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Therapeutic targets for chronic obstructive pulmonary disease (COPD)

L.A. Sorbera, J. Bozzo, C. Dulsat, N. Serradell, E. Rosa
Prous Science, Provenza 388, 08025 Barcelona, Spain

CONTENTS

Abstract

Chronic obstructive pulmonary disease (COPD) is a common, chronic inflammatory lung disease associated with progressive airflow obstruction. It has become apparent that, unlike asthma, antiinflammatory therapies are ineffective in improving chronic symptoms and reducing inflammation, lung function decline and airways remodeling. However, the understanding of the mechanisms involved in the development and progression of COPD has grown significantly in recent years, leading to the identification of a number of promising therapeutic targets. Specific drugs have been developed that are directed against targets involved in remodeling, mucus production and chronic inflammation, and therefore potentially effective in preventing the lung tissue damage and progressive decline in lung function associated with the disease. In the interest of facilitating access to information on the principal targets for therapeutic intervention in COPD, this article presents those targets that are currently under active investigation.

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease associated with progressive airflow obstruction. Smoking is the main risk factor and the prevalence of COPD is increasing worldwide. COPD actually refers to a set of symptoms including chronic cough, expectoration, exertional dyspnea and a significant, progressive reduction in expiratory airflow that may or may not be partly reversible (1, 2). COPD includes disorders such as chronic obstructive bronchitis and emphysema; some classifications also include asthmatic bronchitis. Patients suffering from COPD experience poor gas exchange within the lungs, which results in decreased oxygen levels in the blood, increased levels of carbon dioxide and shortness of breath. Moreover, chronic airflow obstruction in COPD is complicated by the loss of lung elasticity resulting from enzymatic destruction of the lung parenchyma. Although predominantly affecting the lungs, COPD also has significant systemic effects, of which the most prevalent is systemic inflammation (3).

COPD is often unrecognized and widely underdiagnosed, particularly in the mildest and most easily treatable stages of the disease. Moreover, the clinical significant of COPD in those patients correctly diagnosed is frequently underestimated. According to the American Lung Association (ALA), 16 million Americans have been diagnosed with some form of COPD, while another 16 million are undiagnosed (4, 5).

The goals of effective COPD management are to prevent disease progression, relieve symptoms, improve exercise tolerance, health status and quality of life, prevent and treat complications and exacerbations, and reduce dyspnea, nocturnal symptoms, the use of rescue medication and mortality. These goals should be achieved with minimum side effects from treatment, a special challenge in a disease such as COPD in which comorbidities are extremely common (6, 7).

Several pharmacological approaches are currently used to treat COPD, including bronchodilators (β_2-adrenoceptor agonists, anticholinergic agents, xanthines), corticosteroids, expectorants and long-term oxygen therapy, as well as smoking cessation therapy, cardiovascular drugs, etc., when indicated. Novel long-acting inhaled bronchodilators, phosphodiesterase inhibitors, protease inhibitors and retinoids are being developed as future therapeutic agents which may effectively promote tissue regeneration (6-8).

The search for effective treatment strategies for COPD continues, with special attention focused on the identification of novel targets for drug development. Those targets currently under active investigation are discussed below (see Figure 1). Table I shows a selection of products under active development for each target.

