Intrapulmonary airway smooth muscle is hyperreactive with a distinct proteome in asthma

Gijs Ijpma[1,2], Linda Kachmar[1,2], Alice Panariti[1,2], Oleg S. Matusovsky[3], Dara Torgerson[2,4], Andrea Benedetti[1,5,6] and Anne-Marie Lauzon[1,2]

Affiliations: [1]Dept of Medicine, McGill University, Montreal, QC, Canada. [2]Meakins–Christie Laboratories, Research Institute of the McGill University Health Centre, Montreal, QC, Canada. [3]Dept of Kinesiology and Physical Education, McGill University, Montreal, QC, Canada. [4]McGill University and Génome Québec Innovation Centre, Montreal, QC, Canada. [5]Dept of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada. [6]Respiratory Epidemiology and Clinical Research Unit, McGill University Health Centre, Montreal, QC, Canada.

Correspondence: Anne-Marie Lauzon, 1001 Decarie Blvd. EM3.2236, Montreal, QC, H4A3J1, Canada. E-mail: anne-marie.lauzon@mcgill.ca

Cite this article as: Ijpma G, Kachmar L, Panariti A, *et al*. Intrapulmonary airway smooth muscle is hyperreactive with a distinct proteome in asthma. *Eur Respir J* 2020; 56: 1902178 [https://doi.org/10.1183/13993003.02178-2019].

ABSTRACT Constriction of airways during asthmatic exacerbation is the result of airway smooth muscle (ASM) contraction. Although it is generally accepted that ASM is hypercontractile in asthma, this has not been unambiguously demonstrated. Whether airway hyperresponsiveness (AHR) is the result of increased ASM mass alone or also increased contractile force generation per unit of muscle directly determines the potential avenues for treatment.

To assess whether ASM is hypercontractile we performed a series of mechanics measurements on isolated ASM from intrapulmonary airways and trachealis from human lungs. We analysed the ASM and whole airway proteomes to verify if proteomic shifts contribute to changes in ASM properties.

We report an increase in isolated ASM contractile stress and stiffness specific to asthmatic human intrapulmonary bronchi, the site of increased airway resistance in asthma. Other contractile parameters were not altered. Principal component analysis (PCA) of unbiased mass spectrometry data showed clear clustering of asthmatic subjects with respect to ASM specific proteins. The whole airway proteome showed upregulation of structural proteins. We did not find any evidence for a difference in the regulation of myosin activity in the asthmatic ASM.

In conclusion, we showed that ASM is indeed hyperreactive at the level of intrapulmonary airways in asthma. We identified several proteins that are upregulated in asthma that could contribute to hyperreactivity. Our data also suggest enhanced force transmission associated with enrichment of structural proteins in the whole airway. These findings may lead to novel directions for treatment development in asthma.