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Mechanisms of Reduced Glucocorticoid Sensitivity in Bronchial Asthma

Yasuhiro Matsumura
Akishima Hospital
Japan

1. Introduction

Although glucocorticoids (GCs) are among the most widely used compounds for treating asthma, patients with severe asthma sometimes have uncontrolled symptoms despite GC therapy. These patients have an impaired response to GCs, and may demonstrate a temporal reduction in GC reactivity when asthma deteriorates. Although it can be difficult to differentiate truly GC-resistant (GC-R) asthma (Hakonarson et al., 2005), it may correspond to severe asthma. It is defined as persistence of airway obstruction associated with an increase of less than 15% in the forced expiratory volume in 1 second (FEV1) following 2-week high-dose prednisolone administration, as evaluated mainly by reversibility of airflow obstruction (Corrigan & Loke, 2007; Woolcock, 1996). A definition referring to the inhalation route remains obscure (Hakonarson et al., 2005).

Co-administration of certain drugs, e.g. rifampicin, phenytoin and phenobarbital, which may possibly reduce steroid availability by affecting steroid metabolism through CYP3A4, should always be considered by clinicians.

Many processes involved in inflammation escape GC modulation, and resistance to the anti-inflammatory effects of these compounds is mediated via several mechanisms.

2. Actions of GCs

GCs upregulate mRNAs of molecules that suppress inflammatory cytokines and downregulate mRNAs of various inflammatory cytokines and chemokines. GCs increase gene expression of GC-induced leucine zipper (GILZ), mitogen-activated protein kinase phosphatase-1 (MKP-1), and the RNA-binding protein tristetraprolin. Expression of lipocortin-1, interleukin (IL)-10, IL-1 receptor antagonist, and inhibitor-κBα (I-κBα) is also induced. GCs suppress expression of epithelial-derived cytokines and chemoattractants that promote inflammatory cell recruitment. Cytokine expressions is inhibited through reversal of histone acetylation at sites of cytokine gene expression by direct interaction of GC receptors (GRs) with nuclear factor kappa B (NF-κB)-associated coactivators or by recruitment of histone deacetylases (HDAC) to the activated transcription complex.

Low concentrations of dexamethasone (DEX) reportedly rapidly regulate intracellular pH, Ca^{2+} and cAMP-dependent protein kinase activity, and inhibit Cl^- secretion in bronchial epithelial cells via nongenomic mechanisms (Urbach et al., 2006).