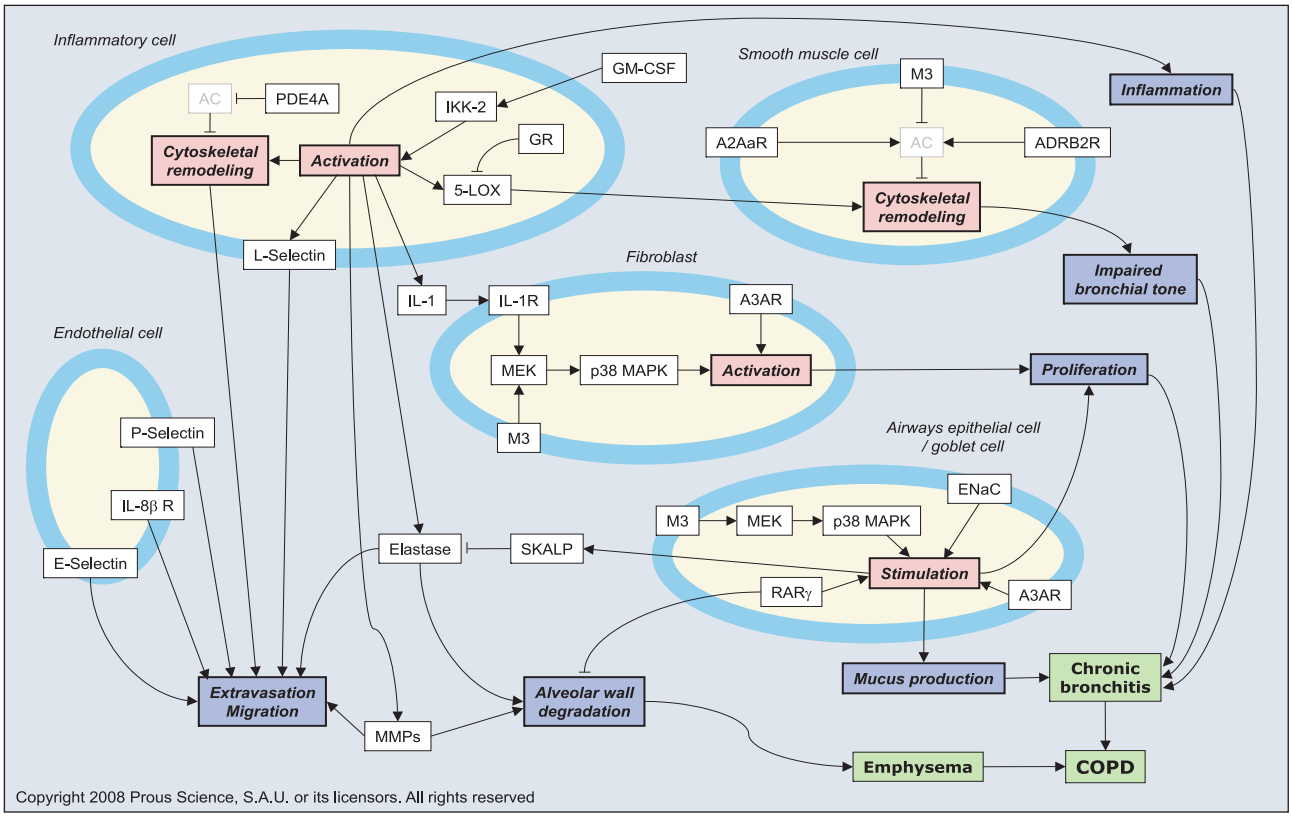

Fig. 1. Diagram showing an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of chronic obstructive pulmonary disease (COPD) and their biological actions (arrow: positive effect; dash: negative effect). A2AaR, adenosine A_{2A} receptor; A3AR, adenosine A_3 receptor; ADRB2R, β_2-adrenoceptor; ENaC, epithelial sodium channel; GM-CSF, granulocyte-macrophage colony-stimulating factor; GR, glucocorticoid receptor; IKK-2, IκB kinase 2 (IKK-B); IL-1R, IL-1 receptor; IL-8βR, chemokine CXCR2 receptor (IL-8 receptor β); 5-LOX, 5-lipoxygenase; M3, muscarinic M_3 receptor; p38 MAPK, p38 mitogen-activated protein kinase; MEK, MAP kinase kinase (MAP2K); MMPs matrix metalloproteinases; PDE4A, phosphodiesterase type 4A; RARγ, retinoic acid receptor gamma; SKALP, elafin precursor (skin-derived peptidase inhibitor 3).

Targets

Adenosine receptors (A_{2A}, A_3)

Adenosine is a naturally occurring purine nucleoside consisting of the nitrogenous base adenine linked to the sugar ribose. The nucleoside is an intermediate product of adenosine triphosphate (ATP) metabolism and is present in many cell types (*e.g.*, neuronal populations, platelets, neutrophils, mast cells and bronchial and vascular smooth muscle cells). Adenosine is released during metabolic stress conditions such as hypoxia or ischemia to elicit strong inflammatory responses. For example, it mediates bronchoconstriction via modulation of inflammatory mediator release from mast cells and may influence the function of other cell types involved in airways inflammation, such as neutrophils, eosinophils, lymphocytes and macrophages. Adenosine production is greatly enhanced under conditions of local hypoxia such as in inflammatory conditions like asthma and COPD, and elevated levels of adenosine have been found in bronchoalveolar lavage, blood and exhaled breath condensate of patients with chronic airways inflammation. Thus, adenosine is strongly implicated in the pathogenesis of chronic inflammatory disorders and modulation of adenosine activity could therefore be exploited as an effective therapeutic approach in the treatment of COPD.

