Medical Xpress

Researchers develop functional, transplantable rat liver grafts

June 13 2010

A team led by researchers from the Center for Engineering in Medicine at Massachusetts General Hospital (MGH) has developed a technique that someday may allow growth of transplantable replacement livers. In their report that will be published in *Nature Medicine* and is receiving early online release, the investigators describe using the structural tissue of rat livers as scaffolding for the growth of tissue regenerated from liver cells introduced through a novel reseeding process.

"Having the detailed microvasculature of the liver within a biocompatible, natural scaffold is a major advantage to growing liver tissue in a synthetic environment," says Basak Uygun, PhD, research associate at the MGH Center for Engineering in Medicine (MGH-CEM) and the paper's lead author. "Our technique of 'decellularizing' organs leaves the vascular system intact, which facilitates repopulation of the structural matrix and the subsequent survival and function of the introduced liver cells."

Liver transplantation is the only effective treatment for liver failure but is greatly limited by the shortage of donor organs. Each year 4,000 individuals who might have survived with a liver transplant die in the U.S. The shortage of donor livers and other organs is a major force behind the emerging field of tissue engineering and regenerative medicine. Efforts to build tissues from the ground up have not yet approached the goal of transplantable replacement organs, and replacing the liver - in which each cell is a metabolic factory requiring constant, direct contact with the vascular system - has been particularly challenging.

The current report describes a refinement of an approach to re-engineering replacement rat hearts that was reported in 2008 by University of Minnesota researchers. Since liver tissue is much more delicate than the muscular structure of the heart, the MGH-CEM team developed a gentler way of flushing living cells out of the liver's structural matrix, which is primarily made of connective tissue like collagen. After the cells were removed, the lobular structure of the liver and its extracellular matrix remained. Containing specific biochemical signals and cues that would direct liver cells to travel to the correct location and resume function - something quite difficult to replicate using synthetic methods - the matrix also maintained the organ's intricate network of blood vessels.

Another novel technique was used to reintroduce hepatocytes, the cells that carry out most of the liver's primary functions, into the decellularized matrix. The MGH-CEM approach actually caused cells to penetrate the vascular network and become embedded in the matrix, leaving major vessels clear to carry the essential blood supply. The repopulated matrix displayed normal liver function for up to 10 days in culture, and recellularized grafts were successfully connected to the circulation of live rats with minimal cellular damage and normal hepatocyte function.

"As far as we know, a transplantable liver graft has never been constructed in a laboratory setting before," explains Korkut Uygun, PhD, of the MGH-CEM, the paper's senior author. "Even though this is very exciting and promising, it is a proof-of-concept study only. Much more work will be required to make long-term functional liver grafts that can actually be transplanted into humans. We haven't been able to go beyond several hours in the rats, but it's a great start."

Martin Yarmush, MD, PhD, director of the MGH-CEM and a co-author of the Nature Medicine study, explains that the quarter of a million donor livers discarded each year because they are not suitable for transplantation would be an obvious source of supply for the creation of whole-organ scaffolds. "There is great potential for constructing full-fledged liver lobes containing animal or human cells, but several thorny issues must first be tackled, including formation of a layer of endothelial cells to line graft blood vessels," he says. "Given enough careful work, this approach could ultimately revolutionize tissue engineering and provide real working grafts for the liver and other complex tissues." Yarmush and Korkut Uygun both have faculty appointments at Harvard Medical School.

Provided by Massachusetts General Hospital