# Epigenomics analysis reveals surprising new clues to insulin resistance

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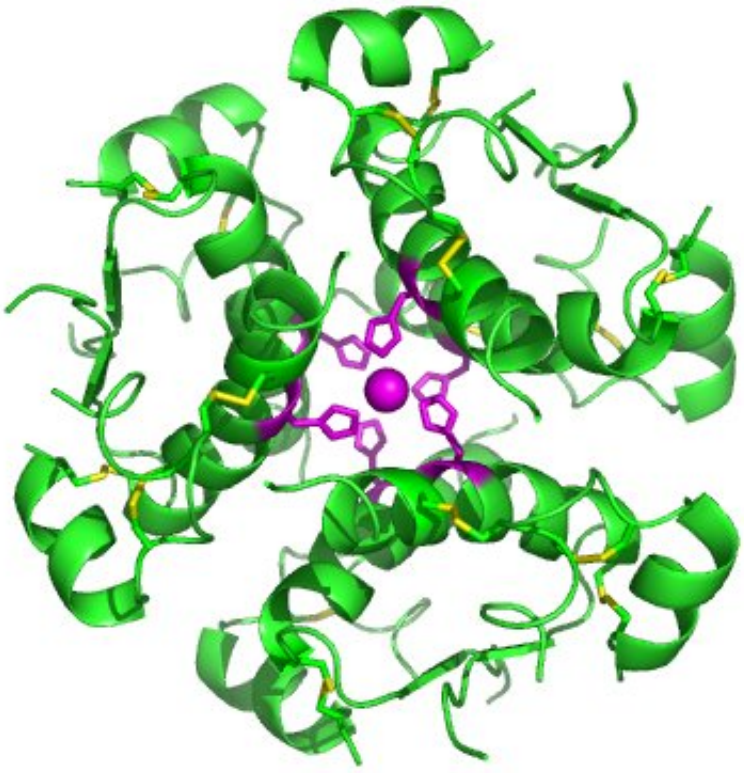

High-resolution model of six insulin molecules assembled in a hexamer. Credit: Isaac Yonemoto/Wikipedia

In studying the cellular structure and function of insulin, a research team led by investigators at Beth Israel Deaconess Medical Center (BIDMC) has uncovered previously unknown steps in the development of insulin

resistance, a hallmark of type 2 diabetes. Reported in the January 2015 issue of *Nature Cell Biology*, their surprising new findings identify two transcription factors—the glucocorticoid receptor (GR) and the vitamin D receptor (VDR) - that play a key role in insulin resistance, providing some of the first evidence that changes in the cellular nucleus underlie the condition and offering a promising new route for the development of drug therapies for type 2 diabetes.

"We wanted to understand what was initially happening to cause the body to become unresponsive and stop 'listening' to insulin," explains senior author Evan Rosen, MD, PhD, of the Division of Endocrinology, Diabetes and Metabolism at BIDMC and Professor of Medicine at Harvard Medical School. "Insulin resistance has been intensively studied for decades, but most work has focused on rapid events that happen in cells immediately after the hormone is produced. Through epigenomic mapping, we have now identified events that take longer to develop and that involve previously unsuspected biological pathways. Perhaps most importantly, we found that these pathways work completely in the nucleus of the cell by regulating the expression of key target genes, a process that was felt by many to be irrelevant to the development of this widespread condition."

Previous investigations of insulin resistance have focused almost exclusively on proteins and cellular functions at or near the surface of cells, where insulin binds. However, epidemiological and molecular data have suggested that events leading to insulin resistance might also take place in the nucleus, where the DNA blueprint is stored.

One such piece of evidence comes from an observation surrounding fetal programming, says Rosen. "Fetal programming centers on a person's exposure in utero," he explains. "So, for example, whether a fetus has received too few or too many nutrients from the mother can lead to a person becoming obese or diabetic in adulthood, and this in turn can be

passed along to the next generation. There is a lot of evidence that insulin resistance can be passed on this way and this type of intergenerational event almost certainly develops in the nucleus."

Epigenomic modifications refer to changes in the structure of DNA that are distinct from mutations and can be passed from cell to cell as cells divide, and passed from one generation to the next. By mapping these modifications, scientists are able to gain important insights into the cell's nuclear function.

To better understand how the epigenome is altered in states of insulin resistance, the research team treated fat cells with one of two chemicals, the steroid dexamethasone or the cytokine tumor necrosis factor-alpha (TNF). "By their nature, these agents would be predicted to cause almost opposite effects in cells, and yet we know that both cause insulin resistance," says Rosen. "This provided us with a unique opportunity to see how each agent was affecting the epigenome of cells. Then by focusing on changes that were shared by the two treatments, we could discern which epigenomic events might be at the core of insulin resistance." Because the types of epigenomic changes being analyzed occur at locations where transcription factors bind, the team was able use their data to infer which transcription factors might be involved in the development of insulin resistance.

"The glucocorticoid receptor [GR] and the vitamin D [VDR] receptor fit the bill," says Rosen. A subsequent series of experiments confirmed that the GR and VDR receptors were indeed cooperating and working together to cause insulin resistance.

"Our findings were unanticipated for several reasons," says Rosen. "First, TNF is a strong inducer of inflammation, while the GR protects against inflammation. Showing that TNF exerts at least some of its actions via the GR is somewhat heretical. Additionally, higher vitamin D

levels have been correlated with better insulin sensitivity, so it was surprising to see the VDR associated with insulin resistance. These results call into question some of the basic assumptions surrounding the relationship between vitamin D and metabolic health. Most importantly, these data tell us that we have an awful lot still to learn about the basic mechanisms by which diabetes is triggered, and they reveal new ways in which we can approach drug therapy for this disorder."

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