

Images in Allergy and Immunology

Philippe Joubert, DVM, MSc, and
Qutayba Hamid, MD, PhD, Editors

Role of airway smooth muscle in airway remodeling

Editor's note: This feature, Images in allergy and immunology, is designed to highlight current concepts of the immunopathology of allergic diseases and other common immunologically mediated diseases. The presentation will appear as sets of images that involve cross-pathology, histopathology, and molecular pathology and will cover a range of topics of interest to allergists and immunologists.

Increase in smooth muscle mass is a key structural change that occurs in the large and small airways of asthmatic subjects (Figs 1 and 2). The mechanisms underlying the increase in airway smooth muscle mass are still unknown. Some reports described hyperplasia of airway smooth muscle cells (ASMCs) in asthmatic airways,¹ whereas other studies found an increase in ASMC size.² More recently, migration of ASMCs toward the epithelium (Fig 3) and from surrounding bundles has been raised as a potential contributor to the increased smooth muscle mass (Fig 4).³ Whether this phenomenon occurs *in vivo* remains unknown.

In addition to their contractile function, ASMCs have been shown to be involved in regulating immune response through the release of several mediators, including cytokines, chemokines, and growth factors (Figs 5 and 6).⁴ They express and release eotaxin in response to T_H2 cytokines. They also produce monocyte chemoattractant protein (MCP) 1, MCP-2, MCP-3, and RANTES when stimulated with pro-inflammatory cytokines, such as IL-1 β and TNF- α . These chemokines have been involved in the patho-

From Meakins-Christie Laboratories, McGill University, Montreal, Quebec, Canada.

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Reprint requests Qutayba Hamid, MD, PhD, Meakins-Christie Laboratories, McGill University, 3626, St-Urbain, Montreal, Quebec, Canada, H2X-2P2.

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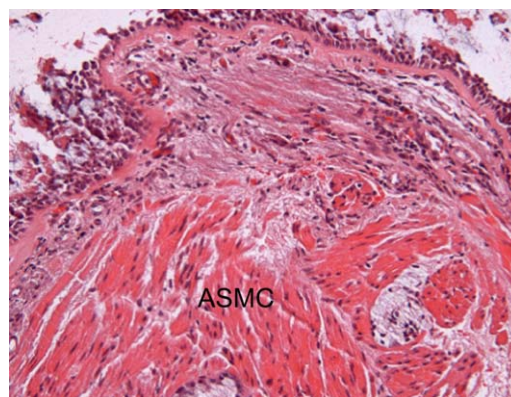


FIG 1. Increase in smooth muscle mass in the large airway of a subject with severe asthma. Hematoxylin and eosin staining; magnification 200 $\times$.

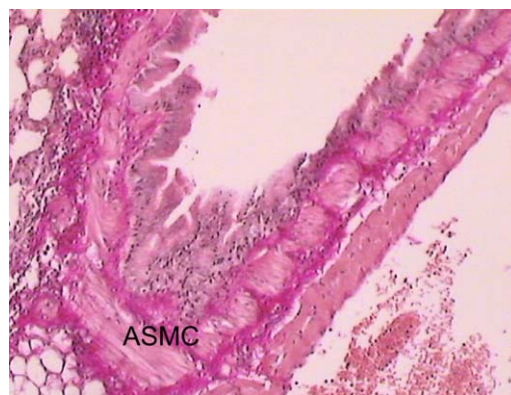


FIG 2. Increase in smooth muscle mass in the small airway of a subject with severe asthma. Hematoxylin and eosin staining; magnification 200 $\times$.

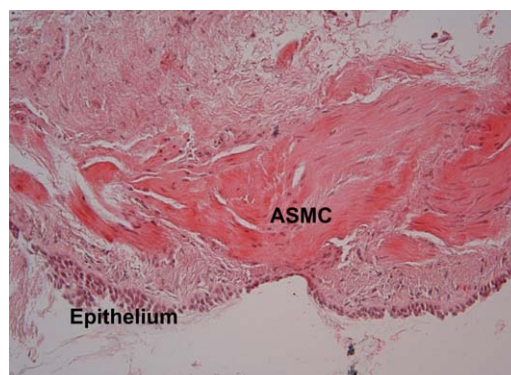


FIG 3. Hematoxylin and eosin preparation from a biopsy specimen of an asthmatic subject shows smooth muscle bundles close to the epithelium.

