Pulmonary Pharmacology & Therapeutics 26 (2013) 64–74

Contents lists available at SciVerse ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Pro-inflammatory and immunomodulatory functions of airway smooth muscle: Emerging concepts

Yuxiu C. Xia [a], Naresh Singh Redhu [b], Lyn M. Moir [c,d], Cynthia Koziol-White [e], Alaina J. Ammit [f], Laila Al-Alwan [g], Blanca Camoretti-Mercado [h,1], Rachel L. Clifford [i,*,1]

[a] Department of Pharmacology, University of Melbourne, Parkville, Victoria, Australia
[b] Department of Immunology, Faculty of Medicine, University of Manitoba, Winnipeg, MB, Canada
[c] Cell Biology Group, Woolcock Institute of Medical Research, Glebe, NSW 2037, Australia
[d] Respiratory Research Group, Discipline of Pharmacology, The University of Sydney, Sydney, NSW 2006, Australia
[e] Airways Biology Initiative, Division of Pulmonary, Allergy and Critical Care, Department of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
[f] Respiratory Research Group, Faculty of Pharmacy, University of Sydney, Australia
[g] Meakins-Christie Laboratories and Respiratory Division, Department of Medicine, McGill University, 3626 rue St. Urbain, Montreal, QC, Canada H2X 2P2
[h] Department of Medicine, Committee on Molecular Pathogenesis and Molecular Medicine, Committee on Clinical and Translational Sciences, Institute of Integrative Physiology, University of Chicago, Chicago, IL 60637, USA
[i] Division of Respiratory Medicine and Nottingham Respiratory Research Unit, University of Nottingham, Clinical Sciences Building, City Hospital, Nottingham, NG5 1PB, United Kingdom

ARTICLE INFO

Article history:
Received 27 February 2012
Received in revised form
8 May 2012
Accepted 9 May 2012

Keywords:
Allergy
Asthma
Chemokine
Chronic obstructive pulmonary disease
Hyperresponsiveness
Infection
Interleukin
Pattern-recognition receptors
Signaling

ABSTRACT

Airway smooth muscle (ASM) is the main regulator of bronchomotor tone. Extensive studies show that in addition to their physical property, human airway smooth muscle (ASM) cells can participate in inflammatory processes modulating the initiation, perpetuation, amplification, and perhaps resolution of airway inflammation. Upon stimulation or interaction with immune cells, ASM cells produce and secrete a variety of inflammatory cytokines and chemokines, cell adhesion molecules, and extracellular matrix (ECM) proteins. These released mediators can, in turn, contribute to the inflammatory state, airway hyperresponsiveness, and airway remodeling present in asthma. As our knowledge of ASM myocyte biology improves, novel bioactive factors are emerging as potentially important regulators of inflammation. This review provides an overview of our understanding of some of these molecules, identifies rising questions, and proposes future studies to better define their role in ASM cell modulation of inflammation and immunity in the lung and respiratory diseases.

1. Introduction

The airway smooth muscle is the main regulator of bronchomotor tone and thus, of the opening of the airways and airflow. Over the last 20 years extensive studies have shown that in addition to their mechanical function, ASM cells can participate in inflammatory mechanisms. ASM cells can interact with inflammatory cells and elicit (patho)physiological responses from the ASM myocyte. For instance, activated T lymphocytes adhere to ASM cells via integrins and CD44 and induce ASM cell DNA synthesis, a marker of cell proliferation [1]. Anti-CD3 activated T cells interact with naïve human ASM cells and increase myocyte constrictor responsiveness to acetylcholine as well as impair myocyte relaxation responsiveness to isoproterenol [2]. Moreover, resting T cells can also adhere to IgE-activated ASM cells suggesting that a dynamic interaction involving bi-directional signaling exists between these cell types [2]. ASM cells can also attach to eosinophils and neutrophils through VCAM-1 and ICAM-1, and TNFα pretreatment of ASM myocytes increases eosinophil and neutrophil adhesion [3,4].

ASM cells are able to respond to and secrete various cytokines and chemokines [5–7] known to regulate inflammation and immune responses in COPD and asthma. Although numerous pathways stimulated by these mediators within the ASM cell have been recognized and a vast array of bioactive molecules secreted by

* Corresponding author. Tel.: +44 (0)1158231723.
E-mail address: r.clifford@nottingham.ac.uk (R.L. Clifford).
[1] Equal contribution.

1094-5539/$ – see front matter © 2012 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.pupt.2012.05.006

activated ASM myocytes identified, new mechanisms of activation and novel released factors are emerging. Furthermore, the roles of factors in normal and pathological ASM biology are being described or redefined as new methodological approaches become available and as our understanding of the ASM cell and of asthma strengthens.

In the present review we discuss some mediators that are relatively new to the ASM field including Thymic Stromal Lymphopoietin Protein (TSLP) and its receptor TSLPR which are expressed by ASM cells; interleukin-33 (IL-33), a novel IL-1 family member whose expression is increased in severe asthma; IL-17 that is upregulated in asthma and induces secretion of IL-8 and IL-6; C–C chemokine receptor type 1 (CCR1), a receptor mainly expressed on immune cells but recently identified on ASM cells; and IL-13, a Th2 cytokine known to regulate the expression of genes in ASM cells that are involved in inflammation, remodeling and airway hyperresponsiveness. We discuss in more detail the role of IgE and post-infection as potential regulators of ASM cell-induced inflammation. Finally, as many questions still remain unanswered, we propose future studies and directions of research to further elucidate the role of ASM in the regulation of airway inflammation and immunomodulation.

