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Novel Strategies for the Treatment of Asthma

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A B S T R A C T

Asthma is characterized as allergic inflammatory responses with airway hyper-responsiveness, both clinical and experimental studies suggest that eosinophils and Th2 type lymphocytes are the key role in the induction of airway inflammation and mucosal injury, The chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. New pyrrolidinone derivatives are metalloproteinase inhibitors to be used for treating cancer, Alzheimer's disease, asthma, rhinitis and rheumatoid arthritis. These Compounds are potent inhibitors of MMP12.

Keywords: Asthma, Rhinitis and rheumatoid arthritis, Alzheimer's disease, cancer.

A R T I C L E I N F O

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1. Introduction

Asthma is characterized by allergic inflammatory responses with airway hyper-responsiveness, and its prevalence is increasing in many countries as one of the important socio-medical problems [1]. Both clinical and experimental studies suggest that eosinophils and Th2 type lymphocytes play a key role in the induction of airway inflammation and mucosal injury, which closely links to non-specific hyper-responsiveness in asthma [2]. In fact, inhaled corticosteroids markedly suppress the airway hyper-responsiveness and asthma symptoms along with decreased eosinophils infiltration in the airways. Clinical trials with anti-IL-5 antibody for the treatment of asthma, however, failed to show the clinical improvement despite apparent decrease in eosinophils of the peripheral blood, and hence, posed some doubt about the critical role of this inflammatory cell [3,4]. It is now proved that asthma is a

heterogeneous and complex airway disease that involves both inflammatory and "non-inflammatory" processes [5,6].

Definition: Asthma is the most common chronic inflammatory disease of the airways characterized by reversible airflow obstruction, and bronchospasm.

2. Pathophysiology and Pathogenesis

Airflow limitation in asthma is recurrent and caused by a variety of changes in the airway including broncho constriction, airway edema, airway hyper-responsiveness, and airway remodeling.

Bronchoconstriction

In asthma, the dominant physiological event leading to clinical symptoms is airway narrowing and a subsequent interference with airflow. In acute exacerbations of asthma, bronchial smooth muscle contraction (broncho constriction) occurs quickly to narrow the airways in response to exposure to a variety of stimuli including allergens or irritants. Allergen-induced acute broncho constriction results from an IgE-dependent release of mediators from mast cells that includes histamine, tryptase, leukotrienes, and prostaglandins that directly contract airway smooth muscle. Aspirin and other nonsteroidal anti-inflammatory drugs can also cause acute airflow obstruction in some patients, and evidence indicates that this non-IgE dependent response also involves mediator release from airway cells. In addition, other stimuli (including exercise, cold air, and irritants) can cause acute airflow obstruction. The mechanisms regulating the airway response to these factors are less well defined, but the intensity of the response appears related to underlying airway inflammation. Stress may also play a role in precipitating asthma exacerbations. The mechanisms involved have yet to be established and may include enhanced generation of pro-inflammatory cytokines.

Airway Edema

As the disease becomes more persistent and inflammation more progressive other factors limit airflow. These include edema, inflammation, mucus hyper-secretion and the formation of inspissated mucous plugs. These latter changes may not respond to usual treatment.

Airway hyper-responsivenes

The degree to which airway hyper-responsiveness can be defined by contractile responses to challenges with methacholine (Provocholine) correlates with the clinical severity of asthma. The mechanisms influencing airway hyper-responsiveness are multiple and include

• Inflammation
• Dysfunctional neuroregulation
• Structural changes

Inflammation appears to be a major factor in determining the degree of airway hyper-responsiveness. Treatment directed toward reducing inflammation can reduce airway hyper-responsiveness and improve asthma control.

Airway Remodeling

Airflow limitation may be only partially reversible in some individuals. Permanent structural changes can occur in the airway, which are associated with a progressive loss of lung function that is not prevented by or fully reversible by current therapy.

