

Influence of histamine on monocyte-derived dendritic cells with

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What is known until today about the effects of histamine?

Norito Katoh: Histamine is an important mediator involved in various physiological and pathological conditions including immediate hypersensitivity reaction and inflammation by its effect of vasodilatation and increased capillary permeability (1). Recently, new immunomodulatory functions of histamine were discovered (2), (i) histamine augments antigen-receptor mediated T and B cell proliferation, (ii) histamine

enhances Th1-type responses by triggering H1 receptor (H1R) whereas Th1- and Th2-type responses are negatively regulated by H2R, and (iii) histamine alters the repertoire of cytokines and chemokines secreted by mature dendritic cells (DCs) that induces the polarization of naïve CD4⁺ T cells towards Th2 phenotypes. Therefore histamine may contribute to other mechanisms involved in the allergic inflammation.

Has histamine an influence on differentiation of dendritic cells?

Norito Katoh: A lack of appropriate exogenous stimuli induces monocytes to undergo apoptosis, whereas under the influence of distinct signals such as proinflammatory cytokines these cells differentiate into macrophages or DCs (3). Macrophages can perform phagocytosis and produce proinflammatory or anti-inflammatory cytokines that regulate inflammatory reactions (4). In contrast, DCs display the capacity to initiate primary and secondary T cell responses and the most efficient professional antigen presenting cells. These fundamental functional divergences may be of importance for their putative regulatory role of monocyte-derived DCs (MoDCs) and macrophages in tissues, and consequently for the outcome of local inflammatory responses. We examined the effect of histamine, a prototypic mediator of allergic inflammation, on the GM-CSF and IL-4-driven differentiation of monocytes into monocyte-

derived dendritic cells which typically showed CD1a⁺CD14⁻ phenotype (5). Monocytes from healthy adult donors were cultured with GM-CSF and IL-4 in the presence or absence of histamine, and the phenotypes and function of these cells were analyzed. Histamine induced the generation of CD1a⁺CD14⁺ cells, which exhibited cytological and phenotypical characteristics of DCs, showed enhanced phagocytic activity and cytokine-producing capacity, but demonstrated weak allo-stimulatory capacity compared with CD1a⁺CD14⁻ MoDCs. The inhibitory effects of histamine on CD1a⁺CD14⁻ MoDC differentiation were antagonized by an H2 receptor antagonist, but not by H1 and H3 receptor blockers, and were mimicked by an H2 receptor agonist. Culture supernatant of histamine-treated monocytes also inhibited CD1a⁺CD14⁻ MoDC differentiation, which was restored by the removal of IL-10.

What are the differences between CD1 positive/CD14 negative and CD1negative/CD14 positive dendritic cells?

Norito Katoh: DCs comprise heterogeneous populations with different morphologies and molecules expressed as a function of their maturation stage. In the dermis, dermal DC (DDCs) express varying levels of CD1a and therefore several subpopulations of DDCs can be distinguished according to their differential expression of CD1a and CD14. DDCs migrated from skin explants have been subdivided into three groups; CD1a⁺CD14⁻, CD1a⁺CD14⁻ and CD1a⁺CD14⁺ (6, 7). According to the reports, CD1a⁺CD14⁺ DDCs showed increased phagocytic activity and weak T cell stimulatory potential. However, CD14⁺CD1a⁻ DDCs described by Nestle et al (6) are positive for intracellular FXIIIa, whereas those reported by Larregina et al (7) is negative for FXIIIa. Our study showed that histamine prevents the IL-4/GM-CSF-driven differentiation of monocytes into CD1a⁺CD14⁻ MoDCs, but induced their differentiation into CD1a⁺CD14⁺FXIIIa⁺ cells which exhibited increased phagocytic activity and weak allo-stimulatory capacity. It is thus suggested that the cells generated in the presence of histamine in this study are similar to DDCs described by Nestle et al (6).

Do you think that there is a direct link between histamine and the exacerbation of allergic disease?

Norito Katoh: Increased expression of molecules involved in Ag capture (mannose receptor, CD11b) and decreased expression of costimulatory molecules (CD80, CD40) in histamine-treated DC, may correlate with their impaired antigen presenting function to T lymphocytes and a higher endocytic activity. These phenotypic and functional features suggest that histamine-induced DCs are immature DC, and may be in a transitional state of differentiation either toward mature CD1a⁺CD14⁻ DDCs and macrophages. It has been known that antigen presentation by

immature DC leads to the generation of T cells with regulatory function. Alternatively, IL-10 produced by histamine-treated monocytes and DCs via H2R may induce regulatory properties of T cells because IL-10-treated DCs lead to antigen-specific anergy in CD4⁺ T lymphocytes which is characterized by inhibited proliferation, reduced production of IL-2, and antigen-specific suppressor activity (8). Taken together, the appropriate use of HR antagonists or the use of selective agonists to induce CD1a⁺CD14⁺ DCs may be promising therapeutic tools against allergic disease.

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