Steroid Resistance in Asthma: Mechanisms and Potential Therapies

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Overview

- Pathophysiology
- Distinct type of asthma/inflammation
- Improve current steroids
- Induced steroid insensitivity
  - Th2 cytokines
  - Infections, IL-17
- Approaches to restore steroid responsiveness
  - Novel anti-inflammatory approaches
  - Reversal of steroid insensitivity

Asthma pathophysiology

(Busse and Lemanske, NCIW, 2001)
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Clinical phenotypes of asthma

- Anti-TNF - responsive
- Xolair - responsive
- Anti-IL-5 - responsive
- Antibiotic - responsive
- Anti-IL-4 - responsive

Bel EH. Curr Opin Pulm Med 2004; 10: 44-50
Wenzel S, Lancet 2006; 366: 804-813

Severe
- Anti-TNF - responsive
- Anti-IL-5 - responsive
- Anti-IL-4 - responsive
- Xolair - responsive
- Antibiotic - responsive

Nair P et al., 2009
Haldar et al., 2009

Patients with >3% sputum eosinophils despite steroids

Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia
Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma

Nair P et al., 2009
Haldar et al., 2009

Cumulative number exacerbations

Am J Respir Crit Care Med 183: 1007-1014, 2011

- Changes in FEV₁ or PC₂₀ Metacholine challenge: anti-IL-13 is shown to be not so different from placebo
- However, in NEJM Aug 2011: some beneficial effects in a subset of asthmatic patients on lung function (those who had clear evidence for excessive activation of IL-13 in the airways)
Effect of anti-TNFα in patients with refractory asthma

- Despite the promising early effects, improvement in patients who had activated TNF in Berry MA et al., *N Engl J Med*. 2006; 354(7): 697-708...

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A Randomized, Double-blind, Placebo-controlled Study of Tumor Necrosis Factor-α Blockade in Severe Persistent Asthma

*Am J Respir Crit Care Med* 179: 549-558, 2009

- No dose dependent beneficial effect of anti-TNF therapy
- A dose dependent increase in severe detrimental side effects

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Spectrum of steroid responsiveness

- Mild
- Moderate
- Severe
- Steroid dependent
- Resistant

- Asthma control
- Inhaled steroids (mg)
- Oral steroids

- Systemic side effects

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Costs of severe asthma

Prevalence Costs
Severe >50%
Moderate
Mild

How steroids work: can we improve current steroids?

Classical mechanism of glucocorticoid action

Glucocorticoid Anti-inflammatory mediators
Cell membrane

mRNA

Nucleus GRE Steroid-responsive target genes

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Dexamethasone induction of MKP-1 in human macrophages

Molecular actions of glucocorticoids

Dissociation of corticosteroid effects
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GR immunolocalisation in sputum cells

Epithelial cell

Cytoplasm

Nuclear

Macrophage

Cytoplasm

Nuclear

Usmani et al., AJRCCM 2005

Effect of FP & salmeterol on GR translocation

- 8 steroid naïve asthmatics, cross-over
- Inhaled single drug dose, sputum induction

Weersink et al., AJRCCM 1997

- Protection from an AMP challenge is greater with a combination and greater than additive
- An enhanced anti inflammatory effect with combination of Fluticasone and Salmeterol
Relative steroid insensitivity is not confined to the airways

Skin blanching response to topical budesonide

Dex fails to suppress selected gene expression in BAL macrophages from severe SD asthma

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Effect of dexamethasone on TNFα-induced GM-CSF production in PBMC

Enhanced GRβ expression is associated with steroid resistance

- Dominant negative isoform of GR
  - Mainly localised to nucleus
  - Does not bind GC ligands
- Expression increased in patients with severe asthma
- Induced by factors associated with severe asthma
- Not seen in all patients with severe asthma
  - Same is true for most drivers of steroid insensitivity

Mitogen activated kinases (MAPKs) affect steroid responsiveness

Activated during the inflammatory response
  - Cell- and stimulus-dependent manner
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IL-2/IL-4 affect GR Kd: role of p38 MAPK

IL-2/IL-4 induce dex-insensitivity in PBMCs

GR nuclear translocation is reduced in IL-2/IL-4 
treated U937 cells: role of p38 MAPK

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Inhibition of p38 MAPK enhances Dex suppression of LPS-induced cytokine release

Combination of new safer MAPK inhibitors with a topical steroid may enable steroids to be effective in patients with severe disease with reduced risk of side-effects

