Eosinophil-Related Disease and the Skin

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Eosinophils are bone marrow-derived cells that infiltrate skin and mucous membrane in a broad spectrum of primary and reactive inflammatory diseases and malignancies. The eosinophil has potent proinflammatory activities, particularly, through the effects of its toxic granule proteins. In addition, eosinophils have prothrombotic and profibrotic activities. Eosinophil participation in the pathogenesis of certain diseases without identifiable intact eosinophil infiltration may not be recognized because eosinophil degranulation is poorly visualized on hematoxylin-and-eosin–stained histopathology sections. Eosinophil-related pathophysiology can involve virtually every component of skin. Commonly recognized dermatoses associated with eosinophils are arthropod bite and sting reactions and drug eruptions, "bugs and drugs." Skin involvement is common in eosinophil-related systemic diseases including the hypereosinophilic syndromes. Eosinophil-related pathophysiology may play a key role in numerous disorders that, therefore, may benefit from therapies targeted to reduce or eliminate eosinophils. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1462-82)

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BACKGROUND

Historical notes

Paul Ehrlich was a histology prodigy who lived during a time when the field of chemistry was blossoming in Europe. Ehrlich extended his understanding of the chemistry of dyes used for staining organic fabrics to develop techniques for staining cells and tissues, recognizing that he could distinguish cells by their variable tinctorial properties. In 1879, he designated the "eosinophil" as the cell that demonstrated intense staining of its cytoplasmic granules with the acidic dye, eosin. Ehrlich also described how to recognize the neutrophil, basophil, mast cell, and lymphocyte, and how to quantitate cells in blood. He further identified increased eosinophils in urticaria, with medication exposure, and in "pemphigus" (probably the disease we now know as pemphigoid, which was not clinically distinguished from pemphigus until more than half a century later). He documented various other disorders associated with peripheral blood eosinophilia including asthma, helminthiasis, and malignant tumors. He prophetically surmised that the bone marrow was the site of eosinophil development, and that "the phenomenon of eosinophilia is dependent on the circulation of a substance which has a chemotactic action on eosinophils, and which serves to release preformed eosinophils from the bone marrow into the blood."[1]

Homeostasis and roles in immunity

Eosinophils are formed in the bone marrow and circulate as mature cells in blood. Other than gastrointestinal tract distal to the esophagus and lymphoid tissues (including spleen, thymus, and lymph nodes), eosinophils are not normally found in human organs and tissues, including skin.[2] Eosinophil infiltration, however, characterizes a number of pathological states, especially parasitic infections and allergic reactivity. Cytokines, including IL-5 and eotaxins (eotaxin-1 or C-C motif ligand 11 [CCL11], eotaxin-2 or CCL24, and eotaxin-3 or CCL26), are known to mediate eosinophil development and participation in inflammation. However, why eosinophils are found normally in certain uninflamed tissues and what the mechanism for basal eosinophil regulation is, including circadian cycling of peripheral blood eosinophils, have remained unexplained until recently with the identification of innate lymphoid cells (ILCs). Long-lived type 2 ILCs, also known as ILC2s, now designated as part of the "T_H2 franchise,"[3] are resident in peripheral tissues and regulate tissue eosinophil accumulation and basal eosinophilopoiesis through homeostatic and stimulated cytokine expression.[4-6] ILC2s secrete IL-5 constitutively and are induced to coexpress IL-13 during type 2 inflammation, resulting in localized eotaxin production and eosinophil accumulation. Studies regarding interactions of skin ILCs with other cell types reveal that dermal ILCs interact selectively and strongly with mast cells.[6,7] An emerging understanding of ILC2s with accompanying eosinophil activities in atopic dermatitis[5] and allergic respiratory disease[8] helps explain associated tissue remodeling and fibrosis.[9] Interactions of eosinophils with nerves may partly explain pruritus, *vide infra*,[10,11] and other neurophysiological aberrations in eosinophil-infiltrated tissues. Epithelial and endothelial expression, considered structural cell factors as compared with immunologic cell (lymphocyte) factors, and interactions also likely influence eosinophils in homeostasis.[12,13] Eosinophilic spongiosis is a common presentation in areolar inflammation of female breast compared with other skin,[14] potentially related to differential innate immunologic expression.

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Abbreviations used
ALHE- Angiolymphoid hyperplasia with eosinophilia
CCL- C-C motif ligand
CCR3- C-C chemokine receptor type 3
DRESS- Drug reaction with eosinophilia and systemic symptoms
ECP- Eosinophil cationic protein
EDN- Eosinophil-derived neurotoxin
EGPA- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
eMBP1- Eosinophil major basic protein 1
EMS- Eosinophilia myalgia syndrome
EPO- Eosinophil peroxidase
GM-CSF- Granulocyte-macrophage colony-stimulating factor
H&E- Hematoxylin and eosin
HES- Hypereosinophilic syndromes
IgG4-RD- IgG4-related disease
ILC- Innate lymphoid cell
ILC2- Type 2 ILC
MMP-9- Matrix metalloproteinase-9
PAF- Platelet activating factor
RANTES- Regulated on activation, normal T cell expressed and secreted
TLR- Toll-like receptor
TOS- Toxic oil syndrome

