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Gautam Damera
University of Pennsylvania

Omar Tliba
School of Pharmacy, Thomas Jefferson University

Reynold A. Panettieri, Jr.
University of Pennsylvania

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Airway Smooth Muscle as an Immunomodulatory Cell

Gautam Damera,[1] Omar Tliba[1,2] and Reynold A. Panettieri, Jr.[1]

[1]Pulmonary, Allergy and Critical Care Division, Airways Biology Initiative, University of Pennsylvania, Philadelphia, PA, USA; [2]Department of Pharmaceutical Sciences, School of Pharmacy, Thomas Jefferson University, Philadelphia, PA, USA

Address for Correspondence:
Reynold A. Panettieri, Jr., M.D., Pulmonary, Allergy and Critical Care Division, Airways Biology Initiative, University of Pennsylvania, 125 South 31st Street, TRL Suite 1200, Philadelphia, PA 19104-3403, USA, Phone: 215-573-9860, Fax: 215-746-1224, E-Mail: rap@mail.med.upenn.edu

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Abstract

Although pivotal in regulating bronchomotor tone in asthma, airway smooth muscle (ASM) also modulates airway inflammation in asthma. ASM myocytes secrete or express a wide array of immunomodulatory mediators in response to extracellular stimuli, and in chronic severe asthma, increases in ASM mass may also render the airway irreversibly obstructed. Although the mechanisms by which ASM secretes cytokines and chemokines are shared with those regulating immune cells, there exist unique ASM signaling pathways that may provide novel therapeutic targets. This review provides an overview of our current understanding of the proliferative as well as synthetic properties of ASM.

Key Words

Synthetic function, airway remodeling, mesenchymal cells, airway hyperresponsiveness, hyperplasia, hypertrophy

1. Introduction

Asthma occurs in about 1 in 20 Americans; in children, recent estimates suggest an incidence as high as 10%. Although asthma typically induces reversible airway obstruction, in some patients airflow obstruction can become fixed. The bronchoconstriction evoked by smooth muscle shortening promotes airway obstruction and constitutes the hallmark of asthma. Although airway smooth muscle (ASM) functions as the primary effector cell that regulates bronchomotor tone, ASM may undergo hypertrophy and/or hyperplasia and modulate inflammatory responses by secreting chemokines and cytokines. This review addresses current studies focusing on molecular and cellular mechanisms by which ASM cells modulate inflammatory cell function and responses in asthma.

The variety of cell types that reside in or infiltrate through the inflamed submucosa potentially undergo cell-cell interactions. Eosinophils, macrophages and, particularly, lymphocytes may initiate or perpetuate the asthma diathesis by secreting pro-inflammatory mediators or by expressing cell adhesion molecules (CAMs) that may act directly or indirectly on ASM. Although many cell-cell interactions likely contribute to airway hyperresponsiveness in asthma, evidence supports that T cells, mast cells and ASM can directly interact via CAMs. In response to cytokines such as IL-1β, TNFα and IFNγ, ASM cells express a host of cell adhesion molecules that promote interactions among ASM and inflammatory cells. The capacity for ASM cells to respond and secrete a myriad of cytokines and growth factors potentially impugns ASM as an immunomodulatory cell as detailed in Table 1. Further advances in understanding the immunoregulatory potential of ASM revealed that cytokines also up-regulate the expression of Toll-like receptors (TLRs) in ASM cells as described in Figure 1. These receptors serve as pattern-recognition molecules that modulate innate and adaptive immune and inflammatory responses to microbial infection, tissue injury or inflammation as described in Tables 1 and 2. In this section, we will review the recent advances describing immunomodulatory functions of ASM cells.

2. Adhesion Molecules

The expression and activation of a cascade of cell adhesion molecules (CAMs) that include selectins, integrins, and CD31, as well as the local production of chemoattractants, evoke leukocyte adhesion and transmigration into lymph nodes and sites of inflammation involving non-lymphoid tissues. The subsequent interactions of the infiltrating leukocytes with other cell

types in the bronchial submucosa or with the ECM that may sustain the inflammatory response remain unclear. Infiltrating inflammatory cells bind to airway structural cells through specific CAMs and, as a consequence, perpetuate airway inflammation [1]. In addition to mediating cell contact, some of the CAMs may also function as co-stimulatory molecules contributing to the activation of structural cells [2].

