



Review article

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# AIRWAY SMOOTH MUSCLE IN ASTHMA

## SUMMARY

Asthma is a disease characterized, in part, by reversible airflow obstruction, hyperresponsiveness and inflammation. Traditional concepts concerning airway inflammation have focused on the effects of inflammatory mediators, cytokines and chemokines secreted by these cells. Airway smooth muscle, the major effector cell responsible for bronchomotor tone has been viewed as a passive tissue responding to neurohumoral control and inflammatory mediators. New evidence, however, suggests that airway smooth muscle may secrete cytokines and chemokines and express cell adhesion molecules that are important in modulating submucosal airway inflammation.

*Key words:* asthma, inflammation, bronchoconstriction, smooth muscle

## INTRODUCTION

Bronchial asthma is a disease characterized by bronchial hyperreactivity, airway inflammation and airway obstruction. Airway smooth muscle (ASM) cells responsible for bronchomotor tone have often been regarded as a somewhat passive cells, simply responding to neurogenic signals and inflammatory mediators. One of the factors that may contribute to the exaggerated airway narrowing in asthma is an abnormality of the airway smooth muscle. This abnormality could take the form of an increase in the amount of muscle or an alteration its pharmacological reactivity (1).

Increasingly, airway smooth muscle is viewed as more than just the assembly of contractile elements. It is both a target of inflammation and a major contributor to the local inflammatory response. Airway smooth muscle cells are playing an important interactive role with inflammatory and structural cells in the response to injury and repair of the airways (2) (figure 1).

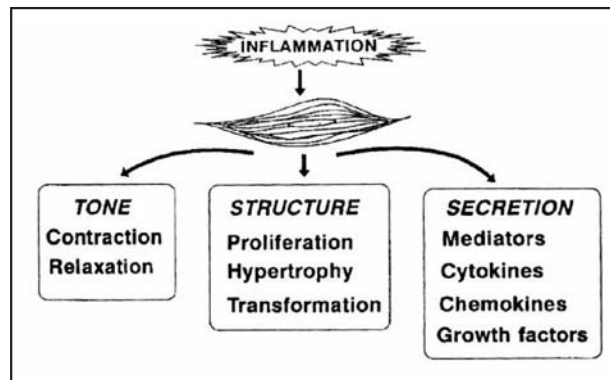


Figure 1. Functions of airway smooth muscle

## BRONCHOCONSTRICTION

ASM functions as the primary effector cell that regulates bronchomotor tone. ASM tone is

largely determined by the intracellular calcium ion concentration ( $\text{Ca}^{2+}$ ) (3). Activation of ASM cells by bronchoconstrictors results in a rapid rise in  $\text{Ca}^{2+}$  due to the release of calcium from intracellular stores. Because the increase in cytosolic calcium directly regulates the initiation and development of ASM contraction, changes in calcium homeostasis may promote bronchial hyperresponsiveness in asthma (4). Following stimulation of airway smooth muscle by classical contractile agonists such as histamine or methacholine, initiation of contractile response depends upon stimulation of phospholipase C-dependent pathways (5). Following binding of agonist to receptor in the cell membrane, the associated G protein which exists as a heterotrimeric complex of  $\alpha$ ,  $\beta$  and  $\gamma$  subunit dissociates: the free subunit stimulates phospholipase C (PLC) which in turn catalyses the breakdown of phosphatidylinositol biphosphate (PIP<sub>2</sub>) (6). This results in the formation of the two intracellular messengers diacylglycerol (DAG) and inositol triphosphate (IP<sub>3</sub>). IP<sub>3</sub> is able to release calcium from intracellular stores, whereas DAG in addition to activating protein kinase C may also be able to stimulate calcium entry (7). The rise in cytosolic free calcium levels leads to contraction of the airway smooth muscle cell (8). ASM may be constricted directly by agonists such as histamine, cysteinil leukotrienes, thromboxane and acetylcholine that activate receptors on the smooth muscle cell (direct bronchoconstriction). Bronchoconstriction may also be induced by agonists that release constrictors from other cells. Thus, adenosine and allergen cause bronchoconstriction through the release of mediators (histamine and cysteinil leukotriens) from mast cells, whereas bradykinin releases bronchoconstrictors (acetylcholine, tachykinins) from airway nerves (indirect bronchoconstriction) (9).

