Researchers Identify Genetic Switch Critical for Cell Survival in Hypoxia

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Researchers at the University of California, San Diego School of Medicine have identified a critical metabolic "switch" in fruit flies that helps oxygen-deprived cells survive.

Hypoxia-induced injury occurs in the case of heart attack, stroke or other neurological or respiratory conditions which diminish the supply of oxygen to vital tissues and organs. Scientists know that most life forms are able to somehow suppress non-essential activity in order to survive oxygen deprivation, but they didn't know why or how this metabolic slowdown occurred.

"A transcriptional suppressor called *hairy* is crucial for reducing the mismatch between supply and demand of oxygen," said Dan Zhou, Ph.D., Assistant Professor of Pediatrics at UC San Diego, and first author on the study, to be published in the October 17 issue of the *Public Library of Science (PLoS) Genetics.*

Because cellular mechanisms in fruit flies are very similar to those in human cells, the research team developed a strain of fly called *Drosophila melanogaster* that developed a tolerance to severe hypoxic conditions through adaptive changes over many generations. They then studied the genome of the "tolerant" flies to see which genes were activated or suppressed during severe hypoxia.

In looking at more than 13,000 or about 90 percent of the known genes in the genome of the fruit fly, the researchers were able to examine the difference in gene expression profiles between the hypoxia-tolerant and normal *Drosophila melanogaster*.

"We discovered that the *hairy* gene binds to and shuts off, or suppresses, activation of many genes," said Gabriel G. Haddad, M.D., Professor of Pediatrics and Neurosciences, Chair of Pediatrics at UC San Diego School of Medicine and Physician-in-Chief at the Rady Children's Hospital, San Diego. "When *hairy* is activated, it puts the brakes on various signaling pathways in the cell, enabling the cells to become resistant to the low-oxygen environment."

The *hairy* switch appears to put into motion a sort of "brown out" in the cells, allowing them to conserve power for critical functions. "While there are multiple pathways that contribute to the ability of this strain of flies to tolerate hypoxia, our study demonstrates that *hairy* -mediated metabolic suppression plays a critical role," said Haddad.

The researchers hope that by better understanding how the *Drosophila* cells have developed a strategy for survival under the stress of hypoxia, they may be able to help human cells and tissues adapt and survive under low oxygen situations caused by disease.

Additional contributors to the study include Jin Xue of the Departments of Pediatrics at UC San Diego and Rady Children's Hospital, San Diego; James C.K. Lai, College of Pharmacy, Idaho State University; Nicholas J. Schork, Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla; and Kevin P. White, Institute for Genomics and Systems Biology, Departments of Human Genetics and Ecology and Evolution, The University of Chicago.

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