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EFFECT OF MUTAGENS ON THE STABILITY OF MITOCHONDRIAL GENOME *

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Abstract

In our study, we explored how various mutagenic agents impact mitochondrial DNA (mtDNA) stability. We analyzed 2448 whole-genome sequencing samples, focusing on induced pluripotent stem cells exposed to environmental mutagens. Not all agents affected mtDNA content, but 13 increased mutations approximately twofold. The dominant mutation type was G>A, and 1,2-dimethylhydrazine (DMH) stood out as a distinctive mutagen.

The question of what factors influence the mutation rate of the mitochondrial genome remains an ongoing puzzle. Specifically, there's a discrepancy concerning the role of reactive oxygen species (ROS) produced by mitochondria in mtDNA instability. The central issue revolves around whether mitochondrial membranes permit mutagens from the environment to traverse and induce mutations.

In our study, we set out to explore the impact of various mutagenic agents on mtDNA stability. Here are the key steps and findings:

We analyzed 2448 whole-genome sequencing (WGS) samples from the study conducted by Kucab et al. in 2019 [1]. In that study, induced pluripotent stem (IPS) human cells were exposed to 79 known or suspected environmental carcinogens or were maintained in different control media. To process the data, we realigned the CRAM files to the human reference genome (hg38). Subsequently, we selected only the reads aligned to the mitochondrial chromosome (chrM) and unmapped reads. These were further trimmed using TRIMMOMATIC (ver. 0.39). The trimmed reads were then aligned to hg38 using BWA MEM, and somatic mutation calling was performed with MitoHPC (ver. of 6 March 2024). We specifically focused on mutations with an allelic frequency (AF) less than 0.15.

As it turns out, not all mutagenic agents affected mitochondrial ploidy. Among the agents tested, 16 increased mtDNA content, while 27 decreased it. Interestingly, their effects were not linked to the chemical nature of the agents or their biological roles. Only 13 agents significantly increased the quantity of mutations in mtDNA, approximately twofold compared to the control (water). Notably, in six cases, this increase was concentration-dependent. The dominant mutation type observed was G>A. One particular mutagen stood out: DMH. This agent, known for its role in alkylation, left a distinctive signature on mtDNA.

In our research, we devised a classification system for mitochondrial mutagens based on their chemical nature and functional impact within mitochondria [2]. However, intriguingly, we haven't yet discovered compelling evidence that specific chemical classes or functional roles directly dictate the mutation spectrum. Instead, we're leaning toward the idea of indirect damage to mtDNA—perhaps arising from reactive oxygen species (ROS) formation.

Overall, while mutations in mitochondrial genomes appear to be largely unaffected by environmental mutagens, some agents do influence mitochondrial copy numbers, leading to an overall increase in mutations.

In summary, our study sheds light on the complex interplay between mutagenic agents, mitochondrial stability, and the delicate dance of mtDNA mutations.

References

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