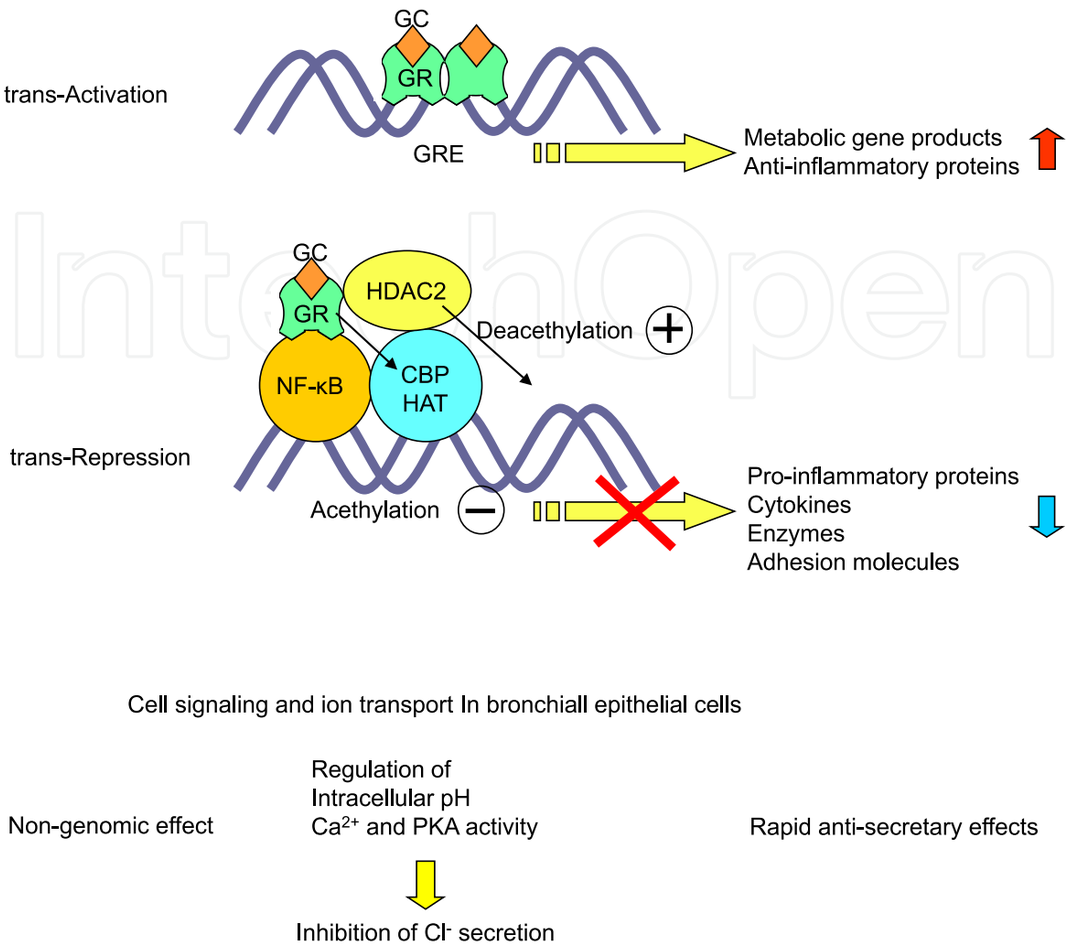

Fig. 1. **Anti-inflammatory actions of GC**
Trans-Activation: GRs bind to GREs and activate genes encoding β2-adrenergic receptors and anti-inflammatory proteins, such as secretory leukoprotease inhibitor (SLPI), MKP-1, IκB-α, and GILZ.
Trans-Repression: GRs inhibit transcription factors such as NF-κB and AP-1. GRs bind to co-activators, such as cAMP-response element-binding protein (CREB)-binding protein (CBP), and thereby inhibit HAT activity. GRs also recruit HDAC2 to the NF-κB -activated inflammatory gene complex.
Nongenomic effect: GCs rapidly regulate intracellular pH, Ca^{2+} and cAMP-dependent protein kinase (PKA) activity and inhibit Cl^- secretion in human bronchial epithelial cells, suggesting GC modulate secretion.

3. Transcription factors

Overexpression of chemokines and cytokines induces inflammatory processes in the airways of asthmatics. These mediators are downstream targets of transcription factors that antagonize steroid signaling via competition with GR-associated co-activators. This mutual transcriptional activity competition between GR and other regulators is among the mechanisms contributing to GC-R asthma.

3.1 GRs

GRs belong to the steroid/thyroid/retinoic acid nuclear receptor superfamily of transcription factor proteins.

Anti-inflammatory actions of GCs are often attenuated in inflamed tissues and differ among tissues. Ligand-dependent downregulation of GR expression via proteasomes was apparent in a respiratory epithelial cell line as compared to keratinocyte-like and hematopoietic cell lines, and was enhanced by lipopolysaccharide (LPS) via activation of p38 mitogen-activated protein kinase (MAPK), c-Jun N-terminal (JNK) and cyclin-dependent kinases (Hirasawa et al., 2009).

GRs are phosphorylated on specific serine residues after hormone binding and also by several kinases and phosphatases as a substrate. Although the precise roles of each specific phosphorylation event remain unclear, GR phosphorylation is involved in its stability, subcellular localization, interactions with coregulators, and transcriptional responses. Phosphorylation of GR on one or more residues adds increasing complexity to GC signaling and may explain how GR differentially regulates subsets of genes in various cell types. GR phosphorylation patterns via enhanced kinase activities of p38 MAPK, JNK, and GSK-3 in diseased cells contribute to different GC signaling within normal and diseased tissues (Bantel et al., 2002; Galliher-Beckley et al., 2008; Irusen et al., 2002; Itoh et al., 2002; Rogatsky et al., 1998; Szatmáry et al., 2004; Wang et al., 2004). GC-induced alterations in GR phosphorylation status are suggested to be associated with acquired GC resistance (Galliher-Beckley & Cidlowski, 2009).

Although phosphor-Ser226-GR reportedly associates with endogenous GRE-containing promoters and remains transcriptionally active, most studies suggest that Ser226 phosphorylation of GR attenuates GR signaling (Ismaili & Garabedian, 2004). Furthermore, JNK-mediated phosphorylation of GR at Serine 226 blunted hormone signaling by enhancing nuclear export of GR (Itoh et al., 2002). Activation of p38 MAPK by IL-2 and IL-4 induces GR phosphorylation and reduces ligand-binding affinity of GR in the nucleus (Irusen et al., 2002). Reduced GR ligand-binding affinity induced by IL-2/IL-4 (Kam et al., 1993; Sher et al., 1994) can be blocked with specific p38 MAPK inhibitors, suggesting that p38 MAPK inhibitors may reverse GC insensitivity (Irusen et al., 2002). IL-2/IL-4 pretreatment and p38 MAPK activation may affect the expression and/or activity of phosphatases, thereby inhibiting DEX-induced S211 phosphorylation of GR, which serves as a biomarker for activated GR in vivo, and preventing GR nuclear translocation in response to hormones (Goleva et al., 2009).

