Recent Research and Developmental Strategy of Anti-Allergic Drugs

Hiroichi NAGAI

Abstract: The purpose of this review is to summarize the recent advances in the research and development of anti-allergic drugs. Extensive research over the past decade has provided information about the onset and treatment of allergic diseases, including bronchial asthma, allergic rhinitis and atopic dermatitis. Recent studies also revealed that allergic inflammation is the basic pathophysiology of allergic diseases and is closely associated with their progression and exacerbation. Our understanding of the mechanism of allergic inflammation has improved as a result of immunological and molecular biological studies. While much effort has been paid to developing new anti-allergic drug, allergic disease has yet to be completely conquered. More extensive research will allow the development of new anti-allergic drugs for rescuing the patients. This article provides an overview of recent advances in the research and developmental strategy of anti-allergic agents.

Keyphrases: allergy, anti-allergic drug, asthma, atopic dermatitis, Th2 cytokine

I. Introduction

Allergic diseases, including bronchial asthma, allergic rhinoconjunctivitis and atopic dermatitis, have become a major burden in all over the world [1-3]. Pathomechanistic studies have indicated that allergic inflammation contributes to onset of acute and/or chronic symptoms of allergic diseases. Despite our understanding of the underlying mechanism, there are some therapeutic problems because the prevalence of allergic diseases has increased dramatically in recent decades [4-8]. A significant amount of research is currently focused on explaining the reason why this rise in the number of cases of allergic diseases [9-13].

Bronchial asthma, a typical allergic disease, is thought to be caused by subchronic eosinophilic epithelial desquamative inflammation of the airway. Other allergic diseases such as allergic rhinitis and atopic dermatitis are also inflammatory diseases, as indicated by the names. Thus, allergic inflammation is the basic pathophysiology of allergic diseases and is closely associated with progress and exacerbation of the diseases.

Based on the information described above, a suitable target for the therapeutic treatment of allergic diseases might be the suppression of allergic inflammation. As shown in Fig. 1, allergic inflammation is initiated by the activation of adaptive immune response. This adaptive immune system is affected by innate immune system including natural killer T (NKT) cells, myeloid dendritic cells (DC) and toll-like receptor (TLR). The allergic immune response results from allergen impact on the mucosal surface. Whole allergen is taken up by antigen-presenting cells and peptides are presented to T cells, resulting in T cell activation and elaboration of cytokines. This is the onset of immune response to produce immunoglobulin. In a Type I allergic reaction, immunoglobulin E (IgE) is produced, which is fixed to the mast cell through Fce receptor. Cross-linking of allergen-specific IgE leads to the release of histamine, leukotrienes (LTs) and prostaglandin D2 from mast cells. These chemical mediators introduce immediate phase reaction such as airway smooth muscle contraction,
sneezing and itching in the tissues. Interleukin-4 (IL-4), IL-13 and other mediators including chemokines are generated and released almost 3 to 12 hours after the antigen-antibody combination. Chemokines attract the eosinophils to the allergic lesion. Eosinophil recruitment leads to the release of toxic proteins and mediators, such as protease and LTs, causing edema and epithelial cell damage. Then, tissue remodeling, the repair of injured tissue, occurs. From these basic concepts, current therapeutic approaches have focused either on the treatment of allergic inflammation or the rapid relief of severe symptoms. The former kind of therapeutics are called “controller” and the later type are called “reliever.” The typical controller is topical glucocorticoid and the reliever is a bronchodilator and anti-histamine.

There are numerous discussions concerning a suitable nomenclature of anti-allergic drug. The nomenclature can reflect the target cells and molecule which participate at the onset and development of allergic diseases. Therefore, in this manuscript, anti-allergic drugs involve anti-histamines, LT inhibitors, thromboxane inhibitors, Th2 cytokine inhibitors, mast cell stabilizers and glucocorticoids (Table 1). The recent advances of therapeutic agents for allergic diseases will be described latter in this review.

