Role of the Histamine H_4-Receptor in Bronchial Asthma

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Contents

Abstract

Histamine is a pro-inflammatory mediator with a prominent role in allergic diseases. Antagonists at the histamine receptor subtype 1 are central in anti-allergic therapies, with the exception of allergic asthma, where they are clinically without effect. The latest identified histamine receptor subtype 4, which is expressed mainly in hematopoietic cells, now provides a reasonable target for new therapeutic strategies inhibiting histamine function. The pathophysiology of allergy, esp. allergic asthma, and in its context the effects of antagonists at the histamine receptor subtype 4 in preclinical and clinical settings are discussed in this chapter.

Keywords

Allergy • Asthma • Dendritic cell • Sensitization • T cell

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1 Allergy

Allergy is the inadequate reaction of the immune system to innocuous environmental substances, such as grass pollen, referred to as allergens. Upon contact with the immune system, allergens trigger a complex immune response. In case the immune response is characterized by the excessive production of allergen-specific immunoglobulin E (IgE) and inflammatory symptoms appear immediately after allergen contact, the allergy is classified as a *type 1* hypersensitivity reaction. The pathogenesis of allergy can be subdivided into two phases: initially, the contact between allergen and immune system results in sensitization of the host against the allergen. Within this sensitization phase, allergen-specific T cells, mostly of the Th2 phenotype, and allergen-specific plasma cells that produce allergen-specific antibodies mainly of the IgE isotype are generated. Upon re-exposition of the sensitized host to the allergen, IgE-occupied mast cells and basophil granulocytes (basophils) immediately degranulate, referred to as effector phase. Due to degranulation, a series of preformed mediators such as histamine, heparin, or prostaglandins is released, which eventually elicit the immediate clinical allergic symptoms such as coughing, sneezing, or itching. Also the life-threatening condition of anaphylaxis is mediated by allergic mechanisms, essentially as described.

2 Allergic Response

2.1 Allergic Sensitization

Sensitization occurs upon contact between an allergen and the immune system, mechanistically being highly similar to the process of immunization. If the immune system encounters the allergen for the very first time, the following immune response occurs without any major symptoms for the host. Similar to antigens, allergens are engulfed by mainly dendritic cells (DCs), which together with other cell types constitute the group of professional antigen-presenting cells (APC). Following engulfment, the allergen is processed into fragments, which are loaded onto MHC II molecules. These allergen/MHC II complexes appear on the surface of DC and can be recognized by the T cell receptor (TCR) of allergen-specific naïve $CD4^+$ T helper (Th0) cells (Fig. 1). The interaction between DC and Th0 cells, which also involves cellular contacts by costimulatory molecules, and the predominant presence of interleukin (IL)-4 activate the Th0 cells for polarization into type 2 effector T helper (Th2) cells. Under these conditions, Th1 and Th17 cells, which are able to inhibit Th2 cell activity by the release of specific mediators, are less frequently polarized. Th2 cells are defined by their production of IL-4, IL-5, and IL-13, which besides other functions direct differentiation of allergen-specific B cells into IgE-producing plasma cells (Vroman et al. 2015). Allergen-specific IgE antibodies circulate throughout the body and eventually bind to Fcε-receptors (FcεR) on tissue-resident mast cells and basophils, which are predominantly located

