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Desmoglein Binding Properties are Regulated by Plakophilins

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Desmosomes are highly organized protein complexes required for strong intercellular adhesion of keratinocytes. To maintain desmosome integrity, desmosomal cadherins provide intercellular mechanical coupling with their extracellular domains whereas plaque proteins such as plakophilins (Pkp), plakoglobin and desmoplakin mediate the anchorage to the intermediate filament cytoskeleton. In addition, Pkp isoforms are involved in the regulation of desmosomal turnover and several signaling pathways and are thereby crucial for desmosomal adhesion. However, their contribution to binding properties of desmosomal cadherins has not been elucidated yet. Here, we used murine keratinocytes lacking either Pkp1 or Pkp3 (Pkp1 k.o. / Pkp3 k.o.) and characterized Dsg1 and 3 binding properties in comparison to wildtype cells (Pkp wt). Both, Pkp1 and 3 k.o. cells showed compromised intercellular adhesion and reduced membrane levels of Dsg1 and Dsg3. Consistent with these findings, the amount of Dsg3 oligomers detected by membrane-impermeable extracellular crosslinking was drastically reduced in both, Pkp1 and 3 k.o. cell lines. Along the same line, binding frequencies of both, Dsg1 and Dsg3-dependent binding events as well as binding strength and the step position of Dsg3 interaction, the latter of which represents a measure for cytoskeletal anchorage, were drastically reduced in Pkp1 and 3 k.o. cell lines. Further, Dsg1 binding frequency was higher at cell borders compared to cell surface in wt but not in Pkp1 and Pkp3 k.o. cells, indicating a Pkp-dependent control of Dsg1 membrane positioning. Moreover, alteration of p38MAPK signaling, a central signaling pathway for the regulation of desmosomal adhesion, correlated with intercellular adhesion in all cell lines. However, Pkp3 k.o. cells showed reduced activity of p38MAPK under untreated conditions as well as a diminished response to the p38MAPK activator anisomycin, indicating an important role of Pkp3 for p38MAPK signaling. Taken together, these data suggest (1) that Pkps are important for localization and binding of desmosomal cadherins and (2) that Pkp3 may participate in the regulation of desmosomal adhesion via p38MAPK signaling.

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