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Study results suggest cell-free DNA may be involved in inflammation in obese patients

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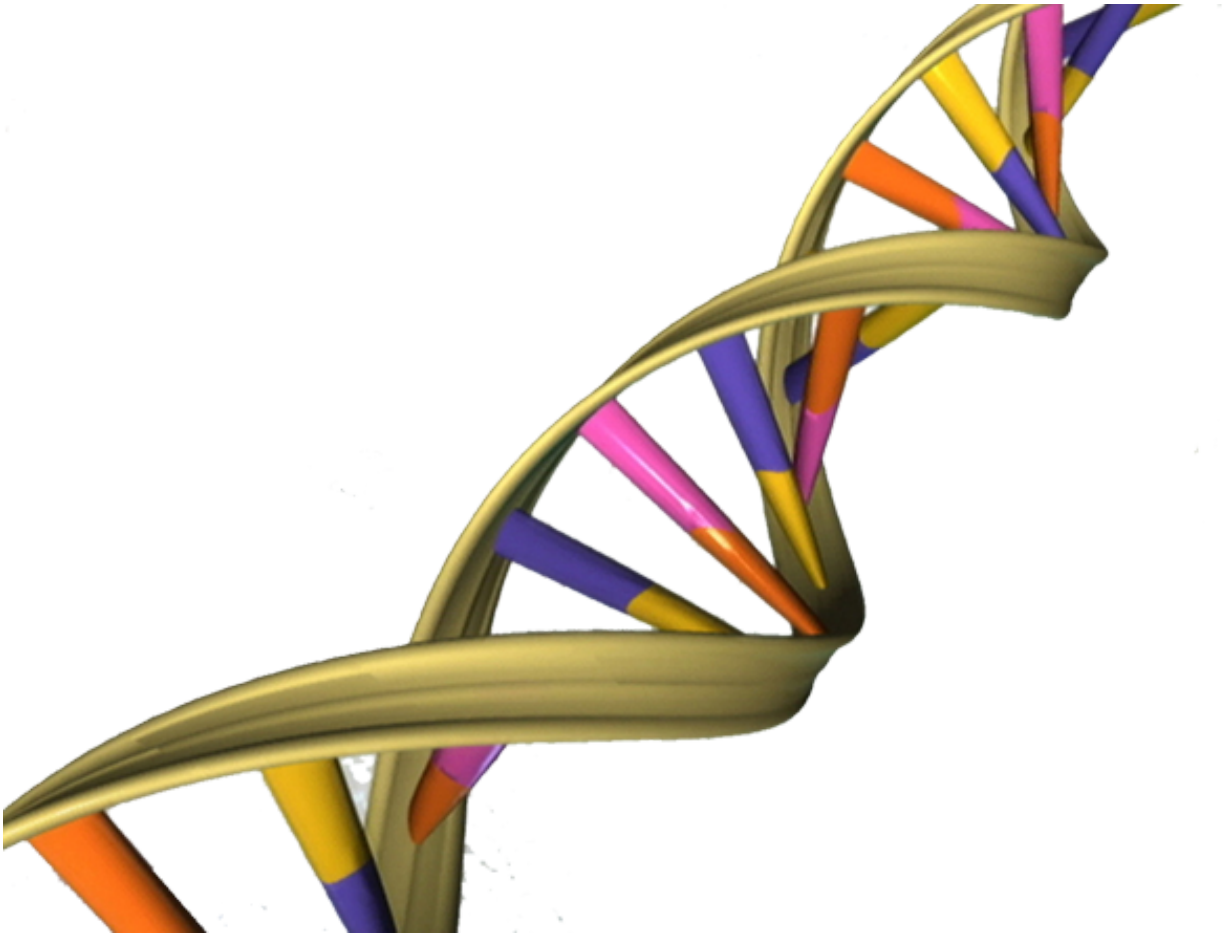

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

(Medical Xpress)—A team of researchers affiliated with multiple facilities in Japan has found that as fat cells die due to an increase in obesity, more cell-free DNA is released into tissue causing inflammation. In their paper published in the journal *Science Advances*, the team describes their study of mice, inflamed tissue and Toll—like receptor 9 (TLR9).

Doctors have known for quite some time that as people gain weight, they become more susceptible to chronic inflammation and that there is a link between it and the protein TLR9. They have also known that there is a link between obesity, inflammation and insulin resistance, which of course is the underlying cause of diabetes. In this new effort, the researchers have found that as people become obese and more and more cell-free DNA is released into nearby tissue as fat cells degenerate and break apart, the result is inflammation, an increased expression of TLR9 and insulin resistance. To come to these conclusions, the team conducted tests with mice that involved causing them to express more or less TLR9—higher levels were found in obese mice, but reducing the levels, even in obese mice, led to less inflation and insulin resistance.

More specifically, the researchers found that the expression of TLR9 had an impact on the amount of accumulation of macrophages in murine fat tissue. Mice that were made obese, but who were caused to express less TLR9, had less accumulation of macrophages in their fat tissues, than those with higher levels of TLR9, which caused them to be more sensitive to insulin. Reintroducing TLR9, on the other hand, caused the inflammation and insulin resistance to rebound. This suggests that developing a therapy that reduces TLR9 levels in humans may help to reduce inflammation due to obesity.

The team also found that *people* with higher than normal levels of visceral fat in their blood also had increased levels of cell-free DNA suggesting the findings in mice likely compare to humans. They also

note that it is still not clear why it is that certain fat cells die off as people become obese or whether the cell-free DNA that circulates in the body has any sort of impact on other tissue types.

More information: S. Nishimoto et al. Obesity-induced DNA released from adipocytes stimulates chronic adipose tissue inflammation and insulin resistance, *Science Advances* (2016). DOI: 10.1126/sciadv.1501332

Abstract

Obesity stimulates chronic inflammation in adipose tissue, which is associated with insulin resistance, although the underlying mechanism remains largely unknown. Here we showed that obesity-related adipocyte degeneration causes release of cell-free DNA (cfDNA), which promotes macrophage accumulation in adipose tissue via Toll-like receptor 9 (TLR9), originally known as a sensor of exogenous DNA fragments. Fat-fed obese wild-type mice showed increased release of cfDNA, as determined by the concentrations of single-stranded DNA (ssDNA) and double-stranded DNA (dsDNA) in plasma. cfDNA released from degenerated adipocytes promoted monocyte chemoattractant protein-1 (MCP-1) expression in wild-type macrophages, but not in TLR9-deficient (Tlr9−/−) macrophages. Fat-fed Tlr9−/− mice demonstrated reduced macrophage accumulation and inflammation in adipose tissue and better insulin sensitivity compared with wild-type mice, whereas bone marrow reconstitution with wild-type bone marrow restored the attenuation of insulin resistance observed in fat-fed Tlr9−/− mice. Administration of a TLR9 inhibitory oligonucleotide to fat-fed wild-type mice reduced the accumulation of macrophages in adipose tissue and improved insulin resistance. Furthermore, in humans, plasma ssDNA level was significantly higher in patients with computed tomography–determined visceral obesity and was associated with homeostasis model assessment of insulin resistance (HOMA-IR), which is the index of insulin resistance. Our study may provide a novel

mechanism for the development of sterile inflammation in adipose tissue and a potential therapeutic target for insulin resistance.