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Airway smooth muscle in asthma: Linking contraction and mechanotransduction to disease pathogenesis and remodelling

Peter B. Noble [a, 1], Chris D. Pascoe [b, 1], Bo Lan [b, c, 1], Satoru Ito [d, 1], Loes E.M. Kistemaker [e, 1], Amanda L. Tatler [f, 1], Tonio Pera [g, 1], Bindi S. Brook [h, 1], Reinoud Gosens [e, 2], Adrian R. West [i, j, *, 3]

[a] School of Anatomy, Physiology and Human Biology, University of Western Australia, WA, Australia
[b] Center for Heart Lung Innovation, University of British Columbia, BC, Canada
[c] Bioengineering College, Chongqing University, Chongqing, China
[d] Department of Respiratory Medicine, Nagoya University, Aichi, Japan
[e] Department of Molecular Pharmacology, University of Groningen, The Netherlands
[f] Division of Respiratory Medicine, University of Nottingham, United Kingdom
[g] Center for Translational Medicine, Thomas Jefferson University, Philadelphia, PA, USA
[h] School of Mathematical Sciences, University of Nottingham, United Kingdom
[i] Department of Physiology, University of Manitoba, MB, Canada
[j] Biology of Breathing, Manitoba Institute of Child Health, MB, Canada

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ABSTRACT

Asthma is an obstructive airway disease, with a heterogeneous and multifactorial pathogenesis. Although generally considered to be a disease principally driven by chronic inflammation, it is becoming increasingly recognised that the immune component of the pathology poorly correlates with the clinical symptoms of asthma, thus highlighting a potentially central role for non-immune cells. In this context airway smooth muscle (ASM) may be a key player, as it comprises a significant proportion of the airway wall and is the ultimate effector of acute airway narrowing.

Historically, the contribution of ASM to asthma pathogenesis has been contentious, yet emerging evidence suggests that ASM contractile activation imparts chronic effects that extend well beyond the temporary effects of bronchoconstriction. In this review article we describe the effects that ASM contraction, in combination with cellular mechanotransduction and novel contraction-inflammation synergies, contribute to asthma pathogenesis. Specific emphasis will be placed on the effects that ASM contraction exerts on the mechanical properties of the airway wall, as well as novel mechanisms by which ASM contraction may contribute to more established features of asthma such as airway wall remodelling.

1. Introduction

Asthma is an obstructive airway disease that affects an estimated 300 million people globally, with a principal functional abnormality of airway hyper-responsiveness (AHR) [1] that leads to recurrent symptomatic episodes of wheezing, breathlessness, chest tightness and coughing [2]. Asthma is widely regarded to be initiated as a chronic allergic and/or inflammatory disorder involving the infiltration and activation of Th-2 and Th-17 lymphocytes, eosinophils, neutrophils and mast cells within the airway wall [3]. Subsequently, chronic inflammation is believed to promote significant structural changes that are collectively termed airway wall remodelling; this encompasses airway smooth muscle (ASM) hypertrophy and hyperplasia, sub-epithelial fibrosis, microvascular remodelling, airway epithelial cell (AEC) metaplasia, and mucous cell hyperplasia [4,5].

Despite significant research many aspects of asthma pathogenesis remain unclear, and there is strong evidence that allergy and inflammation may not be a major driver of disease in a large

* Corresponding author. John Buhler Research Centre, Room 560, 715 McDermot Avenue, Winnipeg, MB R3E3P4, Canada.
E-mail address: Adrian.West@umanitoba.ca (A.R. West).
[1] Equal contributors, listed according to sequence of contributions in manuscript.
[2] Supervising author.
[3] Lead and contributing author.

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proportion of patients. In asthmatic and non-asthmatic subjects the degree of inflammatory changes in response to acute allergen exposure poorly correlate with changes in airway responsiveness [6,7], and there is strong evidence that many mild and moderate asthmatics do not have eosinophilic infiltration as assessed by sputum cytology, lavage and/or bronchoscopy [8,9]. Similarly, individuals with familial eosinophilia present with hypereosinophilic syndrome yet exhibit a lower prevalence of asthma than matched family members [10], while some severe asthmatics demonstrate eosinophilia, but levels of the Th-2 cytokines thought to drive asthma are not elevated [11]. Furthermore, while glucocorticoid treatment improves the health of the majority of patients, to the best of our knowledge no clinical trial has yet demonstrated complete reversal of AHR [12]. Lastly, there is also evidence that structural remodelling may not necessarily be progressive [5], that aspects of remodelling correlate with asthma severity far better than the degree of eosinophilia [13], and that many features of remodelling may precede clinical symptoms [14,15]. This has led to the widespread realisation that asthma is a strongly multifactorial disease, deriving from numerous pathogenic factors. To acknowledge this, and potentially improve/personalise treatment options for such a heterogeneous disease, a number of distinct asthmatic phenotypes have been proposed that derive from different (non)immune pathologies, namely eosinophilic, neutrophilic and mixed inflammatory, as well as paucigranulocytic asthma where inflammatory cell counts are within the normal range [16–18].