Table 1 Anti-allergic drugs

<table>
<thead>
<tr>
<th>Antihistamines</th>
<th>1st, 2nd and 3rd generation</th>
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<tbody>
<tr>
<td>Leukotriene inhibitor</td>
<td>5-lipoxygenase or FLAP inhibitor, Cys LT1 or LTB4 receptor antagonist</td>
</tr>
<tr>
<td>Thromboxane A2 (TxA2) inhibitor</td>
<td>TxA2 synthetase or receptor inhibitor, TxA2 and LT receptor dual antagonist</td>
</tr>
<tr>
<td>Th2 cytokine inhibitor</td>
<td>Th2 cytokine production or receptor inhibitor, Neutizing agent</td>
</tr>
<tr>
<td>Mast cell stabilizer</td>
<td>Topical or Oral active drug</td>
</tr>
<tr>
<td>Glucocorticoid (GC)</td>
<td>Topical, Oral or Injection</td>
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II. Antihistamines

Despite the recent discovery of numerous mediators involved in allergic inflammation, histamine remains a pleiotropic mediator involved in different allergic condition. During the past decade, there have been major advances in our understanding of histamine, histamine receptors and histamine H1 antagonists. For many years, histamine receptors have been characterized using a pharmacological approach. Recently, a cDNA clone encoding the H1 receptor has been cloned in human leukocytes and the structure of the H1 receptor protein has been deduced along with several other histamine
receptors (Fig. 2). These findings improved the development of new antihistamines, especially H1 receptor antagonists.

The first-generation antihistamines were defined by their H1 receptor blocking activity, and despite pronounced unwanted side-effects they are still widely used. The problems with systemic side-effects, especially sedation and dry mouth, stimulated the pharmacological research to develop a second generation of drugs that were ostensibly free of these properties and more efficacious.

The second-generation antihistamines are called non-sedating H1 antagonists because of their low penetration through the blood-brain barrier (Fig. 3). Compared with the first generation agents, they are known for their minimal central nervous system effect. Many of the second generation antihistamines undergo extensive first pass metabolism in the liver by the cytochrome p450 (CYP) enzymes. Drugs such as ketoconazole, erythromycin and azithromycin, which affect the activity of CYP, can lead to build up of the parent antihistamine compound, thus increasing the risk of side-effects. It has been demonstrated that the ingestion of grapefruit juice can inhibit isoenzyme CYP3A4 in the liver. Thus grapefruit juice may increase the concentration of antihistamines, such as terfenadine, loratadine and astemizole which are metabolized by CYP3A4.

Fig. 3 Structural formulas of classical and new generation H1-antagonists
Additionally, life-threatening adverse cardiac side effects, QT prolongation and torsades de points, venricular tachyarrhythmia have been demonstrated to be associated with the use of some second-generation antihistamines. These effects are due to the direct blockade of a specific class of potassium channels controlling the repolarization phase of the cardiac action potential and are not related to the blockade of H1 receptor. Thus this cardiotoxicity by second-generation antihistamines is not a class effect.

As a direct result of these problems, a third-generation antihistamines has emerged \(^{26}\). The term ‘third generation’ or ‘multifunctional’ antihistamine was employed by Hanifin, Sabbah, Caproni et al. and ourselves \(^{27-30}\) for describing the pharmacological profiles of ketotifen, terfenadine and cetirizine, respectively. However, clear criteria of what this term means are still uncertain. In 2003, a Consensus Group on New Generation Antihistamines (CONGA) has been set up with the support of the ‘British Society for Allergy and Clinical Immunology’ to address the meaning of the third-generation antihistamines. An internal expert panel of scientists and clinicians outside the pharmaceutical industry convened to form a CONGA and reported in 2003 \(^{36}\). An exclusive summary was produced with recommendations in six areas as indicated in Table 2.

