New way found by which metabolism is linked to the regulation of DNA

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A research team at the Faculty of Medicine & Dentistry at the University of Alberta have discovered a new way by which metabolism is linked to the regulation of DNA, the basis of our genetic code. The findings may have important implications for the understanding of many common diseases, including cancer.

The DNA wraps around specialized proteins called histones in the cell's nucleus. Normally, histones keep the DNA tightly packaged, preventing the expression of genes and the replication of DNA, which are required for cell growth and division. In order for these critical functions to take place, histones need to be modified with the attachment of an acetyl-group, donated by a critical molecule called acetyl-CoA. This attachment relaxes the DNA, allowing for DNA replication and gene expression. This mechanism is called "epigenetic regulation of DNA" and is important for normal functions (like the growth of an embryo or brain functions) or in common diseases like heart failure or cancer. Until now, how the nucleus generates acetyl-CoA for histone acetylation had remained elusive.

The research team, lead by postdoctoral fellow Gopinath Sutendra and professor Evangelos Michelakis in the Department of Medicine, discovered that an enzyme thought to reside only within mitochondria, called Pyruvate Dehydrogenase Complex (PDC), can actually find its way into the nucleus and do what it is designed to do in the mitochondria: generate acetyl-CoA. When in mitochondria, PDC uses the carbohydrates from our diet to generate acetyl-CoA for energy

production. When in the nucleus, PDC can produce acetyl-CoA for histone acetylation.

"Although this jumping of an enzyme from one organelle into another in the cell is not unheard off, our results were quite surprising", Sutendra says. "We wanted to measure acetyl-CoA levels and PDC in the mitochondria because that's where we thought they were. But accidentally we had the nuclei isolated at the same time and we saw PDC in the nucleus. So we asked, 'what is PDC doing there?' And that started it all."

"We were surprised that, despite the recognized importance of histone acetylation in cell biology and medicine, and despite the efforts by many to develop drugs that regulate histone acetylation, the source of acetyl-CoA in the nucleus had remained unknown," Michelakis says. "Sometimes the answers to important biological questions are just next to you, waiting to be discovered," he adds.

The team found that the translocation of PDC into the nucleus made cancer cells grow faster, an observation that may lead to additional strategies in the war against cancer. Yet, because the findings relate to how our DNA is regulated in general, this work may have far broader implications for many physiologic or pathologic conditions where epigenetic regulation is critical. "We are very excited about this new pathway linking energy production (the process known as metabolism) with gene regulation," the researchers say.

The work is published in the July 3, 2014, issue of the journal *Cell*. Michelakis is particularly proud of the fact that this is the product of a team that is entirely based at the University of Alberta. Many young researchers in the Department of Medicine like Adam Kinnaird, Peter Dromparis and Roxane Paulin were critical members of the team that also included technicians (Trevor Stenson, Alois Haromy, Kyoko

Hashimoto) and researchers from the NanoFAB facility (Nancy Zhang, Eric Flaim). The work was funded by the Canadian Institutes for Health Research and the Hecht Foundation (Vancouver, Canada).

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