Sensitivity to GCs could reflect the degree of GC-induced GR nuclear translocation (Matthews et al., 2004). The IL-2/IL-4 combination alters GR nuclear translocation in T cells, an effect reversed by IFN-γ via inhibition of p38MAPK activation, suggesting critical role of INF-γ for maintaining GC sensitivity (Goleva et al., 2009). Combined budesonide and formoterol can stimulate GR and promote its translocation to the nucleus (Roth et al., 2002).

GRβ is an alternatively spliced form that binds to DNA but cannot be activated by GC, and reportedly antagonizes the trans-activating activity of GRα. GRβ expression is significantly increased in some patients with GC-R asthma and GRβ might be involved in GC resistance (Goleva et al., 2006; Hamid et al., 1999; Kelly et al., 2008; Pujols et al., 2001; Sousa et al.,

2000). CD38 expression upregulates the GRβ isoform, becoming insensitive to GC action thus providing a novel in vitro cellular model for ascertaining how GC resistance develops in primary cells (Tliba et al., 2006). A recent study demonstrated that GRβ promotes steroid insensitivity by controlling HDAC2 expression by inhibiting GC response elements in its promoter (Li et al., 2010). Hypoxia impairs anti-inflammatory actions of GCs by decreasing expression of GRα, but not GRβ, in A549 cells (Huang et al., 2009). However, the role of GRβ in modulating sensitivity to GCs remains controversial.

FK506-binding protein 51 (FKBP51) expression might affect clinical responsiveness to GCs (Denny at al., 2005; Reynolds et al., 1999; Vermeer et al., 2004a; Vermeer et al., 2004b). FKBP51 is an immunophilin chaperone protein residing in the cytoplasm before GC binding. GC dissociates GR from chaperone complexes, translocates GR to the nucleus, and modulates transcription. FKBP51 overexpression inhibits GR signaling by impairing nuclear translocation (Wochnik et al., 2005) and reducing GC binding (Denny et al., 2000). FKBP51 was induced by GCs (Rogatsky et al., 2003; Vermeer et al., 2003), suggesting FKBP51 to function in a negative-feedback loop limiting GR signaling. Airway epithelial cells collected from asthmatics showed high FKBP51 expression associated with a poor GC response (Woodruff et al., 2007).

3.2 Activator protein-1 (AP-1)

AP-1 expression is enhanced in asthmatic airways by Th2 cytokines (Demoly et al., 1992). GC resistance was associated with inability of GCs to deactivate JNK MAPK, as reflected by elevated phosphorylated c-Jun and c-fos gene expression in GC resistance and coinciding with decreased GR-AP-1 interaction intensity in steroid-resistant asthmatics as compared with peripheral blood mononuclear cells (PBMC) (Adcock et al., 1995; Takahashi et al., 2002), monocytes and T lymphocytes (Lane et al., 1998), immunohistochemical analysis of the tuberculin-mediated cutaneous response (Sousa et al., 1999), and bronchial biopsies (Loke et al., 2006) from GC-responsive patients.

3.3 NF-κB

NF-κB, a homo- or heterodimer consisting of subunits from the Rel family of proteins comprised of c-Rel, NF-κB1 (p50), NF-κB2 (p52), Rel A (p65), and Rel B, is activated by a broad range of inflammatory and environmental stimuli, e.g. tumor necrosis factor-α (TNF-α), IL-1β, IL-2, leukotriene B4, allergens, mitogens, LPS, viral infection, oxidative stress, and reactive oxygen exposure. The inflammation target is the prevalent heterodimer NF-κB p65-p50. p50 can increase DNA binding and p65 confers transcriptional regulation.

In patients with bronchial asthma, like other inflammatory diseases, NF-κB activity is increased. Increased activity has been reported in airway epithelial cells, submucosal cells, and sputum macrophages (Caramori et al., 2009; Hart et al., 1998; Vignola et al., 2001). Increases in activated p65, phosphorylated IκBα (p-IκBα), and IκB kinase β (IKKβ) have been documented in PBMC from subjects with severe uncontrolled asthma (Gagliardo et al., 2003). Rhinovirus infection activates NF-κB, leading to cytokine production and expression of adhesion molecules (Papi & Johnston, 1999; Zhu et al., 1996; Zhu et al., 1997), exacerbating asthma and steroid refractoriness. Excess active NF-κB in severe uncontrolled

asthma, which may reflect inflammatory stimuli, may impair the anti-inflammatory actions of GCs by interacting with GR.