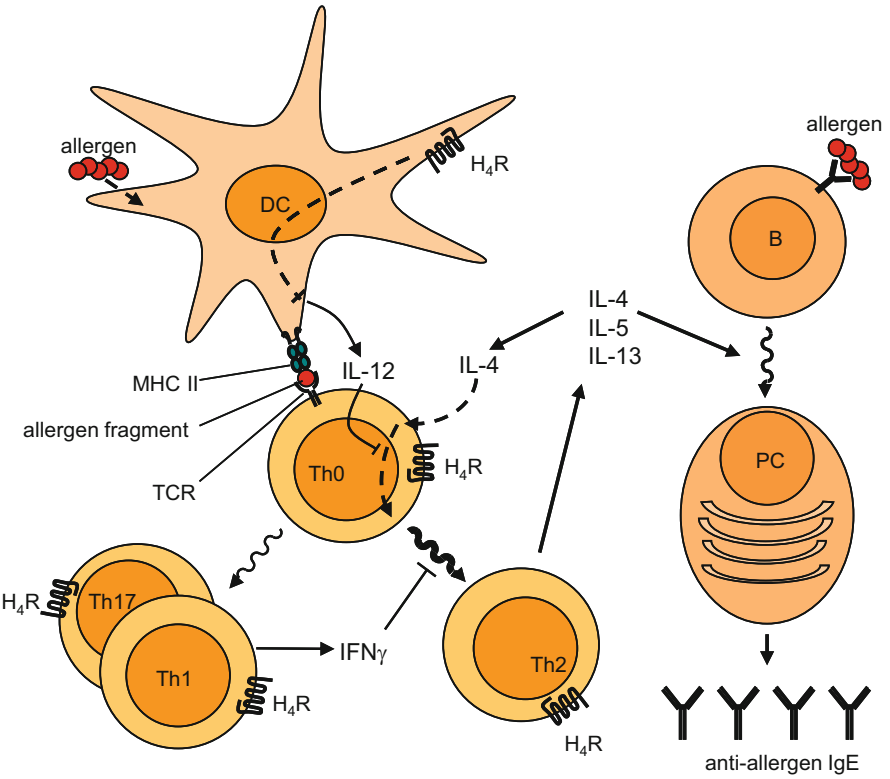

Fig. 1 Allergic sensitization. In the periphery, allergen is sampled by dendritic cells (DC) and then processed into fragments. Allergen-loaded DC migrate to draining lymph nodes, where they present allergen fragments via major histocompatibility complex type II (MHC II) molecules. The allergen fragment/MHC II complex is recognized by specific T cell receptors (TCR) and, thus, activates naïve $CD4^+$ T cells (Th0). Due to a Th2-favoring cytokine milieu, i.e., high concentration of interleukin (IL)-4, Th0 cells mainly polarize into type 2 helper T cells (Th2), which produce the cytokines IL-4, IL-5, and IL-13. Histamine modulates this process via the DC-expressed H_4R, while at least in mice H_4R on T cells do not seem to be involved. Mechanistically it can be hypothesized that DC-expressed H_4R inhibit IL-12 production, which blocks Th2 cell development and favors Th1 cell polarization. Eventually, Th2 cell-derived IL-4 may auto-amplify the polarization of Th2 cells and promotes the development of activated allergen-specific B cells (B) into plasma cells (PC) secreting allergen-specific immunoglobulin (Ig)E

near to the body's surfaces, e.g., bronchial and intestinal mucosae. By this mechanism the mast cell acquires an armed, thus sensitized, status (Reber et al. 2015).

2.2 Allergic Reaction

Upon every other contact to the same allergen, the allergen enters the body's surface and directly binds to the IgE molecules on mast cells and basophils. The

