Clinical Commentary Review

Eosinophils: Friends or Foes?

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List of Design Committee Members: Michael J. Chusid, MD (author); Michael Schatz, MD, MS (editor)

Learning objectives:

1. To understand the physical, enzymatic, biochemical, and hormonal characteristcs that make the eosinophil a central player in normal and pathologic states.

2. To understand the positive roles the eosinophil plays in the immune defense network, as well as its possible regulatory role in inflammatory states.

3. To understand the harmful role the eosinophil may play in clinical eosinophilic conditions and how to potentially ameliorate such negative effects.

4. To recognize the new, non-immune roles being proposed for eosinophils in healthy individuals.

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The roles eosinophils are recognized to play in health and disease continue to evolve. Formerly, eosinophils were believed to fill a primary role in host defense against helminths, an intermediary one in the propagation of allergic conditions, and a pathologic one in clinical conditions characterized by systemic eosinophilia and eosinophilic infiltration of target organs. Eosinophils are increasingly understood to be positioned centrally within mammalian immune and inflammatory networks, possessing receptors for an array of inflammatory mediators and capable of producing numerous proinflammatory and homeostatic mediators. The concept has emerged that eosinophils play a major role in the modulation of allergic inflammation and in the repair of damaged tissues in diseases characterized by eosinophilic infiltration. Possible new emerging roles for eosinophils include neoplasm surveillance, tissue remodeling during puberty and pregnancy, and the restructuring of adipose tissue. The eosinophil granulocyte line appeared hundreds of millions of years ago during the evolutionary process and continues to be retained by all vertebrate species. This is strong evidence that although all the beneficial roles of eosinophils have yet to emerge, eosinophils, on balance, must be considered friends and not foes. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1439-44)

Key words: *Eosinophil; Eosinophilia; Eosinopenia; Hypereosinophilic syndrome; Helminth; IL-5*

INTRODUCTION

First described as a distinct cellular element almost 150 years ago, the nature and function of the human eosinophil and its role in human health and disease remain murky today. Are eosinophils aggressive effector cells in the immune system, whose primary role is to protect the host against invasion and disease produced by metazoan parasitic invaders, or are they dangerous

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Abbreviations used
ECP- eosinophil cationic protein
EDN- eosinophil-derived neurotoxin
EPO- eosinophil peroxidase
MBP-1/MBP-2- major basic protein 1/2
MPO- myeloperoxidase
PMNL- polymorphonuclear leukocyte

remnants from an earlier evolutionary era, and rogue inducers of collateral damage in bystander tissues? Does their presence fulfill other roles required for the optimal health and function of their hosts? Are eosinophils friends, enemies, or something in between?

There has been an explosion of interest in eosinophilic granulocytes over the last 4 decades. Before that, eosinophils were viewed as niche defenders in the immune system, focused on multicellular parasitic invaders, primarily intestinal helminths.[1,2] Eosinophils were recognized as possessing a fearsome collection of toxic substances required for their apparent major role. These agents seemed to play an important part in the tissue damage noted in various clinical conditions characterized by eosinophilia and aggregations of eosinophils within targeted tissues. The presence of eosinophils and their participation in various allergic and immune-mediated conditions further suggested an important role for eosinophils in the propagation and potentiation of allergic-type processes within the host.[3]

Recently, a more nuanced understanding of eosinophils and their critical role in maintaining immune regulatory and modulatory systems has emerged. Careful investigation of seemingly well-established and newly recognized roles of the eosinophil has turned conventional wisdom on its head. In animal models, the presence of eosinophils has been associated with prolonged parasite survival rather than their death. In other studies, instead of increasing severity of allergic and hypersensitivity reactions, eosinophils seem to play a role in downregulating local inflammation, and not in increasing it.

Instead of uncontrolled, noxious effector cells filled with the intracellular equivalent of a bag of hand grenades primed for indiscriminate release within vulnerable tissues, eosinophils are now recognized as critical components in a complex regulatory network, modulating local and systemic immune and inflammatory responses in concert with other elements of the immune system, including polymorphonuclear leukocytes (PMNLs), lymphocytes, and macrophages.[4-6] This concept was comprehensively outlined in the "LIAR hypothesis" by Lee et al,[7] suggesting that eosinophils were responsible for Local Immunity And/or Remodeling/Repair in both health and disease.

