How skin falls apart: The pathology of autoimmune skin disease is revealed at the nanoscale

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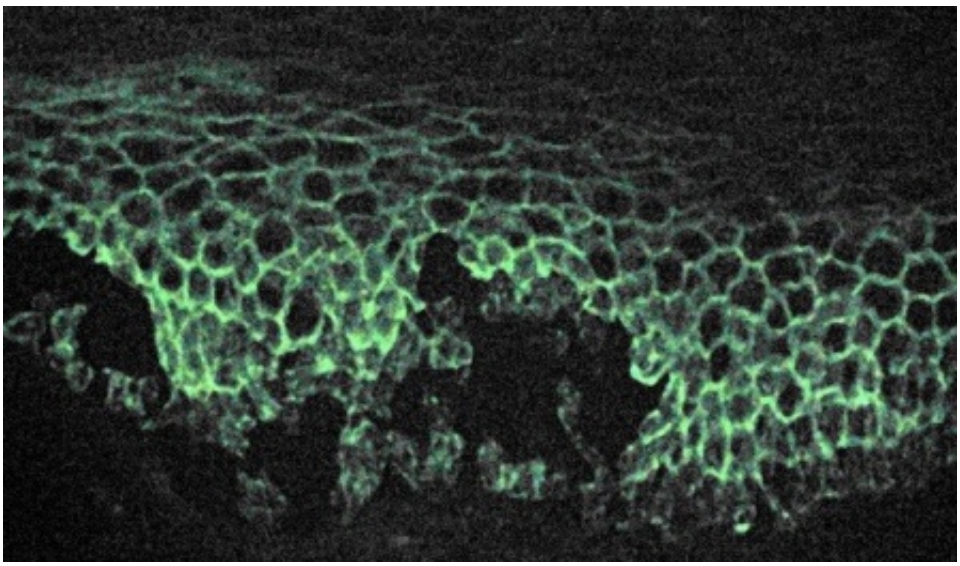

UB researchers have pinpointed important changes in cellular behavior that occur in Pemphigus Vulgaris, the rare, blistering skin disease shown in this microscopic image.

(Medical Xpress)—University at Buffalo researchers and colleagues studying a rare, blistering disease have discovered new details of how autoantibodies destroy healthy cells in skin. This information provides new insights into autoimmune mechanisms in general and could help develop and screen treatments for patients suffering from all autoimmune diseases, estimated to affect 5-10 percent of the U.S.

population.

The research, published in *PLoS One* on Sept. 8, has the potential to help clinicians identify who may be at risk for developing Pemphigus vulgaris (PV), an autoimmune skin disorder, by distinguishing pathogenic (disease-causing) autoimmune antibodies from other nonpathogenic autoimmune antibodies.

PV results in the often painful blistering of the skin and mucous membranes. Generally treated with corticosteroids and other immunosuppressive agents, the condition is life-threatening if untreated.

"Our work represents a unique intersection between the fields of biology and engineering that allowed for entirely new investigational strategies applied to the study of clinical disease," says Animesh A. Sinha, MD, PhD, Rita M. and Ralph T. Behling Professor and chair of the Department of Dermatology in the UB School of Medicine and Biomedical Sciences and senior author on the study.

The immediate application of the research, Sinha explains, is in helping scientists pinpoint important changes in cell behavior.

"These changes could be the differentiation of stem cells or the development of metastases in cancer or, as we are studying it, the point at which a cell is going to implode because it's under autoimmune attack," he says.

Sinha's research team, in collaboration with scientists at Michigan State University, describe the use of atomic force microscopy (AFM), a technique originally developed to study nonbiological materials, to look at cell junctions and how they rupture, a process called acantholysis.

"It has been very difficult to study cell junctions, which maintain the

skin's barrier function by keeping cells attached to each other," says Sinha. "These junctions, micron-sized spots on cell membranes, are very complex molecular structures. Their small size has made them resistant to detailed investigation."

Sinha's interest lies in determining what destroys those junctions in Pemphigus Vulgaris.

"We haven't understood why some antibodies generated by the condition cause blisters and why other antibodies it generates do not," says Sinha.

By studying the connections between skin cells using AFM and other techniques that probe cells at the nanoscale, Sinha and his colleagues report that pathogenic antibodies change structural and functional properties of skin cells in distinct ways.

"Our data suggest a new model for the action of autoantibodies in which there are two steps or 'hits' in the development of lesions," says Sinha. "The first hit results in the initial separation of cells but only the pathogenic antibodies drive further intracellular changes that lead to the breaking of the cell junction and blistering."

The researchers examined the cells using AFM, which requires minimal sample preparation and provides three-dimensional images of cell surfaces.

The AFM tip acts like a little probe, explains Sinha. When tapped against a cell, it sends back information regarding the cell's mechanical properties, such as thickness, elasticity, viscosity and electrical potential.

"We combined existing and novel nanorobotic techniques with AFM, including a kind of nanodissection, where we physically detached cells from each other at certain points so that we could test what that did to

their mechanical and biological functions," Sinha adds.

Those data were then combined with information about functional changes in cell behavior to develop a nanomechanical profile, or phenotype, for specific cellular states.

He also envisions that this kind of nanomechanical phenotyping should allow for the development of predictive models for cellular behavior for any kind of cell.

"Ultimately, in the case of autoimmunity, we should be able to use these techniques as a high-throughput assay to screen hundreds or thousands of compounds that might block the effects of autoantibodies and identify novel agents with therapeutic potential in given individuals," says Sinha. "Such strategies aim to advance us toward a new era of personalized medicine".

Provided by University at Buffalo