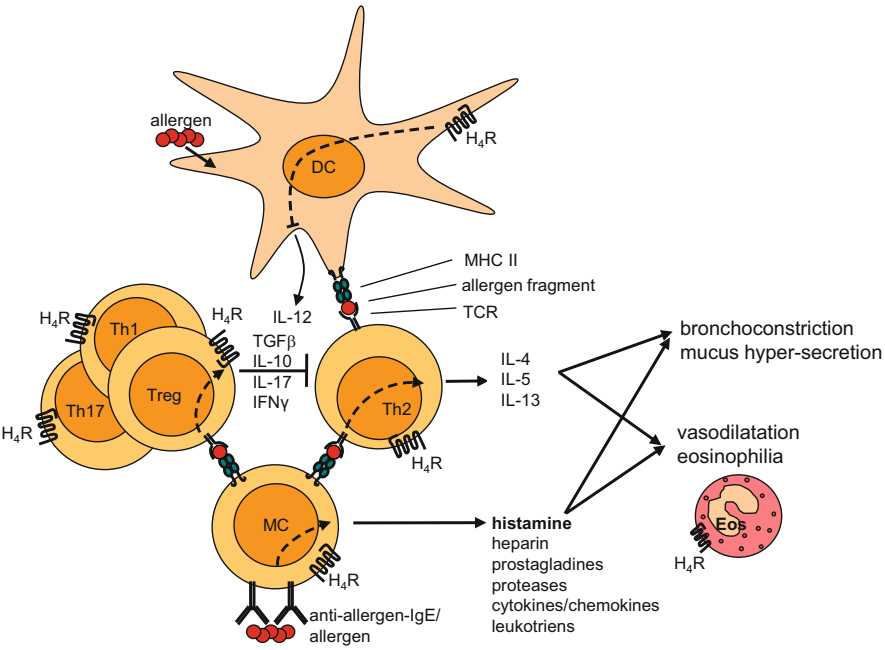

Fig. 2 Allergic reaction (effector phase). Allergen-specific IgE molecules bound to mast cells (MC) which are located near the body's surface bind the allergen and thereby activate the MC to release mediators inducing the allergic symptoms. Histamine via the H_4R regulates migration of MC and thereby may affect this process. In parallel, IgE-bound allergen can be ingested, fragmented, presented via major histocompatibility complex type II (MHC II) molecules, and recognized by T cell receptors (TCR) of effector Type 2 T helper cells (Th2). Similarly, the allergen can be sampled, processed, and presented by local dendritic cells (DC). The activated effector Th2 cell then locally produces large amounts of interleukin (IL)-4, IL-5, and IL-13, which promote the induction of allergic symptoms. Histamine via H_4R may modulate this process since it affects migration of eosinophils, thus the symptom eosinophilia

interaction of multiple IgE molecules with the same allergen leads to cross-linking of FcεR followed by degranulation of the cells (Fig. 2). As a consequence, granule-derived pro-inflammatory mediators such as histamine, proteases, and prostaglandins are released immediately. Moreover, mast cells and basophils start to produce other mediators such as chemokines, cytokines, and leukotriens. These mediators cause allergic symptoms such as redness, rashes, sneezing, and anaphylaxis (Reber et al. 2015). In parallel, DCs sample allergen, process, and present it to effector Th2 cells, a mechanism which can be effectuated also by mast cells after ingestion of IgE-bound allergen. This leads to the local activation of Th2 cells, resulting in the secretion of Th2-type cytokines, supporting the allergic symptoms.

2.3 Allergic Asthma

Asthma is a chronic disease of the airways showing up with very heterogeneous phenotypes, one of which is allergy based (Wenzel 2012; Woodruff 2013). Common features are airway inflammation; airflow obstruction due to airway smooth muscle constriction, mucus hypersecretion, and mucus cell metaplasia; airway hyperresponsiveness (AHR); and airway remodeling. The maturation, activation, and recruitment of eosinophils into the bronchial wall and the airway lumen are key events in the pathogenesis of allergic asthma (Jacobsen et al. 2007; Jacobsen et al. 2014). Eosinophilia in asthma is orchestrated by Th2 cells, mainly through the regulated production of IL-5 (Fig. 2). Moreover, also the innate arm of the immune system, i.e., epithelial cells and group 2 innate lymphoid cells (ILC2), which produce IL-5 and other Th2-type cytokines, too, contribute to eosinophilia in the airways (Liu et al. 2015; Klein Wolterink et al. 2012). If the cellular infiltration in the airways is composed of mostly eosinophils, this is indicative for mild or moderate asthma. In contrast, severe asthma is accompanied by infiltration with eosinophils and also neutrophils. Neutrophils are not activated by Th2-type mechanisms, but mainly by Th17 cells (Cosmi et al. 2011), indicating that in chronic asthma, the sensitization-generated Th2 cell bias is not stable and may shift toward Th1/Th17 cell activation.

