

# Histamine in chronic allergic responses

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**Summary.** In addition to its well-characterized effects in the acute inflammatory and allergic responses, histamine has been shown to affect chronic inflammation and regulate several essential events in the immune response. Histamine can selectively recruit the major effector cells into tissue sites and affect their maturation, activation, polarization, and effector functions leading to chronic inflammation. On the other hand histamine acting through its receptor (HR) type 2 positively interferes with the peripheral antigen tolerance induced by T regulatory (Treg) cells in several pathways. Histamine also regulates antigen-specific T<sub>H</sub>1 and T<sub>H</sub>2 cells, as well as related antibody isotype responses. These findings provide suitable explanation for the observations in the experimental model of asthma showing that allergic inflammatory responses and bronchial hyperresponsiveness may be susceptible to HR1 blockade. Apparently, the various effects of histamine on immune regulation are due to differential expression and regulation of 4 histamine receptors and their distinct intracellular signals. In addition, differences in affinities of these receptors is highly decisive on the biological effects of histamine and drugs that target histamine receptors. This article highlights novel discoveries in histamine immunobiology and discusses their relevance to the allergic inflammatory responses.

**Key words:** Histamine, Histamine receptors, T cells, T regulatory cells, Tolerance, Dendritic cells, Antibodies, Allergy, Airway function.

## Introduction

Histamine, which is synthesized and released by human basophils, mast cells, neurons and lymphocytes (2-[4-imidazole]-ethylamine) was discovered as an uterine stimulant in different extracts more than 100 years ago. Its smooth muscle stimulating and vasodepressor action was shown in the first experiments by Dale and Laidlaw [1], who also found that the effects of histamine mimicked those occurring during anaphylaxis. Histamine is one of the most intensely studied molecules in medicine. Substantial evidence has been accumulated about its metabolism, receptors, signal transduction, physiological and pathological effects. However, the complex interrelationship and crosstalk by histamine, its receptors and other G-protein coupled receptors remain to be elucidated.

## Histamine receptors

The pleiotropic effects of histamine are mediated by four subtypes of receptors (histamine receptor (HR) 1, HR2, HR3, and HR4) (Table 1). All of these receptors belong to the G-protein-coupled receptor family. Specific activation or blockade of histamine receptors has led to a tremendous increase in the knowledge of the roles of histamine in physiology and disease mechanisms.

In the studies to find histamine receptor blocking agents, classical models of G-protein-coupled receptors require the occupation of receptors by an agonist to initiate activation of signal transduction pathways. Recently, the expression of G-protein-coupled receptors in recombinant systems revealed a constitutive spontaneous receptor activity, which is independent of receptor occupancy by an agonist [2]. Like most other G-protein-coupled receptors, histamine receptors exist as a balance between

Table 1. Histamine receptors, expression, coupled G proteins and activated intracellular signals.

Histamine receptors	Expression	Activated intracellular signals	G proteins
HR1	nerve cells, airway and vascular smooth muscles, hepatocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes, DC, T and B cells	Ca <sup>+2</sup> , cGMP, phospholipase D, phospholipase A <sub>2</sub> , NFκB	G <sub>q/11</sub>
HR2	nerve cells, airway and vascular smooth muscles, hepatocytes, chondrocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes DC, T and B cells	adenylate cyclase, cAMP, c-Fos, c-Jun, PKC, p70S6K	Gα <sub>s</sub>
HR3	histaminergic neurons, eosinophils, DC, monocytes low expression in peripheral tissues	enhanced Ca <sup>+2</sup> , MAP kinase, inhibition of cAMP	G <sub>i/o</sub>
HR4	high expression on bone marrow and peripheral hematopoietic cells, eosinophils, neutrophils, DC, T cells, basophils, mast cells, low expression in nerve cells, hepatocytes peripheral tissues, spleen, thymus, lung, small intestine, colon and heart	Enhanced Ca <sup>+2</sup> , inhibition of cAMP,	G <sub>i/o</sub>

