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Letter to Editor

Fibroblasts as tissue-specific mesenchymal stem cells: A re-evaluation

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ABSTRACT

This letter explores the evolving concept of fibroblasts as tissue-resident mesenchymal stem cells, challenging their classical definition by highlighting their phenotypic plasticity, multipotent capacity, and role in tissue homeostasis and regeneration.

Key words: Fibroblasts, Mesenchymal Stem Cells, Tissue Niche, Plasticity, Regeneration, Differentiation

Dear Editor

The traditional dichotomy between fibroblasts as simple stromal cells and mesenchymal stem cells (MSCs) as defined multipotent progenitors is increasingly difficult to sustain. We propose a paradigm shift: viewing fibroblasts not as terminally differentiated cells, but as a diverse population of tissue-specific MSCs that are primed by their unique microenvironment.

Phenotypic and Functional Overlap

The International Society for Cellular Therapy (ISCT) criteria for MSCs—plastic adherence, tri-lineage differentiation, and expression of specific surface markers (CD73, CD90, CD105)[1] —are remarkably met by numerous fibroblast populations[2]. Dermal, gingival, and cardiac fibroblasts, among others, have demonstrated the ability to differentiate into adipogenic, chondrogenic, and osteogenic lineages under appropriate conditions *in vitro*[3–5]. Furthermore, their shared immunomodulatory functions, particularly the suppression of T-cell proliferation, blur the functional distinctions between the two cell types[6]. This suggests that the standard ISCT criteria may be insufficient to delineate a true MSC from a multipotent fibroblast.

The Tissue-Specific Niche Defines Function

The critical factor that may define a fibroblast as a tissue-specific MSC is its niche. Fibroblasts from different anatomical locations exhibit distinct transcriptional profiles, largely governed by developmental HOX code expression. This ”positional memory” dictates their specific role in tissue homeostasis and repair. A dermal fibroblast is specialized for skin repair and ECM remodeling, while a periodontal ligament fibroblast is primed for cementogenic and osteogenic tasks. Rather than being a separate entity, the classical bone marrow MSC can be viewed as one specific, and perhaps more primitive, member of a broader family of mesenchymal progenitor cells, with fibroblasts representing their specialized, tissue-committed counterparts.

A Spectrum of Plasticity

The relationship is best described as a dynamic spectrum. Upon tissue injury, resident fibroblasts can be ”re-activated” or ”de-differentiated,” acquiring a more primitive, MSC-like state with enhanced proliferative and multipotent capabilities. This plasticity is a key regenerative mechanism. The converse is also true; MSCs introduced into a specific tissue niche can adopt a fibroblastic phenotype and function. This bidirectional interconversion strongly argues against a rigid classification.

Unresolved Questions and Future Directions

Key questions remain. If fibroblasts are indeed tissue-specific MSCs, what are the definitive markers that confirm their stemness versus a terminally differentiated state? Are the observed differences in differentiation potency merely a reflection of their degree of niche-specific commitment? Resolving these questions requires single-cell transcriptomic and epigenetic analyses of fibroblast populations across tissues to identify subpopulations with true stem cell properties.

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ABBREVIATIONS

ECM: Extracellular Matrix, **MSC:** Mesenchymal Stem/Stromal Cell, **ISCT:** International Society for Cellular Therapy

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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