Tissue-engineering researchers create replacement knee ligaments from recipients' own cells

November 3 2009

(PhysOrg.com) -- In a development that could lead to more complete recovery from torn anterior cruciate ligament (ACL) injuries in humans, University of Michigan researchers have grown and repaired knee ligaments in rats from bone marrow stem cells harvested from the rats' own bones.

The U-M researchers have tissue-engineered an advanced graft that includes an elastic ligament section in the center to accommodate joint motion and bone portions on the ends for more effective integration and attachment to the native bone of the injured knee.

Their ligament design emphasizes stretchiness over initial strength, which appears to be more important for viability of the ligament and in allowing patients to regain their original mobility, says Ellen Arruda, a professor in the Department of Mechanical Engineering, the Department of Biomedical Engineering and in Macromolecular Science and Engineering.

Other methods for ACL repair, including approaches that involve tissue engineering, aim to match or exceed the previous stiffness of the ligament.

"In our paradigm-shifting approach, we recognized that stiffness and strength aren't the most important requirements. The critical property being overlooked is extensibility," Arruda said. "A ligament is not being asked to support a patient's weight. It's being asked to stretch and to help stabilize a joint."

It's estimated that surgeons reconstruct 50,000 knees each year due to sports-related ACL injuries. Today, they either replace the torn ligament with a transplant from a cadaver or graft a section of ligament from another part of the patient's leg.

These methods work, but they have drawbacks, says Lisa Larkin, associate professor in the Department of Molecular & Integrative Physiology and the Department of Biomedical Engineering. They require permanent screws to hold the new ligament in place. And while the replacement ligament stabilizes the knee, it tends to remain stiff, never fully integrating with the surrounding tissue. Within 12 years of reconstruction, close to 70 percent of patients develop osteoarthritis. This is especially problematic for injured children and adolescents, Larkin says.

"The graft never fully develops the function of the ligament it's replacing," Arruda said. "It's sitting in there like a spring. It stabilizes the knee, but it's stiffer than it really needs to be, so the biomechanics are never fully restored."

Other tissue-engineering approaches exist that involve seeding the patient's own cells on a scaffold that guides the growth of a new ligament. While scaffold-based methods deliver ligaments that provide immediate strength to the knee, they are not very flexible and may not always provide the best environment for remodeling in response to mechanical strains.

As a result, cell death and weakening of the scaffold-based ligament often occurs over time. The scaffold-less tissue-engineering methods of

Arruda and Larkin show promise for bypassing these side effects. Because of the compliance (stretchiness) of the ligament portion of their new composite ligament, no screws would be required. Stitches would hold the graft in place while the ligamentous mid-section stretches during knee movement. The bony ends would be inserted into small holes drilled into the adjacent bones.

Because it would be made of the patient's own cells, the bone-ligament-bone configuration would integrate more seamlessly into the joint. It would continue to grow, reacting to knee movement by stiffening and eventually restoring the correct mechanical forces to all ligaments in the knee.

In this experiment, Arruda, Larkin and their colleagues removed and examined the rats' knee one or two months after ligament replacement. They found that the new, engineered composite ligaments had integrated with the surrounding bone. They had grown additional collagen fibers, which means they were becoming more robust. Blood vessels had penetrated into the engineered ligament. Upon comparison, they found that the new ligaments were similar to those in young rats.

"The mechanical properties of the ligament increased in the body. Its organization improved. It went from having uniform mechanical properties before it went into the body to becoming mechanically complex in the body," Arruda said. "It took on the mechanical functional gradient of native tissue. This tells us the body knows it's a ligament and it's trying to adapt."

More information: Arruda and Larkin are co-authors on a paper about the research that appears in the October edition of the American Society of Mechanical Engineers' *Journal of Biomechanical Engineering*. The paper is called, "Morphological and Functional Characteristics of Three-Dimensional Engineered Bone-Ligament-Bone Constructs Following

Implantation."

Provided by University of Michigan (news : web)