Recent studies in ASM tissues *in vitro* and *in vivo* suggest that specific CAMs mediate cell-cell interactions. *In situ* hybridization and immunohistochemical analyses of lung tissue have revealed that ASM expresses a wide variety of CAMs *in vivo* [3, 4]. Specifically, after LPS stimulation of rat lungs, enhanced ICAM-1 expression both at the protein and mRNA levels was reported in ASM [3]. Using *in vivo* human bronchial tissue transplanted onto the flank of SCID mice, Lazaar and colleagues [4] demonstrated a marked increase in ICAM-1 and VCAM-1 expression after the injection of TNFα, a cytokine that is produced in considerable quantities in asthmatic airways [5]. Further *in vitro* studies confirmed the expression of ICAM-1 and VCAM-1 on cultured ASM that was inducible by a wide range of inflammatory mediators such as TNFα, IL-1β or IFNγ [4, 6]. Although the function of CAMs on ASM remains incompletely defined, surface expression of CAMs on ASM could play a pivotal role in regulating ASM cell interactions with a variety of inflammatory cells relevant for asthma pathogenesis [4, 7-9]. Other studies suggest that activated T cells avidly adhere to cultured ASM, an interaction that is mediated through ICAM-1, VCAM-1 and CD44 [4]. The latter interaction enhances T cell binding, increases bronchoconstrictor responses to acetylcholine and impairs relaxation responses to isoproterenol [7]. More recently, investigators demonstrated that CD4+ T cells interact with ASM *in vivo*. Adoptive transfer of CD4+ T cells from sensitized rats markedly increased ASM mass and inhibited apoptosis of airway myocytes in naïve recipients after repeated allergen challenge. Additionally, genetically modified CD4+ T cells expressing enhanced GFP were localized by confocal microscopy to be juxtaposed to the ASM. These findings are clinically relevant and imply that CD4+ T cells may directly modulate ASM function through cell-cell interactions *in vivo* [10]. Furthermore, other inflammatory cells including eosinophils [8] and recently neutrophils [9] have been demonstrated to adhere to ASM *in vitro*. The attachment of such cells to ASM decreased in the presence of anti-ICAM-1 and VCAM-1 antibodies. Further, studies exploring mast cell-ASM interactions *in vivo* in subjects with asthma also demonstrated that cell-cell attachment could modulate and alter ASM cell

function [11]. In addition, cell-cell interactions can occur apart from CAM expression. For instance, mast cell-ASM interactions occur via membrane bound stem cell factor on ASM [12, 13]. The identification of the critical regulatory sites that modulate CAM expression on airway myocytes and disruption of cell-cell adherence would provide new therapeutic approaches to alter airway remodeling in patients with chronic airflow obstruction.

2.1. Cytokine and chemokine expression

Cytokines and chemokines play a central role in regulating inflammatory and immune responses in chronic lung diseases such as asthma and COPD. *In vivo* studies using selective inhibitors as well as neutralizing antibodies against various cytokines and chemokines demonstrate their prominence in antigen-induced airway inflammation (leukocyte infiltration) and hyperresponsiveness in animal models [14-16]. Studies in sensitized knock-out or transgenic mice also illustrate the importance of cytokines in inducing abnormal airway changes [17]. ASM may provide a potential target for cytokines secreted by immunocytes. In human ASM cells, cytokines alter pro-inflammatory gene expression in an autocrine or paracrine manner [18]. Evidence convincingly demonstrates that ASM cells secrete a number of cytokines and chemoattractants as detailed in Table 1.

IL-6, a pleiotropic cytokine, may induce smooth muscle cell hyperplasia [19] and modulate B and T cell proliferation and immunoglobulin secretion. The effect of IL-6 as an ASM mitogen is controversial and may be species-dependent [20]. Mast cell proliferation, however, is induced by IL-6 when the mast cells are adherent to ASM [12]. IL-6 secretion by ASM cells is inducible by multiple stimuli, including IL-1β, TNFα, TGFβ and sphingosine-1-phosphate [21-25]. Interestingly, transgenic expression of IL-6 in the murine lung evokes a peribronchiolar inflammatory infiltrate but promotes airway **hyporesponsiveness**. This intriguing dual role for IL-6 in controlling local inflammation and in regulating airway reactivity [26, 27] is consistent with the known ability of IL-6 to inhibit TNF and IL-1β secretion. ASM cells may also play a role in promoting both the recruitment and survival of eosinophils by secretion of GM-CSF and IL-5 [28-30], although the secretion of IL-5 by ASM remains somewhat controversial. Finally, additional cytokines that are secreted by human ASM cells include IL-1β, IFNβ and other IL-6 family cytokines, such as leukemia inhibitory factor and IL-11, which are secreted following exposure of ASM cells to viral particles [23, 24, 31-33].

