Keynote Lectures

Role of epithelial barrier in allergic diseases

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Immune system is a highly interactive networking, which makes its decisions on the basis of input from all tissues, infections, normal flora bacteria and many or even any environmental agents. General rules of immunity versus tolerance as well as co-evolutionary development applies to allergen-specific immune response, because rules for regulators and effectors has probably been developed in a co-evolutionary manner with helminths, mites, insect venoms, foods and other allergens. There are multiple proposed roles of tissues in immune regulation and chronicity in asthma, atopic dermatitis and chronic rhinosinusitis, such as continuous low level of tissue inflammation takes place during remissions, which increases during exacerbations; prevention of basal epithelial cell death from apoptosis (full epithelial recovery occurs, when submucosal inflammation is suppressed); apoptototic cell death of highly activated suprabasal epithelial cells is the mechanism of eczema/spongiosis and epithelial shedding; drainage of inflammation to mucosal lumen by opening of tight junctions; drainage of inflammation by lymphatic vessels; suppression of submucosal inflammation by various regulatory cell subsets, Treg cells, Breg cells, regulatory DC, regulatory NK cells etc.; continuous angiogenesis and remodeling of tissue cells; basement membrane (*Lamina reticularis*) tickening takes place in asthma to make a physical barrier between disease-inducing factors (allergens/ environment) and cells of the immune system; ILCs exist in mucosal surfaces and may play an essential role not only in immune effector processes, but also in regulation of tissue responses. Group 2 innate lymphoid cells (ILC2s) may play a role in asthma development independent of the adaptive immune system. Bronchial epithelial leakiness has been shown to be involved in asthma, however the role of ILC2 in the regulation of bronchial epithelial tight junctions (TJs) and barrier function was not known. Therefore, we sought to determine the role of ILC2s in bronchial epithelial TJ barrier. Co cultures of human ILC2s and air-liquid interface (ALI) cultures of primary bronchial epithelial cells were used to determine the measurement of transepithelial resistance (TER), paracellular flux, TJ mRNA and protein expressions and

cytokines. To analyze the in vivo relevance of barrier disruption by ILC2s, the effect of ILC2s on TJs was examined using a murine model of IL-33-induced airway inflammation in wt, Rag-$2^{-/-}$, Rag-$2^{-/-}\gamma c^{-/-}$, and RORα-deficient Staggerer (Ror$\alpha^{sg/sg}$) mice, which is specifically deficient for ILC2s. ILC2s significantly reduced the TER and increased FITC-dextran permeability in ALIs after co-cultures, suggesting the induction of epithelial leakiness. Consistently, ILC2s disrupted TJ proteins as well as decreased the expression of the mRNA of claudin-1, claudin-4, occludin and ZO-1. Neutralization of IL-13, but not IL-4 restored the impaired epithelial barrier function by ILC2s, suggesting that ILC2s induced human bronchial epithelial TJ barrier disruption through IL-13. The intranasal administration of recombinant IL-33 to wild-type and Rag-$2^{-/-}$ mice triggered TJ disruption in an ILC2- and IL-13-dependent manner as demonstrated by the analysis of cellular infiltration, broncho-alveolar lavage cell counts, lung mRNAs and confocal microscopy, whereas Rag-$2^{-/-}\gamma c^{-/-}$ and Ror$\alpha^{sg/sg}$ mice, which lack ILC2s did not recapitulate the response. These data demonstrate for the first time that ILC2s target bronchial epithelial TJ barrier as a novel mechanism in asthma pathogenesis. In conclusion, the balance between inflammation inducing factors, epithelial barrier, keep away factors, wash away factors and suppression factors plays a decisive role in the remission, exacerbation and chronicity of allergic inflammation, the same mchanisms seem to play roles in many different types of inflammations.