The gene that starts it all

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The formation of a human embryo starts with the fertilization of the oocyte by the sperm cell. This yields the zygote, the primordial cell that carries one copy each of the maternal and paternal genomes. However, this genetic information starts being expressed only after the zygote divides a couple of times. But what triggers this process, called "zygotic genome activation", was unknown until now. EPFL scientists have just found that members of the DUX family of proteins are responsible for igniting the gene expression program of the nascent embryo. Published in *Nature Genetics*, this discovery is a milestone for developmental biology.

Alberto de Iaco, a postdoc in the lab of Didier Trono at EPFL, drew upon a seemingly irrelevant study of patients suffering from a form of muscular dystrophy where mutations lead to the production in muscle cells of a protein called DUX4, which is normally detected only at the earliest stage of human embryonic development.

De Iaco also found that when DUX4 is forcibly produced in muscle cells, it turns on a whole set of genes that are expressed during zygotic genome activation. This was what first suggested that DUX4 could be the key regulator of this seminal event.

To confirm this, the researchers analyzed publicly available data to determine what components of the human genome are expressed during the first few days of embryonic development. They found that DUX4 is one of the very first genes expressed at this stage, releasing a high concentration of its protein product just before zygotic genome

activation.

In line with this lead, the scientists could show that the DUX4 protein binds to the regulatory region of genes that are induced during zygotic genome activation, stimulating their expression.

Next, they looked at mouse embryonic stem cells, which contain the mouse version of the DUX4 gene (called simply DUX). When in culture, a small fraction of these cells exhibit a any given time the gene expression pattern of 2-cell stage embryos, before cycling back to the features of more advanced embryonic cells. But when the EPFL researchers deleted the DUX gene, this process stopped, the appearance of the 2-cell stage-like subpopulation was suppressed.

The final piece of evidence came when the EPFL scientists removed the DUX gene from fertilized mouse oocytes using CRISPR/Cas9 genome editing. This prevented zygotic genome activation altogether, and precluded the growth of embryos beyond the first couple of cell divisions.

The study points to DUX4, and by extension the DUX family of proteins, as the master regulator responsible for kick-starting genome expression at the earliest stage of embryonic life in humans, mouse and probably all placental mammals.

"An old enigma is solved," says Didier Trono. "The study sheds light on what triggers the genetic program that ultimately makes us what we are. It can also help us understand certain cases of infertility and perhaps guide the development of new treatments for DUX-related muscle dystrophies".

He and his team are now curious about what could unleash, in the first few hours of our embryonic life, the ephemeral yet so crucial production

of this master regulator.

More information: Alberto de Iaco, Evarist Planet, Andrea Coluccio, Sonia Verp, Julien Duc and Didier Trono. DUX-family transcription factors regulate zygotic genome activation in placental mammals. *Nature Genetics* 01 May 2017. DOI: 10.1038/ng.3858