Special Lecture

Novel mechanisms of eosinophilic inflammation in severe asthma

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Bronchial asthma is a chronic disorder characterized by airway inflammation, reversible airway obstruction, and airway hyperresponsiveness. Eosinophils are believed to play important roles in the pathogenesis of asthma through the release of immune reactive mediators such as their specific granule proteins, cysteinyl leukotreines, radical oxygen species, and a variety of cytokines including TGF-beta, GM-CSF and IL-25. In severe diseases of eosinophilic asthma, anti-IL-5 mAb partly reduces exacerbations and use of oral corticosteroids, indicating roles of eosinophils and IL-5 in the development of this type of asthma.

For eosinophils to accumulate into the asthmatic airways, they have to adhere to and then migrate across the pulmonary microvasculature. Historically, it is well known that these processes are controlled by the Th2-immune pathways. Th2 cytokines IL-4 and IL-13, for example, upregulate the expression of endothelial adhesion protein VCAM-1, which is a selective and powerful adhesive ligand for circulating eosinophils, Additionally. IL-4 and IL-13 generate CC-chemokines from epithelial cells, airway smooth muscle cells and even airway fibroblasts. Activated Th2 cells also release IL-5 which enhances survival and functions of eosinophils. Fortunately, these actions by Th2-immune system are sensitive to corticosteroid treatment.

Recently, accumulating evidence has established that corticosteroid-resistant ILC2 (Group 2 innate lymphoid cells) are major cellular sources of IL-5 in the airways of severe asthma, suggesting that anti-IL-5 treatment exerts benefits mainly via blocking this specific cytokine providing from ILC2. Moreover, even in the absence of IL-5, it is noteworthy that alternative pathways can effectively maintain eosinophilic inflammation in asthma. Cysteinyl leukotrienes can directly provoke eosinophilic infiltration and activation in the airways of asthma. Recently, we found that periostin is able to induce adhesion and activation of effector functions of eosinophils. Surprisingly, even Th1-immune system-associted molecules such as IFNs and IP-10 can sufficiently induce eosinophils inflammation.

Finally, neutrophils activated by IL-8-induced transmigration or endotoxin can induce the transmigration of eosinophils. Therefore, various mechanisms are involved in the eosinophilic airway inflammation of severe asthma and hence development of therapeutic strategies against them will be desirable in the near future.