The action of adenosine is mediated via four distinct purinergic G-protein-coupled receptor subtypes (A_1, A_{2A}, A_{2B} and A_3) and biological responses are determined by the different pattern of receptor distribution in specific cells. Both the A_{2A} and A_{2B} receptors are coupled to G_s, which activates adenylate cyclase, resulting in increases in intracellular cAMP. Activation of these receptors via specific agonists could therefore represent an effective treatment strategy for inflammatory diseases such as COPD. The A_3 subtype is coupled to $G_{i/o}$ and is expressed in eosinophils and mucus-producing cells. This receptor type regulates lung eosinophilia and mucus production in an environment of elevated adenosine and its antagonism has been suggested to be effective for the treatment of COPD and asthma (9-11).

β_2-Adrenoceptor

The β_2-adrenoceptor together with the α_1-, α_2-, β_1- and β_3-adrenoceptor subtypes constitute the adrenoceptor family of G-protein-coupled receptors that bind catecholamines (*i.e.*, epinephrine, norepinephrine). The

Table I: Targets and products being actively investigated for COPD (from Prous Science Integrity®).

Target	Product/Patent	Source	Phase
Adenosine A_{2A} receptor	UK-432097	Pfizer	II
Adenosine A_3 receptor	SAR-137272	sanofi-aventis	Preclinical
β_2-Adrenoceptor	Salmeterol xinafoate	GlaxoSmithKline	L-1990
	Formoterol fumarate	Novartis/Schering-Plough	L-2001
	Salbutamol sulfate	GlaxoSmithKline	L-2002
	Indacaterol	Novartis	III
	159802	GlaxoSmithKline/Theravance	II
	642444	GlaxoSmithKline/Theravance	II
	961081	GlaxoSmithKline/Theravance	II
	Carmoterol hydrochloride	Chiesi	II
	Milveterol hydrochloride	GlaxoSmithKline/Theravance	II
Chemokine CXCR2 receptor	PS-291822	Pharmacopeia/Schering-Plough	II
	SCH-527123	Schering-Plough	II
Elafin precursor	Elafin	Proteo Biotech	I
Epithelial sodium channel	P-680	Parion Sciences	Preclinical
Glucocorticoid receptor	Fluticasone furoate	GlaxoSmithKline	II
Granulocyte-macrophage colony-stimulating factor	MT-203	Micromet	Preclinical
IL-1	Canakinumab	Novartis	II
IL-1 receptor	Dom-0400	Domantis	Preclinical
Leukocyte elastase	AZD-9668	AstraZeneca	I
	Recombinant α_1-antitrypsin	Arriva Pharmaceuticals	I
Matrix metalloproteinases	AZD-1236	AstraZeneca	I
	Ilomastat	Arriva Pharmaceuticals	Preclinical
MAP kinase kinase	WO 2005023759	Array BioPharma	Preclinical
p38 Mitogen-activated protein kinases	856553	GlaxoSmithKline	II
Muscarinic M_3 receptor	Tiotropium bromide	Boehringer Ingelheim	L-2002
	Aclidinium bromide	Almirall/Forest	III
	Darotropium bromide	GlaxoSmithKline	II
	CHF-5407	Chiesi	Preclinical
Phosphodiesterase type 4	Roflumilast	Mitsubishi Tanabe Pharma/Nycomed	III
	256066	GlaxoSmithKline	II
	Oglemilast	Forest	II
	OX-914	Orexo	II
	Tetomilast	Otsuka	II
	TPI-1100	Topigen Pharmaceuticals	I
	ELB-353	elbion	Preclinical
Retinoic acid receptor gamma	R-667	Roche	II
Selectins	Bimosiamose	Revotar Biopharmaceuticals	II

β_2-adrenoceptor subtype is widely distributed (lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, skeletal muscle) and directly associated with the class C L-type calcium channel $Ca_v1.2$. This receptor-channel complex contains G_s, which activates adenylate cyclase, causing an increase in intracellular cAMP. Activation of this receptor type generally causes sympathetic effects such as relaxation of bronchial and vascular smooth muscle. Agonists of this receptor may therefore be effective in the treatment of COPD and asthma (12, 13).