3.4 GATA-3

The zincfinger transcription factor GATA-3 is essential for expression of the IL-4, IL-5 and IL-13 genes (Ray & Cohn, 1999; Zhu et al., 2006). Upon activation, GATA-3 is phosphorylated by p38 MAPK and translocates from the cytoplasm to the nucleus via the nuclear import protein importin-α. GCs inhibit GATA-3 function by rapidly blocking GATA-3 nuclear translocation via preferential binding to shared importin-α and also by inhibiting p38 MAPK via MKP-1 induction (Barnes, 2008).

3.5 CCAAT enhancer-binding protein (C/EBP)

C/EBP belongs to the basic region-leucine zipper transcription factor family. C/EBP-α, which binds the zinc finger motif of single active GR molecules and translocates to the nucleus, modulates GR function allowing induction of key anti-inflammatory mediators (Roth et al., 2004). Airway smooth muscle (ASM) cells from asthmatics are deficient in C/EBP-α, seemingly due to reduced translation controlling factor eukaryotic initiation factor-4E (eIF-4E) (Borger et al., 2009), resulting in poor inhibition of smooth muscle proliferation in vitro (Borger et al., 2007; Roth & Black, 2009). Budesonide plus formoterol simultaneously activates GR and C/EBP-α, resulting in synergistic stimulatory effects on p21 promoter activity and additive inhibitory effects on serum-induced proliferation (Roth et al., 2002).

3.6 Interferon regulatory factor-1 (IRF-1)

Recent investigations demonstrated elevated IRF-1, an early response gene involved in diverse transcriptional regulatory processes, in cells exposed to multiple cytokines that reduce GC responsiveness. IRF-1 promotes GC insensitivity in human ASM cells by interfering with GR signaling (Tliba et al., 2008). Inhibition of GR function by IRF-1 involves its interaction with transcriptional co-regulator GR-interacting protein 1 (GRIP-1). Under GC-R conditions, cytokines enhance expression of IRF-1, depleting GRIP-1 from the GR complex, thereby reducing transcriptions of GR-dependent genes such as MKP-1 and promoting expressions of IRF-1-dependent pro-inflammatory genes such as CD38 (Bhandare et al., 2010). As IRF-1 expression is markedly increased after viral infections, suppressive effects of IRF-1 on GC signaling may explain the reduced GC responsiveness in asthmatics experiencing viral infections (Kröger et al., 2002; Vianna et al., 1998; Yamada et al., 2000).

4. Chromatin modification; histone acetyltransferase (HAT) and HDAC

Reduced HDAC activity and reciprocally increased HAT activity are reported to be among the mechanisms underlying reduced GC sensitivity in bronchial asthma patients (Ito et al., 2002a). Patients with severe asthma have diminished GC sensitivity of PBMC compared to those with nonsevere asthma, associated with reduced HDAC activity paralleling impaired GC sensitivity (Hew et al., 2006). HDAC2 deacetylates GR, enabling p65–NF-κB association and subsequent attenuation of pro-inflammatory gene transcription (Ito et al., 2006). Low-dose theophylline restores HDAC activity in vivo (Ito et al., 2002b).

