Too much retinoic acid disrupts development in zebra fish embryos

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Researchers at the University of Washington (UW) in Seattle are learning how excessive exposure to retinoic acid leads to severe birth defects. Retinoic acid is found in some prescription drugs for severe acne.

The UW studies were conducted in zebrafish, whose transparent bodies make visible the steps of embryonic growth and which function as an important model system for understanding human embryonic development. In observing the developmental pathways disrupted by too much retinoic acid, the scientists learned how embryos protect an important population of progenitor cells from the retinoic acid their own bodies produce.

Progenitor cells are less primitive than stem cells. Progenitor cells, however, still have the ability to develop into cells with a variety of forms and functions, but within a more limited set of options.

The recent basic scientific findings on how the body guards such cells not only have implications in understanding the development of embryos, but also the tenacity and spread of abnormal growths -- like cancer -- and the regenerative potential of the body.

The researchers noted that a rising number of studies have shown that stem cells and progenitor cells exist in niches inside embryos, as well in adults. These niche environments are essential for supporting and maintaining the populations of these cells long term.

Reporting in the Dec. 15 issue of Genes *& Development*, Dr. Benjamin J. Martin, UW senior fellow in biochemistry, and Dr. David Kimelman, UW professor of biochemistry, described their work on a type of progenitor cell that resides at the most posterior end of the embryo during its early formative stages.

The researchers explained that in vertebrates -- including humans -- all of the body of the embryo, except the head, grows through the progressive release of cells from the posterior progenitor population, called the tailbud. The tailbud continues to release progenitor cells as the embryo lengthens and divides into primitive segments. These segments, known as somites, are destined to form the bones of the spinal column (the vertebrae) and most of the musculature of the body. These types of cells are called mesoderm because they occupy the middle layer between the skin and the gut.

In 2008 Martin and Kimelman showed that maintaining this mesodermal population of tailbud cells depends on a self-regulating loop of molecular events and signals. They learned how Brachyury, one of the proteins that enables an embryo to follow the developmental blueprint plans encoded in its DNA, acts as an essential controller of this loop. They also found out why Brachyury is critical for the formation of the posterior progenitor population.

Brachyury means "short tail' due to the effect on mice of missing one of two copies of the gene for this protein. Researchers studying mice had known since the late 1920s that a complete lack of Brachyury during embryonic development causes severe defects in embryos, but the underlying reasons behind this effect were unknown.

Martin and Kimelman conducted studies that showed that Brachyury regulates an essential signaling protein called Wnt, which is well known for its important roles in embryonic development, stem cells, and cancer.

When there is a defect in Brachyury, embryos fail to produce Wnt. This in turn means the posterior progenitor population can no longer exist, resulting in embryos that are so severely truncated that they can't survive.

Retinoic acid, the UW researchers realized, is also a cell signal that can affect body formation. Adding retinoic acid to the embryos of vertebrates (animals with backbones) causes severe truncation of the posterior end of the animal, an effect that on the surface appears to be similar to a lack of Brachyury or loss of Wnt signaling.

In their latest paper, published this week, Martin and Kimelman showed how adding retinoic acid to zebrafish embryos interferes with the function of the self-regulating loop of molecular events that maintains the mesodermal progenitor cells in the tailbud. Retinoic acid specifically blocks the production of Brachyury, and thereby causes the Wnt signal to fade. The result is a lethal truncation of the embryo.

The researchers also discovered that normally Brachyury protects those progenitor cells from retinoic acid naturally produced within the embryo's primitive segments. It does so by activating the manufacture of an enzyme that destroys retinoic acid. Surprisingly, the mesodermal progenitor cells work as a collective to destroy the retinoic acid in the vicinity, with each of the cells helping to protect its neighbors.

"Usually stem cells are sustained and protected by a special population of niche cells," the researchers noted. "In this case the mesoderm progenitor cell population serves as both the niche support cells and the progenitor cells, without dividing these functions into two separate cell types." These cells, it appears, are a community of like individuals who can take care of each other.

While Martin and Kimelman specifically looked at zebra fish in this study, they noted work by other researchers showing that Brachyury loss

and retinoic acid treatment causes similar sorts of truncated embryonic growth in other types of vertebrates.

"It's likely that the same mechanisms we recently discovered are common to all vertebrates," they wrote. They suggested that the expression of Brachyury in the progenitor domain was a vertebrate adaptation conserved during evolution because it allows the progenitor cells to be sustained during the long process of dividing the embryo into primitive segments, which in some species can take many days.

The researchers note that their findings could provide clues about certain forms of cancer. In the past few years, scientists have found that Brachyury occurs in excess in some types of cancerous tumors. The role of Brachyury in these tumors has been uncertain.

The overproduction of the Brachyury protein, Martin and Kimelman said, may be creating a cancer cell niche that maintains high Wnt signaling and low retinoic acid signaling, both of which have been extensively demonstrated to be key components of cancer growth. As they cancer cell spreads to a new part of the body, it is also creating an environment that helps it survive in what otherwise might be unfavorable conditions.

The results of their most recent study may be important in realizing how Brachyury-producing cancer tumors enlarge and then send tumor cells to take root elsewhere.

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