EMBO Rep. 2017 Mar;18(3):451-463. doi: 10.15252/embr.201642931. Epub 2017 Feb 7.

L-OPA1 regulates mitoflash biogenesis independently from membrane fusion

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PMID: 28174208 PMCID: PMC5331265 DOI: 10.15252/embr.201642931

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Abstract

Mitochondrial flashes mediated by optic atrophy 1 (OPA1) fusion protein are bioenergetic responses to stochastic drops in mitochondrial membrane potential ($\Delta\psi_m$) whose origin is unclear. Using structurally distinct genetically encoded pH-sensitive probes, we confirm that flashes are matrix alkalinization transients, thereby establishing the pH nature of these events, which we renamed "mitopHlashes". Probes located in cristae or intermembrane space as verified by electron microscopy do not report pH changes during $\Delta\psi_m$ drops or respiratory chain inhibition. *Opa1* ablation does not alter $\Delta\psi_m$ fluctuations but drastically decreases the efficiency of mitopHlash/$\Delta\psi_m$ coupling, which is restored by re-expressing fusion-deficient OPA1^{K301A} and preserved in cells lacking the outer-membrane fusion proteins MFN1/2 or the OPA1 proteases OMA1 and YME1L, indicating that mitochondrial membrane fusion and OPA1 proteolytic processing are dispensable. pH/$\Delta\psi_m$ uncoupling occurs early during staurosporine-induced apoptosis and is mitigated by OPA1 overexpression, suggesting that OPA1 maintains mitopHlash competence during stress conditions. We propose that OPA1 stabilizes respiratory chain supercomplexes in a conformation that enables respiring mitochondria to compensate a drop in $\Delta\psi_m$ by an explosive matrix pH flash.

Keywords: OPA1; bioenergetics; membrane fusion; mitoflash.