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EDITORIAL

Introduction: B cell-mediated autoimmune diseases

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This issue of Seminars in Immunopathology centers on the role of autoantibodies and B lymphocytes in various autoimmune diseases. B lymphocytes and autoantibodies play a crucial role in the pathogenesis of an increasing number of diseases. They may serve as antigen-presenting cells, produce pro-inflammatory cytokines, and—most notably—plasma cells as their terminal differentiation state represent the source of autoantibodies that are believed to be often the drivers of immunopathology. When looking closely, however, in many autoimmune diseases, the exact mechanisms of autoantibody-driven pathogenesis are less than clear. Binding of target structures by autoantibodies, activation of the complement cascade with the release of chemotactic and pro-inflammatory peptides and binding of immune complexes by innate immune cells via Fc-receptors and initiation of inflammatory responses are discussed to play crucial roles in antibody-driven autoimmune diseases. In addition, a growing number of diseases or subsets thereof are obviously caused by receptor-binding and their function-modulating antibodies. However, depending on the kind of autoimmune disease, different mechanisms or combinations thereof may govern pathogenesis. For multiple autoimmune diseases, the specificity of autoantibodies serves as an important criterion for diagnosis. These classical "biomarkers" are usually poorly or not at all correlated with disease activity and manifestations, either because we do not yet have sufficient understanding of the most relevant autoantibody specificities or even posttranslational modifications of the autoantigens or because additional immunological and non-immunological processes are the crucial determinants for the pathogenesis of a certain autoimmune disease.

A second, antibody-independent, role of B-lymphocytes in modifying autoimmune diseases has been noticed much more recently triggered by the substantial clinical success of therapeutic depletion of B lymphocytes with monoclonal antibodies in some autoimmune diseases. These clinical improvements that go along with relatively modest reductions in autoantibody levels in the serum provided direct clinical evidence for important, sometimes even crucial, antibody-independent roles of B lymphocytes for the autoimmune disease process. B lymphocytes are excellent antigen-presenting cells for the antigen that the B cell receptor recognizes and therefore can enhance or even initiate T cell-driven autoimmune responses. In addition, B lymphocytes can produce substantial amounts of cytokines, both pro- and anti-inflammatory ones.

This issue covers several aspects of antibody-dependent and antibody-independent functions of B lymphocytes in autoimmune diseases. Tiburzy et al. give an overview about plasma cells in the immunopathology of autoimmune diseases. Long-lived plasma cells that need very specific microenviromental niches for their longevity are responsible for autoantibody production which is refractory to treatment and represent a challenge for the therapy of antibody-mediated autoimmune diseases. The complexity of different stages of differentiation and tissue-specific heterogeneity is high among plasma cells. In addition, there is good evidence that plasma cells and their immediate precursors, the plasmablasts, can produce important cytokines, exhibiting so far underestimated functions in autoimmune diseases.

Kao et al. focus on the dichotomy of inhibitory and activating Fcγ receptors that integrate positive and negative

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signals via the binding of immune complexes. Interfering with the interaction of autoantibodies with cellular FcγRs represents an attractive therapeutic target for autoimmune diseases, and Kao et al. summarize the mode of action of two enzymes that selectively inactivate the IgG molecule, either by preventing Fcγ receptor binding or by hydrolyzing the IgG molecule. In addition, new insights in novel-immunomodulating activities of intravenous immunoglobulins are reviewed. Modifications of the glycan structures on the IgG molecules are intensively discussed in the context of future therapies against antibody-mediated autoimmune conditions.

Five reviews in this issue focus on the current knowledge about the pathogenic role of autoantibodies and the possible antibody-independent aggravating role of B lymphocytes in specific autoimmune diseases. Van der Vlag and Rekvig discuss the enigmatic role of anti-dsDNA autoantibodies in the pathogenesis of the systemic lupus erythematosus, particularly in lupus nephritis. Bax et al. summarize the pathogenic potential of anti-citrullinated protein antibodies and more recently discovered autoantibodies against carbamylated proteins in the disease pathogenesis of rheumatoid arthritis. The B cell-mediated pathogenic aspects in ANCA-associated vasculitides are the focus of the review of Jennette and Falk. An interesting crosstalk of activated neutrophils secreting activating factors for B cells is discussed. The rather unexpected positive response on the clinical development of multiple sclerosis and neuromyelitis optica after application of rituximab in these patients points to an important function of B lymphocytes in these autoimmune diseases. Krumbholz and Meinl discuss the pro-inflammatory and regulatory B cell effector functions, defects in B cell tolerance, and the B cell fostering microenvironment in the CNS. Yet another pathogenic mechanism of autoantibodies is discussed in the review by Wallukat and Schimke. Agonistically acting autoantibodies binding to and activating G-protein-coupled receptors are important pathogenic factors in diseases of the cardiovascular system. The authors also summarize recent evidences that this type of autoantibodies might also be associated with other diseases like glaucoma and Alzheimer's disease.

The use of monoclonal antibodies that specifically target B cells, in particular anti-CD20 and ant-BLyS antibodies, have demonstrated the efficacy of this approach for the treatment of human autoimmunity, but questions remain open, how these B cell-targeted therapies work and why in certain autoimmune diseases clinical benefit is unpredictably moderate. In the review by Iñaki Sanz, the clinical response after these novel therapies are correlated with the role of different B cell subsets in SLE particularly.

In conclusion, autoantibody and antibody-independent functions of B lymphocytes in autoimmune diseases are complex and not entirely understood. New therapy regimens targeting B cells and plasma cells offer the unique opportunity to better understand their function when thoroughly analyzed during and after therapy. The application of new methodologies designed to support systems scale analysis of the human immune system combined with detailed pathological studies in these patients should improve further a rational design of B cell-directed therapies.