Inhibition of sonic hedgehog signalling via MAPK activation controls chemotherapy-induced alopecia

IS Haslam1,2, G Zhou1,2, X Xie1, X Teng1, Y Nan1, E Smart1, D Rutkowski1, J Wiese1,2, Y Zhou1, Z Huang1, Y Zhang1, N Farjo1, R Farjo1, Q Wang1,2 and Z Yue1 1 Dept of Biological Chemistry, University of California Irvine, Irvine, California, United States, 2 Developmental and Cell Biology, University of California, Irvine, Irvine, California, United States.

The migration of wound-edge keratinocytes is part of the wound response, crucial for complete wound closure. Despite significant advances, the molecular mechanisms that orchestrate cell-cell adhesion between migrating keratinocytes are not fully characterized. During wound re-epithelialization, keratinocytes at the wound edge undergo series of cellular modifications. These cellular modifications require a loosening of cell-cell adhesion for effective migration. Mice lacking the epidermal transcription factor Grainyhead Like-3 (GRHL3) exhibit impaired wound healing and an increased adhesion between keratinocytes at the wound edge. The increased cell-cell adhesion in Krt14-Cre Grhl3fl/fl wounds coincides with high expression of the adhesion junction protein E-Cadherin and downregulation of the newly identified wound-response gene Fascin (FSCN1). Gene expression analysis of isolated wound-edge keratinocytes shows significant downregulation of Fscn1 mRNA expression in Krt14-Cre Grhl3fl/fl wounds. In addition, ATAC-seq on Krt14-Cre Grhl3fl/fl wound-edge keratinocytes shows loss of wound-specific peaks near Fscn1 gene, in a region that is highly enriched for GRHL3 motifs. Together, these data elucidate a novel wound-specific FSCN1-E-cadherin pathway controlled by GRHL3 that is required for cell-cell loosening between migrating keratinocytes during wound re-epithelialization. This pathway is altered in chronic diabetic wounds in mice.

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