Embryology study offers clues to birth defects (w/Video)

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Gregg Duester, Ph.D., professor of developmental biology at Burnham Institute for Medical Research (Burnham), along with Xianling Zhao, Ph.D., and colleagues, have clarified the role that retinoic acid plays in limb development. The study showed that retinoic acid controls the development (or budding) of forelimbs, but not hindlimbs, and that retinoic acid is not responsible for patterning (or differentiation of the parts) of limbs. This research corrects longstanding misconceptions about limb development and provides new insights into congenital limb defects. The study was published online in the journal *Current Biology*.

In studies of mice and zebrafish, the team found that retinoic acid suppresses the gene fibroblast growth factor 8 (Fgf8) during the period when forelimb budding occurs, creating a suitable environment for the creation of forelimb buds.

"For decades, it was thought that retinoic acid controlled limb patterning, such as defining the thumb as being different from the little finger," said Dr. Duester. "However, we have demonstrated in mice that retinoic acid is not required for limb patterning, but rather is necessary to initiate the limb budding process. We also found that retinoic acid was unnecessary for hindlimb (leg) budding, but was needed for forelimb (arm) budding."

Congenital birth defects of the arms, legs, hands or feet result from improper development of limb bud tissues during embryogenesis. These processes are regulated by signaling molecules that control the growth and differentiation of progenitor cells by regulating specific genes. One

of these signaling molecules is retinoic acid, a metabolite produced from vitamin A (retinol), which plays a key role in the development of limbs and other organs. Dr. Duester's lab was instrumental in identifying Raldh2 and Raldh3, the genes responsible for retinoic acid synthesis, and has shown that retinoic acid is only produced by certain cells at precise stages of development.

In the study, the team of scientists showed that mice missing the Raldh2 and Raldh3 genes, which normally die early and do not develop limbs, could be rescued by treatment with a small dose of retinoic acid. However, forelimb development was stunted, suggesting that retinoic acid is required for forelimb but not hindlimb development. In zebrafish, the forelimb (pectoral fin) is also missing in retinoic acid-deficient embryos, but they were able to rescue fin development by treating such embryos with a drug that reduces fibroblast growth factor activity, thus supporting the hypothesis that retinoic acid normally reduces this activity.

By providing a more complete understanding of the molecular mechanisms involved in normal limb development, these findings may lead to new therapeutic or preventative measures to combat congenital limb defects, such as Holt-Oram syndrome, a birth defect characterized by upper limb and heart defects.

Source: Burnham Institute (news : web)