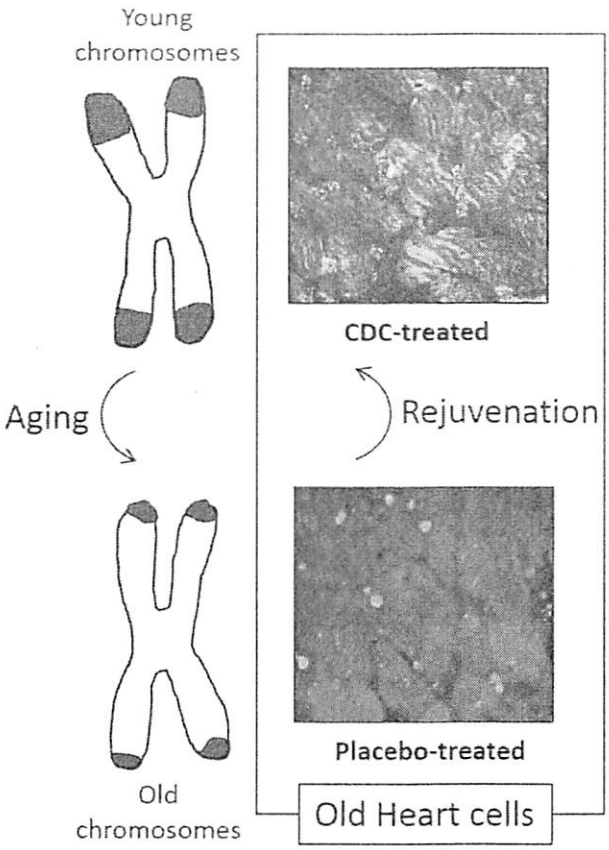
STEM CELL INJECTIONS REJUVENATE AGING RAT HEARTS

Posted by Stem Cells Daily | Aug 15, 2017 | News | 0 |



Researchers at the Cedars-Sinai Heart Institute have shown that injecting cardiac stem cells from young rats into the hearts of old rats can help to reverse the natural cardiac aging process. Results from the studies, led by Eduardo Marbán, M.D., Ph.D., director of the Cedars-Sinai Heart Institute, suggest that similar treatments might one day be used to prevent age-related heart function decline and cardiovascular disease in humans. The Cedars-Sinai studies are reported in the *European Heart Journal*, in a paper entitled "Cardiac and Systemic Rejuvenation after Cardiosphere-Derived Cell Therapy in Senescent Rats."

As we get older the likelihood of developing cardiovascular disease increases. Cell senescence underpins the cardiac aging process, and this is characterized by the shortening of

telomeres, the end caps on our chromosomes. Telomere shortening is associated with heart dysfunction and hypertrophy, impaired cardiomyocyte proliferation, interstitial fibrosis, and reduced regenerative capacity.

Dr. Marbán's team completed the world's first human cardiac stem cell infusion back in 2009 as part of a Phase I trial in heart attack patients. In the latest animal studies, the researchers tested whether cardiosphere-derived cells (CDCs) from newborn rats could reverse or hold back aging in the hearts of old animals. CDCs are cardiac progenitor cells that can differentiate into the three primary cardiac cell types—cardiomyocytes, endothelial cells, and and smooth muscle cells.

The researchers injected CDCs directly into the hearts of aged rats that had undergone echocardiogram testing, treadmill stress tests, and blood analyses at baseline. Equivalent tests were then carried out a month after the stem cell injections. The results of these and other analyses showed that the CDC treatment led to improved heart function and structure and boosted exercise capacity by about 20%.

CDC injections also led to a range of non-cardiac-specific effects, such as speeding hair growth, reducing systemic levels of inflammatory biomarkers, improving renal function, and helping to prevent weight loss secondary to cachexia or sarcopenia. Notably, stem cell therapy was associated with lengthening in heart cell telomeres, resulting from activation of the enzyme telomerase. Promisingly, rejuvenating effects were also seen when human heart cells

from older donors were co-cultured with young CDCs.

Genetic analysis identified treatment-related changes in the expression of 37% of the 168 genes implicated in tissue aging and cellular senescence pathways, primarily those involved in cell cycle control and immune response. "Most of the CDC-related changes (85.5%) directionally recapitulated the gene expression patterns of young animals," the authors write in their published paper.

"The way the cells work to reverse aging is fascinating," Marbán commented. "They secrete tiny vesicles that are chock-full of signaling molecules such as RNA and proteins. The vesicles from young cells appear to contain all the needed instructions to turn back the clock."

What the researchers don't yet know is whether stem cell therapy can also extend life, and there is still a lot more work to do, admits Lilian Grigorian-Shamagian, M.D, Ph.D., co-primary investigator and the first author of the study. "We have much to study, including whether CDCs need to come from a young donor to have the same rejuvenating effects and whether the extracellular vesicles are able to reproduce all the rejuvenating effects we detect with CDCs."

Dr. Marbán was previously at the Johns Hopkins University, where he pioneered the process for growing cardiac-derived stem cells. The technology has since been licensed by the Johns Hopkins and Cedars-Sinai to Capricor Therapeutics. Capricor's lead allogeneic cardiac cell therapy candidate, CAP-1002, is in clinical

development for treating heart disease associated with Duchenne muscular dystrophy and has also been evaluated for adult cardiology indications.

Given that CDCs have already proven safe in human testing, Dr. Marbán's team projects that it may be relatively quick to progress the cardiac rejuvenating CDC therapy into the clinic. "The present findings motivate further translational studies of rejuvenation by CDC therapy," the authors conclude. "If such follow-up studies are promising, progress to clinical testing may be highly feasible...."

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