FEATURE

New Approaches to Corticosteroid Resistance

Written by Maria Vinall

Peter J. Barnes, DM, DSc, National Heart and Lung Institute, Imperial College, London, United Kingdom, spoke about how steroids suppress inflammation, why in some diseases there is variability of response, and what new approaches are on the horizon to deal with steroid resistance.

Glucocorticoids (corticosteroids; steroids) are among the world's most widely prescribed drugs. They are effective in many inflammatory and immune diseases, but they also fail in some seemingly similar diseases. Understanding why this happens requires an understanding of the inflammatory process.

Inflammation involves the increased expression of many inflammatory proteins (eg, cytokines, chemokines, enzymes, receptors, and adhesion molecules), most of which are regulated by transcription through the activation of proinflammatory transcription factors. The genes are switched on through acetylation of core histones and remodeling of the chromatin structure to allow active gene transcription. Steroids work by suppressing this process. They block transcription of inflammatory genes by reversing histone acetylation.

Inflammatory gene activation can be reversed through histone deacetylation. There are 11 histone deacetylases (HDACs) in humans. Although all 11 HDACs reverse histone acetylation and switch off gene transcription, only HDAC-2 switches off inflammatory genes. HDAC-2 is also heavily recruited by corticosteroid receptors into activated inflammatory genes to mediate suppression of inflammation by steroids [Ito K et al. *Mol Cell Biol.* 2000]. Both asthma and chronic obstructive pulmonary disease (COPD) are associated with airway inflammation characterized by inflammatory gene expression that is driven by proinflammatory transcription factors. Asthma is extremely sensitive to steroids, and in most patients it can be controlled by very low doses. By contrast, COPD is completely resistant to steroids. Corticosteroid resistance is also a major barrier to therapy for a number of other severe inflammatory diseases, including severe rheumatoid arthritis (RA), inflammatory bowel disease, diabetes, atherosclerosis, and multiple sclerosis.

Peer-Reviewed Highlights From the

American College of Rheumatology Annual Meeting

November 14–19, 2014
Boston, MA

Alveolar macrophages from nonsmokers, smokers, and patients with COPD show significantly different levels of HDAC activity with markedly lower levels in smokers and COPD patients [Ito K et al. *FASEB J.* 2001]. An examination of the lungs of patients with COPD found the expression of HDAC-2 to be extremely reduced with corresponding increases in interleukin (IL)-8 and marked increases in histone acetylation of IL-8 genes, which correlated with a reduction in HDAC-2 [Ito K et al. *N Engl J Med*. 2005].

Unlike in nonsmoking asthma patients, in whom inflammation is switched off through recruitment of HDAC-2, leading to suppression of inflammatory genes, in smoking asthma patients, oxidative stress generates peroxynitrate, which reduces HDAC-2, leaving these patients resistant to steroids. These patients have enhanced inflammation, which is why they have more severe or refractory disease. Inhibition of oxidative stress-dependent PI3 kinase delta (PI3K-δ) activation by a selective inhibitor or theophylline provides a novel approach to reversing corticosteroid insensitivity in COPD [To Y et al. *Am J Resp Crit Care Med.* 2010].

Theophylline activates HDAC, markedly potentiates steroid effects, and reverses steroid resistance [Cosio BG et al. *J Exp Med.* 2004; Ito K et al. *PNAS.* 2002] by directly targeting PI3K-δ (which is increased in COPD) and reducing its enzyme activity [To Y et al. *Am J Resp Crit Care Med.* 2010]. Other drugs that can also inhibit this pathway include nortriptyline, macrolide antibiotics (like solithromycin), and selective PI3K-δ inhibitors, as well as drugs that work further down the pathway.

NrF2 is a key transcription factor that regulates oxidative stress through the regulation of multiple antioxidant genes [Ishii Y et al. *J Immunol.* 2005; Rangasamy T et al. *J Clin Invest.* 2004]. NrF2 is increased in smokers due to the oxidative stress, but in COPD patients, who have even

more oxidative stress, it is not increased because it becomes acetylated. The key regulator of this acetylation is HDAC-2 [Malhotra D. *Am J Resp Crit Care Med*. 2008]. When HDAC-2 is reduced by oxidative stress, it leads to acetylation of NrF2, which impairs its transcriptional activation properties, leading to reduced expression of antioxidants, which further enhances oxidative stress, driving this inflammatory pathway.

This can be overcome by drugs that activate NrF2, some of which are naturally occurring substances like sulforaphane (found in broccoli). In COPD macrophages exposed to sulforaphane, the HDAC levels are increased, approaching normal [Malhotra D et al. *J Clin Invest*. 2011]. Sulforaphane is rather toxic and nonspecific, so investigators are searching for more effective NrF2 activators.

The fact that steroids do not work very well in COPD and severe asthma has led to the search for new anti-inflammatory treatments such as PDE4 inhibitors, sp38 MAP kinase inhibitors, IKK-2 (NF-κB) inhibitors, and pan-JAK inhibitors. Some of these are likely also being considered for RA, but there is a high risk of side effects, and thus inhaled delivery may be needed.

Prof Barnes proposes an alternative approach to addressing corticosteroid resistance, which is to restore steroid sensitivity. He suggests that this could be done by repurposing existing therapies, including low-dose oral theophylline, oral nortriptyline, or macrolides, or by developing new therapies, which could include inhaled P13Kσ, P13Kγ/σ, or nonantibiotic macrolides. He believes that these studies could move ahead quickly because some of the drugs are already available and in some cases they are inexpensive. Two large long-term controlled trials with theophylline in COPD are underway: the TWICS study [ISRCTN27066620] using low-dose oral theophylline (plasma concentration of about 5 mg/L) plus low-dose inhaled steroid, and the TASCS study [NCT02261727] with low-dose oral theophylline plus low-dose oral steroid (prednisone 5 mg). These findings may have clinically relevant applications in rheumatology.

The editors would like to thank the many members of the 2014 American College of Rheumatology presenting faculty who generously gave their time to ensure the accuracy and quality of the articles in this publication.