genesis of asthma through the recruitment of eosinophils, mast cells, and T_H2 lymphocytes. Expression of cytokine receptors by ASMCs has also been described. Hakonarson et al⁵ and Laporte et al⁶ have described the surface expression of T_H2 cytokine receptors, such as

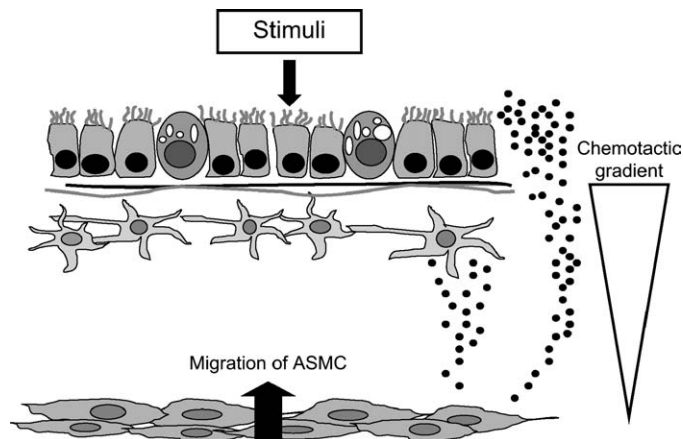


FIG 4. Model representing the migration of ASMCs toward the epithelium, possibly mediated by chemokines.

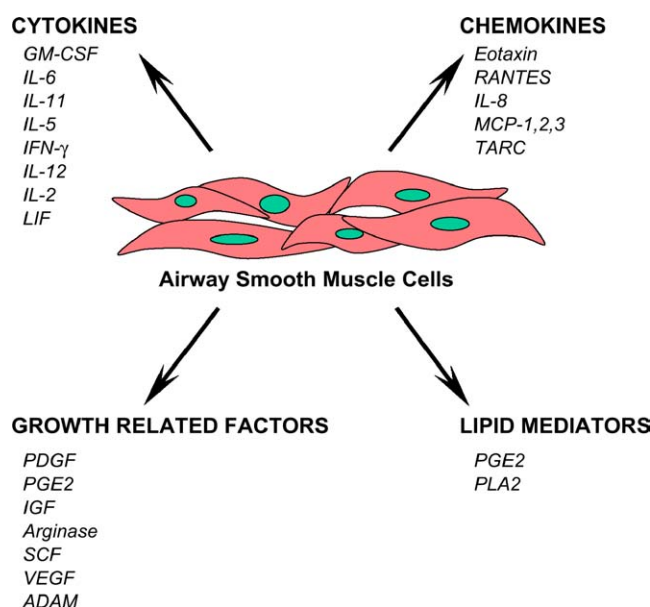


FIG 5. ASMCs express a wide variety of mediators involved in asthma pathogenesis, including cytokines, chemokines, growth factors, and lipid mediators. *LIF*, leukocyte inhibitory factor; *TARC*, thymus- and activation-regulated chemokine; *PDGF*, platelet-derived growth factor; *PGE2*, prostaglandin E₂; *SCF*, stem cell factor; *VEGF*, vascular endothelial growth factor; *ADAM*, a disintegrin and metalloprotease; *PLA2*, phospholipase A₂.

IL-4, IL-5, and IL-13. The expression of C-C chemokine receptors, including CCR1 and CCR3, was reported recently in ASMCs (Figs 7 and 8). These 2 chemokine receptors have been involved in the release of eotaxin and the induction of migration of ASMCs.

Increased deposition of extracellular matrix proteins is a feature of asthma. This phenomenon is believed to modify the physical properties of the airways.⁷ ASMCs have been shown to release a number of extracellular matrix proteins,⁸ including collagen I, collagen III, lumican, and versican (Fig 9). These proteins were shown to be upregulated in the asthmatic airways.

In the last few years, laser capture microdissection has emerged as a very powerful tool to study gene expression in different cell populations in asthma (Fig 10). In particular, protocols allowing PCR analysis of mRNA by ASMCs from tissue specimens, such as biopsy specimens of the lung or resected pieces of the lung, have been described. Fig 11 shows the expression of CCL15 mRNA by ASMCs captured from biopsy specimens of subjects with asthma.

