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The immunobiology of eosinophils—it's a whole new world out there: an interview with Dr. Peter F. Weller

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Abstract

The manuscript “Eosinophils mediate early alum adjuvant-elicited B cell priming and IgM production” was selected as a Pivotal Advance because it addresses an important and novel function of mouse eosinophils. Although eosinophils are traditionally perceived as end-stage degranulating cells, the results of numerous recent studies have broadened our perspective on eosinophil effector function. In this work, Wang and Weller demonstrate that eosinophils stimulate early B cell responses, notably the production of antigen-specific IgM.

Dr. Weller, you have had a long and productive career focused in part on the biology and physiology of the enigmatic eosinophil. What brought you to this interest and what has sustained it?

PFW: I have a longstanding interest in the biology of helminthes and host-parasite interactions. As a physician trained in infectious diseases and allergy/immunology, the prominence of eosinophilia in both helminthic and allergic diseases has always caught my interest. Over the years, the roles that have been considered for eosinophils have varied tremendously. At one time, eosinophils were thought to be major participants in down-regulating allergic responses by neutralizing mast cell mediators. Subsequently, there was a primary focus on the roles of eosinophils as helminthotoxic effector cells. Thereafter, the attention shifted to eosinophils and their contributions to the pathogenesis of asthma and allergic disease based in part on eosinophil degranulation and the release of cationic granule proteins.

More recently, however, our understanding has evolved so that we now see that eosinophils are more complex than simply end-stage effector cells. Among these more intriguing findings, we now know that eosinophils synthesize and secrete at least three dozen cytokines which are stored preformed in granules and vesicles (in contrast to most lymphocytes that need to activate cytokine synthesis via transcription) and that eosinophil “degranulation” was not simply due to wholesale granule exocytosis. Moreover, recent studies have revealed unanticipated roles for eosinophils in development (such as breast ductal involvement) and novel eosinophil localization (such as in the thymus). These observations have encouraged us to consider potential functional roles for eosinophils in more varied developmental and immunologic responses.

Most researchers still view eosinophils as cells that act on their own, releasing cytotoxic mediators in conjunction with parasitic and allergic disease states. You and your group were among the first to recognize that eosinophils had the potential to interact with other leukocytes, first with studies describing eosinophils as antigen-presenting cells, and now demonstrating

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that eosinophils can modulate B cell responses. How did this concept—that eosinophils might interact with cells directing acquired immune responses—occur to you?

PFW: We have always kept an open mind to the possibility that eosinophils were not simply end-stage effector cells. The late Professor Paul Beeson, whose research team helped to delineate the T cell dependence of eosinophilia, encouraged me to think broadly about the functional capacities of eosinophils. Professor Beeson recalled the early thinking about lymphocytes as simply uninteresting. As our studies and those of others have peeled away the onion skin surrounding eosinophils, we began to see that eosinophils were also not so simple, and certainly not uninteresting. For instance, we found that eosinophils express both CD4 and IL-2 receptors, enabling them to respond to IL-16 and IL-2, respectively. Similarly, the recognition that eosinophils synthesized and stored cytokines within intracytoplasmic vesicles encouraged us to consider possible immunomodulatory functions, specifically interactions with other leukocytes, including T cells. For example, eosinophils that contribute to tissue granulomas formed around helminth eggs might be major sources of immunomodulatory of cytokines. Likewise, eosinophils recruited into the airways in experimental allergen challenge or in naturally occurring asthma express MHC-II protein, not generally found on peripheral blood eosinophils, which suggested to us that they might be sampling airway allergens and serving as antigen-presenting cells.

In the Discussion section, you note that eosinophil interactions with B cells and subsequent IgM responses may have an impact on host responses to parasitic infection. Given the controversy regarding the role of eosinophils in parasitic disease, this finding may shed light on an important and crucial element—can you discuss this further?

PFW: As noted above, eosinophils and their cationic granule proteins do function *in vitro* as helminthotoxic effector cells. With a desire to identify a beneficial and relevant role for eosinophils, much interest has focused on host responses to helminth infections. Despite an enormous amount of effort and study using IL-5-deficient and IL-5 overexpressing mouse strains and, more recently, mouse strains devoid of eosinophils, experimental infection studies have not provided a simple or uniform demonstration that eosinophils provide host defense against helminthic parasites. In considering host-immune responses to helminths, a number of considerations should be kept in mind. Helminths have co-evolved with mammalian hosts, often in a host species-specific fashion, and usually are chronic, morbid but not necessarily lethal infections. Thus, helminths, likely varying with their developmental life cycle stages, persist successfully by evolving in conjunction with host immune responses. Likely, anthelmintic immune responses are complex and multi-factorial and extend beyond singular roles of eosinophils as helminthotoxic effector cells. However, prior studies by Abraham and colleagues [1] identified a role for eosinophil-dependent IgM synthesis in the early response to *Strongyloides* larval infections. Our findings, which indicate that eosinophils enhance early B cell IgM synthesis, would certainly be in accord with this work.

Can you speculate on what is occurring at the molecular level (i.e., what eosinophils might be doing to B cells) that results in IgM synthesis? In other words, what components of eosinophils are responsible for this effect?

PFW: Further studies aimed at defining molecular mechanisms are clearly needed. With their rich armamentarium of preformed cytokines, it is very tempting to hypothesize that specific eosinophil-derived cytokines are involved. At the same time, eosinophils also contain rich stores of cationic proteins, which also may be candidates for as yet unrecognized signaling functions for responses of other local leukocytes [2].

Going back to you and your career—of your many contributions to the field of immunology, parasitology, and leukocyte biology, what do you consider to be the most important?

PFW: In looking back on our contributions, what strikes me is that there was no single contribution that was most important. Rather, we, often in parallel with other research groups, have advanced our understanding of the functional responses of eosinophils and helped to delineate the cellular mechanisms underlying those responses. Among our most crucial findings, we were one of the first groups to identify eosinophils as a source of the paracrine mediator, leukotriene C₄. Likewise, our identification of functional CD4 and IL-2 receptor expression on eosinophils suggested broader function with respect to responses to lymphokines. Our recognition of eosinophils as sources of cytokines, including TGF- β and TGF- α , and the rapid identification by others that eosinophils were sources of multiple other cytokines helped to expand our collective consideration of the potential diversity of roles of eosinophils and their means of mediator release, especially in comparison with other leukocytes that lack preformed cytokine stores. Finally, our studies of the roles of intracellular lipid bodies as sites of regulated eicosanoid-formation are identifying roles for cys-teiny1 leukotrienes as intracellular regulators of granule secretion.

Is there anything more that you would like to add?

PFW: I would like to be certain to credit those who over the years have been engaged in advancing these studies in our research group. Of course, much credit goes to Dr. Hai Bin Wang, the first author on this Pivotal Advance manuscript. I also would like to acknowledge many colleagues within our lab group and our collaborators who have helped contribute to these advances. I am also very pleased to see that so many of our trainees are developing independent investigation-based careers advancing studies of leukocyte biology. Likewise, the global community of researchers who have focused on studies of the immunobiology of eosinophils are to be acknowledged for their contributions to unraveling the functions of eosinophils. Personally, I have shared the excitement and funding travails of our research endeavors with an excellent independent researcher, my wife, Dr. Anne Nicholson-Weller.

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Biography

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