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Organelles in focus

Mechanisms of communication between mitochondria and lysosomes

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ABSTRACT

Mitochondria and lysosomes have long been studied in the context of their classic functions: energy factory and recycle bin, respectively. In the last twenty years, it became evident that these organelles are much more than simple industrial units, and are indeed in charge of many of cellular processes. Both mitochondria and lysosomes are now recognized as far-reaching signaling platforms, regulating many key aspects of cell and tissue physiology. It has furthermore become clear that mitochondria and lysosomes impact each other. The mechanisms underlying the cross-talk between these organelles are only now starting to be addressed. In this review, we briefly summarize how mitochondria, lysosomes and the lysosome-related process of autophagy affect each other in physiology and pathology.

1. Introduction

Mitochondria and lysosomes are "ground zero" for a number of devastating genetic diseases. The research efforts to understand the molecular consequences of mitochondrial and lysosomal malfunction have traditionally been studied by focusing specifically on the affected organelle. This led to an overall understanding of how mitochondria and lysosomes are affected at biochemical, ultrastructural and phsyiological levels, by different genetic mutations that cause mitochondrial diseases or lysosomal storage diseases.

Recently, several studies addressed how the defects in these organelles affect cellular signaling pathways, eventually modulating gene expression. These studies uncovered some of the mechanisms responding to organelle malfunction and how they are linked to pathology development. However, the prevailing context for the interpretation of these data is that defects in one organelle affect cellular signaling. It remains however unclear how defects in one organelle, particularly mitochondria or lysosomes, lead to perturbations in other cellular organelles both via cellular signaling and gene expression.

In recent years, several studies have pointed out that genetic defects affecting mitochondrial proteins can result in secondary perturbations in lysosomes and, similarly, genetic defects in lysosomal proteins can lead to mitochondrial perturbations. The mechanisms underlying the interdependence between mitochondria and lysosomes are currently object of intense research, and will be discussed in more detail in the following sections.

2. Cell physiology – mitochondria-lysosome crosstalk

The cross-talk between organelles can involve direct physical contacts or signaling pathways (Raimundo, 2014). While contact sites between mitochondria and vacuole were identified in yeast, in mammalian cells there is so far no evidence of such interaction (Elbaz-Alon et al., 2015). In addition to signals and to contact sites, the interaction between mitochondria and lysosomes has another level of complexity: the degradation of damaged mitochondria by selective autophagy, referred to as mitophagy (Youle and Narendra, 2011). This process is, of course, dependent on lysosomal function, and therefore it is no surprise that most of the studies addressing the interaction between mitochondria and lysosomes involve the autophagic pathway.

2.1. Mitochondrial malfunction affects lysosomes

TFAM is an essential protein for mitochondrial DNA (mtDNA) replication and transcription, and also confers stability and protection to mtDNA, in a manner similar to how histones stabilize nuclear DNA (Gustafsson et al., 2016; Bonawitz et al., 2006). The genetic deletion of TFAM is embryonically lethal in mice, and the level of TFAM is usually correlated with the amount of mtDNA. Thus, loss of TFAM results in loss of mtDNA and therefore inability to assemble a functional respiratory chain (Larsson et al., 1998). It was recently found that in TFAM-/- T-lymphocytes, the expected defects in mitochondrial function were compounded by perturba-

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tion in lysosomal function (Baixauli et al., 2015). The amount of lysosomes in TFAM-/- T-lymphocytes was increased relatively to the wild-type animals, but their function was impaired: the pH was estimated to be higher (less acidic), and there was accumulation of sphingomyelin and autophagy intermediates, consistent with decreased lysosomal function (Baixauli et al., 2015). The increase in lysosome number was attributed to activation of the transcription factor TFEB, a mediator of lysosomal biogenesis, but no causal effect was demonstrated and the mechanisms leading to TFEB activation were not addressed. It also remains to be clarified which mechanisms underlye the lysosomal dysfunction – i.e., why a program of lysosomal biogenesis is not resulting in functional lysosomes.

The effect of mitochondrial malfunction on TFEB signaling was further explored in few other studies. Nezich and colleagues focused on the effect of mitophagy on lysosomal biogenesis (Nezich et al., 2015). They induced mitophagy by a 10-h treatment of Parkin-expressing HeLa cells with complex III inhibitor antimycin A, or with the uncoupler valinomycin (Nezich et al., 2015). Under these conditions, TFEB relocated to the nucleus, a necessary step for its transcriptional function. Interestingly, the mitophagy-induced translocation of TFEB to the nucleus requires both PINK1 and Parkin, in contrast with starvation-induced TFEB translocation (Nezich et al., 2015). The translocation of TFEB was initially proposed to be regulated by phosphorylation, by mTORC1 and ERK, and dephosphorylation by calcineurin (Medina et al., 2015; Settembre et al., 2012). The authors tested if the lower phosphorylation was due to a decrease in mTORC1 activity, which was partially decreased in mitophagy-inducing conditions (Nezich et al., 2015). The activity of AMPK, an energy stress sensor and repressor of mTORC1, was increased. Nevertheless, both AMPK and mTORC1 were insensitive to the presence or absence of PINK1 and parkin (Nezich et al., 2015). The authors checked if manipulating the Ragulator, a protein complex located in the lysosome that when active recruits and activates mTORC1, and observed that a constitutively active Ragulator blocks TFEB nuclear translocation triggered by starvation or by mitophagy, while a dominant negative Ragulator is sufficient to induce robust TFEB nuclear translocation, regardless of Parkin or mitophagy induction (Nezich et al., 2015). Interestingly, mitophagy-triggered TFEB nuclear translocation is dependent on autophagosome formation, in contrast with starvation-induced relocation of TFEB to the nucleus (Nezich et al., 2015). This study carefully addressed the mechanism of TFEB activation by mitophagy, and presents three pivotal findings: (1) there are different mechanisms of TFEB activation by mitochondrial malfunction and starvation; (2) the regulation of TFEB nuclear translocation is not as simple as originally thought, and requires further research, and (3) there is redundancy between TFEB and other microphtalmia family transcription factors, particularly MITF and TFE3.