3 The Histamine H_4-Receptor

3.1 Identification of the Histamine H_4-Receptor

About 15 years ago, several groups simultaneously discovered the H_4R due to its genomic similarity to the H_3R (Oda et al. 2000; Morse et al. 2001; Liu et al. 2001; Nguyen et al. 2001; Nakamura et al. 2000; Hough 2001). Initially, it was proposed that H_4R are expressed exclusively on cells of hematopoietic origin such as dendritic cells (DCs), T cells, mast cells (MC), and eosinophils (Gutzmer et al. 2002; Hartwig et al. 2015; Hofstra et al. 2003; Reher et al. 2012). This proposal, however, is nowadays being challenged, since evidence is accumulated that H_4R is expressed also by certain cells of non-hematopoietic origin (Adderley et al. 2015; Rossbach et al. 2011; Yamaura et al. 2009). Due to its mainly hematopoietic expression and taking into account that histamine is a pro-inflammatory mediator, it was tempting to speculate that H_4R are involved in inflammation and immune responses. This hypothesis was underscored by the observation that some inflammatory disorders in which histamine is most probably involved cannot be controlled by antagonists selective for H_1R or H_2R. Thus, an effort was made to analyze whether the H_4R is the missing link between histamine and these disorders (Jutel et al. 2002; Venable et al. 2005; Zhang et al. 2007; Seifert et al. 2013). One of these diseases is allergic asthma, where fairly high concentrations of histamine can be detected in the lungs of patients or of model

animals, while the anti-allergic H_1R-selective antihistamines lack any efficacy (Calhoun et al. 1998; Hannon et al. 2001; Sirois et al. 2000).

3.2 Histamine H_4-Receptor Antagonists

The advent of the H_4R solved some issues about unexplainable pharmacological observations made with ligands which have been supposed to be specific for histamine receptor subtypes other than the H_4R. These ligands such as clobenproprit, Rα-methylhistamine, thioperamide, imetit, and 4-methylhistamine were found to possess affinity for and activity on the H_4R as well. R-α-methylhistamine and imetit, both originally described as agonists at the H_3R, are agonists at the H_4R, too, albeit a lesser potency. The same holds true for thioperamide but being an antagonist at both receptor subtypes. The situation of clobenpropit is a bit more complex, since it is antagonistic at the H_3R while it is an agonist at the H_4R. Lastly, the formerly identified H_2R-selective agonist 4-methylhistamine is a bispecific agonist at the H_2R and the H_4R (Seifert et al. 2013).

The first commonly available selective antagonist at H_4R is the compound JNJ 7777120 (5-chloro-2-[(4-methylpiperazin-1-yl)carbonyl]-1*H*-indole) (Thurmond et al. 2004; Seifert et al. 2011; Jablonowski et al. 2003). JNJ 7777120, as well as its analog JNJ 10191584, has become a very useful tool to analyze the H_4R function in vitro and in vivo. In the mouse model of acute peritonitis, JNJ 7777120 prevented the massive neutrophil influx, indicating that in vivo the H_4R function probably is pro-inflammatory (Thurmond et al. 2004). Concerning the use of JNJ 7777120 in vivo, esp. in chronic models, caution has to be paid since JNJ 7777120 possesses an only short half-life time (1–2 h), limiting its effects to only a couple of hours (Neumann et al. 2013). This problem, however, can be solved either by repeated application or by a continuous application of JNJ 7777120 over a prolonged period, e.g., via implanted osmotic pumps. Moreover, based on in vitro data, concerns about its antagonistic, thus anti-inflammatory, function have been raised (Schnell et al. 2011; Rosethorne and Charlton 2011). However, data probably reflecting these concerns in vivo have been documented only once: in the model of experimental autoimmune encephalomyelitis (EAE), where JNJ 7777120 exacerbates the disease (Ballerini et al. 2013), while in all other model systems tested, JNJ 7777120 provided a clear anti-inflammatory effect. The data provided by Ballerini et al. (2013), however, could also point to an anti-inflammatory role of H_4R specifically in EAE and maybe other Th1/Th17-mediated diseases. This interpretation fits well also in the hypothesis that H_4R enhances a Th2-type immune response; thus its inhibition shifts the bias toward Th1 and/or Th17 activity. Finally, although the concerns discussed above have arisen and other ligands selective for the H_4R such as UR-PI376, UR 60427, and ST 1006 have been developed, nowadays JNJ 7777120 has become the gold standard for experimental H_4R antagonism.

