

Researchers uncover mechanism that regulates human pluripotent stem cell metabolism

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Human pluripotent stem cells, which can develop into any cell type in the body, rely heavily on glycolysis, or sugar fermentation, to drive their metabolic activities.

In contrast, [mature cells](#) in children and adults depend more on cell mitochondria to convert sugar and oxygen into carbon dioxide and water during a high energy-producing process called oxidative [phosphorylation](#) for their metabolic needs.

How cells progress from one form of energy production to another during development is unknown, although a finding by UCLA stem cell researchers provides new insight for this transition that may have implications for using these cells for therapies in the clinic.

Based mostly on visual appearance, it had been assumed that [pluripotent stem cells](#) contained undeveloped and inactive mitochondria, which are the energy-producing [power plants](#) that drive most cell functions. It was thought that stem cell mitochondria could not respire, or convert sugar and oxygen into carbon dioxide and water with the production of energy. This led most scientists to expect that mitochondria matured and gained the ability to respire during the transition from pluripotent stem cells into differentiated body cells over time.

Surprisingly, UCLA stem cell researchers discovered that pluripotent

stem cell mitochondria respire at roughly the same level as differentiated body cells, although they produced very little energy, thereby uncoupling the consumption of sugar and oxygen from [energy generation](#). Rather than finding that mitochondria matured with [cell differentiation](#), as was anticipated, the researchers uncovered a mechanism by which the stem cells converted from glucose fermentation to oxygen-dependent respiration to achieve full differentiation potential.

The four-year study appears in the Nov. 15, 2011 issue of *The [EMBO Journal](#)*, a peer-reviewed journal of the European Molecular Biology Organization. Teitell collaborated with Carla Koehler, a UCLA professor of chemistry and biochemistry, for the study.

"A lot of attention is being paid to the role of metabolism in pluripotent stem cells for making properly differentiated cell lineages for research and potential clinical uses," said study senior author Dr. Michael Teitell, a researcher with the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA and a professor of pediatrics, pathology and laboratory medicine, and bioengineering.

The initial question prompting our study was whether metabolism in pluripotent stem cells and cancer cells, which also rely heavily on glycolysis, were molecularly similar," he said. "This question led us to study the details of energy-generation by mitochondria in pluripotent stem cells."

Cells make energy in the form of ATP mainly in two ways, by glucose uptake and fermentation in the cytoplasm or by using respiration, in which glucose and oxygen are consumed to make carbon dioxide and water to fuel [cell functions](#). Teitell and his team expected that pluripotent stem cells could not respire because of prior reports on the immature appearance and paucity of mitochondria.

Teitell's team found that the molecular complexes responsible for respiration, called the electron transport chain, in the mitochondria of pluripotent stem cells were functional, and yet the cells instead relied on glycolysis for [energy production](#). The researchers speculated that there were one or more unknown regulators that kept the stem cells from respiring, since the electron transport chain was functional.

Jin Zhang, a graduate student and first author of the study, discovered that a protein called uncoupling protein 2 (UCP2), was highly expressed in the stem cells. He also found that UCP2 blocked respiration substrates derived from sugar from gaining access to the mitochondria, instead shunting them to the glycolytic and biosynthesis pathways located in the cytoplasm, inhibiting the stem cell's ability to respire as a method for generating energy.

As pluripotent stem cells were driven to develop into mature cell types, UCP2 expression was shut off, allowing respiration substrates to enter the mitochondria for energy generation, switching the cells from [glycolysis](#) to oxidative phosphorylation. Manipulating UCP2 expression, by keeping it switched on in differentiating cells, disturbed their maturation, a finding that could make them unsuitable for clinical use and also pointing to the importance of properly functioning metabolism for generating safe, high quality cells.

Teitell and his team confirmed these findings in both human embryonic stem cells and in induced pluripotent stem cells, which are mature body cells that are genetically reprogrammed to have similar abilities and attributes as the pluripotent embryonic stem cells.

"A main question that evolved during the study was whether it was the process of pluripotent stem cell differentiation that was altering the pattern of metabolism, or was it the change in the pattern of metabolism that altered the process of differentiation, a typical chicken-or-the-egg

question," Teitell said. "We over-expressed UCP2 in the stem cells and showed that metabolism patterns changed before markers of pluripotency or cell maturation changed, indicating that changes in metabolism affect changes in differentiation and not the other way around, at least for UCP2. This was important, to show causation for metabolic changes in driving the process of cell differentiation. However, it still leaves open the key question of exactly how manipulating cell metabolism controls cell differentiation, a question we are working hard to address."

Since metabolism in pluripotent [stem cells](#) and cancer cells appear quite similar, Teitell said the finding could potentially be used to target UCP2 in malignant tumors that express it, of which there are many. Silencing UCP2 could force cancer cells to respire, which might impair their ability to grow quickly.

Provided by University of California - Los Angeles Health Sciences

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