REGENERATIVE MEDICINE

Self-directed articular resurfacing: a new paradigm?

Daniel A. Grande and Nicholas A. Sgaglione

Tissue engineering to repair diseased or injured cartilage could be revolutionized by the development of a novel cell-homing strategy that overcomes several barriers inherent in the use of existing techniques.

In an August 2010 issue of the *Lancet*, Lee and co-workers[1] describe a method for coaxing the body's own reservoirs of stem cells to migrate into a specially designed, anatomically accurate scaffold that promotes cell attachment, matrix elaboration, and subsequent biological whole joint resurfacing. The findings represent an important advance over previous tissue engineering concepts, which have relied on the implantation of exogenous cells to effect repair, as endogenous stem cells were thought to be too few in number or incapable of long-range migration to be equivalent to implanted cells in this setting.

Articular cartilage injuries are notoriously problematic for the orthopedic surgeon to treat successfully in a reproducible manner. These injuries are common, and are present in approximately 60% of knee joints upon arthroscopic examination.[2] Cartilage, primarily because of its avascular morphology and the isolation of its resident cells within a dense collagen and proteoglycan-rich matrix, lacks the capability for self-repair. The practical gold-standard for the treatment of focal defects—microfracture chondroplasty[3]—involves penetrating the subchondral plate to allow bleeding, and with it the migration of marrow stromal cells; however, the resultant repair is a mix of tissue generally acknowledged to be mechanically and biochemically inferior to native hyaline cartilage tissue.

In the search for an alternative to microfracture chondroplasty, the field of cartilage repair has seen notable success with the use of cell transplantation as the *sine qua non* for achieving true hyaline cartilage regeneration in focal defects of cartilage. A well-accepted formula for repair is the local delivery of cells such as differentiated chondrocytes,[4] or more recently mesenchymal stem cells,[5] from various tissue compartments. These cell-based therapies are expensive, not necessarily cost-effective, and require complex manufacturing practices. Furthermore, they can require multiple procedures for the harvest, culture, and subsequent implantation of cells. These characteristics are a barrier to the widespread clinical adoption of cell-based therapies, in spite of the superior structural regeneration achieved.[6] The results of the recent study by Lee and co-workers are transformative, not only because of the clinical implications for how we may treat orthopedic injuries but also because they are more far-reaching—multiple disciplines could benefit from the findings of this set of experiments.

In the study, a complete rabbit humeral head was fabricated using photolithographic technology with biocompatible materials that incorporated a penetrating network of specific-diameter pores to enable optimum cell access (Figure 1).[1] The entire scaffold was then loaded with the potent morphogen transforming growth factor β3 (TGF-β3) to assist in guiding resident host-endogenous stem cell chemotaxis and differentiation. The tissue regenerated by use of this strategy was clearly characterized as hyaline cartilage by all of the currently accepted and rigorous criteria for its definition, including the material properties of the regenerated hyaline cartilage and the presence of type II collagen in the extracellular matrix. This achievement represents a significant advancement in our ability to effectively control and direct the neogenesis of an entire joint surface, and the integration of subchondral bone, without the addition of exogenous cells. Whereas many previous investigations have attempted cartilage regeneration in one form or another, Lee *et al.* have apparently gone to extensive lengths to optimize the multitude of parameters necessary to demonstrate the successful regeneration of hyaline cartilage.

The innovations of the study are multifold and incorporate several different technological disciplines including engineering, orthopedic surgery, biomaterials, and regenerative

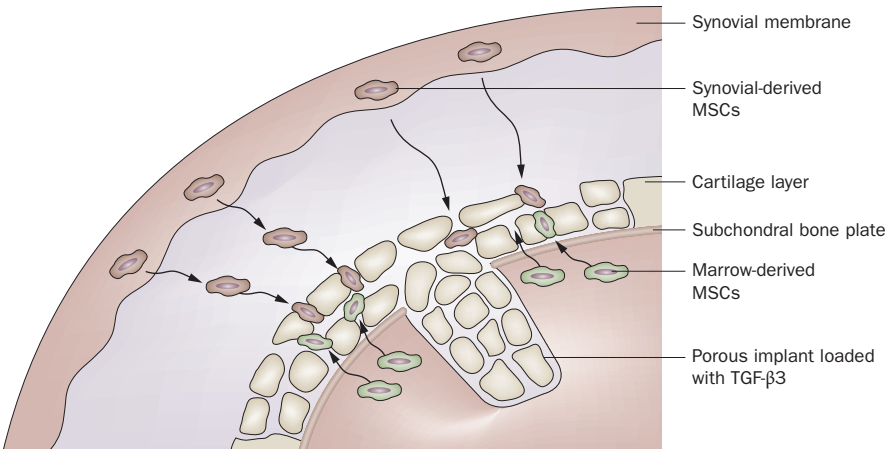

Figure 1 | A cell-homing approach to joint-surface regeneration. An anatomically accurate scaffold loaded with TGF-β3 facilitates the homing of host-endogenous MSCs to the articular surface, where the MSCs differentiate to generate hyaline cartilage. In this model, cell recruitment is from both the synovial membrane as well as the marrow compartment. Abbreviations: MSC, mesenchymal stem cell; TGF-β3, transforming growth factor β3.