Airway remodeling involves an activation of many of the structural cells, with consequent permanent changes in the airway that increase airflow obstruction and airway responsiveness and render the patient less responsive to therapy. These structural changes can include thickening of the sub-basement membrane, sub-epithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation, and mucous gland hyperplasia and hyper-secretion (Box 2). Regulation of the repair and remodeling process is not well established, but both the process of repair and its regulation are likely to be key events in explaining the persistent nature of the disease and limitations to a therapeutic response.

Features of Airway Remodeling

- Inflammation
- Mucous hyper-secretion
- Sub-epithelial fibrous
- Airway smooth muscle hypertrophy
- Angiogenesis (blood vessel proliferation and dilation)

Pathophysiologic Mechanisms in the Development of Airway Inflammation

Airway inflammation involves an interaction of many cell types and multiple mediators with the airways that eventually results in the characteristic pathophysiological features of the disease: bronchial inflammation and airflow limitation that result in recurrent episodes of cough, wheeze, and shortness of breath.

The processes by which these interactive events occur and lead to clinical asthma are still under investigation. Moreover, although distinct phenotypes of asthma exist (e.g., intermittent, persistent, exercise-associated, aspirin-sensitive, or severe asthma), airway inflammation remains a consistent pattern. The pattern of airway inflammation in asthma, however, does not necessarily vary depending upon disease severity, persistence, and duration of disease. The cellular profile and the response of the structural cells in asthma are quite consistent.

Inflammatory Cells Lymphocytes

An increased understanding of the development and regulation of airway inflammation in asthma followed the discovery and description of subpopulations of lymphocytes, T helper 1 cells and T helper 2 cells (Th1 and Th2), with distinct inflammatory mediator profiles and effects on airway function. After the discovery of these distinct lymphocyte subpopulations in animal models of allergic inflammation, evidence emerged that, in human asthma, a shift, or predilection, toward the Th2-cytokine profile resulted in the eosinophilic inflammation characteristic of asthma. In addition, generation of Th2 cytokines (e.g., interleukin-4 (IL-4), IL-5, and IL-13) could also explain the overproduction of IgE, presence of eosinophils, and development of airway hyper-responsiveness. There also may be a reduction in a subgroup of lymphocytes—regulatory T cells—which normally inhibit Th2 cells, as well as an increase in natural killer (NK) cells that release large amounts of Th1 and Th2 cytokines. T lymphocytes, along with other airway resident cells, also can determine the development and degree of airway remodeling. Although it is an oversimplification of a

complex process to describe asthma as a Th2 disease, recognizing the importance of n families of cytokines and chemokines has advanced our understanding of the development of airway inflammation.

Mast cells

Activation of mucosal mast cells releases broncho constrictor mediators (histamine, cysteinyl leukotrienes, prostaglandin D2). Although allergen activation occurs through high-affinity IgE receptors and is likely the most relevant reaction, sensitized mast cells also may be activated by osmotic stimuli to account for exercise-induced bronchospasm (EIB). Increased numbers of mast cells in airway smooth muscle may be linked to airway hyper-responsiveness. Mast cells also can release a large number of cytokines to change the airway environment and promote inflammation even though exposure to allergens is limited.

Eosinophils

Increased numbers of eosinophils exist in the airways of most, but not all, persons who have asthma. These cells contain inflammatory enzymes, generate leukotrienes, and express a wide variety of pro-inflammatory cytokines. Increases in eosinophils often correlate with greater asthma severity. In addition, numerous studies show that treating asthma with corticosteroids reduces circulating and airway eosinophils in parallel with clinical improvement. However, the role and contribution of eosinophils to asthma is undergoing a reevaluation based on studies with an anti-IL-5 treatment that has significantly reduced eosinophils but did not affect asthma control. Therefore, although the eosinophil may not be the only primary effector cell in asthma, it likely has a distinct role in different phases of the disease.

Neutrophils

These are increased in the airways and sputum of persons who have severe asthma, during acute exacerbations, and in the presence of smoking. Their pathophysiological role remains uncertain; they may be a determinant of a lack of response to corticosteroid treatment. The regulation of neutrophil recruitment, activation, and alteration in lung function is still under study, but leukotriene B4 may contribute to these processes.

