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Emerging airway smooth muscle targets to treat asthma

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ABSTRACT

Asthma is characterized in part by variable airflow obstruction and non-specific hyperresponsiveness to a variety of bronchoconstrictors, both of which are mediated by the airway smooth muscle (ASM). The ASM is also involved in the airway inflammation and airway wall remodeling observed in asthma. For all these reasons, the ASM provides an important target for the treatment of asthma. Several classes of drugs were developed decades ago which targeted the ASM – including β-agonists, anti-cholinergics, anti-histamines and anti-leukotrienes – but no substantially new class of drug has appeared recently. In this review, we summarize the on-going work of several laboratories aimed at producing novel targets and/or tools for the treatment of asthma. These range from receptors and ion channels on the ASM plasmalemma, to intracellular effectors (particularly those related to cyclic nucleotide signaling, calcium-homeostasis and phosphorylation cascades), to anti-IgE therapy and outright destruction of the ASM itself.

1. Introduction

Asthma is a common respiratory disease that affects approximately 235 million people worldwide (WHO, Fact Sheet No 307 May 2011). It is characterized by airflow obstruction, airway inflammation and airway remodeling. Classically, the airway smooth muscle (ASM) cell was believed to contribute to the pathogenesis of asthma through its contractile properties: airway hyperresponsiveness (AHR), one of the main characteristics in asthma, refers to excessive narrowing of ASM induced by stimuli which in otherwise normal individuals cause only limited airway narrowing. However it is now widely accepted that ASM also functions as an immunomodulatory cell and contributes to the airway inflammation and structural alterations associated with the disease. Thus, an increase in ASM bulk not only exacerbates airway contraction resulting in increased airway narrowing but it may also be a major driving force of disease progression. Since the ASM plays such a central role it is reasonable to assume that targeting it may be beneficial for the treatment of asthma.

Although current asthma therapies, namely glucocorticoids and β2-adrenoceptor (β2AR) agonists, which abrogate airway inflammation, reverse bronchoconstriction and improve quality of life, are effective in controlling disease symptoms in the majority of patients, a considerable population of patients with poorly controlled asthma remains. Furthermore, these life-long therapies only treat the symptoms and they have little or no effect on the structural alterations associated with asthma. Taken together, these points highlight the need for the development of new or improved therapies. It is only with a greater understanding of the cellular and molecular mechanisms that regulate ASM function that we can begin to develop new treatment strategies for asthma.

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Abbreviations

AHR	airway hyperresponsiveness
ASM	airway smooth muscle
β2AR	β2-adrenoceptor
BTR	bitter taste receptor
Ca^{2+}	calcium
$[Ca^{2+}]_i$	intracellular calcium
cAMP	cyclic 3′5′-adenosine monophosphate
CCL	chemokine (C–C motif) ligand
cGMP	cyclic 3′5′-guanosine monophosphate
COPD	chronic obstructive pulmonary disease
CPA	cyclopiazonic acid
CTGF	connective tissue growth factor
CXCL	chemokine (C–X–C motif) ligand
DAG	diacylglycerol
EGFR	epidermal growth factor receptor
ER	endoplasmic reticulum
FPP	farnesyl pyrophosphate
GGPP	geranylgeranyl pyrophosphate
GPCR	G protein-coupled receptors
HMG	hydroxy-methylglutaryl
IL	interleukin
JAK	janus kinase
MAPK	mitogen-activated protein kinase
MMP	matrix metalloproteinase
NCX	sodium–calcium exchanger
NFκB	nuclear factor kappa B
Non-RTK	non-receptor tyrosine kinase
PDE	phosphodiesterase
PDGFR	platelet-derived growth factor receptor
PI3K	phosphatidylinositol 3-kinase
PKC	protein kinase C
PKG	protein kinase G (cGMP-dependent protein kinase)
PM	plasma membrane
PMCA	plasma membrane Ca^{2+} ATPase
PTEN	phosphatase and tensin homolog deleted on chromosome ten
ROC	receptor-operated channels
ROCK	Rho associated coiled coil-forming protein kinase
RTK	receptor tyrosine kinase
SERCA	sarcoplasmic reticulum calcium-ATPase
SH2	Src homology domain 2
SOCC	store-operated calcium channels
SR	sarcoplasmic reticulum
STIM-1	stromal interaction molecule 1
TGFβ	transforming growth factor beta
TNF	tumor necrosis factor
TH2	T helper type 2
TRP	transient receptor potential
TSLP	thymic stromal lymphopoietin
VDCC	voltage-dependent calcium channels
VEGFR	vascular endothelial growth factor receptor

