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Impact of histamine on dendritic cell functions

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Abstract

A rapidly growing body of evidence highlighted that histamine, a small biogenic amine, is implicated in the regulation of DC (dendritic cell) functions. It is well established that DCs represent the most potent antigen-presenting cells of the body, linking innate and acquired immunity and regulating the outcome of immune responses. Signals, associated with ongoing inflammation and uptake of foreign antigens, promote maturation of DCs and activation of T-cell responses in secondary lymphatic organs. These bone marrow-derived cells patrol continuously all over the body. During their persistent migration, several mediators may influence the behaviour and functions of DCs. Histamine, produced by mast cells, basophils or DCs themselves, may have an important role in the life cycle of DCs. From the differentiation, through their never-ending circulation, until the induction of T-cell response, histamine is present and influences the life cycle of DCs. Here, we summarize recent progress in histamine research with respect to DC functions. We also point out some controversial aspects of histamine action on DCs.

Keywords: antigen presentation; dendritic cell (DC) differentiation; histamine; migration; T-cell polarization

1. Introduction

Histamine [2-(1H-imidazole-4-yl)ethylamine] is a multifunctional, small-sized biogenic amine that regulates a multitude of cellular responses, and plays diverse roles in physiological and pathological processes. This important endogenous molecule was discovered and characterized by Dale and Barger a century ago, in 1910. Histamine, probably an ancient mediator, has been used for communication between different types of cells in biological systems for a long period of time. In mammalian cells, it is synthesized exclusively from the amino acid L-histidine by the enzyme HDC (histidine decarboxylase). Mast cells and basophil granulocytes located in connective tissue and in blood respectively are the major sources of granule-stored histamine. However, many other cells, including DCs (dendritic cells), express the HDC enzyme, and are capable of secreting this small molecule. Histamine exerts its diverse biological effects via four specific membrane receptors, H_1, H_2, H_3 and the lastly discovered H_4 receptor. All histamine receptors are heptahelical, G-protein-coupled molecules showing divergent expression in various tissues and cell types. Thus, depending on the cell source, histamine may have both paracrine and autocrine effects on histamine receptor expressing cells.

Bone marrow-derived DCs, localized in different tissues and organs of the body, differentiate into cells heterogeneous both phenotypically and functionally. In the periphery, DCs phagocytose or endocytose antigens and may be stimulated by inflammatory factors through their TLRs (Toll-like receptors). Ligand binding of TLRs is followed by the expression of co-stimulatory molecules and migration of DCs to secondary lymphoid organs where they present the processed cytosolic or extracellular antigens to cytotoxic or Th cells respectively. By secreting numerous cytokines, DCs initiate and modulate immune responses. While circulating in the body, DCs are under the regulatory effects of different chemokines, cytokines or even low molecular mass histamine.

The in vivo investigation of DCs is troublesome even in mice, since DCs represent sparsely distributed cells in the organism. This is why most of the results are obtained from in vitro experiments with murine or human DCs. Of note, one has to take into account that there are remarkable differences between the phenotypes of human and mouse DCs. The cells used for experiments are predominantly DCs differentiated in vitro from bone marrow or blood monocytes. In some experiments, authors investigate also primary DCs isolated from spleens of mice or from human blood.

After the differentiation protocol, iDCs (immature DCs), similar to human myeloid-related DCs [including epidermal LCs (Langerhans cells) and the interstitial DCs], are obtained. mDCs (mature DCs) are derived from iDCs on stimulation with LPS (lipopolysaccharide).

This minireview highlights the significance of histamine in the life cycle of DCs. We summarize the effects of histamine on relevant DC functions such as differentiation, antigen capture, presentation, migration and cytokine production.

2. Histamine synthesis and expression of histamine receptors by DCs

HDC, the only histamine synthesizing enzyme, is expressed at both RNA and protein levels in human DCs differentiated in vitro from peripheral blood monocytes. Histamine itself has also been

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detected intracellularly in DCs (Szeberenyi et al., 2001). To date, the release of newly synthesized histamine (also referred to as 'nascent histamine') has been shown only in the case of murine (Dunford et al., 2006; Amaral et al., 2007) and not human DCs.

