Symposium 1: Immunity and pathogenesis of AR and CRS

Dysregulated innate immunities in chronic rhinosinusitis

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Introduction

Chronic rhinosinusitis (CRS) is caused by dysregulated immunologic responses to external stimuli, which induce various inflammatory mediators from inflammatory cells including innate lymphoid cells (ILCs) and T lymphocyte as well as epithelial cells. TSLP, IL-25 and IL-33, which are mainly secreted in the epithelial cells in response to external stimuli, act on type 2 ILCs and Th2 cells, inducing IL-4, IL-5, and IL-13. These inflammatory mediators are novel potential therapeutic targets for recalcitrant CRS. This lecture reviews recent publications regarding innate cytokines and ILCs in CRS and nasal polyps.

Epithelial barrier function and epithelial cytokines

The epithelial barrier is the first line of defense; its breakdown can play a significant role in allowing external stimuli to enter nasal tissue and provoke immune responses.[1] Functional and mechanical defects have been reported in nasal polyps (NP). Protease activated receptor (PAR) contributes to the production of cytokines and chemokines from the epithelium in response to external stimuli such as bacteria, fungi, and allergens.[2,3] Epithelial barrier destroyed by protease activities enables allergens to pass physical epithelial barriers, culminating in allergen sensitization.[4] It also signals epithelial cells to secrete innate cytokines, then, facilitates the inducing of eosinophilic inflammation. Epithelial-derived innate cytokines such as IL-25, IL-33, and TSLP may also participate in the evolution of NP.[5] IL-33 is secreted by immune cells such as macrophages and dendritic cells as well as epithelial cells.[6] Full-length IL-33 is extracellularly released when

epithelial cells undergo necrosis and necroptosis via tissue damage caused by external stimuli. Biologically active full-length IL-33 plays a role in mucosal inflammation recruiting neutrophils via chemokines including CXCL-1 and CXCL-2.[7-9] Of interest, a splice variant of IL-33 missing exons 3 and 4, which localizes to the cytoplasm of epithelial cells, is actively released and strongly related to Th2 inflammation whereas full length is not.[10] Several studies sought to investigate the expression and role of IL-33 in CRS. There have been conflicting results on the expression of IL-33 in CRS. It was reported that IL-33 mRNA was highly expressed in nasal mucosa but was not elevated in NP or other inflamed areas of the sinuses in CRSwNP.[11-13] A significant upregulation of ST2 expression was demonstrated in ethmoid mucosa from CRSwNP but the concentration of IL-33 protein was not significantly different between nasal polyp and control tissue.[14] Authors recently demonstrated IL-33 was upregulated in other CRS tissues compared to eosinophilic NP and correlated with Th1/Th17 cytokines.[6] IL-33 may contribute to inducing different types of inflammation under various microenvironments.

IL-17E, also known as IL-25 is released by Th2 cells, mast cells, eosinophils as well as epithelial cells. It is produced? and stored in the cytoplasm of the epithelial cells as results of external stimuli such as protease, house dust mite, and allergen protease.[15] IL-25 transcript levels are reported to increase in CRS tissues including NP and correlated with disease severity and blood eosinophila,[13,16] whereas one earlier study reported that IL-25 and GATA-3 transcripts were decreased in NP versus control tissues.[12] Additionally, IL-17RB(+) polyp-derived Th2 cells were identified in NP, which co-expressed ST-2 and enhanced IL-5 and IL-13 production in response to IL-25 and IL-33.[17] Protein levels of IL-25 were up-regulated in non-eosinophilic NP as well as eosinophilic NP.[5, 18] Of note, the fact that IL-25, known as a cytokine involved in diverse Th2-mediated diseases, is also correlated with inflammatory mediators involved in Th1 and Th17 responses in Asian subjects suggests that it may play diverse roles in polypogenesis besides promoting Th2 inflammation.[16,19] Blockade of IL-25 reduced the burden of NP in a mouse model of NP and represented a potential novel therapeutic target.[19]

TSLP is well known to be induced in airway epithelial cells by viruses, TLR3 agonists, protease, and pro-inflammatory cytokines.[20-23] IL-1β and TNF-α regulate TSLP transcript expression in an NF-κB-dependent manner.[22] Several researchers demonstrated that TSLP mRNA was overexpressed in eosinophilic NP and associated with Th2 inflammation.[24-26] TSLP induces the differentiation of naïve T cells into effector Th2 cells via enhancement of OX40L-OX40 axis on the interaction between dendritic cells and CD4 T cells.[27] TSLP protein is post-translationally modified by endogenous protease. The cleaved TSLP shows higher activity, producing IL-5 when stimulated with IL-1β, than the full-length form.[24] Of interest, authors recently demonstrated that TSLP production was induced by periostin in epithelial cells under Th2 high inflammatory condition like eosinophilic NP.[28] Until now, TSLP has been consistently reported to have a pathological role in eosinophilic NP unlike IL-25 and IL-33.

Innate lymphoid cells

Epithelial-derived cytokines such as IL-25, IL-33, and TSLP exert effects on type 2 innate lymphoid cells (ILC2s).[29] Innate lymphoid cells (ILCs) are lymphocyte-like cells but lack markers of mature lymphocytes and do not express allergen-specific T cell receptors. ILC2s are regarded as innate counterparts of Th2 cells because both share the same functional module on the basis of their mutual production of signature cytokines such as IL-5 and IL-13.[30] For example, GATA-3 is a key transcription factor that has parallel roles in the development and function of both Th2 cells and ILC2s.[31] Moreover, STAT-6 is also an important factor for Th2 polarization and has a role in the post-developmental role in ILC2s, though it is not required for the development of ILC2s.[30] Interestingly, IL-33- and IL-25-activated ILC2s can induce eosinophilic airway inflammation accompanied by airway hyper-responsiveness even in recombination-activating gene (Rag) knockout mice, which means ILC2s function independent of acquired immunity.[32, 33] ILC2s are abundant and also have a close relationship with higher tissue and blood eosinophilia in NP, clinically related to worsening nasal symptom scores and asthma comorbidity.[34, 35] A recent study reported that there was spatial co-localization between ILC2s and eosinophils in NP. A co-culture of eosinophils and ILC2s augmented the activation of eosinophils and prolonged their survival, and in return, pre-activated eosinophils enhanced IL-5 production of ILC2s in an IL-4 dependent manner.[36] Of note, ILC2s have a functional plasticity responsive to environmental cues including viral infection. Mouse ILC2s in the lung undergo T-bet-mediated plasticity in response to infection including influenza virus, respiratory syncytial virus, Haemophilus influenza, and Staphylococcal aureus.[37] Human ILC2s can be converted into ILC1s by IL-12 and reversed by IL-4,[36] or into IFN-γ/IL-13 dual-producing ILC1s in response to both IL-1β and IL-12.[38] T cells that are able to produce both IFN-γ and IL-13 induce enhanced airway hyper-responsiveness compared to conventional Th2 cells.[39] Thus, ILC2 plasticity may contribute to disease heterogeneity which might lead to recalcitrancy and exacerbations of inflammatory diseases.

Conclusion

With the advent of an era with biologicals, endotyping helps to select patients suitable for each biological which can be a breakthrough in treating NP. Although targeting acquired immunity, for example T cell subsets, has made an active progress, targeting epithelial cell-derived innate cytokines such as TSLP, IL-33, and IL-25 may provide novel opportunities in managing allergic diseases including NP.

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