Mathematical modelling of airway smooth muscle cell proliferation and apoptosis in asthma

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Background

Asthma remains an area of considerable unmet medical need despite the availability of medicines that are effective for large numbers of patients; no cures exist and available therapies may be ineffective in some patients with moderate/severe forms of the disease. It is estimated that 300 million people currently suffer from the disease globally, and that by 2025 this figure will be closer to 400 million. Few new drugs have made it to the clinic in the last 50 years, with many which perform well in preclinical animal models of asthma, failing in humans due to lack of safety and efficacy. The failure to translate promising drug candidates from animal models to humans has led to questions about the utility of the *in vivo* studies and demand for more predictive models and tools based on the latest technologies. The NC3Rs (www.nc3rs.org.uk) and MRC held a joint workshop with experts from academia and the pharmaceutical industry to devise a new disease modelling framework to better understand human asthma, and accelerate the development of safe and efficacious new asthma drugs that go beyond symptomatic relief. The development of more powerful mathematical modelling approaches was considered an integral part of this framework.

Health condition

The last 20 years has seen considerable advances in our understanding of the pathological basis of asthma at cellular, molecular and genetic levels, however the fundamental causes of the disease and the reasons for increased prevalence rates remain unclear. What was once considered a single disease is now recognised as a complex and heterogeneous syndrome made up of a collection of sub-phenotypes (e.g. viral induced, allergic, non-allergic, intrinsic, extrinsic, occupational, persistent, seasonal, exercise induced, nocturnal and steroid resistant) with differing immunology, pathology, clinical expression, response to treatments, and long-term outcomes; the severity of which can be affected by the patient's age, genetic background and environmental factors. More recently cluster analysis applied to asthma of varying severity has led to further disease substratification.

Airway smooth muscle and asthma

The role of airway smooth muscle (ASM) in asthma is extremely important since it is widely recognised as the key determinant of airway narrowing in the disease, and as an emerging effector of airway inflammation and remodelling, contributing to airway hyperresponsiveness (AHR) [1]. There is however a lack of mechanistic information on human asthma, especially of AHR, despite intensive research in numerous species which has led to questions being raised about the utility of current animal models for studying this aspect of the disease. Key questions still remain regarding ASM effects on extracellular matrix organisation and smooth muscle turnover, including ASM proliferation rates, where excess smooth muscle in the airways originates, and the role of apoptosis in normal and diseased smooth muscle turnover.

Study group challenge

As stated above, the exact role of ASM in asthma remains uncertain. An increase in ASM mass may exacerbate airway contraction resulting in more pronounced airway narrowing, but ASM myocytes also produce biologically active agents like pro- and anti-inflammatory mediators, cell adhesion molecules, lipid mediators, chemokines and cytokines suggesting they also play an active role in the pathophysiology of asthma [2].

ASM turnover:

Recent thermoplasty approaches support the theory that ASM plays a prominent role in asthma. Reducing ASM mass in asthma patients in this way reduced AHR to an inhaled constrictor and modestly increased flow rates that persisted for almost a year. These findings suggest other more practical methods to reduce ASM mass should be explored, including ridding the airways of smooth muscle by stimulating apoptosis of ASM [3,4]. However in order to do this, ASM myocyte turnover rates, and apoptotic and survival characteristics in health and disease need to be better defined.

The airway epithelium produces a cocktail of mitogenic mediators, including platelet-derived growth factor, epidermal growth factor, fibroblast growth factor, TGF-β, TNF-α, and IL-1β. These proliferative factors encourage the ASM to migrate from the anti-proliferative environment of the ASM bundle towards the epithelium, contributing to the remodelling seen in the airways of asthmatics [3,5]. This has been further supported by recent studies using chemokines upregulated in asthmatic airways – IL-8, RANTES, eotaxin, and MIP-1α – which increased ASM proliferation and migration, and suppressed apoptosis [6].

Perhaps surprisingly however, proteases released by neutrophils (important components of airway inflammation) have been shown to degrade the matrix to which myocytes attach, causing myocytes to detach and subsequently apoptose [4]. Other mediators such as decorin [7] and Fas [8] play a role in normal ASM turnover, which becomes dysregulated under pathophysiological conditions.

The challenge:

Determine the extent to which cell proliferation and apoptosis participates in the turnover rates of human ASM cells in normal and diseased tissue; including the nature of apoptotic and survival characteristics of the ASM, and the signals that the ASM receives under pathophysiological conditions.

It is anticipated this approach will integrate existing human and animal data to develop new innovative models which will better predict ASM turnover and its role in asthma whilst reducing reliance on animals.

References:

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