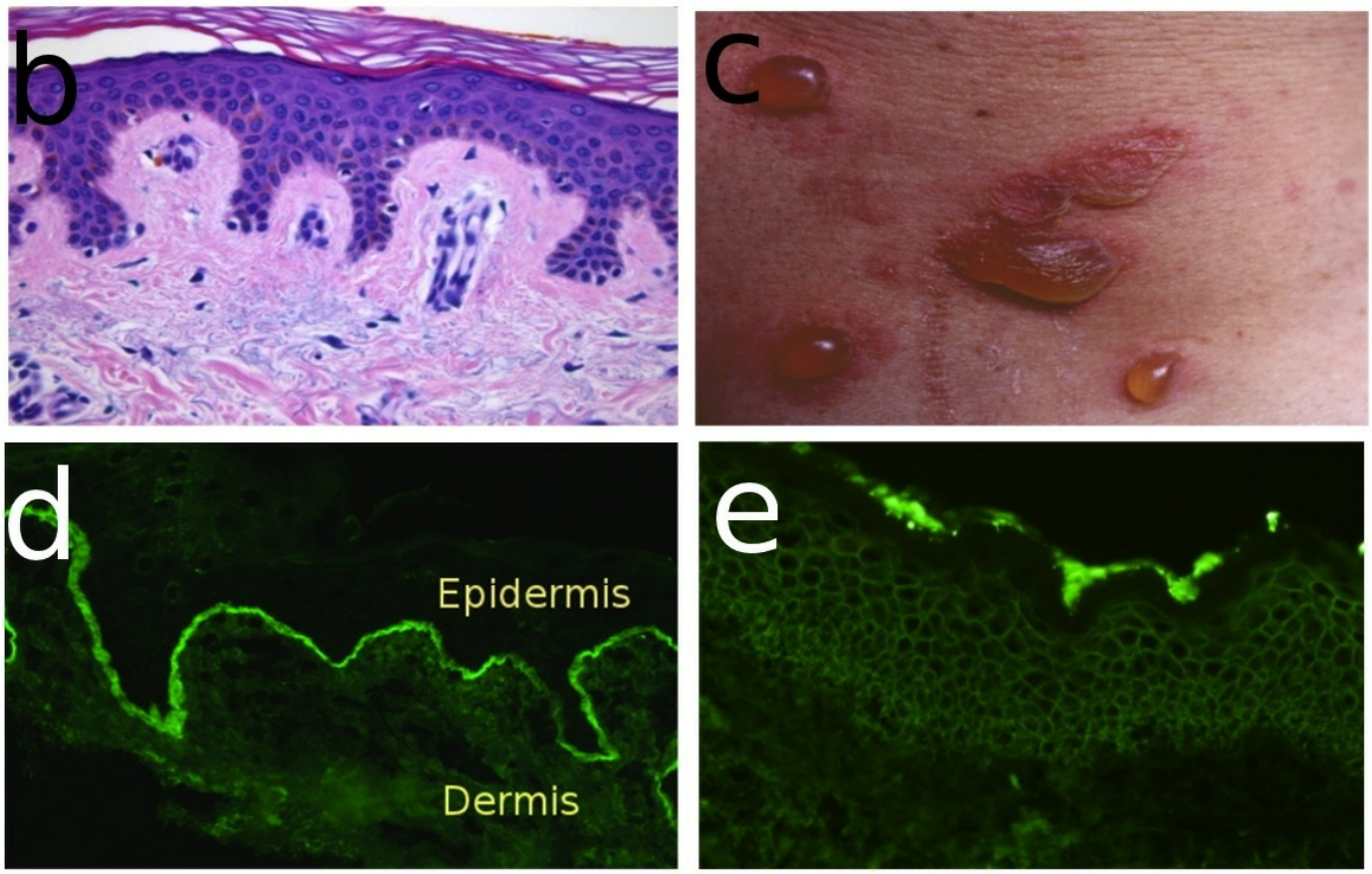
Healthcare industry BW

Autoimmune diseases – when the body sheds its skin

Most people believe that snakes and insects are the only animals able to shed their skin. However, autoimmune diseases of the largest human organ, i.e. the skin, can have a similar effect by creating blisters, scars, peeling and wet wounds. Dr. Cassian Sitaru from the University of Freiburg Medical Centre specifically focuses on blistering autoimmune dermatoses. Using disease models in Petri dishes and laboratory mice, Sitaru and his team hope to find out in more detail how antibodies attack their own organism.

