Fibroblast Heterogeneity and its Role in Keloid pathogenesis Implication for targeted drug development

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Running Title
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BACKGROUND

Keloids are pathological scars resulting from abnormal wound healing. While clinical features vary by anatomical location, the underlying molecular mechanisms contributing to site-specific fibrosis remain poorly understood. Recent research suggests fibroblast heterogeneity and lipid-inflammation signaling play roles in fibrotic disease progression, but their spatial distribution within keloids and therapeutic implications require investigation.

METHODS

Keloids are pathological scars resulting from abnormal wound healing. While clinical features vary by anatomical location, the underlying molecular mechanisms contributing to site-specific fibrosis remain poorly understood. Recent research suggests fibroblast heterogeneity and lipid-inflammation signaling play roles in fibrotic disease progression, but their spatial distribution within keloids and therapeutic implications require investigation.

RESULTS

We identified ten major cell lineages, with fibroblasts exhibiting the most significant site-specific divergence. Chest fibroblasts were enriched in fatty acid and cholesterol metabolism, showing upregulation of arachidonic acid pathway enzymes and receptors localized to pro-inflammatory and secretory-reticular subsets. Earlobe fibroblasts demonstrated higher mesenchymal-transition and matrix remodeling. Pseudotime analysis revealed a chest-biased lineage with early PLA2G2A-PTGES-PTGFR axis activation. CellChat identified dense chest-centered networks involving PPIA-BSG and CXCL12-CXCR4, both promising pharmacological targets. Earlobe lesions preferentially engaged MDK/PTN-LRP1/SDC1 signaling pathways associated with tissue remodeling

CONCLUSİON AND RELEVANCE

Regional tissue microenvironments influence fibroblast fate in keloid disease. Integrated spatial and single-cell transcriptomic profiling identifies site-specific fibroblast programs and suggests potential therapeutic strategies for fibrotic skin disease.