

Protein That Shuttles RNA Into Cell Mitochondria Discovered



Researchers at UCLA's Jonsson Comprehensive Cancer Center and the departments of Chemistry and Biochemistry and Pathology and Laboratory Medicine have uncovered a role for an essential cell protein in shuttling RNA into the mitochondria, the energy-producing "power plant" of the cell. (Credit: Maureen Heaster)

The import of nucleus-encoded small RNAs into mitochondria is essential for the replication, transcription and translation of the mitochondrial genome, but the mechanisms that deliver RNA into mitochondria remain poorly understood.

In the current study, UCLA scientists show a new role for a protein called

polynucleotide phosphorylase (PNPASE) in regulating the import of RNA into mitochondria. Reducing the expression of PNPASE decreased RNA import, which impaired the processing of mitochondrial genome-encoded RNAs. Reduced RNA processing inhibited the translation of proteins required to maintain the electron transport chain that handles oxygen to produce energy in the form of adenosine triphosphate, the energy currency of a cell. With reduced PNPASE, unprocessed mitochondrial RNAs accumulated, protein translation was inhibited and energy production was compromised, leading to stalled cell growth.

The study appears Aug. 5, 2010, in the peer-reviewed journal *Cell*.

"This discovery tells us that PNPASE regulates the energy producing function of mitochondria by mediating cytoplasmic RNA import," said Dr. Michael Teitell, a professor of pathology and laboratory medicine, a Jonsson Cancer Center researcher and co-senior author of the study. "The study yields new insight for how cells function at a very fundamental level. This information provides a potential new

pathway to control mitochondrial energy production and possibly impact the growth of cells, including certain types of cancer cells."

Mitochondria are described as cellular power plants because they generate most of the energy supply of the cell. In addition to supplying energy, mitochondria also are involved in a broad range of other cellular processes, such as signaling, differentiation, death, control of the cell cycle and growth.

The study could have implications for studying and treating certain cancers, which rely on cellular energy to grow and spread, as well as mitochondrial disorders such as neuromuscular diseases. The study could also result in new ways to think about attacking neurodegenerative disorders, such as Parkinson and Alzheimer diseases, which have recently been linked to the function of mitochondria.

"When we're talking about looking for ways to cure cancer, we fundamentally need to understand what makes cells grow and die and the mitochondrion is right at the heart of these issues," said Carla Koehler, a professor of chemistry and biochemistry, Jonsson Cancer Center researcher and co-senior author of the study. "This new and novel pathway for transporting RNA into the mitochondria is shedding new light on the evolving role and importance of mitochondria function in normal physiology and a wide variety of diseases. If we can understand how this pathway functions in healthy cells we could potentially uncover defects that help in transforming normal cells into cancer cells."

PNPASE was identified in 2004 by Teitell and his team as they attempted to find proteins that interact with TCL1, a human lymphoma-promoting cancer gene that has been used to generate genetic models of lymphocyte cancer. Mass spectrometry uncovered PNPASE, which had a signature sequence that suggested that it trafficked into and localized within the mitochondria of cells.

Once localized, Teitell, Koehler and post-doctoral fellow Geng Wang turned their attention to the function of PNPASE, which generated the unexpected results reported in this study. Prior to their discovery, it was not known what pathway was used to get RNA into the mitochondria. PNPASE mediates the movement of RNA from the cell cytoplasm, the area of the cell enclosed by the cell membrane, into the matrix of mitochondria, where the mitochondrial genome is located. The protein acts as receptor and binds to cytoplasmic RNAs that have a particular stem-loop signature sequence, mediating import, Teitell said.

Without this RNA import, the cell lacks the machinery to assemble the mitochondria's energy source, Koehler said.

"The cell would lose most of its ability to make energy," she said. "It would be crippled. Mitochondria are fantastically complex and our study reveals another cellular pathway in which these tiny but important powerhouses participate in essential cell activities, such as the generation of energy essential for life."

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