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Contact: Mary Parlange
mary.parlange@epfl.ch
41-216-937-022
[Ecole Polytechnique Fédérale de Lausanne](#)

Who gives stem cells their marching orders?

Researchers from the Swiss Institute for Experimental Cancer Research (ISREC) have shown that a single gene involved in embryonic development is responsible for two seemingly contradictory activities -- maintaining stem cells after the embryo has implanted in the mother's uterus, and later providing cues to direct their differentiation in a coordinated fashion when the time is ripe.

The development of an embryo from a few seemingly identical stem cells is a truly awesome feat of nature. As they bathe in a chemical soup they've manufactured themselves, stem cells react to subtle changes in chemical concentration, moving apart and taking on distinct identities. The million-dollar question: How do these cells -- all initially the same, and exposed to the same environment -- end up acting in such different ways, and in so orchestrated a manner? Understanding the choreography involved in this mysterious cellular signaling dance is crucial to our ability to coax stem cells to grow into specific tissues outside the body. And it is also important if we are to understand and perhaps correct what goes wrong when the chemical signaling system goes awry and stem cells become cancerous.

Research has shown that the chemical soup in the developing embryo contains a protein factor called Nodal, a powerful "master chef" that controls the activity of a whole host of important regulatory genes. The ISREC group showed that embryos already need Nodal when they attach to the wall of the uterus, to expand their pool of stem cells, and to let individual cells know where they are with respect to their neighbors. However, to carry out these tasks, the Nodal protein must be cleaved by specific enzymes. The enzymes act as a sort of regulatory switch, increasing the stem cells' production of Nodal and preventing them from differentiating too early. Using mice engineered to carry an altered form of the protein, the ISREC group showed that if this switch is blocked, Nodal has the opposite effect: it triggers a cascade of molecular signals which stimulate differentiation.

In an article appearing in the September issue of the journal *Developmental Cell*, the researchers explain how cleaved and uncleaved forms of the Nodal protein act together to let the stem cells know where to move and what to become, once the embryo has reached a critical size. "Whole blocks of chemical "programs" are triggered in a cascading fashion, with Nodal there to maintain the source of a concentration gradient," explains EPFL (Ecole Polytechnique Fédérale de Lausanne) professor Daniel Constam, lead researcher on the project. Constam adds that cells respond differently depending on the amount of time they have been exposed to the Nodal signal.

One hallmark of aggressive cancer cells is their unspecified nature, similar to that of embryonic stem cells. Constam and his colleagues think that the signaling pathways used by tumor cells to migrate and invade new territory might be similar to those used in the embryonic development of the organism. Recent research from Northwestern University seems to confirm this, showing that aggressive melanoma cells secrete the Nodal protein. Understanding the activity of this gene in embryonic development may hold the key to finding a way to control its activity in tumor cells. "We need to separate the aspects of Nodal function, and how this protein is regulated by the cell at the molecular level," says Constam. "The embryo holds the key to this understanding."

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Paper:

BenHaim, N, Lu, C, Pescatore, L, Mesnard, D, Bischofberger, M, Naef, F, Robertson, EJ, Guzman, M, and Constam, DB (2006): *The Nodal precursor acting via activin receptors induces mesoderm by maintaining a source of its convertases and BMP4*. *Developmental Cell* 11: 1-11, September 2006

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