Cellular pathway linked to diabetes, heart disease

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Cardiac researchers at the University of Cincinnati (UC) have found that a certain cellular pathway is linked to obesity-related disorders, like diabetes, heart disease and fatty liver disease.

These findings, being presented at the American Heart Association's Arteriosclerosis, Thrombosis and Vascular Biology (ATVB) 2012 Scientific Sessions in Chicago, April 19, 2012, could lead to a potential molecular target for metabolic diseases in humans.

Building on previous research, Tapan Chatterjee, PhD, and researchers in the division of cardiovascular diseases at UC found that genetically "deleting" the enzyme histone deacetylase 9 (HDAC9) completely protected mice against the health consequences of high-fat feeding, like elevated blood sugar, cholesterol levels and fatty liver disease.

Chatterjee says HDAC9 has been found to lead to obesity-induced body fat dysfunction.

"Failure of fat cells to differentiate and properly store excess calories in obesity is associated with adipose tissue (fat) inflammation, fatty liver disease, insulin resistance, diabetes and increased cardiovascular diseases," he says. "We know that dysfunctional fat tissue is the underlying culprit in obesity-related diseases.

"Caloric intake promotes HDAC9 down-regulation to allow the conversion of precursor fat cells to 'functional' fat cells, capable of

efficiently storing excess calories for future use and also maintaining whole-body lipid and glucose stability," Chatterjee continues. "Unfortunately, during chronic over-feeding, the HDAC9 level is up-regulated in fat tissue, thereby blocking the conversion which leads to adipose tissue dysfunction and the onset of diseases such as diabetes, liver disease, high blood pressure and heart disease—the nation's No. 1 killer."

Chatterjee says that in previous studies, researchers found that elevated HDAC9 expression in fat cells was the underlying molecular culprit for dysfunctional fat tissue during obesity.

"In this study, we used 'knockout' mouse models to test this theory," he says. "Deleting the HDAC9 gene completely prevented mice from developing obesity-related diseases during chronic high-fat feeding. These results mean the discovery of a potential molecular culprit in obesity-related disease development."

Chatterjee says emerging evidence from his laboratory indicates that unhealthy dietary habits over a long period of time promote specific changes in a human's epigenetic structure—meaning changes in the gene structure that influences its function—to switch HDAC9 expression to a higher level.

"This switch paves the way for development of a chronic disease state, despite subsequent dietary intervention," he says. "We are currently focusing our attention to design drugs to reverse such epigenetic changes to bring HDAC9 expression down and restore normal fat cell function in obese individuals, representing a novel treatment strategy for obesity-related disease conditions."

Provided by University of Cincinnati Academic Health Center