MedicalXpress

Study reveals a common genetic link in fatal autoimmune skin disease

June 19 2014

Autoimmune disease occurs when the body's own natural defense system rebels against itself. One example is pemphigus vulgaris (PV), a blistering skin disease in which autoantibodies attack desmoglein 3 (Dsg3), the protein that binds together skin cells. Left untreated, PV can be fatal, as skin layers slough off and leave the body vulnerable to dehydration and infection. Researchers from the Perelman School of Medicine at the University of Pennsylvania recently found a shared genetic link in the autoimmune response among PV patients that provides important new clues about how autoantibodies in PV originate. Full results of the new study are available today in *Nature Communications*.

To better understand the nature of the immune response in PV, the researchers cloned anti-Dsg3 monoclonal autoantibodies (mAbs) from four unrelated PV patients. In characterizing the mAbs, they identified a particular gene, VH1-46, that was used by PV antibodies across all four patients.

"This was a very striking finding, because the common gene suggests common mechanisms for developing the disease," said senior author Aimee Payne, MD, PhD, the Albert M. Kligman Assistant Professor of Dermatology at Penn Medicine. "Most people have common antibody gene responses to infections and vaccinations, so when we first started these studies, we suspected this might be the case for PV, we just didn't know which gene it was going to be."

To investigate further, the team set out to determine the nature and frequency of mutations in the complementarity determining regions (CDRs) of the VH1-46 autoantibodies. CDRs are the parts of the antibody that determine its specific antigen target. The researchers found that with very few CDR mutations, or even none at all, VH1-46 mAbs could bind with the Dsg3 protein. This suggests that the inherent tendency of some VH1-46 antibodies to bind Dsg3 could underlie the cascade of events that ultimately lead to PV.

While it's unlikely that the VH1-46 link solves the entire puzzle of PV's origins, it's an important step pointing in the right direction. Payne explains, "We don't think that VH1-46 is everything in PV, because we know that by the time patients show up with full-blown disease, multiple autoantibodies are causing the disease. However, the key is that we find VH1-46 autoantibodies in all of the patients we have studied, which suggests that it may be one of the earliest autoantibodies that appears."

Among the next steps for the research team will be to continue to probe the development of VH1-46 anti-Dsg3 antibodies, specifically whether they cross-react to microbes such as viruses or bacteria. "That could indicate that autoimmunity was mistakenly triggered during the course of an appropriate immune response to infection," says Payne. "Although we don't think this paper is going to immediately affect therapy, we believe that continuing along these lines of study will allow us to better understand how to improve current therapies or develop new strategies to treat disease," she notes. "We're at a really exciting time right now where we have the technologies to be able to address important questions about how PV occurs."

Provided by University of Pennsylvania School of Medicine

Citation: Study reveals a common genetic link in fatal autoimmune skin disease (2014, June 19)