<u>Autocrine IFNβ secretion regulates ASM inflammatory gene expression</u>

In ASM cells, TNFα activates JAK1 and Tyk2, and STAT1- and STAT2-dependent gene expression via the autocrine action of IFNβ [34]. Autocrine IFNβ differentially regulates TNFα-induced inflammatory gene expression by suppressing IL-6 expression and promoting RANTES secretion. Although functional cross talk between IFNγ and TNFα occurs in other cell types (mostly hemopoietic cells), this study was the first to demonstrate secretion of IFNβ by TNFα in airway structural cells. Collectively, the autocrine secretion of IFNβ is a novel signaling component by which TNFα regulates ASM function in human ASM cells.

NF-κB activation modulates IFN signaling in ASM cells

IFNs interact with other inflammatory mediators such as TNFα and promote the synergistic release of inflammatory mediators from ASM cells [35]. In some instances, IFNs may antagonize TNFα inflammatory responses by inhibiting the NF-κB pathway. IFNγ inhibits TNFα-induced NF-κB-dependent genes including IL-6 and eotaxin in ASM cells [36], and IFNγ suppressed TNFα–inducible gene expression that includes: vascular endothelial growth factor [37], IL-17 receptor [38]), and TLR3 expression [39]. Multiple mechanisms underlying IFN inhibitory effect on NF-κB pathways have been proposed including inhibition of NF-κB DNA binding, prevention of IκB degradation, or regulation of TNF-α receptor 1 via STAT interaction [35]. The use of trichostatin A, a specific histone deacetylase inhibitor, reverses IFNγ inhibitory effects on TNFα–inducible genes and NF-κB-dependent gene expression in ASM cells [36]. These findings suggest that IFNγ negatively regulates expression of TNFα–induced pro-inflammatory genes by impairing NF-κB function via transcriptional repression through increased histone deacetylase activity. A better understanding of the inhibitory mechanisms exerted by IFNγ on TNFα–inducible inflammatory genes may offer new insight into the design of alternative approaches for the treatment of airway inflammation in asthma.

The combination of TNFα and IFNγ can also enhance secretion of some pro-inflammatory mediators. For example, these cytokines, when used together, synergistically induce ASM production of chemokines that have been implicated in mast cell migration to ASM [40]. These include CXCL10 (IP10) production via NF-κB [41] and fractalkine [42]. Thus, the interaction of interferon with pathways dependent on NF-κB is complex and further research is necessary.

Chemokine expression in ASM cells

Chemokines play a central role in the recruitment and trafficking of inflammatory cells along diffusion gradients. After the initiation of injury or inflammation, chemokines provide a diffusion gradient for cell trafficking [18]. Chemokines can be categorized by their molecular structure and by the degree of selectivity for distinct inflammatory cell populations [43]. For example, eotaxin, RANTES (Regulated on Activation, Normal T cells Expressed and Secreted) and IL-5 primarily recruit eosinophils, although eotaxin and RANTES affect other cell types; CXCL8 markedly recruits neutrophils; monocyte chemotactic proteins (MCPs) recruit monocytes; thymus- and activation-regulated chemokine (TARC) recruits lymphocytes; and stem cell factor recruits mast cells. Many of the aforementioned chemokines, which act to recruit and activate leukocytes, are found in bronchoalveolar lavage fluid and lung tissue of subjects with asthma. Using murine models of allergen-induced airway hyperresponsiveness, neutralizing MCP-5, eotaxin, RANTES and MCP-1 dramatically reduced airway hyperresponsiveness as well as leukocyte migration [14]. Intranasal delivery of a recombinant poxvirus-derived viral CC-chemokine inhibitor protein also improves pulmonary function and decreases inflammation of the airway and lung parenchyma [44]. In a chronic allergen exposure murine model, the administration of CCR3 antagonist reduced eosinophil numbers in the airway wall tissue that was accompanied by a decrease in airway remodeling parameters [16]. Together these studies demonstrate that *in vivo* chemokines promote and perpetuate airway inflammation during allergen exposure.

