

A Simulation of the Accumulation of Mitochondrial DNA Mutations with Age

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ABSTRACT

The number of cells with high levels of mutated mitochondrial DNA (mtDNA) increases with age. Since the loss of wild-type mtDNA compromises the energy generation in the cell, this accumulation of mutated mtDNA is one possible source of the general decline in cellular effectiveness with increasing age. We have simulated the development of new mitochondrial DNA mutations with age [4]. The simulation follows the development of the entire population of mtDNA molecules in individual post-mitotic cells over the maximum human lifespan. The formation of new mtDNA mutations is modelled by allowing a small probability of an error whenever each mtDNA molecule is replicated. In this model we assume that there is no replicative bias favoring the mutated mtDNA, so the population of mtDNA in the cell changes with time just through random genetic drift [2, 3, 1]. Our results show that this model is sufficient to cause the accumulation over a human lifespan of a significant number of cells with high mtDNA mutation levels. The model results also show that in the simulated cells that develop high mutation levels these mutated mtDNA are almost always a clonal expansion from a single mutation event, and not the result of a series of separate mutations. While many new mutations events occur in the simulated cell over a lifespan almost all of these mutations are rapidly lost through genetic drift. Only in very rare cases does a new mutation randomly drift to high levels. We will discuss the relationship of this model to ageing and the late development of other diseases caused by mtDNA mutations.

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