As for its use in humans, another complication appears with JNJ 7777120, since it demonstrated signs of adrenal toxicity (as discussed by Rob Thurmond in Chap.

18 of this issue). Thus, a new antagonist, JNJ 39758979, (R)-4-(3-amino-pyrrolidin-1-yl)-6-isopropyl-pyrimidin-2-ylamine, has been developed, which was submitted to clinical trials. JNJ 39758979 showed efficacy in reducing both histamine-induced pruritus in healthy volunteers (Kollmeier et al. 2014) and itch sensitization in atopic dermatitis patients (Ohsawa and Hirasawa 2014). Unfortunately, the phase II trial was terminated due to severe unwanted effects in some of the study patients. Other clinical studies using different H_4R-selective antagonists in a variety of diseases can be found in the database clinicaltrails.gov. These comprise the use of PF-03893787 in allergic asthma, of UR-63325 in allergic rhinitis, and of JNJ 39758979 in persistent asthma. However, although these studies were already completed in the years 2010, 2011, and 2014, respectively, the results obtained are still elusive. A newer study using JNJ 38518168, generically named toreforant, in plaque-type psoriasis is currently (October 2015) in the phase of recruitment. Thus, antagonizing H_4R activity in humans provides a therapeutic benefit, at least against pruritus; however, the advent of an antagonist with the potential to be approved seems to be far away.

This disappointing conclusion may also reflect an additional problem with H_4R ligands and their translation from preclinical, thus, animal models, esp. in mice, to clinical trials. When comparing mouse and human H_4R pharmacologically, it appears that their affinities to selective ligands differ quite massively (Strasser et al. 2013). The human H_4R binds the endogenous ligand histamine with an about 10-times higher affinity ($K_D \sim 7$ nM) than does the murine H_4R ($K_D \sim 60$ nM), while JNJ 7777120 has a comparable affinity to both receptor orthologs ($K_I \sim 5$ nM and 4 nM, respectively). Thus, to compete with histamine at the H_4R, in humans about 10-times higher effective concentrations of JNJ 7777120 would have to be achieved as those determined in mice. Since such differences apply also to other H_4R ligands as well as to other cross-reacting receptor systems, esp. in the histamine-histamine receptor system based on mouse data, it is quite impossible to predict the sum of effects in humans.

3.3 Histamine H_4-Receptor Deficient Mice

Soon after the identification of the H_4R, C57Bl/6 mice lacking expression of this receptor ($H_4R^{-/-}$) were generated by replacing most of exon 1 and part of intron 1 of the Hrh4 gene by a neomycin resistance gene cassette (Hofstra et al. 2003). In mast cells obtained from $H_4R^{-/-}$mice, histamine-induced calcium mobilization and chemotaxis, which both occurred in wild-type mast cells, were absent. Notably, in mouse mast cells degranulation was unaffected by the absence of H_4R expression (Hofstra et al. 2003), while human mast cells seem to directly respond to H_4R activation by degranulation (Jemima et al. 2014). For analyses of allergic diseases, the disrupted Hrh4 locus was backcrossed onto the BALB/c strain (Hartwig et al. 2015; Dunford et al. 2006). Untreated, these mice macroscopically do not demonstrate phenotypical alterations (e.g., viability, Mendelian ratio, gender ratio, growth) compared to their wild-type counterparts (C. Kloth & D. Neumann,

unpublished observations). When applying $H_4R^{-/-}$mice to models of inflammatory diseases, symptoms were generally ameliorated in comparison to wild-type mice (Neumann et al. 2014). However, cellular and molecular mechanisms underlying the protective effect are not well elaborated and may differ depending on the model used.