**Table 2** Summary of present status and recommendations for third generation antihistamines by CONGA

1) The anti-inflammatory or anti-allergic properties should be demonstrable in vivo in humans, at therapeutic doses and under natural exposure to the offending allergens
2) The therapeutic index of an antihistamine, defined as its benefit-risk ratio, is a more important concept than either potency (preclinical studies) or efficacy (clinical trials)
3) The lack of cardiac toxicity must be retained in the development of novel congeners that enter the market in the future
4) The drug should not affect any CYP (enzyme function), should not displace protein bound medications and should not affect active transport mechanism (e.g. P-glycoprotein)
5) Non-sedative properties should be defined by measuring a) incidence of subjective sleepiness; b) objective cognitive and psychomotor function; c) proton emission tomography (PET) measurement of H1 receptor occupancy
6) A new antihistamine based on the theoretical properties should however be proven to have distinct clinical advantage over existing drugs


Published information concerning H1 antihistamines suggests that none of them can be classified as a true third-generation antihistamine. Rationalization is required to develop a new class of antihistamines.

III. Leukotriene inhibitors

LTs are derived from membrane constituent arachidonic acid and show a multiple biological described in Table 3 \(^{31}\). Especially, LTs play a role to induce many allergic symptoms, including airway smooth muscle contraction, hypersecretion, eosinophilia and airway wall remodeling \(^{32-35}\).

The role of LTs in cardiovascular disease and cancer is the interesting subject of recent investigation. However, the theme of this article is not focused on them. So the role of LTs in allergic disease will be discussed here.

As for the role of LTs in allergic reaction, cys LTs and LTB4 play an important role for the onset of allergic inflammation as show in Fig. 4. One explanation is the role of LTs in dendritic cells (DC) migration \(^{36}\) and another is the participation of LTs in the pathological action of IL-13 \(^{37}\). Recent studies by Robbiani et al. \(^{36}\) indicated that LTs play a role in the antigen-stimulated migration of DC through the activation of multi-drug resistance-associated protein 1 (MRP1) and chemokine (CCL19). This suggests that LT may play a role in the acceleration of antigen presentation in adaptive immune response. In addition, IL-13 induced an airway remodeling in mice through the generation of LT which is the main cause for the onset of airway hyperreactivity, eosinophilia and MUC5AC production. This suggests that IL-13 plays an important role in the onset of airway hyperreactivity and contributes to the stimulation of LTs generation.

Evidence from several sources indicates an additional role for LTs in allergic diseases. After the identification of chemical structures of LTs, extensive efforts have been made for cloning of the cysteiny LT (cys-LT) receptors. It is noteworthy that the launch of LT antagonists preceded the identification and cloning of cys-LT receptors. On this basis, many researchers
Table 3 Biological actions of LTs associated with diseases
(By M. Peters-Golhen and W. R Hendersor, 2007)

<table>
<thead>
<tr>
<th>Cells</th>
<th>Allergy</th>
<th>Cardiovascular Disease</th>
<th>Cancer</th>
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</thead>
<tbody>
<tr>
<td>Leukocyte</td>
<td>Increases recruitment of T cells,</td>
<td>Increases monocytes and T cell recruitment</td>
<td>Increases recruitment of monocytes and reactive oxygen species</td>
</tr>
<tr>
<td></td>
<td>eosinophils and mast cells</td>
<td>Increases differentiation of MCP or form cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increases TGF responses, cytokines or</td>
<td>Increase chemokines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>chemokines</td>
<td>(e.g. MCP-1 and MCP-10) and protease</td>
<td></td>
</tr>
<tr>
<td>Dendritic cell</td>
<td>Increases cell recruitment and activation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelial cell</td>
<td>Increase mucus release and goblet cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>Increase contractility and proliferation</td>
<td>Increase contractility and proliferation</td>
<td></td>
</tr>
<tr>
<td>Endothelial cell</td>
<td>Increase vascular permeability</td>
<td>Increase initial hypoxia and</td>
<td>Increase vascular permeability and angiogenesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>increase chemokines</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Increase thrombosis</td>
<td></td>
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<tr>
<td>Malignant cell</td>
<td></td>
<td></td>
<td>Increases proliferation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increases transcriptional activity of oncogenic genes</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Increases expression of adhesion molecules</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decrease apoptosis to increase tumor cell survival</td>
</tr>
</tbody>
</table>

![Diagram](image)

Fig.4 The 5-lipoxygenase (5-LO) pathway of arachidonic acid (AA) and inhibitors
FLAP: 5-lipoxygenase activating protein, 5-HPETE: 5-Hydroperoxyeicosatetraenoic acid, DC: dendritic cell, Inh: Inhibition

initiated programs to find either inhibitors of LT biosynthesis or selective receptor antagonists.