The presence of histamine receptors may be monitored directly (at RNA and protein levels) or indirectly (concluding from the effects of numerous different histamine receptor agonists and antagonists on various DC functions). The indirect proofs will be discussed later in this paper at specific DC cellular processes. With respect to histamine receptor expression in DCs, data are rather conflicting. It is well documented by most authors that H_1, H_2 and H_4 receptor mRNAs and proteins are expressed in both human and mouse DCs (Caron et al., 2001; Gutzmer et al., 2002; Damaj et al., 2007; Amaral et al., 2007). In contrast, data about the presence of H_3R (H_3 receptor) are more controversial (Idzko et al., 2002; Gutzmer et al., 2005). Interestingly, neither H_1R nor H_2R was found on the surface of either *in vitro* differentiated LCs or those isolated from human epidermis. This was probably the result of the effect of TGFβ1 (transforming growth factor β1) specifically applied for LC differentiation (Ohtani et al., 2003). On the other hand, expression of the lastly discovered H_4R by both *in vitro* generated, monocyte-derived LCs (mRNA and protein) and primary LCs from murine and human skin samples (Dijkstra et al., 2008; Gschwandtner et al., 2010) was documented.

Observations proving that DCs express both histamine receptors and their ligand, histamine, support the concept that DCs may be under the influence of histamine derived not only from professional histamine-synthesizing cells but also from DCs themselves.

3. Effect of histamine on *in vitro* differentiation and maturation of DCs

Differentiation to iDCs is a complex, highly regulated process. The discovery that GM-CSF (granulocyte/macrophage colony-stimulating factor) is a key cytokine for the differentiation of haemopoietic progenitors, enabled generation of large number of *in vitro* differentiated DCs in both human and mouse systems.

Both HDC protein expression and intracellular histamine content were found to be increased during cytokine-induced *in vitro* differentiation of DCs from human peripheral blood mono-cytes. In parallel with this, the expression of some relevant cell surface DC markers (CD80, CD86, CD40, CD45 and CD11c) was elevated too. Some of these effects could be effectively inhibited by the blockade of *de novo* histamine production, in-hibition of histamine binding or compromising intracellular interaction of histamine with cytochrome *P*-450 moieties. All these data indicate a substantial role of histamine in *in vitro* DC differentiation (Szeberenyi et al., 2001). Another research group has detected similar inhibitory effect of histamine on CD1a (lipid binding and presenting membrane protein) expression during *in vitro* DC differentiation that was antagonized by an H_2R antagonist (Katoh et al., 2005).

After differentiation, a variety of factors of viral or bacterial origin (such as LPS or cytokines such as IFNγ (interferon γ), IL-1β (interleukin-1β), TNFα (tumour necrosis factor α) may induce terminal maturation of DCs. No effect of histamine was detected in LPS-driven maturation of monocyte-derived iDCs (Mazzoni et al., 2001).

4. Endocytosis

iDCs have an extraordinary ability to sample the surrounding environment. They use different mechanisms for antigen capture such as phagocytosis of bigger particles, macropinocytosis (which occurs constitutively in DCs and allows continuous internalization of antigens present in fluid phase) and receptor-mediated endocytosis (which involves the internalization of soluble antigens after clustering of receptors in clathrin-coated pits).

After histamine challenge, an elevated FITC-labelled latex bead phagocytosis by human monocyte-derived DCs was measured (Katoh et al., 2005). Other authors reported that phagocytosis of FITC-OVA (ovalbumin)-coated latex beads by murine DCs were not stimulated by histamine (Amaral et al., 2007). At the same time, their results show that histamine is able to modulate endocytosis by mouse iDCs: endocytosis of soluble HRP (horseradish peroxidase) and FITC-OVA is markedly increased by histamine. Enhancement of endocytosis is completely suppressed by an H_2R antagonist, but not with H_1R and H_3R/H_4R antagonists.

One may conclude from these data that the ability of histamine to increase antigen uptake depends on the form of antigen and/or mechanism of antigen internalization by DCs (Amaral et al., 2007).

5. DC migration

Migration is an important and indispensable feature of DCs. iDCs migrate to both body surfaces and interstitial spaces, where they easily make contact with self- or foreign antigens. After antigen challenge, migration of DCs is also necessary to activate T-cells, and thus link innate and adaptive immune responses.

In human monocyte-derived iDCs (but not in mDCs) histamine, H_1R and H_3R agonists induce intracellular Ca^{2+} mobilization and F-actin polymerization in a dose-dependent manner (Idzko et al., 2002). Damaj et al. (2007) also showed that histamine mobilized intracellular Ca^{2+} in human monocyte-derived DCs. This was inhibited by an H_3R/H_4R antagonist.