Although a variety of cells are impugned to secrete chemokines, new evidence suggests that ASM may be a prominent source of chemokines in the submucosa. Immunohistochemical and *in situ* hybridization studies revealed that MCP-1, RANTES and fractalkine (FKN) are expressed in ASM of bronchial biopsies in subjects with asthma [40, 45, 46]. CXCL10, a potent chemokine for activated T cells, NK cells and mast cells that bind to CXCR3, is also expressed in ASM in subjects with asthma or COPD [41, 47]. Expression of CXCL10 in ASM cells and CXCR3 (the CXCL10 receptor) in mast cells was seen in ASM *in vivo* [47]. In murine models of allergen-induced airway hyperresponsiveness, eotaxin, an eosinophil specific chemokine mediator, is markedly expressed in ASM tissue [48]. The expression of chemokine receptors also exists in ASM as demonstrated in subjects with asthma who express strong immunoreactivity for CCR3 (eotaxin receptor) [49], a receptor that has been previously linked to the pathogenesis of asthma [50]. To further understand the mechanisms by which chemokines are expressed, *in vitro*

studies showed that in response to specific inflammatory mediators, cultured ASM cells also express and secrete a variety of chemokines such as eotaxin, RANTES, CXCL8, MCP-1, -2 and -3, and TARC [51]. Although the precise physiological relevance of chemokine receptor expression in ASM remains unclear, there is no doubt that the chemokine levels increase in bronchoalveolar lavage fluid in subjects with asthma, and, in part, the increased levels may be mediated by ASM. The identification of the infiltration of mast cells into ASM bundles may also suggest that mast cells diffuse via gradients of chemokines to the submucosa [11]. Activated ASM supernatant from subjects with asthma exhibits chemotactic activity for purified lung mast cells and subsequently elicits their migration toward ASM. The precise mechanisms by which this occurs remain unclear but can serve as a new therapeutic target in decreasing airway infiltration of immunocytes and inflammatory cells in asthma. Blocking CXCL10 decreased mast cell migration into the ASM bundles [11], and in parallel studies, El-Shazly and colleagues [40] demonstrated that FKN also facilitated smooth muscle-induced mast cell chemotaxis. Thus, it is likely that a variety of chemoattractants are involved in vivo.

Several studies have identified molecules that stimulate chemokine secretion by ASM as summarized in Figure 1. For example, the antimicrobial protein human cathelicidin antimicrobial peptide LL-37, produced by mast cells and neutrophils, stimulates IL-8 secretion by ASM cells. The LL-37 effect was dependent on activation of ERK1/2, p38, and the Src signaling pathways [52]. Other studies investigated the role of ECM on ASM cells in modulating chemokine release [52, 53]. Compared with cells obtained from normal volunteers, ASM cells from subjects with asthma express an increased amount of eotaxin, and enhanced autocrine fibronectin secretion requires engagement of $\alpha 5\beta 1$ integrin [52]. Others showed that fibronectin and type I collagen enhanced IL-1β–dependent ASM secretion of eotaxin and RANTES release via a $\beta 1$ integrin-dependent mechanism [53]. These data suggest that the ECM environment surrounding the ASM cell amplifies chemokine release and enhances cellular infiltration during inflammation and remodeling. For instance, vasoactive intestinal peptide, a 28 amino acid peptide hormone, has been shown to modulate FKN, a CXC3 chemokine, function in ASM cells [40]. In several cell types, FKN is expressed as a soluble or membrane-bound moiety [54] that induces both migration and adhesion of leukocytes. Vasoactive intestinal peptide modulates subcellular distribution of FKN, which in turn could favor the adhesion of ASM cells to FKN expressing mast cells [54]. Collectively, these studies support the potential role of ASM cells not only as

regulators of airway inflammation but also as modulators of airway leukocyte infiltration and retention.