Pemphigus is a group of blistering autoimmune diseases that affect the skin and mucous membranes. These autoimmune diseases are characterised by acantholysis, which is the loss of intercellular connections in the upper skin layer (epidermis), resulting in the loss of cohesion between keratinocytes. In healthy people, keratinocytes adhere closely to one another, an adhesion that is mediated by key-lock protein pairs of the cadherin group. In pemphigus, the patient's body attacks the cadherins with weapons that are normally used against foreign intruders. These molecules, the antibodies, bind to the cadherins between two keratinocytes, with the result that the key-lock principle becomes ineffective. The cells become separated from each other, and blisters that slough off and turn into sores are formed. "A hundred years ago or so, around 90 percent of patients suffering from an autoimmune disease of this kind would die," said Dr. Cassian Sitaru, a dermatologist at the Department of Dermatology and the Centre for Biological Signalling Studies (bioss) at the University of Freiburg with a major interest in the scientific elucidation of medical issues.

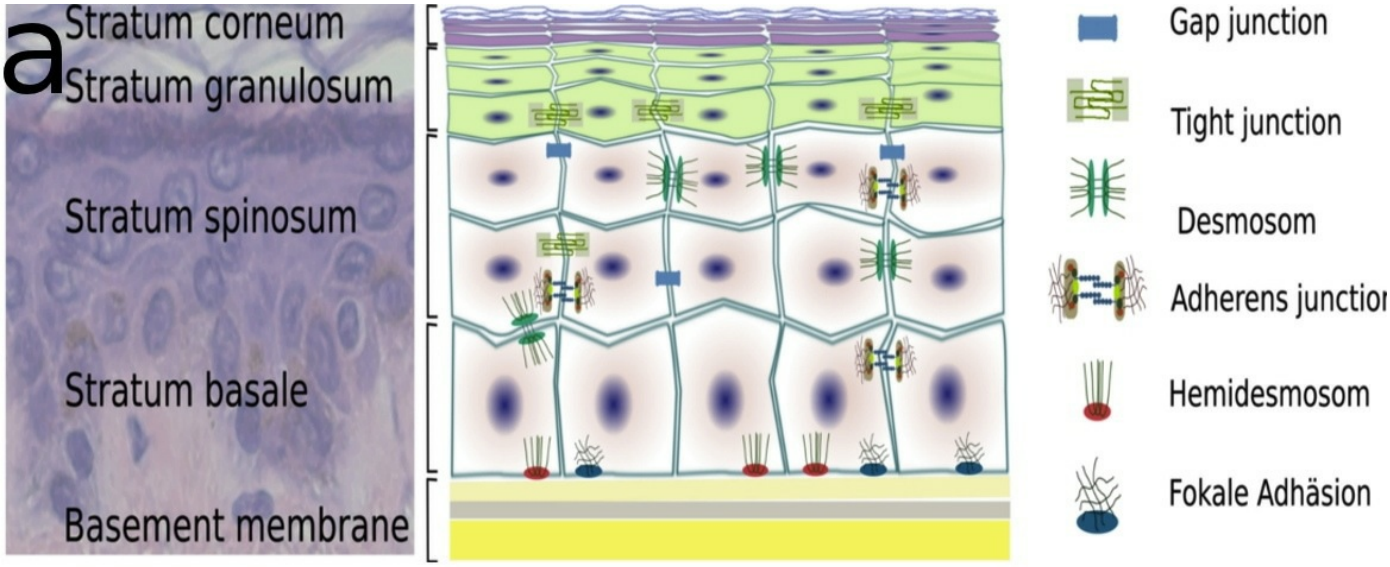


Acantholysis refers to the loss of cohesion between cells in the epidermis, resulting in the formation of blisters c). Image b) shows how the epidermis (purple) and the dermis (pink) are kept together. In d) and e), autoantibodies cause the epidermis to separate from the basal membrane (green line) between the epidermis and the dermis, resulting in hollow spaces between the two skin layers.

