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Hexokinase 1 rings prevent mitochondrial fission during energy stress

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Background: To meet cellular needs, metabolic enzymes must constantly adapt to changes in substrate availability. It is unknown how changes in substrate availability impact the subcellular location of the mitochondrial-bound enzyme hexokinase 1 (HK1). To answer this question, we use live-cell imaging and a substrate-free perfusion buffer.

Results: HK1 surprisingly clustered into ring-like structures that constricted mitochondria during glucose depletion. HK1-rings rapidly disassembled upon glucose readdition. The formation of HK1-rings was observed in multiple cell types and was confirmed with immunofluorescence. Using genetically encoded biosensors, we observed that the appearance of HK1-rings correlated more tightly with mitochondrial ATP than with cytosolic glucose levels, indicating that a lack of energy and not glucose drives the formation of HK1-rings. A single point mutation in the ATP-binding site increased that probability of HK1-ring formation. In contrast, mutating bulky residues in the mitochondrial binding domain abolished the formation of HK1-rings. HK1-rings were localized at mitochondrial fission sites, characterized by the contact with endoplasmic reticulum. Finally, we could demonstrate that HK1-rings prevented mitochondrial fission during energy stress.

Conclusion: HK1 forms rings in response to changes in substrate availability and may help cells in resisting energy stress by preventing mitochondrial fission.