medicine. Notably, the researchers resurfaced not just a focal defect but an entire joint surface, which broadens the technology's application beyond the treatment of sports injuries into the arena of osteoarthritis, a critically large and unmet clinical need. The reliance on the body's own cell population for effecting the regenerative process by cell-homing and recruitment negates the need for complicated exogenous-cell-based therapies, effectively providing the clinician with readily available implants in the operating room.

Although Lee *et al.* demonstrate how this mechanism of regeneration can be successful in principle, and have thus opened a new paradigm for effecting cartilage regeneration, there remain important unanswered questions that will need to be addressed before this technology can gain widespread clinical acceptance. First, the optimization of growth factor dosage, as well as other synergistic combinations, such as growth factor 'cocktails' capable of further enhancing the quality of the resultant cartilage tissue, need further evaluation. Second, the rabbit model, although a good testing ground for proof-of-concept studies, might not be translatable to models of larger weight-bearing joints or indeed humans. Rabbit studies have typically shown excellent short-term results, but a degradative process seems to occur in the 6–12 month range. Third, the ideal biomaterial combination is also a critical component to success. Of particular interest is the actual source of the cells homing to the morphogen-loaded scaffold. It is likely that these cells are emanating from both the subchondral bone marrow as well as the synovial lining membrane. To what extent each of these cell populations contributes to the overall repair, and what environmental cues each needs to differentiate down their respective pathways, whether bone or cartilage, remain to be answered.

By successfully demonstrating whole-joint resurfacing by cell-homing, Lee *et al.* have shown the promise of this technology. Thus, they have opened a new avenue of investigation that is likely to provide further and substantial improvements in healthcare.

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Competing interests
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GENETICS

Rare genes for autoimmunity—the new kids on the block

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Genome-wide association studies of human diseases have uncovered large numbers of common genetic variants with small effect sizes; however, rare genetic variants with large effect sizes might have greater relevance with respect to disease heritability. The identification and characterization of rare variants—such as those recently discovered in *SIAE*—is, therefore, likely to be a major endeavor in the field in the coming years.

Genome-wide association studies (GWAS) have identified >2,000 common genetic variants associated with various human diseases.[1] However, these common genetic variants confer small effect sizes, as measured by their estimated odds ratios, and collectively account for only a modest fraction of total disease heritability. This is certainly true of the GWAS-elucidated genes in rheumatic autoimmune diseases.[2,3] By contrast, rare genetic variants can exhibit considerably larger effect sizes than common genetic variants, and might have a more direct and profound impact on disease pathogenesis. It also seems likely that these rare genetic variants, particularly if highly penetrant, might be more predictive of disease than commonly occurring regulatory variants.

A study by Surolia *et al.*[4] has identified *SIAE* as the latest addition to the class of autoimmunity genes with rare variants, a list that includes *TREX1* and *IFIH1*. *SIAE*, which encodes sialate *O*-acetylesterase, has an autoimmunity-associated odds ratio >8, clearly dwarfing the odds ratios associated with autoimmunity genes previously identified by GWAS.[2,3] Sialate *O*-acetylesterase deacetylates sialic acid at the 9-OH position and promotes the binding of sialic acids to CD22, a negative regulator of B-cell receptor signaling. The subsequent phosphorylation of CD22 by the tyrosine-protein kinase Lyn is followed by the recruitment and activation of tyrosine-protein phosphatase non-receptor type 6 (also known as SHP-1). These effects ultimately dampen calcium flux induced by the B-cell receptor, with important consequences for B-cell tolerance.[5,6] Indeed, mice with mutations in components of this pathway develop lupus-like autoimmunity.[5–8] Collectively, these observations underline the obligatory role of this molecular pathway in regulating humoral immune responses and preventing humoral autoimmunity.

The role of sialate *O*-acetylesterase and its associated molecular cascade in autoimmune diseases other than systemic lupus erythematosus is unclear and warrants further study. Rare loss-of-function *SIAE* variants were predominantly associated with rheumatoid arthritis and type 1 diabetes.[4] The fact that cell-surface expression of 9-*O*-acetyl sialic acid is increased on activated B cells from patients with defective *SIAE* variants[4] suggests that sialate *O*-acetylesterase can also act in a B-cell-intrinsic manner in other autoimmune diseases. B-cell depletion therapy is effective in several autoimmune