Many non-immune cells including airway nerves [19] and epithelial cells [20] are hypothesised to contribute to asthma pathogenesis. However the cell that arguably has the greatest capacity to influence airway physiology and drive the formation of a disease state is the ASM cell. Even within the immune-linked pathologies the sheer volume of ASM in the airway wall makes it the largest target and the largest potential source of secreted inflammatory mediators [21]. However, the contractile activity of ASM presents an ideal candidate for contributing to non-immune pathologies since ASM is the principal effector of acute airway narrowing [22]. It was originally believed that a pathological defect (i.e., enhancement) of ASM contractile function was primarily responsible for asthma, although a lack of consistent findings makes this hypothesis problematic (see table 2 in Ref. [23] for review). More recently, an improved understanding of ASM mechanics, cellular mechanotransduction pathways, and the identification of contraction-inflammation synergies have highlighted new ways in which ASM contraction may significantly alter airway structure and function.

In this article, we review the historical and contemporary evidence indicating that ASM contraction, while not necessarily presenting an inherent contractile defect in asthma, significantly contributes to clinical symptoms and disease pathogenesis. Specifically, we will consider the transient and long term effects that ASM contraction has on the mechanical properties of the airway wall, independent of inflammation-driven structural remodelling, a phenomenon we will collectively define in this review as 'mechanical remodelling'. Next, we will discuss the cellular mechanotransduction pathways by which alterations in the mechanical environment may contribute to the mechanical and structural remodelling process. Recent evidence will be presented as to how contractile signalling, particularly through muscarinic receptors, may synergise with conventional inflammatory pathways by causing cytokine release (i.e. transforming growth factor beta [TGF-β]) or by enhancing TGF-β related pathways within the cell. Finally, we will discuss mathematical modelling approaches that aim to describe how these disparate short and long term effects of ASM contraction and altered airway mechanics need to be integrated with traditional inflammatory-driven processes to produce a more comprehensive understanding of the disease state.

2. Contraction-linked mechanical remodelling

The structural properties and the dynamic mechanical behaviour of the airway wall are abnormal in asthma. There is considerable evidence to suggest that the airway wall is stiffened in asthma [24–26], although not all studies draw the same conclusion [27–29]. The intuitive explanation for airway stiffening in asthma is structural remodelling secondary to inflammatory processes, specifically thickening of the ASM layer and structural wall compartments [30], and the deposition of extracellular matrix (ECM) proteins and proteoglycans [31,32]. In asthmatic subjects the distensibility of the airway wall is inversely correlated to the thickness of the basement membrane [33]. However changes in airway mechanics can occur without structural remodelling, a process which may be initiated by ASM contractile activation. These short-term changes (i.e. seconds to hours) can occur through an active contractile component of stiffening, force generation and shortening consistent with classic Ca^{2+}-dependent actomyosin crossbridge cycling, but also through increasing passive stiffness of cytoskeletal elements that can augment force generation or prevent airway strain even in the absence of contractile activation. Collectively, we refer to these pathways and their physiological consequences as mechanical remodelling.

Contractile activation of ASM by numerous mediators initiates a broad cascade of signalling and biomechanical events, although we will consider pathways relating to neuronally derived acetylcholine (ACh) (Fig. 1 and Ref. [34]). Briefly, canonical cholinergic signalling involves activation of the M_3 muscarinic receptor, which when coupled with $G_{\alpha q/11}$ activates phospholipase C, which in turn produces inositol triphosphate, liberating Ca^{2+} from the sarcoplasmic reticulum. Ca^{2+} then binds to calmodulin and activates myosin light chain kinase (MYLK), which in turn phosphorylates the 20-kDa myosin regulatory light chain (MLC_{20}) and allows for actomyosin crossbridge cycling and binding. These contractile events are closely associated with enhanced polymerisation of actin which is regulated by M_3-mediated activation of the small GTPase RhoA through multiple intermediates. This critical contraction/mechanotransduction effector facilitates actin polymerisation through N-WASp and Arp2/3 [35], but may also work through Rho associated

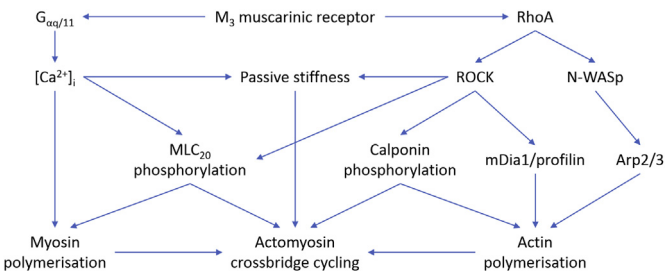

Fig. 1. A high level overview of the signalling pathways downstream of cholinergic activation of ASM, with a focus on potential mediators of mechanical remodelling. Canonical M_3 muscarinic receptor activation of $G_{\alpha q/11}$ increases $[Ca^{2+}]_i$ and phosphorylates MLC_{20}, simultaneously promoting myosin polymerisation and allowing for actomyosin crossbridge cycling. Additional muscarinic receptor activation of RhoA through multiple signalling intermediates facilitates actin polymerisation via N-WASp and Arp2/3, as well as through ROCK, mDia1/profilin and calponin phosphorylation pathways. Passive stiffness of ASM is modifiable by ROCK through Ca^{2+}-dependent and Ca^{2+}-independent mechanisms, and ROCK further promotes MLC_{20} phosphorylation. Each of myosin polymerisation, actin polymerisation and passive stiffness elements contribute to the mechanical properties of ASM cells, and facilitate or augment force production by actomyosin crossbridges.

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