

Emerging role of lysosomal calcium store as a hub of neuroprotection

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Filled with more than 60 different types of hydrolases, the acidic organelle lysosome governs cellular digestion by removing damaged organelles and catabolic products (Xu and Ren, 2015). Beyond the canonical role in the intracellular degradative pathways, lysosome precedes nutrient sensing, autophagy, immune cell signaling, metabolism and membrane repair. Of note, most of these necessary functions are Ca^{2+} -dependent. In this respect, lysosome is now being considered as a dynamic organelle deputed to Ca^{2+} storing and homeostasis (Patel and Muallem, 2011). Accordingly, lysosomal channels and transporters regulate not only lysosomal ion homeostasis, membrane potential, catabolite export, membrane trafficking, and nutrient sensing, but also the whole cellular Ca^{2+} homeostasis (Xu and Ren, 2015). Interestingly, dysfunction of lysosomal channels may underlie the pathogenesis of many lysosomal storage diseases, other metabolic disorders and some neurodegenerative diseases (Xu and Ren, 2015). Furthermore, lysosomes continuously communicate and exchange ions with the main intracellular calcium stores, including endoplasmic reticulum (ER) and mitochondria (Tedeschi et al., 2019a). In this respect, we have recently demonstrated a functional interplay between these tiny organelles and the ER through the unique ER Ca^{2+} sensor, STIM1 (Tedeschi et al., 2021). Therefore, it is not surprising that lysosomal dysfunction, determining organellar Ca^{2+} dyshomeostasis, may underlie various neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS). It has been recently postulated that channelopathy-like mechanisms may contribute to disease progression via pathological alterations in motor neuron intrinsic biophysical properties (Deardorff et al., 2021). In line with this view, we have demonstrated the involvement of a cation-permeable channel localized on lysosomal membrane and belonging to the mammalian mucolipin transient receptor potential (TRP) subfamily, TRPML1 or mucolipin-1, in the pathogenesis of amyotrophic

lateral sclerosis/Parkinson-dementia complex (ALS/PDC), a Guamanian form of the disease (Tedeschi et al., 2019b). In this study we found that a progressive downregulation of TRPML1 occurs in motor neurons exposed to the cyanobacterial neurotoxin beta-methylamino-L-alanine (L-BMAA), mainly involved in the disease etiology through an oral ingestion (Dunlop et al., 2021). On the other hand, an early pharmacological stimulation of TRPML1 can efficiently rescue motor neurons from L-BMAA toxicity by counteracting ER stress and autophagy impairment (Tedeschi et al., 2019b). Therefore, we suggest that boosting autophagy via TRPML1 activation could represent a new therapeutic avenue to explore in searching for new effective drugs in ALS.

Furthermore, in other neurological diseases, in which autophagy is hyperactivated, such as during stroke, we have hypothesized that TRPML1 should be inhibited in order (i) to reduce the early removal of partially damaged organelles by the autophagic machinery and (ii) to preserve organellar calcium homeostasis. In line with this view, we have recently shown that neuronal TRPML1 protein is downregulated during ischemic preconditioning (Tedeschi et al., 2021), a brief non-lethal exposure to low-oxygen conditions able to induce ischemic tolerance through the preservation of ER Ca^{2+} homeostasis (Secondo et al., 2019). This could be interpreted as a protective mechanism to hamper excessive Ca^{2+} loss from lysosome and from its intracellular partner, the ER. In fact, we observed a persistent upregulation of TRPML1 Ca^{2+} -releasing activity during the reoxygenation phase of the ischemic insult that leads to hypoxic neuronal death. Interestingly, under persistent hypoxic conditions, we measured a significant organellar Ca^{2+} leak thus highlighting the harmful and all-encompassing role played by dysfunctional lysosomal Ca^{2+} homeostasis during neurodegeneration. Of note, we showed a fair interaction between STIM1 sensor and TRPML1 channel in the control of both ER and lysosomal Ca^{2+} filling state not only under normoxia, but also during low-

oxygen conditions. This may throw light on the necessity of a continuous balance between STIM1 expression and TRPML1 function to preserve the complex and dynamic regulation of neuronal Ca^{2+} homeostasis under either normoxic or hypoxic conditions.

Lysosome-mediated catabolic degradation is regulated by nutrient status (Settembre et al., 2013). In fact, nutrient starvation not only inhibits mTOR-mediated growth (Yu et al., 2010), but it also activates transcription factor EB (TFEB), mainly involved in the lysosomal biogenesis and identified as the master regulator of autophagy (Settembre et al., 2013). Considering the main role of TRPML1-mediated Ca^{2+} releasing activity in TFEB activation to promote autophagic flux (Medina et al., 2015), we identified the role of the lysosomal channel in the autophagy control at neuronal level (Tedeschi et al., 2019b). In accordance with our results, TRPML1 could be considered the way to switch-on or switch-off the autophagic flux in neurons. Accordingly, TRPML1 stimulation boosts autophagy in ALS motor neurons thus preserving mitochondrial activity and preventing ER stress (Tedeschi et al., 2019b), whereas TRPML1 downregulation prevents ischemic neuronal death hampering organellar Ca^{2+} leak (Tedeschi et al., 2021).

In conclusion, we suggest that lysosome and its machinery may be considered a hub of neuroprotection (**Figure 1**) since: (i) the tiny organelle stabilizes the global ionic balance in virtue of the strict interaction with the ER, and (ii) it controls the autophagic process through TFEB.

We claim that many efforts should be dedicated to this specific field in order to synthesize, characterize and identify new molecular entities able to pharmacologically modulate TRPML1 activity and lysosomal function thus treating those neurodegenerative illness characterized by autophagy dysfunctions.

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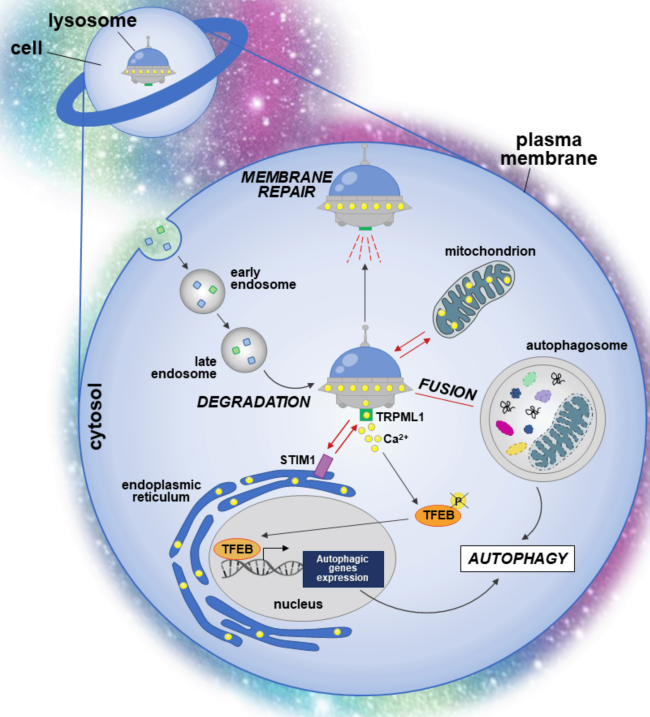


Figure 1 | The lysosome-centered theory.

Schematic representation of the main lysosomal functions within the cell, where the tiny organelle lysosome plays a major role in membrane repair, autophagosome formation, TFEB activation through Ca^{2+} -releasing activity of TRPML1 channel, endoplasmic reticulum refilling and lysosomes-mitochondria crosstalk. TFEB: Transcription factor EB.

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