Increase in smooth muscle mass is not restricted to asthma. This phenomenon is also observed in other respiratory diseases, including chronic obstructive pulmonary disease.⁹

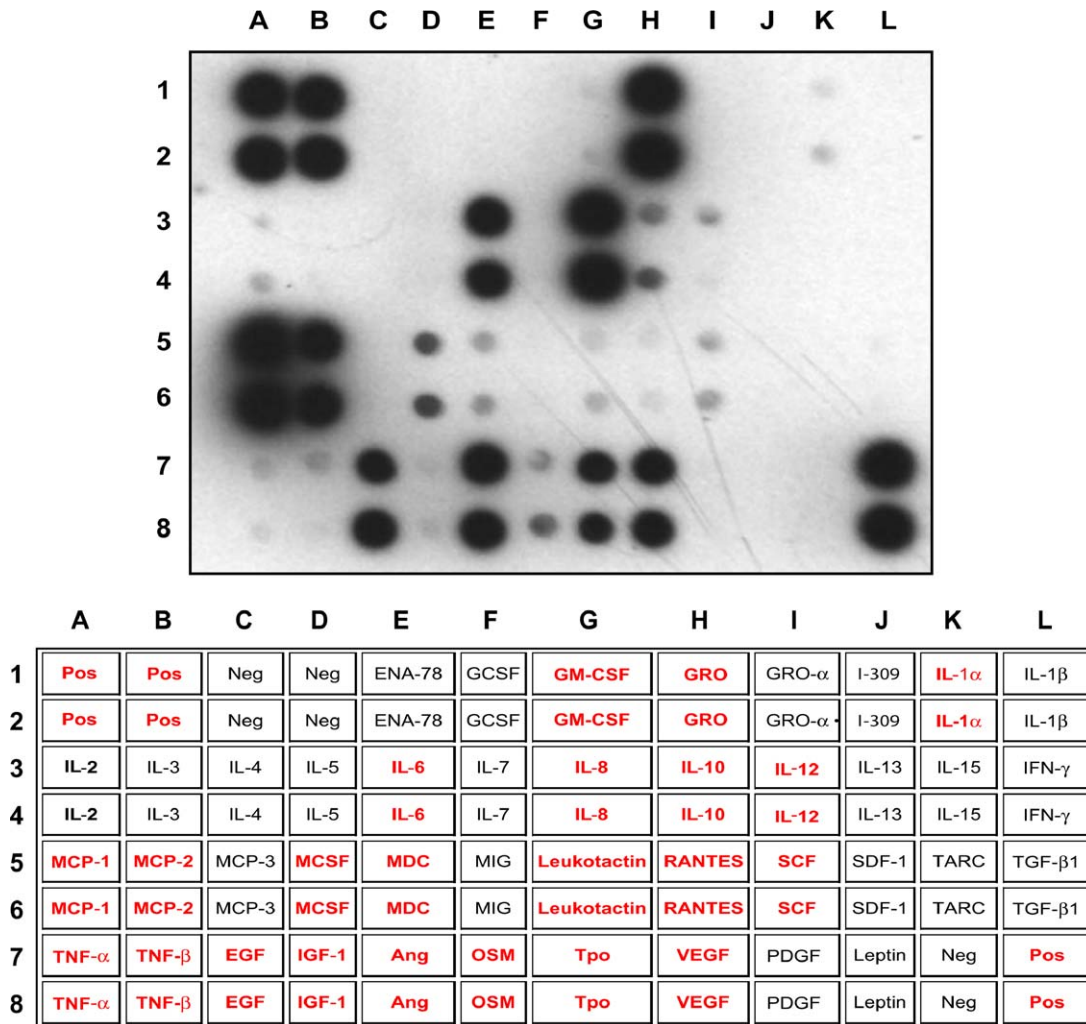


FIG 6. Example of the potential of ASMCs to produce cytokines and chemokines. Protein array of supernatant obtained from ASMCs shows immunoreactivity (in red in the table) to a number of cytokines and chemokines. *Pos*, Positive; *Neg*, negative; *MCSF*, macrophage colony-stimulating factor; *IGF-1*, insulin-like growth factor 1; *MDC*, macrophage-derived chemotactic factor; *Ang*, angiopoietin; *GCSF*, granulocyte colony-stimulating factor; *MIG*, monokine induced by IFN-γ; *OSM*, oncostatin M; *GRO*, growth-related oncogene; *VEGF*, vascular endothelial growth factor; *SCF*, stem cell factor; *PDGF*, platelet-derived growth factor; *SDF-1*, stromal cell-derived factor-1; *TARC*, thymus- and activation-regulated cytokine.

