Using dynamic bioreactors to engineer tendon grafts for anterior cruciate ligament reconstruction

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Video Abstract

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Abstract

A new approach for engineering tendon tissue to help heal tears to the anterior cruciate ligament, or ACL, may produce better outcomes than traditional repair methods. Typically, ACL reconstruction involves replacing the torn ligament with a graft. But autografts carry a risk of donor site morbidity, and allografts can lead to poor graft incorporation as well as the possibility of disease transmission. Now, researchers based in the Republic of Korea have combined tissue engineering and stem cell technology to produce lab-grown grafts that can help overcome many of these limitations. To engineer the grafts, the team started with small pieces of tendon that were surgically extracted from pigs. The tissues were decellularized to provide a fresh scaffold for the growth of new cells – specifically, human bone marrow-derived stem cells. The reseeded constructs were placed in custom-designed, dynamic bioreactors, which simultaneously applied tension and torsion to the growing tissue. This allowed the stem cells to mature within an environment that mimicked the mechanical forces produced by the knee. The tissues responded favorably to the mechanical conditioning. Compared to fresh tendons cultured in static incubators and reactor-cultured tendons that had not been recellularized, the reseeded tendons showed higher expression of tendon-specific biomarkers. They also had significantly higher levels of the extracellular matrix proteins collagen and glycosaminoglycan, supporting that the stem cells had acquired the traits of tendon cells. The dynamic bioreactors also enhanced the grafts' biomechanical properties – one of the most important requirements for an ACL graft. After 7 days in dynamic culture, the engineered tendons showed a significant increase in ultimate tensile load – calculated as the maximum load before failure – compared to freshly harvested tendons grown in static culture. Moreover, when used to repair a model of ACL rupture, the ultimate tensile load of the engineered grafts reached 80% of that measured in native ACL by 12 weeks after implantation. The grafts also appeared to be safe, producing no evidence of inflammation or immune reaction. Although these findings must still be replicated in humans, they serve as an important proof of concept that tendon tissue engineering using dynamic bioreactors holds promise for translation into clinical applications.