Chemokine CXCR2 receptor

The chemokine CXCR2 receptor (IL-8 receptor type II, IL-8 receptor β, $IL8R_B$) is one of two G-protein-coupled receptor subtypes (α and β) for IL-8, an ELR^+ (Glu-Leu-Arg) chemokine produced by monocytes, fibroblasts and endothelial cells that mediates the activation and chemotaxis of T-cells, monocytes and neutrophils. Overexpression of IL-8 appears to be involved in the airways inflammation characteristic of COPD, as well

as cystic fibrosis, asthma, the common cold and rheumatoid arthritis. Antagonism of this receptor could prevent recruitment of pathogenic cells into inflamed lungs, thus preventing the development of COPD (14-16).

E-selectin

E-selectin is a cellular adhesion molecule (CAM) and CD antigen (CD62E) expressed only on endothelial cells and activated by cytokines. It plays a crucial role in inflammation, mediating leukocyte recruitment to the sites of injury or, more specifically, neutrophil, monocyte and memory T-cell adhesion to cytokine-activated endothelial cells. E-selectin recognizes sialylated carbohydrate groups present on the surface proteins of certain leukocytes; these carbohydrates include members of the Lewis X or Lewis A family expressed on monocytes, granulocytes and T-lymphocytes. Neutrophilic inflammation is a pathogenic feature of COPD and inhibition of E-selectin may be an effective therapy for the treatment of this disease (17, 18).

Elafin precursor (SKALP)

Elafin precursor (peptidase inhibitor 3, skin-derived antileukoproteinase, SKALP) is a serine protease and leukocyte (neutrophil) elastase inhibitor produced in the airways epithelial cells that protects these same cells from leukocyte elastase. It is also upregulated in the epidermis of several inflammatory skin diseases. The pathogenesis of COPD is thought to involve an imbalance between protease and antiprotease activity in the lung. SKALP possesses the endogenous function of conferring protection against leukocye elastase at inflammatory sites and suppression of SKALP production may enhance airways inflammation and increase resulting lung damage. Activation of this enzyme could therefore be an effective therapy for COPD (19).

Elastases

The elastases are a family of serine proteases that hydrolyze elastin. Leukocyte (or neutrophil) elastase (EC 3.4.21.37) is a member of this family, a major component of lung elastolytic activity and a stimulant of mucus secretion. It also induces release of IL-8 from epithelial cells and therefore may prolong inflammation. Macrophage elastase, or MMP-12 (EC 3.4.24.65), hydrolyzes soluble and insoluble elastin and specifically cleaves 14-Ala- | -Leu-15 and 16-Tyr- | -Leu-17 in the insulin B-chain. Neutrophils and leukocyte elastase, macrophages and macrophage-derived metalloproteinases, lymphocytes, tumor necrosis factor α (TNF-α) and oxidants have all been shown to play a role in the pathogenesis of emphysema and COPD. Thus, inhibition of elastase is a potential approach to the treatment of COPD, as well as acute respiratory distress syndrome (ARDS) and cystic fibrosis (20, 21).

Epithelial sodium channel (ENaC)

This channel is a non-voltage-gated, amiloride-sensitive, membrane-bound, constitutively active ion channel also known as SCNN1 (sodium channel, non-voltage-gated 1) that together with Na^+/K^+-ATPase is involved in transepithelial Na^+ transport and is considered rate-limiting for Na^+ reabsorption in many tissues. These channels are found on the apical membrane of polarized epithelial cells of many tissues and are also permeable to lithium (Li^+) and protons. For example, they are expressed by epithelial cells that line the distal part of the renal tubule, the distal colon, the ducts of several exocrine glands and the lung. The channels are heteromultimeric proteins composed of three homologous subunits (α-, β- and γ ENaC or SCNN1A, SCNN1B and SCNN1G) that have been proposed to be arranged in either a $2\alpha\beta\gamma$ or a higher ordered configuration; a δ subunit (SCNN1D) can replace the α subunit. In the lung, these channels regulate airways surface liquid volume and the efficiency of mucociliary clearance. Mutations of ENaC can result in pulmonary disease. Moreover, ENaC blockers may be effective in the treatment of symptoms of COPD (22-24).