their inactive and active conformations, agonists stimulating the active and inverse agonists (antagonist in the old terminology) the inactive one. An agonist with a preferential affinity for the active state of the receptor stabilizes the receptor in its active conformation leading to continuous activation signal via the HR1. An inverse agonist with a preferential affinity for the inactive state, stabilizes the receptor in this conformation and consequently induces an inactive state, which is characterized by blocked signal transduction via the HR1 [3]. In reporter gene assays, constitutive HR1-mediated nuclear factor (NF)-κB activation has been shown to be inhibited by many of the clinically used H1-anti-histamines, indicating that these drugs are inverse HR1-agonists [3]. Constitutive activity has now been shown for all four histamine receptors [3]. The G<sub>q/11</sub>-coupled HR1 is responsible for many symptoms of allergic disease. Studies in different species and several human cells demonstrated that inhibition of characteristic features of the cells by primarily cAMP formation dominates in HR2-dependent effects of histamine.

HR3 has been identified in the central and peripheral nervous system as pre-synaptic receptors controlling the release of histamine and other neurotransmitters. The

control of mast cells by histamine acting on HR3 involves neuropeptide-containing nerves and might be related to a local neuron-mast cell feedback loop controlling neurogenic inflammation [4]. Dysregulation of this feedback loop may lead to excessive inflammatory responses and suggests a novel therapeutic approach by using HR3 agonists.

Human HR4 is functionally coupled to protein G<sub>i/o</sub>, inhibiting forskolin-induced cAMP formation like the HR3 [5]. HR4 shows high expression in the bone marrow and peripheral hematopoietic cells, neutrophils, eosinophils and T cells, and moderate expression in spleen, thymus, lung, small intestine, colon, and heart [5]. Both basophils and mast cells express HR4 mRNA [6]. H4-receptor activation promotes the accumulation of inflammatory cells (particularly eosinophils and mast cells) to sites of allergic inflammation. Related to high homology between the two receptors, presently available HR3 agonists and antagonists are also recognized by the HR4 [5]. The H1 antagonists, doxepin, cinnarizine, and promethazine have been recently reported to exhibit high affinity binding to the H<sub>4</sub> receptor (Nguyen et al., 2001). HRs have been found to form dimers, and even oligomers, which allow cooperation between HRs and other G protein-coupled receptors. The affinity of

histamine binding to different histamine receptors varies significantly, with  $K_i$  values ranging from 5-10 nM for the  $H_3$  and  $H_4$  receptors to 2-10  $\mu$ M for the  $H_1$  and  $H_2$  receptors [7,8]. Thus, the effects of histamine upon receptor stimulation can be very complex.

## Histamine and inflammation

The interaction of histamine with the HR1 mediates a variety of effects associated with anaphylactic symptoms [9]. However, increasing evidence suggests that it influences several immune/inflammatory and effector functions [10,11].

Histamine contributes to the progression of allergic-inflammatory responses by enhancement of the secretion of proinflammatory cytokines like IL-1 $\alpha$ , IL-1 $\beta$ , IL-6 as well as chemokines like RANTES or IL-8, both in several cell types and local tissues [12-15]. Histamine induces the CC chemokines, monocyte chemoattractant protein 1 and 3, RANTES and eotaxin in explant cultures of human nasal mucosa via HR1, suggesting a prolonged inflammatory cycle in allergic rhinitis between the cells that release histamine and their enhanced migration to nasal mucosa [16]. Endothelial cells express functional HR1 and HR2 and increased adhesion molecule expression such as ICAM-1, VCAM-1 and P-selectin was demonstrated by histamine infusion via HR1 [17-19]. Histamine regulates the expression of its own receptors on endothelial cells and influences the overall inflammatory reaction [20].

Histamine regulates granulocyte accumulation to tissues in distinct ways. Allergen-induced accumulation of eosinophils in the skin, nose and airways is potently inhibited by H1-antihistamines [21]. The effect of histamine on eosinophil migration may differ according to the dose. Whereas high doses inhibit eosinophil chemotaxis via HR2, low doses enhance eosinophil chemotaxis via HR1 [22]. Recently, it has been shown that the histamine receptor responsible for the selective recruitment of eosinophils is HR4 [23]. Histamine possesses all the properties of a classical leukocyte chemoattractant (i.e., agonist-induced actin polymerization, mobilization of intracellular calcium, alteration in cell shape, and upregulation of adhesion molecule expression). The eosinophils chemoattractive ability of histamine is weak when compared to the potent CCR3-active  $\beta$ -chemokines, eotaxin and eotaxin-2 [22-25]. However, histamine upon activation of the HR4 induces enhanced migration of eosinophils towards eotaxin and eotaxin-2 [24,25]. On the other hand, the potential of histamine alone to act as an eosinophil chemoattractant *in vivo*, might be augmented by other factors, such as growth factors or cytokines like IL-5, the cytokine specific for the differentiation, activation, and survival of eosinophils [23]. Triggering of HR4 also induces chemotaxis of mast cells [26]. Experiments in mice showed that mast cells from wild-type and HR3-

