

The inheritance of viable mitochondria

Mitochondria cannot be produced de novo by the cell, but are inherited across generations. Their peculiar genetics (multiple genomes per cell, no meiosis, replication independent from cell cycle, high mutation rate) and the possible exposition to Reactive Oxygen Species (ROS) are predicted to produce a fast accumulation of deleterious mutations, a phenomenon known as Müller's ratchet. Nonetheless, mitochondrial genomes persist accurately over million years. How is a viable mitochondrial genetic information preserved? To answer this question we review the following relevant topics: 1) the sources of mtDNA mutation (replication and ROS); 2) the origin of mitochondrial membrane potential; 3) the activity of germ line mitochondria; 4) the mitochondrial bottleneck; 5) mtDNA drift and selection. Finally we discuss such topics in the light of an unusual biological system (Doubly Uniparental Inheritance of mitochondria, DUI), in which also sperm mtDNA is regularly transmitted to the progeny.



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Liliana Milani & Fabrizio Ghiselli

Department of Biological, Geological and Environmental Sciences (BiGeA)
University of Bologna, Bologna, Italy

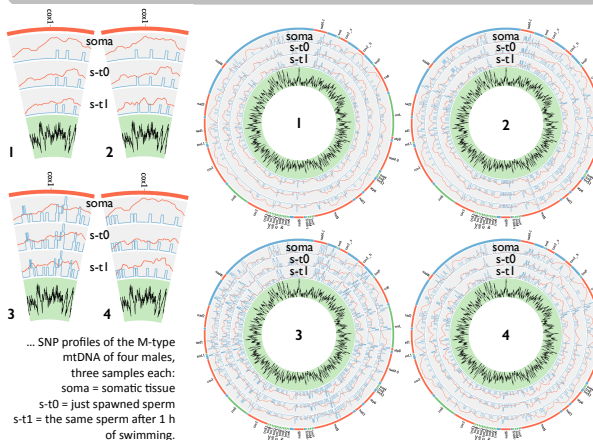
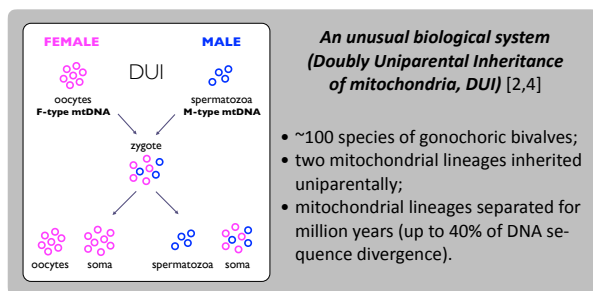


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How is a viable mitochondrial genetic information preserved?

The "division of labour" (DOL) hypothesis postulates that male gametes maximize energy production for motility by sacrificing mitochondrial DNA (mtDNA) to oxidative phosphorylation (OXPHOS) and its mutagenic by-products, while non-motile female gametes repress OXPHOS, thus being somewhat inactive [1].

However, many studies failed to support a causal link between high OXPHOS activity and generation of hazardous amounts of ROS, so caution is advised [2]. The high energy demand for flagellar movements may even produce a lower amount of ROS (compared to "basal" ROS production), as documented during high exercise activity [3].



Activity of gamete mitochondria

According to the presence of high inner membrane potential ($\Delta\psi_m$) (Fig. 1), mitochondria of both gamete types are active [2]. Sperm mitochondria are active both in species that do not transmit sperm mitochondria and in DUI species. So, high mitochondrial activity does not necessarily imply mtDNA damage (Fig. 2) and may actually promote the inheritance of mitochondria [2,5].

Although DUI might seem just a weird exception to a quite conserved biological "rule", molecular and phylogenetic evidence suggests that it evolved from Strictly Maternal Inheritance (SMI) (DUI can revert to SMI under some circumstances) so, most likely, the two systems share the same basic molecular mechanism of mitochondrial inheritance [2,5,6].

Is the DUI system undermining the DOL hypothesis?

Exceptions to SMI might represent a challenge for the division of labour DOL hypothesis. It is clear that the long evolutionary persistence of DUI indicates that the mtDNA transmitted through sperm can be a viable genetic template.

Two possibilities by which the DOL would still hold true easily come to mind [6]:

- DUI species might use alternative energy-production pathways and/or produce less ROS;
- DUI species might have evolved specific mechanisms of ROS scavenging and/or mtDNA protection.

An **alternative hypothesis to DOL** to explain how viable mitochondria are transmitted through generations is that the most active mitochondria are inherited. A combination of drift and selection on germ line mtDNA population might be responsible for the maintenance of viable mitochondrial genetic information, and mitochondrial activity would be the phenotype under selection [2].



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liliana.milani@unibo.it

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STAGE	LEVEL	TARGET	MECHANISM
Gametogenesis	Organelle	mtDNA	Autophagy of unfit mitochondria Selection of high $\Delta\psi_m$ mitochondria (Baijani body mitochondria or sperm mitochondria) Replication advantage of wild-type mtDNA
Gametogenesis	Cell	mtDNA	Apoptosis of unfit cells
Fertilizing gametes			Fertilization failure
Zygote	Organism	mtDNA	Development failure
Early embryos		nuclear genes for mitochondrial function	

Selection on mitochondrial functions [2]



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fabrizio.ghiselli@unibo.it