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JNK activation is not repressed by prednisolone in SR asthma

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Induction of steroid insensitivity by TCR co-stimulation requires MEK activation  

MAPK inhibitors may offer a therapeutic solution for glucocorticoid resistance  

Infection and steroid responsiveness

Corticosteroid-resistant asthma is associated with classical antimicrobial activation of airway macrophages  

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Superantigen-induced GR insensitivity requires ERK activation and loss of GR nuclear import

Li et al., JACI 2004

RV-induced steroid resistance in asthma

Al-Ramli et al., JACI 2009

IL-17 expression is increased in severe asthma

Al-Ramli et al., JACI 2009
IL-17 attenuates steroids effects in mice

McKinley L et al., JI 2008

- Presence of IL-17 can modulate the ability of Dex to functionally reduce airway hyperresponsiveness
- In WT animals there is clear induction of hyperresponsiveness which is suppressed by Dex and Dex reduces T_{h}2 type inflammatory responses
- In the presence of over expression of IL-17 steroids no longer effective at suppressing airway hyperresponsiveness and they no longer suppress TH2 mediated inflammation and increase the presence of neutrophiles within the airways of these animals

Loss of anti-inflammatory mediators in steroid refractory severe asthma

↓ Proinflammatory cytokines
IL-1β, TNF-α, IL-6, GM-CSF

↓ Chemokines
IL-8, MIP-1α, RANTES, eotaxin

↓ Inflammatory enzymes
iNOS, COX-2

↓ Allergen responses
MHCII, CD23, B7-1, B7-2

↓ Th2 cytokines
IL-4, IL-13, IL-5

↑ Antiinflammatory proteins
IL-1R antagonist, TIMPs

IL-10: master inhibitory cytokine
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Vitamin D enhances IL-10 production from dex-stimulated CD4+ T-cells

Xystrakis et al., 2005

Vitamin D ingestion enhances IL-10 production from dex-stimulated CD4+ T-cells

Xystrakis et al., 2005

Patients who had been given therapeutic doses of vitamin D3 had an increased ability to produce IL-10 mRNA/protein

Smoking reduces steroid function in asthma

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Smoking and steroid responses in asthma
Chalmers GW et al., Thorax 2002

- Measured the ability of steroids to enhance lung function in asthmatic non-smokers and smokers
- Non smokers: steroids increased lung function and reduced Sputum Eos.
- Smokers: Fluticasone no longer had an ability to enhance lung function and there was no anti-inflammatory effect of steroids

Cigarette smoking inhibits the inflammatory response to corticosteroids in asthma

Altered glutathione homeostasis in children with severe asthma: ELF measurements

Fitzpatrick et al., JACI 2009

Oxidative stress prevents GR nuclear translocation in human fibroblasts
Okamoto et al., JBC 1999

- The increase in oxygen load seen in the airways of patients with severe asthma may be important
- The presence of H₂O₂ can prevent the ability of Dex to induce GR nuclear translocation
- This is reversed by the presence of an antioxidant NAC

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Oxidative stress induces steroid insensitivity in macrophages

Correlation between inhibitory effect of dex and HDAC activity in BAL macrophages

Cigarette smoke reduces HDAC activity in macrophages
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HAT and HDAC activity in asthmatic biopsies

Reduced HDAC and increased HAT activity in asthmatic children

Low dose theophylline enhances dexamethasone function under conditions of oxidative stress

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Randomisation strategy – smoking asthma

Smoking asthma – lung function (PEF)

Steroid responsiveness in severe asthma: summary

- CR is a syndrome – GWAS/unbiased analysis
- No single cause
  - Cytokine/mediator effects
  - GR affinity
  - GRβ expression
  - MAPK expression/activity
  - GR co-factor association
  - IL-10/IL-12 expression
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Heterogeneity of ‘causes’ of CS insensitivity: relevance to airways disease

- Microbial factors
- Allergens
- Smoking
- Obesity
- Vitamin D3

- Viruses, LPS, superantigens
- IL-2, IL-4, IL-13
- MAPK
- MAPK
- IL-1β
- HDAC, Suv39H1
- IL-10

Corticosteroid Insensitivity

Relationship between drivers of steroid resistance

- P38 MAP
- Th2 cytokines
- IL-17
- GR
- HDAC2
- GRβ

Conclusions

- CR is a syndrome
- Understanding pathophysiology of patients will
  - lead to novel anti-inflammatory treatments
  - lead to new combinations that enhance steroid actions
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