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Airway smooth muscle: A modulator of airway remodeling in asthma

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Asthma is a disease characterized, in part, by airway hyperresponsiveness and inflammation. Although asthma typically induces reversible airway obstruction, in some patients with asthma, airflow obstruction can become irreversible. Such obstruction might be a consequence of persistent structural changes in the airway wall caused by the frequent stimulation of airway smooth muscle (ASM) by contractile agonists, inflammatory mediators, and growth factors. Traditional concepts concerning airway inflammation have focused on trafficking leukocytes and on the effects of inflammatory mediators, cytokines, and chemokines secreted by these cells. Recent studies suggest that ASM cells might modulate airway remodeling by secreting cytokines, growth factors, or matrix proteins and by expressing cell adhesion molecules and other potential costimulatory molecules. These ASM cell functions might directly or indirectly modulate submucosal airway inflammation and promote airway remodeling. (J Allergy Clin Immunol 2005;116:488-95.)

Key words: *Asthma, signal transduction, smooth muscle, proliferation, synthetic function*

Chronic severe asthma is characterized by inflammation of the airways and growth of airway smooth muscle (ASM) cells. In patients with asthma, cytokines and growth factors promote myocyte proliferation and deposition of extracellular matrix (ECM) that, in part, constitute the process of airway remodeling. Pathologically, angiogenesis and microvascular remodeling are prominent features of chronic severe asthma, changes that are likely mediated by multiple factors. We will discuss the potential for ASM to influence the remodeling process through its ability to synthesize and secrete inflammatory mediators and ECM, as well as express adhesion molecules and other immunomodulatory proteins.

Abbreviations used

ADAM: A disintegrinase and metalloproteinase
ASM: Airway smooth muscle
ECM: Extracellular matrix
ERK: Extracellular signal-regulated kinase
GPCR: G protein–coupled receptor
LTD_4: Leukotriene D_4
MCP: Monocyte chemotactic protein
MMP: Matrix metalloproteinase
PDGF: Platelet-derived growth factor
PI3K: Phosphatidylinositol 3-kinase
RTK: Receptor tyrosine kinase
STAT: Signal transducer and activator of transcription
VEGF: Vascular endothelial growth factor

INCREASED SMOOTH MUSCLE MASS

Myocyte hyperplasia

ASM mitogens act through different receptor-operated mechanisms. Although growth factors induce ASM cell mitogenesis by activating receptors with intrinsic protein receptor tyrosine kinase (RTK) activity, contractile agonists released from inflammatory cells mediate their effects through activation of G protein–coupled receptors (GPCRs). Importantly, synergy can occur between RTK and GPCRs to promote human ASM mitogenesis.[1]

The mechanisms regulating smooth muscle proliferation have been the subject of numerous reviews.[2] Phosphatidylinositol 3-kinase (PI3K) and extracellular signal–regulated kinase (ERK) activation appear to be the dominant signal transduction pathways for RTK-, GPCR-, or cytokine-stimulated growth of ASM cells (Fig 1). PI3K phosphorylates membrane phosphoinositides, which function as second messengers and activate downstream

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effector molecules to regulate cell-cycle protein expression and thus modulate cell-cycle traversal.[3] Activation of PI3K is critical for ASM cell-cycle progression,[4-6] although other signaling events are also necessary to promote maximal ASM growth responses.[7] For example, inhibition of ERK activity attenuates mitogen-induced DNA synthesis in ASM cells, suggesting that activation of ERK is also required for proliferation.[8,9]

D-type cyclins (cyclins D1, D2, and D3) are key regulators of G_1 progression in mammalian cells, and consequently, cyclin D1 has been the most widely studied cyclin in ASM biology. In human ASM corticosteroids reduce mitogen-stimulated increases in cyclin D1 protein.[10] Corticosteroid binding to the glucocorticoid receptor results in activation of the transcription factor C/EBPα and subsequent increased expression of the cyclin-dependent kinase inhibitor $p21^{WAF/Cip1}$, thus providing a potential mechanism for the antiproliferative effect of glucocorticoids on ASM cell growth.[11-13] A recent study suggests that ASM cells derived from patients with asthma lack expression of C/EBPα and are therefore resistant to the effects of glucocorticoids on proliferation.[14] Although cyclin D1 expression might be necessary for cell growth, it is not sufficient. For example, IFN-γ inhibits ASM growth without modulating growth factor–induced upregulation of cyclin D1.[15]

