

Hunt for the protein TGM1 led to disease discovery

December 14 2021



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By searching for the protein TGM1 among patients with various autoimmune skin diseases, researchers have successfully identified a separate disease that can be linked to autoimmunity against TGM1. This

backward method demonstrates a new way of identifying autoantigens as markers for serious diseases. By letting autoantigens point to the disease, diagnosis and treatment can be facilitated, according to the study now published in *PNAS*.

Sometimes research begins from the opposite end. To find the cause or symptom of a [disease](#), it is common to study many affected patients to find a common denominator. This study, however, did the opposite. The researchers started with the protein transglutaminas 1 (TGM1), which belongs to a [protein family](#) with many known autoantigens. Autoantigens are the body's own proteins that the [immune system](#) reacts against in [autoimmune diseases](#). TGM1 is in the skin. TGM1 has been previously linked to a hereditary skin disease and now the researchers wanted to know if TGM1 was also involved as an autoantigen in acquired [skin diseases](#). They searched for it in patients with a wide range of autoimmune and unexplained skin diseases.

"Eventually, they found a match. We saw that patients with the cancer-associated and severe blister-causing [skin](#) disease paraneoplastic pemphigus presented antibodies against TGM1. We confirmed the findings in a larger group of patients and could conclude that TGM1 antibodies were completely specific for paraneoplastic pemphigus," says Nils Landegren, [medical doctor](#) and researcher specializing in autoimmune diseases at Uppsala University, who led this study conducted together with researchers at Karolinska Institutet and Osaka City University, Japan.

Over 500 patients with various diseases participated in the study.

Autoimmune diseases occur when the immune system reacts incorrectly. Instead of protecting the body against viruses and bacteria, it attacks the individual's own body. In autoimmune diseases, the immune system's cells and antibodies react against the body's own proteins, known as

autoantigens. Knowing which autoantigens are associated with a specific disease is important, both to understand the disease mechanisms and to be able to diagnose autoimmune diseases and to give [patients](#) the correct treatment.

Traditionally, research has focused on individual diseases to identify autoantigens. In this new study published in *PNAS*, the researchers took the opposite approach: they focused on the suspected autoantigen and then conducted a broad search for a matching disease. The study illustrates a new approach to identifying biomarkers. The researchers believe that this approach can be used in studies of all sorts of autoimmune diseases, and that this could be a way to leverage the growing amount of openly available data on gene expression and function.

"We believe that TGM1 antibodies can be valuable as a diagnostic marker in investigations of blister-forming diseases. Patients that test positive should be quickly investigated to eliminate the possibility of undiscovered cancers," says Landegren.

More information: A gene-centric approach to biomarker discovery identifies transglutaminase 1 as an epidermal autoantigen, *Proceedings of the National Academy of Sciences* (2021). [DOI: 10.1073/pnas.2100687118](#)

Provided by Uppsala University

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