Molecular & Cellular Oncology ›
Volume 6, 2019 - Issue 3

Open access

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Author's Views

USP30: protector of peroxisomes and mitochondria

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Article: 1600350 | Received 12 Mar 2019, Accepted 25 Mar 2019, Published online: 16 Apr 2019

Cite this article https://doi.org/10.1080/23723556.2019.1600350 Check for updates

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KEYW

Mitophagy

Selective ed or dysfunctional organelles. Even though selective autophagy is necessary for normal

cellular function, and its dysregulation results in many human diseases,[1] surprisingly little is known about how selective autophagy of different substrates is regulated.

Peroxisomes are metabolic organelles responsible for, amongst other things, metabolizing fatty acids and scavenging reactive oxygen species.[2] However, dysregulation in peroxisome homeostasis results in a rare class of genetic disorders, Peroxisome Biogenesis Disorders (PBDs).[3] While the low peroxisome number and function was previously thought to be caused by reduced peroxisome biogenesis, a recent study has shown that the most common form of the disease is caused by increased degradation.[4] Regulation of pexophagy is therefore essential to prevent disease, and thus formed the basis of our study.[5]

Peroxisomes, like mitochondria, are degraded through selective autophagy, termed pexophagy and mitophagy respectively. Pexophagy can be induced by various stimuli, but the focus of our study was amino acid starvation induced pexophagy. Amino acid starvation, through inhibition of mammalian target of rapamycin (mTOR), results in the stabilization of the E3 ligase PEX2 on peroxisome membranes.[6] PEX2 acts to ubiquitinate membrane proteins, resulting in peroxisomal degradation. This serves as the first regulatory step to ensure peroxisomes are not lost under basal conditions.

It has been shown that mitophagy, in addition to the regulation offered by recruitment of the E3 ligase Parkin to damaged organelles, is also negatively regulated by a deubiqu t previously been sho describing the role uncta that did not c ized with peroxiso dy aimed to characte

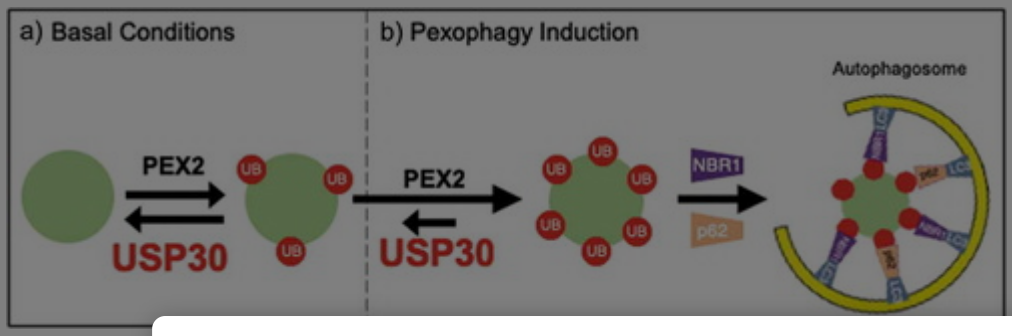
We b g that over-expre re than the mitocho) which is ER retai isome membra suggesting that USP next found that ove hagy upon amino a MP34-USP30,

but not TOM20-USP30, was able to demonstrate this inhibition, suggesting that USP30 is acting directly at the peroxisome.

To determine whether UPS30 functions to prevent basal pexophagy, we used siRNA mediated knockdown to understand its role under basal conditions. We found that USP30 depletion resulted in increased autophagy dependent peroxisome loss. In addition, co-depletion of PEX2 resulted in an abolishment of the peroxisome loss seen in USP30 depleted cells, suggesting that USP30 acts in opposition to PEX2 and is required to keep basal pexophagy to a minimum. (Figure 1(a))

Figure 1. USP30 regulates basal pexophagy.

a) Under basal conditions, USP30 and PEX2 work in opposition to maintain peroxisome homeostasis. b) During pexophagy induction, USP30 can no longer maintain low peroxisome ubiquitination, autophagy receptors NBR1 and sequestosome 1 (p62) are recruited to facilitate engulfment by the autophagosome and peroxisomes are lost.



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and found that it can rescue the loss of peroxisomes, suggesting a potential therapeutic approach in combatting this disease.

During the revision of our manuscript, a study was published by Sylvie Urbé's group demonstrating that endogenous USP30 localizes to the peroxisome where it regulates basal pexophagy.[8] Our work adds to their work by the identification of the E3 ligase, and at least two of UPS30's substrate. Together, these studies demonstrate the novel role of USP30 in pexophagy.

Many questions still remain unanswered. First and foremost, why would the cell have a single regulator for both pexophagy and mitophagy. This gives rise to the question of targeting and regulation. Peroxisomes and mitochondria are degraded under different conditions, one example being amino acid starvation which induces pexophagy while protecting mitochondria.[9] Is there any condition, therefore, that would induce an upregulation of USP30, or a change in its cellular distribution, to allow for degradation of one organelle over the other? We and Urbé's group have shown that USP30 is targeted to the mitochondria and peroxisome independently. Is this difference in targeting a mechanism by which USP30 differentially regulates these two organelles? Or is USP30 differentially regulated on its target organelle?

Finally, we've shown that USP30 is able to increase peroxisomes in PEX1 G843D fibroblasts, suggesting a potential therapeutic approach in disease. While continuing to evaluate
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