

Role of basophils and histamine during the immune response

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Our laboratory has been involved in histamine research and histamine-cytokine interactions during the immune response ever since we discovered that bone marrow cells generate important amounts of this mediator in response to a cytokine, which we identified as IL-3. Phenotypical characterization of this cell subset, which represents around 0.1% of total bone marrow cells, led to the characterization of cells displaying ultrastructural features of immature basophils. Even though they did not express the Fc RI on their membrane at this stage of maturation, they could be purified on the basis of their low density, low granular content, lack of mature lineage markers and high rhodamine-123 retention. Using *in situ* hybridization, we established that IL-3 induced increased histidine decarboxylase, both on transcriptional and protein levels, among this sorted population, together with IL-4, and IL-6, a cytokine profile that is typical for the basophil lineage. More recently, we have set up an *in vitro* culture method, performed with total bone marrow cells, which give rise to a highly enriched basophil population that can be purified completely by electronic sorting of Fc RI⁺c-kit⁻ cells and conserve the same functional characteristics as freshly isolated bone marrow cells (Fig. 1).

Even though basophils have been discovered more than a hundred years ago, their specific physiological functions remain largely unknown. Up to now, they have been mostly associated with the detrimental effects accompanying allergic immune responses and it has only recently been proposed that basophils are probably the most important source of IL-4 at the onset of the immune response, thus orchestrating the development of a Th2 phenotype. It has also been shown that basophil activation does not necessarily depend on Ag-specific IgE cross-linking but can occur through parasitic, bacterial, endogenous or environmental antigens. This central position of basophils in the Th1/Th2 cytokine network is illustrated in Fig. 2. The comprehension of these interactions in experimental models like allergic asthma and parasite infection remains a major objective of our research.

To date, due to the scarcity of basophils, little is known about their negative regulation. We have shown in a murine model that the pro-Th1 cytokines IL-12 and IL-18 promote their Fas-dependent apoptosis through activated NK cells. More recently, we have provided evidence for the expression of a bidirectional transporter, identified as organic cation transporter-3 (OCT-3), in the basophil membrane, through which histamine can enter and exit the cell and downregulate its own synthesis and that of concomitantly produced IL-4, IL-6 and IL-13, once it has attained a critical intracellular concentration. We are presently investigating how the lack of this transport system in genetically engineered mice affects disease progression in a murine model of allergic asthma. We are also looking for a pharmacological means of blocking OCT-3 to increase intracellular levels of newly synthesized histamine in basophils. In turn, this would trigger the negative feedback signal and inhibit histamine and cytokine production, thus attenuating their deleterious effects during allergic responses (Fig. 3).

References

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Fig. 2 Pro-Th2, anti-Th1 activity of basophils



