Update on glucocorticoid action and resistance

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Extensive development of inhaled and oral glucocorticoids has resulted in highly potent molecules that have been optimized to target activity to the lung and minimize systemic exposure. These have proved highly effective for most asthmatic subjects, but despite these developments, there are a number of subjects with asthma who fail to respond to even high doses of inhaled or even oral glucocorticoids. Advances in delineating the fundamental mechanisms of glucocorticoid pharmacology, especially the concepts of transactivation and transrepression and cofactor recruitment, have resulted in better understanding of the molecular mechanisms whereby glucocorticoids suppress inflammation. The existence of multiple mechanisms underlying glucocorticoid insensitivity raises the possibility that this might indeed reflect different diseases with a common phenotype, and studies examining the efficacy of potential new agents should be targeted toward subgroups of patients with severe corticosteroid-resistant asthma who clearly require effective new drugs and other approaches to improved asthma control. (J Allergy Clin Immunol 2006;117:522-43.)

Key words: *Severe asthma, steroid resistance, glucocorticoid receptor, molecular mechanisms, future therapies*

All patients with asthma have a specific pattern of inflammation in the airways that is characterized by degranulated mast cells, an infiltration of eosinophils, and an increased number of activated T_H2 cells.[1] It is believed that this specific pattern of inflammation underlies the clinical features of asthma, including intermittent wheezing, dyspnea, cough, and chest tightness. Approximately 100 known inflammatory mediators are increased in asthma and include lipid mediators, inflammatory peptides, chemokines, cytokines, and growth factors.[2] There is increasing evidence that structural cells of the airways, such as epithelial cells, airway smooth muscle cells, endothelial cells, and fibroblasts, are a major source of inflammatory mediators in asthma.[3]

Suppression of this inflammation by glucocorticoids controls and prevents these symptoms in the vast majority of patients,[4] and if used appropriately, these patients usually have no problems in terms of adverse effects. However, 5% to 10% of asthmatic patients do not respond

Abbreviations used

AHR: Airway hyperresponsiveness
AP-1: Activator protein 1
ARE: Adenylate-uridylate–rich element
BAL: Bronchoalveolar lavage
CBP: Cyclic AMP response element binding protein (CREB) binding protein
CD: Corticosteroid dependent
COPD: Chronic obstructive pulmonary disease
CR: Corticosteroid resistant
CS: Corticosteroid sensitive
GR: Glucocorticoid receptor
GRE: Glucocorticoid response element
HAT: Histone acetyltransferase
HDAC: Histone deacetylase
HFA: Hydrofluoroalkane
HuR: Hu antigen R
ERK: Extracellular signal–regulated kinase
IκBα: Inhibitor of nuclear factor κB
IKK: Inhibitor of NF-κB kinase
IRF-3: Interferon response factor 3
JAK: Janus-associated kinase
JNK: c-Jun N-terminal kinase
Kd: Dissociation constant
LBD: Ligand binding domain
MAPK: Mitogen-activated protein kinase
MKP-1: Mitogen-activated protein kinase phosphatase 1
NF-κB: Nuclear factor κB
NLS: Nuclear localization sequence
NO: Nitric oxide
Nrf2: Nuclear erythroid 2 p45-related factor 2
pMDI: Pressurized metered-dose inhaler
SOCS: Suppressor of cytokine stimulation
SRC-1: Steroid receptor coactivator 1
STAT: Signal transducer and activator of transcription
TCR: T-cell receptor
TTP: Tristetrapolin

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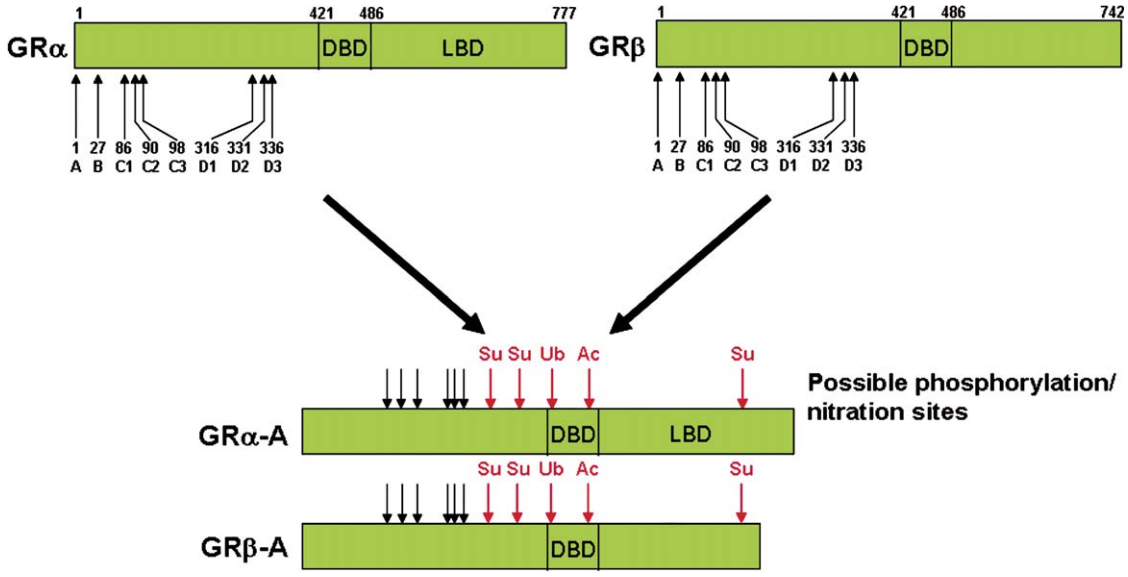

