

DO WE REALLY NEED CARTILAGE TISSUE ENGINEERING?

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INTRODUCTION: Typical cell-based cartilage repair techniques rely on the implantation of chondrocytes in suspension (ACI) or seeded on specific scaffolds (MACI). In the medium term, the resulting repair tissue is often fibrocartilaginous, lacking the biochemical and mechanical properties of hyaline cartilage and thus possibly affecting the durability of the clinical outcome. Engineered cartilaginous tissues, where cells are embedded within a hyaline-like extracellular matrix, could not only have superior handling at the time of implantation, but also provide the appropriate cues to induce hyaline cartilage regeneration. In this lecture, we will review a few examples generated using in vitro and in vivo pre-clinical models, addressing the possible advantages of grafting pre-developed cartilaginous tissues.

ECTOPIC DEVELOPMENT

Monolayer-expanded human articular chondrocytes (HAC) were seeded into Hyaff-11[®] meshes (FAB). Constructs were directly implanted subcutaneously in nude mice for up to 8 weeks or pre-cultured in media promoting proliferation or differentiation for 2 weeks prior to implantation. As compared to direct implantation of freshly seeded scaffolds, pre-culture of constructs in *differentiating medium*, but not in *proliferating medium*, supported an enhanced in vivo development of engineered cartilage, as assessed histologically, biochemically and biomechanically¹

RESPONSE TO INFLAMMATORY SIGNALS

Monolayer-expanded HAC were cultured in pellets for 3 or 15 days in chondrogenic medium and assessed for the production of anabolic and pro-inflammatory cytokines in response to IL-1 β treatment. By increasing culture time, cells released lower amounts of IL-8 and MCP-1 and higher amounts of TGF β -1. As compared to HAC cultured for 3 days, those cultured for 15 days responded to IL-1 β releasing lower MMP-1 and MMP-13 amounts²

RESPONSE TO MECHANICAL LOADING

HAC expanded in monolayers were seeded on different polymeric scaffolds, cultured for different durations and exposed or not to dynamic deformation. Upon application of

compression, changes in glycosaminoglycan (GAG) synthesized, accumulated, and released were significantly positively correlated to the GAG content of the constructs prior to loading, and resulted in improved tissue quality only in the most developed tissues^{3,4}.

ORTHOTOPIC IMPLANTATION IN GOATS

Engineered cartilage was generated by culture of autologous articular chondrocytes in Hyaff-11[®] meshes for 2 days, 2 weeks or 6 weeks and implanted on top of hydroxyapatite/Hyaff-11[®] sponges into goat osteochondral defects for 8 months. Additional experimental groups included defects that left untreated or treated with cell-free scaffolds. Modified O'Driscoll scores indicated poor cartilage repair for untreated and cell-free treated groups. Instead, the use of cells improved cartilage repair, and grafts cultured for 2 weeks performed better than those generated in 2 days⁵.

CONCLUSIONS: The reviewed studies indicate that, as compared to scaffolds freshly seeded with cells or immature tissues, more mature engineered cartilaginous tissues would have the potential to support superior cartilage repair. This could be due to a combination of (i) the intrinsic capacity to develop, (ii) the resistance to inflammatory processes, (iii) the modality of transduction of loading to cells. These pre-clinical evidences prompt for randomized, prospective trials where the performance of mature engineered cartilage grafts is compared to that of typical ACI or MACI techniques.

REFERENCES

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