

Review

Effects of histamine on Th1/Th2 cytokine balance

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Abstract

Atopic asthma is a chronic inflammatory disorder of the airways where upon exposure to allergens, the body mounts an immune response. This disease is associated with an increase in the number of Th2 (T helper type 2) cells and Th2 cytokines and a decrease in the number of Th1 (T helper type 1) cells and Th1 cytokines.

Histamine plays an important role in the pathogenesis of atopic asthma through differential regulation of T helper lymphocytes. Histamine enhances the secretion of Th2 cytokines such as IL-4 (interleukin-4), IL-5, IL-10 and IL-13 and inhibits the production of Th1 cytokines IL-2 and IFN γ (interferon- γ) and monokine IL-12. It has been shown that histamine can modulate the cytokine network through upregulation of PGE₂ (prostaglandin E₂) and NO (nitric oxide). Histamine also affects cytokine production via H2 receptors and through the activation of PKA (protein kinase A). We have also demonstrated that the Jak-STAT (Janus kinase-signal transducers and activators of transcription) pathway is involved in histamine-mediated regulation of Th2 cytokines IL-5, IL-10, IL-13 and Th1 cytokine IFN γ .

While standard treatment of asthma consists of β -receptor agonists and inhaled corticosteroids, the elucidation of histamine's control over the cytokine network and the Th1/Th2 balance provides a basis for the potential use of antihistamines in the prevention and treatment of atopic asthma. Several other anti-allergic agents to modulate the Th1/Th2 balance are under current investigation based on this paradigm. These include cytokines, cytokine antagonists, anti-IgE, and vaccinations. As more advances are made in our understanding of histamine and its control over the Th1/Th2 balance, the use of new therapeutic targets such as these will play a prominent role in disease management.

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Keywords: Th1/Th2; Histamine; Asthma

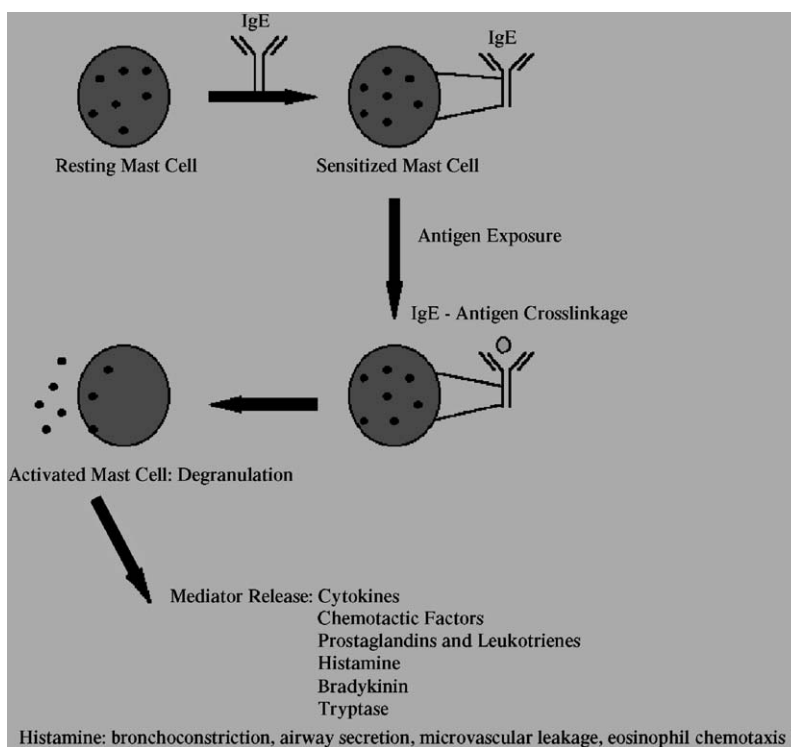
1. Asthma and its immunoregulation

The term *asthma* is of Greek origin, meaning “panting”, which refers to a chronic inflammatory disorder of the airways. Symptomology of asthma is caused by two major physiologic components: airway hyperresponsiveness and airflow obstruction [1]. The

degree of airway hyperresponsiveness is important as it correlates with the severity of asthma. Airflow obstruction is caused by a variety of changes including acute bronchoconstriction, airway edema, chronic mucous plug formation, and airway remodeling [1]. While the etiology of asthma is complex and may involve a number of triggering factors such as external allergens, irritants, cold, stress, and exercise, the manifestation is universal. The disease is characterized by shortness of breath, wheezing, and forced inhalation [2].

