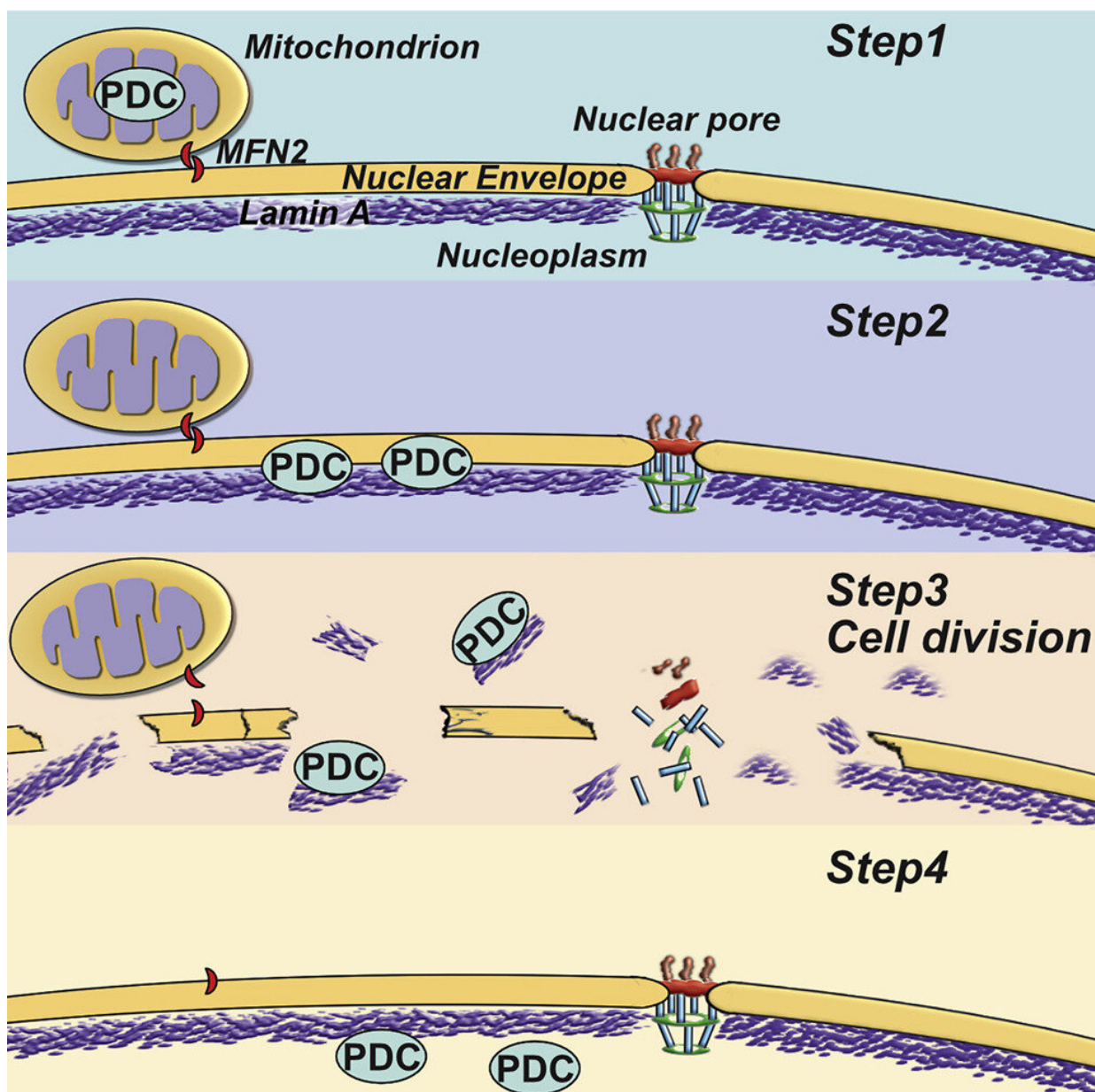


Two new studies yield clues to the metabolic mysteries of why some cancers grow out of control and spread

May 5 2022, by Gillian Rutherford



Graphical abstract. Credit: *Molecular Cell* (2022). DOI: 10.1016/j.molcel.2022.02.003

Researchers working in a U of A laboratory have uncovered two previously unknown ways that metabolism triggers cancer cell growth, uncovering potential new pathways for diagnosis and treatment.

