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Study examining how toxicity of fatty acids links obesity and diabetes

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Though it generally is known that obesity dramatically increases the risk for type 2 diabetes, the biological mechanisms for that connection still are unclear.

Backed by several grants from the National Institutes of Health (NIH), James Granneman, Ph.D., professor of psychiatry and behavioral neurosciences and pathology in Wayne State University's School of Medicine, is examining the nature of those mechanisms, specifically how the toxicity of lipids, or fatty acids, links obesity and diabetes.

As people become obese, their adipose tissue, which stores energy from food, loses its ability to do so, releasing toxic lipids, or free fatty acids (FFAs), which make their way to muscles and the liver. The FFAs then interfere with insulin's ability to promote the use of glucose as a fuel by cells in the muscle and liver. As a result, the pancreas is stimulated to produce more insulin, but diabetes can occur if the pancreas is unable to meet the higher demand. Some 20 million people in the United States suffer from type 2 diabetes and its complications.

"It's not how fat you are that causes diabetes, but rather how well your adipose tissue functions to handle toxic fatty acids," said Granneman, whose laboratory is part of WSU's Center for Integrative Metabolic and Endocrine Research (CIMER).

Understanding cellular mechanisms for storing and releasing fatty acids in adipose tissue, muscle and the liver is important to understanding the

pathophysiology of lipotoxicity, he said.

Granneman is working with colleagues on four NIH-funded projects that address how adipose tissue handles fatty acids and the mechanisms by which that process occurs. The work has direct implications for metabolic and cardiovascular diseases.

The first project, funded by $1.37 million over four years, investigates basic mechanisms of lipolysis, or how fat and muscle cells break down stored triglycerides into fatty acids. This work includes the development of techniques to image the process of lipolysis in live cells at high resolution. Victoria Kimler, a CIMER research associate, now is collaborating with the National Center for Microscopy and Imaging Research in San Diego to use high-resolution 3-D electron tomography to understand the structure and organization of lipid storage in fat-storing cells and in cardiac muscle at nanometer resolution.

Another study, recently funded by a two-year, $375,000 grant, is aimed at developing techniques to directly visualize FFA within live cells. An earlier project developed a "sensor" prototype based on the interaction of two proteins. The new project will create a second-generation sensor so that the production, metabolism and signaling of FFA can be observed in live cells in real time. Fellow CIMER researcher Todd Leff, associate professor of pathology in WSU's School of Medicine, is helping Granneman pursue applications beyond fat cell signaling.

"Once we develop this second-generation sensor, we'll make it available to the broader scientific community so they can use it in their own studies," Granneman said, adding that fat accumulation in the liver (hepatic steatosis) is a particularly big problem whose study could benefit from such a sensor.

The fourth project, funded by a separate $1.5 million grant, involves

methods for improving the function of adipose tissue and is being undertaken by WSU pathology graduate students Emilio Mottillo and Yun-Hee Lee. The research investigates how excessive fatty acid production triggers inflammation and impairs normal adipose tissue function. It also is exploring ways to develop anti-obesity drugs that convert tissue that normally stores fat into the energy-burning type.

"This includes exciting new work that has identified stem cells in fat tissue that give rise to cells with the fat-burning phenotype," Granneman said. "The work has therapeutic implications for both metabolic disease and for restorative medicine, since we can successfully isolate the cells and transplant them into animals."

Overall, he said, the projects have allowed insights into the basic mechanisms of lipolysis and suggested novel approaches for therapeutic intervention. Based on these insights, Granneman and collaborators at the Scripps Research Institute are screening chemical libraries for compounds that might be developed into anti-obesity therapeutics.

"We now have identified compounds that have the expected biochemical activity and are hopeful that some might be used as chemical leads for anti-obesity drugs," he said.

Provided by Wayne State University