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Scheme 1. The mechanism of immunologic response in asthma. Resting mast cells have Fc receptors that bind to IgE (immunoglobulin E). In atopic asthma, IgE is produced in lieu of IgG (immunoglobulin G). Upon second exposure to an allergen or antigen such as pollen, mold, spores, or dust, there is an IgE-mediated release of chemical mediators from mast cells including cytokines, histamine, prostaglandins, and leukotrienes. These mediators lead to pathological symptoms ranging from rash to bronchospasm to anaphylactic shock.

According to the 1997 National Health Interview Study by the National Center for Health Statistics and the Center for Disease Control and Prevention, it was estimated that 25.7 million people had been diagnosed with asthma. This number increased to 26.3 million in 1998. The highest prevalence of this disease occurs in children 5–17 years of age. Unfortunately, the overall age-adjusted death rate from asthma has increased from 0.9 per 100,000 people in 1979 to 1.4 per 100,000 people in 1998, a 55.6% increase [3].

Atopic asthma is a chronic inflammatory disorder of the airways where upon exposure to allergens, the body mounts an immune response. This response involves many cell types including T lymphocytes, macrophages, neutrophils, and epithelial cells [1]. The mediators released from these cells include, but are not limited to, histamine, cytokines, leukotrienes, prostaglandins, bradykinin, and tryptase. These mediators cause an array of pathologic and physiologic symp-

toms including bronchial hyper-responsiveness and obstruction of airflow (Scheme 1).

In the United States, it is estimated that atopic asthma affects 3 million children and 7 million adults [4].

2. Histamine

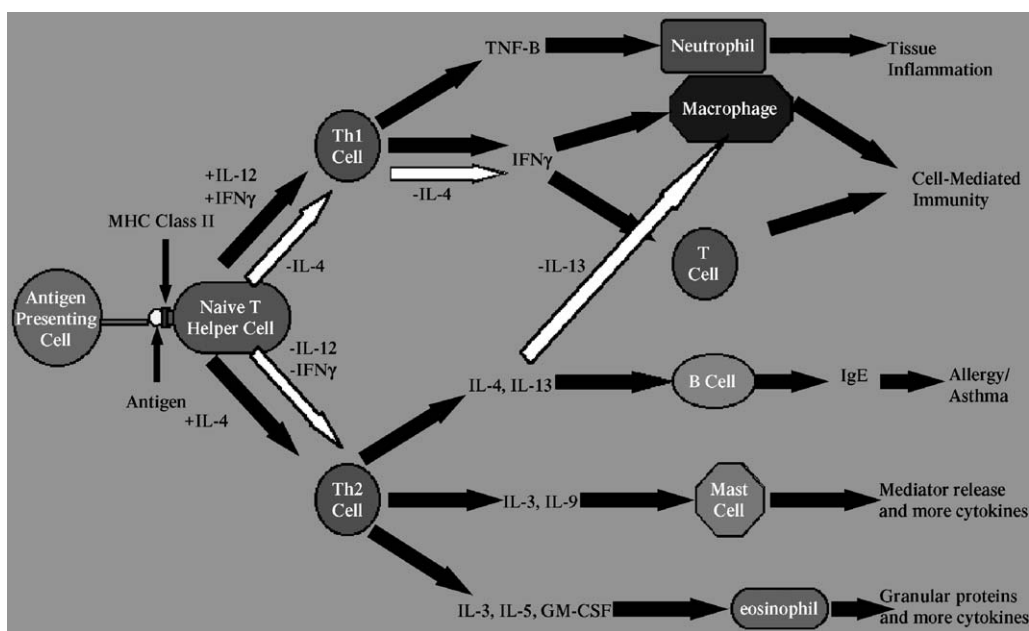
Histamine, or β -aminoethylimidazole, plays an important role in the pathogenesis of atopic asthma. Histamine was first discovered as a contaminant in extracts of ergot resulting from bacterial action. Its name is derived from the Greek word for *histos* or tissue. The first pharmacological properties attributed to histamine were discovered in 1910 by Dale and Laidlaw. They found that histamine stimulated smooth muscles and had potent vasodepressor action. In 1927, Best et al. discovered that this compound was naturally

derived from the human body when they isolated histamine from samples of liver and lung [5].

