Extreme makeover: Scientists explore new way to change cell's identity

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Even cells aren't immune to peer pressure. Scientists at the Stanford University School of Medicine have now shown that skin cells can be coaxed to behave like muscle cells -- and muscle cells like skin cells -- solely by altering who they hang out with: the relative levels of the ingredients inside the cell.

The fickleness of the cells, and the relative ease with which they make the switch, provide a glimpse into the genetic reprogramming that must occur for a cell to become something it's not.

"We'd all like to understand what happens inside the black box," said Helen Blau, PhD, the Donald E. and Delia B. Baxter Professor and member of Stanford's Stem Cell Biology and Regenerative Medicine Institute. "These types of experiments will help us to identify the earliest regulators of reprogramming."

Harnessing these genetic makeovers will allow scientists to better understand how to induce specialized adult cells to revert to a stem-cell-like state in a process called induced pluripotency. These newly pluripotent, or iPS, cells, which can then be encouraged to branch out into a variety of other cell types, have shown increasing promise as possible therapies for disorders like diabetes. But Blau's experiments suggest an intriguing alternative to iPS: that of enticing specialized adult cells to move sideways from one developmental fate to another without requiring a dip into the stem cell pool.

Blau, who directs the Baxter Laboratory of Genetic Pharmacology at the medical school, is the senior author of the research, which is published in the May issue of the FASEB Journal. She and her laboratory members fused mouse muscle cells with human skin cells to create hybrids called heterokaryons. In heterokaryons, the nuclei of each cell type remains distinct, and the influence of one on the nature of the other can be clearly distinguished. They then examined the hybrids to see if they began to look and act more like muscle cells, skin cells or something in between.

The researchers use species-specific differences to track the unique gene-expression profiles of each cell type. They found that if the muscle cell nuclei outnumbered the skin cell nuclei, the skin nuclei began to express muscle-specific genes within a few hours of fusion. When the skin cell nuclei were more numerous, the muscle cell nuclei switched to express skin-specific genes. What's more, the heterokaryons themselves assumed the morphology of the ruling cell type — flat and roundish like skin cells or long and skinny like muscle cells.

"We were especially pleased to see that the muscle cells could begin to act like skin," said Blau, whose laboratory had previously shown in similar experiments that muscle cells can influence the fate of other cells. "But now we know it can go both ways."

The outnumbered nuclei assumed their new identities both quickly and decisively — there was a telling lack of cells expressing characteristics of both muscle and skin.

"It's all or nothing," said Blau. "At a certain threshold, a switch is flipped and the cell becomes committed to a specific fate." Although the precise molecular regulators of such a switch have not yet been identified, Blau speculates that proteins or small RNAs in the cytoplasm of the predominant cell modify the gene expression program of the minority

nuclei.

In addition to homing in on these regulators, the researchers are repeating the experiment with a variety of different cell types. "This shows that it can be done," said Blau. "Currently, inducing pluripotency in adult cells is time consuming and inefficient. We'd like to improve on that, or explore ways to skip that step altogether. We're coming at the problem from all angles."

Source: Stanford University Medical Center (news : web)