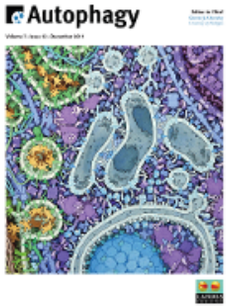
Autophagy



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ISSN: 1554-8627 (Print) 1554-8635 (Online) Journal homepage: https://www.tandfonline.com/loi/kaup20

Together we are stronger

Fusion protects mitochondria from autophagosomal degradation

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To cite this article: Angelika S. Rambold, Brenda Kostelecky & Jennifer Lippincott-Schwartz (2011) Together we are stronger, Autophagy, 7:12, 1568-1569, DOI: 10.4161/auto.7.12.17992

To link to this article: https://doi.org/10.4161/auto.7.12.17992

Autophagy 7:12, 1568–1569; December 2011; © 2011 Landes Bioscience

Together we are stronger

Fusion protects mitochondria from autophagosomal degradation

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Starvation induces a protective process of self-cannibalization called autophagy that is thought to mediate nonselective degradation of cytoplasmic material. We recently reported that mitochondria escape autophagosomal degradation through extensive fusion into mitochondrial networks upon certain starvation conditions. The extent of mitochondrial elongation is dependent on the type of nutrient deprivation, with amino acid depletion having a particularly strong effect. Downregulation of the mitochondrial fission protein Drp1 was determined to be important in bringing about starvation-induced mitochondrial fusion. The formation of mitochondrial networks during nutrient depletion selectively blocked their autophagic degradation, presumably allowing cells to sustain efficient ATP production and thereby survive starvation.

Keywords: autophagy, mitochondria, fission, fusion, starvation, PKA, Drp1

Submitted: 08/16/11

Revised: 09/02/11

Accepted: 09/06/11

http://dx.doi.org/10.4161/auto.7.12.17992

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Punctum to: Rambold AS, Kostelecky B, Elia N, Lippincott-Schwartz J. Tubular network formation protects mitochondria from autophagosomal degradation during nutrient starvation. Proc Natl Acad Sci USA 2011; 108:10190–5; PMID:21646527; http://dx.doi.org/10.1073/pnas.1107402108

Autophagy is a highly conserved degradation pathway that can be induced by a variety of stimuli such as infection, cell stress or limited nutrient availability. During starvation, cells become heavily dependent on autophagy for survival. As autophagosomes are formed, they engulf cytoplasmic material that is eventually degraded in the lysosome. Recycled breakdown products, like sugars, fatty acids and amino acids, are used to drive the cell's metabolism and provide building blocks for biomolecules during nutrient-scarce conditions.

While substrates are selectively targeted for autophagosomal degradation during basal conditions, during starvation autophagy has traditionally been considered nonselective. Initially, en masse degradation might seem reasonable to ensure the continuous flow of metabolic precursors in a starving cell. But is it expedient to degrade mitochondria, the most efficient cellular ATP producer and source of autophagosomal membrane? It seemed counterintuitive that mitochondria would be degraded during starvation, given that they are essential for optimal energy production and autophagosome biogenesis. This led us to hypothesize that a mechanism might exist to protect mitochondria from autophagosomal degradation specifically during starvation.

To determine whether mitochondrial changes occur during starvation, we investigated mitochondrial dynamics upon complete nutrient depletion. Although it was known that mitochondria could adopt a diverse range of morphologies, from individual roundish spheres to highly interconnected networks, their morphological characteristics during starvation were unknown at the onset of our study. Unexpectedly, we observed the formation of a highly fused mitochondrial network upon nutrient depletion. Changes in morphology are first observed as early as 30 min after nutrient depletion, leading to large, interconnected mitochondrial networks after 90 min in up to 80% of cells. This network formation is conserved in a variety of different cell types including embryonic fibroblasts, kidney cells and various cells of cancerous origin.