Another study demonstrated a similar effect of histamine regarding actin polymerization in iDCs; however, data about the implicated receptors were controversial. According to Gutzmer et al. (2002, 2005), H_2R and H_4R agonists trigger F-actin polymerization, an effect that can be antagonized by specific receptor antagonists.

Several independent research groups established that histam-ine (Gutzmer et al., 2005; Damaj et al., 2007) or histamine agonists (Idzko et al., 2002; Gutzmer et al., 2005) are strong chemotaxins for iDCs. In contrast, they are ineffective for mDCs, as suggested by the observation that mDCs did not migrate in response to

histamine challenge (Idzko et al., 2002). By using specific receptor antagonists the involvement of both H_3R (Idzko et al., 2002; Damaj et al., 2007) and H_1R (Idzko et al., 2002) has been shown in the modulation of migration.

In vivo studies revealed that LC migration to draining lymph nodes was modulated by mast cell-derived histamine, and this effect was blocked by an H_2R antagonist (Jawdat et al., 2010).

Mouse DC migration was impaired by an H_4R antagonist; upon *in vivo* administration of JNJ7777120, a reduced number of labelled DCs were demonstrated in the lymph nodes (Cowden et al., 2010). Histamine, via H_2R, also promotes PGN (peptidoglycan)-induced accumulation of DC subsets in lymph nodes (Dawicki et al., 2010). In a skin DC migration assay, both histamine and an H_4R agonist induced an enhanced chemotaxis that was blocked by H_1R and H_4R antagonists. These results were confirmed by *in vitro* migration experiments using bone marrow-derived mouse DCs (Bäumer et al., 2008).

Thus, based on both *in vivo* and *in vitro* data, histamine, via different receptors, modulates DC migration.

6. Antigen presentation

In the periphery, iDCs, characterized by high level of endocytic activity, internalize diverse foreign or self-antigens. For effective antigen presentation, beside antigen capture, another stimulus, for example via TLRs, is also required. The captured antigens are processed by the cell, and loaded on to MHC class I or II molecules. Meanwhile DCs migrate into secondary lymphoid organs. During their migration DCs undergo substantial modulations both of their phenotype and function, a process referred to as DC maturation. Secondary lymphoid organs are sites of antigen presentation to naive CD4+ or CD8+ T-cells. Maturation results in an increased expression of MHC class I, class II and co-stimulatory molecules (such as CD80 and CD86).

Even though an increasing body of evidence supports the notion that histamine has an impact on antigen presentation, this essential immunological process needs further investigation, especially because most results are obtained from murine experiments.

Expression of co-stimulatory and accessory molecules (CD40, CD80 and CD86) and MHC class II, involved in effective antigen presentation, are enhanced transiently by histamine on human monocyte-derived iDCs. Furthermore, H_1R and H_2R antagonists prevented histamine-induced CD86 expression (Caron et al., 2001). Mazzoni et al. (2001) also reported a moderate, but consistent, increase in CD86, CD80 and MHC class II expression, however, histamine had no effect on the expression of CD40.

Splenic DCs of $HDC^{-/-}$ mice kept in histamine-free conditions, displayed a more efficient *in vitro* antigen presentation as compared with cells from wild-type mice. This difference was not a result of an altered distribution of DCs between or within the major functional sub-populations or to major changes in the co-stimulatory molecule profile (e.g. CD40, CD80 and CD86) (Jelinek et al., 2007).

DCs present antigens not only in a 'conventional way' but also cross-present foreign antigens very efficiently. Cross-presentation is the process by which extracellular antigens (normally presented in association with MHC class II molecules) are routed for presentation on MHC class I molecules, enabling extracellular antigens to activate CD8+ T-cells. This pathway may lead either to tolerization or activation of antigen-specific CD8+ T-cells. Histamine markedly improved cross-presentation of soluble OVA, but not that of OVA-coated latex beads in mouse iDCs. Thus it seems that the ability of histamine to increase cross-presentation is dependent on the form of the antigen and/or the mechanisms through which the antigen is internalized by DCs, since cross-presentation of the pinocytosed, but not of the phagocytosed, OVA was facilitated by histamine. Interestingly, the expression of MHC class II, but not of MHC class I, was increased after histamine treatment, and the stimulation of cross-presentation was prevented by H_3R/H_4R antagonists (Amaral et al., 2007).

