

Clinical and Experimental Allergy

Histamine as an immune modulator in chronic inflammatory responses

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In addition to its dominant role in type I hypersensitivity reactions, histamine influences several immune/inflammatory and effector functions [1, 2]. Histamine can selectively recruit the major effector cells into tissue sites and affect their maturation, activation, polarization, and other functions leading to chronic inflammation [3]. Histamine also regulates monocytes, dendritic cells, T cells, and B cells, as well as related antibody isotype responses. 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 [1, 2]. In addition, the differences in affinities of these receptors for histamine are highly decisive in the biological effects of histamine and drugs that target histamine receptors.

Histamine possesses all the properties of a classical leucocyte chemoattractant, including agonist-induced actin polymerization, mobilization of intracellular calcium, alteration in cell shape, and up-regulation of adhesion molecule expression. *In vivo*, allergen-specific wild-type but not histamine H₁ receptor-deficient CD4⁺ T cells were recruited to the lungs of naïve recipients following inhaled allergen challenge [3]. Histamine inhibits neutrophil chemotaxis due to histamine H₂ receptor-triggering, which is mimicked by impromidine (histamine H₂ receptor agonist), but not by β -histine (histamine H₁ receptor agonist) [4]. Histamine contributes to the progression of allergic-inflammatory responses by enhancement of the secretion of pro-inflammatory cytokines such as IL-1 α , IL-1 β , IL-6 as well as chemokines such as RANTES or IL-8, in several cell types and local tissues [5–8]. Histamine induces the CC chemokines, monocyte chemoattractant protein 1 and 3, RANTES, and eotaxin in explant cultures of the human nasal mucosa via the histamine H₁ receptor, suggesting a

prolonged inflammatory cycle in allergic rhinitis between the cells that release histamine and their enhanced migration to nasal mucosa [9].

The immunoregulatory effects of histamine on antigen-presenting cells such as dendritic cells and monocytes have been well documented. In monocytes stimulated with Toll-like receptor-triggering bacterial products, histamine inhibits the production of pro-inflammatory IL-1-like activity, TNF- α , IL-12, and IL-18, but enhances IL-10 secretion, through histamine H₂ receptor stimulation [5, 10–12]. Histamine also down-regulates CD14 expression via H₂ receptors on human monocytes [13]. The inhibitory effect of histamine via H₂ receptors occurs through the regulation of ICAM-1 and B7.1 expression, leading to the reduction of innate immune responses stimulated by lipopolysaccharide [14]. Histamine induces an intracellular Ca⁺⁺ flux, actin polymerization, and chemotaxis in immature dendritic cells due to stimulation of histamine H₁ receptor and histamine H₃ receptor subtypes. Maturation of dendritic cells results in the loss of these responses. In maturing dendritic cells, however, histamine dose-dependently enhances intracellular cAMP levels and stimulates IL-10 secretion, while inhibiting the production of IL-12 via the histamine H₂ receptor [15]. Interestingly, although human monocyte-derived dendritic cells express both histamine H₁ and H₂ receptors and can induce CD86 expression by histamine, human epidermal Langerhans cells express neither histamine H₁ nor histamine H₂ receptors, mainly because of the effect of transforming growth factor- β [16].

The balance between production and death is important in the control of cell numbers within physiological ranges. Cell accumulation in the tissues may be a consequence of either increased cell production or decreased cell death. Because apoptosis of cells is a powerful mechanism for deleting the cells, it raises the interesting possibility that unequal apoptosis of effector cells may lead to preferential deletion of one subset over another [17]. The effect of histamine on the life span of immune-competent cells has

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not been investigated so far. Soga et al. [18], in this issue, show that histamine affects the monocyte life span via the H₂R. These findings provide additional evidence supporting the immunomodulatory effect of histamine on monocytes. Histamine prevents monocytic apoptosis in a dose- and time-dependent manner and this effect is mediated by the H₂R and cAMP pathway. This phenomenon results in part from the histamine-induced endogenous production of IL-10. These results may indicate that the H₂R signals prolong the life span of monocytes and infiltration to the site of inflammation in modalities such as chronic allergic disorders including asthma and atopic dermatitis. In addition, recent studies suggest that histamine may play an important role in the modulation of the cytokine network in the lung via the histamine H₂ receptor, histamine H₃ receptor, and histamine H₄ receptor that are expressed in distinct cells and cell subsets [19, 20]. Apparently, due to the same signal transduction patterns, β_2 adrenergic receptors may function in a manner similar to the histamine H₂ receptor in humans [21].

Endogenous histamine is actively synthesized during cytokine-induced dendritic cell differentiation [22]. Histamine actively participates in the functions and activity of dendritic cell precursors as well as their immature and mature forms. Dendritic cells express all four histamine receptors [23–25]. Dendritic cells mature from monocytic and lymphoid precursors and acquire dendritic cell 1 and dendritic cell 2 phenotypes, which in turn facilitates the development of Th1 and Th2 cells, respectively. In the differentiation process of monocyte-derived dendritic cells, histamine H₁ receptor, and histamine H₃ receptor act as positive stimulants that increase antigen-presentation capacity and Th1-priming activity. In contrast, the histamine H₂ receptor acts as a suppressive molecule for antigen-presentation capacity, enhances IL-10 production and induces IL-10-producing T cells or Th2 cells [11, 15, 26].

It has been demonstrated that differential patterns of histamine receptor expression on Th1 and Th2 cells determine reciprocal T cell responses following histamine stimulation [27]. Th1 cells show predominant, but not exclusive expression of the histamine H₁ receptor, while Th2 cells show increased expression of the histamine H₂ receptor. Histamine enhances Th1-type responses by triggering the histamine H₁ receptor, whereas both Th1- and Th2-type responses are negatively regulated by the histamine H₂ receptor, due to activation of different biochemical intracellular signals [27]. In mice, deletion of histamine H₁ receptor results in suppression of IFN- γ and dominant secretion of Th2 cytokines (IL-4 and IL-13). Histamine H₂ receptor-deleted mice show up-regulation of both Th1 and Th2 cytokines. In addition, IL-3 stimulation significantly increases histamine H₁ receptor expression on Th1, but not on Th2 cells. Furthermore, it has been shown that histamine stimulation induced IL-10 secretion through the histamine H₂ receptor [28]. Increased IL-10

production in both dendritic cells and T cells may account for an important regulatory mechanism in the control of inflammatory functions by histamine.

In conclusion, the emerging pattern of immune regulation by histamine is very complex and calls for further investigation. Histamine and four different histamine receptors constitute a multi-faceted system with distinct functions of receptor types due to their differential expression, which changes according to the stage of cell differentiation and influences of the microenvironment.

Acknowledgements

The author's laboratories are supported by the Swiss National Foundation Grant: 32-105865 and Global Allergy and Asthma European Network (GA²LEN) and the Polish National Science Committee Grant 1387/P05/2000/19.

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