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Study shows how embryos regulate vitamin A derivatives

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Human embryos that get too much or too little retinoic acid, a derivative of Vitamin A, can develop into babies with birth defects. New research at UC Irvine shows for the first time how embryonic cells may regulate levels of retinoic acid, giving scientists insight into how it acts as a signal between cells to control development of the brain, limbs and many other tissues in embryos.

Thomas Schilling, Richard White, Qing Nie and Arthur Lander of UCI studied the behavior of retinoic acid in zebrafish embryos, which often are used in genetic studies as models for human development because the transparent embryos are easy to examine and develop rapidly. The zebrafish genome also has been completely sequenced.

Retinoic acid is important to human health. In addition to its vital role in embryo development, it is used to treat patients with certain types of leukemia, and it is included in many acne medications because of its profound effects on skin cells. Vitamin A is found naturally in many foods, including liver, carrots, broccoli, kale and sweet potatoes.

“Vitamin A in the diet gets converted into retinoic acid, which scientists have known since the 1960s has amazing effects on cells and tissues,” said Schilling, associate professor of developmental and cell biology at UC Irvine. “If you don’t get enough Vitamin A in your diet – or if you get too much – your body compensates for that. Our study helps explain how this regulation occurs.”

This study appears Nov. 20 in the journal *Public Library of Science Biology*.

Within a certain range, cells can regulate levels of retinoic acid. Schilling and his colleagues found that if the level becomes too high, an enzyme called cyp26a1 degrades the excess and brings it back to normal. When levels drop too low, proteins called fibroblast growth factors, or FGFs, stop the retinoic acid from degrading as rapidly.

“Those two things work together to keep the whole system adjusted to the right level,” Schilling said. “Retinoic acid induces its own degradation, and FGFs, also present in the embryo, have the opposite effect by inhibiting retinoic acid degradation.”

Zebrafish embryos used in this study were genetically engineered to be unable to make enough retinoic acid. The UCI scientists implanted tiny retinoic acid-soaked beads, which gradually released retinoic acid into the embryos. Using genetically altered fish embryos in which cells become fluorescent in response to retinoic acid when illuminated with an ultraviolet light, the scientists tracked how the retinoic acid moved within the embryos. This study is among the first to examine the distribution of retinoic acid.

These data were analyzed in a mathematical model based on the different biological components of the embryo. This type of collaboration between biologists and mathematicians is key to understanding how signals work and act together in complex biological systems.

Previously, scientists focused on where retinoic acid is made within an embryo, “but now we’re hoping the results of our study will shift the focus of research to how the degradation of retinoic acid is controlled,” Schilling said. Hopefully this someday will help scientists better predict

how retinoic acid behaves in the human body, leading to more effective drug treatments.

Source: University of California - Irvine