Functional Role of Eosinophils in Gastrointestinal Inflammation

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KEYWORDS

• Eosinophil • Esophagitis • Eosinophilic gastroenteritis
• Inflammatory bowel disease

Eosinophil accumulation in the gastrointestinal (GI) tract is a common feature of numerous GI disorders including classic immunoglobulin (Ig)E-mediated food allergy,[6] eosinophilic gastroenteritis (EGE),[7] allergic colitis,[8] eosinophilic esophagitis (EE),[9,10] inflammatory bowel disease (IBD),[11] and gastroesophageal reflux disease.[12,13] The function of eosinophils in GI inflammation remains an enigma. Eosinophils can potentially initiate GI antigen-specific immune responses by acting as antigen-presenting cells (**Fig. 1**). Eosinophils express major histocompatibility complex class II molecules and relevant costimulatory molecules (CD40, CD28, CD86, B7.1, and B7.2) and secrete an array of cytokines (interleukin [IL]-2, IL-4, IL-12, and IL-10) capable of promoting lymphocyte proliferation, activation, and helper T cell type 1 or type 2 polarization. In addition, eosinophils can have proinflammatory effects including the up-regulation of GI adhesion systems and the modulation of leukocyte trafficking, tissue remodeling, and cellular activation states by releasing cytokines (IL-2, IL-4, IL-5, IL-10, IL-12, IL-13, IL-16, IL-18, and transforming growth factor [TGF]-β), chemokines (RANTES [regulated on activation normal T-cell expressed and secreted] and eotaxin), and lipid mediators (platelet activating factor and leukotriene C4) (see **Fig. 1**). Finally, eosinophils can serve as major effector cells, inducing tissue damage and dysfunction by releasing toxic granule proteins (major basic protein [MBP], eosinophilic cationic protein [ECP], eosinophil peroxidase [EPO], and eosinophil-derived neurotoxin [EDN]) and lipid mediators.[14] Consistent with multifunctional capabilities, there is accumulating evidence in various eosinophilic GI disorders (EGIDs) that eosinophils may have a dual function (ie, end-stage effector and immunoregulatory).[1,14–18]

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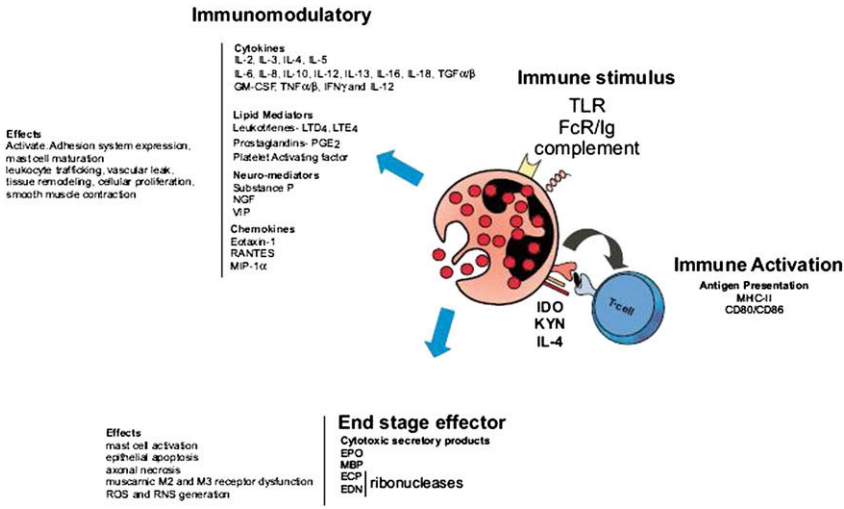

Fig. 1. Eosinophil function in GI inflammation. Eosinophils are bilobed granulocytes with eosinophilic staining of secondary granules. The secondary granules contain four primary cationic proteins: eosinophil peroxidase (EPO), major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN). All four proteins are cytotoxic molecules; in addition, ECP and EDN are ribonucleases. Eosinophils can be activated by immune stimulus by way of toll-like receptor (TLR), immunoglobulin, and complement. In addition to releasing their preformed cationic proteins, eosinophils can also release a variety of cytokines, chemokines, lipid mediators, and neuromodulators. Eosinophils activate T cells by serving as antigen-presenting cells. Eosinophils can also regulate T-cell polarization through synthesis of indoleamine 2,3-dioxygenase (IDO), an enzyme involved in oxidative metabolism of tryptophan, catalyzing the conversion of tryptophan to kynurenines (KYN), a regulator of T helper cell type 1 and 2 balance. Eosinophils generate an array of cytokines, chemokines, lipid mediators, and neuromodulators that regulate leukocyte trafficking, activation, and maturation; adhesion system expression; collagen synthesis; cellular proliferation; and mucus cell hypersecretion. Eosinophils can also act as an end-stage effector cell, secreting cationic proteins that can regulate mast cell function and generate reactive oxygen species (ROS), reactive nitrogen species (RNS), epithelial cell injury, and muscarnic receptor (M2 and M3) dysfunction. FcR, Fc receptor; GM-CSF, granulocyte-macrophage colony–stimulating factor; IFN, interferon; IL, interleukin; LT, leukotriene; MHC, major histocompatibility complex; MIP, macrophage inflammatory protein; PG, prostaglandin; RANTES, regulated on activation normal T-cell expressed and secreted; TGF, transforming growth factor; TNF, tumor necrosis factor; VIP, vasoactive intestinal peptide. (*Adapted from* Rothenberg ME, Hogan SP. The eosinophil. Annu Rev Immunol 2006;24:149; with permission.)

EOSINOPHIL-DERIVED CYTOKINES

Eosinophils can synthesize and secrete at least 35 important inflammatory and regulatory cytokines, chemokines, and growth factors. Those eosinophil-derived cytokines that have been quantified generally appear to be generated in relatively small amounts, suggesting an autocrine, paracrine, or juxtacrine role in regulating the function of the microenvironment. In some circumstances, however, eosinophils are the chief producers of cytokines such as TGF-β, which is linked with tissue remodeling in a variety of eosinophil-associated diseases such as asthma.[19] Eosinophils store their cytokines intracellularly as preformed mediators in crystalloid granules and small secretory vesicles.[20] This allows the immediate release of these mediators