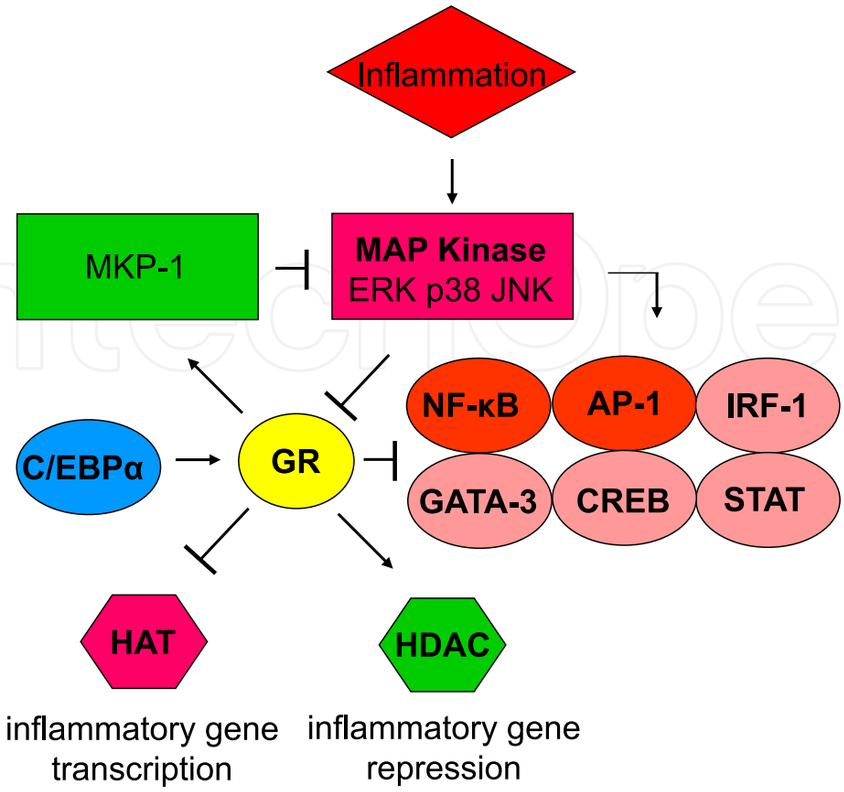

Fig. 2. **Intracellular factors and pathways of GC-R asthma.**
GC acts through switching on the expression of anti-inflammatory genes such as MKP-1 or switching off inflammatory genes through negatively regulate the activity of various other DNA-bound transcription factors, including NF-κB, AP-1 ,CREB, IRF-1, STAT, and GATA-3, via the transrepression mechanism or tethering mechanism. Inflammatory stimulation provokes activation of protein kinase pathways and transcription factors, resulting in attenuation of GR function and reduction of HDAC activity or recruitment.

5. Protein kinase signaling

Intracellular protein kinases are involved in the expression and activation of inflammatory mediators in the airways. MAPK family members, e.g. p38MAPK, JNK and extracellular signal-regulated kinase (ERK), are implicated in airway inflammation via activation of pro-inflammatory transcription factors including AP-1 and NF-κB, or via regulation of stabilization and increased translation of pro-inflammatory cytokine mRNA, dependent on conserved AU-rich elements in the 3′-UTRregion (Dean et al., 2004).

GCs not only induce MKP-1, an endogenous inhibitor of MAPK genes, but also reduce its degradation (Abraham et al., 2006; Clark, 2003). MKP-1 inhibits MAPK pathways and thereby inhibits JNK and to a lesser extent ERK.

Alveolar macrophages from patients with severe asthma show reduced inhibition of cytokine release by DEX with increased p38 MAPK activation, possibly resulting from impaired MKP-1 inducibility (Bhavsar et al., 2008), suggesting that GC insensitivity in severe asthma could be improved by p38 MAPK inhibitors (Bhavsar et al., 2010).

Moreover, GC responses of GC-R patient samples were restored by adding MAPK inhibitors (Goleva et al., 2009; Irusen et al., 2002; Li et al., 2004; Tsitoura & Rothman, 2004). Thus, MAPK-mediated inhibition of GR function appears to be key to GC resistance.

In GC-R asthma patients, increased p38 MAPK phosphorylation corresponds to reduced induction of dual-specificity phosphatases (DUSP) 1 expression (Bhavsar et al., 2008). Taken together, these observations suggest GC unresponsiveness to play central roles in MAPK dysregulation and probably also impaired DUSP1 induction.

Cytokine signaling, including type I interferon signaling, through cognate Jak/signal transduction and activators of transcription (STAT) pathways is reported to be unaffected or even stimulated by GR. Inhibition of JAK/STAT signaling may be of therapeutic benefit in GC-R airway disease (Clarke et al., 2010; Flammer et al., 2010).

PI3K plays an integral role in the immune system, for both mast cells and eosinophil function (Marwick et al., 2010), and may contribute to GC sensitivity by reducing HDAC activity (Ito et al., 2007). Therapeutic inhibition of PI3Kδ is reported to restore GC function in oxidative stress-induced GC-insensitive mice (Marwick et al., 2009).

6. Cytokine-induced GC insensitivity

Inflammatory cytokines alter GC cellular responses. Cytokines from Th2 cells are implicated in the pathogenesis of athma. IL-4 and IL-13 switch B cells to IgE synthesis, IL-5 plays a role in eosinophil maturation and survival, and IL-13 regulates airway hyper-responsiveness (AHR) and mucus hyperplasia**.** A study of bronchoalveolar lavage (BAL) fluid showed significantly greater numbers of cells expressing IL-2 and IL-4 mRNA in GC-R than in GC-sensitive asthmatics (Leung et al., 1995). Bronchial biopsy specimens from GC-R asthma patients revealed overexpression of IL-2, IL-4 and IL-13 and reduced GR affinity of inflammatory cells (Leung et al., 1999; Szefler & Leung, 1997).