In the 1990s, the LT approach moved from concept to proof. This was based on the successful development and subsequent launch of three LT antagonists and one 5-lipoxygenase (5-LO) inhibitor listed in Table 4. Three receptor antagonists display significant structured homology and are highly effective against LTD4. A common feature of clinical trials with these three

Table 4 The inhibitors of leukotrienes

<table>
<thead>
<tr>
<th>5-LO inhibitor</th>
<th>Cys-LT1 antagonist</th>
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<tbody>
<tr>
<td>Zafirlukast</td>
<td>Montelukast</td>
</tr>
<tr>
<td>Zileuton</td>
<td>Montelukast</td>
</tr>
<tr>
<td>Zileuton</td>
<td>Zafirlukast</td>
</tr>
<tr>
<td>Dosis (mg/day)</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>600</td>
</tr>
<tr>
<td>Administration</td>
<td>40</td>
</tr>
<tr>
<td>Synergic effect</td>
<td>10</td>
</tr>
<tr>
<td>Asthma</td>
<td>450</td>
</tr>
</tbody>
</table>

5-LO: 5-lipoxygenase  Cys-LT1 cysteinyl leukotriene 1 receptor
antagonists is an improvement in baseline lung function in asthma patients but not in non-asthma patients. This result demonstrates that antagonists do not have a direct relaxing activity of bronchial smooth muscle. These improvements are generally in the range of 25-50%, although the magnitude of the changes depends on the symptoms which are measured by the severity of disease. In addition, many studies have been carried out with combinations of cys-LT antagonists and inhaled corticosteroid \(^{38-40}\). Generally, treatment of LT antagonists resulted in a lower dose of inhaled corticosteroid, reducing the severity of asthmatic symptoms.

As for 5-LO inhibitors, many compounds have been developed but only one drug, zileuton has been registered for treatment of asthma in the USA. From observations with 5-LO inhibitors, in particular zileuton, it appears that the anti-asthmatic effects of 5-LO inhibition and selective cys-LT1 receptor antagonists in asthma patients are indistinguishable. The successful induction of cys-LT1 receptor antagonists and 5-LO inhibitors for the treatment of bronchial asthma provided clinical data that confirmed the LT hypothesis in asthma, which had taken almost 70 years to evolve since the original discovery of slow reacting substance of anaphylaxis.

Unfortunately the clinical role of LTs in other allergic diseases, such as allergic rhinitis and dermatitis, is still uncertain. Our studies employing 5-LO gene deficient mice suggest the low participation of LTs in allergic dermatitis and IgE production (unpublished data). Further studies to investigate the role of LTs in other allergic diseases, especially nasal obstruction, could expand the therapeutic utility of LT inhibitors.

Moreover, the role of LTB\(_4\) in allergic diseases is still obscure \(^{41-44}\). If more potent and selective LTB\(_4\) receptor antagonist will be discovered, it will be helpful for understanding the role of LTB\(_4\) in allergic diseases.

