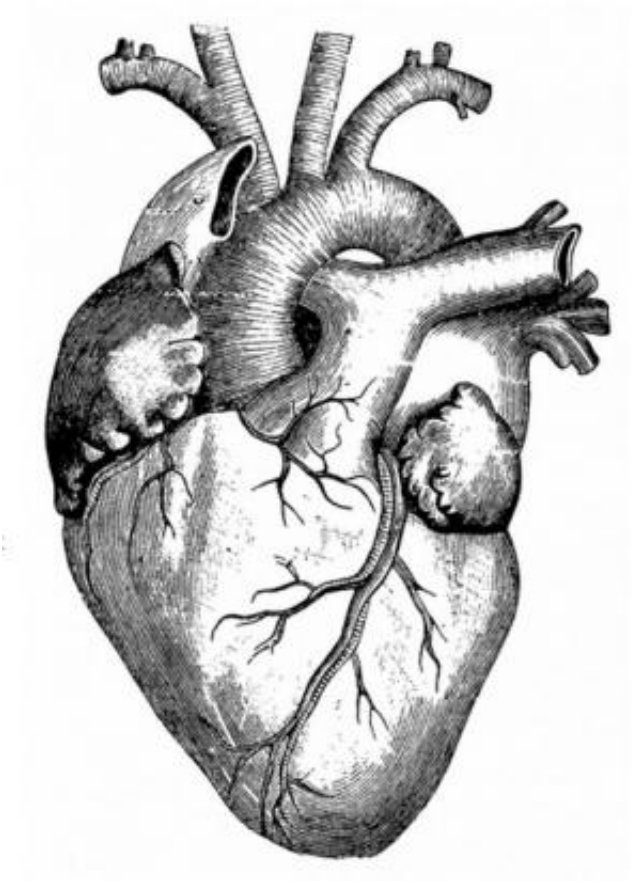
MedicalXpress

Long non-coding RNA molecules necessary to regulate differentiation of embryonic stem cells into cardiac cells

January 25 2013, by Anne Trafton



When the human genome was sequenced, biologists were surprised to find that very little of the genome—less than 3 percent—corresponds to

protein-coding genes. What, they wondered, was all the rest of that DNA doing?

It turns out that much of it codes for genetic snippets known as long non-coding RNAs, or lncRNAs. In recent years, scientists have found that these molecules often help to regulate which genes get turned on or off inside a cell. However, little is known about the specific roles of the thousands of lncRNAs discovered so far.

In a new study, MIT biologists have identified a critical role for a lncRNA they dubbed "Braveheart." This lncRNA appears to stimulate stem cells to transform into heart cells during mouse embryonic stem cell (ESC) differentiation; the researchers suspect that lncRNAs may control this process in humans as well. If so, learning more about lncRNAs could offer a new approach to developing regenerative drugs for patients whose hearts have been damaged by cardiovascular disease or aging.

"It opens a new door to what we could do, and how we could use lncRNAs to induce specific cell types, that's been completely unexplored," says Carla Klattenhoff, a postdoc in MIT's Department of Biology and one of the lead authors of a paper describing the findings in the Jan. 24 online edition of *Cell*.

MIT postdoc Johanna Scheuermann is also a lead author of the paper. Senior author is Laurie Boyer, the Irwin and Helen Sizer Career Development Associate Professor of Biology at MIT.

The researchers zeroed in on the Braveheart lncRNA because they had noticed that it is abundant both in ESCs and in differentiating heart cells. In the new study, they found that without normal levels of the Braveheart lncRNA, mouse ESCs did not develop any of the three major types of heart cells that comprise the cardiovascular system—cardiomyocytes

(which make up cardiac muscle), smooth muscle cells and endothelial cells.

They also showed that Braveheart controls the gene known to be a master regulator of heart-cell differentiation in vertebrate animals. This gene, called MesP1, initiates a cascade of hundreds of genes needed for heart development. However, without Braveheart, this process never gets started.

The researchers found that Braveheart controls the cascade by interacting with a protein complex known as the PRC2 complex, which normally sits on top of DNA, blocking MesP1 and other genes necessary for heart-cell development. When Braveheart interacts with it, the MesP1 network is activated and heart development proceeds.

"This paper is definitely a first step toward what we need to do, which is understand in a more fundamental way the biological role of these noncoding RNAs," says Ramin Shiekhattar, a professor of gene regulation and expression at the Wistar Institute in Philadelphia.

Shiekhattar, who was not part of the research team, adds that important next steps include deciphering in more detail the mechanism of how this lncRNA exerts its effects, and testing what happens when the lncRNA is knocked out in mice.

LncRNAs may also contribute to the species-specific complexity of organs such as the heart, according to the MIT team. This could help explain why the human heart is so much more complex than, for example, the fly heart, even though both species use many of the same cardiac protein-coding genes.

"We think that the added complexity may come from the non-coding portion of the genome, and we think lncRNAs are involved,"

Scheuermann says.

The researchers are now looking for other lncRNAs that function in cardiac development in mice, and are also searching for human lncRNAs involved in heart-cell differentiation. So far they have not found a direct human analog of Braveheart—which is not surprising, Klattenhoff says, because lncRNAs tend to evolve much more rapidly than protein-coding genes. However, they expect to identify many novel lncRNAs that play critical roles in human heart development and to find that mutations in lncRNAs will contribute to cardiovascular diseases.

This story is republished courtesy of MIT News (web.mit.edu/newsoffice/), a popular site that covers news about MIT research, innovation and teaching.

Provided by Massachusetts Institute of Technology