Two potential pathogenic mechanisms

Pemphigus can be treated with corticoids and immunosuppressant drugs, which bring the immune system and hence the generation of autoantibodies to a standstill. Chances of survival increase from around 10 percent to 90 percent. However, the adverse effects of immunosuppressant drugs are devastating, weight gain being one of the least severe effects. Worse effects involve an ineffective immune system being unable to fight off flu viruses and other pathogens. "Our research is therefore focused on the question as to how the therapy and diagnosis of autoimmune diseases of the skin can be improved," said Sitaru whose team is investigating different types of blistering autoimmune diseases. The researchers are interested in finding responses to questions relating to how autoantibodies are generated, which skin structures they bind to and the molecular and cellular consequences of the binding. "With regard to pemphigus, two molecular mechanisms are currently being discussed as a potential explanation for the development of the disease," said Sitaru.

On one hand, it is assumed that the antibodies bind to the cadherin molecule between two cells, resulting in less effective latching properties by changing the conformation of the cadherins and preventing the "key" from fitting properly into the "lock". The other possible mechanism, for which Sitaru and his team have been able to come up with convincing evidence, is the following: the autoantibodies bind to the cadherins, triggering them to transmit a signal into the cell. This signal is translocated into the cell nucleus, where it leads to a change in gene activity and in consequence stops or triggers the production of certain proteins. "These proteins might then affect the properties of the cadherin lock and prevent the cells from adhering to one another," said Sitaru.



The epidermis consists of layers of cells that are "glued" together by way of cell-cell contacts. These cell-cell contacts come in the form of cadherin proteins that fit into each other like a key fits into lock, thereby keeping the cells together.
© Dr. Cassian Sitaru

The researchers from Freiburg have used mass spectrometry and other methods for their investigations and found that cells that come into contact with typical pemphigus autoantibodies change their gene expression pattern, resulting in a change in the composition of the entire proteome. So the aforementioned signalling hypothesis might in fact be true. However, so far it has only been observed in cell cultures in which a single cell layer covers the bottom of the dish. A skin model, which is much closer to the real situation, is a three-dimensional construct, and needs to consist of keratinocytes of the epidermis and so-called fibroblasts that normally form the extracellular matrix, a network of proteins and carbohydrates in which the keratinocytes arrange themselves correctly. Sitaru and his team now plan to use such three-dimensional skin constructs to further develop their techniques and eventually also apply mass spectrometric methods.

A specific test and new drugs?

"We would like to find out what the molecular structures have to look like in order for pathogenic autoantibodies to be able to bind to them," said Sitaru. It is known that not all antibodies that bind to cadherins trigger acantholysis. And this finding might be of vital importance for the diagnosis of the disease. Up until now, patients have been tested for the general presence of autoantibodies; doctors do not look specifically for disease-causing molecules. "One of our long-term goals is to develop a test for the specific detection of pathogenic autoantibodies," said Sitaru.

Another objective relates to the identification of target structures for possible new drugs based on a detailed knowledge of the pathogenic mechanisms. These drugs would render disease-causing autoantibodies harmless without interfering with the whole immune system. Another method of treating the disease is antigen-specific immune apharesis, which involves "washing" the

blood plasma of a patient with a filter that only captures pathogenic autoantibodies. “These are of course pipe dreams,” said Sitaru. The Sitaru team, in collaboration with teams of researchers in Germany and abroad, is working on the elucidation of the structure of the autoantibody targets. This knowledge is an important prerequisite for developing a blood plasma filter, and it will be interesting to see how the research progresses.

Further information:

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