Ability to chart the molecular progress of diabetes brings personalized medicine closer to realization

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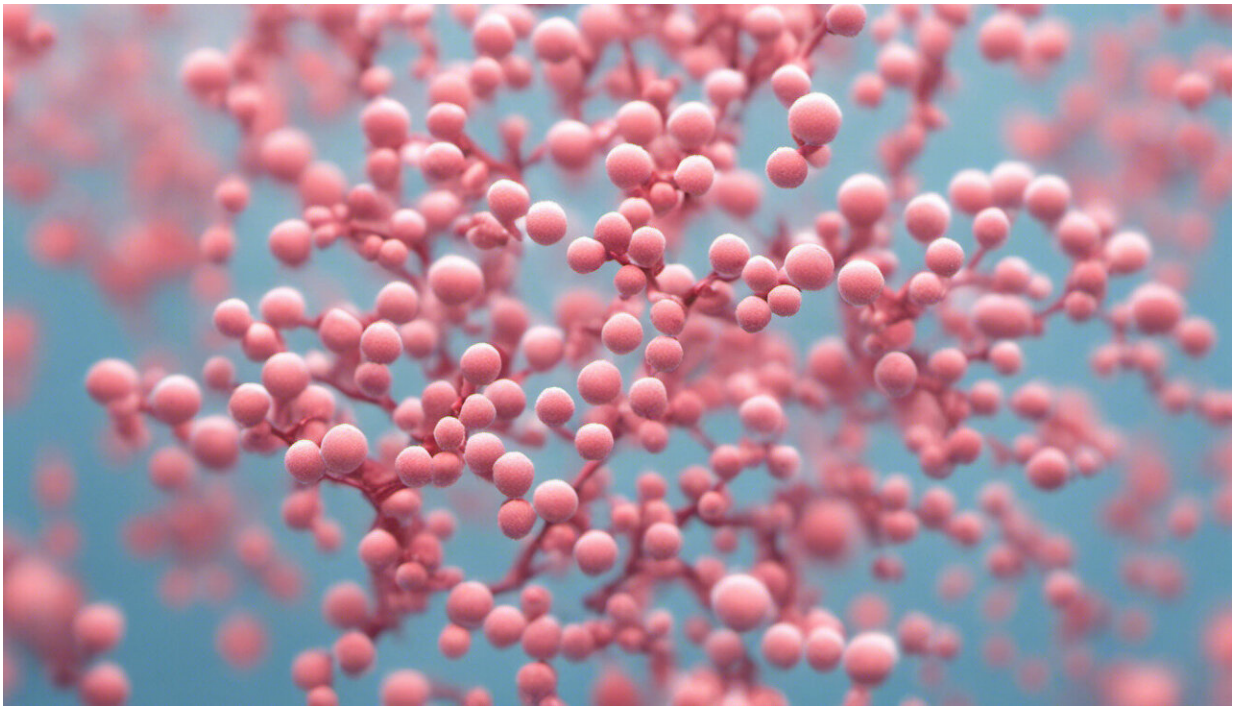

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Researchers in Singapore have succeeded in tracking, for the first time, the molecular changes caused by type 2 diabetes that affect how the body handles glucose production in the liver. In a series of experiments in mice, the researchers introduced a form of the compound pyruvate

that incorporated specially treated carbon nuclei. This allowed the researchers to follow the processing of the compound using magnetic resonance spectroscopy (MRS). In this way, the team, led by Phillip Lee of the Singapore Bioimaging Consortium, showed that the enzyme pyruvate carboxylase plays a key role in the development of diabetes.

The researchers also used their technology to plot the molecular changes induced by diabetes treatment over time. "This facilitates an in-depth understanding of treatment response in each subject and paves the way for personalized treatment," Lee says.

Diabetes is a consequence of the dysfunction of insulin, a hormone that stimulates cellular uptake of glucose from the blood. This process is closely linked to the production of glucose in the liver. Since the 1980s, limited study of the molecular details of glucose production has been possible using MRS to track organic compounds incorporating the rarer type of natural carbon known as carbon-13. Recently a 'hyperpolarized' form of carbon-13—vastly easier to detect using MRS—has become available.

Lee and his co-workers injected hyperpolarized carbon-13-labeled pyruvate into a strain of mice in which type-2 diabetes can be induced simply by changing the diet from normal to high fat. Using MRS, they then traced over time, in both normal and diabetic mice, the compounds into which the hyperpolarized carbon nuclei became incorporated, and in what proportions. Their results provide evidence not only of which biochemical pathways are active, but also which are dominant in normal and diabetic mice.

By comparing the two groups of mice, they were able to show distinct changes in the liver metabolism of diabetic mice over time, particularly the importance of the biochemical pathway dependent on the enzyme pyruvate carboxylase in the development of diabetes. When the

researchers gave the mice drugs typically used to treat diabetes, their technique detected the metabolic changes resulting from the therapy.

"This technology could be used to screen for metabolic disorders associated with other conditions such as heart failure, cancers and brain diseases," Lee says. "We are extending our work to investigate metabolic aberrations in the diabetic heart, and to understand the therapeutic effects of anti-diabetic drugs on cardiac function."

More information: Lee, P., Leong, W., Tan, T., Lim, M., Han, W. & Radda, G. K. In vivo hyperpolarized carbon-13 magnetic resonance spectroscopy reveals increased pyruvate carboxylase flux in an insulin resistant mouse model. *Hepatology* advance online publication, 22 August 2012 (doi: 10.1002/hep.26028). onlinelibrary.wiley.com/doi/10 … 2/hep.26028/abstract

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