Dendritic Cells

These cells function as key antigen-presenting cells that interact with allergens from the airway surface and then migrate to regional lymph nodes to interact with regulatory cells and ultimately to stimulate Th2 cell production from naïve T cells.

Macrophages

Macrophages are the most numerous cells in the airways and also can be activated by allergens through low-affinity IgE receptors to release inflammatory mediators and cytokines that amplify the inflammatory response.

Resident Cells of the Airway

Airway smooth muscle is not only a target of the asthma response by undergoing contraction to produce airflow obstruction but also contributes to it (via the production of its own family of pro-inflammatory mediators). As a consequence of airway inflammation and the generation of growth factors, the airway smooth muscle cell can undergo proliferation, activation, contraction, and hypertrophy events that can influence airway dysfunction of asthma.

Epithelial Cells

Airway epithelium is another airway-lining cell critically involved in asthma. The generation of inflammatory mediators, recruitment and activation of inflammatory cells, and infection by respiratory viruses can cause epithelial cells to produce more mediators that are inflammatory or to injure the epithelium itself. The repair process, following injury to the epithelium, may be abnormal in asthma, thus furthering the obstructive lesions that occur in asthma.

Inflammatory Mediators

Eotaxin is relatively selective for eosinophils, whereas thymus and activation-regulated chemokines (TARCs) and macrophage-derived chemokines (MDCs) recruit Th2 cells. There is an increasing appreciation for the role this family of mediators has in orchestrating injury, repair, and many aspects of asthma. Cytokines direct and modify the inflammatory response in asthma and likely determine its severity. Th2-derived cytokines include IL-5, which is needed for eosinophils differentiation and survival, and IL-4 which is important for Th2 cell differentiation and with IL-13 is important for IgE formation. Key cytokines include IL-1_ and tumor necrosis factor (TNF), which amplify the inflammatory response, and granulocyte-macrophage colony-stimulating factor (GM-CSF), which prolongs eosinophils survival in airways. Recent studies of treatments directed toward single cytokines (e.g., monoclonal antibodies against IL-5 or soluble IL-4 receptor) have not shown benefits in improving asthma outcomes. Recent studies have also shown leukotriene B4 can contribute to the inflammatory process by recruitment of neutrophils.

Immunoglobulin E (IgE)

It is the antibody responsible for activation of allergic reactions and is important to the pathogenesis of allergic diseases and the development and persistence of inflammation. IgE attaches to cell surfaces via a specific high-affinity receptor. The mast cell has large numbers of IgE receptors. The development of monoclonal antibodies against IgE has shown that the reduction of IgE is effective in asthma treatment. These clinical observations further support the importance of IgE to asthma.

Implications of Inflammation for Therapy

Recent scientific investigations have focused on translating the increased understanding of the inflammatory processes in asthma into therapies targeted at interrupting these processes. Some investigations have yielded promising results, such as the development leukotriene modifiers and Anti-IgE monoclonal antibody therapy. Other studies, such as those directed at IL-4 or IL-5 cytokines, underscore the relevance of multiple factors regulating inflammation in asthma and the redundancy of these processes. All of these clinical studies also indicate that phenotypes of asthma exist, and these phenotypes may have very specific patterns of inflammation that require different treatment approaches. Current studies are investigating novel therapies targeted at the cytokines, chemokines, and inflammatory cells farther upstream in the inflammatory process. For example, drugs designed to inhibit the Th2 inflammatory pathway may

cause a broad spectrum of effects such as airway hyper-responsiveness and mucus hyper-secretion. Further research into the mechanisms responsible for the varying asthma phenotypes and appropriately targeted therapy may enable improved control for all manifestations of asthma, and, perhaps, prevention of disease progression.

