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New diaphragms grown from stem cells offer hope of a cure for common birth defect

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An international collaboration between scientists in Sweden, Russia, and the United States has resulted in the successful engineering of new diaphragm tissue in rats using a mixture of stem cells and a 3D scaffold. When transplanted, it has regrown with the same complex mechanical properties of diaphragm muscle. The study is published in the journal *Biomaterials*, and offers hope of a cure for a common birth defect and possible future heart muscle repairs.

The multidisciplinary team behind the current study includes world-renowned researchers in the field of regenerative medicine and tissue engineering; Paolo Macchiarini, MD, PhD, Director of the Advanced Center for Regenerative Medicine and senior scientist at Karolinska Institutet; Doris Taylor, PhD, Regenerative Medicine Research Director at the Texas Heart Institute; and Mark Holterman, MD, PhD, Professor of Surgery and Pediatrics at the University of Illinois College of Medicine in Peoria, working in collaboration with a research team at the Kuban State Medical University in Russia.

The diaphragm is a sheet of muscle that has to contract and relax constantly to allow breathing. It is also important in swallowing, and acts as a barrier between the chest cavity and the abdomen. Malformations or holes in the diaphragm are found in 1 in 2,500 babies and can cause extreme, often fatal, symptoms.

At the moment, surgical repair of large defects like these involves using an artificial patch, which will not grow with the infant and does not

provide any contraction to assist with breathing. The new technique presented in *Biomaterials* could instead allow such replacements to be grown especially for babies from their own cells, which would provide all the function of diaphragm tissue and would grow with them.

The success of this study also offers hope for the possibility of regenerating heart tissue, which undergoes similar pressure as it contracts and relaxes with every beat.

"So far, attempts to grow and transplant such new tissues have been conducted in the relatively simple organs of the bladder, windpipe and esophagus. The diaphragm, with its need for constant muscle contraction and relaxation puts complex demands on any 3D scaffold; until now, no one knew whether it would be possible to engineer," said Dr. Doris Taylor.

Dr. Paolo Macchiarini adds, "This bioengineered muscle tissue is a truly exciting step in our journey towards regenerating whole and complex organs. You can see the muscle contracting and doing its job as well as any naturally-grown tissue - there can be no argument that these replacements are truly regenerated, and the possibilities that this opens up for the future are enormous."

The field of tissue engineering involves 'growing' new tissues or organs from stem cells on three dimensional 'scaffolds,' which give both structural support and shape to the new tissue and guide the differentiation and proliferation of the stem cells. Engineered new tissues can not only help patients avoid the need for an organ donation, but also the need for the recipient to take immunosuppressant drugs.

In the current study, the researchers took diaphragm tissue from donor rats and removed all the living cells from it using a series of chemical treatments. This process removes anything that might cause an immune

response in the recipient animals, while keeping all the connective tissue - or extracellular matrix - which gives tissues their structure and mechanical properties. When tested in vitro, these diaphragm scaffolds at first appeared to have lost their important rubber-like ability to be continually stretched and contracted for long periods of time. However, once seeded with bone marrow derived alloegenic stem cells and then transplanted into the animals, the diaphragm scaffolds began to function as well as undamaged organs.

The method must now be tested on larger animals before it can be tried in humans, but the hope is that tissue-engineered repairs for congenital diaphragm malformations will be at least as effective as current surgical options with the added benefit of growing with children throughout their lives.

More information: Elena A. Gubareva et al. Orthotopic transplantation of a tissue engineered diaphragm in rats, *Biomaterials* (2015). DOI: 10.1016/j.biomaterials.2015.11.020

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