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Human basophils and their regulation during allergic inflammation

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Asthma is characterized by chronic inflammation of the respiratory tract. To stratify the disease into different entities, asthma endotypes based on different underlying mechanisms have been defined. In allergic asthma, one of the seven endotypes defined so far, Th2 cells and eosinophils have been regarded as driving cells. Recent mouse studies suggest that basophils act as effector and/or immunoregulatory cells that aggravate allergic asthma. However, it has not yet been conclusively elucidated whether human basophils play similar roles. To better understand the regulation of human basophils in allergic asthma, we study the potential of various factors to activate and inhibit human basophils, respectively. As basophil activators, we used members of the GM-CSF family (IL-3, IL-5, GM-CSF). Although all members rapidly activated human basophils, only IL-3 had the capacity to induce sustained responses. The IL-3-mediated sustained effect was concomitant with high and continued expression of IL-3Rα-chain and replenishment of cβ-chain. Interestingly, continuous IL-3 signaling was necessary to induce sustained cellular responses. In contrast, IL-5 and GM-CSF rapidly down-regulated their receptors. To inhibit basophils, we induced apoptosis by addition of IFN-γ, ligands of death-receptors (FasL, TRAIL) or BH3-mimetics, which inhibit anti-apoptotic proteins of the intrinsic pathway. We demonstrate that apoptosis was efficiently induced in resting basophils. In contrast, basophils that have been activated through addition of IL-3 or FcεRI cross-linking, efficiently resisted pro-apoptotic stimuli. We therefore suspect that an allergic environment causes an inefficient induction of apoptosis from human basophils, which can thus contribute to the maintenance of allergic airway inflammation.

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