Eosinophils demonstrate other roles in immune responses. As a granulocyte, the eosinophil is capable of phagocytosing and killing bacteria and other small microbes *in vitro*, although eosinophils cannot effectively defend against bacterial infections when neutrophil function is deficient. Nevertheless, eosinophils may have a role in innate immunity against bacteria using a unique DNA trap mechanism, which may be an important response, particularly in mucosal epithelium. Eosinophils rapidly release mitochondrial DNA when exposed to bacteria, complement component C5a, or C-C chemokine receptor type 3 (CCR3) ligands.[15] The traps contain granule proteins, eosinophil cationic protein (ECP), and eosinophil major basic protein 1 (eMBP1). In the extracellular space, the granule proteins and mitochondrial DNA form structures that bind and kill bacteria both *in vitro* and *in vivo*. Eosinophils, unlike neutrophils, do not undergo cell death during this process. Interestingly, eosinophil extracellular traps are found in a number of inflammatory skin diseases, particularly Wells syndrome, *vide infra*, and in cutaneous infections.[16]

Through major histocompatibility complex class II expression and IL-1α production, eosinophils may function as antigen presenting cells for various viral, parasitic, and microbial antigens, including staphylococcal superantigens, and allergens.[17] Activation of eosinophils via toll-like receptor 7 (TLR7) and TLR9 affects several eosinophil functions; the overall response is influenced by a T_H2-like cytokine milieu.[18] Isolated eosinophil granules, often observed in biopsy specimens from skin lesions, express extracellular domains for IFN-γ receptor and CCR3 and, on stimulation, respond independently as organelles by releasing ECP.[19] The functional diversity of eosinophils in both innate and acquired immunity has abundant ramifications in homeostasis and disease pathogenesis.

PATHOPHYSIOLOGY

Activities and effects of eosinophils

The pathology in eosinophil-related cutaneous disorders, including inflammatory and neoplastic dermatoses, is impacted by eosinophil activity in tissues and blood. Eosinophils express a myriad of cell surface receptors and elaborate numerous biologically active factors that guide their roles in homeostasis and disease. Directly and indirectly, eosinophils influence and are influenced by other cells. Eosinophils elaborate potent toxins that kill cells and damage tissues. Many publications review these activities and the studies on which they are based.[20-28]

Eosinophils circulate transiently in blood (8-18 hours) and are constantly replenished to maintain a stable pool. Eosinophil infiltration in tissues is determined by a unique combination of factors relevant to adhesion, migration, and homing. Blood vessels are regulated by cytokines, chemokines, and other biologically active factors to express ligands with which eosinophils interact, and proinflammatory peptides and cytokines, including IL-1, commonly induce cell surface receptor expression on both eosinophils and endothelial cells that prompts eosinophils to tissue sites. Epithelial-derived cytokines, particularly IL-33, may influence inflammatory mechanisms by activating ILC2s, inducing the development of T_H2 cells and activating other cells with high receptor levels, including mast cells, basophils, and eosinophils.[13] IL-33 also may be a product of structural cells such as endothelial cells and fibroblasts as well as dendritic cell, mast cells, and monocytes.[13]

Eosinophils are recruited to and activated in tissues by cytokines from the T_H2 subset of T cells, which produces IL-4, IL-5, IL-10, and IL-13, as well as by cytokines that also are produced by T_H1 cells, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-3. Members of the C-C chemokine gene superfamily are chemotactic for eosinophils and include the eotaxin family, eotaxins 1, 2, and 3 (CCL11, CCL24, CCL26), and regulated on activation, normal T cell expressed and secreted (RANTES) (CCL5), which signal primarily through CCR3. Eotaxins 1, 2, and 3 are chemotactic specifically for eosinophils, while RANTES also is chemotactic for monocytes, T lymphocytes, natural killer cells, and basophils (but not neutrophils). In addition to chemotactic properties, the eotaxins and RANTES induce production of reactive oxygen species by eosinophils, indicating that they have both chemotactic and functional activation effects. As eosinophil chemoattractants, eotaxins are stronger than RANTES, and eotaxins 1 and 2 also have greater ability to induce reactive oxygen species by eosinophils than do eotaxin 3 and RANTES. Eotaxins 1, 2, and 3 and RANTES are produced by dermal fibroblasts, and RANTES also is produced by keratinocytes, well positioning these mediators for participation in cutaneous inflammation.

After movement across vessels, eosinophils are present in the extracellular matrix, where cell surface integrins recognize as receptors substances that exert effects on eosinophil activity, such as fibrous proteins (in particular, fibronectin, laminin, and collagen) and glycosaminoglycans (especially hyaluronic acid and chondroitin sulfate). Integrin expression, specifically CD11b/CD18 (MAC-1), is critical for eosinophil effector functions, including degranulation. Mast cell—derived cytokines contribute to eosinophil activation and vice versa with bidirectional interactions.[29] Human natural killer cells, which respond to some of the same chemokines as eosinophils, also produce IL-5.