Another study addressing the effect of mitophagy on lysosomal biogenesis, using SH-SY5Y neuroblastoma cells (Ivankovic et al., 2015), finds similar results, with increased TFEB nuclear localization resulting in lysosomal biogenesis, as measured by increase in lysosomal enzymes. In this study, an induction of PGC1 alpha is also observed, possibly via TFEB, resulting in compensatory mitochondrial biogenesis (Ivankovic et al., 2015). Finally, in fibroblasts prepared from mice in which AIF, OPA1, or PINK1 were deleted, all leading to mitochondrial dysfunction, there is accumulation of dysfunctional, swollen lysosomes, which is dependent on mitochondrial reactive oxygen species (Demers-Lamarche et al., 2016). One interesting mechanistic link between mitochondrial malfunction and TFEB activation was recently proposed to involve the activation of the lysosomal Ca^{2+} export channel TRPML1, which is activated in the presence of increased levels of mitochondrial reactive oxygen species (ROS) (Zhang et al., 2016). When mitochondria generate (and, presumably, release) higher levels of ROS, TRPML1 exports more Ca^{2+} to the cytoplasm, which causes the activation

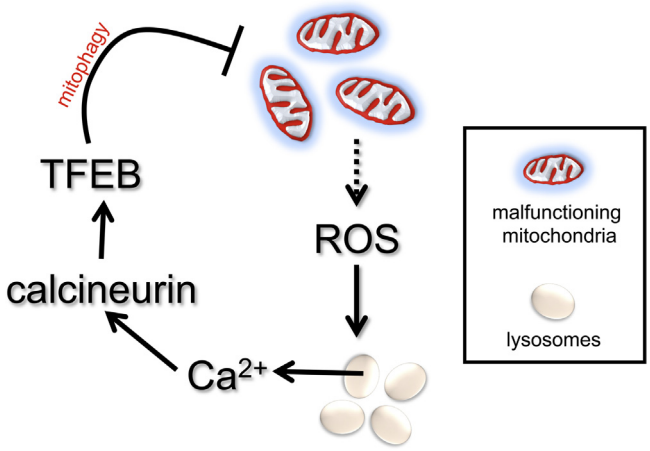

Fig. 1. Mitochondrial stress affects lysosomes. Different types of mitochondrial stress in proliferating cells result in lysosomal saturation and also in a TFEB-associated program of lysosomal biogenesis. The increase in lysosomal biogenesis is likely to serve both as a measure to compensate the lysosomes that became dysfunctional due to the mitochondrial stress, as well as to increase the lysosomal capacity for autophagy, which would enhance the removal of damaged mitochondria and thus solve the source of the stress.

of the Ca^{2+}-dependent phosphatase calcineurin, and calcineurin-dependent TFEB dephosphorylation and activation, which in turn increases the cellular capacity for mitophagy (Zhang et al., 2016).

Altogether, mitochondrial malfunction in proliferating cells, either *in vivo* or in culture, triggers TFEB signaling. It is however less evident if and how increased TFEB signaling coalesces into effective lysosomal biogenesis, since in the TFAM-/- T-cells the lysosomes were dysfunctional despite increased TFEB levels.

While the studies mentioned address the impact of mitochondrial malfunction on lysosomal activity and biogenesis in proliferating cells, it is less clear what happens in post-mitotic tissues. One recent study using a mouse model of amyotrophic lateral sclerosis (ALS) has shed some light on this matter (Xie et al., 2015). Accumulation of damaged mitochondrial in motor neurons (MNs) is one of the pathological hallmarks of ALS (Kong and Xu, 1998). Mice overexpressing superoxide dismutase 1 carrying an ALS-causing patient mutation ($SOD1^{G93A}$) present mitochondrial dysfunction (Kong and Xu, 1998). Recently, it was shown that in mice expressing SOD1G93A specifically in the motor neurons, the mitochondrial dysfunction is compounded by lower lysosomal mass and lower autophagic capacity (Xie et al., 2015). It remains unclear if the ensuing lysosomal deficits in the SOD1G93A mice are mediated via the TFEB/MITF transcription factors or by other mechanisms. While other models need to be tested, the data available so far seems to suggest that the effect of mitochondrial malfunction on lysosomes is different in proliferating cells and post-mitotic tissues (summarized in Fig. 1). Further studies will certainly help to clarify the picture.

2.2. *Lysosomal malfunction affects mitochondria*

Lysosomal storage diseases (LSDs) are severe pathologies that arise due to mutations in genes encoding lysosomal proteins (Parenti et al., 2015). These diseases provide the context to address the impact of lysosomal malfunction in other cellular systems, namely mitochondria, for the purpose of this review. Indeed, lysosomal storage diseases have been shown recently to not only compromise the function of lysosomes but also impact the function of other organelles in the cell. This evidence suggests a potential crosstalk between organelles in the pathogenesis of LSDs. Selak and colleagues, for instance, have reported partial reductions in relative