Reduction in antibody gene rearrangement in B cells related to type 1 diabetes, lupus

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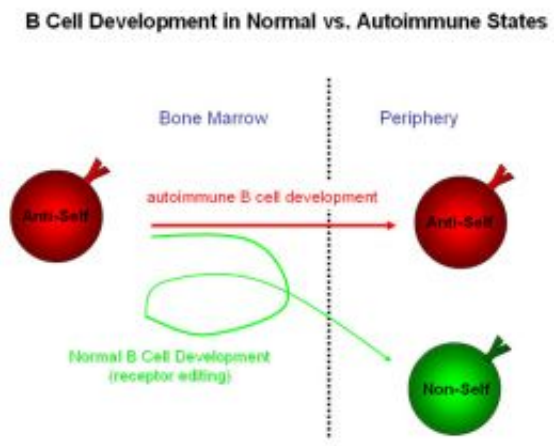

When B cells produce antibodies, self-binding or anti-self antibodies are often formed (red-colored cells). Such anti-self cells must be eliminated, either by cell death or by revising the specificity of the antibody through a process called receptor editing. When successful, receptor editing produces a B cell that is non-self binding (green-colored cell). The Penn study documented lower levels of antibody gene rearrangements in B cells from some patients with autoimmune disease, suggesting a defect in this early B-cell tolerance checkpoint. Credit: Nina Luning Prak, M.D., Ph.D, Univeristy of Pennsylvania School of Medicine

(PhysOrg.com) -- More drafts usually mean a better product and so it also seems to go with the human immune system. As B cells develop, genes rearrange to allow antibodies to recognize different foreign invaders or pathogens. But sometimes antibodies are created that

recognize and attack the body's own cells. These self-reactive antibodies, like early drafts of a manuscript, must be edited into versions that won't attack self. This process is called receptor editing and is important for central or early B cell tolerance, which occurs while B cells are still developing in the bone marrow.

A research team led by Nina Luning Prak, M.D., Ph.D, Assistant Professor in the Department of Pathology and Laboratory Medicine at the University of Pennsylvania School of Medicine, has discovered that this editing process may go awry in people with certain types of autoimmune diseases.

Prak and her colleagues, including the study's first author, Penn MD-PhD student Anil Panigrahi, observed that the amount of antibody edits in the development of B cells is related to two types of autoimmune disease, lupus and type 1 diabetes. The findings, which appeared online this month in the *Journal of Experimental Medicine*, have implications for new tests and more personalized treatments for autoimmune diseases.

The investigators found a lower level of antibody editing in mouse models and in blood samples from lupus and diabetes patients. In the samples from autoimmune patients, 30 percent had low editing levels, a high proportion, but also indicative that not all autoimmunity is caused by errors in editing. A targeted, personalized approach may be necessary to treat these complex diseases, according to the researchers. New assays derived from this study to assess the level of editing may help direct appropriate therapies.

"Right now we have a very crude approach to treating autoimmunity: depleting or inactivating circulating B or T cells wholesale," explains Prak. "Editing errors develop before B cells leave the bone marrow. However, treatments such as B-cell depletion might be less likely to

work in patients with editing errors because the self-attacking B cells can be regenerated rapidly as they develop in the bone marrow."

The researchers found a way to look at the editing history of B cells in the human and mouse samples, by monitoring the frequency of a non-functional light chain genetic rearrangement in the B cell antibody, which is termed RS. The investigators surmise that a decrease in RS levels indicates that B cells that react with self can evade editing of their self-reactivity and that defects in editing, in turn, may lead to an increased risk of developing autoimmune disease.

The measurement of RS frequency is independent of antibody specificity and, because it is non-functional and irrevertible, it can be used to monitor the level of antibody gene rearrangement in any B cell population and in any autoimmune disease. The team is now interested in testing if RS frequency is altered in other autoimmune diseases and if a low RS level in an apparently healthy person is predictive of future autoimmunity. The RS assay may also be of use to clinicians who treat patients with established autoimmunity and to researchers who are mapping genes that are associated with different underlying causes of autoimmunity.

In addition to Nina Luning Prak and Anil Panigrahi, Penn co-authors are Noah G. Goodman, Robert A. Eisenberg, Michael R. Rickels, and Ali Naji.

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