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KEY WORDS:
alveolar macrophage · monocyte · lung · pathogenesis · H5N1 · cytokine

Editorial: **Is histamine the missing link in chronic inflammation?**

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RECEIVED FEBRUARY 20, 2012; REVISED MARCH 24, 2012; ACCEPTED MARCH 25, 2012. DOI: 10.1189/jlb.0212093

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Histamine elicits pleiotropic actions, largely through binding to four currently known GPCRs, designated as H_1R–H_4R, and it has been implicated in inflammation for over 80 years. H_1R and H_2R antagonists (antihistamines) attained blockbuster status for the treatment of allergy and gastrointestinal diseases, respectively, but they have proved to be significantly less effective or ineffective in chronic inflammation. The discovery of the H_3R and H_4R some years ago and their respective primary expression in the CNS and in hematopoietic cells revived the interest of the global scientific community and the pharmaceutical industry in histamine research and exposed attractive perspectives for the potential therapeutic exploitation of these new drug targets [1]. Importantly, a century after histamine was first linked to allergies, the identification of the H_4R at the turn of the millennium led to intense research over the last decade, which offered renewed hope that this is the missing link in tackling chronic inflammation [2] and even exposed additional roles for the "older" H_1Rs and H_2Rs. The consequences of the novel concept—that histamine exerts immunomodulatory actions in inflammation through H_4R signaling—and the potential exploitation of this activity for a range of the major, poorly treatable chronic inflammatory diseases are currently the subject of worldwide evaluation. Yet, our understanding of the functional mission of histamine in the multiple interconnected systems that constitute the immunological responses and inflammatory signals remains incomplete.

In this issue of the *Journal of Leukocyte Biology*, Gschwandtner et al. [3] explored the cross-talk of histamine, IL-27, and chemokine CXCL10 in an attempt to identify an essential regulatory pathway, which is critical for the pathogenesis of allergy and inflammatory skin diseases, such as chronic eczema and psoriasis. The authors showed that histamine selectively down-regulates the production of IL-27 in isolated human peripheral monocytes, whereas stimulation of skin keratinocytes with supernatants from these cell cultures down-regulates CXCL10 secretion (**Fig. 1**). In initial experiments, histamine reduced IL-27, but not IL-6, TNF-α, and IL-10 production, at mRNA and protein levels, at early rather than late timepoints, regardless of the TLR that drove monocyte activation. The functionality of the histamine-induced IL-27 down-regulation in monocytes was illustrated by the consequent decreased activation of keratinocytes. Although an underlying signaling mechanism was not revealed, the effects of histamine in reducing IL-27 production appeared not to rely on Stat1, Erk1/2, and NF-κB phosphorylation, despite the described regulation of these signaling molecules by histamine in other cell types [2]. Subsequent investigations focused on the identification of the type(s) of histamine receptors that mediated the response. With the use of selective, pharmacologically active agents, as well as bone marrow-derived DCs from BALB/c $H_4R^{-/-}$ mice, the authors document the orchestration of these concerted immunological responses by H_2R and H_4R.

The complexity of chronic inflammation-driven disorders is highlighted by the extensive literature on the interplay among the signals triggering inflammatory responses, the large repertoire of immune cell subsets and mediators shaping the phenotypic variations in inflamed tissues, and the downstream cascades underlying the initiation, propagation, and perpetuation of the response [4]. In particular, chronic inflammatory skin diseases are characterized by erythematous and pruritic skin lesions infiltrated by various cell types, including monocytes and T_H cells, eliciting the differentiation of specialized DC subsets through largely unexplored mechanisms [5]. The increased histamine levels in inflamed skin and the functional expression of histamine receptors on infiltrating immune cells, keratinocytes, and sensory neurons support the

Abbreviations: EU COST=European Union European Cooperation in Science and Technology, H_1R—H_4R=histamine H_1—H_4 receptor, $H_4R^{-/-}$=H_4R knockout mouse, IDEC=monocyte-derived inflammatory dendritic epidermal cell, Treg=regulatory T cell

