DECODING MECHANISMS THAT REGULATE RE-EPITHELIALIZATION

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During normal wound healing, keratinocytes are the first dermal cell type to respond to the injury, covering the wound bed to establish a barrier for immune defense and provide structural and mechanical support for dermal regeneration. Failure of this re-epithelialization process results in the development of chronic wounds, which are associated with substantial medical costs. During re-epithelialization, keratinocytes can utilize multiple mechanisms to fill the space, including migration, proliferation, and hypertrophy. Additionally, individual keratinocytes are influenced by numerous factors in the wound microenvironment, including substrate mechanics and growth factors to direct these cellular decisions. To determine which individual cell behaviors represent the most promising targets to engineer re-epithelialization, we have examined collective and individual responses of HaCaT keratinocytes to changes in substrate mechanics and growth factors and utilized computational modeling to predict the hierarchy of factors driving wound closure. Our results suggest that migrational persistence is the key parameter for effective wound closure. We have further examined biomaterials-based methods to direct migrational persistence, and identified a mechanism by which immobilization of EGF induced strong migrational persistence through the activation of PLCg1 specifically in keratinocytes on the leading edge. Ongoing work is examining this process in more detail to determine the mechanism responsible for leading edge-specific activation of PLCg