Classification: Asthma is defined by the Global Initiative for Asthma as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. These episodes are usually associated with widespread, but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment".[13]

Table 1: Clinical classification of severity

Severity in patients ≥ 12 years of age [14]	Symptom frequency	Night time symptoms	% FEV_1 of predicted	FEV_1 Variability	Use of short-acting β_2 agonist for symptom control
Intermittent	≤2 per week	≤2 per month	≥80%	<20%	≤2 days per week
Mild persistent	>2 per week but not daily	3–4 per month	≥80%	20–30%	>2 days/week but not daily
Moderate persistent	Daily	>1 per week but not nightly	60–80%	>30%	Daily
Severe persistent	Throughout the day	Frequent (often 7×/week)	<60%	>30%	Several times per day

Asthma is clinically classified according to the frequency of symptoms, forced expiratory volume in 1 second (FEV_1), and peak expiratory flow rate. Asthma may also be classified as atopic (extrinsic) or non-atopic (intrinsic), based on whether symptoms are precipitated by allergens (atopic) or not (non-atopic).[4]

Updated Understanding of Asthma Pathogenesis:

Role of Airway Remodeling

Airway remodeling in asthma has been implicated as a significant pathological change that includes sub-epithelial fibrosis, goblet cell hyperplasia, smooth muscle cells proliferation and microvascular changes. Such structural alterations observed in asthmatic airways are believed to be related to the severity and therapeutic outcomes of asthma [7, 8].

Sub-epithelial Fibrosis and its Molecular Pathogenesis

Bronchial sub-epithelial fibrosis is considered to be an important part of airway remodeling. A significant correlation was found between sub-epithelial layer thickness and degree of airway hyper-reactivity [9]. Increased deposition of collagens type I, III and V is thought to be induced by fibroblasts under the basement membrane. Fibroblasts, especially so-called myofibroblasts, are increased in the Airways of asthmatic patients, and the number of myofibroblasts is correlated with the degrees of airway hyper-responsiveness [10,11]. Abnormal extracellular matrix (ECM) deposition is induced by imbalance between matrixes Metalloproteinases (MMPs) and tissue inhibitor of matrix Metalloproteinases (TIMPs) [12]. Inflammatory cells such As neutrophils and eosinophils produce and release MMPs and TIMPs. Various ECM produced by myofibroblasts also act as growth and migration factors for fibroblasts. ADAM33 (A Disintegrin and Metalloproteinase 33) has been identified as a gene that is linked to asthma in a Caucasian population [13]. ADAM33 is a membrane-anchored metalloproteinase [14]. The expression of this gene is abundant in airway fibroblasts and smooth muscles. Therefore, this protein may play an important role in airway remodeling. Regulation of fibroblast proliferation is dependent on several growth factors via each specific as well as common signal transduction pathways. In vitro co-culture of bronchial epithelial cells and myofibloblasts as a model of airway remodeling of asthma has been reported, and when bronchial epithelial cells are damaged, growth factors [platelet-derived growth factor (PDGF), fibroblast growth Factor-2 (FGF-2), insulin-like growth factor-1 (IGF-1), transforming growth factor (TGF)-b, endothelin-1 (ET-1)] and secreted by bronchial epithelial cells and these factors control myofibloblast proliferation and migration [15].-b 1 stimulates or inhibits proliferation depending on the condition of fibroblast cultures. In addition, prostanoids TGF are involved in negative signals for fibroblast proliferation. We found that Th2 cytokines, IL-4 and IL-13 cell growth of normal lung fibroblasts, and a potent cyclooxygenase inhibitor indomethacin increased proliferation up to the level reached by the action of IL-4 or IL-1316].Regulatory mechanisms of how fibroblasts differentiate into myofibroblasts have been studied. A potent fibrogenic growth factor TGF-b is known to induce myofibroblastic differentiation [17]. We found that IL-4 and IL-13 can directly induce differentiation of lung fibroblasts [16].Importantly, such phenotypic differentiation was not attenuated by dexamethasone (DEX), a potent corticosteroid. As a Th1 type cytokine, interferon (IFN)-g counteracted the effect of IL-4 and IL-13, and attenuated the expression of a-smooth muscle actin (SMA), a marker of myofibroblasts [16]. This result suggests that intervention to the Th1-Th2 imbalance in asthmatic airways can be beneficial for airway remodeling.

