Mitochondrial calcium uniporter, MiRNA and cancer
Live and let die

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Mitochondria receive calcium (Ca²⁺) signals from endoplasmic reticulum (ER) and decode them into pro-apoptotic inputs, which lead to cell death. Therefore, mitochondrial Ca²⁺ overload is considered a fundamental trigger of the apoptotic process, and several oncogenes and tumor suppressors modify the activity of protein involved in Ca²⁺ homeostasis to control apoptosis. The identification of the channel responsible for mitochondrial Ca²⁺ entry, the Mitochondrial Ca²⁺ 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 Ca²⁺ 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 Ca²⁺ regulation in cancer cell survival.

In the last two years, the discovery of the pore-forming subunit of the mitochondrial Ca²⁺ uptake channel (Mitochondrial Calcium Uniporter, MCU) and its regulatory subunits, termed MICU1 (mitochondrial calcium uptake 1) and MCUR1 (mitochondrial calcium uniporter regulator 1), opened a new era for the study of mitochondrial Ca²⁺ regulation and its key role in a variety of processes, including cell death. In the presence of an apoptotic stimulus, mitochondria receive Ca²⁺-mediated inputs that induce the release of a number of pro-apoptotic factors from the mitochondria. Several oncogenes and tumor suppressors manipulate Ca²⁺ to exert their anti/pro-apoptotic activities. For example, Akt and Bcl-2 regulate ER Ca²⁺ flux to avoid mitochondrial Ca²⁺ overload and apoptosis; in contrast, pro-apoptotic genes, such as Fhit and PML, act at mitochondrial and ER levels, respectively, to promote mitochondrial Ca²⁺ accumulation. Although the connection between mitochondrial Ca²⁺ increase and apoptosis is widely accepted, the mechanistic role of mitochondrial Ca²⁺ 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. Dysregulation of miRNA expression could lead to a variety of human disorders, including cancer. 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, gastric adenocarcinoma, epidermal growth factor receptor-positive lung adenocarcinoma and prostate carcinoma and has been reported to target different regulators of the apoptotic pathway, such as...
Interplay between the modulation of Ca\textsuperscript{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\textsuperscript{2+} stores) repression generates a positive feedback loop to drive the hypertrophic response, a process that is primarily Ca\textsuperscript{2+} dependent.\textsuperscript{21} In the same cellular setting, miR-214 protects the mouse heart from ischemic injury by controlling Ca\textsuperscript{2+} overload and cell death through the repression of the mRNA encoding sodium/calcium exchanger 1 (Ncx1), a key regulator of Ca\textsuperscript{2+} influx.\textsuperscript{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.\textsuperscript{23}

In conclusion, the interplay between intracellular Ca\textsuperscript{2+} and miRNAs might be a key aspect in several pathological conditions. Specifically, the suppression of mitochondrial Ca\textsuperscript{2+} entry by cancer-related miR-25 represents the first study of the control of the mitochondrial uniporter by miRNA\textsuperscript{24} 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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