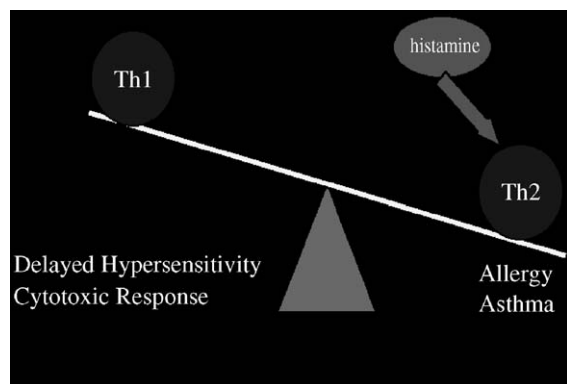
Though mast cells in the immune system serve as the predominant storage site for histamine in humans, it is present in almost all tissues in amounts ranging from 1 µg/g to more than 100 µg/g [5]. While the focal point of this discussion is centered on the immune system, histamine also regulates diverse bodily functions in a variety of tissues. In the central nervous system, histamine functions as a neurotransmitter by binding to H1 (histamine type 1 receptors) to decrease appetite and increase wakefulness. Through binding to H2 (histamine type 2 receptors), histamine induces the release of gastric acid from the parietal cells in the gut and also increases the output of pepsin and intrinsic factor. In the cardiovascular system, histamine causes dilation of the blood vessels through both H1 and H2 receptors leading to flushing, lowered total peripheral resistance, increased capillary permeability, and a fall in systemic blood pressure. Histamine also relaxes smooth muscle. The role of H3 (histamine type 3

receptors) in humans is less understood. It is certain, however, that H3 receptors function as feedback inhibitors in the central nervous system and are present in the cardiovascular system as well [5]. Furthermore, the discovery of a novel H4 receptor has been recently reported in humans and lower species including mouse, rat, and guinea pig [6]. The H4 receptor is reportedly found in peripheral blood leukocytes, spleen, thymus, small intestine, colon, and bone marrow [7]. This receptor is G protein coupled, down-regulates intracellular cAMP levels, and is closely related to the H3 receptor [7,8].

In the immune system, histamine is an important mediator of allergic disease, asthma, and inflammation. The development of some allergic reactions, infections and tumors are associated with excessive histamine production [9]. Histamine modulates the activity of immunocompetent cells, including T lymphocytes, by binding to histamine receptors on their cell surface [10]. There is great variance in response to histamine between human T lymphocyte subsets based



Scheme 2. Th1 and Th2 cells: role of cytokines and their effector functions. Various cytokines can control the differentiation of naïve T helper cells into Th1 and Th2 cells. Th1 cytokine IFN γ and monokine IL-12 are important for the differentiation of naïve T helper cells into Th1 cells, while Th2 cytokine IL-4 is crucial for the differentiation into Th2 cells. Each T helper subset has its own unique cytokine secretion profile. Th1 cells secrete predominantly IL-2, IL-3, IFN γ , TNF β (tumor necrosis factor β), and GM-CSF that ultimately leads to tissue inflammation, cytotoxic response, and delayed hypersensitivity. Th2 cells secrete IL-3, IL-4, IL-5, IL-10, IL-13, and GM-CSF that ultimately perpetuate allergic disease and asthma.



Scheme 3. Histamine's influence on the Th1/Th2 balance. Th1 cells control delayed hypersensitivity and cytotoxic response while Th2 cells control allergic disease and asthma. In normal or nonatopic patients, there is a critical balance between the number of Th1 and Th2 cells and their respective cytokines. However, in an atopic patient or someone secreting histamine, there is a T helper cell imbalance. Histamine controls allergic disease and asthma by increasing the number of Th2 lymphocytes and Th2 cytokines while reducing the number of Th1 lymphocytes and Th1 cytokines.

on receptor distribution [11]. For instance, suppressor T cells are more responsive to histamine than T helper cells or cytotoxic T cells [11]. Likewise, the response to histamine in T helper cells and cytotoxic T cells is greatly increased after mitogenic stimulation [11]. In humans, histamine suppresses the proliferation of mixed T lymphocytes through H2 receptors [10,12]. Histamine also suppresses class I specific cytotoxicity in human cytotoxic T lymphocytes through H2 receptors, but at higher concentrations, increases class II specific cytotoxicity [13]. It has been demonstrated that histamine and its derivatives can inhibit the immune response by augmenting the activity of T suppressor cells through H2 receptors and natural suppressor cells through H1 receptors [14–16].