Both papers come out of the laboratory shared by Evangelos Michelakis, professor and associate chair of research in the Faculty of Medicine & Dentistry and Canada Research Chair in Applied Molecular and Mitochondrial Medicine, and Gopinath Sutendra, associate professor of medicine, Alberta Innovates Health Solutions Translational Health Chair in Cardio-Oncology and member of the Cancer Research Institute of Northern Alberta.

Cancer has long been thought of as a genetic disease, but it is now known that environment and metabolism are also factors. Michelakis's research is focused on how mitochondria are involved. Mitochondria are control centers within [cells](#) that turn nutrients and oxygen into energy. They sense whether there is enough supply and decide whether the cell will live or die.

"The mitochondria process the food and the oxygen that we take in and they make energy and other molecules, and they can make decisions," explains Michelakis, who is also a 2021 Killam Professor. "When the balance is favorable, they say, "OK, cell, grow, grow, grow. If you are cancer, go for it, become big; if you are a sick cell, repair yourself; and if there's not enough fuel, just die."

This "survival circuit" was developed in the first bacteria that existed on Earth to monitor the often harsh chemical and climatic environment. Understanding how and why it operates is key to understanding why some [cancer cells](#) become aggressive and resist treatment, Michelakis says.

When the mitochondria do not function properly in cancer cells, they can promote [cell proliferation](#), interfere with natural cell death, increase blood supply and facilitate the spread of tumors to new sites in the body.

A mystery solved, a paradigm shifted

For the first paper, published in the journal *Molecular Cell*, the team used super-high-resolution imaging and other molecular techniques to reveal how a [mitochondrial enzyme](#) (called pyruvate dehydrogenase complex or PDC) crosses into the nucleus of a cancer cell by taking advantage of damaged lamin, proteins that line the nucleus, which hosts our DNA.

The presence of this enzyme in the nucleus enhances a process called [histone acetylation](#), which is essential for the genetic reprogramming that is needed to transform a regular cancer cell into an aggressive metastatic cancer cell.

Michelakis and his team were the first to identify mitochondrial enzymes in cell nuclei in 2014. The enzyme molecule was previously believed to be too large to pass through the nuclear surface. "Our paper essentially solves that mystery by showing another mechanism," Michelakis explains.

An editorial in the same issue of the journal called the discovery a "[paradigm shift](#)" in our understanding of how mitochondria control genetic changes within the nucleus of diseased cells.

"This pathway gives a different level of understanding of how cancer utilizes metabolism to its advantage," Michelakis says. "Cancer cells have to reprogram themselves constantly to become resistant to harsh conditions like chemotherapy. This pathway shows a major way that may allow the cancer cells to do that."

A key to metastasis

The second paper, published in *Cell Reports*, identifies a metabolic stress-induced [protein](#) previously thought to be active only in neurons (cells of the nervous system) which acts as a brake on metastasis. When the protein is suppressed or missing in lung, prostate or other cancer cells, for example, the researchers found those cells were more likely to reprogram, transform, metastasize and spread.

This protein (called Collapsin Response Mediator Protein 2A or CRMP2A) can now be used as a biomarker to predict which cancers will become more aggressive, guiding clinicians on whether to treat patients with chemotherapy, for example, or just "watch and wait."

Since the effect of the protein is reversible, it also provides a new target for potential cancer treatments.

"This research sheds new light on what makes cancer cells transform into this more aggressive type of cell that metastasizes," Michelakis says.

Michelakis, Sutendra and their teams have already started looking for ways to manipulate the gene for CRMP2A from [cancer](#) cells.

"It opens a very unexpected window in developing tools that people were not thinking about before," he says. "It's a very novel concept."

More information: Sotirios D. Zervopoulos et al, MFN2-driven

mitochondria-to-nucleus tethering allows a non-canonical nuclear entry pathway of the mitochondrial pyruvate dehydrogenase complex, *Molecular Cell* (2022). [DOI: 10.1016/j.molcel.2022.02.003](https://doi.org/10.1016/j.molcel.2022.02.003)

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