The Role of Eosinophils in Angiostrongyliasis: Multiple Roles for a Versatile Cell?

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Abstract

Human infection with the rat lungworm, Angiostrongylus cantonensis*, is characterized by a vigorous eosinophil response that gives the disease its name, eosinophilic meningitis. The actual role eosinophils play, both protective and destructive, in this infectious process is still largely a mystery. Research since 2002 has indicated that eosinophils are a multifaceted granulocyte that contributes to a wide range of physiological and pathological processes depending on their location and activation status. This article suggests an expanded role for eosinophils as both classic antiparasitic effector cells and as immune regulatory cells in eosinophilic meningitis caused by* Angiostronglyus cantonensis.

Keywords

Angiostrongylus cantonensis*, Cerebrospinal fluid, Eosinophilia, Food, Immunology, Meningitis, Parasitology*

Background

Dr Paul Ehrlich, using a newly discovered dye, eosin, discovered eosinophils in the blood of humans and other animals in 1879. The cells were named eosinophilic granulocytes because of their reddish orange staining properties.[1] Eosin binds highly basic proteins that constitute the granules of these cells. These granules can be classified into four different populations: crystalloid granules, primary granules, small granules, and secretory vesicles. The largest are the crystalloid granules that store the majority of granule proteins in eosinophils. These granules contain an array of cationic proteins, designated major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), and eosinophil-derived neurotoxin (EDN), and are arranged as a crystalloid core consisting of MBP-1 (and MBP-2) and a matrix of the ECP, EDN, and EPO proteins. Differential release of these proteins is mediated by directed exocytosis and degranulation.[2,3]

Search Strategy and Selection Criteria

For this short review, PubMed was searched for reports published in English between May 2002 and May 2012 with the search terms "eosinophil," "eosinophilic meningitis," and "*Angiostronglyus cantonensis*." Although publications from the past ten years were mainly selected, commonly referenced and highly regarded previous publications were not excluded. Reference lists of articles identified by this search strategy were also searched and relevant reports selected.

Function

Most eosinophils in the human body are distributed in the mucosal tissues and the classical view of eosinophil function is that they are terminally differentiated granulocytes primarily involved with either the destruction of helminthic pathogens, such as intestinal and tissue nematodes and schistosomes, or associated with the disease process of allergic diseases, such as asthma.[3] Since 2002 this narrow view of eosinophil function has given way to a broader concept of the role eosinophils play in the maintenance of immune homeostasis, in part because of the production of a wide range of diverse proinflammatory and regulatory cytokines and chemokines and functions such as antigen presentation.[4,5] This evolving role for eosinophils in the host immune response has these cells capable of both an effector function as well as participating in tissue repair and immunoregulation.[6]

Disease Process

Human disease with the rat lungworm, *Angiostrongylus cantonensis*, is associated with three main clinical entities, meningitis, encephalitis, and ocular involvement because of the presence of the organisms in these tissues.[7-9] The initial infectious process begins with ingestion of infective third stage larvae (L3) that penetrate the gut lumen. This allows the parasites to enter the circulatory system where they eventually gain access to the central nervous system (CNS).[9] The presence of the parasites in the CNS results in a clinical syndrome characterized by eosinophils in the cerebrospinal fluid (CSF).[10] While there are a number of different etiologies for eosinophilic meningitis, the most common infectious cause is *A. cantonensis*.[11] The predominant clinical feature of eosinophilic meningitis due to *A. cantonensis* is headache followed by development of a variety of meningeal signs and symptoms that include neck pain/stiffness, fever, nausea, and vomiting.[12,13] Imaging studies, such as magnetic resonance imaging (MRI), of patients with eosinophilic meningitis have demonstrated abnormalities in many but not all patients. These abnormalities, while not pathognomonic for this infection, tended to present as single or multiple enhancing lesions of the leptomeninges and parenchyma of the brain.[14,15] These changes have been attributed to the migration of the parasite, inflammation, or granuloma formation from dead or dying worms.[12,13,15,16]

