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Researchers safely regenerate failing mouse hearts with programmed embryonic stem cells

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Mayo Clinic researchers have safely transplanted cardiac preprogrammed embryonic stem cells into diseased hearts of mice successfully regenerating infarcted heart muscle without precipitating the growth of a cancerous tumor -- which, so far, has impeded successful translation into practice of embryonic stem cell research.

The Mayo study is the first known report establishing a successful, tumor-resistant approach to growing new heart tissue from an embryonic stem cell source. The study is published in the February issue of the *Journal of Experimental Medicine*.

Embryonic stem cells have the potential to become any cell type in the body. But directing the stem cells to regenerate targeted tissue is a process that hasn't yet been perfected. Scientists continue to closely scrutinize stem cell strategies to establish even safer and more effective treatments for disease.

"Embryonic stem cells are like a stealth fighter jet that flies virtually undetectable by radar," says the study's first author, Atta Behfar, M.D., Ph.D., a clinician-investigator fellow in the Mayo Graduate School of Medicine. "The host body doesn't recognize embryonic stem cells, which it allows to multiply freely in an unimpeded fashion."

The Mayo study is the first known report of a successful strategy for

programming embryonic stem cells to suppress cancer genes, to mature into heart cells (also known as cardiomyocytes) and to successfully fix injured hearts without causing tumors to develop. The study removes a critical obstacle towards translation of regenerative technology into developing new therapies for people with heart disease.

“Embryonic stem cells have an unequaled potential for repair, yet it has been uncertain whether we can drive them to safely regenerate the tissue we would like to replace,” says Andre Terzic, M.D., Ph.D., a stem cell specialist and lead investigator of the study. “Our objective was to repair heart muscle by avoiding the limitations intrinsic to embryonic stem cells, i.e., potential tumor growth.

“In this study, we have successfully programmed embryonic stem cells to safely generate new cardiac muscle tissue, leading potentially to new therapy,” Dr. Terzic says.

The Study

Researchers transplanted mouse embryonic stem cells into infarcted hearts of mice. Consistent with the risk for uncontrolled growth, a significant number of recipient mouse hearts developed tumors. To avoid tumor formation, researchers secured guided differentiation of stem cells to produce cardiopoietic cells, or cardiac specified cell precursors rather than any cell type. Treatment with cardiopoietic cells proved to have no tendency to develop into cancer. Tumor-free heart repair occurred in all treated mice. Two months after cardiopoietic stem cell transplantation, scientists reported a 35 percent improved output in treated hearts.

The threat of tumor growth associated with embryonic stem cell transplants was eliminated by restricting expression of oncogenes and pluripotency genes through transgenic manipulation of tumor necrosis

factor alpha (TNFa), a genome reprogramming protein. Researchers found that over-expressed TNFa promoted guided control of cardiac embryonic stem cells to drive the cardiogenesis process.

Researchers discovered approximately 15 proteins whose production was dramatically increased after TNFa stimulation. These proteins, when combined into a “cocktail,” secured guided differentiation of embryonic stem cells, producing cardiac progenitors called cardiopoietic cells. Such guided heart precursor cells did not form tumors, even though they were transplanted at doses that would otherwise carry a high risk for tumorigenesis with embryonic stem cells.

“Our goal is to apply these findings to adult stem cells, and in our next step create the first human cardioprogenitor stem cells as a tool for therapies in the future,” Dr. Terzic says.

Source: Mayo Clinic