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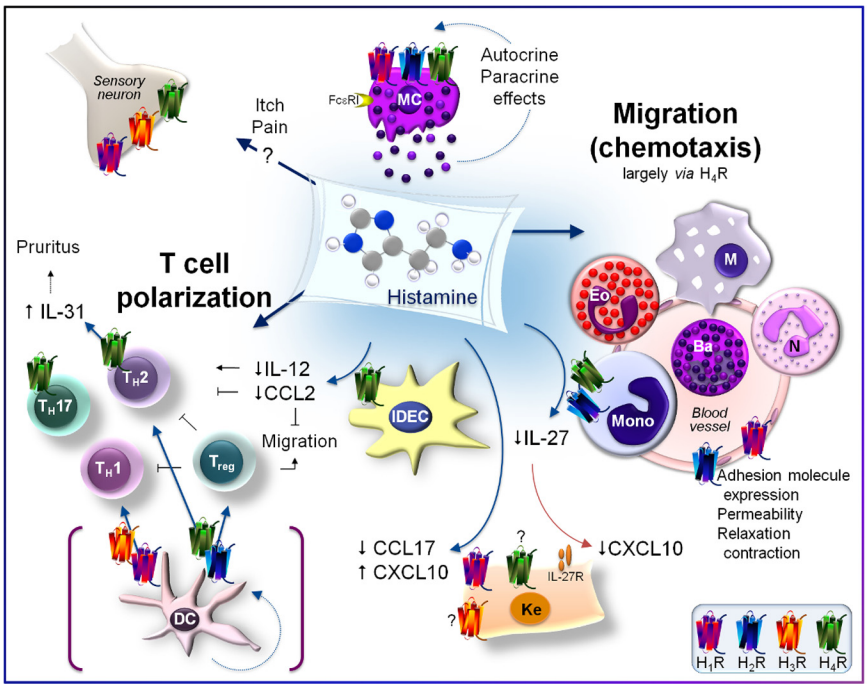

Figure 1. Schematic overview of the influence of histamine on multiple interconnected components in the skin. Differential expression and stimulation of H_1R–H_4R can alter pro- and anti-inflammatory signals and may orchestrate the transition from acute to chronic inflammation reflected by the repertoire of secreted cytokines and chemokines (see text for details). Ba, Basophils; Eo, eosinophils; FcεRI, high-affinity IgER; Ke, keratinocytes; M, Macrophages; MC, mast cells; Mono, monocytes; N, neutrophils.

hypothesis that histamine contributes to the pathogenesis of these disorders and influences the course of inflammation and pruritus [6, 7]. In cultures of human keratinocytes expressing the H_1R and H_2R, but not the H_3R and H_4R, H_1R-mediated suppression of CCL17 (T_H2 chemokine) and enhancement of CXCL10 (T_H1 chemokine) production (Fig. 1) suggested that histamine may act as a negative-feedback signal for T_H2-dominant skin inflammation [8]. It is worth noting that the use of H_1 antagonists for the treatment of itch, which frequently complements many skin disorders, is well documented; however, antihistamines targeting the H_1R and H_2R are of limited therapeutic value in chronic diseases, such as atopic dermatitis [6].

Interestingly, histamine involvement in regulating the T_H2 to T_H1 shift during transition from acute to chronic skin inflammation is reflected by the increased H_4R expression on IDECs, stimulated with IFN-γ, and by the H_4R-mediated down-regulation of CCL2 (MCP-1, T_H2 chemokine) [7]. In this case, H_4Rs seem to dictate a negative-feedback mechanism that avoids a T_H2-dominant environment. Along this line of research, the studies of Gschwandtner et al. [3] expand the topicality of this concept and support a growing body of evidence pointing to the contribution of the network of histamine receptors in modulating T_H polarization through modification of the cytokine and chemokine milieu at sites of inflammation (Fig. 1). In agreement with the down-regulation of IL-12, reported previously by the same group [7], the findings that H_2R and H_4R activation down-regulates IL-27, and consequently, CXCL10 production implies that the H_4R affects the T_H1 as well as the T_H2 phenotype. Although studies in H_2R-deficient mice were not performed, the contribution of H_2Rs in the observed histamine-mediated effects deserves careful consideration. In addition to the well-established regulation of gastric acid secretion, H_2Rs modulate a range of immune system activities, including mast cell degranulation, regulation of T_H1, T_H2, and Treg functions, as well as suppression of T cell proliferation in nonallergic patients [4]. In parallel to the development of dual-action H_1R/H_4R antagonists, aiming to clarify their therapeutic potential in itch and pain [1], the development of dual-action H_2R/H_4R ligands would provide more accurate tools to assess the potential of histamine receptors to shape pro- or/and anti-inflammatory signals in chronic skin diseases [6].

