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Review

The role of the complement anaphylatoxins in the recruitment of eosinophils

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Abstract

Eosinophils are blood and tissue immune cells that participate in a diverse range of activities normally beneficial for the host defense, but in circumstances of untoward inflammatory conditions these cells can be responsible for pathological responses. Accordingly the transit of eosinophils from the blood to tissues is a subject of considerable importance in immunology. In this article we review how the complement anaphylatoxins, C3a and C5a bring about eosinophil extravasation. These mediators do not merely provide a chemotactic or haptotactic gradient but are responsible for orchestrating innumerable responses by other cells types, including of endothelial cells, mast cells, and basophils in order to create an environment that is conducive for eosinophil infiltration. C5a has the capacity to prime the endothelium directly to present P-selectin, and C5a stimulated generation of eosinophil hydrogen peroxide and other oxidants can cause additional upregulation of endothelial P-selectin and ICAM-1. Moreover, the anaphylatoxins have the ability to recruit mast cells and basophils and can stimulate these cells to release IL-4 and IL-13, which by augmenting endothelial VCAM-1, convey some selectivity for eosinophils. The anaphylatoxins also have the capability to evoke the release and activation of eosinophil MMP-9, which is employed by this cell type to digest its way past the subendothelial matrix. Finally, because C3a and C5a can stimulate the generation of nitric oxide along with the secretion of histamine and LTC4 from several cell types, the anaphylatoxins can bring about an increase in vascular permeability that facilitates eosinophil accumulation at sites of allergic inflammation.

Keywords: Eosinophils; Complement; Anaphylatoxins; C3a; C5a

Abbreviations: CCP modules, Complement Control Protein modules; CR1, Complement Receptor 1; ECM, Extracellular Matrix; ECP, Eosinophil Cationic Protein; EDN, Eosinophil Derived Neurotoxin; EPO, Eosinophil Peroxidase; GlyCAM-1, Glycosylation dependent Cell Adhesion Molecule-1; GM-CSF, Granulocyte Macrophage Colony Stimulating Factor; ICAM, Intracellular Adhesion Molecule; iNOS, inducible Nitric Oxide Synthase; LFA, Leukocyte Function associated Antigen; LPS, Lipopolysaccharide; mAb, monoclonal Antibody; MMP, Matrix degrading MetalloProtease; PAF, Platelet Activating Factor; PDGF, Platelet Derived Growth Factor; PSGL-1, P-Selectin Glycoprotein Ligand-1; MAdCAM-1, Mucosal Address in Cell Adhesion Molecule-1; MBP, Major Basic Protein; MCP, Monocyte Chemotactic Protein; NGF, Nerve Growth Factor; PECAM, Platelet Endothelial Cell Adhesion Molecule; RANTES, Regulated upon Activation of Normal T-cell Expressed and Secreted; TGF, Transforming Growth Factor; TNF, Tumor Necrosis Factor; VLA, Very Late Antigen; VCAM, Vascular Cell Adhesion Molecule.

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Contents

1. Introduction

The eosinophil is a differentiated non-dividing immune cell that has its origin in the bone marrow. Eosinophils mature from multipotent hematopoietic cells of a myeloid lineage by a process dependent on IL-3, IL-5, and GM-CSF [1]. The normal range of eosinophil numbers in human peripheral blood is between 150 and 300 cells per microliter, but these values can increase several fold during conditions of allergy or parasitic infection. The content of eosinophils in blood represents a small fraction of these cells in the body as large pools of eosinophils are found in the bone marrow and at mucosal sites of the gastrointestinal (especially the lamina propria), respiratory, and reproductive tracts [2–5], as well as in developing breast tissue [6]. Thus the eosinophil is correctly viewed as a tissue cell, which is found in the blood as it transits from the bone marrow to mucosal sites. Review articles dealing with the biology of eosinophils have been published recently [7–9].

When viewed by electron microscopy (Fig. 1), the eosinophil is seen as a granulated cell of 8–10 μm in diameter with a bilobal nucleus containing condensed marginated chromatin. Ribosomes and mitochondria are scarce, and most thin sections fail to show a clear exhibition of rough endoplasmic reticulum or Golgi. A trilamellar membrane encloses the densely staining secondary granules, which are an impressive characteristic of the eosinophil, and this cell also contains primary granules, lipid bodies, and a variety of small vesicles [10]. The core of the secondary granules consists predominantly of crystalloid major basic protein (MBP), while the matrices are enriched with eosinophil cationic protein (ECP) (EC 3.1.27.–), eosinophil derived neurotoxin (EDN) (EC 3.1.27.5), and eosinophil peroxidase (EPO) (EC 1.11.1.7) [10].

MBP, ECP, EDN, and EPO are all basic proteins. MBP is an arginine rich polypeptide of 117 amino acids having a folding design similar to that of a C-type lectin [11]. ECP and EDN are both toxic ribonucleases [12,13],

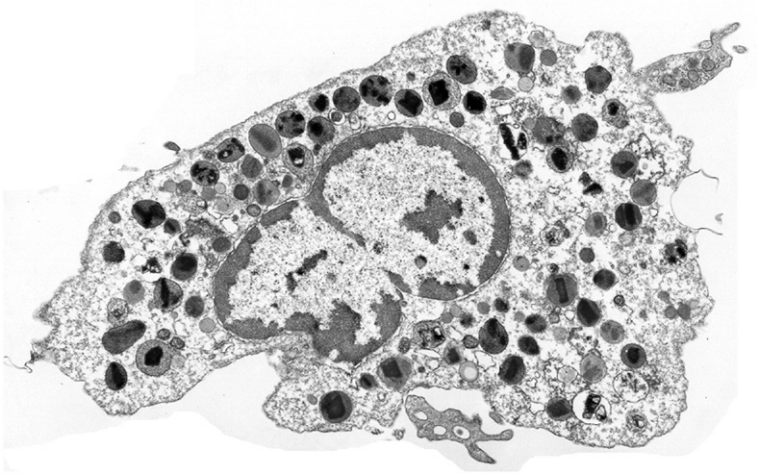

Fig. 1. Transmission electron microscopy of an eosinophil. The cell is about 10 μm long and contains a bilobal nucleus. Characteristic densely staining secondary granules contain crystalline cores of MBP.