2. Expression of novel immunomodulatory molecules and their receptors in ASM cells

2.1. Thymic stromal lymphopoietin protein (TSLP)

TSLP is a novel IL-7-like pro-allergic cytokine considered as a driver of Th2 immune responses [8]. Human ASM cells from both asthmatic and COPD patients produce TSLP *in vivo* [9,10]. In culture, TSLP is released from ASM cells after stimulation with the pro-inflammatory molecules tumor necrosis factor-α (TNFα) and IL-1β [9,11], the Th2 cytokine IL-4, β2-adrenergic receptor agonists [12], cigarette smoke extract, and IgE [13]. The mechanism of TSLP production primarily involves the activation of the p38 and ERK1/2 mitogen activated protein (MAP) kinase pathways, as well as the nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) transcription factors [14,15] (Fig. 1).

TSLP-stimulated myeloid dendritic cells are able to release pro-inflammatory mediators and prime naïve CD4+ T cells in an antigen-specific manner resulting in their polarization into Th2 inflammatory cells [16]. In addition, TSLP induces proliferation of human airway epithelial cells [17], CD4+ T cells [18], and CD8+ T cells [19]. Because mast cells and CD4+ T cells localize in close proximity to ASM bundles in asthma [20,21], it is enticing to speculate that TSLP may contribute to the increased number of ASM cells observed in asthma. However, a recent report suggests that TSLP does not affect ASM cell proliferation, but rather increases mast cell-derived cytokine/chemokine production [10]. This supports the idea of cell-specific effects of this novel immunostimulatory protein.

ASM cells from mild allergic asthmatics express the TSLP receptor TSLPR [22], raising the interesting possibility of an autocrine mechanism of action. *In vitro*, TSLPR activation in ASM cells leads to augmented levels of eotaxin-1/CCL11, IL-6, and CXCL8/IL-8 [22] as well as increased intracellular calcium (Ca^{2+}) mobilization, suggesting a plausible role of TSLP in ASM contraction [23] (Fig. 1). Therefore, ASM cells are both a rich source of TSLP and a target of TSLP action, indicating that TSLP/TSLPR interaction on ASM may modulate airway inflammatory responses [15]. Moreover, ASM cell-derived TSLP may participate in dendritic cell-T cell mediated adaptive immune responses within the airways. Future efforts should be directed to understand additional triggers of TSLP release from ASM cells, its underlying signaling mechanism(s), and the functional outcome of TSLPR-mediated ASM cell activation. In particular, the role of TSLP in modulating ASM cell contraction, proliferation, and migration needs to be investigated (Fig. 1).

2.2. Interleukin-33 (IL-33)

IL-33 is a recently discovered cytokine that belongs to the IL-1 superfamily and utilizes the ST2 receptor, a member of the IL-1

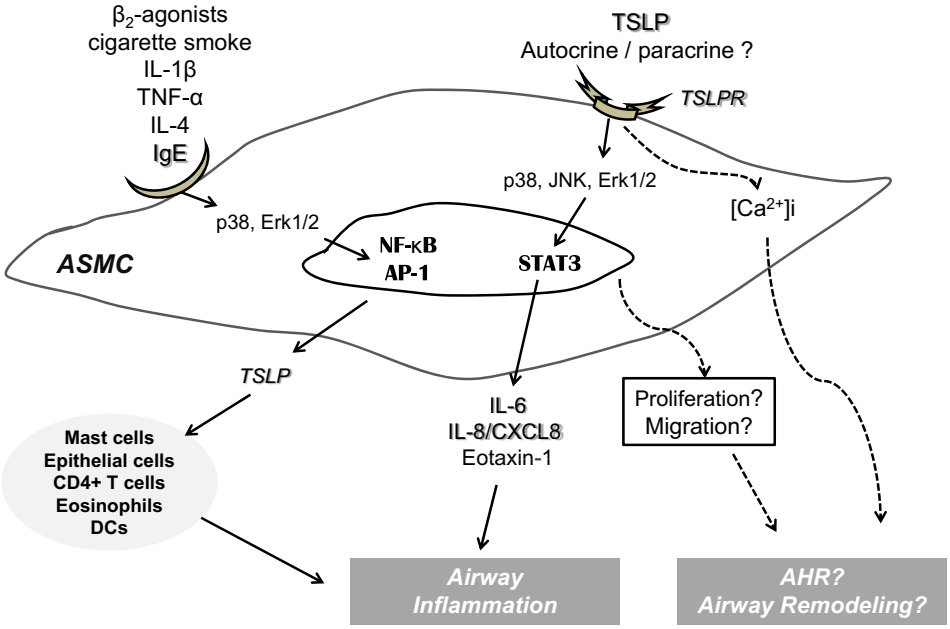

Fig. 1. Potential autocrine/paracrine activation of human ASM myocytes by TSLP, and the role of IL-6 and IL-8. Various triggers such as β2-adrenergic agonists, cigarette smoke extract, pro-inflammatory and Th2 cytokines, and IgE induce high levels of TSLP release from ASM cells. This response utilizes the MAPK, NF-κB, and AP-1 signaling pathways. Released TSLP can activate multiple inflammatory cells including granulocytes and dendritic cells (DCs), which could promote a Th2-dominant allergic immune response. ASM cells also express a functional TSLP receptor, which raises the possibility of TSLP/TSLPR-mediated autocrine/paracrine activation of ASM. Production of IL-6, IL-8 and eotaxin as well as calcium mobilization by TSLP stimulation could, in turn, modulate airway inflammation, remodeling and responsiveness to constrictors.