Symposium 1: Immunity and pathogenesis of AR and CRS

Distinct role of dendritic cells in AR

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1. Introduction

Allergic rhinitis (AR) is one of the most common diseases globally. Classical symptoms of AR are nasal itching, sneezing, rhinorrhea, and nasal congestion. AR is also frequently associated with asthma, which is found in 15% to 38% of patients with AR, and nasal symptoms are present in 6% to 85% patients with asthma. In addition, AR is a risk factor for asthma, and uncontrolled moderate-to-severe AR affects asthma control. AR reduces the quality of life of many patients, impairing sleep quality and cognitive function and causing irritability and fatigue.

2. Immune system

The immune system protects the host from pathogens, allergens, and chemicals that enter through mucosal surfaces. Diverse responses against these stimuli induce different types of immune response by various T helper (Th) cells. CD4+ Th cells comprise a diverse category of immune cells, including Th1, Th2, Th17, and T regulatory cells. These different types of Th cell have distinct cytokines and transcription factor profiles with distinct immune responses. For example, CD4+ Th1 responses are induced by intracellular bacteria and viruses, resulting in secretion of interferon γ (IFN-γ) and expression of signal transducer and activator of transcription (STAT)-4. On the other hand, Th2 cells produce cytokines such as interleukin (IL)-4, IL-5, IL-13, and IL-10 and express transcription factors, such as GATA binding protein-3, STAT-5, and STAT-6.

Advances in immunology have revealed a fundamental role of the innate immune system in sensing pathogens and tuning the quality of Th responses. Th1 cells attack intracellular pathogens with cell-mediated immune responses, whereas Th2 cells protect against extracellular pathogens predominantly by helping with

humoral responses. When the Th1 and Th2 cell responses are over-reactive, the Th1 pathway induces organ-specific autoimmune diseases, such as arthritis and type 1 diabetes, whereas the Th2 pathway can predispose a host to systemic autoimmune diseases, such as allergy and atopic dermatitis.

3. Dendritic cell

Differentiation of Th cells into Th1 or Th2 cells is under the control of antigen-presenting cells (APCs), mostly dendritic cells (DCs). When DCs are exposed to intracellular pathogens, they move to lymph nodes and secrete IL-12, resulting in differentiation of naïve T-cells into Th1 cells. Those Th1 cells release IFN-γ, which restimulates the DCs to produce IL-12, resulting in differentiation of naïve T-cells into Th1 through an autocrine loop. Like that of Th1 cells, maturation of Th2 cells is initiated by IL-6 released from DCs, and these Th2 cells produce IL-4 to generate more Th2 cells through an autocrine loop to naive T-cells. Several cell types produce cytokines to mature Th2 cells and induce Th2 immune responses. Diverse pattern recognition receptors (PRRs) are involved, and multiple signaling pathways are elicited. However, the fundamental roles of DCs in the Th2 immune responses including allergic rhinitis associated with these factors are not apparent.

4. cAMP pathway in dendritic cell for Th2 differentiation

Cyclic adenosine monophosphate (cAMP, cyclic AMP) is a second messenger important in many biological processes. cAMP is a derivative of adenosine triphosphate (ATP) and used for intracellular signal transduction in many different organisms, conveying the cAMP-dependent pathway. Knockout (KO) of *Gnas*, the gene that encodes Gαs in mouse CD11c+ cells, and the subsequent decrease of cAMP in mouse DCs were recently reported to provoke the Th2 immune response with an allergic phenotype, whereas increased cAMP has been found to induce Th17 immunity. In this study, adoptive transfer of BMDCs from the Gnas KO mice induced Th2 immune responses, such as increased IL-4 and elevated IgE, and a PKA-selective cAMP agonist eliminated the Th2 phenotype in these mice. These results indicate that the Th2-biased effects of low cAMP concentration in DCs are regulated via PKA signaling and that cAMP/PKA signaling is an attractive target for the development of DC-directed therapy for Th2 immune diseases.

5. Conclusion

DCs interact with multiple types of immune and structural cells, show distinct subsets, bind to specific receptors according to the pathogen or allergen, and transfer stimuli through diverse signaling pathways to

elicit Th2 immune responses. Although DC-related Th2 immune responses are too complex to identify a single main target factor and many aspects have not been revealed, newly discovered areas, such as cAMP/PKA signaling, illuminate the possibility of regulating Th2 immunity in the near future.

References

1. Neurath MF, Finotto S, Glimcher LH. The role of Th1/Th2 polarization in mucosal immunity. Nat Med 2002;8: 567-573.
2. Paul WE, Zhu J. How are T(H)2-type immune responses initiated and amplified? Nat Rev Immunol 2010;10: 225-235.
3. Pulendran B, Tang H, Manicassamy S. Programming dendritic cells to induce T(H)2 and tolerogenic responses. Nat Immunol 2010;11:647-655.
4. Tang H, Cao W, Kasturi SP, et al. The T helper type 2 response to cysteine proteases requires dendritic cell-basophil cooperation via ROS-mediated signaling. Nat Immunol 2010;11:608-617.
5. Kim TH*, Lee J*, Murray F, Li X, Choi SS, Broide DH, Corr M, Lee J, Webster NJ, Insel PA, Raz E. Cyclic AMP in dendritic cells induce and regulate Th2 immunity and allergic asthma. Proc Natl Acad Sci U S A. 2015 Feb 3;112(5):1529-34.