receptor-deleted mice migrated in response to histamine, while mast cells from the HR4-deleted mice did not. Thus, chemotaxis of eosinophils and mast cells via histamine is triggered mainly through the HR4. The HR4-mediated chronic inflammatory effects of histamine may be aborted by administration of HR4 antagonists, and combination therapies with the HR1 antagonists are a promising approach.

Histamine inhibits neutrophil chemotaxis due to HR2 triggering, which is mimicked by impromidine (HR2 agonist), but not by betahistidine (HR1 agonist). In addition, histamine inhibits neutrophil activation, superoxide formation and degranulation via HR2 [27].

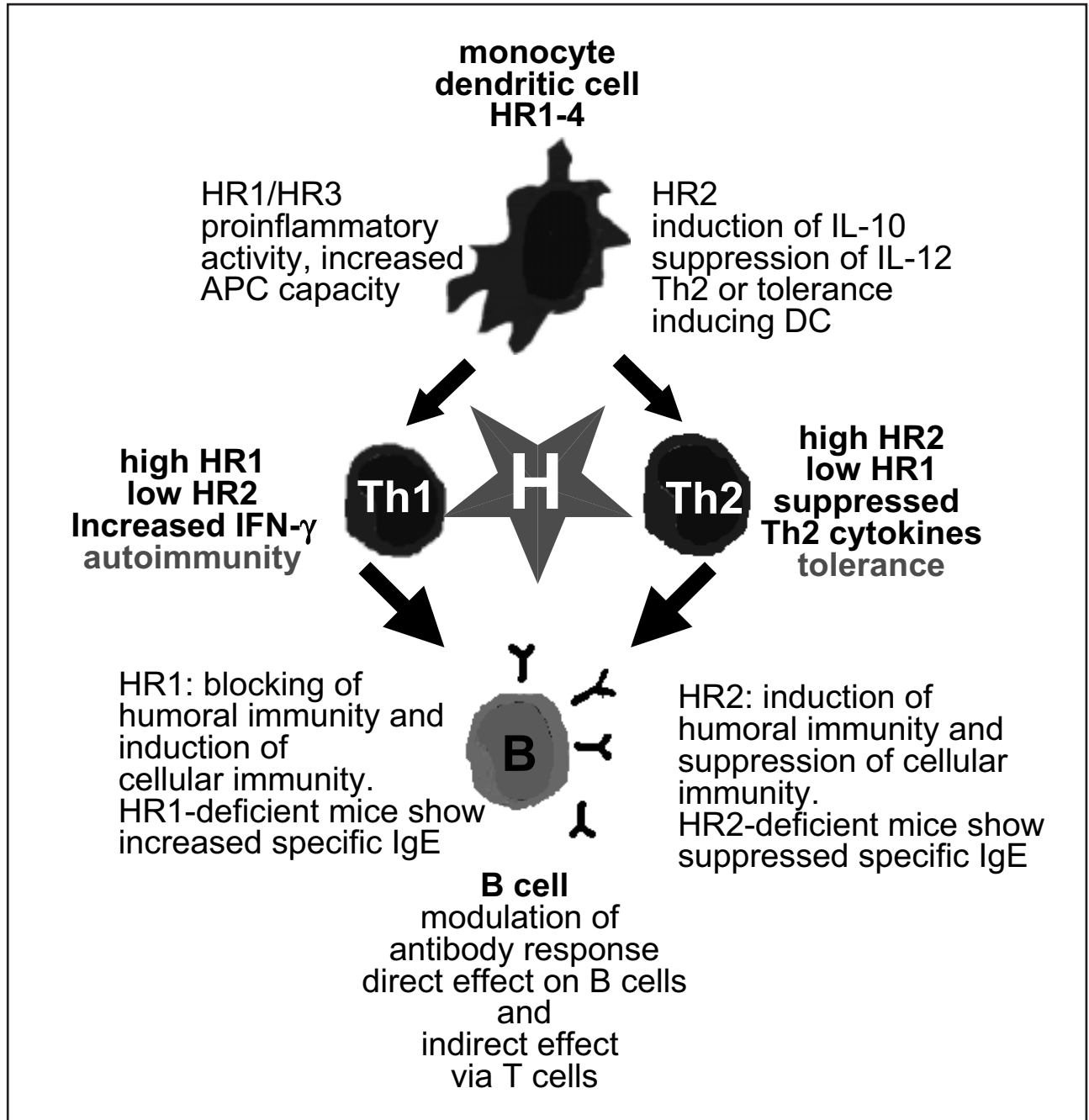
Down regulation of NF- $\kappa$ B, which acts as a potent transcription factor in initiating inflammation, may represent a possible mechanism for H1-anti-histamines to inhibit inflammatory cell accumulation [28]. Low concentrations of H1-antihistamines, cetirizine and azelastine have been demonstrated to down-regulate NF- $\kappa$ B expression in parallel to inhibition of pro-inflammatory cytokines [29]. A recent study with HDC-deficient and mast cell-deficient mice showed that histamine mainly derived from non-mast cells plays an essential role in the angiogenesis and generation of inflammatory granulation [30].

