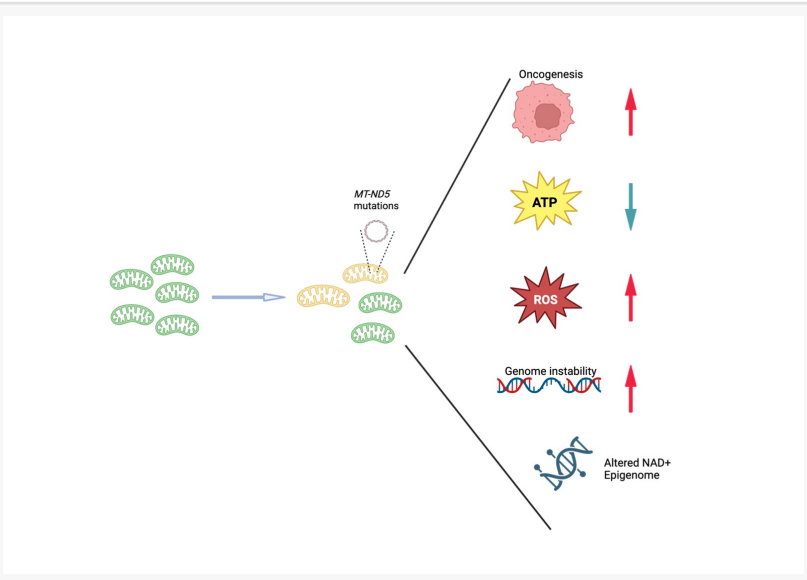
Heteroplasmic de novo MT-ND5 truncating mutations: Implications for mitochondrial function in oncogenesis

GA, UNITED STATES, May 19, 2025 /EINPresswire.com/ -- With mitochondrial DNA (mtDNA) base editing tools, this study controlled the nuclear background to investigate the causal effect of mtDNA mutations. Co-existence of wild-type and mutant mtDNA (heteroplasmy) in MT-ND5 was introduced. Enhanced oncogenic potential was confirmed with in vitro and in vivo assays. They reported compromised mitochondrial respiration and increased glycolytic activity, often termed as the Warburg effect following the mutations. By tracking cellular phenotypes during the MT-ND5 heteroplasmy decay, they reasoned that the increased glycolytic activity was to rescue NAD+ depreciation. Increased ROS level, genome instability, altered NAD+ epigenetics are the likely factors drove oncogenesis post MT-ND5 mutations.



Heteroplasmic MT-ND5 mutations introduce systematic impact on cells. By Yuanyuan et al., generated by BioRender.com.

Mitochondria are semi-autonomous organelles containing their own DNA (mtDNA), which exhibits a higher mutation rate compared to nuclear DNA. Accumulation of mtDNA mutations is associated with aging and has been observed in various cancers. However, the causal role of these mutations in oncogenesis remains unclear.

A recent study led by Dr. Zhenglong Gu, Director of the Center for Mitochondrial Genetics and Health at Fudan University and Courtesy Professor at Cornell University, reports new insights into this issue. Published in the KeAi journal Mitochondrial Communications, Gu's research demonstrates that heteroplasmic mutations in the mitochondrial gene MT-ND5 can drive cancer initiation. MT-ND5 encodes a critical subunit of mitochondrial complex I, essential for oxidative phosphorylation. De novo MT-ND5 mutations were introduced, and the full molecular etiology post-MT-ND5 mutations was examined.

Gu and his team found that low to moderate levels of MT-ND5 heteroplasmy are sufficient to impair mitochondrial function, leading to increased reactive oxygen species (ROS) production and elevated oncogenic potential. “This increased oncogenic potential was examined using both in vitro and in vivo assays,” explains Gu. “Heteroplasmic MT-ND5 mutated cells exhibited a metabolic shift towards glycolysis, known as the Warburg effect.”
Notably, this metabolic reprogramming appears to be a compensatory mechanism to restore NAD levels rather than to meet energy demands, as NAD levels did not recover even when MT-ND5 heteroplasmy decreased. The researchers proposed that elevated ROS and altered NAD metabolism are key factors promoting oncogenesis.

“Additionally, we investigated how deleterious mtDNA mutations are retained and tolerated by cells,” says Gu. “By longitudinally tracking heteroplasmy levels and associated mitochondrial phenotypes, we gained deeper insights into the mechanisms of mtDNA quality control. This approach sheds light on how cells manage and maintain mitochondrial genome integrity over time.”

The findings establish a causal relationship between specific mtDNA mutations and cancer initiation. "In our previous review in Life Medicine, we discussed the accumulation of mitochondrial DNA mutations with aging in tumor origin. In this study, we reveal the causal relationship of mtDNA mutations to oncogenesis,” adds Gu.

The researchers note that further studies are needed to evaluate the interactions of multiple mtDNA mutations with the nuclear background in oncogenesis. “Nevertheless, our study highlights the often-overlooked role of mtDNA in the complex process of oncogenesis and represents a significant step toward precision medicine for cancer prevention and prediction,” concludes Dr. Gu.

References
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Lucy Wang
BioDesign Research
email us here