Prenatal vitamin A deficiency tied to postnatal asthma

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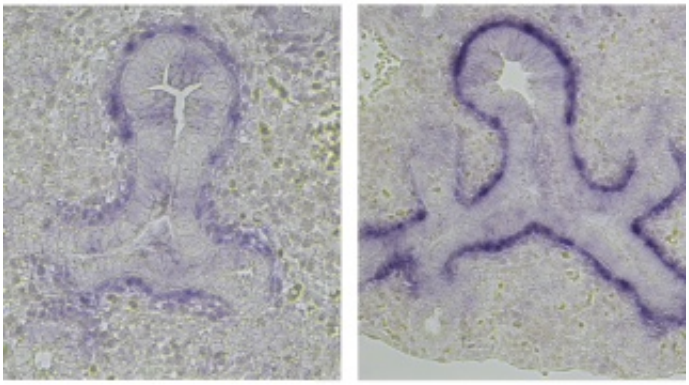

Vitamin A deficiency during fetal development can lead to excessive growth of smooth muscle surrounding the airways, making the lungs overly reactive to stimulation from the environment later in life and thus at risk to develop asthma. In these cross-sectional images of the lungs of embryonic mice, the dark stains represent smooth muscle. The left image is from a mouse whose mother was fed sufficient vitamin A, while the right image is from a mouse whose mother was fed insufficient vitamin A. Credit: Lab of Wellington V. Cardoso, M.D., Ph.D./Columbia University Medical Center

A team of Columbia University Medical Center (CUMC) investigators led by Wellington V. Cardoso, MD, PhD, has found the first direct evidence of a link between prenatal vitamin A deficiency and postnatal airway hyperresponsiveness, a hallmark of asthma. The study, conducted in mice, shows that short-term deficit of this essential vitamin while the lung is forming can cause profound changes in the smooth muscle that

surrounds the airways, causing the adult lungs to respond to environmental or pharmacological stimuli with excessive narrowing of airways. The findings were published online in the *Journal of Clinical Investigation*.

"Researchers have long wondered what makes some people more susceptible than others to developing asthma symptoms when exposed to the same stimulus," said Dr. Cardoso, senior author, director of the new Columbia Center for Human Development, and a faculty member in the Division of Pulmonary Allergy Clinical Care Medicine. "Our study suggests that the presence of structural and functional abnormalities in the lungs due to vitamin A deficiency during development is an important and underappreciated factor in this susceptibility."

"More generally," Dr. Cardoso said, "our findings highlight a point often overlooked in adult medicine, which is that adverse fetal exposures that cause subtle changes in developing organs can have lifelong consequences."

Previous studies had shown that retinoic acid (RA)—the active metabolite of vitamin A—is essential for normal lung development. Until now, however, little was known about the impact of prenatal RA deficiency on postnatal airway function.

In an earlier study, Felicia Chen, MD, a member of Dr. Cardoso's team and first author of the current paper, identified a number of genes regulated by RA signaling in fetal lung development. Additional analysis showed the abnormal presence of genes involved in the formation of smooth muscle when RA signaling was disrupted. This finding prompted the researchers to take a closer look at the effects of vitamin A deficiency on the development of the smooth muscle that surrounds airways as they continued to form and branch.

The researchers used a mouse model in which they could control when and in what amount vitamin A would reach the developing fetus through maternal diet. "We timed the vitamin A deficiency to the middle of gestation, coinciding with the period of formation of the airway tree in the fetus," Dr. Cardoso said. Fetuses that were deprived of vitamin A were found to have excess smooth muscle in the airways, compared with controls.

In a subsequent experiment, the mice were again deprived of vitamin A during the same developmental stage, but returned to a normal diet after that stage and until adulthood. "When the animals reached adulthood, they appeared normal—that is, they had no problems typically associated with vitamin A deficiency," said Dr. Cardoso. "However, pulmonary function tests showed that their lungs were clearly not normal." When the mice were challenged with methacholine, a chemical that causes the airway to contract, their response was significantly more severe than that of controls.

Additional experiments determined that, during development, RA utilization largely occurs where the bronchial tubes branch to form new generations of airways. As each new tube is formed, it is surrounded by smooth muscle. According to the researchers, RA signaling temporarily inhibits the development of smooth muscle in airways in areas that are still branching, preventing precocious and excessive formation of these cells. "If an animal is deprived of vitamin A, RA signaling is disrupted and smooth muscle overdevelops," said Dr. Cardoso.

Finally, the study showed that the structural and functional changes in the airways occurred in the absence of inflammation. "This does not imply that inflammation is not an important component of pulmonary conditions characterized by hyperresponsiveness, such as asthma," said Dr. Cardoso. "But it reminds us of the multifactor origin of asthma and indicates an additional, structural component that cannot be overlooked.

The findings underscore the importance of sufficient vitamin A in the diet, which remains a significant challenge in developing countries. The study also has potential clinical implications in the developed world. "Most pregnant women in the U.S. are probably getting enough vitamin A in their diet, but it's possible that their babies are not making proper use of it," said Dr. Cardoso. "The body has a very complex system for processing vitamin A, and this system is prone to interference from outside factors, such as cigarette smoke and alcohol. We need to understand more precisely how early exposures of the fetus to adverse environmental factors can interfere with crucial developmental mechanisms, such as the one we found linking vitamin A to airway structure and function."

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