#### BRONCHODILATATION

Following binding of agonist to receptor, the associated stimulatory G protein (G<sub>s</sub>) dissociates freeing the stimulatory subunit. G<sub>s</sub> is able to activate adenylyl cyclase (AC), which catalyses the breakdown of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP); this in turn activates protein kinase A (PKA), leading to the dissociation of the catalytic subunit. (7) The catalytic subunit is able to phosphorylate key targets within the cell, leading to relaxation. Several endogenous products are bronchodilators, either by activating bronchodilator receptors on ASM (epinephrine, vasoactive intestinal peptide, prostacyclin) or via the release of endogenous bronchodilators such as NO or PGE<sub>2</sub>.

#### PROLIFERATION

In chronic asthma there is an increase in ASM bulk, which appears to be due to an increase in cell number (hyperplasia) and increase in cell size (hypertrophy). This contributes to increased thickness of the airway wall in asthma and leading structural changes in the airway wall, which contribute to the development of persistent airway obstruction and increased non-specific airway hyperresponsiveness in asthma (1).

Evidence has shown that exposure of airway smooth muscle to cytokines or growth factors alter contractility, calcium homeostasis and induces smooth muscle cell hypertrophy and hyperplasia. ASM growth is itself under regulatory control by a large number of growth factors and kinases. Promoters of airway smooth muscle growth include epithelial-derived growth factor (EGF), insulin-like growth factor (IGF-1), histamine, endothelin-1, thromboxane, and leukotriene 4 (LT<sub>4</sub>) (10,11). Other agents decrease proliferation of ASM. Thus, PGE<sub>2</sub>, NO and  $\beta_2$  agonists are anti-proliferative, due to an increase in cAMP. Transforming growth factor  $\beta_1$  (TGF- $\beta_1$ ) has an anti-proliferative effect, although the molecular mechanisms are not yet certain. Heparin also blocks proliferation of ASM.

#### SECRETORY FUNCTION

While the contractile and proliferative properties of ASM cells have been recognized for a long time, it is only recently that the enormous capacity for ASM cells to produce inflammatory mediators has been recognized. This is consistent with the demonstration that other structural cells, such as airway epithelial cells and fibroblasts, also have the capacity to produce several types of inflammatory mediators. These structural cells may serve as an important source of cytokines in chronic asthma and may drive the chronic inflammatory process (9).

An inducible form of cyclooxygenase, COX-2, has an increased expression in asthmatic airways. This induction is likely to be mediated by activation IL- $\beta$ , TNF- $\alpha$  and INF- $\gamma$ . The predominant cyclooxygenase products of COX-2 in human ASM are PGE<sub>2</sub> and prostacyclin. Since PGE<sub>2</sub> inhibits proliferation of ASM, this suggests a feedback control system to inhibit proliferative responses to inflammatory stimulation (12).

NO may be produced by many structural and inflammatory cells at sites of inflammation, through the induction of inducible NO synthase (iNOS). NO, like PGE<sub>2</sub> may have an anti-proliferative effect on ASM, and it is of interests that iNOS and COX-2 are induced by the same inflammatory stimuli.

A number of studies now show that airway smooth muscle cells are secretors of a number of cytokines and chemokines and may therefore contribute to the persistence of chronic inflammation in asthma. Thus, ASM produces granulocyte macrophage colony-stimulating factor (GM-CSF) in response to IL-1 $\beta$ , TNF- $\alpha$  and IFN- $\gamma$ . ASM also expresses the genes for the chemokines RANTES and IL-8 and releases these chemokines in response to inflammatory cytokines and may therefore participate in the recruitment of inflammatory cells into the airways (13) (figure 2).

