Long-Term Hypoxia in Flies Shown to Result in Permanent DNA Changes

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In an important study that may shed light on human ability to adapt to hypoxia, or inadequate levels of oxygen, researchers at the University of California, San Diego School of Medicine have proven that the genome of flies exposed to long-term hypoxia are changed to permanently affect gene expression. Their findings, to be published online by the journal of the *Proceedings of the National Academy of Sciences* (PNAS) the week of January 24, 2011, may lead to new targets for development of therapies for hypoxia-induced disease in humans.

Hypoxia-induced injury not only occurs due to oxygen deprivation at very high or low altitudes, but can also occur in cases of heart attack, stroke or other neurological or respiratory conditions which diminish the supply of oxygen to vital tissues and organs.

Because cellular mechanisms in fruit flies are very similar to those in human cells, the scientists studied populations of Drosophila melanogaster generated through long-term laboratory selection over 200 generations. These flies are capable of tolerating severe, normally fatal hypoxia, and pass their hypoxia tolerance trait to subsequent generations – the trait persisting even in the absence of hypoxic stress, which suggests a genetic rather than a physiological mechanism is at play in adaption.

Using high-throughput screening, the researchers compared the genomics of these flies with those of normal controls, and were able to identify a number of specific DNA regions, mostly on the X-chromosome, related to hypoxia resistance.

Several of these regions contained genes encoding or regulating a particular pathway called the Notch pathway, previously shown to be over-activated during exposure to hypoxia in both flies and mice. They confirmed the contribution of Notch activation using a specific y-secretase inhibitor called DAPT, which significantly reduced survival in the hypoxia-tolerant strain. In addition, they observed that flies with absent or loss-of-function Notch mutations showed a significant reduction in tolerance to hypoxia. In contrast, gain-of-function mutations resulted in over-expression of the Notch domain and greatly increased hypoxia tolerance.

The study was conducted by Gabriel G. Haddad, MD, chair of the UCSD Department of Pediatrics and Physician-in-Chief at Rady Children's Hospital-San Diego and Dan Zhou, PhD, of the UCSD Department of Pediatrics. Rady Children's is a research and teaching affiliate of the UCSD School of Medicine.

"We set out to pinpoint the genomic regions responsible for the change in sequence, and prove that it was the DNA changes which led to gene expression and subsequent adaptation," said Haddad, who recently received a $10 million grant from the National Institute of Health's Heart, Lung and Blood Institute to study hypoxia tolerance. "We confirmed that change in the DNA, and not just a change in gene expression, results from long-term hypoxia exposure."

"The findings are promising because we know that more than 70 percent of genes are conserved between flies and humans. We now want to see if we can discover the pathways in humans that allow survival in high altitudes," said Zhou, adding that the scientists are now studying human cells from individuals in mountainous areas of Ethiopia, Kazakhstan, Tibet and Peru. "This roadmap will lead us to better understand how tissues adapt to low oxygen levels, and could lead to new therapies to treat human diseases such as stroke, obstructive sleep apnea and pulmonary hypertension."

Additional contributors to the paper include Nitin Udpa, Merril Gersten, DeeAnn W. Visk, Ali Bashir, Jin Xue, Kelly A. Frazer, James W. Posakony, Shankar Subramaniam and Vineet Bafna, all of UC San Diego.

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