

Isolation and Characterization of a Fibroblast Sub-Population Responsible for Cutaneous Scarring in the Ventral Dermis

Tripp Leavitt, Michael S. Hu, Graham G. Walmsley, Ulrike M. Litzemberger, Ryan C. Ransom, Elizabeth R. Zielins, Derrick C. Wan, Howard Y. Chang, H. Peter Lorenz, Michael T. Longaker

Purpose: Recent studies have demonstrated the functional heterogeneity of fibroblasts, particularly in terms of their activities during wound healing. Both location within the dermis¹ and embryonic lineages² provide a means by which we may now identify the sub-populations of fibroblasts chiefly responsible for connective tissue deposition during scar formation in the dorsal dermis. However, whether these findings translate to the ventral dermis have yet to be elucidated.

Methods: *Prrx1*^{Cre}/*Rosa26*^{mTmG} mice, were used to trace two fibroblast lineages restricted to the ventral dermis. Fibroblasts of different embryonic lineages—based on *Prrx1* expression—were isolated from ventral fetal and adult dermis at a series of time points, including the late-gestational transition from scarless to scar-forming wound healing. ATAC-seq (Assay for Transposase-Accessible Chromatin with high throughput sequencing) was also performed in isolated pre- and post-gestational fibroblasts.

Results: Histological analysis revealed that the *Prrx1*-positive lineage contributed to the majority of connective tissue during scar formation. Flow cytometry demonstrated a shift in fibroblast sub-populations over the course of gestation. Differential transcriptional activity shown by ATAC-seq further demonstrated the heterogeneous nature of fibroblasts within the ventral dermis.

Conclusions: As in the dorsal dermis, fibroblasts of the ventral dermis demonstrate functional heterogeneity. Further studies may allow targeting of specific sub-populations to improve wound healing.

1. Lichtenberger BM, Mastrogriannaki M, Watt FM. Epidermal [beta]-catenin activation remodels the dermis via paracrine signalling to distinct fibroblast lineages. *Nat Commun.* 2016;7.
2. Rinkevich Y, Walmsley GG, Hu MS, et al. Skin fibrosis. Identification and isolation of a dermal lineage with intrinsic fibrogenic potential. *Science.* 2015;348(6232):aaa2151.