Glucocorticoid receptor (GR)

The glucocorticoid receptor (GR) is a nuclear hormone receptor of the NR3 class, also known as type II glucocorticoid receptor, that exists as a dimer coupled with chaperone molecules (*e.g.,* heat shock proteins HSP90 and HSP65). The chaperone molecules are shed subsequent to ligand binding. The receptor occurs mainly in two alternative splice variants encoding GRα and GRβ. The receptor binds cortisol and corticosterone, and also aldosterone and deoxycortisone, but with less affinity. The activated receptor then binds nuclear hormone response elements and also affects transcription via protein-protein interactions with other transcription factors such as activator protein-1 (AP-1) and nuclear factor-κB (NF-κB). Activation can result in potent antiinflammatory activity, as well as regulation of several cardiovascular, metabolic, immunological and homeostatic responses. Synthetic GR ligands may be effective as a treatment for COPD and other inflammatory conditions, such as asthma, arthritis, dermatitis, allergic reactions, hepatitis, systemic lupus erythematosus, inflammatory bowel disease (IBD), sarcoidosis, Alzheimer's-type dementia and for glucocorticoid replacement in Addison's disease or other forms of adrenal insufficiency (25, 26).

Granulocyte-macrophage colony-stimulating factor (GM-CSF)

GM-CSF is a cytokine secreted by macrophages, T-cells, mast cells, endothelial cells and fibroblasts that acts as a white blood cell growth factor and can stimulate stem cells to produce granulocytes (*i.e.,* neutrophils, eosinophils and basophils) and monocytes, and is therefore involved in immune and inflammatory responses.

Patients suffering from COPD have increased levels of this proinflammatory cytokine. Neutralization of GM-CSF would prevent activation of inflammatory cells and thus attenuate the release of airways neutrophilic and remodeling mediators. Inhibiting GM-CSF may therefore be effective for reducing lung inflammation in COPD (27, 28).

IKK-B

IKK-B (IκB kinase 2, IKK-β, IKK-2) is a protein serine/threonine kinase (EC 2.7.11.10) that phosphorylates IκB, a cytoplasmic inhibitor, targeting it for proteasomal degradation and allowing the nuclear translocation of NF-κB. It is composed of α, β and γ subunits, the latter not having kinase activity but presumed to play a regulatory role. IKK-B regulates several inflammatory genes, such as those for TNF-α, IL-1 and CAMs, and the proinflammatory mediators NF-κB and AP-1 appear to be activated in airways diseases. Inhibitors of IKK-B block the NF-κB activation cascade, thus attenuating inflammatory responses, and may therefore be effective in the treatment of inflammatory airways diseases such as COPD, asthma and cystic fibrosis (26, 29-31).

IL-1

The IL-1 superfamily includes IL-1α, IL-1β and IL-1 receptor antagonist (IL-1RA). IL-1α and IL-1β are proinflammatory cytokines that are involved in inflammatory and immune responses and IL-1RA competes for receptor binding with these two isotypes, thus blocking inflammatory and/or immune activation. Both isotypes are secreted by monocytes, macrophages and/or accessory cells early during an immune response and they activate T- and B-cells, stimulate T-cell proliferation and enhance T- and B-cell responses to antigens. Overproduction of IL-1 has been implicated in several diseases, including COPD, rheumatoid arthritis, type 1 diabetes, Alzheimer's disease and IBD, and inhibitors of this cytokine may be effective treatment options for these disorders (14, 32).

IL-1 receptor (IL-1R)

IL-1R is the cytokine receptor that binds members of the IL-1 superfamily (see above). Two subtypes have been identified —type I (CD121a) and type II (CD121b)— which are involved in many cytokine-induced immune and inflammatory responses. Antagonism of these receptor subtypes may be effective in the treatment of inflammatory diseases such as COPD (14, 32).