IV. Thromboxane A2 (TXA2) inhibitors

TXA2 is unstable at physiological condition, the biological half-life is less than 1 minute and the plasma concentration is less than 100 pg/ml. Therefore, the precise role of TXA2 in allergic disease is obscure for long time. However, there is some evidence from basic research and clinical reports to indicate that TXA2 is involved in the onset and development of allergic diseases \(^{45-47}\). TXA2 causes a constriction of airway smooth muscle. And recent studies indicate that TXA2 play a role in allergic rhinitis, especially rhinorrhea and rhinostenosis \(^{48-50}\). Moreover, Shin et al. \(^{51}\) reported the association of TXA2 receptor (TBX2A2R) with atopy and asthma. There are two types of TXA2 inhibitor in clinical use in Japan, including one TXA2 synthetase inhibitor (ozagrel) and two TXA2 receptor antagonists (ramatroban and seratrodust). All these TXA2 inhibitors are employed for the treatment of bronchial asthma. The efficacy of these agents in asthma treatment is still under discussion, but the effectiveness of ramatroban in allergic rhinitis is noteworthy. Because of the strong expression of TXA2 receptor mRNA in the nasal mucosa of allergic rhinitis patients and the positive relationship between TXA2 receptor polymorphism and IgE production \(^{52}\), the anti-allergic action of TXA2 receptor antagonist might be anticipated. From the extensive basic and clinical investigations concerning the efficacy of ramatroban in allergic rhinitis, the drug showed a potent therapeutic activity to several nasal symptoms, especially, nasal obstruction. Since several investigators including ourselves, revealed the efficacy and antagonistic action of ramatroban against the CRTH2, one of the prostaglandin D2 receptor, interest in the role of CRTH2 in the onset of nasal obstruction has increased \(^{48,50}\). However, further studies are necessary to fully determine the efficacy of these anti-CRTH2 agents.
Suplatastat tosilate (IPD)

Fig. 5 Chemical structure of suplatastat tosilate (IPD) and its action during Type I allergic reaction

V. Th2 cytokines inhibitor

Many investigators indicated that Th2 polarized immunity is a main course of allergy. Recent advances in understanding the immunology of Th2 cells have opened up the possibility of specific immunomodulation to control allergic diseases. Much effort has been paid to suppress the allergic diseases by employing modulator of Th2 polarized immunity. Our laboratory, in collaboration with a pharmaceutical company, has investigated suplatastat, a Th2 cytokine inhibitor. Suplatastat initiates the suppression of IgE antibody production and eosinophilia by the interfering with Th2 cytokine production. In addition, suplatastat inhibits the activation of chloride ion channel on eosinophils resulting in cell death (unpublished data). The chemical structure and pharmacological profile of suplatastat are summarized in Fig. 5. This is the first trial to apply the T cell immunomodulator as a remedy for allergic diseases.

VI. Mast cell stabilizer

The role of mast cell in allergic disease is evident. It has been suggested that stabilization of mast cell is a key mechanism to protect the allergy. Cromoglicate is the first agent to have a mast cell stabilizing activity and shows a clinical efficacy against some allergic diseases including bronchial asthma, allergic rhinitis and atopic eye disease. Cromoglicate may be distinguished from other drugs used in the treatment of allergy, such as β2-adrenergic stimulants, antihistamines and glucocorticoids, because it is ineffective if given after antigen-challenge whereas the latter groups of drugs are effective after antigen stimulation. The clinical efficacy of cromoglicate is widely recognized, but this drug is not absorbed by oral administration. It is only effective if applied directly to the airway mucosa by inhalation. This disadvantage promote to develop oral active mast cell stabilizers which inhibit the release of allergic mediator after antigen provocation. Our laboratory, in collaboration with a pharmaceutical company, has developed tranilast, 3', 4' dimethoxy cinnamoyl-anthranilic acid, the first orally usable mast cell stabilizer. It showed efficacy and usefulness in the treatment of allergic asthma, rhinitis and skin diseases as shown in Table 5. Then, many pharmaceutical companies developed oral active mast cell stabilizers as an anti-allergic agent. They show
Table 5: Anti-allergic action of tranilast in basic research

1. Inhibition of immunological mediator, release from sensitized human or animal lung tissues
2. Inhibition of allergen-induced histamine release from leukocytes of sensitized patients *ex vivo*
3. Inhibition of allergic reaction in airway or skin in human or experimental animal models by oral administration

An effectiveness for the treatment of allergic diseases but the potency is almost relatively weak or mild. Therefore, their clinical usage has been limited. Most of agents inhibit the functions of eosinophils, neutrophils and platelets and these actions of drugs, together with the inhibition of mast cell function, seem to be the best explanation to data of the anti-allergic effect of the drugs.

