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Relevance of Keratin Alterations and Desmoglein 3 Internalization in the Autoimmune Skin Disease Pemphigus Vulgaris

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Pemphigus vulgaris (PV) is a potentially lethal autoimmune disease characterized by blister formation of the skin and mucous membranes and is caused by autoantibodies against desmoglein (Dsg) 1 and Dsg3. Dsg1 and Dsg3 are linked to keratin filaments in desmosomes, adhering junctions abundant in tissues exposed to high levels of mechanical stress. The binding of the autoantibodies leads to internalization of Dsg3 and a collapse of the keratin cytoskeleton – yet, the relevance and interdependence of these changes for loss of cell-cell adhesion and blistering is poorly understood. In live-cell imaging studies, loss of the keratin network at the cell periphery was detectable starting after 60min of incubation with immunoglobulin G fractions of PV patients (PV-IgG). These rapid changes correlated with loss of cell-cell adhesion detected by dispase-based dissociation assays and were followed by a condensation of keratin filaments into thick bundles after several hours. Dsg3 internalization started at 90min of PV-IgG treatment, thus following the early keratin changes. By inhibiting casein kinase 1 (CK1), we provoked keratin alterations resembling the effects of PV-IgG. Although CK1-induced loss of peripheral keratin network correlated with loss of cell cohesion and Dsg3 clustering in the membrane, it was not sufficient to trigger the internalization of Dsg3. However, additional incubation with PV-IgG was effective to promote Dsg3 loss at the membrane, indicating that Dsg3 internalization is independent from keratin alterations. Vice versa, inhibiting Dsg3 internalization did not prevent PV-IgG-induced keratin retraction and only partially rescued cell cohesion. Together, keratin changes appear very early after autoantibody binding and temporally overlap with loss of cell cohesion, suggesting a crucial role for initial loss of cell cohesion in PV.

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