Mutations can spur dangerous identity crisis in cells

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As our bodies first form, developing cells are a lot like children put on the school bus with their names and addresses pinned to their shirts.

The notes identify one as a future heart cell, another as a liver cell, a third as a neuron. And that's what they each grow up to be.

But once those cells reach adulthood, changes to those original marching orders caused by aging, disease and other stressors like smoking can precipitate a kind of identity crisis, researchers at the University of Michigan Health System have found.

The cells start to forget things like which genes are supposed to be turned on and which turned off. This can lead to significant changes in their ability to function.

While microscopic, these changes can still have profound impacts on living beings. When this type of mutation was purposefully introduced into the heart muscle cells of mice, the normal functioning of the heart's electrical systems were disturbed, at times leading to dangerous arrhythmia, a new U-M study shows.

The results, published in the July issue of the Journal of Clinical Investigation, bring us one step closer to developing treatments for issues associated with aging or chronic diseases in which cells lose their ability to maintain a stable pattern of gene expression, says senior study author Gregory R. Dressler, Ph.D., collegiate professor of pathology research at

the U-M Medical School.

"We're excited about this research because it suggests that these mutations can be the cause of disease as well as the result," says lead author Adam B. Stein, M.D., an assistant professor of cardiology at U-M.

Stein, Dressler and their colleagues are working in a relatively new area of research known as "epigenetics." It's well known that human beings pass a life code, bound up in the double helix of our DNA, from one generation to the next. What's less well understood is that they also transmit sets of instructions – written in proteins and enzymes – that tell each cell of the body which genes should be expressed, that is, which should be turned on and which turned off, Dressler says. (Epigenetic means, basically, a trait that is inherited but not encoded directly in the DNA.)

Early on, when all the cells in an embryo are an undifferentiated mass of stem cells, these instructions lay out the master plan. Like children groomed for the Olympic greatness, their destinies are spelled out for them: nerve, muscle, bone.

"What scientists didn't know was whether those instructions, once in place, must be maintained after a cell reaches maturity," Dressler explains. "We wanted to find out what happens when you remove some of the imprinting machinery that tells the heart cell that it's a heart cell."

The researchers found that those instructions matter quite a bit.

"What we found was that it's important for the body to keep telling the heart cell, 'You're a heart cell, you're a heart cell,' " says Dressler, who notes the research was the first time this mechanism has been studied in a living mammal. "When you knock out a piece of those instructions, the

heart cell starts to forget who it is. These changes start off small, but over time they can have big effects on the organism."

Moreover, although they can be caused by environmental factors, negative changes like those that led to arrhythmia in the mice could potentially be passed down through the generations.

"The idea that cell state is a stable phenomenon is what's being challenged here," says Dressler. "We believe these findings could eventually lead to drug treatments to fight this type of cell destabilization."

More information: "Loss of H3K4 methylation destabilizes gene expression patterns and physiological functions in adult murine cardiomyocytes," Journal of Clinical Investigation, July 2011.

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