VII. Glucocorticoids

Glucocorticoids (GCs) are the most effective agents currently used to treat the chronic allergy. However systemic usage of GCs is limited in fear of side effects. Therefore, the topical application of GCs is recommended in several allergic diseases such as bronchial asthma, allergic rhinitis, atopic dermatitis and others. Inhaled GCs are the most common agent for the management of bronchial asthma. In Japan, now, three inhaled GCs, beclomethasone dipropionate (BDP), fluticasone propionate (FP) and budesonide, are available for clinical use (Fig. 6). Recently, long acting β₂ agonist and glucocorticoid combined inhalator and ciclesonide were introduced for the treatment of chronic asthma. Asthma treatment guideline in many countries recommended the usage of an inhaled corticosteroid plus a long-acting inhaled β₂-agonist as the preferred maintenance therapy for moderate and severe persistent asthma. An inhaler combination formulation is at least equivalent to its components administered separately and is superior to monotherapy with salmeterol or inhaled corticosteroid in both paediatric and adult populations. Ciclesonide is a novel non-halogenated inhaled corticosteroid that is not directly active, but it is cleaved by endogenous esterases in the airway to activated drug substance 54, 75). Thus, ciclesonide is an on-site activated drug. Because of this character the drug has highly topical potency but essentially no oropharyngeal side effects and suppression of endogenous cortisol. This is the first inhaled GC having a high topical potency without causing any systemic cortisol suppression.

These developments of inhaled GC improved the quality of asthma management. Regarding the therapy of nose or skin allergic diseases by GCs, a soft drug is

![Chemical structure of inhaled glucocorticoid](image-url)
extensively investigated. A soft drug is active by itself, rapidly and predictably inactivated during its systemic has therapeutic efficacy at the site of application, and its uptake and distribution.

Much effort has been paid to develop a new soft GS as an anti-allergic drug by several pharmaceutical companies, some effective drug will be available in the near feature.

VIII. Future anti-allergic drugs

Although topical GCs are very effective at controlling allergic diseases, symptoms recur when GCs are withdrawn and there is an increase in markers of inflammation, and immune response. Thus strategies for the immunomodulation are attractive since they may offer the prospect of long-term disease modification and prevention. Future strategy aimed at down regulation of the allergic response can be classified many targets as indicated in Table 6. While there are numerous possible strategies to develop a new drug, our interest is focused on the concept of Th2 dependent allergic inflammation in the diseases.

Regarding the suppression of Th2 response, there are some new trials targeting Th1 response stimulation, cytokine suppression and other regulatory molecules.

One of Th1 stimulator is a plasmid vector containing genes that encode allergen, namely a DNA vaccine. This vaccine decreases Th2-mediated responses, enhance Th1 mediated responses and suppress the allergic responses in animal models. Other trials have employed a virus-like particle to induce interferon producing CD8+ T cells and mucosal DNA vaccines to induce tolerance. For example, the main peanut allergen gene expression vector when administered orally caused higher fecal IgA and serum IgG2a and lowered serum IgE titer and resulted in decreased anaphylactic symptoms. Whether this approach is efficacious will be determined in further studies.

A particular approach for enhancement of Th1 mediated response has been the administration of synthetic oligodeoxynucleotides with immunostimulatory sequences. Strong stimulation was driven by sequences containing methylated CpG motifs that are more highly expressed in microbial rather than vertebrate DNA, and so are recognized as foreign by the Toll-like receptor in innate immunity. These motifs indicate the function as Th1 promoting adjuvant capable of switching the usual Th2 response toward Th1 response. Preclinical results are promising, but the outcome of clinical trials for allergic diseases is pending.