The effects of histamine on T helper lymphocytes are differential and complex. T lymphocytes, especially T helper lymphocytes, play an important role in the pathogenesis of atopic asthma. Helper T cells can be divided into two subsets based on their cytokine profile and different functions: T helper type 1 cells (Th1) and T helper type 2 cells (Th2). Both subsets play distinctive roles in the development, initiation, and regulation of the immune response. Th1 cells are involved in delayed type hypersensitivity and cytotoxic response while Th2 cells regulate allergic disease

by activating B cells and regulating IgG and IgE secretion (Scheme 2).

Th1 cells secrete primarily IL-2 (interleukin-2), IFN γ (interferon γ), IL-3, and GM-CSF (granulocyte-macrophage colony stimulating factor), while Th2 cells predominantly secrete IL-3, IL-4, IL-5, IL-10, IL-13, and GM-CSF. The pathogenesis of asthma is perpetuated by an imbalance of cytokines released from T helper cells. Histamine downregulates the proliferation of T helper type 1 lymphocytes, which control cytotoxic response and delayed-type hypersensitivity. Histamine upregulates the proliferation of T helper type 2 lymphocytes, which control allergic disease and asthma [17]. Histamine regulates the development of an allergic state by enhancing the secretion of Th2 cytokines such as IL-4, IL-5, IL-10 and IL-13 and by inhibiting the production of Th1 cytokines IL-2 and IFN γ and monokine IL-12 (Scheme 3) [9,18–27]. We have demonstrated that histamine dose-dependently upregulated the secretion of Th2 cytokines IL-5, IL-10, and IL-13 and downregulated the secretion of Th1 cytokines IL-2 and IFN γ in cloned murine T helper cells [23–26,28]. In the same cell line, histamine had no effect on the secretion of Th2 cytokine IL-4 (unpublished observations).

3. Cytokines

Cytokines are low molecular weight proteins released from cells that regulate important biological processes including cell growth, cell activation, inflammation, immunity, tissue repair, and fibrosis. Interferons (IFN α , IFN β , IFN γ) are cytokines associated with potent antiviral activity. While IFN γ possesses the least antiviral activity, this T helper type 1 cytokine is important for the activation of T cells and plays an important role in immunoregulation and cytotoxic response. Interleukins (IL-1 through IL-20) were given this name in 1981 because of their release from and action upon leukocytes. Interleukins act predominantly on T cells and B cells in the immune system. The primary actions of the individual interleukins are varied and range from proliferation, activation, division, and differentiation of various immune cells. IL-2, a Th1 cytokine, controls the differentiation of naïve T helper cells into Th1 cells while IL-4, a Th2 cytokine, controls the differentiation of naïve T helper cells into Th2 cells.

IL-4, along with Th2 cytokine IL-13, also plays a central role in the promotion of an allergic inflammatory eosinophilic reaction in allergic diseases through IgE isotype switching [29]. IL-13 also inhibits the production of inflammatory cytokines, induces B cell proliferation and differentiation, including IgE production and enhances expression of CD23 and MHC class II molecules (major histocompatibility complex class II) [30–32]. Th2 cytokine IL-5 also plays an important role in allergic disease by controlling the movement, maturation, and proliferation of eosinophils. Th2 cytokine interleukin-10 downregulates cellular immune response and affects the outcomes of viral diseases via inhibition of the production of Th1 cytokines. Aside from interferons and interleukins, there are other cytokines such as GM-CSF (granulocyte-monocyte colony stimulating factor) that regulate hemopoiesis and inhibitory cytokines such as TGF (transforming growth factor) that stimulate connective tissue and collagen formation but downregulate immune function. Cytokines exert their actions by binding to cytokine receptors on cells. Many cytokine receptors show sequence homology and even share identical subunits.

Th1 cells secrete primarily IL-2, IFN γ , IL-3, and GM-CSF, while Th2 cells predominantly secrete IL-3, IL-4, IL-5, IL-10, IL-13, and GM-CSF. The pathogenesis of asthma is perpetuated by an imbalance of cytokines released from T helper cells.

