

Embryonic Stem Cell Differentiation Is Driven By Metabolic Changes

May 21, 2012

JR Schoenborn

Embryonic stem cells (ESC) hold great promise for regenerative medicine and for facilitating our understanding of early animal development. To advance the use of ESC-based therapies, a better understanding of the mechanisms that regulate ESC pluripotency and differentiation is necessary.

Mouse and human ESC are both derived from the inner cell mass (ICM) of pre-implantation embryos, and both are capable of self-renewal and differentiation into the three germ lineages: ectoderm, endoderm, and mesoderm. However mouse and human ESC use different signaling pathways to maintain pluripotency.

Compared to mouse ESC, human ESC are more closely related to mouse epiblast stem cells (EpiSC), which are derived from a more mature embryonic stage following implantation into the uterine lining. Recent cell culture, proteomic, transcriptomic, and epigenetic analyses support the similarity in regulation and function of mouse EpiSC and human ESC.

Drs. Daciana Margineantu and David Hockenbery of the Clinical Research Division and their colleagues at the University of Washington now show that mouse ESC and EpiSC switch their metabolic regulation as a result of HIF1-alpha signaling. The authors first showed that mouse EpiSC and human ESC have lower mitochondrial respiration than mouse ESC, and are dependent on glycolysis for their survival. In contrast, mouse ESC were able to shift between glycolysis and respiration. The reduced mitochondrial respiration observed in EpiSCs and human ESCs correlated with decreased expression of the complex IV cytochrome c oxidase (COX) family members, which are involved in electron transfer during respiration.

To define how this switch in gene expression and metabolism occurs during the transition from mouse ESC to EpiSC, the authors identified a HIF1-alpha driven gene signature in EpiSC but not ESC. HIF1-alpha is a basic helix-loop-helix transcription factor that is essential for cellular responses to hypoxia. Ectopic expression of HIF1-alpha in an ESC cell line was sufficient to cause morphological and metabolic changes similar to those in EpiSC.

To maintain the renewal and pluripotency capabilities of EpiSC in culture, growth conditions require the protein Activin. In contrast, mouse ESC that are exposed to Activin shift to an EpiSC phenotype.

The authors demonstrated that Activin signaling caused stabilization of HIF1-alpha, thus modulating expression of several metabolic genes, including downregulation of COX family members. Ultimately, these changes in gene expression caused phenotypic alterations in lineage markers that define the developmental transition from mouse ESC to EpiSC.

Because cancer cells frequently show a metabolic switch, known as the Warburg effect, understanding the regulation of this switch may improve our understanding of key regulators of the rapid tumor cell growth and division, as well as the frequent de-differentiation observed in cancer cells.

[Zhou W, Choi M, Margineantu D, Margaretha L, Hesson J, Cavanaugh C, Blau CA, Horwitz MS, Hockenbery D, Ware C, Ruohola-Baker H.](#) 2012. HIF1alpha induced switch from bivalent to exclusively glycolytic metabolism during ESC-to-EpiSC/hESC transition. *EMBO Journal* 31:2103-16.

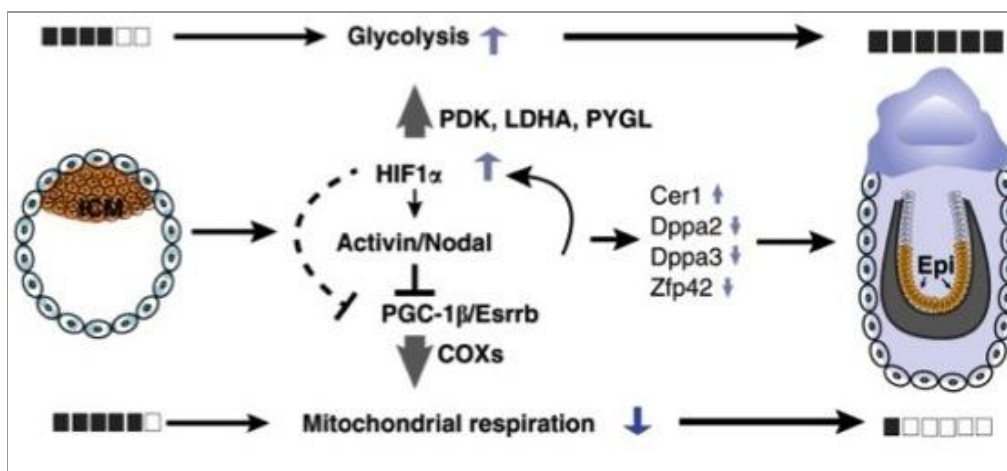


Image courtesy of the authors

The transition from an embryonic stem cell (ESC) to an epiblast stem cell (EpiSC) is associated with a metabolic transition that is characterized by reduced metabolic respiration and increased glycolysis in the more mature EpiSC. The authors define the role of HIF1-alpha and Activin in the downregulation of COX family proteins, which are involved in electron transfer during respiration.