## Immunoregulatory effects of histamine

### Antigen presenting cells

Dendritic cells (DC) are professional antigen-presenting cells that mature from monocytic and lymphoid precursors and acquire DC1 and DC2 phenotypes, which in turn facilitates the development of Th1 and Th2 cells, respectively. Endogenous histamine is actively synthesized during cytokine-induced DC differentiation, which acts in autocrine and paracrine fashion and modifies DC markers [31]. Histamine actively participates in functions and activity of DC precursors as well as their immature and mature forms (Figure 1). Immature and mature DCs express all four HR, however comparison of their levels of expression has not yet been studied [32-35]. In the differentiation process of DC1 from monocytes, HR1 and HR3 act as positive stimulants that increase antigen-presentation capacity and proinflammatory cytokine production and TH1 priming activity. In contrast, HR2 acts as a suppressive molecule for antigen-presentation capacity, enhances IL-10 production and induces IL-10-producing T cells or TH2 cells [36-38].

In monocytes stimulated with Toll-like receptor-triggering bacterial products histamine inhibits the production of pro-inflammatory IL-1-like activity, TNF $\alpha$ , IL-12 and IL-18 but enhances IL-10 secretion, through HR2 stimulation [12,38,39,40]. Histamine also



*Figure 1.* In lymphatic organs and subepithelial tissues of allergic inflammation, histamine regulates monocytes, dendritic cells, T cells and B cells. Monocytes and dendritic cells express all known HRs. HR1 and HR3 induce proinflammatory activity and increased APC capacity, whereas HR2 plays a suppressive role on monocytes and monocyte-derived dendritic cells (DC). Th1 cells show predominant, but not exclusive, expression of HR1, whereas Th2 cells show upregulation of HR2. Histamine induces increased proliferation and IFN- $\gamma$  production in Th1 cells. Th2 cells express predominant HR2, which acts as the negative regulator of proliferation, IL-4 and IL-13 production. Histamine enhances Th1-type responses by triggering the HR1, whereas both Th1- and Th2-type responses are negatively regulated by HR2. These distinct effects may suggest roles of HR1 and HR2 on T cells for autoimmunity and peripheral tolerance, respectively. Histamine also modulates antibody production. Histamine directly effects B cell antibody production as a co-stimulatory receptor on B cells. HR1 predominantly expressed on Th1 cells may block humoral immune responses by enhancing Th1 type cytokine IFN- $\gamma$ . In contrast, HR2 enhances humoral immune responses. Allergen-specific IgE production is differentially regulated in HR1- and HR2-deficient mice. HR1-deleted mice show increased allergen-specific IgE production, whereas HR2-deleted mice show suppressed IgE production.

downregulates CD14 expression via H2 receptors on human monocytes [41]. The inhibitory effect of histamine via H2-receptor appears through the regulation of ICAM-1 and B7.1 expression, leading to the reduction of innate immune response stimulated by LPS [42].