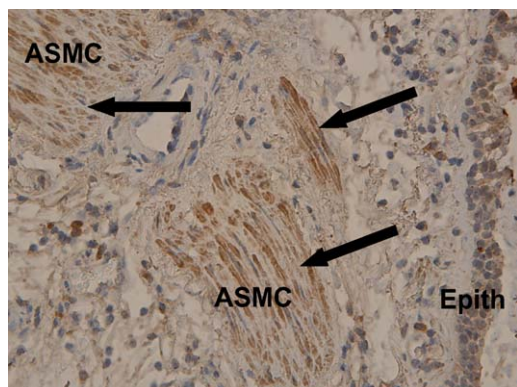


FIG 7. CCR3 immunostaining from a biopsy specimen of an asthmatic subject shows positive signal in smooth muscle bundles. Diaminobenzidine method; magnification 400×. *Epith*, Epithelium.

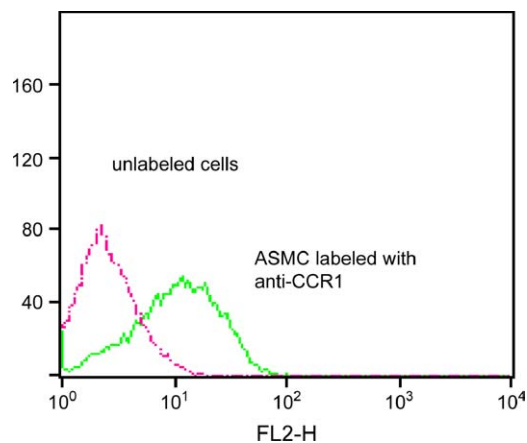


FIG 8. Flow cytometric analysis of cultured ASMCs with an anti-CCR1 coupled with phycoerythrin.

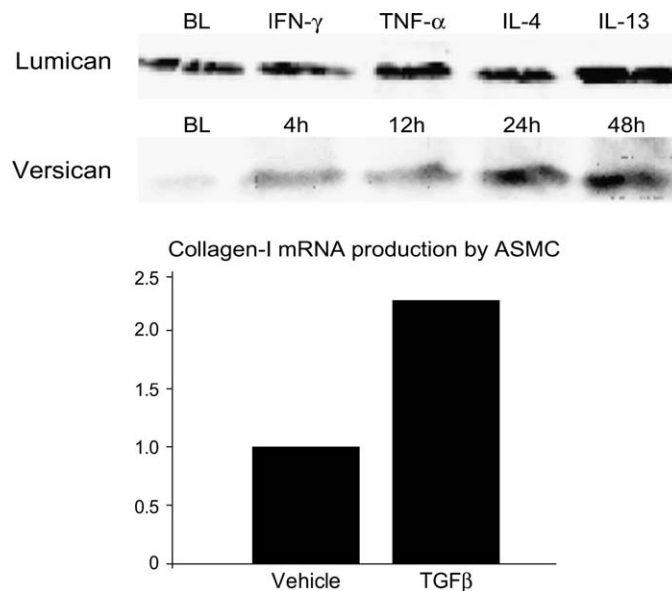


FIG 9. Western blotting and real-time PCR analysis of extracellular matrix protein production by cultured ASMCs. Lumican production was assessed after stimulation with different cytokines for 48 hours, and versican production was evaluated after stimulation with IL-25 in a time-dependent manner. Messenger RNA collagen production was quantified by using real-time PCR after 24 hours of stimulation with TGF-β. BL, baseline.

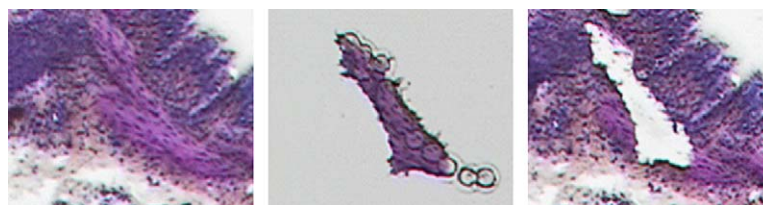


FIG 10. Example of a laser capture microdissection of ASMCs in a biopsy specimen obtained from an asthmatic subject.

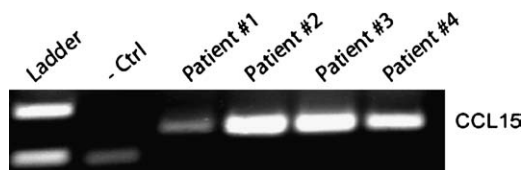


FIG 11. RT-PCR for CCL15 expression performed on mRNA extracted from laser capture microdissection on biopsy specimens from asthmatic subjects. Ctrl, Control.

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