2.2. Toll-like receptors

Mammalian Toll-like receptors (TLRs) are cell surface molecules that evoke inflammatory responses in recognition of bacterial and viral components as described in Figure 1. Airway infections due to viruses exacerbate asthma and prompted investigators to study whether activation of TLRs in the airways promotes airway inflammatory responses. Accordingly, several TLR and TLR ligands have been associated with the asthma diathesis [55]. A specific interest has focused on TLR function in ASM cells since microbial products such as lipopolysaccharide, a major component of the external membrane of gram-negative bacteria, modulate ASM hyperresponsiveness to contractile agonists in some species [42, 56].

The interaction of ASM cells with immune cells such as monocytes and mast cells dramatically amplifies TLR-mediated local inflammatory responses. In studies involving co-cultures of peripheral blood monocyte/ASM cells, enhanced TLR2- and TLR4-mediated IL-6, CCL2, and CXCL8 secretion has been reported [57]. Monocytes also play a role in the initiation of inflammatory responses, and interaction with stromal cells could amplify such effects. Additionally, treatment of ASM cells with poly(I:C), a synthetic analog of inosine that resembles dsRNA of viruses, stimulates the recruitment of mast cell lines to ASM cells [57]. Oliver et al. showed that rhinovirus infection enhanced IL-8 release from asthmatic ASM, suggesting that post viral infection, activation of mast cells together with TLR-driven pathways in ASM contribute towards ASM exacerbations [58]. These observations suggest that ASM cells could modulate inflammatory responses during viral and microbial infections.

2.3. Mechanisms inhibiting ASM synthetic function

Effects of intracellular cAMP-elevating agents on cytokine-induced synthetic responses

In asthma, β-agonist bronchodilators increase intracellular cAMP ($[cAMP]_i$) and stimulate cAMP-dependent protein kinase in ASM. In a similar manner, prostaglandin E_2 (PGE_2), which is produced in large quantities at sites of inflammation, increases $[cAMP]_i$ in human ASM cells and is a potent and effective bronchodilator [59]. $[cAMP]_i$-mobilizing agents in ASM cells also modulate cytokine-induced synthetic function [60]. In TNFα-stimulated ASM cells, expression of both eotaxin and RANTES is effectively inhibited by isoproterenol, PGE_2, dibutyl $[cAMP]_i$, or the phosphodiesterase inhibitors rolipram and cilomast [21, 61, 62]. TNFα-

induced interleukin (IL)-8 secretion is inhibited by the combination of $[cAMP]_i$-mobilizing agents [63]. Similarly, S-1-P, which activates a Gs protein-coupled receptor and increases $[cAMP]_i$, abrogates TNFα-induced RANTES secretion in ASM cells [22]. In contrast to the effects of $[cAMP]_i$ on chemokine secretion, pharmacologic agents that increase $[cAMP]_i$ stimulate secretion of IL-6 in human ASM cells [21] and modulate basal IL-6 promoter activity [64]. More recently, investigators show that increases in cAMP abrogate secretion of GM-CSF by ASM cells, and that cyclo-oxygenase inhibitors that reduce PGE_2 enhance cytokine-induced secretion of GM-CSF [65, 66]. Accordingly, phosphodiesterase type IV inhibitors, which reduce GM-CSF secretion *in vitro*, also reduce antigen-induced airway hyperresponsiveness [66, 67]. Activation of $[cAMP]_i$-dependent pathways inhibits, in part, TNFα-mediated induction of both ICAM-1 and VCAM-1 expression, as well as inhibiting adhesion of activated T cells to ASM cells. The basal expression of ICAM-1 and VCAM-1, as well as the binding of activated T cells to unstimulated ASM, was resistant to increases in $[cAMP]_i$ [6]. Thus, cytokine-induced expression of cellular adhesion molecules and T-cell adhesion to ASM cells are modulated by changes in $[cAMP]_i$. Taken together, current evidence suggests that some but not all pro-inflammatory functions in ASM cells are inhibited by $[cAMP]_i$-mobilizing agents.

