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Jefferson researchers uncover new way nature turns genes on and off

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Peering deep within the cells of fruit flies, developmental biologists at the Kimmel Cancer Center at Thomas Jefferson University in Philadelphia may have discovered a new way that genes are turned on and off during development.

If they're right, and the same processes are at work in higher organisms, including mammals, the findings could eventually have implications for improving the understanding of a range of diseases, including childhood cancer.

Reporting in the journal Cell, Alexander Mazo, Ph.D., professor of biochemistry and molecular biology at Jefferson Medical College, Svetlana Petruk, Ph.D., and their co-authors focused on pieces of genetic material called non-coding (nc)RNAs. About two-thirds of the human genome is converted into such RNAs (the better known messenger RNAs are translated into proteins), though the function of the majority is unknown. The researchers detailed a possible mechanism by which ncRNAs briefly control the functioning of homeotic, or HOX, genes, which guide the master developmental plan of the organism.

"We think that this new mechanism operates early in embryogenesis," says Dr. Mazo.

According to Dr. Mazo, the researchers found that one of the likely mechanisms behind ncRNAs' ability to regulate essential coding genes is through a "transcription interference" mechanism. "Such mechanisms

are known in bacteria and yeast, but not much is known in higher organisms," he explains.

In the fruit fly, HOX gene activity is maintained by genes and proteins in the Trithorax group (TrxG). These proteins are thought to act through so-called maintenance elements, one of which, in a nearby region, bxd, is located between two HOX genes, Ubx and abd-A. Dr. Mazo explains that several "long" ncRNAs are transcribed through bxd maintenance elements. They were thought to be expressed in the same cells as Ubx, and to regulate HOX gene coding sequence expression. But the researchers found something different: ncRNAs instead can repress Ubx activity by blocking its activity in certain types of cells in the developing embryo.

"Importantly, non-coding RNAs are very tightly developmentally regulated, as we show in case of bxd RNAs," Dr. Mazo notes. "These create an enormous potential to regulate the neighboring coding genes in a time- and tissue-specific manner. This is a new type of transcriptional regulation mechanism for higher eukaryotes, and it is very likely that it is conserved in mammals."

Understanding the details of the TrxG system could someday have implications for ALL,
a dangerous type of childhood leukemia. The disease stems from gene rearrangements in
utero. MLL, the gene that is affected in humans, corresponds to Trithorax in fruit flies.
"ALL is thought to be a disease of misregulated HOX genes," says Dr. Mazo.

HOX gene groups have long been known to be "transcriptional regulators" that control
the multitude of genes involved in embryonic development, Dr. Mazo

says. He and his
group would like to ultimately better understand the early stages of such development.

Source: Thomas Jefferson University