IL-33, described as a promoter of Th2 immunity and systemic inflammation (Schmitz et al., 2005), is expressed at higher levels in ASM cells of asthmatics. DEX failed to abrogate TNF-α-induced IL-33 expression (Préfontaine et al., 2009).

TNF-α, a pro-inflammatory cytokine, is often associated with conditions that might activate innate immunity in the lung. Upregulation of the TNF-α axis in bronchial asthma with reduced sensitivity was reported (Berry et al., 2006; Howarth et al., 2005; Morjaria et al., 2008). TNF-α is produced by Th1 cells and macrophages and to a lesser extent mast cells in ASM, possibly inducing AHR. TNF-α is increased in BAL and bronchial biopsy specimens from severe asthma patients and is associated with GC-R (Howarth et al., 2005). TNF-α suppresses GC responsiveness in monocytes (Franchimont et al., 1999) and upregulates pathways involved in chronic airway remodeling and subepithelial fibrosis (Sullivan et al., 2005). TNFα upregulates the ERK1/ERK2 and p38MAPK pathways and induces expression of CXCL8, a neutrophil chemoattractant. Activation of the ERK1/ERK2 MAPK cascade is completely insensitive to actions of GCs in ASM cells and is involved in neutrophil recruitment contributing to inflammation (Robins et al., 2011).

Cytokines associated with Th1 immunity rather than allergic Th2 responses may contribute to the pathogenesis of severe GC-R asthma (Heaton et al., 2005). Th1 cells induce steroid-resistant AHR through an INF-γ/TLR4-MyD88-dependent mechanism after LPS-priming of

the innate host defense system (Yang et al., 2009). Although interferon γ (IFN-γ), a Th1 cytokine, prevented airway inflammation, some studies suggest that Th1 cells, secreting IFN-γ, might cause severe airway inflammation (Cui et al., 2005; Hansen et al., 1999). Sputum IFN-γ levels were markedly increased in airway cells obtained by sputum induction in patients with moderate to severe asthma and nonallergic asthma (Truyen et al., 2006). IFN-γ is expressed by an increased percentage of cells in the airways of severe asthmatics (Shannon et al., 2008).

TNF-α and IFN-γ synergistically enhance transcriptional activation of interferon- γ -inducible protein-10 (CXCL10), a potent chemoattractant for mast cells and T lymphocytes, cells implicated in asthma pathophysiology and elevated in patients suffering viral exacerbation of asthma, in human ASM cells via STAT-1, NF-κB and the transcriptional coactivator CREB-binding protein. Abrogation of JAK2 and subsequent STAT-1 signaling was more effective than fluticasone in an in vitro model of steroid-resistant inflammation, suggesting JAK/STAT signaling inhibition to be of therapeutic benefit in GC-R (Clarke et al., 2010).

Dysregulation of INF-γ producing Th1 cells or IL-10-producing regulatory T cells can counterbalance the number of Th2 cells. IL-10, a potent anti-inflammatory and immunosuppressive cytokine, appears to correlate inversely with the incidence and/or severity of asthma (Akdis et al., 2004; Borish et al., 1996; Heaton et al., 2005; Lim et al., 1998). Induction of IL-10 synthesis may contribute to the clinical efficacy of GCs in allergy and asthma. CD4+ T cells from GC-R asthmatics show markedly reduced capacity to synthesize IL-10, which inhibits pro-inflammatory cytokine production, antigen presentation, T cell activation and mast cell and eosinophil function, following in vitro stimulation in the presence of DEX, as compared with those from GC-sensitive patients with similar disease severity (Hawrylowicz et al., 2002).

Thus, GC-R asthma is associated with an altered cytokine gene expression profile; i.e. failure to suppress production of inflammatory cytokines and to induce production of anti-inflammatory cytokines.

Dehydroepiandrosterone (DHEA) can reverse cytokine imbalances associated with asthma, possibly preventing and attenuating allergic airway inflammation. Clinically, a steroid-sparing effect is observed with DHEA. DHEA and its analogs might prove useful in reversing relative GC-insensitivity in patients with GC-R asthma (Kasperska-Zajac, 2010).

7. Inflammatory cells

In severe asthma, pathological features different from those in mild-to-moderate asthma include mixed Th2/Th1 phenotypes with possible Th17 or regulatory T cell involvement. This type of asthma is GC-refractory.