Glucocorticoids modulate cytokine-induced synthetic responses

Although glucocorticoids (GCs) are effective anti-inflammatory agents in asthma, the precise mechanisms by which GCs improve lung function in asthma remain unclear. Most anti-inflammatory effects of GCs are mediated via the glucocorticoid receptor alpha isoform (GRα), which suppresses expression of inflammatory genes through mechanisms known as transactivation or transrepression [68]. Alternative splicing mechanisms induce transcription of another glucocorticoid receptor isoform, namely GRβ [69]. Cytokine-induced secretion of RANTES [21, 70, 71], monocyte chemoattractant protein [71], eotaxin [62], GM-CSF [30] and IL-6 [25] is abrogated by corticosteroids. In conjunction with $[cAMP]_i$-mobilizing agents, steroids additively inhibit chemokine and cytokine secretion [64]. It also appears that corticosteroids inhibit specific cytokines, altering unique transcription factor expression. For instance, dexamethasone inhibits TNFα-induced RANTES secretion by affecting the activator protein-1 (AP-1) site. In contrast, dexamethasone has little effect on TNFα- or IL-1β-induced NF-κB activation in human ASM cells [72]. Furthermore, cytokine-induced ICAM-1 expression in ASM cells, which is completely dependent on NF-κB activation, was unaffected by

dexamethasone, with IL-6 secretion only modestly inhibited [64]. In contrast, IL-1β-induced cyclo-oxygenase 2 expression was completely abrogated [72-74]. The anti-inflammatory potential of steroids in asthma is not solely due to their effects at NF-κB sites but is also due to their regulatory effects at other transcription factors such as AP-1. In addition, steroids can regulate GM-CSF expression by reducing mRNA stability [75].

ASM glucocorticoid sensitivity

The treatment of ASM cells with a combination of IFNs and TNFα impairs steroid inhibition of gene expression such as CD38, RANTES and ICAM-1 by a mechanism involving the up-regulation of GRβ isoform [76]. Although the mechanism of synergy remains unknown, steroids augment IFNγ/TNFα-induced FKN and TLR2 expression in ASM [39, 42]. Despite that the pathological role of the GRβ isoform is not well understood, existing reports demonstrate a correlation between steroid resistance in individuals with asthma and the expression levels of GRβ [77]. More importantly, increased GRβ expression in the airways has been detected in patients who died of asthma [78]. Based on the ability of GRβ to act as a dominant-negative inhibitor of steroid action in other cell types [79], the role of GRβ in steroid insensitivity in inflammatory diseases has been suggested [80]. GRβ overexpression in ASM cells also prevents GC-induced transactivation and inhibits cytokine-induced pro-inflammatory gene expression [76].

In a GRβ-independent manner, short-term treatment of ASM cells with IFNs and TNFα partially inhibits steroid transactivation through the cellular accumulation of IRF-1 [81]. IRF-1 is an early response gene involved in diverse transcriptional regulatory processes [82], and an association exists between IRF-1 polymorphisms and childhood atopic asthma [83]. Early steroid dysfunction seen after short incubation with IFNs and TNFα was rescued by enhancing IRF-1 cellular levels using constitutively active IRF-1 that inhibited glucocorticoid response element (GRE)-dependent gene transcription [81]. Reducing IRF-1 cellular levels using siRNA approaches in TNF/IFN-treated ASM cells also restored GC transactivation. These findings demonstrate that IRF-1 may serve as a GRβ-independent mechanism modulating cytokine-induced steroid insensitivity. Since expression of IRF-1 is increased after viral infections [84] and since IRF-1 suppresses steroid signaling in ASM cells [81], IRF-1 may mediate reduced steroid responsiveness seen in patients with asthma experiencing viral infections [85].

3. Conclusions

In summary, ASM contributes to the pathogenesis of asthma at multiple levels beyond its contractile functions. ASM, exposed to a variety of mediators and cytokines, can undergo phenotypic changes and secrete chemokines and cytokines, which may participate in or even perpetuate the mucosal inflammatory changes via the activation and recruitment of inflammatory cells. These new findings may provide unique therapeutic targets to decrease cell migration/infiltration and disrupt cell-cell adherence, and may ultimately reverse either airway remodeling or ongoing airway inflammation. Further elucidation of the cellular and molecular mechanisms that regulate non-contractile functions of ASM will offer new therapeutic targets in the treatment of asthma, chronic bronchitis and emphysema.

