

# Research helps clarify how obesity leads to type 2 diabetes, cancer

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New findings about the biological links between obesity, insulin resistance and type 2 diabetes may also shed light on the connection between obesity and cancer, says a scientist at The University of Texas at Dallas.

In a study published online June 5 in the journal *Cell*, UT Dallas' Dr. Jung-whan (Jay) Kim and colleagues at the University of California, San Diego found that a protein called HIF-1 alpha plays a key role in the development of [insulin resistance](#) and type 2 diabetes in obese mice.

The researchers genetically engineered mice to lack the HIF-1 alpha protein within the animals' [fat cells](#), or adipocytes. The animals still made HIF-1 alpha in other types of cells and tissues in their bodies. Although the mice became obese when fed a high-fat diet, they did not develop insulin resistance and diabetes to near the extent that genetically normal, obese mice did.

"There is clearly a greater chance among the obese human population to develop insulin resistance and diabetes. We still don't know the exact mechanism, but now we know that HIF-1 alpha is very active in the pathogenesis of these diseases from obesity," said Kim, a co-lead author of the study who conducted the research while a postdoctoral researcher at UC San Diego and the Salk Institute for Biological Studies. He joined the UT Dallas faculty as an assistant professor of molecular and cell biology in 2013.

Kim said the findings about HIF-1, which stands for hypoxia inducible factor-1, are significant not only for their possible application to fighting insulin resistance and diabetes, but also cancer. Here's why:

Cells in the body normally consume oxygen to produce energy. But if oxygen levels decrease, for example during strenuous exercise or at high altitudes, cells enter a condition called hypoxia, or low oxygen. With oxygen in short supply, cells switch their metabolism. Instead of energy, the cells produce reactive oxygen species, which are molecules that can damage or kill cells. To help mitigate the damage, hypoxic cells activate HIF-1 alpha, which in turn shuts down the production of [reactive oxygen species](#) and signals inflammatory cells to migrate to the hypoxic areas.

"Organisms need to be able to temporarily adapt to the stress of hypoxic conditions until the situation changes, so when inflammatory cells see this kind of signal, they come to the hypoxic area to do their normal job, which is to basically eat damaged cells," Kim said.

In obesity, however, fat cells are in a chronic state of hypoxia.

"If you look at adipose, or fat tissue, in the obese, there is massive and chronic inflammation," he said. "It's a defense mechanism. The [inflammatory cells](#) are really good guys, but as obesity persists, inflammation becomes chronic.

"HIF-1 alpha is important for hypoxia adaptation, but it's constantly activated in the obese, and that's where it turns bad," Kim said. "In the obese, HIF-1 is aberrantly and chronically elevated and is the master regulator of ominous chronic inflammation."

To study the effect HIF-1 alpha might have on the development of insulin resistance and diabetes, Kim and his colleagues used genetic engineering techniques to completely remove, or "knock out" HIF-1

alpha from adipose tissue in [obese mice](#).

"Once we knocked out HIF-1, everything got better," he said. "The fat cells survived and the mice remained obese, but we saw less inflammation in the fat tissue. These mice responded better to insulin than their normal counterparts, which means insulin sensitivity was improved and glucose tolerance was improved."

Kim said several pharmaceutical companies are developing HIF-1 alpha inhibitors to block the protein from functioning, which might one day result in medications to treat [type 2 diabetes](#) and insulin resistance in [obese people](#). But the primary reason the pharmaceutical industry is already investigating HIF-1 alpha inhibitors is cancer.

"Tumor cells grow really fast, but the blood vessels that feed them oxygen cannot grow fast enough, so tumor cells become hypoxic," Kim explained. "The [tumor cells](#) have to develop some sort of mechanism to survive under hypoxic stress, and that's HIF-1 alpha."

"If you can inhibit HIF-1 alpha in a tumor cell, you can kill the cell, and that's why pharmaceutical companies are interested in HIF-1 inhibitors."

Kim said one motivation for the *Cell* study was to gain a better understanding of the links between [obesity](#) and cancer.

"There is a clear correlation between the two, but it's not clear why obese people have a greater chance of developing certain cancers," he said. "If you look at breast cancer, the glands that produce milk are completely surrounded by fat cells."

"Tumor tissue is hypoxic. Obese tissue is hypoxic. HIF-1 alpha is important in both conditions. I'm very motivated to study the interaction between [breast cancer cells](#) and fat [cells](#)."

Provided by University of Texas at Dallas

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