Poster Prize of the Day of BioMedical Research 2024
Stem Cell Project Prize

Mechanostructural signaling in Pemphigus vulgaris upon uncoupling of transadhesion

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Pemphigus vulgaris (PV) is a severe blistering skin disease caused by autoantibodies targeting in majority of patients desmoglein 3 (Dsg3) or Dsg3/Dsg1, which are desmosomal adhesion molecules expressed by keratinocytes. The binding of these antibodies uncouples extradesmosomal Dsg3 transadhesion which triggers cellular signaling pathways inducing blister formation in the epidermal stem and progenitor cell compartment. To investigate the identified pathogenic signaling molecules responsible for keratinocyte adhesion loss and blister development, we first conducted a thorough systematic review. The collective research on PV signaling indicates that anti-Dsg3 antibodies alter the mechanical, structural and biochemical properties of keratinocytes, highlighting the need to establish a comprehensive signaling network for therapeutic purposes. Our study utilized scRNA-seq and live cell phenotyping alongside functional approaches such as keratinocyte dissociation assay (KDA) and immunofluorescence microscopy of 2D human primary epidermal keratinocytes treated with AK23, an experimental pathogenic anti-Dsg3 antibody. scRNA-seq analysis revealed increased proliferation as confirmed by Ki67 immunofluorescence staining and KDA combined with an inhibitor of proliferation (5-fluorouracil). Additionally, amongst others, gene expression changes related to altered replication and cell cycle progression, Rho GTPase modulation and actomyosin contraction, as well as WNT inhibition, supporting earlier findings. These approaches combined with gene knockout further demonstrated that the loss of adhesion induced by AK23 is associated with pathogenic activation of mechanosensitive ion channels (Piezo1 and TRPV3), shifting cell fate towards proliferation, necessitating transcriptional regulation. Interestingly, E-cadherin did not play a significant role in this process. Taken together, our findings suggest that the alteration of keratinocyte mechanical properties by AK23 modulates electrical signaling, shifting the fate of keratinocyte subpopulations from stemness or differentiation towards proliferation, reminiscent of a wound healing phenotype. They also identify extradesmosomal Dsg3 as a mechanical sensor in epithelial tissue providing the basis for multiple pharmacological treatment options in PV patients.