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ANALYSIS OF THE BIOLOGICAL FUNCTION OF TRMT61B IN A CANCER, CHROMOSOMAL INSTABILITY CONTEXT

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Chromosomal instability is one of the most widespread features of carcinogenesis and is the main cause of aneuploidy and tumor heterogeneity that results in drug resistance, aggressiveness and, therefore, poor patient prognosis. In an effort to search for CIN-related cancer biomarkers with clinical value, a potential candidate, named TRMT61B, was identified. Although it is known that this RNA methyltransferase modulates mitochondrial translation by catalyzing the formation of N1-methyladenine in various mitochondrial tRNAs, rRNAs and mRNAs, its cellular function and connection with cancer is poorly understood.

A TRMT61B loss-of-function model using several shRNAs was studied in CIN-high and CIN-low human melanoma cell lines as well as in two immortal, untransformed cell lines. The absence of this protein led to markedly reduced proliferation, slightly increased cell death, accumulation of the LC3B-II autophagy marker and mitochondrial function impairment in CIN-high conditions, whereas in no-CIN and CIN-low contexts the effect is less prominent and heterogeneous. In a parallel fashion, CRISPR/Cas9 mediated TRMT61B knockout reproduces most of the alterations associated with TRMT61B loss induced by the shRNA approach, reinforcing the key role played by TRMT61B in the physiology of cancer cells. Interestingly, overexpression studies of TRMT61B performed in different immortal cell lines, also indicate a reduced proliferation effect that argue in favor of maintaining a strict control of TRMT61B expression levels as a requirement for proper cellular homeostasis.

Different works have demonstrated a cross-talk between mitochondrial impairment and chromosomal instability, being the first causative of the second. Considering that there might be thresholds from which higher or lower levels of CIN are deleterious, the results obtained in this work support a putative role of TRMT61B in buffering CIN high effects, allowing tumor cell survival. Further work is needed to confirm this function of TRMT61B and its potential as a therapeutic target.

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