4. Signal transduction

4.1. NO and PGE₂

It is clear that histamine affects the production of cytokines from Th1 and Th2 lymphocytes. The distinct signal transduction mechanisms involved, however, are less clear. It has been shown that histamine can modulate the cytokine network through upregulation of PGE₂ (prostaglandin E₂) and NO (nitric oxide). In the immune system, PGE₂ functions to inhibit T lymphocyte proliferation, suppress natural killer cell proliferation, and selectively modulates cytokine production [33–37]. Nitric oxide, in the immune system, can be synthesized from inducible nitric oxide synthase (iNOS) induced in murine macrophages by proinflammatory cytokines TNF α ?, IL-1, and IFN γ [38]. Nitric oxide may also modu-

late the signaling between macrophages and T lymphocytes [39].

It was recently demonstrated that histamine increases the synthesis and release of IL-10 from macrophages through PGE₂ and NO [27]. However, in Th1 and Th2 cells, NO is differentially produced. It has been shown that in cloned murine T helper lymphocytes, Th1 cells but not Th2 cells can be activated by specific antigens to produce NO [40]. T helper lymphocytes produce PGE₂. The effectiveness of the leukotriene pathway is being used clinically today.

Leukotrienes, products of arachidonic metabolism, are secreted from mast cells and eosinophils and induce numerous biological effects including augmentation of neutrophil and eosinophil migration, neutrophil and monocyte aggregation, leukocyte adhesion, increased capillary permeability, and smooth muscle contraction. These effects contribute to the inflammation, edema, mucous secretion, and bronchoconstriction during an acute asthma attack. There are four leukotrienes that are physiologically active: LTB₄, LTC₄, LTD₄, and LTE₄. Zileuton is a leukotriene modifier that inhibits the enzyme 5-lipoxygenase and thus prevents leukotriene B₄, C₄, D₄, and E₄ formation. On the other hand, montelukast and zafirlukast are competitive and selective inhibitors of the receptors that leukotriene D₄ and E₄ bind to. Leukotrienes act as potent bronchoconstrictors, much more so than histamine, which impacts the efficacy of leukotriene antagonists relative to antihistamines in the treatment of asthma.

4.2. Protein kinase A pathway

Histamine also affects cytokine production via H₂ receptors and through the activation of PKA (protein kinase A) [28,41,42]. H₂ (histamine type 2) receptors are linked to adenylate cyclase, the enzyme that converts ATP (adenosine triphosphate) to cAMP (cyclic adenosine monophosphate). After cAMP levels are elevated, cAMP-dependent PKA is activated [43,44]. PKA-dependent regulation of IL-4, IL-5, IL-10, IL-17, and TNF secretion by cAMP-elevating agents has been demonstrated [23,45–48]. The PKA pathway is also involved in histamine-mediated regulation of both Th2 cytokines IL-10, IL-13, and Th1 cytokine IFN γ [24–26].

4.3. Janus kinase signal transducers and activators of transcription pathway

Cytokines themselves are able to modulate effector cytokine production by T lymphocytes [49–52]. Cytokine-induced signal transduction is controlled by numerous transcription factors. Cytokines released after activation of TCR (T cell receptor) interact with cytokine receptors on mononuclear cells and activate these cells via a Jak-STAT (Janus kinase and signal transducers and activators of transcription) pathway [53,54]. After phosphorylation, transcription factors are translocated from the cytoplasm into the nucleus and bind to the cytokine responsive elements of DNA [55]. Studies indicating that STAT6-deficient mice do not generate Th2 cells and that STAT4-deficient mice do not generate Th1 cells have demonstrated the importance of STAT factors in T helper lymphocyte cytokine signaling [56]. It has also been shown that Th1-like monokine IL-12 is capable of repressing STAT6 DNA binding, which led to downregulation

of Th2 cytokines IL-4 and IL-5 [57]. Likewise, through the use of tyrphostin AG490, a protein tyrosine kinase inhibitor of Jak2, Jak3, STAT1, STAT3, and STAT5 [58–60], we have recently demonstrated that the Jak-STAT pathway is involved in histamine-mediated regulation of Th2 cytokines IL-5, IL-10, IL-13, and Th1 cytokine IFN γ [26,61].