L-selectin

The CAM L-selectin, also known as CD62L, is another member of the selectin family of proteins and is expressed on leukocytes. It is constitutively expressed but is shed upon cellular activation as a result of cleavage mediated by ADAM17 (a disintegrin and metalloproteinase domain 17), a membrane-bound metalloproteinase. It has been identified as a peripheral lymph node homing receptor and several ligands (*e.g.*, glycosylation-dependent cell adhesion molecule 1 [GlyCAM-1], CD34, mucosal addressin cell adhesion molecule 1 precursor [MAdCAM-1]) have been identified on lymph node high endothelial venules (HEVs); however, the ligand for L-selectin on inflamed venular endothelium has not been identified. L-selectin recognizes sialylated carbohydrate groups present on the surface proteins of certain leukocytes; these carbohydrates include members of the Lewis X or Lewis A family expressed on monocytes, granulocytes and T-lymphocytes. Neutrophilic inflammation is a pathogenic feature of COPD and inhibition of L-selectin may represent an effective therapy for the treatment of this and other airways diseases (17, 18).

5-Lipoxygenase

This enzyme (EC 1.13.11.34) catalyzes the first oxidation step in arachidonic acid metabolism, resulting in the synthesis of leukotrienes (LTs), which primarily act as mediators of inflammatory and allergic reactions. The enzyme's activity is regulated in a complex manner and involves different signaling pathways. It can be activated by an increase in intracellular Ca^{2+} concentration, diacylglycerols, phosphorylation by mitogen-activated protein kinase (MAPK)-activated protein kinase 2 (MAPKAP kinase 2, MAPKAPK-2) and extracellular signal-regulated kinases (ERKs), while protein kinase A (PKA) and glutathione peroxidase have been found to suppress its function. Several inflammatory disorders, including COPD, asthma, arthritis and IBD, are associated with elevated levels of LTB_4; eicosanoids generated through the 5-lipoxygenase pathway may also be primary mediators of allergic rhinitis, idiopathic pulmonary fibrosis, atherosclerosis, atopic dermatitis, acne and ischemia-related organ injury. Modulation of LTB_4 synthesis could be achieved via inhibition of 5-lipoxygenase, which would block the synthesis of 5-hydroperoxyeicosatetraenoic acid (5-HPETE) and the subsequent synthesis of eicosanoids (*e.g.,* cysteinyl leukotrienes, LTB_4), which are instrumental in the promotion of the pulmonary inflammatory response and bronchospasm. Thus, these agents may be effective in the management of COPD (33, 34).

Matrix metalloproteinases (MMPs)

The MMPs are a family of zinc-dependent enzymes also known as matrixins that catalyze the hydrolysis of peptide chains and therefore have the ability to degrade a variety of proteins (*i.e.,* elastin, collagen, proteoglycans, laminin, fibronectin) of the extracellular matrix. They are functionally categorized into three groups according to their substrate target —collagenases, stromelysins and gelatinases, which degrade fibrillar collagen, proteoglycans and glycoproteins, and denatured and basement membrane collagens, respectively. MMPs are produced by neutrophils, alveolar macrophages and airways

epithelial cells and have been implicated in several clinical inflammatory conditions, such as COPD and asthma, where inhibition would block extravasation, migration and alveolar wall degradation. Inhibitors may also be effective as a treatment for rheumatoid arthritis, IBD, stroke and multiple sclerosis, and for preventing tumor growth and metastasis (14, 35, 36).

MAP kinase kinase (MEK, MAP2K)

MAP kinase kinase (MEK, MAP2K; EC 2.7.12.2) is a member of the MAPK signal transduction cascade that occurs upstream of MAPK and serves to stimulate the enzymatic activity of MAPK. MAPKs, also known as extracellular signal-regulated kinases (ERKs), are activated (*i.e.*, via rapid phosphorylation on threonine and tyrosine residues) by a wide variety of extracellular signals and thus serve as an integration point for multiple biochemical pathways. The MAPK signaling cascade is initiated by extracellular signaling, which activates (*i.e.*, phosphorylates) MAP kinase kinase kinase (MKKK, MAP3K). Activated MAP3K phosphorylates MEK, which then stimulates MAPK. MEK/ERK inhibitors inhibit mucin secretion, which could be potentially effective as a treatment for the airways mucus hypersecretion seen in COPD and other respiratory disorders such as asthma and cystic fibrosis. MEK inhibitors have also been shown to inhibit muscarinic receptor-induced human lung fibroblast proliferation, which is also a major contributor to the pathology of COPD (37-41).

