Fat associated with chemical changes in DNA that may help explain obesity-related disease

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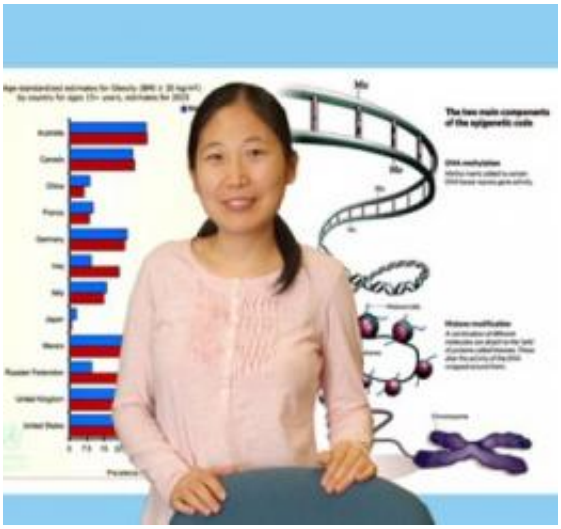

The research of Dr. Xiaoling Wang, genetic epidemiologist at the Medical College of Georgia's Georgia Prevention Institute, is providing insight as to how fat causes disease. Credit: Phil Jones, Campus Photographer

Fat appears to associate with some distinctive chemical changes in the DNA – a finding that may help explain why obesity can increase the risk for chronic problems such as cardiovascular disease and diabetes, researchers report.

The finding, published in *BMC Medicine*, may one day help identify those at risk and reduce it, according to Dr. Xiaoling Wang, genetic epidemiologist at the Medical College of Georgia's Georgia Prevention

Institute.

"Losing fat is very difficult; we know that. We also know it causes many diseases so we want to identify and target pathways to reduce those diseases," Wang said.

Fat used to be viewed as essentially padding and a ready energy source but scientists are learning it's more like a factory that makes chemicals and compounds such as hormones and proteins. Studies comparing two groups of obese versus lean teens found higher levels of chemical change, or methylation, in a portion of the UBASH3A gene and lower levels in part of the TRIM3 gene.

Both genes are known to have roles in regulating the immune system, which is often dysregulated in obese individuals. Dysregulation can result in a level of chronic inflammation that contributes to diseases such as cardiovascular disease, diabetes and cancer. Methylation can impact immune function by affecting gene expression levels which ultimately impacts downstream functions of the proteins produced by genes.

"You need to know disease pathways to find novel medications," Wang said. "We generally know they have a dysregulation of the immune function, but we didn't know the specific site." She believes she found at least two sites in the UBASH3A and TRIM3 gene. Her initial search was broad: a genome-wide screen of seven obese and seven lean teens that enabled her to identify genes most different between the two. She ranked the differences and, in a much larger study of 46 obese and 46 lean controls, looked at the same sites in the top six genes and found again the distinctive methylation pattern in UBASH3A and TRIM3.

Wang now wants to clarify whether fat causes the DNA changes or vice versa and confirm that the changes contribute to the immune dysfunction associated with obesity.

She notes that because obesity does not always lead to related diseases, it's important to have a way to not just intervene, but to identify those most at risk. Factors such as fitness, body shape and environment probably are also predictors for related disease.

"... (T)he public health message of 'eat less and exercise more' appears to have fallen on deaf ears," Drs. Paul W. Franks and Charlotte Ling of Sweden's Skåne University Hospital, Lund University write in an accompanying editorial. "Thus, despite the apparently simple explanation and remedy for obesity, this knowledge is not enough. We are saddled with a challenge, which is to unravel the mechanisms by which obesity emerges and to understand how its presence causes disease and death, with the hope that somewhere within the details hides the solution to the problem." They note that Wang's study provides "tentative evidence" that DNA methylation at the two gene sites may be implicated in obesity-related disease.

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