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Skin and Bones (and Cartilage): The Dermal Fibroblast Connection

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A recent report by Sommar et al.¹ published in the *Journal of Plastic, Reconstructive & Aesthetic Surgery* provided evidence that dermally derived human fibroblastic cells, cultured as three-dimensional constructs on macroporous gelatin microcarriers encapsulated in platelet-rich plasma, were able to undergo induced osteogenic and chondrogenic differentiation *in vitro*, as demonstrated using histological, biochemical, and immunohistochemical analyses. The authors suggested that human dermal fibroblasts represent a convenient cell source for bone and cartilage tissue engineering. The reported findings are thus of relevance to the general field of regenerative medicine.

Tissue engineering and regenerative technologies are of particular importance in the musculoskeletal field, in view of the prevalence and burden of degenerative diseases that involve the articular joints and intervertebral discs, age-related diseases such as osteoporosis, and physical trauma related pathologies, such as fractures and tears, that impact bone, cartilage, and other soft tissues, including ligaments and tendons. While conventional reconstructive approaches developed in the last several decades have been effective in restoring physical activities and improving the lives of patients, there are inherent limitations. For example, artificial joints constructed from biomaterials, including titanium or chrome-cobalt alloys and ultra-high-molecular-weight polyethylene, result in stress shielding and the production of wear debris particulates that eventually compromise bone quality, leading to ultimate failure and the need for revision surgery.² Thus, while biomaterials are able to simulate some of the tissue characteristics, the quality and success of repair is ultimately dependent on the biological activities of the tissue and the constituent cell types. Thus, more biological and cellular reparative approaches are being actively sought, with the emergence of a new scientific discipline - tissue engineering.

Tissue engineering is the application of principles of life science and engineering to create tissue substitutes capable of restoring function to diseased or injured tissues, and requires three basic components – cells, scaffold, and biological signals (Figure 1).³ For cells, the current major technical challenges include sourcing, adequacy in quantity and quality, and phenotypic stability and requirements. In addition, for a number of safety and ethical reasons, autologous cells are generally preferred over allogeneic cells. The study by Sommar et al.¹ is thus directly relevant to this issue.

The main finding of the study is that human dermal fibroblasts, isolated using a relatively simple procedure, have the ability to differentiate into osteoblasts and chondrocytes, constituent cell types of bone and cartilage, respectively. The possibility of using autologous

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cells is thus highly feasible. However, it should be noted that the findings on the osteogenic and chondrogenic potential of dermal fibroblasts are not novel, since there have been a number of previous reports on osteogenic and chondrogenic differentiation of dermal fibroblasts.⁴⁻⁵ In addition, differentiation was induced using traditional osteogenesis and osteogenesis culture medium supplements/conditions,⁶ and was characterized primarily on the basis of histological and immunohistochemical parameters. Thus, no new mechanistic information can be derived on the biological pathways or signals responsible for the initiation and regulation of osteogenic and chondrogenic differentiation of the dermal fibroblasts.

Another aspect of this study is the application of a commercial biomaterial scaffold (CultiSpher-GL), a macroporous gelatin-based microcarrier, to produce three-dimensional constructs using dermal fibroblasts. A number of hydrogels, including alginate, agarose, collagen, and polyethylene glycol, have been used to produce three-dimensional stem cell-based constructs that support guided differentiation.⁷ Because no direct comparison was made in this study between CultiSpher-GL and these other more commonly used hydrogels in terms of cell proliferation and differentiation, there is no specific evidence to support the advantage of this particular biomaterial for cell-based tissue engineering, particularly regarding long-term biocompatibility and tissue reactions *in vivo*, including inflammatory and immune reactions. Mechanical characteristics, which are not measured in this study, represent another key requirement for functional skeletal tissue engineering. It is noteworthy that three-dimensional cartilaginous constructs derived from adult bone marrow mesenchymal stem cells, even after extensive induced chondrogenic differentiation, exhibit inferior mechanical properties compared to those derived from chondrocytes.⁸ The underlying reason for this difference is not known, and how dermal fibroblasts compare to other adult stem cells in this regard remains to be seen.

Cell-based tissue engineering is one of the most promising approaches in regenerative medicine. Adult stem cells are particularly attractive, since autologous sources are possible, minimizing safety and ethical complications.⁹ For adult dermal fibroblasts to be considered, a direct comparison to bone marrow derived mesenchymal stem cells, the de facto gold standard, must be carried out. In addition, efficient and reproducible cell isolation and expansion procedure must be adapted, and characterization parameters must be established that are predictive of the differentiation capabilities of each batch of cell isolates and the phenotype stability of the differentiated cells. For biomaterial scaffolds to be directly applicable for three-dimensional tissue construct, desirable properties include ease of cell seeding, optimal biodegradability, support of cell expansion and guided differentiation, and biocompatibility. Another requirement of a functional skeletal tissue-engineered construct is that it must exhibit mechanical properties that are appropriate for and compatible with subsequent tissue function, such as load bearing and joint articulation. Another challenge in regenerative technologies is multiphasic tissue engineering, because most tissues and organs are made up of multiple differentiated cell types distributed in structurally and spatially defined manner. A number of approaches have been taken to accomplish this goal, e.g., three-dimensional biomaterial printing for osteochondral tissue engineering.¹⁰ Finally, a major issue that must be taken into consideration in developing functional tissue engineering is the inherent differentiation fate and stability of the starting cell types; in other words, a judicious choice of the starting cell type(s), seeded into a three-dimensional scaffold in a spatially guided manner, may in fact be exploited to facilitate the engineering of the optimal multiphasic tissue. In this regard, it is critical to ascertain these differentiation characteristics of adult stem cells derived from various sources, including bone marrow, adipose, bone, ligament, as well as dermal fibroblasts, such that placement of specific cell type(s), that have well characterized and predictable differentiation phenotypes, into three-dimensionally

specific sites in an appropriate biomaterial scaffold can be carried out to enhance the engineering of multiphasic tissue constructs.

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Sommar *et al.*¹ reported that primary human dermal fibroblasts seeded into a three-dimensional biodegradable microcarrier can differentiate *in vitro* into osteoblasts and chondrocytes, and form three-dimensional bone- and cartilage-like constructs, respectively. Skeletal tissue engineering application of these cells awaits more in-depth characterization of their native and differentiated phenotypes as well as the rationale choice of a suitable biomaterial scaffold.

Figure 1.

Tissue engineering application of mesenchymal stem cells, illustrated using different approaches to articular cartilage repair. (A) Injection of a suspension of native mesenchymal stem cells, either directly without expansion or after culture expansion, into the joint space, where they encounter all intra-articular tissues. (B) Matrix-guided approach to repair deep cartilage defects in osteoarthritis, involving cell-seeding into biodegradable scaffold for controlled local application. (C) Cells recombinantly modified via gene transduction *ex vivo*, selected/expanded *ex vivo*, and injected directly into the joint space or seeded into matrix and implanted into cartilage defects, for global or local release of therapeutic transgene products. (Modified from Reference 9.)