Editorial

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Editorial on the Fibroblast Heterogeneity

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Editorial

Fibroblasts are the cells that make up connective tissue's extracellular matrix and are responsible for preserving the structural integrity of most tissues. Fibroblasts are thought to have functional specialisation based on their organ of origin, body site, and spatial placement, according to researchers. Several studies have recently revealed the existence of fibroblast subtypes in mice. The mammalian dermis has proven to be an accessible and tractable system for dissecting these interactions.

Fibroblasts are specialised cells found in mesenchymal-derived connective tissues such as the heart, lung, gastrointestinal tract and muscle. Dermal and nondermal fibroblasts have diverse gene expression patterns and fibroblasts generated from different anatomical regions, such as the neural crest, lateral plate mesoderm, and dermatomyotome have different developmental origins. Furthermore, the architecture of the dermis varies significantly at different body regions, which is linked to a distinct risk of disease processes including the production of keloid scars.

Different patterns of Hox gene expression reflect the developmental origin of the cells and are connected with differences in appearance and behaviour in cultured fibroblasts generated from different body regions. As a result, changes in fibroblast behaviour between body sites are likely due to a combination of innate variances as well as the role of factors such as mechanical stress, which varies throughout body regions.

Fibroblast heterogeneity can be classified by developmental stage, tissue of origin, and tissue microenvironment. The skin of mammals has proven to be a particularly tractable tissue with which to investigate these issues. The epidermis is a stratified squamous epithelium that sits on top of the dermis, which is a mesenchymal tissue. The dermis, like other mesenchymal tissues, contains a diverse range of cell types, including blood vessel components [endothelial cells, smooth muscle cells, and blood vessel–associated fibroblasts], eccrine and apocrine sweat glands, lymphatic vessel components, neurons, sensory receptors, and immunological cells that live in the tissues. Because these other cell types are so numerous in the adult dermis, fibroblasts are a minority cell type.

The developmental lineage, molecular phenotype, and adaptability in response to wound signals have all been used to define fibroblast heterogeneity in wound healing. Fibroblast lineages differ in their embryonic expression of patterning genes like Engrailed-1 and Prrx-1, which are homeobox transcription factors; lineage-positive fibroblasts respond to wounds, but lineage-negative fibroblasts do not.

Fibroblasts can be easily distinguished by their molecular phenotype (surface markers, omics signatures, and so on), but dynamic gene expression in the wound environment complicates this process.

It is now known that fibroblasts exhibit phenotypic plasticity in response to wound signals, but whether this plasticity is sustained in human wound healing remains to be shown. Recent research has demonstrated that fibroblasts are extraordinarily heterogeneous cells, but the best lens for studying this variety (lineage, phenotypic, and adaptability), as well as its relevance to human biology, is yet unknown. In this opinion piece, we discuss recent advances in our understanding of fibroblast heterogeneity during skin wound healing, as well as outstanding concerns that need to be answered before these results may be effectively applied to reduce scarring in patients.

Cancer fibroblasts

Fibroblasts in the stroma of solid tumours perform a similar role in supporting tumour cell proliferation and regulating the tumour microenvironment as they do in cutaneous wound healing. In fact, these Cancer-Associated Fibroblasts (CAFs) recapitulate wound-healing gene expression pathways in a mechanism known as the "serum response," which is conserved across diverse tissue and tumour types. Significant heterogeneity exists across fibroblasts from different tumour kinds and locales, as well as between species, just as it does in wound healing and fibrosis. As a result, fibroblasts are extremely difficult to target therapeutically in the context of cancer, despite their crucial involvement in disease progression.

In skin malignancies, there is a lot of fibroblast heterogeneity. In melanoma, for example, fibroblasts expressing the cell surface marker CD26 are an essential subpopulation of cells contributing to tumour stroma ECM deposition; reduction of the CD26-positive fibroblast subpopulation inhibited tumour growth in a mouse xenograft model of melanoma.CAFs are known to express a number of chemokines linked with both local immunosuppression and tumour growth in basal cell carcinoma. Even fibroblasts in cancer-free, sun-damaged areas around patients' tumours have cancer-associated gene expression patterns, implying that these cells may aid tumour growth.

Dermal fibroblasts heterogeneity

Dermal fibroblasts are the major cell type in the skin's dermal layer. These cells originate from distinct locations of the embryo and reside in unique niches in the dermis. Different dermal fibroblasts exhibit distinct roles in skin development, homeostasis, and wound healing. Therefore, these cells are becoming attractive candidates for cell-based therapies in wound healing.

Tissue examination at a single-cell level has revealed amazing new details about the cellular heterogeneity of several organs, including an unanticipated diversity among fibroblasts. With sequencing costs falling and sensitivity and sequencing depth rising, we can expect a slew of new publications revealing fibroblast subpopulations in all tissues (e.g. including synovium or bone-marrow). To comprehend and compare fibroblast heterogeneity in different organ systems and across species, new stratification methodologies based on functional variety rather than the expression of specific marker genes are required.