Some experimental results, including those of our own, indicate the efficacy of interferons or IL-12 against the

<table>
<thead>
<tr>
<th>Target</th>
<th>Approach</th>
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<tr>
<td>T cell modulator</td>
<td>(Th2) GATA-3, FOG-1, CD28, CTLA-4</td>
</tr>
<tr>
<td></td>
<td>(Th1) CpG oligodeoxynucleotides, T-bet</td>
</tr>
<tr>
<td></td>
<td>(T) Macrocyclic immunosuppressant</td>
</tr>
<tr>
<td>Cytokines</td>
<td>TNF antagonist, GM-CSF antagonist, IL-4 antagonist, IL-5 antagonist,</td>
</tr>
<tr>
<td></td>
<td>IL-13 antagonist, IL-10, IL-12, IL-18, IFN-γ</td>
</tr>
<tr>
<td>Chemokines</td>
<td>Th2 related chemokines receptor antagonist, CCR-3 antagonist, IL-8 receptor antagonist</td>
</tr>
<tr>
<td>Adhesion molecule</td>
<td>VLA-4 antagonist, selectin antagonist, ICAM-1 and VCAM-1 antagonists</td>
</tr>
<tr>
<td>Allergen</td>
<td>Epitopes, TCR activation status receptors</td>
</tr>
<tr>
<td>IgE antibody</td>
<td>Humanized anti-IgE antibodies</td>
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allergic inflammation\textsuperscript{81}. Contrary to basic research, these cytokines are ineffective for the clinical treating allergic diseases\textsuperscript{82}. These cytokines, along with related targets, will have to be monitored in near feature. In addition to Th1 related cytokines, Th2 cytokines including IL-5 are the target molecule for anti-allergic agents. As for IL-5 suppression, there are many experiments to support the effectiveness of anti-IL-5 monoclonal antibody at inhibiting allergic diseases\textsuperscript{83-85}. We have demonstrated the efficacy of anti-IL-5 monoclonal antibody for allergic airway wall remodeling, but not for allergic airway hyperreactivity in experimental animals\textsuperscript{85}. Our data is confirmed by some clinical studies. Holgate et al.\textsuperscript{86} reported ineffectiveness of IL-5 monoclonal antibody in airway hyperreactivity but found it to be effective in the therapy for allergic eosinophilia. Moreover recent studies by Kay et al. indicated the effectiveness of anti-IL-5 antibody on airway wall remodeling in asthmatic patients. These results stimulated a discussion about the role of IL-5 and eosinophils in the development of allergic asthma. Long term treatment of anti-IL-5 will be necessary to establish the role of IL-5 and eosinophils in bronchial asthma. Regarding the role of eosinophils, our recent studies employing the inhibitors of eosinophil chemotaxis indicate the efficacy of eosinophil inhibitors for anti-asthmatic treatment (unpublished data).

Some investigators reported that IL-13 and IL-9 are potent pathological substances for allergic diseases. Therefore, these two cytokines are target molecules for anti-allergic agents. In fact, mice lacking the gene for IL-13 and IL-9 showed low hyperresponsiveness and airway inflammation, respectively. However, there has been no report about the efficacy of the inhibitors against these cytokines in clinical trial.

Moreover, the use of humanized anti-IgE antibodies has become a new therapeutic strategy for allergic diseases\textsuperscript{87,88}. Treatment with anti-IgE antibodies leads to a decrease in serum IgE and in the number of high-affinity IgE receptors on mast cells and basophiles. These decreases lead to a low excitability of the effector cells reducing the release of inflammatory mediators. Anti-IgE antibody is expected to be a promising strategy in near feature.

IX. Conclusion

The aim of this article is to offer a state-of-the-art description of recent advances in research and development of new therapeutics for allergic disease. Extensive research on the mechanism of allergy and therapeutics to combat allergic disease will give us an opportunity to find new strategies for establishing effective treatments. Continued research on the molecular mechanism of allergic disease will inevitably generate new forms of therapy and new anti-allergic drugs.

X. Acknowledgement

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XI. References