Airway Smooth Muscle Cells:

Mechanisms of Proliferation and Hypertrophy

Airway narrowing in asthma is the result of spasms of airway smooth muscles (ASM). Hypertrophied ASM lead to the severe airway narrowing. ASM cell size is greater in Patients with severe asthma as compared with that in control subjects [18]. Regulatory mechanisms of proliferation of airway smooth muscle cells have been investigated. Nitric oxide and prostaglandin (PG) E2, which

are released by bronchial epithelial cells, inhibit proliferation of smooth muscle cells [19,20].,TGFb, IGF-I have growth stimulating activity [21], which are also released by bronchial epithelial cells. ASM cells of bronchial asthma themselves produce connective tissue growth factor (CTGF) in response to Stimulation with TGF-b [22].CTGF release by smooth muscle cells may contribute to the increased production of fibronectin and collagen deposition in the remodeled airway wall. ASM in asthma release less endogenous PGE2 than Normal smooth muscle cells [23].Infiltrated inflammatory cells including eosinophils affect proliferation of smooth muscle cells via TGF-b, PDGF, and tumor necrosis factor (TNF) a [24]. Mast cell infiltration in airway smooth muscle layer is a unique feature in asthma [25]. Mast cell-derived histamine and induce proliferation of smooth muscle cells [26].

Vascular Components

Airway remodeling also include changes of vascular components in the airway. Increased vascularity, vasodilation, and micro vascular leakage occur, which are related to the increased airway wall thickness. Even among patients with mild asthma, increased number of small vessels insubmucosal layer was reported, and this fact suggests that angiogenesis is a component of the chronic airway remodeling in asthma [31].

Airway Remodeling as a Result of Dys-regulated Epithelial Mesenchymal Tropic Units

Above-mentioned data strongly suggest that airway epithelial cell, fibroblast and smooth muscle cell closely interact with each other and exquisitely regulate the repair process and/or remodeling. In the asthmatic airways, dys-regulated repair process might result in structural and functional changes known as remodeling. In the regeneration of epithelial cells, EGF plays an important role, and it is reported that the expression of EGFR (epidermal growth factor receptor) is up regulated in asthmatic bronchial epithelium, while proliferation of the epithelium dose not take place appropriately .This observation suggests that bronchial epithelial cells in asthma lack in functional response to the binding of EGF .In contrast, negative growth factors such as TGF-b seem play an important role in epithelial repair of asthma. While intrinsic fragility and impaired proliferation of epithelial cells might be a cause of epithelial damage and subsequent profibrogenic growth factor production, much has yet to be clarified to explain the precise mechanism of remodeling. Above mentioned progress in the understanding of the Molecular mechanisms of airway inflammation and remodeling in asthma leads us to re-evaluate the present and future drugs for asthma treatment. Although complex and heterogeneous processes are involved, one can understand that certain signal transduction pathways play pivotal roles as final common processes, and thus, it is crucial to determine the target molecule(s) and route of administration for proper drug design.