5. Th1/Th2 balance in atopic asthma

An imbalance in the Th1/Th2 ratio is associated with many disease states. In allergic asthma, it is thought that there is an increase in the number of Th2 cells and Th2 cytokines and a decrease in the number of Th1 cells and Th1 cytokines. A recent study by Kou et al. [62] examined the changes in Th1/Th2 ratios and cytokine profiles of asthmatic children during acute attacks and at convalescence. The investigators found higher levels of Th2 cytokine IL-5 and lower levels of Th1 cytokine IFN γ in asthmatic patients versus normal

Table 1
Conventional therapy in the treatment of atopic asthma

Class	Mechanism of action	Effectiveness
Corticosteroids (inhaled and systemic)	Anti-inflammatory: decrease the formation, release, and activity of inflammatory mediators such as kinins, histamine, liposomal enzymes, prostaglandins, and leukotrienes Inhibit margination and subsequent cell migration to area of injury Reverse dilation and decrease vessel permeability Decrease serum extravasation, swelling, and discomfort	Very effective anti-inflammatory response
Cromolyn/Nedocromil	By altering the function of delayed chloride channels: inhibit cough, inhibit late response of eosinophils, and prevent mast cell degranulation after antigen contact and subsequent release of chemical mediators such as histamine, leukotrienes, and prostaglandins	Effective prophylaxis for adults and children; drugs of choice for childhood asthma
B ₂ agonists	Relax bronchial smooth muscle, increase mucociliary transport, decrease edema and airway activity, and inhibits release of mediators from mast cells	Most effective bronchodilators
Methylxanthines	Bronchodilation and anti-inflammatory mediated by the inhibition of phosphodiesterase, inhibition of adenosine receptors, or inhibition of the late phase response to antigen challenge	Somewhat effective bronchodilators, clinical potency limited by low therapeutic index
Leukotriene modifiers	Prevent formation of leukotrienes (zileuton) or inhibit leukotriene receptors (montelukast and zafirlukast) Reverse augmentation of neutrophil and eosinophil migration, neutrophil and monocyte aggregation, leukocyte adhesion, capillary permeability, and smooth muscle contraction	Less-effective anti-inflammatory response
Anticholinergics	Block acetylcholine-mediated contraction of bronchial smooth muscle and decrease mucous production	Somewhat effective, only reverse cholinergic-mediated bronchoconstriction
H1 and H2 receptor antagonists	Inhibit immune cell proliferation and shift the Th1/Th2 cytokine balance by upregulating Th1 cytokines and downregulating Th2 cytokines	Least effective; however, with potential use in the prevention of atopic disease

controls. Likewise, they determined that the Th1/Th2 ratio in asthmatic patients was significantly lower than controls both during an acute attack and during convalescence. It has also recently been suggested that an imbalance between Th1-like monokine IL-12 and Th2 cytokine IL-13 may induce the allergic phenotype [63]. Interestingly, it has also been shown that there is a strong correlation between Th2 cytokine IL-13+ lymphocytes in core blood from newborns and the development of wheezing and/or asthma during the first year of life [64]. Based on these findings, the importance of the Th1/Th2 paradigm cannot be ignored when investigating alternate therapeutic strategies to treat atopic asthma.

6. The potential role of antihistamines in the prevention/treatment of atopic asthma

Despite recent advances in understanding the etiology and pathogenesis of asthmatic disease, the clinical treatment of asthma still poses a major challenge. The elucidation of histamine's control over the cytokine network and the Th1/Th2 balance provides a basis for the potential use of antihistamines in the prevention and treatment of atopic asthma. Today, asthma is routinely treated with inhaled β -receptor agonists and inhaled corticosteroids. Table 1 summarizes conventional drug classes used in the treatment of atopic asthma.

Prior to the advent of inhaled corticosteroids 20 years ago, however, first-generation antihistamines were frequently utilized [65]. Though effective in reducing bronchial response, antihistamines are less effective than corticosteroids in the treatment of asthma [65].

Recent studies have demonstrated that both H1 and H2 receptor antagonists have the ability to modulate cytokine secretion profiles and the Th1/Th2 balance. For instance, H1 receptor antagonist terfenadine has been shown to not only inhibit cell proliferation, but also to diminish secretion of Th2 cytokines IL-4 and IL-5 in human peripheral blood mononuclear cells [66]. Likewise, it was shown in patients with allergic rhinitis that H2 receptor antagonist ranitidine increased Th1 cytokine IFN γ and decreased Th2 cytokine IL-4 [67]. In the ETAC [68] study, cetirizine, a H1 receptor antagonist with the ability to downregulate eosinophil recruitment, has been shown to reduce the incidence of asthma by half in certain sensitized

infants with atopic dermatitis. This study indicated that certain antihistamines with unique immunomodulating properties were effective in the prevention of atopic asthma.