FIG 1. The GR can produce 8 distinct products (A, B, C1, C2, C3, D1, D2, and D3) by use of alternative translation initiation sites corresponding to methionine residues at 1, 27, 86, 90, 98, 316, 331, and 336. These alternative proteins can be produced from both GRα and GRβ transcripts. Posttranslational modification of GRs, particularly by means of phosphorylation and nitration, alters GR function and contributes to the potential for diverse function in distinct tissues. Other modifications, such as ubiquitination *(Ub)*, sumoylation *(Su)*, and acetylation *(Ac)*, are also shown.

well to glucocorticoid treatment, and these subjects account for approximately 50% of the total health care costs of asthma.[5,6] These subjects include patients with severe asthma, who are at increased risk of dying from asthma and who have continued morbidity from both their disease and the oral corticosteroids that are often used to treat it.[5,6] Furthermore, despite the availability of effective and relatively cheap treatments, there is still a considerable degree of undertreatment of severe asthma. For example, a European survey showed that only approximately 25% of patients with severe asthma were receiving inhaled corticosteroids.[7] In this review we will cover glucocorticoid receptor (GR) structure and function, limitations of glucocorticoid therapy, clinical characteristics of patients with severe treatment-insensitive asthma, and mechanisms underlying this insensitivity. Finally, we will discuss current treatment strategies and the potential for novel stand-alone or add-on therapies being developed that might be suitable for this group of subjects.

GLUCOCORTICOID ACTION

Structure of the GR and its gene

Glucocorticoids exert their effects by binding to a ubiquitously expressed 777-amino-acid GR that is localized to the cytoplasm of target cells. GR is a modular transcription factor in which specific domains play selective roles (Fig 1).[4] Although unliganded GR is thought to remain in the cytoplasm, evidence with nuclear export inhibitors suggests that a rapid active cycling of GR between the nucleus and cytoplasm might occur.[8,9] 2 GR isoforms (α and β) were originally described (Fig 2), with the nuclear GRβ having a dominant negative effect on GRα through the formation of GRα/GRβ heterodimers.

Yudt and Cidlowski[10] originally proposed the existence of additional isoforms of GR through use of different initiation sites within exon 2. Thus 4 distinct isoform of GR were proposed GRα-A, GRα-B, GRβ-A, and GRβ-B, depending on the methionine codon used and the GR N-terminus (Fig 1). Interestingly, GRα-B has twice the biologic activity of GR-αA *in vitro*, and this suggests that differential expression in various cell types might explain distinct cellular responsiveness.[10] To complicate things further, however, it has recently been reported that each single GR mRNA species can produce up to 8 functional GR N-terminal isoforms through leaky ribosomal scanning and shunting mechanisms (Fig 1).[11] These GR isoforms display diverse cytoplasm-to-nucleus trafficking patterns and distinct transcriptional activities. Importantly, in these studies the transcriptional responses to dexamethasone closely reflect the identity and abundance of the GR isoforms in human osteosarcoma cells. Advances in gene expression profiling techniques have allowed the effects of mutations in GR to be studied across a range of responsive genes in parallel. Such studies have revealed that different sets of genes are affected in different ways by each mutant.[12] For instance, some genes are dependent on the N-terminal AF-1 domain, whereas for others this activity is redundant. Because expression of some cofactor proteins, such as the peroxisome proliferator-activated receptor (PPAR) γ coactivator 1, is controlled both temporally and spatially,[13] the opportunity for selective modulation of glucocorticoid response through the manipulation of affinity for cofactors becomes apparent.