4 Histamine H_4-Receptor and Asthma

In the lungs of asthma patients as well as of asthma model animals, histamine is detected in fairly high concentrations, indicating its possible pathogenic role. However, the clinically approved antihistamines which block H_1R or H_2R functions lack any effect in asthma. The identification of the pro-inflammatory H_4R thus led to the hypothesis that this receptor subtype is the one mediating the histamine effect in asthma. Genetic evidence for a role of the H_4R in human asthma has been provided by Simon et al. (2012), who demonstrated that some polymorphisms within the Hrh4 gene are associated with asthma induced by infection (Simon et al. 2012). As already discussed above, clinical trials treating asthma patients with antagonistic H_4R ligands have been performed; however, results of these studies have not been published so far (Salcedo et al. 2013). Thus, concerning human asthma, the functional involvement of the H_4R and its possible role as drug target is still elusive.

In mice ovalbumin (OVA)-induced asthma is a commonly used model presenting some features closely resembling human allergic asthma, i.e., eosinophilic inflammation and AHR. Using this model, the contribution of H_4R to the pathophysiology was intensively studied (Hartwig et al. 2015; Neumann et al. 2013; Dunford et al. 2006; Beermann et al. 2012; Cowden et al. 2010). When H_4R function in mice was blocked, either by treatment with a selective antagonist or by genetic ablation, asthmatic symptoms were significantly reduced. Thus, as expected from other models of inflammatory diseases, in the acute asthma model, H_4R demonstrates a pro-inflammatory function, too. Animal models of allergic asthma bear the advantage that the two phases sensitization and allergic reaction, the latter one also being referred to as effector phase, can be clearly distinguished. Thus, in contrast to asthma patients, in animal models also, the sensitization phase can be followed and relevant mechanisms can be analyzed (Fig. 1). Naturally, mice do not develop asthma. Thus, an asthma-like disease has to be experimentally induced, i.e., for sensitization mice are injected with the experimental allergen OVA, which may be formulated with an adjuvant such as aluminum hydroxide (alum), in order to initiate an immune reaction against OVA (Fig. 3). The resulting T cell-dependent immune reaction can be boosted after approx. 2 weeks by an additional systemic injection of OVA. In order to trigger the effector phase, the sensitized mice are challenged topically in the lung either by inhalation of nebulized OVA or by intranasal delivery of an OVA-containing solution (Fig. 3). Notably, in BALB/c mice this treatment regime using alum/OVA for sensitization

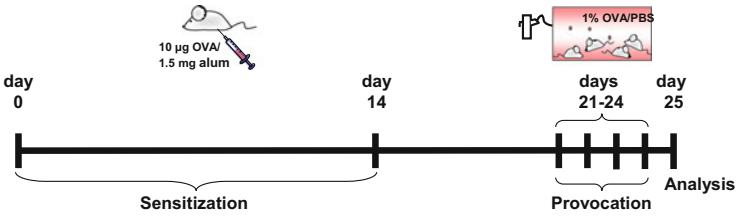

Fig. 3 Ovalbumin-induced acute asthma in mice. To model human asthma, mice are sensitized to ovalbumin (OVA) by two intraperitoneal injections of OVA formulated with aluminum hydroxide (alum) on days 0 and 14. One week later, on days 21–24 mice are daily exposed to a nebulized phosphate-buffered saline (PBS) solution containing OVA. Finally, the mice are analyzed on day 25

most probably results in an asthma-like disease which is independent of mast cells (Lei et al. 2013).

