OPA1 links human mitochondrial genome maintenance to mtDNA replication and distribution

Titre	OPA1 links human mitochondrial genome maintenance to mtDNA replication and distribution
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Résumé en anglais	Eukaryotic cells harbor a small multiploid mitochondrial genome, organized in nucleoids spread within the mitochondrial network. Maintenance and distribution of mitochondrial DNA (mtDNA) are essential for energy metabolism, mitochondrial lineage in primordial germ cells, and to prevent mtDNA instability, which leads to many debilitating human diseases. Mounting evidence suggests that the actors of the mitochondrial network dynamics, among which is the intramitochondrial dynamin OPA1, might be involved in these processes. Here, using siRNAs specific to OPA1 alternate spliced exons, we evidenced that silencing of the OPA1 variants including exon 4b leads to mtDNA depletion, secondary to inhibition of mtDNA replication, and to marked alteration of mtDNA distribution in nucleoid and nucleoid distribution throughout the mitochondrial network. We demonstrate that a small hydrophobic 10-kDa peptide generated by cleavage of the OPA1-exon4b isoform is responsible for this process and show that this peptide is embedded in the inner membrane and colocalizes and coimmunoprecipitates with nucleoid components. We propose a novel synthetic model in which a peptide, including two trans-membrane domains derived from the N terminus of the OPA1-exon4b isoform in vertebrates or from its ortholog in lower eukaryotes, might contribute to nucleoid attachment to the inner mitochondrial membrane and promotes mtDNA replication and distribution. Thus, this study places OPA1 as a direct actor in the maintenance of mitochondrial genome integrity.

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