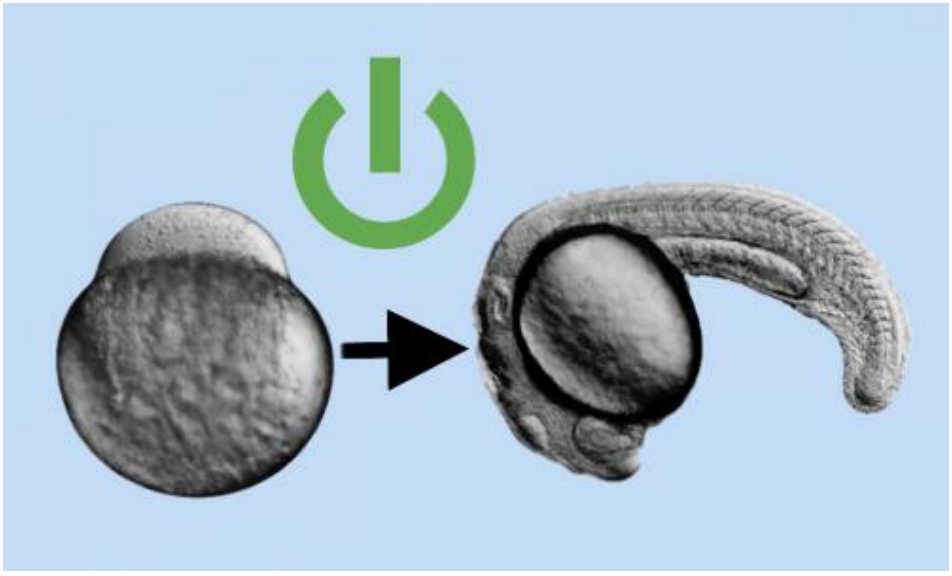
The developmental on-switch



The Pou5f1 protein acts as an on-switch for embryonic development in zebrafish. Credit: Wolfgang Driever

German researchers have demonstrated for the first time why the molecular cocktail responsible for generating stem cells works. Sox2 and Oct4 are proteins whose effect on cells resembles that of an eraser: They remove all of the cell's previous experiences and transform it into a so-called pluripotent stem cell. Like cells in the embryo, this stem cell can then develop into all forms of tissue. The discoverers of this reprogramming technique received the Nobel Prize in Physiology or Medicine in 2012. However, until now scientists did not understand precisely why these proteins can reprogram cells and what function they have in the embryo.

A team from the Department of Developmental Biology and the Cluster of Excellence BIOSS Centre for Biological Signalling Studies, led by Dr. Daria Onichtchouk and Prof. Dr. Wolfgang Driever, has discovered that the Oct4 protein in the zebrafish embryo, which is initially provided by the mother, is responsible for switching on the embryo's genes for the first time, thus initiating the animal's independent development. Young embryonic cells can develop into all tissues and cell types found in the body, just like cultures of the so-called pluripotent stem cells. These multi-talented cells are the focus of much attention in biomedical research because experts hope to use them to regenerate damaged organs without having to resort to embryonic stem cells.

In an article published in the journal *Science*, the Freiburg scientists explain that the zebrafish Pou5f1 protein, which is very similar to the human Oct4 protein, serves as the main starting signal for embryonic development. Pou5f1 awakens the genes after the resting period following fertilization. In all animals, development is initially controlled by proteins from the mother in the egg cell; the genes of the embryo are not activated until some time later. In the zebrafish, for instance, this process is triggered as soon as the embryo has a thousand cells. This "zygotic gene activation" reprograms the cells of the embryo: Specialized, rapidly dividing cells that do not create any new gene products become stem cells. These embryo stem cells can form all cell types – like pluripotent stem cells. In the case of so-called mesodermal cells, which can form blood or muscles, the scientists demonstrate how the Pou5f1 protein sets off the cascade of gene products that create muscle, blood, or bone cells from the embryonic cells. This regulatory network is very similar to that of the pluripotent stem cells.

Researchers have been able to generate pluripotent stem cells for several years now, but have found it difficult to convert them into stable cell types with sufficient reliability – if stem cells are unstable, they can become cancerous. Using the regulatory network discovered in the zebrafish, developmental biologists can now study how particular cell types in the body are created from stem cells and what makes them stable. Scientists require reliable processes for forming stable tissue before it can be used for applications in medicine.

More information: Leichsenring, M. et al. Pou5f1 Transcription Factor Controls Zygotic Gene Activation In Vertebrates, *Science* (online in *Science Express* 15 August 2013). DOI: 10.1126/science.1242527

Provided by Albert Ludwigs University of Freiburg