Baylor College of Medicine

Gene-diet interactions help regulate the body’s daily rhythms

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Our bodies follow a natural 24-hour cycle known as the circadian rhythm that influences everything from sleep to metabolism. While scientists have long known that certain core circadian clock genes help regulate these rhythms, a new study led by researchers at Baylor College of Medicine reveals that there is an additional layer of regulation – diet interacts with an individual's genetic makeup, influencing daily patterns of gene activity in the liver, especially those related to fat metabolism.

These findings, published in *Cell Metabolism*, reveal a previously underappreciated temporal aspect of the interactions between genetics and the environment in regulating lipid metabolism, with implications for individual variations in obesity-associated disease susceptibility and personalized chronotherapy, or the alignment of medical interventions with the body's natural circadian rhythms.

"Our study provides new insights into the question, 'Why do some people gain weight more easily or develop liver problems while others don't, even when they eat similar diets?'" said corresponding author Dr. Dongyin Guan, assistant professor of medicine – endocrinology, diabetes and metabolism and molecular and cellular biology at Baylor. Guan also is a member of Baylor's Dan L Duncan Comprehensive Cancer Center.

"We found that individual genetic differences affect the timing of gene activity in the liver in response to food," said co-first author Dr. Ying Chen, postdoctoral fellow in the Guan lab. "Genes and diet work together to shape the liver's daily rhythm, which in turn can affect how fats are processed and stored."

The researchers studied both human liver samples and two strains of mice with different genetic backgrounds. They looked at how genes in the liver turn on and off throughout the day and how this changes when the mice are fed a high-fat diet.

To explore the underlying molecular mechanisms of this collaboration between diet and genetics, the team also examined 3D interactions between DNA regions. They investigated how 'enhancers,' which are genes that boost gene activity, connect with 'promoters,' which start gene activity, in a time-dependent manner.

Guan and his colleagues found that genetic variation contributes to daily gene

activity patterns in both humans and mice. In humans, thousands of genes showed rhythmic activity only in people with specific gene variants.

“We also found that diet changes the rhythm of gene expression in mouse liver, but differently for different genes,” said co-first author Dishu Zhou, research assistant in the Guan lab. “When mice were fed a high-fat diet, their liver gene activity changed, but not in the same way for all genes. Some genes kept their rhythm, some lost it, and others gained it.”

Remarkably, genetics and nutrition work together to control more than 80% of the rhythmic enhancer-promoter interactions. “We identified gene ESRRγ as a noncanonical clock regulator, meaning that it is not part of the core circadian clock gene family but still plays a significant role in regulating daily rhythms,” Guan said. “Mice lacking ESRRγ lost many of these rhythmic connections in the liver and showed disrupted fat metabolism.”

The findings show that fat metabolism is time-sensitive and gene-dependent. In mice with different genetic backgrounds, the size of fat droplets in the liver changed throughout the day, but only in those with active ESRRγ. This suggests that individual genetic makeup could influence not just how the body handles fat, but when it does so.

This study focused on liver and fat metabolism, but the authors propose that the same principles may apply to other organs and diseases. The findings not only provide an improved understanding of daily metabolic changes but also support the possibility of personalized chronotherapy – tailoring mealtimes or scheduling medication or other treatments based on a person’s genetic profile to optimize health outcomes.

The study collaborators include Panpan Liu, Kun Zhu, Juliet Holder-Haynes, S. Julie-Ann Lloyd, Cam Mong La, Inna I. Astapova, Seunghee Choa, Ying Xiong, Hosung Bae, Marlene Aguilar, Hongyuan Yang, Yu A. An, Zheng Sun, Mark A. Herman, Xia Gao, Liming Pei, Cholsoon Jang, Joshua D. Rabinowitz, Samer G. Mattar and Yongyou Zhang. The authors are affiliated with Baylor College of Medicine, Xiamen University, University of Pennsylvania, Case Western Reserve University School of Medicine,

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