Study Sheds Light On Formation of Tissue-Engineered Vascular Grafts to Repair Heart Defect

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(PhysOrg.com) -- A Yale School of Medicine study provides new understanding of the mechanisms that underlie how tissue engineered vascular grafts (TEVG) work. The paper is published this week in the online Early Edition of the *Proceedings of the National Academy of Sciences*.

TEVG are specially-designed vascular grafts that can be used in congenital heart surgery because they possess growth potential. They are made by seeding an individual's own cells onto a biodegradable tube. As the tube degrades, a blood vessel forms. The study, conducted on mice, could have implications for the treatment of babies and children born with a single ventricle anomaly - a life-threatening congenital heart defect.

The Yale surgeons expanded on an earlier study and human trial conducted in Japan on the use of TEVG as conduits in patients with single ventricles. That study was conducted by researchers from Yale and Tokyo Women's Medical University. Updated results from the trial were recently published in the Journal of Thoracic and Cardiovascular Surgery. Results of the Japanese study are promising and demonstrate the feasibility and utility of using TEVG in congenital heart surgery. The lead author was Toshiharu Shinoka, M.D., Ph.D., now of Yale School of Medicine and a contributing author on the latest PNAS study.

In the PNAS-published investigation, the Yale researchers set out to understand the underlying mechanism of TEVG formation in mice. The tissue-engineered grafts used in both studies differed from older vascular grafts in a critical way. Researchers developed a method of creating mature, living blood vessels by seeding the individual's own bone marrow cells onto a biodegradable tube, or scaffolding. After only a couple of hours of incubation, surgeons were able to implant the seeded scaffolding into the patient.

"After implantation, the seeded blood marrow cells appeared to transform into living blood vessels, very similar to native blood vessels," said lead author on the PNAS paper, Christopher K. Breuer, M.D., associate professor of pediatric surgery at Yale School of Medicine. "Because the vessels were made of the patient's own cells, they are not susceptible to rejection."

In trying to figure out the mechanism of this transformation, the Yale team initially theorized that the bone marrow cells had simply been incorporated into the existing vascular system, but further investigation showed this was not the case. Breuer says his team was startled to discover what was really taking place. "We realized that the grafts appeared to undergo an inflammatory response due to the infiltration of host monocytes - white blood cells that are part of the body's immune system. Rapid recruitment of these monocytes has been shown before to be intricately involved in natural blood vessel formation, or arteriogenesis. In other words, inflammation from the immune system response was instigating the creation of new blood vessels."

In infants born with just one ventricle, the heart cannot adequately supply oxygen to the body. These infants are known as "blue babies" because the lack of sufficient oxygen causes cyanosis, a bluish tinge to the skin. Without surgical intervention, the condition is almost always fatal.

Previous methods of correcting this congenital heart defect have relied upon synthetic grafts which often fail due to thrombosis or clotting of the graft. Because of their artificial composition, they may also require replacement as the child grows.

The Yale team's advance in understanding why tissue-engineered vascular grafts parallel the natural process of vascular formation may have important implications for the growing field of vascular tissue engineering. Yale pediatric cardiologist Alan Friedman, M.D., said, "The revolutionary possibilities established from this work may help define the future of care that we provide to our patients affected by congenital heart disease. These innovations may well change not only the way we think, but the way we practice."

Other authors on the *PNAS* study are Jason D. Roh, Rajendra Sawh-Martinez, Matthew P. Brennan, Steven M. Jay, Lesley Devine, Deepak A. Rao, Tai Yi, Tamar L. Mirensky, Ani Nalbandian, Brooks Udelsman, Narutoshi Hibino, Toshiharu Shinoka, W. Mark Saltzman, Themis R. Kyriakides and Jordan S. Prober of the Interdepartmental Program in Vascular Biology and Therapeutics, and Edward Snyder of the Interdepartmental Program in Vascular Biology and Therapeutics and the Department of Laboratory Medicine, Yale School of Medicine.

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