The Pathogenesis of Systemic Lupus Erythematosus

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Peggy Crow:
Hi, this is Dr. Peggy Crow. I am a rheumatologist at Hospital for Special Surgery and for many, many years, a lupus investigator. I am going to be speaking to you about the pathogenesis of systemic lupus erythematosus (SLE) or lupus. This is a disease that is really grounded in the immune system. So, to the extent that you understand how the immune system functions in the context of responses to microbes in a protective way, I think many of the same lessons apply to how we think about the pathogenesis of lupus. And lupus is a complex disorder. It involves a significant contribution from genetic variance among us and can also be triggered by environmental factors. But at the end, it is really a disease in which the immune system functions in a manner that can be damaging to organs and tissues. One of the most characteristic features of lupus is that patients with lupus make auto antibodies to nucleic acid or nucleic acid binding proteins.

Peggy Crow:
That is a key feature of the disease and probably holds important lessons for understanding disease pathogenesis. But the mechanisms that lead up to production of those antibodies and the way that those antibodies contribute to tissue damage, can be understood by thinking about how the immune system typically works. So, you probably are aware of the innate immune system and the adaptive immune system.

Peggy Crow:
The innate immune system comprises cells and their products that are readily induced by various triggers. The adaptive immune system, which includes T cells and B cells and their products, require a little bit more specific activation by antigens. But both innate and adaptive immune systems come into play in lupus.

Peggy Crow:
The innate immune system involves several cells and their products. One of the big advances over the last 15 or 20 years has been an understanding of the contribution of innate immune system cells and products, particularly the role of type I interferon to lupus pathogenesis. We can get important hints about the important pathways and factors that contribute to lupus pathogenesis if we look in detail at some of the genetic variants that are associated with the disease. So, many of the genes and reasons in the genome that have been shown to be statistically associated with the diagnosis of lupus, 22 pathways that involve innate immune system activation, and particularly production of type I interferon or response to type-I interferon.

Peggy Crow:
Interferon is a family of molecules that are typically activated in the setting of viral infections. But in most patients with lupus, type I interferon is expressed at high levels and is sustained way over time. The effect of that interferon is that many cells of the immune system become activated and altered in their function, very much in a similar way to what we might see in a chronic infection with a virus.

Peggy Crow:
Type I interferon is one of the very important products of the innate immune system, but the adaptive immune system, T cells and B cells, are also key. Type I interferon can help to activate both T cells and B lymphocytes. And what we have learned is that different types of T cells are particularly important in lupus pathogenesis. So, T helper cells and a subset of T helper cells, T follicular helper cells, are important in providing so-called help to B cells and driving B cell differentiation.
Peggy Crow:
T regulatory cells are important cells that regulate the immune response and there is some evidence that the level of activity of T regulatory cells is insufficient in lupus to provide that important level of control. Cytidine deaminase (CDA) T cells may also be important and probably have been insufficiently studied in lupus. There's interest now in the concept of T-cell exhaustion, which is a feature of CDA T cells in some diseases and probably including lupus.

Peggy Crow:
The T cells work in different ways to control and orchestrate the rest of the immune system and a particular key feature of the role of T cells is their interaction with B cells and their role in helping to expand B cells as well as differentiate these cells into auto antibody producing cells.

Peggy Crow:
These cells depend on not only the T cell signals, but help from myeloid cells, macrophages dendritic cells, and their products. One of the important products is a list of B cell activating factor (BAFF). So all of these features, the products of the innate immune system, including type I interferon, different T cell subsets, the interactions between T cells and B cells, and the products of B cells, particularly auto antibodies, are all important features of the immune system that characterizes patients with lupus.

Peggy Crow:
Once auto antibodies are formed, what has been known for many, many years is that immune complexes form. We are particularly interested in thinking about the pathogenesis of lupus nephritis, or kidney disease in lupus patients. It has been well known that immune complexes, which include the auto antibodies and the antigen and sometimes other components, will deposit in kidney tissue, particularly the glomerulus. It can be very important, exactly where in the glomerulus the immune complex is deposited with regard to the kind of damage that follows.

Peggy Crow:
But one of the common locations for deposition of immune complexes is beneath the endothelial cells of the glomerulus and when that occurs, additional inflammatory events come into play. The complement system can be activated, and when that occurs, inflammatory cells are brought into the kidney and can be very, very damaging. The events that occur in the kidney, particularly inflammation, are not self-limited. Even if that inflammation is brought under control often there is a response, the tissue healing and response process, but that can result in scarring.

Peggy Crow:
All these effects come together to generate a complex scenario of immune dysregulation that contributes to the pathogenesis of lupus. All these events are food for consideration of how we might address lupus therapeutically and each of the components that I have mentioned is at least a candidate therapeutic target. So, the type I interferon system is being considered in many ways to think about if we could block it or inhibit its production, inhibiting its activity on target cells.

Peggy Crow:
We are aware of studies to inhibit the function of the professional interferon producing cells, the plasmacytoid dendritic cells. There are efforts to block the interaction of type I interferon with its receptor, as well as efforts to block the signaling process downstream of the type I interferon receptor, for example, with Janus kinase (JAK) inhibitors. But in addition, there are good reasons to think about inhibiting T cells and the T follicular helper cell might be a candidate for targeting inhibitory biologics to block the capacity of those cells to interact with B cells or to block some of their products.

Peggy Crow:
There are efforts to inhibit the activation of so-called T helper type 1 (Th1) cells by blocking some of the cytokines that span those cells, such as interleukin-23 (IL-23), blocking T helper 17 (Th17) cells with similar approaches. And then several ways of either indirectly or directly inhibiting the activation and differentiation of B cells. So, we are aware of the approved drug belimumab, which inhibits the interaction of BLISS or BAFF with B cells. And rituximab, although not FDA approved for the treatment of lupus, is used by some rheumatologists to bring disease under control and in some patients that approach can be effective.
Peggy Crow:
Rituximab will target the CD20 molecule in B cells and is a B cell depleting agent. There are many, many new and innovative approaches for therapy of lupus being considered that directly or indirectly target pathogenic mechanisms. Many of these will target intracellular molecules, such as kinases and I have mentioned targeting the JAK-STAT pathway.

Peggy Crow:
Many others might target soluble molecules. So, all in all, this is a very promising period we are in, in that there's greater and greater understanding of the pathogenesis of lupus, how it can affect tissue, and organ damage. All the research that has been done is leading us to have many good ideas about candidate therapeutic targets. The challenge now is to develop informative study designs for testing of many of these candidate agents and to have appropriate patient enrollment and implementation of clinical trials with informative outcome measures that can teach us which of these new medications is going to be effective in helping patients to have better outcomes.