Symposium 2: Allergen-specific immunotherapy in AR

Mechanisms of inducing and breaking allergen tolerance

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Although it is becoming more clear that the observed increment in the incidence of allergic diseases is due to the loss of peripheral T-cell tolerance to allergens, the mechanisms or specific cytokines or innate immune response stimulating factors involved in such processes remain largely unknown. We sought to identify molecular mechanisms that break allergen-specific T-cell tolerance in human subjects. In allergic patients the immune profile of the tonsils represents the atopic status of patients, with low expression of the TH1 cell-specific transcription factor T-bet and the cytokine IFN-g, as well as IL-10. Human tonsils show very low levels of allergen-induced T-cell proliferation, thus representing a very suitable in vivo model to assess mechanisms of breaking allergen-specific T-cell tolerance. Triggering of Toll-like receptor (TLR) 4 or TLR8 and the proinflammatory cytokines IL-1b or IL-6 break allergen-specific T-cell tolerance in human tonsils and peripheral blood through a mechanism dependent on the adaptor molecule myeloid differentiation primary response gene (88) (MyD88). In particular, myeloid DCs and stimulations that activate them broke the tolerance of allergen-specific CD4+ T cells, whereas plasmacytoid DCs and stimulations that activate them, such as TLR7 and TLR9, did not have any effect. Tolerance-breaking conditions induced by different molecular mechanisms were associated with a mixed cytokine profile with a tendency toward increased levels of IL-13 and IL-17, which are TH2 and TH17 cytokines, respectively.

Certain innate immune response signals and proinflammatory cytokines break allergen-specific CD4+ T-cell tolerance in normally unresponsive subjects, which might lead to the development or exacerbation of allergic diseases after encountering microbes or inflammatory conditions. Respiratory infections with human rhinoviruses (HRV) are strongly associated with asthma exacerbations and pose a severe health risk for allergic individuals. How HRV infections and chronic allergic diseases are linked, and which role HRV plays in the breaking of allergen-specific tolerance is unknown. T regulatory cells (Tregs) play an important role in the induction and maintenance of immune tolerance. Therefore, the aim of this study is to

investigate the effects of HRV on Tregs during asthma exacerbations. Healthy and asthmatic individuals were experimentally infected with HRV16 in vivo. Peripheral blood mononuclear cells (PBMCs) were obtained before infection and three days after infection. Tregs were sorted from the PBMCs according to their flow cytometric profile CD4+CD3+CD25+CD49d-CD127- and were analyzed with next generation sequencing. We have found that on baseline there is a clear difference in Tregs from asthmatics compared to healthy individuals. Tregs from asthmatics show a more Th2 type profile with increased expression of IL13, IL4, IL5, PTGDR2 and reduced FOXP3. Three days after intranasal infection with RV16 in both asthmatics and healthy individuals an antiviral response is induced in T regulatory cells, including upregulation of MX1, STAT1, IFI44L, IRF7/9, OAS3. In healthy individuals there is an additional upregulation of FOS and JUN, and the suppressor molecule SOCS3, while this was not altered or even down regulated in asthmatics. Furthermore, in healthy individuals CCL5 was downregulated, while unchanged in asthmatics. Tregs from healthy and asthmatic individuals show an anti-viral response after RV infection. However there are clear differences between healthy and asthmatic individuals, upon baseline and in response to rhinovirus infection. These differences in response might affect Treg functions, level of inflammation, chronicity and viral clearance. These data suggest that Treg functions might be altered or impaired during HRV infections, which may contribute to asthma exacerbations.