Developmental bait and switch: Enzyme responsible for neural crest cell development

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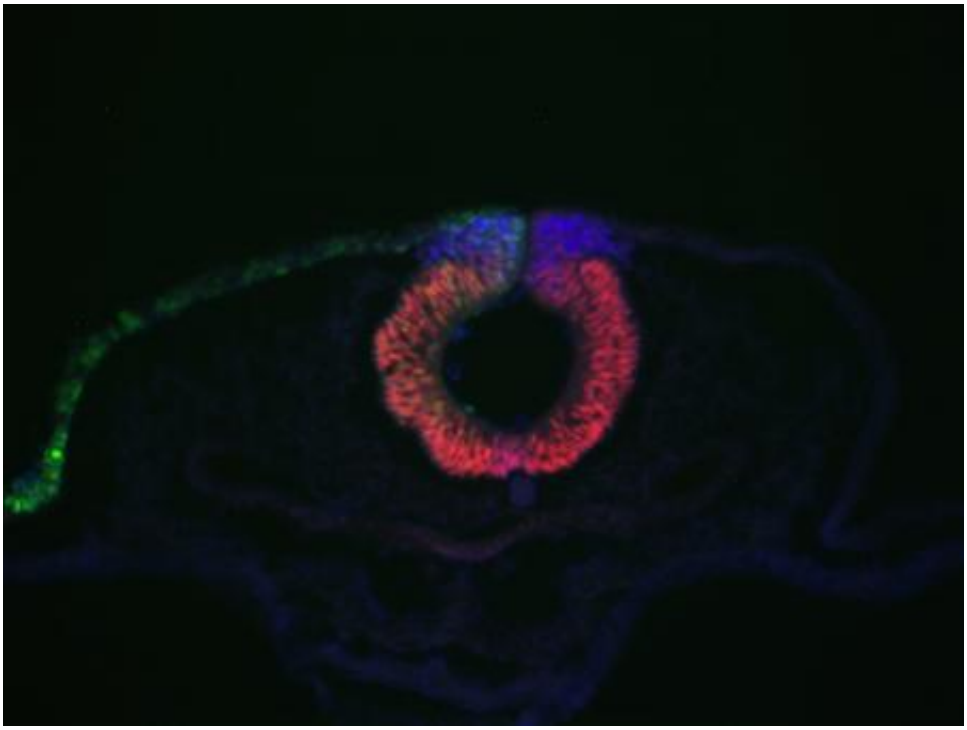

(Phys.org)—During the early developmental stages of vertebrates—animals that have a backbone and spinal column, including humans—cells undergo extensive rearrangements, and some cells migrate over large distances to populate particular areas and assume novel roles as differentiated cell types. Understanding how and when such cells switch their purpose in an embryo is an important and

complex goal for developmental biologists. A recent study, led by researchers at the California Institute of Technology (Caltech), provides new clues about this process—at least in the case of neural crest cells, which give rise to most of the peripheral nervous system, to pigment cells, and to large portions of the facial skeleton.

"There has been a long-standing mystery regarding why some cells in the developing embryo start out as part of the future central nervous system, but leave to populate peripheral parts of the body," says Marianne Bronner, the Albert Billings Ruddock Professor of Biology at Caltech and corresponding author of the paper, published in the November 1 issue of the journal Genes *& Development*. "In this paper, we find that an important type of enzyme called DNA-methyltransferase, or DNMT, acts as a switch, determining which cells will remain part of the central nervous system, and which will become neural crest cells."

According to Bronner, DNMT arranges this transition by silencing expression of the genes that promote central nervous system (CNS) identity, thereby giving the cells the green light to become neural crest, migrate, and do new things, like help build a jaw bone. The team came to this conclusion after analyzing the actions of one type of DNMT—DNMT3A—at different stages of development in a chicken embryo.

This is important, says Bronner, because while most scientists who study the function of DNMTs use embryonic stem cells that can be maintained in culture, her team is "studying events that occur in living embryos as opposed to cells grown under artificial conditions," she explains.

"It is somewhat counterintuitive that this kind of shutting off of genes is essential for promoting neural crest cell fate," she says. "Embryonic development often involves switches in the types of inputs that a cell receives. This is an example of a case where a negative factor must be

turned off—essentially a double negative—in order to achieve a positive outcome."

Bronner says it was also surprising to see that an enzyme like DNMT has such a specific function at a specific time. DNMTs are sometimes thought to act in every cell, she says, yet the researchers have discovered a function for this enzyme that is exquisitely controlled in space and time.

"It is amazing how an enzyme, at a given time point during development, can play such a specific role of making a key developmental decision within the embryo," says Na Hu, a graduate student in Bronner's lab and lead author of the paper. "Our findings can be applied to stem cell therapy, by giving clues about how to engineer other cell types or stem cells to become neural crest cells."

Bronner points out that their work relates to the discovery, which won a recent Nobel Prize in Medicine or Physiology, that it is possible to "reprogram" cells taken from adult tissue. These induced pluripotent stem (iPS) cells are similar to embryonic stem cells, and many investigators are attempting to define the conditions needed for them to differentiate into particular cell types, including neural crest derivatives.

"Our results showing that DNMT is important for converting CNS cells to neural crest cells will be useful in defining the steps needed to reprogram such iPS cells," she says. "The iPS cells may in turn be useful for repair in human diseases such as familial dysautonomia, a disease in which there is depletion of autonomic and sensory neurons that are neural crest–derived; for repair of jaw bones lost in osteonecrosis; and for many other potential treatments."

In the short term, the team will explore the notion that DNMT enzymes may have different functions in the embryo at different places and

times. That's why the next step in their research, says Bronner, is to examine the later role of these enzymes in nervous-system development, like whether or not they effect the length of time during which the CNS is able to produce neural crest cells.

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