Using JNJ 7777120 or JNJ 10191584, the functional relevance of H_4R in both sensitization and effector phase of an acute asthmatic reaction in mice was demonstrated (Beermann et al. 2012; Cowden et al. 2010; Dunford et al. 2006; Thurmond et al. 2008). Application of the H_4R antagonists exclusively during either the sensitization or the effector phase both ameliorated the symptoms of acute asthma and the signs of Th2-type inflammation, indicating that histamine and H_4R are involved in both phases of the asthma model. Addition of an H_1R antagonist to the H_4R antagonist modified the effect obtained with the H_4R antagonist alone, however, dependent on the timing of application. When applied during sensitization, the H_1R antagonist enhanced the effect of the H_4R antagonist, while in the effector phase it reduced it (Beermann et al. 2012). Thus, the murine H_1R and H_4R functions can interact with each other in at least two different qualities, indicating that more than one possible mechanism exists for such interaction.

Cells typically involved in allergic asthma are mast cells and eosinophils. Since both cell types are responsive to H_4R stimulation (Hofstra et al. 2003; Reher et al. 2012; Jemima et al. 2014; Desai and Thurmond 2011), this may provide an explanation why H_4R antagonists are effective in reducing the asthmatic phenotype in mice. Interestingly, the JNJ 7777120 effect on OVA-induced asthma is still observed in mast cell-deficient WBB6F1-Kit^W/$Kit^{W\text{-}v}$ mice (Dunford et al. 2006). This was to be expected, since, in contrast to humans, the lungs of mice, esp. parenchyma and alveoli, are sparsely populated with mast cells. Due to these anatomical bases, the contribution of mast cells to asthmatic responses in mice strongly depends on the protocol used for induction, and, as discussed above, the protocol applied by Dunford et al. (2006) induces a rather mast cell-independent airway inflammation (Lei et al. 2013). Thus, a mast cell-mediated H_4R effect in mouse experimental asthma cannot definitively be excluded; it may be just absent in the model applied.

For human eosinophils, H_4R stimulation has been shown to be a chemotactic signal (Reher et al. 2012; Thurmond et al. 2014; Ling et al. 2004). Although very

likely, the proof whether this observation holds true also for mouse eosinophils is still lacking.

The OVA-induced asthma model is dependent on T cells (Coyle et al. 1995). Direct effects of the H_4R on T cell cytokine production cannot be excluded, at least in humans (Jutel et al. 2001, 2002, 2005). However, in mouse CD4 T cells, H_4R activation does not affect IFNγ production upon in vitro stimulation (Vauth et al. 2012), while it is rather H_2R, which mediates such effects of histamine (Vauth et al. 2012; Krouwels et al. 1998). Accordingly, lack of H_4R expression on CD4 T cells in sensitization of a combined in vitro/in vivo mouse asthma model seems to be without any effect on the disease (Hartwig et al. 2015).

In vitro data point to a potential role of H_4R on T cell priming by DC (Dunford et al. 2006), and in an in vitro/in vivo asthma model, it was demonstrated that H_4R on DC accounts for the ameliorating effect of H_4R blockade (Hartwig et al. 2015). Thus, the effect of H_4R on CD4 T cell polarization toward the Th2 phenotype is rather indirectly mediated via DC, at least in the mice asthma model (Fig. 1). In human DC, a role for H_4R was evaluated in vitro and indicates that it regulates mediator expression as well as migratory behavior (Gschwandtner et al. 2010, 2011). Strikingly, in human DC, H_4R activation inhibits the expression of IL-12 (Gutzmer et al. 2005). Thus, by inhibition of H_4R activation, the Th1-inducing cytokine IL-12 is produced in higher amounts, probably shifting the T cell polarization bias from the Th2 toward the Th1 phenotype, eventually reducing an allergic phenotype (Figs. 1 and 2). Whether this indeed holds true also in vivo, thus in human asthma patients still has to be elaborated.

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