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Tumor-free iPS stem cells for heart cells

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When induced pluripotent stem (iPS) cells were first discovered in 2007 there was a huge interest.[1,2] The iPS cell technique with a minimal number of embryonic transcription factors could turn skin or any other tissue directly into viable embryonic stem cells. It was amazing to able to so simply to turn mature adult cells back into embryonic stem cells. The discovery also avoided the most difficult ethical/political problem of human embryonic stem cells (ES), because no potential human being was involved. It seemed that the pathway to stem cell regeneration was now opened for every disease that needed tissue regeneration including heart disease. Although literally thousands of papers have been published on iPS, there have been no FDA-approved human trials on iPS and heart disease or any other disease. That is because iPS as replacements for embryonic stem cells are faced with the same problem that hES are faced with: they create random tumor masses known as teratomas. Teratomas are tumors of mixed cells that make bone, teeth, hair, gut, and neurons. They are a characteristic of hES. Their presence is even used as a test to define that iPS cells are the same as hES cells. Teratomas make hES and iPS cells too risky to use for human treatment and is one of the main reasons that iPS trials on humans have not been allowed by the FDA.

In their recent paper in *Cell Cycle*, Zhang et al.[3] have a major breakthrough of preventing the possibility of teratomas when using iPS cells for regenerating heart muscle. Heart muscle is destroyed in heart attacks due to a lack of oxygen (myocardial ischemia or MI). Repeated MIs lead to heart failure, because the heart does not have enough cardiomyocytes to keep the heart pumping. Death occurs when the injured heart cannot pump enough blood or respond to increased bodily demands for oxygen. Therefore, the great hope of stem cells is that they can regenerate cardiac tissue, which is particularly critical because of the large number of patients with heart disease.

To overcome the obstacle of teratomas, Zhang et al.[3] reasoned that the iPS stem cells which cause teratomas can be recognized by a transcription factor, Nanog. Nanog correlates with tumorogenicity in iPS cells. They took a recent discovery by Ben-David et al.[5] that in ES cells inhibition of an oleate enzyme, stearoyl-coA desaturase, by a chemical, PluriSin#1, caused undifferentiated ES cells to die. Zhang et al. asked would this treatment work in iPS cells, and would it selectively destroy the Nanog-labeled tumorigenic cells? In a series of experiments, both in cell culture and in mice, they demonstrated that PluriSin#1 does remove the tumorigenic iPS cells. Further they showed that treated iPS cells could be given to mice hearts without causing tumors. The breakthrough by Zhang et al. needs to be repeated for human iPS cells, but it makes stem cells for heart regeneration in humans without the risk of tumors eminently possible.

It has long been believed by scientists that although adult cells like bone marrow-derived cells can be used for heart repair,[6] the embryonic stem cells would be the best choice, because they are natural. Since iPS cells are the closest to ES cells but avoid the ethical–political concerns attached to hES, this discovery overcomes the stumbling block that has held back iPS use in humans. While the authors have carefully shown that pretreatment of iPS cells with PluriSin#1 works for regenerating cardiomyocytes in the heart, the finding could also advance stem cell therapy with iPS for regeneration of other types of cells in other organs for other diseases too.[7]

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