Researcher suggests enzyme crucial to embryonic development

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(Medical Xpress)—Scientists have long recognized retinoic acid – a compound the body produces by metabolizing vitamin A – as crucial to embryonic development. Either too much or too little retinoic acid during gestation can lead to a number of severe postnatal complications and diseases. Consequently, much research has been done on how the body regulates the metabolism of vitamin A, though no clear consensus has emerged.

But new research by Alexander Moise, University of Kansas assistant professor of pharmacology and toxicology, suggests the key to vitamin A metabolism could be an enzyme called dehydrogenase reductase, or DHRS3. According to Moise, this finding could mean a new framework for understanding and treating disorders related to impaired vitamin A metabolism ranging from congenital defects to immune deficiency to skin disorders and blindness.

"Alterations in vitamin A metabolism during pregnancy can lead to various developmental disorders and diseases," said Moise, a faculty member in the KU School of Pharmacy. "That's why we want to better understand the mechanisms by which the body controls retinoic acid balance. We find the enzyme DHRS3 could be crucial to that process."

Moise's findings are available online and will appear this fall in *The FASEB Journal*, the official publication of the Federation of American Societies for Experimental Biology.

Moise's central hypothesis is that retinoic acid regulates its own levels via a homeostatic feedback mechanism – a self-correcting system that maintains equilibrium by balancing the formation of retinoic acid and its breakdown. But current studies have largely ignored the role of enzymes that carry out the reduction of the metabolite retinaldehyde in retinoic acid metabolism.

Moise and his colleagues address this gap and focus on the enzyme DHRS3. In their recent study, the researchers demonstrate that DHRS3-deficient mice saw a 40 percent increase in retinoic acid, which lead to developmental defects, including common human congenital defects such as cleft palate, skeletal defects and defects in heart development. These DHRS3-deficient mice died during gestation.

"We find that DHRS3 is pivotal in the reduction of retinaldehyde and, thus, pivotal in preventing the formation of excess retinoic acid during embryonic development," he said. "Previously, the consensus had been that formation of excess retinoic acid is prevented largely through its breakdown by cytochrome P450 enzymes. Or put another way: While the previous model has been that the body prevents formation of excess retinoic acid by slamming on the brakes, DHRS3 takes the foot off the gas when it comes to vitamin A metabolism."

The specific goal of Moise's current project is to determine the factors that control the formation of retinoic acid in vivo. But longer term, the goal is to discover targets that allow for the manipulation of the levels and activity of retinoic acid in target tissues and to develop improved approaches to prevent and treat congenital disorders, blinding and immune diseases and cancer.

"This could have major implications for thousands, maybe millions, of people each year," he said.

More information: www.fasebj.org/content/early/2 … 227967.full.pdf+html