7. The potential role of cytokines in the prevention/treatment of atopic asthma

The elucidation of the role that specific cytokines play in allergic inflammation provides the basis for alternate cytokine-specific therapeutic strategies. Such strategies include the use of cytokine antagonists (antibodies, soluble cytokine receptors), cytokine receptor antagonists, and attempts to restore the balance of Th1-versus Th2-like cytokines.

8. Th1 cytokines

8.1. IFN γ

Th1 cytokine IFN γ and monokine IL-12 are important for the differentiation of naïve T helper cells into Th1 cells. Histamine inhibits the production of IFN γ in polyclonally activated human blood mononuclear cells reversible by the addition of recombinant Th1 cytokine IL-2 [18,19]. In T cell clones from the bronchoalveolar fluid and blood from asthmatic patients, histamine inhibited IFN γ secretion in 40% of the clones and enhanced IFN γ secretion in only 15% of the clones [21]. Arad et al. [20] reported inhibition of IFN γ in cultured human peripheral blood mononuclear cells. We have found that histamine dose-dependently inhibits IFN γ in cloned murine T helper type 1 lymphocytes [24].

IFN γ downregulated the secretion of certain Th2 cytokines. The local administration of aerosolized recombinant IFN γ in mice prevented antigen-induced eosinophil infiltration into the trachea and normalized airway function [69,70]. Unfortunately, recombinant subcutaneous administration of IFN γ had no benefit in the treatment of steroid-dependent asthma [71].

8.2. IL-12

Elenkov et al. [9] demonstrated that histamine suppressed secretion of Th1-like monokine IL-12 in

LPS (lipopolysaccharide)-stimulated whole blood cultures via the H2 receptor through a release of cAMP. Histamine also inhibits LPS-induced IL-12 production in uncommitted dendritic cells [72].

Atopic asthma has been associated with a deficiency in IL-12 [63]. While systemic administration of IL-12 has serious side effects, localized intranasal treatment in mice inhibited airway hyperresponsiveness and lung eosinophilia after airway challenge and led to a shift from a Th2 inflammatory pattern toward a Th1 reaction [73,74]. This treatment also led to local enhancement of IFN γ and prevention of local IL-4 and IL-5 production. Kips et al. [75] also demonstrated that administration of IL-12 in mice sensitized to ovalbumin abolished airway eosinophilia and hyperresponsiveness without affecting levels of specific IgE.

9. Th2 cytokines

9.1. IL-4

The effects of histamine on the production of IL-4 have not clearly been elucidated to date. Studies in our laboratory have demonstrated no significant effect of histamine on IL-4 secretion in cloned murine Th2 cells (unpublished observations). This lack of effect has also been demonstrated by other investigators [22]. It has also been found in T cell clones from the bronchoalveolar fluid and blood from asthmatic patients that histamine inhibited IL-4 secretion in only 8.5% of the clones and enhanced IL-4 secretion in only 4.3% of the clones [21].

IL-4 plays a central role in the promotion of an allergic inflammatory eosinophilic reaction in allergic diseases through IgE isotype switching. IL-4 is also crucial for the differentiation of naïve T helper cells into Th2 cells. Data in IL-4 knockout mice demonstrate its potential usefulness. It has been shown that sensitization and exposure in IL-4 knockout mice prevents eosinophilia and peribronchial inflammation [76]. Recently, the safety and efficacy of human soluble IL-4 receptor in the treatment of moderate persistent asthma was demonstrated in 62 patients by a decline in FEV(1) [77]. These observations clearly suggest the antagonism of the IL-4 receptor as a potential therapeutic target in asthma.

Another potential therapeutic target in this realm is the modulation of STAT6, transcription factor for IL-4 and IL-13, because it is expressed in abnormally high levels in asthmatic patients [78]. Consequently, the effects of histamine in the regulation of IL-4 could be significant.

9.2. IL-5

It has been demonstrated that histamine dose-dependently upregulates IL-5 in T helper type 2 cells [22]. It has also been found that in T cell clones from the bronchoalveolar fluid and blood from asthmatic patients, histamine inhibited IL-5 secretion in only 14% of the clones and enhanced IL-5 secretion in 30% of the clones [21]. In our laboratory, we have demonstrated that histamine dose-dependently upregulates IL-5 in cloned murine T helper type 2 lymphocytes [86].