Taken together, the recent developments in histamine research have prompted a re-evaluation of the role that histamine plays in immune homeostasis. A large body of preclinical evidence identifies the H_4R as a central player in initiating and propagating immune responses. However, the remarkable cell and tissue variability in histamine-mediated signals and the profound intra- and interspecies differences in potency, selectivity, and off-target effects of H_4R ligands [2, 4, 9] hamper investigations and call for more cautious interpretation of the observed effects in vivo. For instance, the complex pharmacology of H_4R antagonists can be partly attributed to the functional selectivity exhibited by many GPCRs [9]. This may explain the failure of the H_4R antagonist alone to circumvent the effect of histamine on IL-27 production, in contrast to the observed IL-27 up-regulation in $H_4R^{-/-}$ mice [3]. The selection of suitable pharmacological tools and human biological samples as well as the use of in vivo models of disease and knockout animals are essential for reaching conclusions about putative receptor functions, which would allow the cautious extrapolation of the findings to human (patho) physiology. To add further complication, histamine receptors exhibit varying affinities for histamine, which elicits diverse or/and counteracting actions, depending on the levels and the type of activated receptors expressed on the multitude of cells involved in inflammatory responses (Fig. 1) under different experimental or physiological environments [1, 2, 4], whereas recent evidence argues for additional, receptor-independent actions of this biogenic amine [10].

In this versatile system of histamine-driven immunoregulation, commonly represented by the four currently known histamine receptors, further experimentation is needed to address numerous unresolved questions and to clarify conflicting findings to reach more beneficial end-points. For instance, what is the con-

tribution of histamine receptors in important and indispensable DC characteristics, such as maturation or/and migration, and what is the relevance of experimental data to human (patho)physiology? What is the role of the differential expression or activation of histamine receptors on immunocompetent cells in vivo, and how are they functionally related to the large repertoire of cytokines and chemokines implicated in acute and chronic inflammation? What are the molecular mechanisms underpinning histamine receptor cross-talk with immune-relevant pathways, such as TLR signaling and DC chemotaxis, and how would these interactions be useful in identifying more effective therapeutic targets for inflammatory disorders? Finally, it would be interesting to know whether autocrine or paracrine mechanisms are in operation [11], considering that not only the "professional" histamine-synthesizing mast cells but also DCs express histamine and histamine receptors (Fig. 1), yet the putative automodulatory mechanisms remain unknown.

In conclusion, the studies by Gschwandtner et al. [3] highlight the promising value of histamine in orchestrating the complex immune response in dermal inflammation, and more importantly, they raise challenging questions about the mechanisms underlying the multiple interconnected systems that contribute to the pathogenesis of chronic inflammation in vivo.

AUTHORSHIP

E.T. is the chair of the EU COST Action BM0806: Recent Advances in Histamine Receptor H_4R Research, evaluated the available related literature, and critically wrote the commentary.

ACKNOWLEDGMENTS

The work is part of the EU RTD FP7 COST Action BM0806: Recent Advances in Histamine Receptor H_4R Research.

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KEY WORDS:
chemotaxis · histamine receptors · immune cells · immunomodulation · skin · T cell polarization

Editorial: **Route by which monocytes leave the brain is revealed**

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RECEIVED FEBRUARY 29, 2012; REVISED MARCH 21, 2012; ACCEPTED MARCH 30, 2012. DOI: 10.1189/jlb.0212110

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Immunological privilege, whereby allografts survive in the brain for longer periods than in other organs, is an important and much-discussed concept in neuroimmunology. The presence of blood-brain barriers restricts the entry of solutes and inflammatory cells into the CNS, but one of the main reasons advanced for immunological privilege is the lack of conventional lymphatic drainage from the CNS [1]. Despite the absence of classical lymphatics, however, there are well-established routes by which fluid and solutes drain from the CNS to regional LNs [2]. CSF drains from the subarachnoid space via the cribriform plate into nasal lymphatics and

Abbreviations: CLN=cervical LN, CSF=cerebrospinal fluid, dpi=days postinjection, EAE=experimental autoimmune encephalomyelitis, ECL=entorhinal cortex lesion, ISF=interstitial fluid, MS=multiple sclerosis

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