Editorial

Increased airway smooth muscle cells in asthma: mechanisms and therapeutic prospects

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Airway remodeling is a key feature of asthma that can affect all bronchial wall layers and is generally characterized by an epithelial injury, mucus gland hypertrophy, neoangiogenesis, subepithelial and submucosal collagen deposition, and airway smooth muscle mass (1). In their article "Cellular sources of airway smooth muscle cells in asthmatic airway remodeling and their clinical relevance: a narrative review", Li *et al.* described the sources of the increase in the number of airway smooth muscle cells (ASMCs) and therapies targeting the airway smooth muscle remodeling in asthma (2). This topic is particularly of interest since among bronchial remodeling characteristics, airway smooth muscle remodeling appears as a key feature in asthma pathogenesis (1). Indeed, the airway smooth muscle is involved in bronchial contraction and hyperresponsiveness, but also in immune cell recruitment (3,4) and viral infection susceptibility in asthma (5). In addition, an increased airway smooth muscle mass at preschool age is predictive of asthma at school age (6), and is associated with decreased lung function, poor disease outcomes, the number of exacerbations and/or asthma severity in both asthmatic children and adults (7,8). Therefore, the authors rightly pointed out the main interest to identify the sources of the increased number of ASMCs involved in bronchial smooth muscle remodeling to develop new targeted therapy in asthma.

Among the sources of ASMCs in asthmatic airway remodeling, Li *et al.* firstly discussed the controversial role of the increased ASMC proliferation in asthmatics patients (2). Indeed, as stated by the authors, if the increased ASMC proliferation *in vitro* in asthmatics patients compared to non-asthmatics is now well-admitted, its relevance remains unclear due to the divergent results from *in vivo* studies. As mentioned in the review (2), an increased ASMC proliferation *in vitro* has been described by many studies, reviewed by our team in adult asthma (1) and even in preschool wheezing (9). This increased ASMC proliferation can be stimulated by several molecules released by inflammatory and bronchial wall cells, including ASMCs themselves, such as growth factors, cytokines, inflammatory mediators, enzymes, but also by free fatty acids, reactive oxygen species, and mechanical stress (1). This increased ASMC proliferation in asthma is supported by a mitochondria-dependent proliferation enhanced by an altered calcium homeostasis (10-12). In 2010, both Hassan *et al.* and Ramos-Barbon *et al.* confirmed the increased ASMC proliferation *in vivo* on bronchial biopsies, based on the proliferation markers Ki67 and the proliferating cell nuclear antigen (PCNA) and demonstrated an association between ASMC proliferation and asthma severity (13,14). By contrast, other studies did not identify cell proliferation in airway smooth muscle (15) or did not demonstrate a difference between asthmatics and controls (16,17). Nevertheless, these contradictory finding may result from different methodologies used in the above-mentioned *in vivo* studies according to patients inclusion, tissue sampling or processing prior to proliferation assessment, as rightly stated by Li *et al.* (2). In addition, the lack of

increased ASMC proliferation in the biopsies cannot exclude that, such an increased proliferation could have been present in days, weeks, months or years, prior to tissue sampling under the effect of the numerous above-mentioned factors stimulating the proliferation of ASMCs (1).

As mentioned by Li *et al.*, an imbalance between apoptosis and proliferation could also be involved in the increase in ASMCs but is not addressed by the authors in their review (2). Apoptosis is an essential cell death mechanism for the maintenance of morphogenesis and tissue homeostasis whose role in the increase of ASMCs in asthma remains unclear. Indeed, *in vitro* studies and mouse models of asthma initially suggested a decrease in apoptosis of ASMCs in asthma whereas other described no significant difference in spontaneous ASMC apoptosis between asthmatics and controls (1). Moreover, other studies have described an increased expression of apoptosis markers in bronchial smooth muscle in biopsies from asthmatics compared to non-asthmatics (18,19) and in fatal asthma (19). More recently, Fraga-Iriso *et al.*, also described from a mouse model of asthma that inhibition of apoptosis was associated with increased bronchial hyperresponsiveness and disorganized increase in smooth muscle size (20). Indeed, this study suggested that apoptosis would act as a protective mechanism to limit the growth of bronchial smooth muscle. Thus, the airway smooth muscle remodeling would be related with an insufficient increase of ASMC apoptosis.

The asthmatic ASMC hyperplasia may also result from ASMC migration (1), which was not addressed by Li *et al.* (2). ASMC migration is involved in the development of airways and can be induced by a wide range of mediators released by epithelial and inflammatory cells in asthma (1,21). Indeed, we very recently demonstrated an increased ASMC migration toward rhinovirus-infected epithelium (21). Such a migration was related to both an increased CXCL10 production by the epithelium and a decreased CXCR3-B isoform protein expression and activation in ASMCs from patients with severe asthma (21).

As source of ASMCs, Li *et al.* also well addressed the ability of mesenchymal stem cells, myofibroblasts, pericytes and epithelial cells to differentiate or transdifferentiate into ASMCs and their potential role in airway smooth muscle remodeling (2). One should point out the additional recruitment of fibrocytes, derived from the bone marrow, as sources of ASMCs and myofibroblasts. Indeed, fibrocytes can differentiate into myofibroblasts and then into ASMCs, as indicated by the expression of α-smooth muscle actin, and their migration toward airways can be promoted by ASMCs themselves and airway epithelium (1,17,22). Moreover, the role of fibrocytes in airway smooth muscle remodeling is suggested by their presence in airway smooth muscle bundles (17) and the association between circulating fibrocytes and both airway obstruction and annual decline in forced expiratory volume in 1 second in asthmatic patients (22).

In their review, Li *et al.* finally focused on targeted therapy for reducing ASMC numbers and more particularly on epigenetic targeting therapy (i.e., miRNA, bromodomain, extra-terminal domain inhibitor and histone deacetylase inhibitor) (2). Even if we fully agree with the authors that epigenetic targeting therapy may represent attractive prospects in airway smooth muscle treatment, their effects on ASMC proliferation and cytokine proinflammatory secretion, cell differentiation/transdifferentiation into ASMCs, on airway inflammation and on hyperresponsiveness have been described *in vitro* and in animal models of asthma. However, these data need to be confirmed *in vivo* by double-blind, randomized, placebo-controlled clinical trial. By contrast, both the calcium channel inhibitor gallopamil (23), and the prostaglandin D2 type 2 receptor antagonist fevipiprant (24) have been showed to significantly decrease airway smooth muscle mass *in vivo* in double-blind placebo-controlled clinical trials. In addition, it is necessary to clearly indicate that glucocorticoids can decrease some characteristics of bronchial remodeling (e.g., reticular basement thickness, number of bronchial vessels), but are unable to decrease ASMC proliferation in asthma (9,25). Along the same way, bronchodilators were unable to reverse/prevent ASMC proliferation in asthma (unpublished data).

Thus, further studies remain necessary to better understand the mechanisms underlying the increased ASMC number in asthma and the review published by Li *et al.* (2) is an important contribution toward highlighting some of these mechanisms and identifying recent new perspectives.

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