Some asthma patients have neutrophils instead of eosinophils in their sputum. In general, asthma associated with neutrophils tends to show increased airway gland secretion, AHR, tissue destruction and airway remodeling, resulting in a severe condition (Douwes et al., 2002; Wenzel et al., 1998; Wenzel, 2009). Epidermal growth factor receptor (EGFR) (Puddicombe et al., 2000), which correlates with IL-8 (Hamilton et al., 2003; Hamilton et

al., 2005), could contribute to sustained neutrophilic inflammation. Subjects with neutrophilic asthma have increased activation of proteolytic enzymes, such as neutrophil elastase, indicating protease/anti-protease imbalance, as compared with other asthma phenotypes (Simpson et al., 2005). Moreover, it is characterized by a poor response to GC (Green et al., 2002; Pavord et al., 1999; Pavord, 2007). A mouse model suggested GC-R neutrophilic inflammation in acute exacerbation of asthma to be related to impaired nuclear recruitment of HDAC2, leading to ongoing enhanced expression of neutrophil chemoattractant and survival factors (Ito et al., 2008). The neutrophil infiltrates in these patients suggest activation of innate host defense pathways. This is consistent with evidence that infection and allergen exposure function synergistically in the pathogenesis of asthma exacerbations.

In a mouse model, Th17 cells, which play a central role in regulating neutrophilic inflammation during infection, were linked to GC-R AHR (McKinley et al., 2008). IL-17 is reported to be increased in the lungs, sputum, and BAL fluid of asthmatics (Bullens et al., 2006), and its expression level correlates with disease severity (Kawaguchi et al., 2009). IL-17 is especially important for neutrophil recruitment (Pène et al., 2008). Th17 cytokine responses are not sensitive to DEX. Th17 cell-mediated airway inflammation and AHR are steroid-resistant, indicating a potential role of Th17 cells in GC-R asthma. IL-17F plays a pro-inflammatory role in asthma, by activating transcription factors such as C/EBPβ, C/EBPγ and NF-κB.

8. Other novel intracellular mechanisms causing GC-R

Amphiregulin is secreted by human mast cells after exposure to antigens via aggregation of FcεRI, resulting in sputum production. Its expression is not inhibited by DEX. This may explain GC treatment being largely ineffective against sputum overproduction (Okumura et al., 2005).

Cofilin is a novel factor causing GC-R. Cofilin is known to promote actin depolymerization and filament severing. Cofilin 1, the evolutionarily conserved ADF/cofilin family, is crucial for many cellular processes, e.g. cell motility, cell division and membrane organization. The inhibitory action of cofilin on GR may have physiological relevance. Overexpressions of cofilin and actin as well as chemical cytoskeletal disruption changed the subcellular receptor distribution and upregulated c-Jun, possibly explaining the inhibitory mechanism of cofilin-1. Increased cofilin-1 expression is important for regulating GC sensitivity in peripheral blood lymphocytes of patients with severe treatment-resistant asthma (Vasavda et al., 2006).

9. Air way structure and remodeling

The effects of GC on airway remodeling are not completely understood. Airway remodeling is associated with increased deposition of extracellular matrix (ECM) proteins such as type I collagen. Immunoreactivity of type I collagen was not reduced in the submucosa of moderate to severe asthmatics after a 2-week oral GC course (Chakir et al., 2003). Overexpression of AP-1, which is known to be involved in regulating the procollagen-α II promoter by inhibiting its activity, impairs GC inhibition of collagen production by fibroblasts in asthmatics (Jacques et al., 2010).

The ratio of matrix metalloprotease (MMP)-9 to tissue inhibitor of MMP (TIMP)-1 is higher in the lungs of patients with severe asthma. MMP-9 is produced in neutrophils (Cundall et al., 2003). This is poorly inhibited by GCs. Eosinophilic asthma is characterized by active MMP-9 without free elastase (Simpson et al., 2005). DEX upregulates TIMP-1 mRNA in BAL fluid cells from patients with GC-sensitive asthma, but not in cells from those with GC-R asthma. Inability of GC to enhance TIMP-1 production shifts the MMP-9/TIMP-1 ratio in GC-R asthma, potentially promoting proteolytic activity and possibly resulting in abnormal tissue remodeling of airways (Goleva et al., 2007), leading to reduced lung function and β-agonist reversibility in these patients.

10. Environmental and behavioral factors

The classical macrophage activation and induction of LPS signaling pathways along with high endotoxin levels in BAL fluid from GC-R asthma patients suggest LPS exposure to contribute to GC-R asthma (Goleva et al., 2008).

Increased T-cell receptor vβ8+ T cells in BAL fluid of subjects with poorly controlled asthma suggests a role for microbial superantigens (Hauk et al., 1999). Microbial superantigens may contribute to GC insensitivity through induction of GR (Hauk et al., 2000). Microbial superantigens induce human T-cell resistance to GC, via the Raf-MEK-ERK1/ERK2 pathway of T-cell receptor signaling, which leads to GCRα phosphorylation and inhibition of DEX-induced GCRα nuclear translocation (Li et al., 2004). This may occur in exacerbation of asthma symptoms by bacterial infection.