p38 MAPKs

The p38 MAPKs are a class of MAPKs composed of four isoforms —MAPK p38 α (MAPK14), MAPK p38 β (MAPK11, SAPK2), MAPK p38 γ (MAPK12, ERK6, SAPK3) and MAPK p38 δ (MAPK13 or SAPK4)— which are activated by a variety of cellular stresses, including osmotic shock, inflammatory cytokines, lipopolysaccharide (LPS), ultraviolet light and growth factors. They are activated via MAP3K and MEK by phosphorylation at Thr180 and Tyr182. Activated p38 MAPKs have been shown to phosphorylate and activate MAPKAPK-2 and the transcription factors ATF-2, Mac and MEF2. p38 MAPKs may also be involved in mucin secretion and inhibitors of this kinase could be potentially effective as a treatment for the airways mucus hypersecretion seen in COPD and other respiratory disorders, and may also inhibit the lung fibroblast proliferation contributing to the pathology of COPD (39, 40, 42).

Muscarinic M_3 receptor

The muscarinic acetylcholine M_3 receptor is one of five identified membrane-bound G-protein-coupled, 7-transmembrane-spanning acetylcholine receptor (AChR) proteins that mediate the metabotropic actions of ACh in the nervous system and may also exert autocrine activity. They are expressed on vascular and pulmonary smooth muscles and this subtype signals through G_q, resulting in activation of phospholipase C (PLC), upregulation of inositol 1,4,5-trisphosphate (IP3) and increases in intracellular calcium, ultimately causing contraction of smooth muscle such as that observed during bronchoconstriction. Thus, antagonism of the M_3 receptor may be effective in the management of COPD (43, 44).

P-selectin

P-selectin is a CAM also known as CD62P that is involved in acute inflammation and hemostasis. It is expressed by platelets and endothelium and mediates adhesion, an essential process in the initial recruitment of leukocytes to the site of injury during inflammation. The majority of P-selectin-binding lymphocytes are memory cells. P-selectin is stored in intracellular granules and its expression can be rapidly upregulated by several mediators, such as histamine, thrombin and LTC_4. P-selectin binds P-selectin glycoprotein-1 (PSGL1), which is expressed on most leukocytes and also recognizes sialylated carbohydrate groups related to the Lewis X or Lewis A family expressed by monocytes, granulocytes and T-lymphocytes. Neutrophilic inflammation is a pathogenic feature of COPD and inhibition of P-selectin may be an effective therapy for the treatment of this and other airways diseases (17, 18).

Phosphodiesterase type 4 (PDE4)

PDE4 is a phosphodiesterase isozyme (EC class 3.1.4) characterized by high affinity for cAMP and poor affinity for cGMP. Four PDE4 isoforms have been identified (A, B, C and D). PDE4 plays a key role in regulating cAMP content in human airways smooth muscle cells. PDE4 isozymes are abundant in immunocompetent cells, where an increase in cAMP leads to the inhibition of the synthesis and release of proinflammatory mediators, cytokines and active oxygen species. Since PDE4 is the primary cAMP-hydrolyzing enzyme in inflammatory and immune cells (macrophages, eosinophils, neutrophils), inhibition of this isozyme would increase cAMP levels, consequently downregulating the inflammatory response and relaxing airways smooth muscle. Thus, PDE4 inhibitors may be effective as a treatment for inflammatory diseases such as COPD, asthma, rheumatoid arthritis, atopic dermatitis and IBD (45, 46).

Retinoic acid receptor gamma (RARγ)

RARγ is a member of the retinoid receptor superfamily of nuclear receptors that also includes RARα and RARβ, retinoid X receptor (RXR) α, RXRβ and RXRγ, as well as the cytoplasmic receptors (CRABP-I and -II, CRBP-I and -II). RARs are members of the NR1B family which are activated by natural vitamin A (*i.e.*, retinoic acid), synthetic vitamin A agonists, *all-trans*-retinoic acid (tretinoin) and 9-*cis*-retinoic acid. They form heterodimers with RXRs, modulate cell differentiation and proliferation,

and exert antitumor activity. RARγ agonists may be effective in the treatment of emphysema (COPD) in inhibiting alveolar degradation and may serve as potential therapeutics for cancer, psoriasis, acne, macular degeneration, ischemic vascular disorders and obesity (47, 48).

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