SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS SHOW ABSENCE OF KEY OXYGEN-SENSING MOLECULE LEADS TO DEVELOPMENTAL DEFECTS

DALLAS – Nov. 25, 2003 – UT Southwestern Medical Center at Dallas researchers have shown that the absence of a key oxygen-sensing molecule can lead to multiple developmental defects – from an enlarged heart to eye problems.

The researchers generated the first mouse model that lacks entirely a member of an important family of proteins involved in sensing hypoxia, a state of reduced oxygen in the body's cells that is associated with conditions such as heart attacks, stroke and lung disease.

This new model allowed the scientists to take a closer look into the exact physiologic function of these proteins, which was unknown until now, and the model provided clues as to what human diseases may be caused by alterations in these proteins. The researchers reported in the online version of *Nature Genetics* that the absence of this crucial oxygen-sensing molecule leads to developmental defects due to the inability of the mice to respond to high, damaging levels of oxygen-based molecules called reactive oxygen species.

Their knockout mice lacked the gene *Epas1*, which encodes HIF-2α (hypoxia inducible factor 2α), a molecule activated in response to hypoxia. In the mice that lacked HIF-2α, the researchers reported abnormalities including cardiac hypertrophy or enlarged heart, fatty liver, eye defects, serum biochemical abnormalities, and increased oxidative stress – conditions seen in human patients with mitochondrial defects.

"The surprise was that mice lacking the nuclear DNA-encoded *Epas1*/HIF-2α had changes in multiple organs that was suggestive of a mitochondrial disease state," said Dr. Joseph Garcia, assistant professor of internal medicine and senior author of the study. "Both mitochondrial and nuclear DNA mutations can adversely affect these crucial intracellular organelles and lead to widespread abnormalities in humans as well as animal models."

The body has a normal response to hypoxia, which includes turning on specific genes that have protective roles to alleviate the detrimental effects of reduced oxygen in the cells. It likewise has an adaptive response to oxidative stress that involves increasing the expression of genes

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whose function is to eliminate oxygen radicals and their potentially harmful derivatives.

"This study provides evidence that *Epas1*/HIF-2α is an important regulator of gene expression for a particular group of genes involved in oxidative stress response," Dr. Garcia said. "In the absence of *Epas1*/HIF-2α, mice are not able to turn on the expression of these antioxidant genes, and the overall balance of the cell favors a state of oxidant excess, which led us to hypothesize that the mitochondria in the *Epas1*/HIF-2α knockout mice were impaired.

"We attributed the cause of impairment to increased oxidative stress and decreased elimination of reactive oxygen species."

To test their hypothesis, the researchers treated the mice with a chemical compound that mimics the activity of proteins encoded by genes that *Epas1*/HIF2α would normally activate. This chemical compound, which has antioxidant properties, substantially prevented or reversed the organ and metabolic abnormalities in the mice. In addition, treatment of pregnant females with the same molecule led to increased viability in their newborns, suggesting that "therapy that reduces oxidative stress, increases (newborn) survival to birth," the researchers reported.

"This research also has implications for a role of *Epas1*/HIF-2α and possibly other HIF factors in human mitochondrial disorders," Dr. Garcia said. "Their role in other human conditions associated with increased oxidative stress such as aging, cardiovascular disease and diabetes will require future studies."

Other researchers who contributed to the study included Dr. Michael Bennett, professor of pathology and pediatrics; Dr. Kan Ding, postdoctoral researcher in internal medicine; Yavuz Oktay, student research assistant in the Integrative Biology Graduate Program; Dr. James Richardson, professor of pathology; Dr. Marzia Scortegagna, postdoctoral researcher in internal medicine; John Shelton, a research scientist in internal medicine; Arti Gaur, a former research assistant in internal medicine; and researchers at the University of Washington School of Medicine.

The study was funded by the National Institutes of Health, the American Heart Association and the Donald W. Reynolds Foundation.

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