Eosinophilic meningitis is generally a self-limiting disease[12] with mortality rates reported to be less than 1%[11,17] so necropsy studies of human angiostrongyliasis are limited. Published autopsy and subsequent pathologic studies of fatal cases generally show the following features: (1) meningeal infiltration by eosinophils, macrophages, and lymphocytes, (2) distinct tracks within the brain parenchyma associated with cell debris, (3) microthrombi and inflammatory cells that are assumed to be due to the migration of the parasite, and (4) the presence of classic granulomatas surrounding dead worms. Histologically a large numbers of eosinophils have been associated with meningeal infiltration and the granuloma formation but perhaps surpris-

ingly not in close association with viable or well preserved larval worms as would be expected for a direct role in parasite killing.[18-20]

Eosinophilic Response

Understanding of the role eosinophils play in the human immune response to helminthic pathogens is far from complete.[21] Work since 2002 to further elucidate the immunobiology of eosinophils has led to consideration of a broader role for these cells in immunity to helminthic infections.[22,23] The classical view of eosinophils as solely effector cells for parasite killing has given way to the idea that these cells play important roles in regulation of cellular immune responses.[24] Eosinophils could be envisioned to have a number of different functions in response to *A. cantonensis* infections. An example of this diverse functionality can be illustrated in the formation of granulomas around dead or dying *A. cantonensis* larvae. Similar to granulomas observed with schistosomiasis, granulomas in angiostrongyliasis contain large numbers of activated eosinophils that produce T_H2-associated cytokines that drive granuloma development.[25] *In vitro* work involving interleukin 5 (IL-5) knockout mice suggested that eosinophils are involved in the direct killing of the intracranial worms.[26] While a recent mouse study found that blocking the CCR3 chemokine receptor, which is abundant on the surface of eosinophils and is responsible for their activation and chemotaxis, did not affect worm burden as a result of decreasing the number of intracranial eosinophils.[27] Whether these findings can be translated to humans remains to be elucidated,[6] as it is crucial to keep in mind the immunological differences between species and to consider such when applying mouse models to the mechanism of human disease. Presently there is sparse evidence in the literature to directly support the idea of eosinophils participating in the direct killing of *A. cantonensis* larvae in the CNS. Therefore it is equally likely that the recruitment of eosinophils into the brain parenchyma may occur secondarily as a result of parasite death.

Expanded Role for Eosinophils in Eosinophilic Meningitis

It is possible to speculate that the central function of eosinophils may be in tissue remodeling, repair, and, more importantly, immuno-regulation. It is interesting to note that eosinophils express two cytokines: interleukin 12 (IL-12) and gamma interferon (IFN-γ), both of which serve to down regulate T_H2 type inflammatory responses. Indeed, IL-12 has been shown to inhibit allergen-induced T_H2 cytokine responses and eosinophil degranulation.[3] This suggests that eosinophils may have the ability to release cytokines that regulate eosinophil modulated T_H2 type tissue inflammation resulting from migrating parasites.[4] Eosinophils (as well as other immune cells such as T-cells) have also been shown to store, produce, and release neurotrophins such as brain-derived neurotrophic factor (BDNF).[28,29] It has been suggested that locally produced BDNF in the CNS mitigates inflammation-dependent neuronal damage.[30] Furthermore it could be hypothesized that the pathology of human angiostrongyliasis may be due in part to the inability of eosinophils to modulate T_H2 type effector functions such as granuloma formation and inflammation initiated by the migration, death, and disintegration of the *A. cantonensis* larvae. This inability of the eosinophil population to modulate the host inflammatory response may be due to host factors such as polymorphisms in eosinophil cytokine receptor expression, parasite factors such as strain variations in *A. cantonensis*, or a combination of both. Further studies are required to truly appreciate the role eosinophils play in disease associated with human *Angiostrongylus cantonensis* infection.

Conclusion

Understanding of the function of eosinophils has significantly increased over the past few years. However, more research is needed to define their role in *Angiostrongylus cantonensis* infections. Only by understanding this intricate biological role that eosinophils play in eosinophilic meningitis can rational treatment protocols be proposed and tested.

Conflict of Interest

Neither author identifies any conflict of interest.

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