Overcoming Steroid Insensitivity in Respiratory Disease

Edited by

Ian M. Adcock and Kian Fan Chung

National Heart and Lung Institute,
Imperial College London,
London, UK
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Preface

The treatment of chronic inflammatory diseases was revolutionized by the discovery of the therapeutic utility of corticosteroids in the 1950s. Since this time they have been the mainstay of treatment for chronic inflammatory diseases. Their utility has been tempered, however, by the increasing risk of debilitating side effects with higher dose therapy. This is important because a reasonable proportion of patients with severe asthma do not respond well to high doses of inhaled or even oral corticosteroids. Thus 5% of asthmatics who do not respond to corticosteroid therapy account for >50% of the total healthcare costs for asthma. In addition, patients with chronic obstructive pulmonary disease also show little or no responsiveness to conventional corticosteroid therapy.

In the treatment of airways diseases side effects can be limited by targeted delivery to the airway and lung. Significant progress has been made through the use of increasingly selective molecules, and through a variety of lung-targeting strategies. Moreover, the recent developments in our understanding of the molecular and structural mechanisms of corticosteroid actions have suggested that it may be possible to develop a new corticosteroid, with intrinsically different pharmacology, that does not induce many of the pathways involved in the manifestation of side effects. A combination of these developments will enable the design of agents with an enhanced therapeutic index.

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Molecular Mechanisms of Glucocorticoid Receptor Action

Pankaj Bhavsar and Ian M. Adcock

1.1 Introduction

Glucocorticoids are the most effective therapy for the treatment of many chronic inflammatory diseases such as asthma and inflammatory bowel disease (Ito et al., 2006a). In contrast to the situation in asthma, chronic obstructive pulmonary disease (COPD), a common and debilitating chronic inflammatory disease of the lung, is glucocorticoid insensitive (Barnes, 2000a, b; Culpitt et al., 2003).

Glucocorticoids act by binding to cytosolic glucocorticoid receptors (GRs), which upon binding become activated and rapidly translocate to the nucleus. Within the nucleus, GR either induces transcription of genes such as secretary leukocyte protease inhibitor (SLPI) (Abbinante-Nissen et al., 1995) and mitogen-activated kinase phosphatase-1 (Lasa et al., 2002) by binding to specific DNA elements (glucocorticoid response element, GRE) at the promoter/enhancer of responsive genes, or reduces inflammatory gene transcription induced by nuclear factor-kappa B (NF-κB) or other pro-inflammatory transcription factors (Ito et al., 2006a). Binding of GR to p65-NF-κB is crucial for transrepression by glucocorticoids, however, it is not clear how the GR dissociates its ability to control inflammation by suppressing NF-κB from its ability to directly transactivate genes via binding to GRE (Ito et al., 2006b).

In the resting cell, chromatin is tightly compacted to prevent transcription factor accessibility. During activation of the cell this compact inaccessible chromatin is made available to DNA-binding proteins, thus allowing the induction of gene transcription (Lee and Workman, 2007; Li et al., 2007). There is compelling evidence that increased inflammatory gene transcription is associated with an increase in histone acetylation induced by transcriptional coactivators containing...