7. T-cell polarization

DCs are professional antigen-presenting cells, which effectively prime naive antigen-specific T-cells. Based on their ability to favour Th1 or Th2 differentiation, mDCs fall into the categories of either DC1 or DC2 phenotypes, which in turn, facilitate the development of Th1 and Th2 cells respectively. DC maturation is associated with the synthesis of numerous cytokines and chemokines that act on T-cell polarization. The most intensively studied cytokines include the Th1-type IL-12 and the Th2 or T-regulatory type IL-10. The majority of experimental data support that histamine induces an altered cytokine expression in DCs, and favour Th2 polarization. This effect is exhibited even in the presence of IFNγ, a strong DC1 promoting factor (Caron et al., 2001). Histamine inhibited LPS- or IFNγ-induced IL-12 response and the production of some other proinflammatory cytokines such as IL-1β and IL-6. This effect could be antagonized both by H_1 and H_2 receptor antagonists (Caron et al., 2001; Mazzoni et al., 2001; Gutzmer et al., 2002).

At the same time, others demonstrated the involvement of both H_2R and H_3R, but not H_1R in the histamine-induced suppression of IL-12 production. Conversely, relevant Th2 cytokines and LPS-stimulated IL-8 and IL-10 synthesis, were significantly increased in histamine-treated human monocyte-derived mDCs (Mazzoni et al., 2001; Idzko et al., 2002).

After the discovery of H_4R, the possible involvement of this receptor in Th polarization was studied extensively. It was demonstrated that the reduced production of the paramount Th1 cytokine, IL-12p70 was mediated not only by H_2R but also by the lastly found H_4R (Gutzmer et al., 2005). *In vitro* studies indicate that in DCs from $H_4R^{-/-}$ mice and upon the blockade of H_4R of mouse splenic DCs, both cytokine (IL-6) and chemokine production [KC (keratinocyte chemoattractant) and MIP-1α (macrophage inflammatory protein 1α)] are significantly decreased. Furthermore, the ability of H_4R-deficient DCs to induce Th2 responses in T-cells is limited (Dunford et al., 2006).

The migration of Th cells into target organs is regulated by different sets of chemokines. Histamine was shown to up-regulate the production of Th2-attracting chemokines [e.g. CCL17 (CC chemokine ligand 17) and CCL22 (CC chemokine ligand 22)], and down-regulate the IFNγ-induced CXCL10 (CXC chemokine ligand
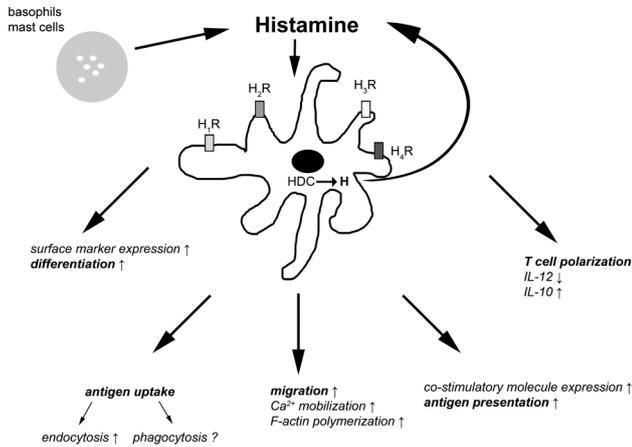
Figure 1 Summary of histamine (H) effects on DC functions

10) production by human monocyte-derived iDCs (McIlroy et al., 2006).

These data show that histamine is involved in Th2 polarization. It down-regulates the production of IL-12 and stimulates the synthesis of certain Th2-attracting chemokines and IL-10 by DCs.

8. Conclusions

Apparently, DCs are the 'conductors' of the immune system, linking innate and adaptive responses in the course of immune processes. DCs are not only critical for the induction of primary immune responses but are also implicated in the induction of immune tolerance, as well as in the regulation of T-cell-mediated immune processes. During their life cycle, patrolling the body, numerous chemical mediators such as cytokines, chemokines and low molecular mass factors may have an influence on DC functions. Histamine seems to be one of the mediators, which has a crucial impact not only on DCs themselves but also on the ultimate outcome of the immune response (Figure 1). DCs, being the most powerful professional antigen-presenting cells, are natural adjuvants and represent promising alternative tools for vaccination. *Ex vivo* antigen-loaded DCs may be used to prime the immune response against infectious agents and cancer cells in experimental animal models and also in patients. Thus lessons of studies on DCs and molecules affecting DC functions, are of substantial clinical relevance.

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