Eosinophilia in Mast Cell Disease

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KEYWORDS

• Eosinophilia • Chronic eosinophilic leukemia (CEL) • Hypereosinophilic syndrome
• Systemic mastocytosis • Tryptase • FIP1L1-PDGFRA fusion • Imatinib

KEY POINTS

- The interplay between mast cells and eosinophils is complicated and those interactions are currently being studied.
- Certain clonal and nonclonal entities exist in which these 2 cell types are increased in tissues and other sites, and in which they play a role in pathogenesis.
- The specific type of clonal disorder is important to diagnose correctly, because treatment needs to be carefully tailored to the specific entity.

INTRODUCTION

Eosinophils and mast cells coexist in tissues in some benign conditions, and also in bone marrow biopsies of patients affected by clonal diseases. Some clonal and nonclonal disorders in which mast cells are affected are also associated with peripheral eosinophilia. These disorders include such varied presentations as allergic and asthmatic disorders, eosinophilic esophagitis (EoE), and both clonal and probably nonclonally expanded lines within the category of malignancies.

Discussed are the complex interplay of eosinophils and mast cells in these disorders. Also what is known about these disorders is described, a schematic in thinking about these disorders in one rubric is offered, and treatment options, which are usually tailored specifically to the patient presentation and underlying disorder, if it can be elucidated, are discussed.

MAST CELL AND EOSINOPHIL BIOLOGY

Mast Cells

Mast cells derive from the pluripotent precursor cell ($CD34^+$, $CD117^+$(Kit)). They develop and mature with the influence of stem cell factor (SCF) via Kit, the

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transmembrane tyrosine kinase receptor for SCF.[1] Many other cytokines, including interleukins (IL) IL-3, IL-4, IL-5, IL-6, IL-9, and IL-15, can potentiate the growth and maturation of mast cells.

Mast cells are a rich source of inflammatory mediators which include histamine, prostaglandin D_2, cysteinyl leukotrienes (LTC_4), platelet activating factor, IL-3, IL-5, IL-6, IL-16, and SCF. Mast cell products that likely provide some interaction with eosinophils include IL-5, which is a potent growth and survival factor, CCL5 (RANTES), which is a chemotactic molecule, chymase (eosinophil apoptosis suppressor), tumor necrosis factor (survival and chemotaxis), heparin (stabilize eotaxins), and Kit, which interacts with eosinophil-derived SCF to induce differentiation, proliferation, and activation of mast cells.[2]

Eosinophils

Eosinophils also derive from the pluripotent $CD34^+$ cell line. Granulocyte-macrophage colony-stimulating factor, IL-3, and IL-5 are all growth factors for eosinophils. IL-5 is the major cytokine that influences eosinophilopoiesis, as well as eliciting their activation and chemotaxis.[3] As discussed above, mast cells do produce both IL-3 and IL-5. Eosinophil mediators include many chemokines and cytokines. A notable feature of eosinophils as a source of cytokines is that they store these cytokines preformed within eosinophil granules and secretory vesicles. Some of these mediators that have potential for mast cell interactions include IL-3, IL-5, IL-6, IL-16, and LTC_4. More recently IL-9 was found to be produced by eosinophils in the context of mast cell interactions in EoE.[4] Platelet activating factor is a known chemoattractant for eosinophils. IL-16, prostaglandin D_2, and LTC_4 are produced by eosinophils and eosinophils express receptors for these agents, enhancing the interaction between mast cells and eosinophils.[5]

Therefore, in addition to interacting with each other, these 2 cells have the capacity to influence the tissue microenvironment, which self-promotes their own existence and attracts cells that help activate and stimulate them into the area (such as TH2 CD4+ T cells, macrophages).

The Mast Cell-Eosinophil Pair

One interesting concept regarding the interaction between them is the existence of the eosinophil and mast cell couplets or pairs, reported in papers from 2011 and 2013.[6,7] The research was mainly done on tissues with allergic inflammation, and the authors found several colocalized pairs of mast cells and eosinophils in human nasal polyps, asthmatic bronchi, as well as in mouse atopic dermatitis tissues. In vitro, they found that the 2 cells form stable conjugates and there is clear membrane contact established between them. Eosinophils were more viable when mast cells were present, dependent on soluble mediators and on physical cell contact (interestingly more so in the presence of SCF-enriched media than in granulocyte-macrophage colony-stimulating factor–enriched media). Mast cells were not as clearly affected or made more viable by eosinophil coculture. They were found to influence each other in a paracrine/physical pathway, using human and murine cells in vitro.[7] This concept is discussed later when discussing the role of anti-IL-5 in EoE.

NONCLONAL DISORDERS IN WHICH BOTH CELLS ARE PRESENT AND LIKELY DRIVE DISEASE PATHOGENESIS

Asthma and Allergic Rhinitis

In allergic disorders, mast cells degranulate in response to immunoglobulin E–mediated allergic stimulation. Mediators released locally recruit eosinophils to cause further damage. Previous work has shown that both cells are present in asthmatic airways