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Regulatory effects of antihistamines on the responses to staphylococcal enterotoxin B of human monocyte-derived dendritic cells and CD4$^+$ T cells

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TARC;
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ELISA;
Proliferation;
ICAM-1;
CD54;
Flow cytometry

Summary

Background: Antihistamines are widely used for the treatment of allergic diseases, such as urticaria and allergic rhinitis. They are also effective for the treatment of diseases in which T cells are mainly involved in the pathogenesis, such as atopic dermatitis (AD) and contact dermatitis. Dendritic cells (DCs) drive polarization of naive T cells into Th1 or Th2 subsets, and are also likely to be involved in AD pathogenesis.

Objectives: The aim of this study was to determine the effects of antihistamines on DCs and CD4$^+$ T cells.

Methods: Human monocyte-derived DCs (MoDCs) and autologous CD4$^+$ T cells were obtained from healthy subjects, and cultured together or independently in the presence of antihistamines. As a stimulant, we used staphylococcal enterotoxin B or the combination of anti-CD3 monoclonal antibody (mAb) and anti-CD28 mAb. The concentrations of cytokines and chemokines in culture supernatants were measured by ELISA. The expression of surface molecules on MoDCs was measured by flow cytometry. Cell proliferation in the cocultures of MoDCs and CD4$^+$ T cells (DC-T cocultures) was measured by a [^{3}H] thymidine incorporation assay.

Results: Antihistamines inhibited the production of IFN-γ, and enhanced the production of IL-4 in DC-T cocultures. Antihistamines inhibited the production of TNF-α, TARC, MDC, IP-10, and Mig from MoDCs. Epinastine, one of antihistamines, suppressed the expression of ICAM-1 (CD54) on MoDCs. Epinastine also inhibited the proliferation of CD4$^+$ T cells cocultured with MoDCs.

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Conclusions: Our findings show that antihistamines regulate immune responses by affecting the interaction between DCs and $CD4^+$ T cells, and further DCs and $CD4^+$ T cells independently, which may partially contribute to the control of allergic diseases such as AD and contact dermatitis.

1. Introduction

Antihistamines are widely used for the treatment of allergic diseases, such as urticaria and allergic rhinitis. Their clinical effect is believed to be mediated by their antagonistic action against histamine, mainly produced by mast cells. On the other hand, antihistamines are also effective for the treatment of diseases in which T cells are mainly involved in the pathogenesis, such as atopic dermatitis (AD) and contact dermatitis [1—3]. Recent studies have suggested that antihistamines may possess additional mechanisms besides their ability to block histamine receptors [4,5], and that antihistamines exert inhibitory action on cytokine production from T cells in vitro and in vivo [6—10].

Previous reports have suggested that Th1-related chemokines such as IFN-γ-inducible protein-10 (IP-10) and monokine induced by IFN-γ (Mig), and Th2-related chemokines such as thymus and activation regulated chemokine (TARC) and macrophage-derived chemokine (MDC), which may facilitate the recruitment of Th1/Th2 cells [11,12], are important molecules in the pathogenesis of AD [13—15]. Therefore, the regulation of these chemokines may be useful in the management and treatment of allergic diseases, including AD.

Dendritic cells (DCs) could also be targets for the treatment of allergic diseases, since they drive polarization of naive T cells into Th1 or Th2 subsets [16], and are likely to be involved in the pathogenesis of the above diseases [17]. Nevertheless, the effects of antihistamines on the functions of human DCs, such as the production of Th1/Th2-related cytokines and chemokines, and the expression of surface markers, are yet to be determined.

In this study, we evaluated the effects of antihistamines on the function of DCs and autologous $CD4^+$ T cells. In certain experiments, $CD4^+$ T cells were cocultured with DCs in vitro, because we considered that T cell stimulation in the presence of DCs, as compared to the stimulation without DCs, may better reflect the physiological conditions in which DCs mainly work as antigen presenting cells. Skin colonization with *Staphylococcus aureus* is an almost ubiquitous feature of AD, with rates as high as 75—90% of lichenified plaques compared with only 5% in skin from healthy donors [18]. *S. aureus* strains producing superantigens were isolated at a high prevalence (37—57%) from AD subjects [19,20]. Staphylococcal enterotoxin B (SEB), one of the superantigens produced by *S. aureus*, has been shown to induce inflammatory reactions following application to intact skin of healthy and atopic subjects [21]. Therefore, we used SEB as a stimulant of immune cells in this study. We observed that antihistamines had considerable effects on DC and T cell function.

2. Materials and methods

2.1. Media, reagents, and antibodies

The medium used was RPMI1640 (Nissui Pharmaceutical, Tokyo, Japan) supplemented with 2 mM L-glutamine (Nacalai Tesque Inc., Kyoto, Japan), 25 mM HEPES (Wako Pure Chemical Industries, Osaka, Japan), 100 U/ml penicillin, 100 μg/ml streptomycin (Meiji Seika, Tokyo, Japan), and 10% heat-inactivated foetal bovine serum (Thermo Electron, Melbourne, Australia), defined as complete medium. Recombinant human GM-CSF and recombinant human IL-4 were purchased from PeproTech (Rocky Hill, NJ, USA). Highly purified staphylococcal enterotoxin B was obtained from Toxin Technology Inc. (Florida, USA). Anti-CD80 monoclonal antibody (mAb) (2D10), anti-CD86 mAb (IT2.2), FITC-conjugated anti-CD54 mAb (MEM-111), and FITC-conjugated anti-HLA-DR mAb (L243) were purchased from BioLegend (San Diego, CA, USA). Anti-CD1a mAb (HI149), anti-CD3 mAb (UCHT1), anti-CD28 mAb (CD28.2), anti-CD83 mAb (HB15e), and FITC-conjugated rat anti-mouse IgG1 antibody (A85-1) were purchased from BD PharMingen (San Diego, CA, USA). Control mouse IgG1 and FITC-conjugated control mouse IgG2a were purchased from DakoCytomation (Glostrup, Denmark). FITC-conjugated anti-CD14 mAb (TÜK4) was obtained from Miltenyi Biotec (Begisch Gladbach, Germany). Anti-CD4 mAb (SFCI12T4D11) was obtained from Beckman—Coulter Immunotech (Villepinte, France). The agents used in this study and their sources were as follows, antihistamines: Epinastine, kindly provided by Nihon Boehringer Ingelheim Co. (Kawanishi, Japan); Ketotifen by Novartis Pharma AG (Basel, Switzerland); Loratadine by Shionogi Co. (Osaka, Japan);