

## Embryonic stem cells shift metabolism in cancer-like way upon implanting in uterus

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This is a microscopic image from the mouse embryonic stem cell metabolism study in Seattle. Credit: Hannele Ruohola-Baker lab

Shortly after a mouse embryo starts to form, some of its stem cells undergo a dramatic metabolic shift to enter the next stage of development, Seattle researchers report today. These stem cells start using and producing energy like cancer cells.

This discovery is published today in *EMBO*, the European Molecular Biology Organization journal.

"These findings not only have implications for <u>stem cell research</u> and the study of how embryos grow and take shape, but also for <u>cancer therapy</u>," said the senior author of the study, Dr. Hannele Ruohola-Baker, University of Washington professor of <u>biochemistry</u>. The study was



collaborative among several research labs in Seattle.

The metabolic transition they discovered occurs very early as the <u>mouse</u> <u>embryo</u>, barely more than a speck of dividing cells, <u>implants</u> in the mother's uterus. The change is driven by low oxygen conditions, Ruohola-Baker explained.

The researchers also saw a specific type of biochemical slowdown in the stem cells' mitochondria – the cells' powerhouses. The phenomenon previously was associated with aging and disease. This was the first example of the same downshift controlling normal early embryonic development.

"This downshift coincides with the time when the germ line, the keeper of the genome for the next generation, is set aside," Ruohola-Baker said.. "Hence reduction of mitochondrial reactive oxygen species may be nature's way to protect the future."

Embryonic stem cells are called pluripotent because they have the ability to renew themselves and have the potential to become any cell in the body. Self-sustaining and versatile are qualities necessary for the growth, repair and maintenance of the body – and for regenerative medicine therapies.

Although they share these sought-after qualities, "Pluripotent stem cells come in several flavors," Ruohola-Baker explained. They differ in subtle ways that expand or shrink their capacities as the raw living material from which animals are shaped.

There's a big reason why the researchers wanted to understand the distinction between the stem cells that make up the inner cell mass of the free-floating mouse embryo, and those in the epiblast, or implantation stage. Mouse embryonic cells at the epiblast stage more closely resemble



human embryonic stem cells -- and cancer cells.

Human stem cells and mouse epiblast stem cells have lower mitochondrial respiration activity than do earlier stage mouse stem cells. This reduction occurs despite the fact that the later stage stem cells have more mature mitochondria. The researchers confirmed that certain genes that control mitochondria are turned down during the transition from inner cells mass to epiblast cells.

Instead, the transitioning cells obtain their energy exclusively from breaking down a sugar, glucose. In contrast, the earlier stage mouse embryonic stem cells have more energy options, dynamically switching from mitochondrial respiration to glucose breakdown on demand.

As the embryo enlarges from a few dividing cells to a dense mass that buries into <u>uterus</u> for further development, oxygen comes at a premium.

The researchers discovered that the low-oxygen conditions activate a transcription factor called hypoxia-inducible factor 1alpha. This factor is sufficient to drive mouse embryonic stem cells to rely exclusively on glucose metabolism for their energy. The next challenge is to reveal whether the metabolic switch is deterministic for the fate of these stem cells, in normal as well as in cancer development.

This forced metabolic switch may determine the functional fate of some of the tiny mass of cells making up the primordial embryo. They transition first into epiblast <u>stem cells</u> and, afterward produce the entire developing embryo.

In <u>cancer cells</u>, the shift to a sugar-busting metabolism is known as the Warburg effect, the researchers explain. The Warburg effect sets in motion the biochemical activities that provide the fuel and materials required for rapid tumor cell growth and division.



The Warburg effect in embryonic cells, the researcher proposed, "may serve a similar function in preparation for the dramatic burst of embryonic growth and for the formation of the layers of the early embryo that later will become organs and other body structures."

Provided by University of Washington

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