To identify which types of starvation could induce mitochondrial elongation, we deprived cells of single nutrients individually. Remarkably, net mitochondrial fusion (over a period of 6 h) is induced in the absence of nitrogen sources

(i.e., amino acids or glutamine), but not serum or glucose. The cellular availability of amino acids might therefore be a determining factor in controlling mitochondrial morphology, and mechanisms regulating amino acid availability could play a role in this process. The master regulator of autophagy, mTOR, tightly controls amino acid recycling, and recent studies from our group support a role for mTOR in regulating mitochondrial dynamics to some extent. Upon pharmacological and genetic inhibition of mTOR, mitochondrial fusion increases under nutrient-rich conditions (unpublished data). This is consistent with published data indicating that mTOR directly controls mitochondrial function. However, neither our data nor any of the studies published thus far identified mitochondrial fusion or fission proteins as mTOR-substrates.

Since the TOR complexes integrate a diverse set of signals and feedback circuits, it is plausible that other signaling pathways cause mitochondrial fusion independent of mTOR inactivation. Two kinases implicated in such signaling pathways are AMPK and PKA, both of which are activated during starvation. Our recent data point to a role for PKA in starvation-induced mitochondrial fusion: overexpression of a Drp1 mutant (with a Ser to Ala mutation at a PKA phosphorylation site), or pharmacological inhibition of PKA effectively inhibits mitochondrial fusion during starvation. Furthermore, the amount of Drp1 localized on the mitochondria is reduced during starvation, consistent with PKA-driven cytosolic sequestration of Drp1.

Having established that nutrient starvation induces mitochondrial network formation, we further asked whether the mitochondrial fusion mechanism spares mitochondria from autophagosomal degradation. To test this hypothesis, we assayed mouse embryonic fibroblasts lacking the essential mitochondrial fusion proteins Mfn1/2 or Opa1 under starvation conditions. Both cell lines were reported to have fragmented mitochondrial morphology under full-nutrient conditions. Interestingly, during starvation mitochondria deficient in either Mfn1/2 or Opa1 do not undergo mitochondrial fusion and are substantially degraded by autophagy. In contrast, wild-type cells show much lower rates of mitophagy, suggesting mitochondrial elongation protects them from autophagosomal turnover.

Although it is clear that fusion blocks mitochondrial degradation by autophagy during starvation, the mechanism of this mitochondrial protection remains unclear. Is the increased size alone sufficient to exclude mitochondria from autophagy or do mitochondrial networks have additional properties that block autophagosomal targeting? Under basal conditions the targeting of mitochondria for autophagic degradation is dependent on three factors: (1) fragmentation, (2) dysfunction, and (3) recognition of the dysfunctional mitochondria through the Pink1-Parkin system. Starvation clearly eliminates the morphological prerequisite, but does it disrupt mitochondrial function? Are fused mitochondria simply not recognized by Pink1-Parkin, or do they evade degradation by downregulation of this specific degradation mechanism? Several studies indicate that mitochondrial networks are characterized by increased ATP production accompanied by reorganization of cristae and changes in ATP synthase oligomerization. Our recent data and evidence from Scorrano and colleagues indicate that fused mitochondria sustain ATP production and enhance cellular survival during starvation. This retention of mitochondrial functionality may make elongated mitochondria a poor substrate for Pink1-Parkin. These lines of evidence indicate that mitochondrial size and functionality may be key factors in reducing mitophagy, but direct studies are needed to conclusively determine how mitochondria are protected during starvation.

Mitochondrial fusion is a very elegant system to fine-tune autophagosomal substrate availability during nutrient-starvation. Subsequently, it will be fascinating to determine how PKA, mTOR and other signaling pathways regulate mitochondrial dynamics and vice versa. It is clear that we still do not understand the potential of mitochondrial dynamics to effect changes in cell function and fate. Ultimately, this study has given us insight into a specific mechanism for mitochondrial protection based on mitochondrial morphological change and may help us understand in the future how changes in mitochondrial dynamics control cellular metabolism, signaling and stress response.