

Researchers unlock mysteries of vitamin A metabolism during embryonic development

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Researchers at Rutgers have unlocked some of the mysteries of how the developing embryo reacts to fluctuations in the amount of vitamin A present in the maternal blood stream. Their results are presented in the February 28 issue of the *Journal of Biological Chemistry*.

The researchers studied the role of LRAT, a protein that facilitates the formation of vitamin A stores in the body, during embryonic development. In particular, they showed how LRAT protects developing tissues from potentially toxic levels of vitamin A that have been ingested by the mother. Although this function of LRAT had previously been hypothesized in adults, this is the first time that its role has been demonstrated during embryonic development.

The developing mammalian embryo is entirely dependent on the maternal circulation for its supply of retinoids, the vitamin A metabolites produced in the body. These are essential nutrients and they control the formation of the embryo's heart, central nervous system, eyes and other important organs and tissues. Malformations of the developing embryo can occur when too little, or too much, vitamin A is consumed by the mother.

“We were looking for the mechanisms that allow the fetus to maintain adequate amount of retinoids, whether the mother has over- or under-consumed vitamin A,” said Dr. Loredana Quadro, an assistant professor in the Department of Food Science and member of the Center for Lipid Research at the Rutgers School of Environmental and Biological

Sciences. “We also looked at the effects of different levels of vitamin A being transferred from the mother to the fetus.”

When vitamin A is ingested, it is converted into retinyl ester (RE) in the intestine from where it is secreted in the bloodstream packaged with other dietary lipids into lipoprotein particles called chylomicrons. The majority of dietary RE reaches the liver, the main body storage site of vitamin A. Under insufficient dietary vitamin A intake, the liver transforms RE into retinol (ROH), which is then secreted into the bloodstream bound to retinol-binding protein (RBP), its sole specific serum carrier, to be delivered to the target tissues. Upon intake through a specific membrane receptor named Stra6, ROH is ultimately converted to retinoic acid (RA), which is the active form of vitamin A. If tissue RA is in excess, it is transformed into inactive forms, such as 4-hydroxy retinoic acid or 4-oxo retinoic acid (OXO-RA) by the action of a specific enzyme named Cyp26A1.

“When we think about vitamin A, we think about one compound,” said Quadro. “But in reality, the term vitamin A comprises a family of different compounds. Each one has a slightly different action, and plays a different role.”

The Rutgers researchers took a closer look at how ROH is metabolized into RE and RA to maintain an optimal balance of retinoids during the formation of the embryo. Mutant mice lacking both RBP and LRAT were generated to perform this study, so as to interfere with the two main pathways of maternal vitamin A delivery to the fetus (ROH-RBP from the liver stores and RE of dietary origin).

“We hypothesized that the lack of ROH-RBP and LRAT would make the embryo more vulnerable to changes in maternal dietary vitamin A intake,” said Quadro “and our data proved this to be correct. Indeed, a severe embryonic vitamin A deficiency is readily attainable when the

mothers are deprived of dietary vitamin A during pregnancy. Therefore, this strain turned out to be a very good model to study how embryonic development is affected by fluctuations in the amount of retinoids present in the maternal diet and hence in the maternal circulation”.

The researchers identified LRAT, Cyp26A1 and Stra6 as the three key molecular players that act in coordination to protect the developing tissues from potentially detrimental levels of vitamin A ingested by the mother. "Understanding vitamin A metabolism in the developing fetus could have broad implications," said Quadro. "Consumption of large doses of dietary supplements and vitamins, including vitamin A, has become a very common practice in recent years, generating the necessity to investigate the effects of high doses of vitamin A intake at different stages of the lifecycle, including pregnancy and development. These studies expand our knowledge of maternal-fetal nutrition and dietary contribution to embryonic development and may ultimately provide new insight into appropriate dietary practices during pregnancy."

The paper was previously published on the *Journal of Biological Chemistry's* web site on December 19, 2007.

Source: Rutgers University

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