Interplay Between Neutrophils and T Cells in an Autoimmune Disease

By Holly Rosenzweig

The Th17 signaling response has emerged as a potential therapeutic target in many inflammatory diseases such as spondyloarthritis and its related diseases including psoriatic arthritis, psoriasis, inflammatory bowel disease, and uveitis. Despite progress in identification of genetic factors and improved characterization of immunological factors involved in arthritis, it remains an enigmatic group of diseases that is often inadequately treated. The role of adaptive immune system, especially T cells, in arthritis has been the subject of intense investigation. Yet, despite CD4+ T cells seemingly being prime candidates of arthritic diseases, it remains unclear exactly how T cell responses are shaped. Thus, evolving concepts of disease mechanisms propose a paradigm wherein a series of cellular interactions that involve both innate and adaptive interactions shape chronic inflammatory disease. As such, a role for innate immunity is being increasingly considered as a key contributor to inflammatory arthritis.

The IL-23/IL-17 axis has been considered a prevailing response in the development of autoimmune disease models, and has been a major focus in spondyloarthritis research and therapies. Production of IL-17 from CD4+ T cells and their differentiation into “Th17 cells” has been well-described. Expression of IL-23 receptor (IL-23R) on their cell surface allows T cells to respond to IL-23, which is critical in their expansion and maintenance. However, recent findings highlight how IL-17 can be produced by innate cells such as neutrophils, which may be an important cellular source of IL-17 in situ. Indeed, neutrophils are the main cellular source of IL-17 in the joints of patients with spondyloarthritis. Thus, the ensuing pathology observed in arthritic disease could involve coordinated events between T cells of the Th17 lineages in addition to innate immune cells such as neutrophils. The involvement of innate cells such as neutrophils could be a previously unconsidered and critical aspect involved in orchestration of the Th17 response.

Using a murine model of spondyloarthritis, wherein mice immunized with the cartilage constituent proteoglycan (PG) develop chronic progressive disease of the peripheral joints, spine, and uveitis (or ocular inflammatory disease), we propose to explore the interplay between neutrophils and antigen-specific T cells in development of disease and their participation in the Th17 response. We know that IL-17 plays an essential role in autoimmune responses of the eye, which is negatively regulated by the Th1 cytokine, IFN-gamma, and the ensuing uveitis can be prevented upon administration of anti–IL-17 blocking antibody. The role of Th17 response in mediating the uveitis aspect of disease is consistent with our data supporting the increased neutrophil infiltrate. In order to understand how the in vivo cellular interaction between neutrophils and T cells shapes “autoimmune” disease, we will use intravital videomicroscopy—an established technique in our lab that allows us to visualize in real-time the cellular trafficking responses within the microvasculature and iris tissue of the eye. We will use T cell receptor-transgenic (TCR-Tg) mice that recognize PG, which we have crossed with DsRed2 fluorescent mice (that have red fluorescent CD4+ T cells) and thereby allow us to visualize antigen-
specific T cell responses. We have also crossed the DsRed2 x TCR-Tg mice with Lys-GFP mice (that have green fluorescent neutrophils), which will allow us to simultaneously monitor the in vivo cellular trafficking responses of neutrophils and PG-specific T cells.

To determine how IL-23 responsiveness is associated with T cell versus neutrophil trafficking in the eye, we would perform studies that involve local injection of IL-23 into the eye. These experiments will be coupled with corresponding studies that involve administration of a blocking antibody to IL-23. The dynamics of neutrophil and T cell trafficking responses would be monitored in vivo within the eye using our intravital videomicroscopy technology throughout the progression of spondyloarthritis. It is critical to relate the in vivo cellular functions to cell phenotype and using multicolor flow cytometry we will examine the extent to which IL-23 impacts the ability of neutrophils versus T cells to infiltrate the eye, the cellular source of IL-17 and other Th17-related cytokines (such as IL-22), which cells differentially express IL-23R, and how their activation state may be impacted. To determine the effects of neutrophils on PG-specific T cells responses, we will administer a neutrophil-depleting antibody and the consequences of neutropenia on T cell responses will be monitored in vivo by intravital videomicroscopy. The onset and severity of uveitis and arthritis will be assessed clinically and by routine histological methods. The extent to which neutrophil-depletion affects the ability of antigen-specific T cell responses of the eye will be further quantified by flow cytometry as described above, and the antigen-specific T cell cytokine response will be measured in splenocyte cultures using multiplex ELISA.

Our ability to visualize in vivo cell trafficking at a site of disease coupled with reagents and support from BD Biosciences puts us in an especially unique position to dissect cellular processes that involve the participation of neutrophils and T cells in the Th17 response modeled in a disease resembling spondyloarthritis. Our background in immunology will allow us to use state-of-the-art technology involving flow cytometry, cytokine blocking experiments, and multiplex ELISA to answer such questions in an inflammatory disease that impacts millions of people worldwide.

The BD Biosciences Research Grant Program aims to reward and enable important research by providing vital funding for scientists pursuing innovative experiments to advance the scientific understanding of disease.

Visit bdbiosciences.com/grant to learn more and apply online.