Histamine induces intracellular Ca<sup>++</sup> flux, actin polymerization, and chemotaxis in immature DCs due to stimulation of HR1 and HR3 subtypes. Maturation of DCs results in loss of these responses. In maturing DCs, however, histamine dose-dependently enhances intracellular cAMP levels and stimulates IL-10 secretion, while inhibiting production of IL-12 via HR2 [37]. Interestingly, although human monocyte-derived dendritic cells (MoDC) have both histamine H1 and H2 receptors and can induce CD86 expression by histamine, human epidermal Langerhans cells express neither H1 nor H2 receptors, mainly because of the effect of TGF- $\beta$  [43].

## Regulation of T cells and antibody isotypes

It has been shown that differential patterns of histamine receptor expression on Th1 and Th2 cells determine reciprocal T cell responses following histamine stimulation (Figure 1) [44]. Th1 cells show predominant, but not exclusive expression of HR1, while Th2 cells show increased expression of HR2. Histamine enhances Th1-type responses by triggering the HR1, whereas both Th1- and Th2-type responses are negatively regulated by HR2, due to activation of different biochemical intracellular signals [44]. In mice, deletion of HR1 results in suppression of IFN- $\gamma$  and dominant secretion of Th2 cytokines (IL-4 and IL-13). HR2-deleted mice show upregulation of both Th1 and Th2 cytokines. In addition, IL-3 stimulation significantly increases HR1 expression on Th1, but not on Th2 cells. Moreover, histamine stimulation has been shown to induce IL-10 secretion through HR2 [45]. Increased IL-10 production in both DC and T cells may account for an important regulatory mechanism in the control of inflammatory functions through histamine.

In mice, histamine enhances anti-IgM induced proliferation of B cells, which is abolished in HR1-deleted mice. In HR1-deleted mice antibody production against a T cell-independent antigen-TNP-Ficoll is decreased [46], suggesting an important role of HR1 signaling in responses triggered from B cell receptors. Antibody responses to T cell-dependent antigens like ovalbumin (OVA) show a different pattern [44]. HR1-deleted mice produced high OVA-specific IgG1 and IgE in comparison to wild type mice. In contrast, HR2-deleted mice showed decreased serum levels of OVA-specific IgE in comparison to wild type mice and HR1-deficient mice. Although T cells of HR2-deficient mice secreted increased IL-4 and IL-13, OVA-specific IgE was suppressed in the presence of highly increased IFN- $\gamma$ .

Thus HR1 and related Th1 response may play a dominant role in the suppression of humoral immune response.

## Peripheral T cell tolerance

Considerable evidence has emerged to suggest that histamine participates in the immune regulation of the inflammatory response in several diseases. Peripheral T cell tolerance characterized by immune deviation to regulatory/suppressor T cells represents a key event in the control of specific immune response during allergen-specific immunotherapy [47]. Although multiple suppressor factors including contact dependent or independent mechanisms might be involved, IL-10 and TGF- $\beta$  predominantly produced by allergen-specific T cells play an essential role [47,48]. Histamine interferes with the peripheral tolerance induced during SIT in several pathways. Histamine induces the production of IL-10 by dendritic cells [37]. In addition, histamine induces IL-10 production by Th2 cells [45]. Furthermore, histamine enhances the suppressive activity of TGF- $\beta$  on T cells [49]. All three of these effects are mediated via HR2, which is relatively highly expressed on Th2 cells and suppresses IL-4 and IL-13 production and T cell proliferation [44]. Apparently, these recent findings suggest that HR2 may represent an essential receptor that participates in peripheral tolerance or active suppression of inflammatory/immune responses.

