Gene directs stem cells to build the heart

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Researchers have shown that they can put mouse embryonic stem cells to work building the heart, potentially moving medical science a significant step closer to a new generation of heart disease treatments that use human stem cells.

Scientists at Washington University School of Medicine in St. Louis report in *Cell Stem Cell* that the Mesp1 gene locks mouse embryonic stem cells into becoming heart parts and gets them moving to the area where the heart forms. Researchers are now testing if stem cells exposed to Mesp1 can help fix damaged mouse hearts.

"This isn't the only gene we'll need to get stem cells to repair damaged hearts, but it's a key piece of the puzzle," says senior author Kenneth Murphy, M.D., Ph.D., professor of pathology and immunology and a Howard Hughes Medical Institute investigator. "This gene is like the first domino in a chain: the Mesp1 protein activates genes that make other important proteins, and these in turn activate other genes and so on. The end result of these falling genetic dominoes is your whole cardiovascular system."

Embryonic stem cells have created considerable excitement because of their potential to become almost any specialized cell type. Scientists hope to use stem cells to create new tissue for treatment of a wide range of diseases and injuries. But first they have to learn how to coax them into becoming specialized tissue types such as nerve cells, skin cells or heart cells.

"That's the challenge to realizing the potential of stem cells," says Murphy. "We know some things about how the early embryo develops, but we need to learn a great deal more about how factors like Mesp1 control the roles that stem cells assume."

Mesp1 was identified several years ago by other researchers, who found that it was essential for the development of the cardiovascular system but did not describe how the gene works in embryonic stem cells.

Using mouse embryonic stem cells, Murphy's lab showed that Mesp1 starts the development of the cardiovascular system. They learned the gene's protein helps generate an embryonic cell layer known as the mesoderm, from which the heart, blood and other tissues develop. In addition, Mesp1 triggers the creation of a type of cell embryologists recently recognized as the heart's precursor.

They also found that stem cells exposed to the Mesp1 protein are locked into becoming one of three cardiovascular cell types: endothelial cells, which line the interior of blood vessels; smooth muscle cells, which are part of the walls of arteries and veins; or cardiac cells, which make up the heart.

"After they are exposed to Mesp1, the stem cells don't make any decisions for several days as to which of the three cell types they're going to become," Murphy notes. "The cues that cause them to make those commitments come later, in the form of proteins from other genes."

Researchers already know a number of the genes that shape the heart later in its development. Murphy plans to start tracing Mesp1's effects from gene to gene—following the falling genetic dominoes, which branch out into the pathways that form the three cardiac cell types.

"If we can find gene combinations that only make endothelium or cardiac or smooth muscle, then that could be applied to tailoring embryonic stem cells for therapies later on," he says.

Source: Washington University

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