SCIENTIFIC SEMINAR

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Nuclear MTHFD2 secures centromere stability and correct chromosome segregation

One-carbon folate metabolism is a pivotal pathway in cancer progression, being indispensable for the de novo synthesis of nucleotides, amino acid homeostasis, DNA and histones methylation, and the maintenance of the cellular redox state. The importance of this metabolic pathway in the control of cancer growth is exemplified by the fact that the mitochondrial one-carbon metabolism enzyme methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) emerged as the metabolic gene most consistently overexpressed in tumors. MTHFD2 supports cell proliferation and survival in vitro and tumor growth in vivo, along with promoting metastatic features such as cell migration and invasion. Besides localizing in the mitochondria, where it performs its canonical function, MTHFD2 has been found in the cellular nucleus, and our group previously showed that it is chromatin-bound. A handful of publications propose distinct roles of this non-canonical nuclear form of MTHFD2, being implicated in cell proliferation, RNA translation and metabolism, and DNA damage repair. However, none of them clearly delineate mechanistically when and why MTHFD2 is required on chromatin. For the very first time, here we show that the nuclear localization of MTHFD2 ensures a successful cell division. After validating that MTHFD2 localize on chromatin in a variety of cell lines, we investigated its nuclear interactome. MTHFD2 nuclear partners are mostly cell cycle regulators involved in centromere and kinetochore stability, including the methyltransferases KMT5A and DNMT3B, which are required for centromeric histones and DNA methylation, respectively. We reasoned that nuclear MTHFD2 could be preserving centromere stability via methylation of histones and DNA. We show that in absence of MTHFD2 DNA become largely hypomethylated and histone marks of centromeric heterochromatin are diminished, resulting in increased centromeric expression. Phenotypically, MTHFD2 knock out cells show reduced mitotic index and increased chromosome misalignment events, which results in 10 fold increase of interphase micronuclei. For the very first time, our study show that the nuclear localization of a mitochondrial metabolic enzyme is physically and enzymatically required to ensure mitotic cell division, corroborating the mounting evidence of the nucleus as a separated metabolic compartment

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EXCELENCIA SEVERO OCHOA

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Atrio 800
12.00H

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