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The desmoglein 3 – plakoglobin connection: the ying and yang in Pemphigus vulgaris

The life threatening autoimmune disease Pemphigus vulgaris (PV) is characterized by blister formation in skin and mucous membranes that occurs secondary to loss of intercellular adhesion (acantholysis) between basal and suprabasal keratinocytes. Acantholysis is induced by autoantibody binding to desmoglein 3 (Dsg3), a transmembrane cadherin glycoprotein which is present at the plasma membrane, both in desmosomes as well as in a non-desmosomal, Triton-soluble fraction. The complete cellular and molecular mechanism leading to acantholysis in PV is still unknown but we have pinpointed distinct signaling pathways that contribute to the pathogenic process. At cell cycle exit and onset of terminal differentiation, non-desmosomal Triton-soluble Dsg3 together with PG, an armadillo protein associated with the cytoplasmic tail of Dsg3, recruit phosphatidylinositol trisphosphate kinase (PI3K) to the plasma membrane of keratinocytes. PI3K recruitment further correlates with activation of the downstream kinase Akt, inhibition of glycogen synthase kinase 3 (GSK3) and translocation of PG to the nucleus where it suppresses, amongst others, c-Myc transcription. C-Myc inhibition is prerequisite for the keratinocyte to exit the cell cycle and initiate terminal differentiation. In contrast, exposure of keratinocytes to pathogenic monoclonal anti-Dsg3 antibody (AK23) disrupts Dsg3/PG/PI3K signaling. Dissociation of PG from Dsg3 coincides with reduced PI3K recruitment and impaired Akt activation, as well as to abrogation of PG-mediated transcriptional repression of c-Myc. This in turn results in c-Myc overexpression and sustained cell proliferation at the expense of terminal differentiation. Demonstrating the pathogenic involvement of this event, inhibition of c-Myc as well as GSK3 are sufficient to prevent acantholysis in mice injected with PV antibodies.

Together these results suggest that acantholysis in PV occurs secondary to compromised signaling through non-desmosomal Dsg3/PG, and as a novelty, that transadhesion between and signaling through Dsg3 receptors is central to onset of the terminal differentiation process. Furthermore, our results exemplify the usefulness of in vitro cell culture models as a tool to unravel cellular and molecular mechanisms of disease.

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