Novel pathophysiologic mechanism responsible for autoimmunity identified

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(Medical Xpress) -- Researchers from Boston University School of Medicine (BUSM) have discovered that human proteins with an affinity for Dermatan Sulfate (DS) have the propensity to become autoantigens. In a companion article, the researchers also found that DS physically interacts with dead cells and that the resulting DS–autoantigen complexes drive autoreactive B-1a cell responses and autoantibody production both in-vitro and in mouse models. These findings, which appear in two back-to-back papers in the May issue of the *American Journal of Pathology*, provide a promising tool for discovery of autoantigens, molecular diagnosis of autoimmune diseases and development of cause-specific therapies.

Autoimmune diseases are the third most common category of disease in the United States after cancer and heart disease; they affect approximately 14-22 million persons. Autoimmune diseases are among the most poorly understood medical conditions, although it is well accepted that they are caused by aberrant immune responses directed at endogenous molecules and tissues of the body. Autoimmune diseases encompass a wide spectrum of clinical presentations, and more than 80 types have been classified, based primarily on systemic or organ-specific involvement. Common systemic autoimmune diseases include systemic lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome; localized diseases include type 1 diabetes, multiple sclerosis, and Graves' disease.

According to the researchers, both precise diagnosis and development of

cause-directed therapies remain challenging. A major hurdle has been the lack of understanding of etiologically inciting molecular and cellular events and key pathophysiologic mechanisms that lead to autoimmunity.

Studying patients with autoimmune diseases, the researchers discovered patient-specific complex autoantigen patterns that were more diverse than previously thought, indicating significant pathological heterogeneity even within traditionally defined clinical entities, such as rheumatoid arthritis or systemic lupus erythematosus. By shotgun sequencing of DS affinity-enriched proteomes extracted from cell lines, they identified more than 200 autoantigens, both novel and previously linked to autoimmunity, including several well-known families of autoantigens related to the nucleosome, ribonucleoproteins, the cytoskeleton and heat shock proteins. We were able to capture the entire known human auotantigen-ome and then some more in a single experiment," explained senior author Michael Roehrl, MD, PhD, an assistant professor of pathology and laboratory medicine at BUSM.

The studies revealed that noncovalent DS-antigen complexes have the unique capability of expanding B-1a. "On the basis of our findings, we propose that DS forms complexes with autoantigens presented by apoptotic or dead cells and that these complexes promote the positive selection and expansion of autoreactive CD5_ B cells and the secretion of autoantibodies," he added.

"It has been a longstanding puzzle why only a small subset (1-2 percent) of all human proteins can become functional antibody targets in autoimmune diseases. Our theory offers a plausible answer to this ontogenic question central to autoimmunity by showing that affinity to DS may be a unifying principle of autoantigens," stated Roehrl.

The researchers believe that further investigation of the molecular activities of DS and DS-binding proteins will lead to a more precise

understanding of the molecular mechanisms driving B-1a cell activation and thus autoimmune disease. Furthermore, Roehrl's laboratory is already using the new discoveries to develop personalized molecular serum testing for patients with autoimmune diseases, an area of medicine that "has not seen significant advances in a very long time and that was ripe for a real breakthrough" according to Roehrl.

Provided by Boston University Medical Center