3. Treatment of Asthma: A future perspective Inhibitors of Transcription Factors

As mentioned above, increased expression of cytokines, chemokines, adhesion molecules and growth factors are the essential features of persistent, chronic asthma with inflammation and airway wall remodeling. Several transcription factors have been implicated in the pathogenesis of asthma ,including the glucocorticoid receptor (GR), nuclear factor kappa B (NF kappa B), Activator Protein-1 (AP-1), Nuclear Factor of Activated T-cells (NF-AT), cyclic AMP Response Element Binding Protein (CREB) as well as signal transducer and activator of transcription(STAT)1 [34] and more recently, the CCAAT/Enhancer Binding Protein (C/EBP), STAT6, Peroxisome Proliferator-activated Receptor (PPAR) and the bZIP transcription factor, nuclear factor E2-related factor 2 (Nrf2) .In clinical practice, inhaled corticosteroids and beta agonists are commonly used for the treatment in asthma and are often used together. Recent evidence suggests that many of the anti-inflammatory actions of corticosteroids are mediated by cross-talk between the activated GR and other transcription factors such as thepro-inflammatory NF kappa B. In a randomized, placebo controlled, crossover study of six weeks' treatment within haled budesonide (400 microg twice daily), terbutaline (1 mg four times daily), and combined treatment were recruited [36]. Biopsy samples of the bronchial mucosa were obtained after each treatment and analysed for the DNA binding activity of GR, CREB, and NF kappaB. Budesonide increased GR activity and decreased NF kappaB activity. No treatment combination altered CREB activity and terbuta-line had no significant effects on any transcription factor. Thus, affects of inhaled cortices teroids might be due to, at least in part, the dual effects on GR and NF kappaB activity in bronchial mucosa.

NF kappaB Inhibitors:

NF kappaB is an inducible transcription factors that plays a central role in the regulation of many immune and inflammatory responses. A variety of signal transduction pathways, originating from various cellular stresses and stimuli, lead to the downstream molecular targets: the NF kappaB/IkappaB complex and its activating kinase (inhibitor of kapp aB kinase, IKK). New Indazole carboxamide derivative or its salt is another inhibitor of IKK2 activity [38].New crystalline mono potassium salt form of 2-((2-(2-methylamino-pyrimidin-4-yl)1H-indole-5-carbonyl)-amino)-3-(phenylpyridin-2-ylamino)-propionic acid is IKK inhibitor [39]. New anilinopyrimidine derivatives are selective inhibitors of IKK, particularly IKK-2 [40].Another invention is related to the co-administration of adehydroepi androsterone (DHEA) congener in combination with a parthenolide, a naturally occurring N kappaB inhibitor, to reduce inflammation.

Although these low-molecular products seem to have a potential to be a novel choice for the treatment of intractable asthma and COPD, it is worrisome to suppress these pivotal transcription processes, since many transcription factors play a central role in tissue and organ homeostasis Cell type specific application of decoy or antisense oligonucleotides or inhaled formulations to antagonize against kappa B, may help to control the inflammatory responses in the affected airways, with little adverse effects.

Macro-Steroids

Erythromycin and its 14-member macrolide analogues have attracted attention for their effectiveness in a variety of airway diseases including diffuse panbronchiolitis (DPB) sinobronchial syndrome, chronic sinusitis and bronchial asthma. In vitro As well as in vivo studies strongly suggested that macrolides have potentials to inhibit expression of inflammatory cytokines and chemokines. In chronic airway inflammation, there is a prominent increase in a variety of cytokines such as IL-1, TNFa, and IL-8. Treatment with 14-ring member macrolide antibiotics Resulted in decreased cytokine levels in the airway lining fluids, suggesting that they have potentials to inhibit cytokine production in the local milieu. In vitro Studies demonstrated that they have, indeed, inhibitory effects on cytokine /chemokine production by several kinds of cells .Recent progress for the elucidation of molecular mechanisms of their unique and novel anti-inflammatory actions indicated that these agents inhibit activation of several transcription factors including NF kappaB and AP- They have also been shown to inhibit fibroblast proliferation, suggesting anti-remodeling activity. Recent reports .showing beneficial effects of anti-TNF alpha receptor antagonist on severe intractable asthma, further suggested therapeutic possibilities of this group of drugs. In this regards, macrolide conjugates with anti-inflammatory activity is interesting New macrolide derivatives are glucocorticoid receptor antagonists which are expected to be useful to treat inflammatory diseases, disorders and conditions, and immune disorders associated with e.g. COPD, asthma and bronchitis. This invention might improve therapeutic action and the use in the treatment of inflammatory diseases and conditions in humans and animals. New decladinosyl macrolide derivatives are cytokine inhibitors used for treating inflammatory disorders e.g. asthma and adult respiratory distress syndrome The present invention relates to novel semi-synthetic macrolides with anti-inflammatory activity. More particularly, the invention relates to 14- and 15-membered macrolide lacking cladinose sugar substituted at the C-3 position, to their pharmaceutically acceptable derivatives, to processes and intermediates for their preparation, to pharmaceutical compositions containing them and to their activity and use in the treatment of inflammatory diseases and conditions in humans and animals, especially those diseases associated with excessive secretion of TNF-alpha, IL-1, IL-6, IL-8, IL-2 or IL-5.