Clinically, bronchial asthma patients who smoke have an impaired GC response as compared to nonsmokers (Chaudhuri et al., 2006). The sputum of asthmatic patients who smoke contains more neutrophils and CXCL8, which is closely associated with severe asthma (Thomson et al., 2004). Smoking increases NF-κB activity, resulting in increased expression of inflammatory genes such as IL-8, MMP and monocyte chemoattractant protein. Smoking can inhibit GR function by suppressing GR-associated HDAC2 activity and expression (Ito et al., 2001). It also reduces the GRα:β ratio in PBMC (Livingston et al., 2004), and GC insensitivity in smokers with asthma may be more generalized, affecting tissue sites other than the airways (Livingston et al., 2007).

In asthma patients, reduced vitamin D levels are associated with impaired lung function, increased AHR and reduced GC responsiveness (Ginde et al., 2009; Sutherland et al., 2010). Impaired induction of IL-10 by GCs in T cells from GC-R asthmatics can be reversed by vitamin D3 and IL-10 (Xystrakis et al., 2006). This may reflect IL-10 increasing GR expression by human $CD4^+$ T cells while vitamin D3 overcomes ligand-induced downregulation of GR. Vitamin D reduced human ASM expression of chemokines, including fractalkine and CX_3C chemokine (Banerjee et al., 2008; Sukkar et al., 2004). Thus, vitamin D may hold promise in treating GC-R asthma.

Asthma appears to be more severe in obese individuals (Moore et al., 2007). Obese asthma patients have increased illness severity and altered responses to conventional therapy, as well as leukotriene antagonists (Sin & Sutherland, 2008), as compared with lean asthmatics. Elevated body mass index is associated with a blunted in vitro response to DEX in asthma patients. MKP-1 induction by GC is impaired in PBMC and alveolar macrophages from obese asthmatics. Increased TNF-α in overweight and obese patients with asthma might be involved in downregulation of MKP-1 (Sutherland et al., 2008).

Extracellular factors	Reported GR-R mechanisms
Viral infection	NF-κB ↑ IRF-1 ↑
Microbial superantigens	GRα phosphorylation ↑
	GRα nuclear translocation ↓
Smoking	NF-κB ↑
	HDAC ↓
	GR α : β ratio ↓
Vitamin D ↓	GR downregulation ↑
	Chemokines ↑
Obesity	TNF-α ↑
	MKP-1 ↓

Table 1. **Extracellular factors and reported mechanisms of GC-R.**
In general, the factors exacerbate asthma symptoms occur largely at the same time the factors of GC-R. Those extracellular factors control the intensity of inflammation,which may explain the very common clinical observation that resistance is relative, and patients often respond to high doses of GCs. GC-R asthma may be attributable mostly to reduced GR function resulting from enhanced activations of AP-1 and NF-κB and upstream kinase pathways, or reduced HDAC activity.

11. Conclusions

The inflammatory processes in asthma are complex and heterogeneous (Anderson, 2008; Gibson et al., 2001). GC insensitivity may contribute to disease severity. GC-R asthma is usually an acquired condition. Variable intensity of inflammation may explain the very common clinical observation that resistance is relative. Reduced GC sensitivity in asthmatics is largely due to altered activation of GR by upstream kinase activity, enhanced activation of AP-1 and NF-κB or reduced HDAC activity, associated with inflammation. Th2 independent mechanisms tend to involve GC-R. Understanding the contributing factors and cellular and molecular mechanisms of GR-asthma is important for identifying new targets for biological intervention.

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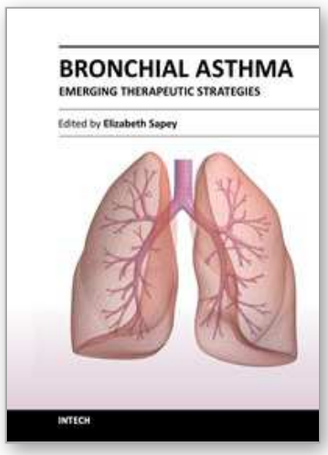

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Asthma remains a serious health concern for millions of people globally. Despite continuing research interest, there have been few advancements that impact clinically on patient care, potentially because asthma has been treated as a homogeneous entity, rather than the heterogeneous condition it is. This book introduces cutting-edge research, which targets specific phenotypes of asthma, highlighting the differences that are present within this disease, and the varying approaches that are utilized to understand it.

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Phone: +385 (51) 770 447
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