“MECHANISMS OF HUMAN EOSINOPHIL CYTOKINE SECRETION”

Professor Peter F. Weller
Professor of Medicine
Harvard Medical School, Boston, MA

Chief, Allergy and Inflammation Division
Vice Chair for Research
Chief, Infectious Disease Division
Department of Medicine,
Beth Israel Deaconess Medical Center

Professor Weller’s research studies, supported principally by longstanding NIH RO1 grants, have focused on delineating basic mechanisms of leukocyte functioning in forms of inflammation. The two principal areas of investigation are: 1) the immunobiology of eosinophilic leukocytes and 2) the intracellular regulation and compartmentalization of inducible mediators of inflammation in neutrophils and other leukocytes. These investigations are pertinent to the roles of eosinophils in allergic and anti-parasite immune responses and to the cellular biology of leukocytes underlying their functions in infectious and immune inflammatory responses. Specific studies include studies of roles of eosinophils as airways antigen-presenting cells pertinent to allergic inflammation.

Abstract

Human eosinophils contain within their cytoplasmic granules and secretory vesicles distinct cationic proteins, (ECP, MBP) and multiple other preformed proteins, including diverse cytokines. Mechanisms governing secretion of granule-derived proteins underlie the biologic activities and functions of eosinophils. Compound exocytosis, whereby the entire granule contents are released extracellularly following fusion of granules with the plasma membrane, may occur when eosinophils interact with large targets, such as helminthic parasites, but otherwise is neither commonly observed in vivo nor parsimonious in providing a means to selectively secrete granule-derived cytokines or other proteins. Instead, secretion of granule contents from within eosinophils occurs by piecemeal degranulation (PMD). Electron microscopically documented alterations in granule morphology within eosinophils in tissue sites demonstrate that PMD occurs in vivo. Within granules, there is an extensive network of membranotubular structures. From this network, granule contents can be selectively mobilized into vesicles, both small round vesicles and longer curved tubular structures, that transport proteins for secretion at the plasma membrane. Some proteins, such as MBP, are transported in the fluid phase of vesicles whereas others, as recognized for the cytokine, IL-4, are transported bound to their cognate membrane-inserted receptor. PMD enables differential mobilization and selective secretion of specific eosinophil granule-derived cytokines and proteins in response to varied stimuli. Another mechanism by which granule-derived proteins may be specifically secreted is based on responses of extracellular eosinophil granules. Intact, membrane-bound granules extruded from eosinophils have been recognized in diverse disorders (e.g., asthma, dermatitis). We demonstrated that cell-free eosinophil granules can function as independent secretory organelles capable of responding a cytokine (IFN-gamma), a chemokine (eotaxin-1), and cysteinyl leukotrienes via cognate membrane-expressed receptors, topologically oriented with ligand-binding domains displayed externally on granule membranes. Granule membrane-expressed receptors, coupled to intragranular signaling cascades, stimulate selective, agonist-elicted secretion of ECP and cytokines from within eosinophil granules.