In this review, we provide an update on existing ASM targets and highlight new and emerging concepts for the treatment of asthma. Space limitations do not allow us to be all inclusive or comprehensive on this subject; instead, we focus particularly on the new directions being pursued by the attendees of the meeting. We begin with stimulation of the ASM by its plasmalemmal receptors for external stimuli – the G protein-coupled receptors, or GPCRs – and several pharmacological concepts related to their function (desensitization; constitutive activity; biased agonism). In addition, we briefly summarize one novel class of GPCR – the bitter taste receptor – given the considerable attention which this family has recently received in the airway field. Next, we consider several diverse signaling events triggered by those GPCRs, including the cyclic nucleotide/phosphodiesterase cascade, elevation of cytosolic calcium concentration via 4 different Ca^{2+}-influx pathways, and activation of various kinases. Finally, we move away from these strategies of treating asthma through control of an excited ASM, by instead now either controlling airway inflammation (anti-IgE therapy), or by removing the ASM entirely (bronchial thermoplasty).

2. G protein-coupled receptors

G protein-coupled receptors (GPCR) on human ASM cells have been a major target for asthma therapy for decades and GPCR ligands still constitute the frontline treatment of asthma today. This widespread clinical use of GPCR ligands is a result of the expanded body of knowledge regarding GPCR identity, localization, downstream signaling pathways, ligand specificity and duration as well as improved methods of administration.

In addition to finding new GPCR targets, the current challenge is to advance the study of GPCR regulation and signaling in human ASM to create new ligands, modify existing ones or target modulators of GPCR function. These approaches are shaped by our growing appreciation of 3 important concepts: (1) GPCR desensitization, (2) constitutively active receptors and (3) biased agonism.

2.1. GPCR desensitization

How GPCR signaling can be manipulated in human ASM to promote a pro-relaxant, anti-inflammatory, anti-proliferative phenotype has long-been the subject of intensive research (see reviews [1,2]). Pharmacological strategies to address this goal have focused on the development of β2AR-selective ligands with optimized efficacy and pharmacokinetic properties. β2AR signaling and functional efficacy is limited by desensitization mechanisms invoked upon exposure to β-agonist. Interestingly, data from Penn, Walker, and colleagues reveals that directly targeting β2AR desensitization mechanisms (via either GRK2/3 inhibition or β-arrestin-2 inhibition/knockout) selectively enhances β2AR signaling in human ASM cells to and augments the relaxant effect of β-agonists on ASM [3,4]. Inhaled corticosteroids in combination with β-agonists constitute the mainstay asthma therapy for many patients and it is interesting to note that preincubation with steroids both restores β-agonist-induced sensitivity and prevents β2-AR desensitization in human precision-cut lung slices [5]. In a follow up study, Panettieri and colleagues revealed that the protective effect of the steroid was not observed for all β-agonists studied and budesonide was found to prevent formoterol- but not salmeterol-induced desensitization of human small airways [6].

2.2. Constitutively active receptors

It is now appreciated that many GPCRs do not sit inactive awaiting stimulation but instead possess a measure of constitutive activity. Thus, in contrast to long-held assumptions, GPCRs are not necessarily on/off switches, but may be active in the unliganded