IL-5 also plays an important role in allergic disease by controlling the movement, maturation, and proliferation of eosinophils, along with IL-3 and GM-CSF. The dominant role of IL-5 in the control of eosinophilia has been demonstrated in several mammalian species as administration of anti-IL-5 suppresses airway eosinophilia induced by allergens [79]. Whether or not the administration of anti-IL-5 can prevent airway hyperresponsiveness in addition to preventing eosinophilia is a matter of controversy that needs to be further investigated [79].

Recently, Ramshaw et al. [80] have generated a monoclonal antibody, BION-1, which binds to a shared receptor subunit (betac) for IL-3, IL-5, and GM-CSF. By inhibiting all three eosinophilopoietic factors, it is anticipated that there will be an inhibition of eosinophil production and feasible therapeutic treatment for asthma.

9.3. IL-10

Elenkov et al. [9] demonstrated that histamine stimulates secretion of Th2 cytokine IL-10 in LPS (lipopolysaccharide)-stimulated whole blood cultures via the H2 receptor through a release of cAMP. Histamine also upregulates the secretion of IL-10 from unstimulated and LPS-stimulated alveolar macrophages [27]. We have reported that histamine

dose-dependently upregulates IL-10 in cloned murine T helper type 2 lymphocytes [25].

Interleukin-10 downregulates cellular immune response and affects the outcomes of viral diseases via inhibition of the production of Th1 cytokines. IL-10 prevents the accumulation and activation of eosinophils and inhibits allergen-induced IL-5 production in animal models of asthma [81]. IL-10 knockout mice exhibited increased airway inflammation and increased synthesis of proinflammatory cytokines [82].

9.4. IL-13

We reported that histamine dose-dependently upregulated IL-13 in cloned murine T helper type 2 lymphocytes [26]. IL-13 plays a central role in the promotion of an allergic inflammatory eosinophilic reaction in allergic diseases through IgE isotype switching [29]. IL-13 also inhibits the production of inflammatory cytokines, induces B cell proliferation and differentiation, including IgE production and enhances expression of CD23 and MHC class II molecules (major histocompatibility complex class II) [30–32]. It has been shown that selective neutralization of IL-13 through a fusion protein in murine models leads to amelioration of the asthma phenotype, including airway hyperresponsiveness, eosinophil recruitment, and mucus overproduction [83]. These data clearly implicate cytokine IL-13 in the pathogenesis of atopic asthma.

Recently, a recombinant IL-13 receptor antagonist called IL-13E13K has been shown to competitively inhibit IL-13- and IL-4-dependent proliferation and to inhibit IL-13-induced STAT6 activation [84]. The authors suggest this may also be a useful tool in the treatment of atopic disease.

9.5. Th1/Th2 modulation

The use of antihistamines to modulate the Th1/Th2 cytokine balance in the prevention of asthma remains attractive, as demonstrated by ETAC study. Aside from the use of antihistamines and cytokines to alter the Th1/Th2 balance, several other strategies are under current investigation. One such strategy is the invention of novel anti-allergic agents to modulate the Th1/Th2 balance. For instance, M50367 is an anti-allergic agent under investigation that has been shown to

downregulate the Th2 response in a murine model of atopic asthma [85]. It has also been proposed that by boosting innate immunity through vaccines, a possible increase in the Th1/Th2 ratio can be achieved [78]. This is currently under investigation. As more advances are made in our understanding of histamine and its control over the Th1/Th2 balance, the use of new therapeutic targets such as these will play a prominent role in disease management.

In summary, asthma has limited therapeutic options. Corticosteroids are currently the mainstay of therapy in asthma; however, their side effects remain a serious concern. Other than steroids, the choices for the treatment of asthma are rather limited. The two newer drugs for the treatment of asthma that are under development include Nuvance™ and olizumab (Xolair®). Nuvance is a soluble IL-4 receptor that can be taken once a week for inhalation and olizumab is a recombinant antibody to IgE. Since Th1/Th2 cytokine imbalance contribute to the etiology and pathogenesis of asthma, understanding these mechanisms will provide novel targets for therapeutic interventions. With the discovery of four different types of histamine receptors, it has become increasingly important to delineate their transduction mechanisms in lymphocytes as well as their effects on cytokine-induced transcription factors such as Janus kinases, STAT factors, c-maf, and GATA-3. Functional differences between Th1, Th2, and Th0 cells may be due to differences in the activation of transcription factors controlling expression of cytokine genes or intracellular pathways controlling cytokine production.

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