BASIC SCIENCE FOR THE CHEST PHYSICIAN

Leukotriene A₄ hydrolase: an anti-inflammatory role for a proinflammatory enzyme

Robert J Snelgrove

ABSTRACT

Neutrophils represent a prominent source of pathology in chronic lung diseases such as COPD, cystic fibrosis and bronchiolitis obliterans syndrome, where they maintain inflammatory (PGP degradation) roles that govern neutrophil recruitment. Lung epithelial cells are indiscriminate in toxicity and can cause significant bystander or ‘collateral’ damage to surrounding host tissue. Accordingly, neutrophils must be readily cleared from a site of infection, with persistent neutrophilia implicated in the pathology of chronic lung diseases such as chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF) and severe asthma. Anti-inflammatory steroids exhibit limited benefits in these diseases and have even been shown to promote neutrophil survival. There is therefore an urgent need to develop novel therapeutic strategies to alleviate neutrophil-mediated pathologies.

Signals that drive neutrophil recruitment and maintenance offer plausible therapeutic targets. Neutrophils are mobilised from the vasculature and into the lung in response to a broad array of chemoattractant signals. For a long time it has been known that fragments of structural proteins such as collagen and elastin that constitute the lung architecture can cause the recruitment of inflammatory cells. Proline-Glycine-Proline (PGP) is a peptide of just three amino acids, generated from collagen, that can recruit neutrophils by mimicking key sequences found in certain other neutrophil chemoattractants such as interleukin 8 (IL-8). PGP is generated from collagen by the sequential action of enzymes called matrix metalloproteinases followed by a secondary enzyme, prolyl endopeptidase. Neutrophils contain the full enzymatic repertoire required to generate PGP from collagen and are therefore capable of driving a self-sustained vicious circle of inflammation. Significant concentrations of PGP have been detected in chronic lung diseases such as COPD, CF and bronchiolitis obliterans syndrome, where they maintain neutrophilic inflammation at a time when other chemoattractant levels have subsided.

A recent paper published in Science describes a novel anti-inflammatory pathway whereby PGP is degraded to switch off neutrophilic inflammation. Influenza infection of mice elicits acute pulmonary neutrophilic inflammation with concomitant release of PGP-generating enzymes but no PGP. Failure to detect PGP was found to be due to the activity of an enzyme being released by cells into the extracellular environment that could degrade this peptide. This enzyme was found to be leukotriene A₄ hydrolase (LTA₄H). LTA₄H is classically recognised for a secondary activity that resides inside cells, where it converts leukotriene A₄ (LTA₄) into leukotriene B₄ (LTB₄). LTB₄ is an extremely inflammatory (LTB₄ generation) and protective enzyme (PGP degradation) that governs neutrophil recruitment. Lung epithelial cells and neutrophils were shown to be capable of releasing extracellular LTA₄H. The release by neutrophils suggests that the same cells normally coordinate the release of PGP-generating and PGP-degrading enzymes in order to resolve neutrophilic inflammation and limit tissue damage (figure IA).

If PGP is normally readily degraded to resolve neutrophilic inflammation, it is rational to question why PGP is present at all in chronic lung diseases with persistent neutrophilia. We demonstrated that cigarette smoke, a major risk factor in the development of COPD, chemically modified PGP by addition of an acetyl group (AcPGP). This modification enhanced the capacity of the peptide to recruit neutrophils and also protected it from

Correspondence to
Robert J Snelgrove, Imperial College London, Leukocyte Biology Section, National Heart and Lung Institute, Exhibition Road, London SW7 2AZ, UK; robert.snelgrove@imperial.ac.uk

Received 21 March 2011
Accepted 24 March 2011
protecting it from degradation by LTA4H while promoting its chemotactic pathway in two ways: (1) chemically acetylating PGP (AcPGP) and potential; and (2) selective abrogation of LTA4H PGP-degrading activity.

2o f2 Snelgrove RJ.

degradation by LTA4H. Furthermore, cigarette smoke selectively abrogated the capacity of LTA4H to degrade PGP while having minimal effect on its ability to generate LTB4 (figure 1B). Thus, cigarette smoke seems capable of driving this enzyme, with dual pro- and anti-inflammatory activities, towards a uniquely proinflammatory phenotype whereby LTB4 and PGP can act in tandem to drive the neutrophilic inflammation and pathology observed in COPD. Furthermore, it is intriguing that significant concentrations of PGP/AcPGP are observed in patients with CF, given the defective cystic fibrosis transmembrane conductance regulator-mediated chloride transport in these patients and the fact that chloride ions have been shown to enhance the capacity of LTA4H to degrade PGP. Ultimately, it may be that PGP degradation by LTA4H and acute neutrophilia are the norm and that PGP only persists when this system is perturbed by exogenous stimuli, such as cigarette smoke, or genetic influence.

It is prudent to question the significance of these findings in the context of therapeutic strategies that seek to inhibit LTA4H to reduce LTB4-mediated pathologies. Targeting enzymes crucial to the generation of LTB4 or blocking its receptor binding seem appealing therapeutic targets. Accordingly, there has been a significant pharmaceutical effort to generate LTA4H inhibitors, with Johnson and Johnson and deCODE having developed lead compounds with the latter now in phase II trials. However, these inhibitors seem unlikely to distinguish between the opposing activities of LTA4H and may inadvertently prevent PGP degradation leading to persistent neutrophilia. This is not to say that LTA4H inhibitors should be disregarded out of hand. Indeed, they have shown excellent therapeutic potential in a number of animal models. LTB4 is an extremely potent proinflammatory mediator with many effects on multiple cell types while PGP is far more limited in both its potency and range, so it may be that PGP is the lesser of two evils. The significance of LTA4H in different instances will also be complicated by the availability of enzymes that generate LTA4 and PGP, or a source of acetylation for PGP. It is feasible that the relative importance of each of the LTA4H pathways will be disease- and even patient-specific, but it would be wise to be vigilant to adverse effects of LTA4H inhibitors when testing their efficacy and safety. A series of studies have shown that the opposing activities of LTA4H reside in distinct but overlapping sites within the enzyme, and thus selective modulation of these activities should prove feasible and could offer novel therapeutic avenues to pursue.5

Funding This work was supported by the Wellcome Trust (082727/Z/07/Z).

Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

REFERENCES
Leukotriene A4 hydrolase: an anti-inflammatory role for a proinflammatory enzyme

Robert J Snelgrove

Thorax  published online April 17, 2011

Updated information and services can be found at:
http://thorax.bmj.com/content/early/2011/04/07/thoraxjnl-2011-200234

These include:

References
This article cites 5 articles, 2 of which you can access for free at:
http://thorax.bmj.com/content/early/2011/04/07/thoraxjnl-2011-200234#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/