PHYSIOLOGY, ANATOMY, AND FUNCTION

Eosinophils are found circulating in the blood of all vertebrates, including reptiles, amphibians, mammals, and fish.[6] In mammals, they comprise 1% to 3% of circulating leukocytes. The eosinophilic granulocytic line differentiates from a pluripotent eosinophil/basophil precursor. The cytokines IL-3, GM-CSF, and especially eosinophil granulocyte-stimulating factor, now known as IL-5, are critical for the stimulation, differentiation, and maturation of the eosinophilic line of granulocytes in the marrow.[8] Once eosinophils reach maturity, primarily IL-5 controls eosinophil egress in the circulation. Migration into tissues is controlled by various cytokines, some specific for eosinophils (eotaxin).[9] Eosinophils are normally found in significant numbers in the bone marrow, the thymus, the alimentary tract exclusive of esophagus, the uterus, and the mammary gland tissues of healthy individuals.[10]

Eosinophils possess amoebic motility that can be directed toward appropriate soluble stimuli. Normally, eosinophils contain about 200 large eosinophilic-straining specific cytoplasmic granules whose contents can be released into the local environment when the cell is activated.[10,11] These granules contain an array of toxic substances unique to the eosinophil, including major basic proteins 1 and 2 (MBP-1 and -2), eosinophil peroxidase (EPO), eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN). Eosinophil granules are crystalloid in structure, consisting of a core composed exclusively of MBP-1, with a surrounding matrix composed of ECP, EDN, and EPO.[11]

It is the release of these unique and toxic substances that has been thought to account for both the antimetazoan activity of eosinophils and their presumed pathologic effect in clinical eosinophilic conditions associated with eosinophil ingress, activation, and degranulation within target tissues. MBP has been demonstrated to be highly toxic to helminths *in vitro* as well as to host tissues. EPO plays a catalytic role in eosinophils similar to that of myeloperoxidase (MPO) in PMNLs. The respiratory burst of both types of phagocytic cells results in the evolution of various oxygen species, including superoxide, singlet oxygen, and hydrogen peroxide. Both EPO and MPO catalyze the production of highly toxic hypohalous acids from evolving hydrogen peroxide and available halide substrates. Hypochlorous acid is the primary antimicrobial agent produced through this process by PMNL MPO. In contrast, hypobromous acid is the major antimicrobial product of eosinophils and their EPO.[12-14] These agents produce nonspecific oxidative stress, with resultant microbial cellular toxicity and apoptosis. They are also capable of inducing collateral oxidative damage to host tissues. ECP, a small basic protein, possesses helminthotoxic, cytotoxic, and ribonuclease activity. EDN, the fourth eosinophil granular enzyme, is a ribonuclease with significant antiviral activity and is also known to induce severe neurotoxicity after injection into the mammalian brain.[2,10]

Eosinophils are an integral component of the innate immune system. They are phagocytic cells capable of chemotaxis, phagocytosis, and antibacterial and antifungal killing rates similar to monocytes and PMNLs.[2,10] Eosinophils even possess antiviral capabilities.[15,16] In addition, they are uniquely capable of killing multicellular parasites, particularly those attempting migration beyond the alimentary canal. Eosinophils possess various surface receptors, allowing detection of infectious agents by nonspecific pathogen-associated molecular pattern receptors and injured cells through damage-associated molecular pattern receptors.[17]

Eosinophils release DNA traps that possess antibacterial activity. Eosinophil traps contain ECP and MBP, but their release does not result in cellular death as occurs with PMNL trap release.[18] Activated eosinophils also have the capacity to secrete various proinflammatory cytokines including IL-5, eotaxins, and GM-CSF. These can serve to potentially perpetuate or amplify an eosinophil-rich inflammatory reaction, increasing local damage related to eosinophil enzyme release[19-21] (Table I).

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