

Scientists identify role of tiny RNAs in controlling stem cell fate

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Researchers at the Gladstone Institute of Cardiovascular Disease (GICD) and the University of California, San Francisco have identified for the first time how tiny genetic factors called microRNAs may influence the differentiation of pluripotent embryonic stem (ES) cells into cardiac muscle.

As reported in the journal *Cell Stem Cell*, scientists in the lab of GICD Director, Deepak Srivastava, MD, demonstrated that two microRNAs, miR-1 and miR-133, which have been associated with muscle development, not only encourage heart muscle formation, but also actively suppress genes that could turn the ES cells into undesired cells like neurons or bone.

“Understanding how pluripotent stem cells can be used in therapy requires that we understand the myriad processes and factors that influence cell fate,” said Dr. Srivastava. “This work shows that microRNAs can function both in directing how ES cells change into specific cells—as well as preventing these cells from developing into unwanted cell types.”

The differentiation of ES cells into heart cells or any other type of adult cell is a very complicated process involving many factors. MicroRNAs, or miRNAs, seem to act as rheostats or “dimmer switches” to fine-tune levels of important proteins in cells. More than 450 human miRNAs have been described and each is predicted to regulate tens if not hundreds of proteins that may determine cellular differentiation.

While many ES cell-specific miRNAs have been identified, the role of individual miRNAs in ES cell differentiation had not previously been determined. The Gladstone team showed that miRNAs can control how pluripotent stem cells determine their fate, or “cell lineage” – in this case as cardiac muscle cells.

Specifically, they found that miR-1 and miR-133 are active at the early stages of heart cell formation, when an ES cell is first “deciding” to become mesoderm, one of the three basic tissue layers in mammals and other organisms. Activity of either miR-1 or miR-133 in ES cells caused genes that encourage mesoderm formation to be turned on. Equally important, they caused other genes that would have told the cell to become ectoderm or endoderm to turn off. For example, expression of a specific factor called Delta-like 1 was repressed by miR-1. Removal of this factor from cells by other methods also caused the cells to begin transforming into heart cells.

“Our findings provide insight into the fine regulation of cells and genes that is needed for a heart to form,” said Kathy Ivey, PhD, a California Institute of Regenerative Medicine (CIRM) postdoctoral fellow and lead author on the study. “By better understanding this complicated system, in the future, we may be able to identify ways to treat or prevent childhood and adult diseases that affect the heart.”

Source: Gladstone Institutes

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