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Enzyme action could be target for diabetes, heart disease treatments

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Cardiac researchers at the University of Cincinnati (UC) have found a new cellular pathway that could help in developing therapeutic treatments for obesity-related disorders, like diabetes and heart disease.

This research is being presented at the American Heart Association's Scientific Session in Chicago Nov. 16.

Tapan Chatterjee, PhD, and researchers in the division of cardiovascular diseases found that action by the enzyme histone deacetylase 9 (HDAC9) can lead to obesity-induced body fat dysfunction and that HDAC9-regulated pathways could be targets for potential treatment options in obesity-related diseases.

"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," Chatterjee says. "We know that dysfunctional fat tissue is the underlying culprit in obesity-related diseases; however, we do not know why fat tissue becomes dysfunctional when a person becomes obese."

Chatterjee says researchers in this study first identified HDAC9 regulator of fat cell differentiation within the living organism.

"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," he says. "Ideally, fat cells should function as a reversible storage site of excess calories and as an endocrine organ to maintain systemic lipid and glucose stability.

"Unfortunately, during chronic over-feeding, we find 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."

Researchers examined various members of the HDAC family of proteins and found that only HDAC9 showed a direct correlation to differentiation of precursor fat cells, both from human and mouse fat tissues.

"HDAC9 down-regulation is necessary for the differentiation of precursor fat cells to mature fat cells; forced up-regulation of HDAC9 by genetic manipulation blocks the differentiation of the precursor fat cells," Chatterjee says. "On the other hand, precursor fat cells from HDAC9 genetic knockout mice showed accelerated differentiation.

"We believe that HDAC9 keeps precursor fat cells in the undifferentiated state; metabolic cues trigger HDAC9 down-regulation allowing conversion of the precursor cells to mature fat cells. We are exploring the cellular signaling mechanism that promotes such down-regulation of this enzyme during the normal fat cell differentiation process."

Chatterjee says researchers were really interested in the tie between increased HDAC9 levels in fat tissue of mice and the caloric overload.

"Fat tissues from these obese mice showed dysfunction, with increased expression of pro-inflammatory agents and decreased expression of

hormones responsible for maintaining whole body lipid and glucose stability," he says. "The fat tissues of these mice are not capable of efficiently storing excess calories and are not able to perform proper endocrine functions.

"The adaptive response fails for some reason during chronic caloric overload, leading to the generation of fat tissue mass that is dysfunctional."

Chatterjee says the HDAC9 level in fat cells is the underlying molecular culprit for dysfunctional fat tissue during obesity.

"We are currently examining HDAC9 knockout mice subjected to chronic high-fat feeding and think that HDAC9 gene removal will protect mice from obesity-linked adipose tissue dysfunction and associated metabolic disorders," he says.

"Identification of HDAC9 as a novel regulator of fat cell differentiation and the finding that elevated HDAC9 levels are associated with adipose tissue dysfunction in obesity are extremely interesting and novel findings," he continues.

Chatterjee's team is pursuing studies to understand how diet regulates HDAC9 levels in fat tissue and how HDAC9 up-regulation can be prevented during diet-induced obesity through pharmacological means.

"Our findings may help lead researchers to targeted therapies that may prevent the development of obesity-related disorders in humans."

Provided by University of Cincinnati