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Mitochondrial calcium uniporter, MiRNA and cancer

Live and let die

Saverio Marchi and Paolo Pinton*

Department of Morphology, Surgery and Experimental Medicine; Section of General Pathology; Interdisciplinary Center for the Study of Inflammation (ICSI); Laboratory for Technologies of Advanced Therapies (LTTA); University of Ferrara; Ferrara, Italy

Mitochondria receive calcium (Ca^{2+}) signals from endoplasmic reticulum (ER) and decode them into pro-apoptotic inputs, which lead to cell death. Therefore, mitochondrial Ca^{2+} overload is considered a fundamental trigger of the apoptotic process, and several oncogenes and tumor suppressors modify the activity of protein involved in Ca^{2+} homeostasis to control apoptosis. The identification of the channel responsible for mitochondrial Ca^{2+} entry, the Mitochondrial Ca^{2+}Uniporter (MCU), together with its regulatory components, MICU1 and MCUR1, provides new molecular tools to investigate this process. Recent data have also shown that miR-25 decreases mitochondrial Ca^{2+} uptake through selective MCU downregulation, conferring resistance to apoptotic challenges. MCU appears to be downregulated in human colon cancer samples, and accordingly, miR-25 is aberrantly expressed, indicating the importance of mitochondrial Ca^{2+} regulation in cancer cell survival.

Keywords: mitochondria, calcium (Ca^{2+}), Mitochondrial Calcium Uniporter (MCU), MicroRNAs (MiRNA), apoptosis, cell death, cancer

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*Correspondence to: Paolo Pinton; Email: pnp@unife.it

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In the last two years, the discovery of the pore-forming subunit of the mitochondrial Ca^{2+} uptake channel (Mitochondrial Calcium Uniporter, MCU)[1,2] and its regulatory subunits, termed MICU1 (mitochondrial calcium uptake 1)[3] and MCUR1 (mitochondrial calcium uniporter regulator 1),[4] opened a new era for the study of mitochondrial Ca^{2+} regulation and its key role in a variety of processes, including cell death. In the presence of an apoptotic stimulus, mitochondria receive Ca^{2+}-mediated inputs that induce the release of a number of pro-apoptotic factors from the mitochondria.[5,6] Several oncogenes and tumor suppressors manipulate Ca^{2+} to exert their anti/pro-apoptotic activities. For example, Akt and Bcl-2 regulate ER Ca^{2+} flux to avoid mitochondrial Ca^{2+} overload and apoptosis;[7,8] in contrast, pro-apoptotic genes, such as *Fhit* and *PML*, act at mitochondrial and ER levels, respectively, to promote mitochondrial Ca^{2+} accumulation.[9,10] Although the connection between mitochondrial Ca^{2+} increase and apoptosis is widely accepted, the mechanistic role of mitochondrial Ca^{2+} homeostasis in tumorigenesis is not fully understood. MicroRNAs (miRNAs) are a class of naturally occurring small noncoding RNAs that are capable of regulating the expression of protein-coding genes at the posttranscriptional level, which consequently leads to a decrease in target protein abundance.[11] Dysregulation of miRNA expression could lead to a variety of human disorders, including cancer.[12] Thus, miRNAs may function as oncogenes or tumor suppressors. Among the oncogenic miRNAs, miR-25 is one of the most studied and well described. miR-25 is 22 nucleotides in length, hosted by the minichromosome maintenance protein-7 (MCM7) gene, and transcribed as part of the mir-106b~25 polycistron; it is overexpressed in several human cancers, including pediatric brain tumors,[13] gastric adenocarcinoma,[14] epidermal growth factor receptor-positive lung adenocarcinoma[15] and prostate carcinoma[16] and has been reported to target different regulators of the apoptotic pathway, such as

BIM,[17] PTEN[16] and TRAIL.[18] Mir-25 also affects Ca^{2+} homeostasis through the specific downregulation of MCU, causing a strong decrease in mitochondrial Ca^{2+} uptake and, importantly, conferring resistance to Ca^{2+}-dependent apoptotic challenges.[19] Prostate cancer cell lines, which exhibit high levels of miR-25, display very low amounts of MCU, and this inverse correlation (high miR-25/low MCU) is also maintained in colon cancer cell lines. Expression of miR-25 inhibitor in HCT116 cells increases mitochondrial Ca^{2+} levels and re-sensitizes cells to apoptosis. A cancer link has been established through the detection of high miR-25 levels in stage II and III colonic adenocarcinoma samples, whereas MCU is virtually undetectable by immunohistochemistry. Other members of the miR-25 family, such as miR-92a and miR-363, have the same effect on MCU expression and Ca^{2+} signaling as miR-25. These observations not only highlight the deep involvement of the whole family in the regulation of Ca^{2+} homeostasis, but also suggest how cancer cell survival, which is favored by MCU downregulation, might be ascribed to the upregulation of all miR-25 family members or strong expression of a singular miR, different from miR-25. Thus, both miR-25-5p, which is the different mature miR that originates from the opposite arm of the same pre-miRNA, and members of the same miRNA cluster, i.e., miR-106b, were predicted to target MCU mRNA, although their activity has not yet been tested. Therefore, the miR-106b~25 cluster might also play an important role in the control of MCU levels.

Regulation of intracellular Ca^{2+} levels by miRNAs might be considered a fundamental aspect in several physio-pathological conditions. In the Ca^{2+}-dependent apoptosis context, which is characterized by sustained Ca^{2+} release from the ER and consequent accumulation at the mitochondrial level,[20] the specific expression of miR-targeting mitochondrial Ca^{2+} effectors, such as miR-25, may be considered one of the most rapid intracellular mechanisms to prevent mitochondrial Ca^{2+} overload and avoid cell death. This process appears to be aberrantly overexpressed in tumors, especially in colon and prostate cancer cells.

Interplay between the modulation of Ca^{2+} levels and miRNAs has also been highlighted in other pathological scenarios. For example, in cardiomyocytes, loss of miR-133a-mediated IP3R II (inositol 1,4,5 trisphosphate receptor, the calcium channel within the membranes of sarco/endoplasmic Ca^{2+} stores) repression generates a positive feedback loop to drive the hypertrophic response, a process that is primarily Ca^{2+} dependent.[21] In the same cellular setting, miR-214 protects the mouse heart from ischemic injury by controlling Ca^{2+} overload and cell death through the repression of the mRNA encoding sodium/calcium exchanger 1 (Ncx1), a key regulator of Ca^{2+} influx.[22] Moreover, miR-708, which is transcriptionally repressed in metastatic breast cancer, targets the ER protein neuronatin to decrease intracellular calcium levels, resulting in decreased cell migration and impaired metastases.[23]

In conclusion, the interplay between intracellular Ca^{2+} and miRNAs might be a key aspect in several pathological conditions. Specifically, the suppression of mitochondrial Ca^{2+} entry by cancer-related miR-25 represents the first study of the control of the mitochondrial uniporter by miRNA[19] and offers initial clues to the relevance of this pathway in human cancers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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