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Table 1: Immunomodulatory proteins expressed by human ASM cells

Cytokines	Chemokines	CAM	Growth Factors	Others
IL-1β	IL-8	ICAM-1	IGF-1	CD40
IL-5	RANTES	VCAM-1	PDGF	HLA-DR
IL-6	Eotaxin	CD44	SCF	FcγRII
IL-17	TARC	LFA-1		FcγRIII
IFNβ	Fractalkine			NO
VEGF	MCP-1,-2,-3			PGE_2
GM-CSF				TLRs
TGFβ				
LIF				
IP10				

Abbreviations:

CD40, CD44: cytoplasmic domain 40, 44; FcγRII, FcγRIII: receptor for Fc region of IgG; GM-CSF: granulocyte macrophage-colony stimulating factor; HLA-DR: human leukocyte antigen-DR; ICAM-1: intercellular adhesion molecule-1; IFN: interferon; IGF: insulin-like growth factor; IL: interleukin; IP10: interferon inducible protein 10; LFA: lymphocyte fusion-associated antigen; LIF: leukemia inhibitory factor; MCP: monocyte chemotactic protein; NO: nitric oxide; PDGF: platelet-derived growth factor; PGE_2: prostaglandin E_2; RANTES: regulated on activation, normal T cells expressed and secreted; SCF: stem cell factor; TARC: thymus- and activation-regulated chemokine; TGF: transforming growth factor; TLRs: Toll-like receptors; VCAM-1: vascular cell adhesion molecule-1; VEGF: vascular endothelial growth factor

Table 2: Novel molecules regulating the immunomodulatory functions of ASM

Stimulus	**Receptor**	**Effects**
PGN, Pam_3CSK_4	TLR2	↑↑ IL-6, CXCL8, eotaxin secretion
LPS, pLPS	TLR4	↑↑ IL-6, CXCL8, eotaxin secretion
DsRNA, poly(I:C)	TLR3	↑↑ IL-6, CXCL8, CXCL10, eotaxin secretion
IL-17	IL-17R	↑↑ CXCL8 and eotaxin secretion, ↑↑ neutrophil chemotaxis
LL-37	Purinergic P2	↑↑CXCL8 secretion
VIP	VIPR	↑↑ Mast cell chemotaxis, ↑↑ fractalkine function
Fibronectin, type I collagen	β1 integrin	↑↑ IL-1β-induced eotaxin and RANTES secretion

Abreviations:

CXCL8: IL-8; CXCL10: IP10; DsRNA: double-stranded RNA; IL: interleukin; IL-17R: IL-17 receptor; LL-37: human cathelicidin antimicrobial peptide LL-37; LPS: lipopolysaccharide; Pam_3CSK_4: synthetic bacterial lipopeptide; PGN: peptidoglycan; pLPS: purified LPS; Poly(I:C): polyriboinosinic polyribocytidylic acid; RANTES: regulated on activation, normal T cells expressed and secreted; TLR: Toll-like receptor; VIP: vasoactive intestinal peptide; VIPR: vasoactive intestinal peptide receptor

Figure Legend

Figure 1

Environmental challenges induce asthma exacerbations that, in part, are mediated by alterations in ASM function. Allergens as well as viruses and bacterial infections are common stimuli for asthma exacerbations. Traditionally, these environmental challenges are thought to be mediated through airway inflammation and trafficking leukocytes. Contemporary thought suggests that structural cells, namely, ASM, in part may modulate inflammatory responses by altering cell adhesion molecule expression or secreting chemokines and cytokines. The paracrine and autocrine secretion of chemokines and cytokines may then also alter the responsiveness of ASM to contractile agonists and agents that promote bronchodilation. Repeated asthma exacerbations may induce chronic alterations in ASM manifested by myocyte hypertrophy and hyperplasia (modified from Tliba and Panettieri, Curr Allergy Asthma Rep 2008; 8:262-8).

Abbreviations:

ASM: airway smooth muscle; CXCL8, CXCL10, CCL2: chemokines; DsRNA: double-stranded ribonucleic acid; ECM: extracellular matrix; FKN: fractalkine; ICAM-1: intercellular adhesion molecule-1; IFNγ: interferon gamma; IL-17: interleukin-17; LL-37: human cathelicidin antimicrobial peptide LL-37; LPS: lipopolysaccharide endotoxin; TNFα: tumor necrosis factor alpha; VCAM-1: vascular cellular adhesion molecule-1; VIP: vasoactive intestinal peptide