Reactive oxygen species might also regulate ASM function. ASM cells express several, but not all, components of the phagocyte nicotinamide adenine dinucleotide phosphate oxidase, and reactive oxygen species can modulate mitogen-induced ASM cell proliferation.[16-19] Additionally, signal transducer and activator of transcription (STAT) 3 has been shown to play an important role in platelet-derived growth factor (PDGF)–induced proliferation of human ASM cells. Activation of JAK2 and STAT3 by PDGF appears to be redox dependent and affects the proliferative response to mitogen independent of ERK activation.[20] Interestingly, IFN-γ and IFN-β activate STAT1/2, JAK1, and Tyk2 in ASM; these cytokines, however, are potent inhibitors of mitogen-induced proliferation, in part through upregulation of the interferon-inducible gene *IFI 16*.[15,21]

Myocyte hypertrophy

There is renewed attention to the role of increased myocyte size or hypertrophy as a mechanism of increased ASM cell mass in asthma. Some mediators, such as IL-1β, IL-6, TGF-β, angiotensin II, and cardiotrophin I, induce cellular hypertrophy *in vitro*, although the mechanisms remain unclear.[22-24] In a primate model of asthma, the airways of monkeys sensitized to house dust mite antigen display an increase in smooth muscle mass, as well as smooth muscle bundle size.[25] Morphologic studies confirm the presence of ASM cell hypertrophy in some, but not all, asthmatic patients.[26] Increased cell size appears to negatively correlate with postbronchodilator FEV_1 and distinguishes between severe persistent asthma and milder disease.[27] In contrast, Woodruff et al[28] obtained bronchial biopsy specimens from patients with mild-to-moderate asthma and studied ASM cell gene expression and cell morphology. These investigators found no evidence for ASM cell hypertrophy, although they did confirm the presence of ASM hyperplasia. More work is needed in this particular area of ASM cell biology.

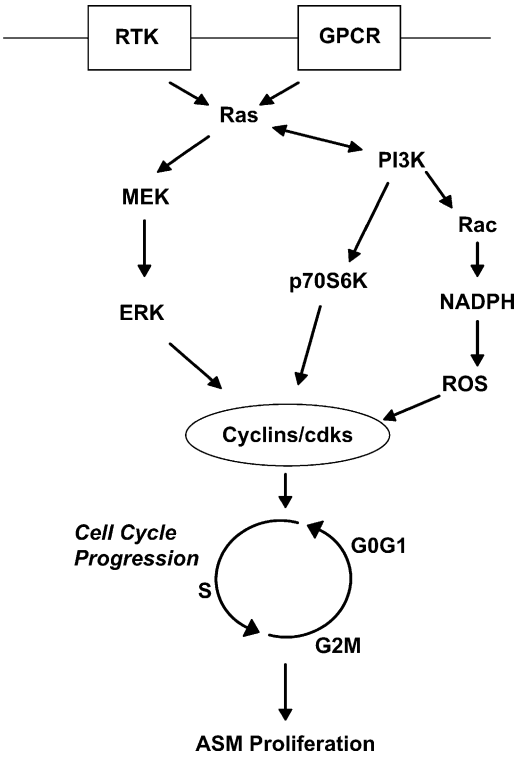

FIG 1. Overview of ASM cell mitogenesis. In this simplified diagram of the intracellular pathways regulating ASM cell mitogenesis, Ras serves as a point of convergence for growth factor RTK and GPCR signaling. Ras activates ERK and PI3K, leading to activation of cyclins and cyclin-dependent kinases *(CDKs)*. Activation of cyclin D1 ultimately leads to cell-cycle progression and cell proliferation. MEK, mitogen-activated protein kinase/ERK; NADPH, nicotinamide adenine dinucleotide phosphate; *p70S6K*, Ribosomal S6 kinase; *ROS*, reactive oxygen species.

Smooth muscle migration

Hyperplasia and hypertrophy are important processes regulating increased smooth muscle mass in asthma. Analogous to vascular smooth muscle migration in atherosclerosis, however, ASM cell migration also likely promotes airway remodeling in chronic asthma. Evidence suggests that proliferating smooth muscle cells migrate along chemotactic gradients. During chronic inflammation, myocyte migration would be promoted by exposure of cells to a variety of cytokines and growth factors, as well as to an altered ECM.

Structurally, myofibroblasts display a phenotype intermediate between fibroblasts and smooth muscle cells, express α-smooth muscle actin, and have the ability to secrete ECM proteins. In addition, myofibroblasts secrete chemokines and prolong eosinophil survival.[29] Although myofibroblasts are found in the lamina reticularis, the