

Immune Regulation by Histamine H₄ Receptors in Skin

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The diverse effects of histamine on immune regulation appear to be due to differential expression and regulation of four types of histamine receptors and their distinct intracellular signals. The differences in cellular expression and affinities of these receptors for histamine determine the biological effects of histamine and the drugs that target histamine receptors. In this issue, Dijkstra *et al.* demonstrate the expression and some of the functions of histamine H₄ receptors on inflammatory dendritic cells in atopic dermatitis skin.

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Histamine is synthesized from L-histidine exclusively by histidine decarboxylase, an enzyme expressed in cells throughout the body, including central nervous system neurons, gastric mucosa parietal cells, mast cells, and basophils (Akdis and Simons, 2006; Jutel *et al.*, 2002). Although contrasting findings have been reported, the histamine H₁-receptor (H₁R) stimulates cells of the immune system by potentiating their proinflammatory activity through increased migration to areas of inflammation, as well as by increasing their effector function. The histamine H₂-receptor (H₂R), on the other hand, appears to be a potent suppressor of inflammatory and effector function. Histamine modulates neurotransmitter release through presynaptic histamine H₃-receptors (H₃R) located on histaminergic and nonhistaminergic neurons in the central and peripheral nervous systems, and it facilitates several proinflammatory activities through the novel histamine H₄-receptor (H₄R). Differences in cellular expression and affinities of these receptors for histamine determine the biological effects of histamine and the drugs that target histamine receptors. H₁R and H₂R have a low affinity in the micromolar range, whereas H₃R and H₄R are high-affinity histamine receptors, with affinities

of 5–10 nM (Akdis and Simons, 2006; Thurmond *et al.*, 2008).

Histamine contributes to the progression of allergic-inflammatory responses by enhancing the secretion of proinflammatory cytokines such as IL-1 α , IL-1 β , and IL-6, as well as chemokines such as RANTES and IL-8, by several cell types and in local tissues (Bayram *et al.*, 1999; Jeannin *et al.*, 1994; Meretey *et al.*, 1991; Vannier and Dinarello, 1993). Histamine possesses all the properties of a classic leukocyte chemoattractant, including agonist-induced actin polymerization, mobilization of intracellular calcium, alterations in cell shape, and upregulation of adhesion molecule expression. Histamine induces the CC chemokines, monocyte chemotactic proteins 1 and 3, RANTES, and eotaxin in explant cultures of human nasal mucosa via H₁R, suggesting a prolonged inflammatory cycle in allergic rhinitis between the cells that release histamine and their enhanced migration to nasal mucosa (Fujikura *et al.*, 2001). In an allergen-induced lung-inflammation model in mice, allergen-specific wild-type but not H₁R-deficient CD4⁺ T cells were recruited to the lungs of naive recipients following inhaled allergen challenge (Bryce *et al.*, 2006).

Histamine exerts a range of effects on many physiologic and pathologic processes, and new roles are still being

discovered. In lesional skin of patients with atopic dermatitis (AD), a special DC type—the inflammatory dendritic epidermal cell (IDEC)—is characterized by the expression of both the low-affinity IgE receptor (CD23, Fc ϵ RII) and the high-affinity IgE receptor (Fc ϵ RI) (Wollenberg and Klein, 2007). These cells disappear with successful topical treatment of the skin. Because of the importance of IDECs in the pathogenesis of AD and a possible interaction of histamine and IDECs in lesions of AD, Dijkstra *et al.* (2008, this issue) investigated the expression and function of H₄R on IDECs. The authors demonstrate that skin IDECs express H₄R at the protein level, as shown by flow cytometry of epidermal cell suspensions and immunofluorescence staining of skin sections from lesional skin of AD patients. The expression of H₄R on monocyte-derived IDECs was upregulated by interferon- γ , but not by IL-4, tumor necrosis factor- α , poly I:C, or combinations of these, thus demonstrating that H₄R has a role in a T helper 1 (Th1)-related cytokine environment in the skin. Previously, high CCL2 levels have been linked to Th2 responses. The upregulation of H₄R by IFN- γ , together with the downregulation of CCL2 by H₄R agonists, suggests a role for H₄R in Th1 responses. It has been demonstrated that differential patterns of histamine receptor expression on Th1 and Th2 cells determine reciprocal T-cell responses following histamine stimulation (Jutel *et al.*, 2001). Th1 cells show predominant, but not exclusive, expression of H₁R, whereas Th2 cells show increased expression of H₂R. Histamine enhances Th1-type responses by triggering H₁R, whereas both Th1- and Th2-type responses are negatively regulated by H₂R (Jutel *et al.*, 2001). The work of Dijkstra *et al.* suggests that downregulation of CCL2 and upregulation of IFN- γ by H₄R may contribute to the shift from a Th2 to a Th1 milieu, as seen in the transition from acute to chronic lesions of AD (Dijkstra *et al.*, 2008). It seems that H₁R and H₄R synergize in this process, in which the upregulation of IFN- γ in T cells leads to keratinocyte apoptosis and eczema formation in AD (Trautmann *et al.*, 2000).

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Histamine participates in activating dendritic cell precursors, as well as both immature and mature forms. Dendritic cells express all four histamine receptors (Caron *et al.*, 2001a; Gutzmer *et al.*, 2002; Idzko *et al.*, 2002). Some H₄R-mediated effects of histamine on antigen-presenting cells have been previously demonstrated by the same group, for example, IL-12 downregulation in human MoDCs (Gutzmer *et al.*, 2005) and CCL2 downregulation in human monocytes (Dijkstra *et al.*, 2007). Endogenous histamine is actively synthesized during cytokine-induced dendritic cell differentiation (Szeberenyi *et al.*, 2001). Dendritic cells mature from monocytic and lymphoid precursors and acquire dendritic cell 1 and 2 phenotypes, which in turn facilitate the development of Th1 and Th2 cells, respectively. In the differentiation process of monocyte-derived dendritic cells, H₁R and H₃R act as positive stimulants that increase antigen-presentation capacity and Th1 priming activity. In contrast, H₂R acts as a suppressive molecule for antigen presentation, enhancing IL-10 production and inducing IL-10-producing T cells or Th2 cells (Caron *et al.*, 2001b; Mazzoni *et al.*, 2001; van der Pouw Kraan *et al.*, 1998). Maturation of dendritic cells results in the loss of these responses. In maturing dendritic cells, however, histamine dose-dependently increases intracel-

Four histamine receptors have unique roles.

lular cAMP levels and stimulates IL-10 secretion, while inhibiting production of IL-12 via H₂R (Mazzoni *et al.*, 2001). Interestingly, although human monocyte-derived dendritic cells express both H₁R and H₂R and can induce CD86 expression by histamine, human epidermal Langerhans cells express neither H₁R nor H₂R, mainly because of the effect of transforming growth factor- β (Ohtani *et al.*, 2003).

In conclusion, the immune regulatory functions of histamine are exciting and important, and new data are emerging. Histamine and the four histamine receptors constitute a multifaceted system, with distinct functions of receptor types due to their differential expression, which changes according to the stage of cell differentiation with influence from the microenvironment. New data on the novel functions of H₄R have opened an exciting new window and may lead to new understanding and novel therapies to treat allergic and other inflammatory diseases.

CONFLICT OF INTEREST

The author states no conflict of interest.

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