SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS SHOW TUMOR-SUPRESSOR GENES LINKED TO INSULIN SIGNALING

DALLAS – June 1, 2001 – Researchers at UT Southwestern Medical Center at Dallas have discovered a link between insulin signaling and certain tumor-suppressor genes that may lead to significant progress in diabetes and cancer research.

In an article published today in the journal *Genes and Development*, Dr. Duojia Pan, assistant professor of physiology, and Dr. Xinsheng Gao, postdoctoral researcher in physiology, describe a genetic link between the tuberous sclerosis (TSC) suppressor genes and insulin signaling.

Tuberous sclerosis affects 1 in 6,000 individuals and is caused by a mutation in either the TSC1 or TSC2 tumor-suppressor genes. The disease is characterized by the widespread development of benign tumors (tubers) that harden as the patient grows older, skin rashes, seizures and developmental delays.

Although it is clear the TSC genes are responsible for this illness, it remains unknown how they normally function to suppress tumor formation.

Pan and Gao examined how the TSC1 and TSC2 genes functioned in relation to the insulin pathway in fruit flies. Fruit flies, or drosophila, have approximately 60 percent of the same disease genes that humans have, and the fly genome is easily mutated. Because flies reproduce and grow so quickly, gene functions can be effectively studied in less time than other animal models.

"We found that the TSC genes are negative regulators of the insulin pathway because when we omit the TSC genes, insulin signaling increases, and thus results in larger cells," Pan said. "The opposite is also true. If we increase the presence of the TSC genes, the insulin signaling decreases, and the end result is smaller cells.

"Our studies have implications for diabetes and cancer in humans. More than 90 percent

(MORE)

of diabetic patients are resistant to the action of insulin. The flies with defective insulin receptors are similar to patients with diabetes. These flies had less insulin signaling, and we were able to cure them by taking out the TSC genes.

"We have shown that by removing one of the two copies of the TSC1 or TSC2 genes normally present in the flies, we can recuperate some of the lost activity of the insulin pathway. Thus, we may be able to recover some insulin signaling in diabetic patients by reducing the activity of the TSC genes," Pan said.

As for cancer patients, the presence of the TSC genes affected the cell size of various organs in the flies. The tubers of TSC patients also contain giant cells. One of the hormone-mediated pathways that play a role in cellular growth involves insulin. Understanding how cellular growth is controlled will ultimately lead to a better understanding of cancer.

Given the link between the TSC genes and insulin signaling, Pan and Gao also believe that tuberous sclerosis may be treated by reducing the activity of the downstream effectors, such as S6 kinase, of the insulin pathway.

"My lab's main interests are in growth control. For instance, why does the left hand grow to be the same size as the right hand? We already knew the insulin pathway is important to size control, but we did not know all the players involved in this pathway," Pan said.

"This study is important because we now understand more about how the TSC genes function. We now know they work as a team, and their function can be studied in relation to vertebrates and humans. Further study of this group may lead to significant progress in diabetes and cancer research," he said.

In the near future, Pan plans to collaborate with researchers in the UT Southwestern Touchstone Diabetes Center to examine this group of genes in diabetic mice.

Pan's research is partially supported by the National Institutes of Health and the American Heart Association.