The long-term protection from honeybee stings by terfenadine premedication during rush immunotherapy with honeybee venom in a double-blind, placebo controlled trial was analyzed [50]. After an average 3 years, 41 patients were re-exposed to honeybee stings. Surprisingly, none of 20 patients who had been given HR1-antihistamine premedication, but 6 of 21 given placebo, had a systemic allergic reaction to the re-exposure by either a field sting or a sting challenge. This highly significant difference suggests that antihistamine premedication during the initial dose-increase phase may have enhanced the long-term efficacy of immunotherapy. Expression of HR1 on T lymphocytes is strongly reduced during ultrarush immunotherapy, which may lead to a dominant expression and function of tolerance-inducing HR2. This indicates a positive role of histamine in immune regulation during SIT [51].

Selective HR2 antagonists have attracted interest because of their potential immune response-modifying activity [52]. Most data suggest that cimetidine has a stimulatory effect on the immune system, possibly by blocking the receptors on subsets of T-lymphocytes and inhibiting HR2-induced immune suppression. Cimetidine has also been used successfully to restore immune functions in patients with malignant disorders, hypogammaglobulinemia and AIDS-related complexes.

## Effects of histamine and antihistamines on airway function

Inhaled and intravenous histamine causes bronchoconstriction as one of the first recognized properties of histamine, which is inhibited by HR1 antagonists. As a manifestation of airway hyperreactivity, asthmatic individuals are more sensitive to the bronchoconstrictor effect of histamine than normal individuals. It has been shown in sensitized mice that treatment with H1R antagonist fexofenadine prevented the development of airway hyperresponsiveness in both the primary sensitization and challenge. Decreases in bronchoalveolar lavage and tissue eosinophilia, lymphocyte numbers, and  $T_H2$  cytokine production were also observed [53]. Similarly, it has been observed that another HR1 antagonist, desloratadine given at the time of exposure to the allergen, inhibited the induction of allergic pulmonary inflammation, and bronchial hyperresponsiveness [54].

Consistently, histamine-induced concentration-dependent release of IL-6 and  $\beta$ -glucuronidase from macrophages isolated from the human lung parenchyma was inhibited by fexofenadine but not by ranitidine, an  $H_2$ -receptor antagonist [55]. Thus long-term treatment with HR1 receptor antagonists can alter disease progression in patients with respiratory allergy associated with tissue damage/remodeling mediated by macrophage and Th2 cell activation.

Although previous studies suggested a basal tone of smooth muscle mediated by histamine binding to HR1, currently constitutive intrinsic activity of the HR1 without any occupation by histamine could be more relevant. Histamine also induces proliferation of cultured airway smooth muscle cells [56].

Difference in histamine response between species has been reported indicating a role for HR2-mediated bronchodilatation in cat, rat, rabbit, sheep and horse [57]. However, in humans, H2-antihistamines such as cimetidine and ranitidine do not cause bronchoconstriction in normal or asthmatic individuals [58,59]. Although there is no direct evidence that it plays a role in pathogenesis, HR2-mediated gastric secretion is impaired in asthma [60]. Rather a beneficial effect of H2-anti-histamines given for the treatment of gastritis was observed in asthma [61]. In addition, recent studies suggest that histamine may play an important role in the modulation of the cytokine network in the lung via HR2, HR3 and HR4 that are expressed in distinct cells and cell subsets [35,62]. Apparently, due to the same signal transduction patterns,  $\beta_2$  adrenergic receptors may function similarly to HR2 in humans [63]. The role of histamine and other redundant G-protein-coupled receptors in the regulation of immune/inflammatory pathways in the lung remain to be intensely focused in future studies.

## Conclusion

Histamine and so far 4 different HRs display a complex system with distinct functions of receptor subtypes and their differential expression, which changes according to the stage of cell differentiation as well as microenvironmental influences. Although contrasting findings have been reported, HR1 stimulates the immune system cells by potentiating their proinflammatory activity for higher migration to inflammation area as well as increased effector functions. On the other hand, HR2 seems to be a potent suppressor of inflammatory and effector functions. The data on the role of HR3 and HR4 in the immune regulation are limited. The observation that H4R activation promotes the accumulation of inflammatory cells to sites of allergic inflammation opens a new window for therapeutic approaches based on combined anti-H1R/anti-H4R blockade or development of selective dual H1R/H4R antagonists. Whether such therapies will provide further benefit to suppression of allergic inflammatory responses as observed after HR1 blockade remains to be elucidated.

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