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In tiny fruit flies, researchers identify metabolic 'switch' that links normal growth to cancer

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As day-old embryos, fruit flies called *Drosophila* enter a stage in which their cells freely divide and proliferate as the insect grows dramatically in size.

This is true for all animals, which undergo most of their growth prior to sexual maturation. Until now, researchers have known nothing about the metabolic state that occurs when cells divide during early development. But in a study published online Tuesday, Feb. 1, 2011, in Cell Metabolism, University of Utah human genetics researchers show that this cell division in *Drosophila* depends on a metabolic state much like when cells run amok to form cancerous tumors. Unlike cancer, however, this cell proliferation in fruit flies and other organisms halts when the animal becomes mature.

Led by Carl S. Thummel, Ph.D., professor of human genetics, the researchers identified a genetic switch that supports cell division and proliferation in growing fruit flies. This switch is controlled by a nuclear receptor and transcription factor (proteins that turn genes on and off) called dERR, which is similar to three human transcription factors known as ERRs (Estrogen-Related Receptors). Two of the ERR transcription factors are associated with breast cancer, leading Thummel to believe that understanding the role of dERR could shed light on how cancer cells proliferate and spread in humans using a metabolic state known as the Warburg effect.

"No one has ever really thought about the metabolic state that supports normal growth during development, or how it might be related to the cell proliferation in cancer," Thummel said. "Our study has a direct relevance for humans. Our findings with dERR suggest that the mammalian transcription factors are doing the same thing."

Although there is probably more than one regulator controlling the metabolic state of cell division and proliferation, identifying the role of dERR is a significant first step in understanding this process. Thummel's study shows that dERR supports cell proliferation by regulating metabolism, the essential function by which people, fruit flies, and other organisms store and use nutrients appropriately.

In fully developed humans and fruit flies most cells are in a metabolic state of homeostasis, where nutrients are used to support normal daily life. To maintain this state, cells turn carbohydrates into ATP, the molecule that is the main source of energy for all organisms. During early development, however, cells must divide and proliferate to form the organs and other tissues that will keep the mature organism alive. To accomplish this, the embryo's metabolic state changes so that instead of producing only ATP, cells use carbohydrates to make proteins, lipids, and nucleotides that support the cell division and proliferation needed for growth.

Employing the method of gene silencing in *Drosophila* pioneered by the U of U's Kent Golic, Ph.D., professor of biology, Thummel and his colleagues in the U human genetics department discovered that dERR plays a central role in *Drosophila* development by switching on a set of metabolic genes that allow cells to divide and proliferate. When the researchers silenced dERR in fruit fly embryos at the stage when cells are starting to divide furiously, metabolism was disrupted, growth was stopped, and the insects died. That's a compelling argument for the important role Estrogen-Related Receptors play in metabolism, cell

proliferation, and, quite possibly, human cancer, according to Thummel.

"The whole metabolic program of the animal is changed when dERR is removed," he said. "It's pretty remarkable that this one transcription factor turns on an entire program that supports growth."

The Warburg effect is similar to the metabolic state of the fruit fly embryos. Instead of using nutrients to make ATP, they make biomass to divide and proliferate without control. A number of studies have shown a close association between ERR receptors and cancer, and Thummel and his colleagues have provided a new context for studying those receptors in mammals.

"Our studies of the single *Drosophila* ERR family member raise the important possibility that mammalian ERRs control the dramatic cellular proliferation associated with cancer through their ability to promote the Warburg effect," the researchers write.

Future studies in the Thummel lab are directed toward understanding how dERR knows when to switch on the metabolic state that supports growth. They also want to understand if it has other functions later in life, when the adult animal is in a state of homeostasis.

Provided by University of Utah