UT SOUTHWESTERN MEDICAL CENTER NEWS

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A relative of anti-aging gene *Klotho* also influences metabolic activity, obesity

DALLAS – April 25, 2007 – A relative of the anti-aging gene *Klotho* helps activate a hormone that can lower blood glucose levels in fat cells of mice, making it a novel target for developing drugs to treat human obesity and diabetes, UT Southwestern Medical Center researchers have found.

In a study available online and in the *Proceedings of the National Academy of Sciences*, the researchers show that a type of Klotho protein binds to receptors for a metabolic hormone in fat cells, forming a "co-receptor" that enables the hormone to stimulate the processing of glucose, the body's main source of fuel. The *Klotho* gene has previously been found to play a role in prolonging the life of mice partly by controlling insulin.

Mice lacking this particular Klotho protein can't stimulate this key metabolic activity, said Dr. Makoto Kuro-o, associate professor of pathology at UT Southwestern and the study's senior author.

"The ability to stimulate the glucose processing is key to proper metabolism, so this Klotho protein, known as beta-Klotho, is a novel target for developing drugs that can enhance or block the metabolic activity of this hormone, which has been shown to be able to lower blood glucose in mice," he said. "Klotho's role in regulating the metabolic activity of the growth hormones is essential."

Dr. Kuro-o and his colleagues originally discovered the *Klotho* gene in 1997, naming it after one of the mythical Greek characters who controlled the length of human life.

The Klotho protein, which is found in several species, acts as a hormone in mice, circulating through the blood and binding to cells. Previous studies have shown that mutant mice lacking the *Klotho* gene appear normal until about a month of age, and then begin showing signs of age, such as skin atrophy, osteoporosis, arteriosclerosis and emphysema. The mice die prematurely at about two months.

Therapies based on *Klotho* could prove to be a way to extend life or slow the effects of aging, so Dr. Kuro-o and his colleagues are trying to uncover more about how *Klotho* works.

In this study, the researchers examined a connection between the presence of Klotho proteins and fibroblast growth factors in the fat cells of mice. Fibroblast growth factors are hormones found in many tissues that are involved in tasks such as wound care and skeletal development.

Certain fibroblast growth factors are active only in fat cells, but it hadn't been known why.

The UT Southwestern researchers discovered that beta-Klotho, which is active in fat cells,

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actually binds to receptors for metabolic fibroblast growth factors. This forms a co-receptor that activates the hormone's metabolic function, Dr. Kuro-o said.

For example, fibroblast growth factor 21, or FGF21, is a hormone in the blood that has been shown to lower blood glucose levels in diabetic and obese mice. In fat cells it binds to the fibroblast growth factor and beta-Klotho co-receptor complex and signals glucose processing; however, without beta-Klotho, FGF21 lacks the ability on its own to bind to its receptors and can't stimulate the metabolic function.

"Klotho's actions determine the metabolic activity of these fibroblast growth factors, making them targets for drugs that either block or enhance the metabolic activity," Dr. Kuro-o said. "Klotho proteins thus will be important players in future therapies for human conditions such as diabetes, obesity and kidney disease."

Other UT Southwestern pathology researchers involved in the study were Drs. Yasushi Ogawa, postdoctoral researcher; Hiroshi Kurosu, instructor; Animesh Nandi, senior research scientist; Kevin P. Rosenblatt, assistant professor; and Masaya Yamamoto, a former instructor who has since returned to Japan. Researchers from the New York University School of Medicine also were involved.

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