PDE4 Inhibitors:

Phosphodiesterase-4 (PDE4) is an important cyclic adenine monophosphate (cAMP) PDE4 plays a significant role in modulating the activity of cAMP, an important second messenger that mediates the relaxation of airway smooth muscle and suppresses inflammatory cell function, thereby attenuating the inflammatory response. Selective inhibitors of this enzyme show a broad spectrum of activity in animal models of COPD and asthma these drugs block the hydrolysis of cAMP via inhibition of PDE4 and are attractive candidates for novel anti-inflammatory drugs. At present, two second-generation PDE4 inhibitors for the treatment of COPD and asthma patients are being tested in clinical Phase III trials. The first compound is the orally active, selective PDE4 inhibitor cilomilast (cis-4 cyano-4-[3- cyclopentyloxy- 4 methoxy phenyl] cyclohexane carboxylic acid) Cilomilast shows high selectivity for cAMP specific PDE4, an isoenzyme that predominates in proinflammatory and immune cells and that is 10-fold more selective for PDE4D than for PDE4A, -B or -C. in vitro, Cilomilast suppresses the activity of several pro-inflammatory and immune cells important in asthma and COPD. Moreover, it is highly active in animal models of these diseases .Another PDE4 inhibitor, roflumilast was suggested to regulate the ECM and therefore processes of airway remodeling in asthma .New pyrazolo-naphthyridinone compounds are PDE4 inhibitors useful for treating many diseases, including respiratory disease especially asthma .New fluorine compounds are other group of PDE4 inhibitors ,which down regulate or inhibit the production of TNF-alpha and therefore might be useful in the treatment of variety of allergic and inflammatory diseases including asthma and COPD.

Modulation of Th1/Th2 Balance:

It has been documented that Th1/Th2 imbalance toward the predominance of Th2 cells play an important role in the airway inflammatory changes of asthma. As mentioned above, modulation of Th1/Th2 balance might also be a useful tool for the prophylactic treatment of airway remodeling. In fact, there is increasing body of literature suggesting that interferon may have a beneficial effect especially in severe persistent asthma .A group of Th1 cytokines including interferon, IL-12 and other related substances, therefore, are worthy to be evaluated.

Other Anti-Inflammatory and Anti-Remodeling Drugs: Other groups of anti-inflammatory and anti-remodeling agents have been patented as potential promising compounds in the treatment of asthma and related inflammatory Airway diseases.

Monocyclic Aroyl pyridinones as Anti-inflammatory Agents: New monocyclic aroylpyridinones are useful for treating acute and chronic inflammatory processes e.g. asthma, chronic obstructive pulmonary disease.

Pyrimidyl Sulphone:

New sulfonamidopyrimidine derivatives are chemokine receptor modulators useful to treat asthma, rheumatoid arthritis, psoriasis and osteoporosis.

Metalloproteinase Inhibitors:

New pyrrolidinone derivatives are metalloproteinase inhibitors to be used for treating cancer, Alzheimer's disease, asthma, rhinitis and rheumatoid arthritis. These compounds are potent inhibitors of MMP12.

4. Conclusion

Most of the drugs for the treatment of asthma have been developed based on the inhibitory activity on allergic airway inflammation and bronchial smooth muscle contraction. Recent progress in the understanding of molecular events in chronic asthma has proved that airway remodeling is a new potential target of asthma treatment. A variety of anti-inflammatory and anti-remodeling compounds have been attracting attention and patented. It

would be vital to determine the target molecule(s) for re-evaluating each compound for novel drug design in this field.

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