Regulation of the retinoic acid gradient in zebrafish embryos

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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 published this week in the open-access journal *PLoS Biology* shows for the first time how embryonic cells may regulate levels of retinoic acid, providing insight into how retinoic acid signaling interacts with other key developmental signals to control development of the brain, limbs, and many other tissues in embryos.

Thomas Schilling, Richard White, Qing Nie, and Arthur Lander of University of California Irvine studied the behavior of retinoic acid in zebrafish embryos. 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, bringing the concentration back to normal. When levels drop too low, proteins called fibroblast growth factors (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. 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.”

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.

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.

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. This may help scientists predict how retinoic acid behaves in the human body, leading to more effective drug treatments.

Citation: White RJ, Nie Q, Lander AD, Schilling TF (2007) Complex regulation of cyp26a1 creates a robust retinoic acid gradient in the zebrafish embryo. PLoS Biol 5(11): e304. doi:10.1371/journal.pbio.0050304. www.plosbiology.org

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