doses or with supplementary therapy.[1] In part, the efficacy of ICSs lies in improving bronchial hyperresponsiveness, in reducing the eosinophilic and lymphocytic inflammation in the airway wall, and in suppressing the expression of multiple inflammatory genes in the airways.[1] There is some evidence that ICS therapy may also reverse, to a certain extent, features of airway wall remodeling, such as

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basement membrane thickness.[1] Persons with asthma who smoke have an impaired response to therapy with both ICSs and oral GCs compared with persons with asthma who do not smoke.[2] Smoking cessation improves basal lung function but requires at least a year to demonstrate any improvement in GC responsiveness with respect to morning peak expiratory flow, but not FEV_1, after receiving therapy with high-dose prednisolone.[2]

In addition, even high doses of GCs have a minimal effect on the inexorable decline in lung function in COPD patients and have only a small effect in reducing COPD exacerbations.[3] This is consistent with the demonstration that therapy with ICSs or oral GCs fails to reduce the numbers of inflammatory cells, cytokines, chemokines, or proteases in induced sputum or airway biopsy specimens from patients with COPD.[3] GCs are also ineffective at suppressing these inflammatory proteins in alveolar macrophages from COPD patients compared to cells from healthy smokers and nonsmokers.[3] This appears to result from a defect in the antiinflammatory effect of GCs, since other antiinflammatory therapies, such as theophylline and resveratrol, have inhibitory effects.[3] GC insensitivity, therefore, presents a profound management problem in persons with asthma who smoke, in patients with severe asthma, and in patients with COPD. These patients also account for a disproportionate amount of health-care costs.[1,3]

Definition of GC Insensitivity in Asthma

GC-resistant or corticosteroid-refractory (CSR) asthma is defined as $< 15\%$ improvement in baseline FEV_1 after a 14-day course of oral prednisolone (40 mg/d) in patients who demonstrate $> 15\%$ improvement in FEV_1 with salbutamol therapy.[1] Furthermore, patients who showed improvements in FEV_1 of $\geq 30\%$ were considered to be GC-sensitive (CSS).[1] This definition has been used in subsequent studies. This definition of CSR asthma probably represents an extreme case, but these patients are useful as a comparison in studies elucidating the mechanisms underlying GC insensitivity in asthma patients. This definition of CSR asthma has been based on the reversibility of airflow obstruction to pharmacologic agents without any accompanying indication as to whether this group of patients is characterized by a particular clinical type, a pattern of asthma, or a specific pathophysiology. Further research in this area is essential, and recent data[4] from the Severe Asthma Research Protocol has begun to address some of these issues. It is important to highlight here that these CSR patients are a subset of those patients with severe asthma and that the terms are not interchangeable, since some CSR patients do not have severe disease and some patients with severe asthma are not GC insensitive.[4]

Pathologic Changes in Asthmatic Airways Associated With GC Insensitivity

Some pathologic characteristics of patients with CSR asthma are becoming clear. The thickness of the airway epithelium and basement membrane in patients with CSR asthma is greater than those in patients with CSS asthma, with both groups showing similar levels of epithelial shedding.[5,6] This difference was associated with an altered expression of markers of epithelial proliferation (*eg*, increased Ki-67 expression, reduced retinoblastoma expression, and reduced expression of Bcl-2 protein, which is a negative regulator of epithelial cell death).[5] The failure of ICS therapy to induce the expression of tissue inhibitor of metalloproteinase-1 in CSR asthmatic patients has been proposed[7] to account, at least in part, for this increase in airway remodeling.

Recently, a number of unbiased techniques, such as the hierarchical clustering of BAL cytokine expression[8] and the analysis of volatile organic components of exhaled breath using an electronic nose,[9] have been used to provide a fingerprint of distinct phenotypes of patients with CSR asthma. Interestingly, in the former study the expression of key cytokines such as interleukin (IL)-2 and IL-4 were associated with the lack of GC responsiveness, which was similar to the findings of earlier studies of biopsy samples from Ito and colleagues and references therein.[1] Some studies[3,10–12] have been performed comparing patients with COPD to healthy smokers, but, as with patients with CSR asthma, further studies using age-matched, disease-severity control subjects in larger groups of patients are needed to determine the usefulness of this approach.

Most of the studies examining patients with CSR asthma have been limited due to the examination of only a few persons, generally 6 to 12 subjects, in each patient group. Furthermore, few details have been provided as to the type of asthma these patients had, apart from their baseline FEV_1 and their response to oral prednisolone.

Molecular Actions of GCs

GCs act by binding to and activating specific cytosolic GC receptors (GRs), which are held in a resting state by a number of chaperone proteins (Fig 1). These activated GRs then have to translocate into the nucleus before they can regulate inflammatory