Preview for "Autophagy compensates for defects in mitochondrial dynamics"

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Introduction

Mitochondria are subcellular organelles that act as the main place of energy generation through oxidative phosphorylation and also involve in multiple cellular processes such as Reactive Oxygen Species (ROS) production and stress response activation in eukaryotic cells (van der Bliek et al., 2017). Mitochondria homeostasis is not only important for maintaining cellular energy metabolism, but they are also involved in many diseases and normal aging processes. Recently, many studies discovered various mechanisms to maintain mitochondria homeostasis. However, how these mechanisms are coordinated is not well understood yet.

Mitochondria dynamics through combination of fusion and fission is important for maintenance of mitochondrial function under different metabolic and environmental conditions. Mitochondria fusion and fission are mainly mediated by dynamin-like guanosine triphosphatases (GTPases) family (Youle and van der Bliek, 2012). In nematode *Caenorhabditis elegans*, mitochondria fusion and fission regulated by dynamin-family proteins including FZO-1 (Ichishita et al., 2008), DRP-1 and EAT-3. These proteins are required to maintain mitochondria morphology and functions; mitochondria are fragmented and are decreased membrane potential by *fzo*-1 mutation whereas *drp-1* mutation elongates mitochondria morphology. The mitochondrial Unfolded Protein Response (UPR^{mt}) is triggered when mitochondria dynamics is disrupted such as *fzo-1*mutation. ATFS-1 is the well-known transcriptional regulator which has dual targeting signal which promote transcription of genes needed for activating UPR^{mt}, such as the mitochondria chaperone *hsp-6* and *hsp-60,* to mitigate mitochondria dysfunction (van der Bliek et al., 2017; Yoneda et al., 2004).

On the other hand, autophagy regulated by *let-363* is a general quality control mechanism that removes dysfunctional cellular components by lysosomal degradation (Long et al., 2002; Mizushima, 2007). The 'Endosomal Sorting Complex Required for Transport' (ESCRT) activity is required to lysosomal endocytosis and affects autophagy. As opposed to *Drosophila melanogaster*, knock-out or knock-down of ESCRT components induce autophagy in *C. elegans* (Djeddi et al., 2012*).*

In this new study Haeussler S, *et al*. (2020), authors want to show and understand the functional relationship between ESCRT and UPR^{mt} or autophagy and UPR^{mt} under disruption mitochondria homeostasis.

Results

Haeussler S, *et al*. (2020) set out to find the regulators of mitochondria-stress induced UPR^{mt} using P*hsp-6*::mtHSP70gfp *(zcls13)* transgene, prevalently used to report UPR^{mt}, in *fzo-1(tmm1133)* worms (Zhang et al, 2018). They used Ahringer RNAi library that covers 87% of the worm genome to identify genes that affect the induction of UPR^{mt} in response to a block in mitochondria fusion. The screen yielded 299 suppressors and surprisingly three genes were components of the endosomal sorting complexes required for transport (ESCRT) machinery. This finding leads authors to focus on connection between ESCRT components and UPR^{mt}. Authors showed that depletion of components of ESCRT-0, -I, -III or VSP-4 ATPase can rescue *fzo-1* induced UPR^{mt}. They questioned whether reduction in ESCRT components affect fragmented mitochondria morphology. The mitochondrial-matrix targeted GFP protein in body wall muscle revealed that ESCRT does not affect mitochondria morphology. Next, they looked at another mitochondria feature, mitochondrial membrane potential. TMRE staining showed decreased mitochondria membrane potential in ESCRT RNAi samples suggesting that the change in membrane potential not mitochondria morphology is rescued by ESCRT depletion in *fzo-1* induced UPR^{mt} .

Inactivation of ESCRT machinery induces autophagy (Djeddi et al. ,2012, Guo et al., 2014). Finding several ESCRT targets in their screen authors looked into the role of autophagy in more detail. They found 143 of the target genes in an additional screening negatively regulate autophagy. This regulation is one directional as either increase or decreased UPR^{mt} changes autophagy. Non-targeted lipid profiling in *fzo-1(tm1133)*, *drp-1 (tm1108)* and *spg-7(ad2249)* animals revealed that levels of short acyl chain decreased while longer chain acyl increased in UPR^{mt} upon autophagy induction.

Future Perspective

The findings of Haeussler S, *et al*. (2020) propose a novel functional connection between the UPR^{mt} and autophagy when the mitochondrial dynamics is disrupted. The induction of autophagy partially restores membrane potential and thereby suppresses UPR^{mt} induced by

the defects of mitochondrial fusion. Interestingly, it's been known that mitochondrial fusion is a membrane potential dependent process that prevents dysfunctional organelles from fusing with each other. In addition, autophagic machinery targets depolarized mitochondria as a quality control mechanism. The hypothesis makes perfect sense that enhanced autophagy eliminates dysfunctional mitochondria and suppresses UPR^{mt}. However, Haeussler et al tried to exclude this possibility by showing Pink-Parkin dependent mitophagy does not play a role in the suppression of *fzo-1*-induced UPR^{mt}, other mitophagy pathways still need to be further investigated.

Lipid profiling of *drp-1* and *fzo-1* worms which are both defective in mitochondrial dynamics showed changes in certain species of triacylglycerols(TGs). Some of the levels of changes as well as UPR^{mt} can be reverted by the induction of autophagy in fzo-1 worms, implying the association of lipid composition with the activation of UPR^{mt}. The compensation role of autophagy under the condition of defective mitochondrial dynamics in the maintaining mitochondrial homeostasis can be attributed to the impact on lipidome. Nonetheless, how specific TGs involve in the regulation of mitochondrial membrane potential still remains enigmatic.

The UPR^{mt} is a transcriptional program that is implicated in several steps, like sensing by changes in membrane potential and protein import efficiency, initiating by nuclear localization of the transcription factor ATFS-1, and activating by the expression of downstream genes. As complicated as it is, the UPR^{mt} is intertwined with other cellular pathways. To study how UPR^{mt} can be integrated into multiple stress response and quality control pathways and how they interact with each other will advance our knowledge of UPR^{mt} in regulating cellular metabolism, development and organismal aging.

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