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Common genetic variant in a tumor suppressor gene linked to obesity and type 2 diabetes

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P53, a tumor suppressor gene that is mutated and inactivated in the vast majority of cancers, has often been described as the "guardian of the genome" because of its protective effects against cancer. Now, researchers at The Wistar Institute are also making the case for p53 as the "guardian of obesity," having found that a variant of the gene is heavily implicated in metabolism, which may lead to obesity and the development of type 2 diabetes. Study results are published in the journal *Cell Reports*.

While p53's role in cancer is undisputed and has been well-established over the course of decades, the gene's role in metabolism is poorly understood. Prior studies have shown that p53's role in metabolism may play an essential role in the gene's tumor suppressor function, and it has also been implicated in heart disease, obesity, and type 2 diabetes.

To understand why this crucial gene functions differently in diverse populations, Maureen Murphy, Ph.D., professor and program leader of the Molecular and Cellular Oncogenesis Program at Wistar, and colleagues have focused on single nucleotide polymorphisms (SNPs), or variations at single points in a DNA sequence. In p53, the most common SNP occurs at amino acid 72, where there is a nucleotide sequence that encodes for one of two amino acids: Proline (P72) or Arginine (R72).

For decades, the R72 variant of p53 was observed in people who lived

farther away from the Equator and in colder winter temperatures, but studies could not conclusively explain why this was happening. Moreover, genome-wide association studies revealed significant associations between the R72 variant and increased body mass index and susceptibility to type 2 diabetes.

Murphy and colleagues studied mice that had either the P72 variant or the R72 variant. They were fed a normal diet for 10 weeks and then given a high-fat diet for eight weeks. While on the normal diet, the R72 variant mice showed a mildly increased weight gain, but there was a much more significant weight gain experienced when the mice were switched to a high-fat diet, with at least 20 percent greater body fat content in the R72 mice than the P72 mice. Glucose tolerance tests showed that following the high fat diet, the R72 mice developed pre-diabetic symptoms and insulin resistance.

To confirm that a high-fat diet exacerbated these metabolic disorders in R72 mice, they fed the two groups a normal diet for 18 weeks instead of switching over to a high-fat diet. No difference in glucose tolerance was observed between the two groups, showing that the high-fat diet was responsible for these negative changes.

"Unlike the majority of other oncogenes and tumor suppressor genes, the p53 gene has genetic variations that change the function of this protein," said Murphy, lead author of the study. "For years, no one understood why such an important tumor suppressor would show genetic variation, much less in response to latitude.

"Now we think we understand why: the R72 variant may have been arisen and been selected for in colder climates because it increases the body's ability to store fat. Unfortunately, this can also lead to increased risk for obesity, fatty liver disease and diabetes."

Murphy and colleagues also identified two genes controlled by p53 that were noticeably different in the livers of the R72 mice compared with the P72 mice: Npc111 and Tnf. Npc111 has been linked to cholesterol absorption while Tnf ¬ is associated with obesity-induced insulin resistance. These genes acted as "early-responders" to a high-fat diet and helped initiate the development of obesity and non-alcoholic fatty liver disease in the R72 mice. Since drugs that specifically inhibit these two genes already exist, they used them as daily treatment for the mice. Using both inhibitors led to significant decreases in weight gain and fat accumulation in R72 mice.

The study may also provide an evolutionary explanation for differences in populations living farther away from the Equator. Human ancestors may have undergone this change in R72 to promote energy storage in cold climates and during times of famine. However, in modern society, the need for this type of variant in our genes is unnecessary, leading instead to increased risk for obesity and type 2 diabetes. Obesity is also a risk factor for certain types of cancer, so these findings may also explain why the R72 variant of p53 might predispose certain people to cancer.

"We showed exactly why the R72 variant of p53 is linked with diseases like obesity and type 2 diabetes," said Che-Pei Pat Kung, Ph.D., a postdoctoral fellow in Murphy's lab and first author of the study. "Not only does this study provide a more solid foundation for the link between p53 and metabolism, but it also shows that targeting Npc111 and Tnf may be effective strategies for the treatment of diabetes."

Wistar's Business Development team will be making the human p53 knock-in mouse models in this paper widely available to both academic and industry development partners interested in exploring the link between p53 and metabolism.

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