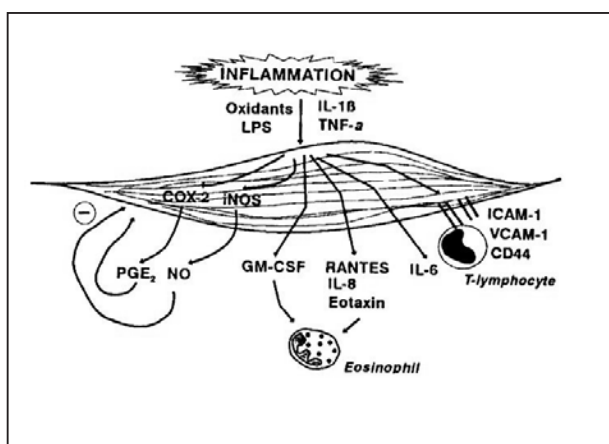


Figure 2. Secretory function of airway smooth muscle

After stimulation with inflammatory mediators, ASM expresses adhesion molecules: ICAM-1 and VCAM-1, resulting in adhesion of inflammatory cells, such as lymphocytes to the myocyte surface (9). Adherence of activated T cells results in expression of major histocompatibility complex class II molecules in ASM cells, indicating a change in phenotype.

#### CELL INTERACTION

There are complex interactions between inflammatory cells and other structural cells in the air-

way. It is likely that there are particular interactions between airway epithelial cells and ASM cells. Epithelial cells may express a large range of mediators in asthmatic airways and these may have an important influence on ASM function (figure 3).

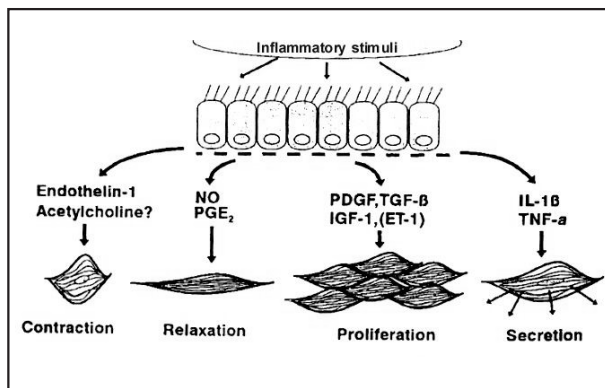


Figure 3. Interaction between airway epithelium and airway smooth muscle

Thus in asthma, epithelial cells may release PGE<sub>2</sub> and NO, which relax ASM and inhibit its proliferation. In addition, epithelial cells also have the capacity to synthesize various growth factors that increase ASM proliferation, including PDGF and EGF (14).

#### CONCLUSION

Airway smooth muscle functions as the primary effector cell that regulates bronchomotor tone. Recent evidence also suggests that ASM may undergo hypertrophy and/or hyperplasia and modulate inflammatory responses by secreting chemokines and cytokines. Also, ASM have an important interactive role with inflammatory and structural cells in the response to injury and repair of the airways in asthma.

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## DISAJNI GLATKI MIŠIĆ KOD ASTME

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### SAŽETAK

Bronhijalna astma je oboljenje koje se karakteriše reverzibilnom opstrukcijom disajnih puteva, hiperreaktivnošću i inflamacijom. Tradicionalni koncept o inflamaciji u disajnim putevima astmatičara fokusira efekte inflamatornih medijatora, citokina i hemokina sekretovanih od strane inflamatornih ćelija. Glatko-mišićne ćelije disajnih puteva, efektorne ćelije odgovorne za bronhomotorni tonus, do sada su smatrane pasivnim ćelijama koje samo pasivno reaguju na nerohumoralnu kontrolu i inflamatorne medijatore. Međutim, novija saznanja pokazala su da ćelije glatkih mišića disajnih puteva mogu sekretovati citokine i hemokine i eksprimirati ćelijske atehzione molekule i da stoga imaju značajnu ulogu u imunomodulaciji procesa inflamacije kod astme.

**Ključne reči:** astma, inflamacija, bronhokonstrikcija, glatki mišić