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Novel link between excessive nutrient levels and insulin resistance

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For quite some time now, scientists suspected the so-called hexosamine pathway — a small side business of the main sugar processing enterprise inside a cell — to be involved in the development of insulin resistance. But they could never quite put their finger on the underlying mechanism.

Now, researchers at the Salk Institute for Biological Studies have uncovered the long-missing molecular link: the enzyme OGT (short for O-linked ß-N-acetylglucosamine transferase), the last in a line of enzymes that shuttle sugars through the hexosamine pathway.

Their study revealed that OGT slams the brake on insulin signaling soon after insulin fires up the machinery that pulls glucose from the blood stream and squirrels it away inside liver or stashes the surplus energy in fat pads.

“For the first time we have a real understanding of how the insulin signaling system is turned on and off,” says Howard Hughes Medical Investigator Ronald M. Evans, Ph.D., a professor in the Salk Institute’s Gene Expression Laboratory, who led the study that appears in the Feb. 21 issue of *Nature*.

He hopes that “this could lead to a new class of insulin-sensitizing drugs that loosen the brake and let insulin work a little bit longer.”

When insulin binds its receptor on the cell surface it sets off a cascade of intracellular signals resulting in the production of PIP3, a specialized

lipid molecule that masterminds a whole army of molecules that work together to synthesize and store carbohydrates, lipids and proteins. “But turning on a physiological process is only half the story,” explains Evans. “You also need instructions that tell the cell to get off the accelerator and put on the brake.”

Postdoctoral researcher and first author Xiaoyong Yang, Ph.D., discovered that PIP3 oversees both. His experiments revealed that within minutes activation of the insulin signaling network coaxes OGT out of the nucleus and into the cytoplasm. It travels to the plasma membrane and hooks up with PIP3.

“It uses a novel PIP3 binding domain to interact with the same lipid that just turned on the system,” describes Xiaoyong. “After OGT is recruited to the plasma membrane it starts turning off the system.”

It accomplishes this task by tagging key members of the insulin signaling network with sugar molecules, specifically O-linked ß-N-acetylglucosamine or O-GlcNAc, which are produced by the hexosamine pathway.

Since the amount of O-GlcNAc is directly tied to availability of glucose, lipids and other nutrients in the bloodstream, the researchers believe that the hexosamine pathway acts as fuel gauge, protecting the body’s cells against the toxic effects of too much glucose and other high-energy molecules.

Excessive quantities of nutrients — the result of a lifestyle where food is plentiful and exercise is optional — drive O-GlcNAc levels up, which in turn dampen the insulin response, paving the way for a relentless progression of insulin resistance.

Though it may not be as simple as that, when Xiaoyong put OGT into

overdrive in the livers of mice, the animals developed insulin resistance and abnormal blood lipid levels, emphasizing the importance of the hexosamine pathway for the development of insulin resistance, the first step towards full-blown type 2 diabetes.

Most people with insulin resistance go on to develop type 2 diabetes within 10 years, unless they lose 5 to 7 percent of their body weight—approximately 10 to 15 pounds for someone who weighs 200 pounds—by making modest changes in their diet and level of physical activity. But making permanent lifestyle changes is difficult and studies predict that one in three Americans born in the year 2000 will develop diabetes in their life time. A similar fate awaits most developed nations.

Source: Salk Institute