NEURAL REGENERATION RESEARCH
www.nrronline.org

Emerging role of lysosomal calcium store as a hub of neuroprotection

Valentina Tedeschi, Agnese Secondo*

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.

The present work was supported by Progetto Speciale di Ateneo (CA.04_CDA_n_103 27.03.2019 to AS) and Programma di finanziamento linea-1 54_2020_FRA to AS.

Valentina Tedeschi, Agnese Secondo*
Division of Pharmacology, Department of Neuroscience, Reproductive and Odontostomatological Sciences, School of Medicine, "Federico II" University of Naples, Naples, Italy

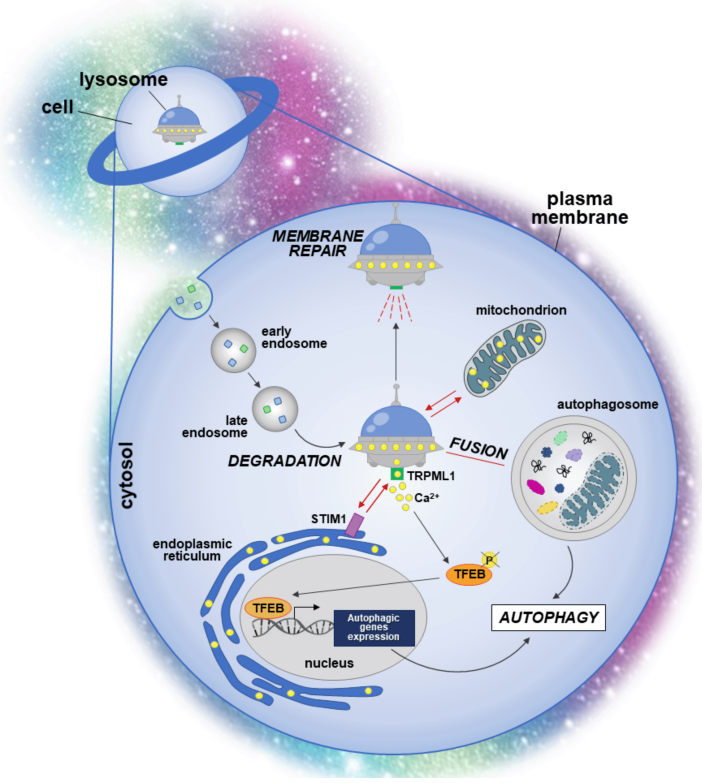

Figure 1 | **The lysosome-centered theory.**
Schematic representation of the main lysosomal functions within the cell, where the tiny organelle lysosome plays a major role in membrane repair, autophagosome formation, TFEB activation through Ca^{2+}-releasing activity of TRPML1 channel, endoplasmic reticulum refilling and lysosomes-mitochondria crosstalk. TFEB: Transcription factor EB.

***Correspondence to:** Agnese Secondo, PhD, secondo@unina.it.
https://orcid.org/0000-0001-5054-4098 (Agnese Secondo)
Date of submission: May 28, 2021
Date of decision: July 16, 2021
Date of acceptance: August 16, 2021
Date of web publication: November 12, 2021

https://doi.org/10.4103/1673-5374.327340
How to cite this article: *Tedeschi V, Secondo A (2022) Emerging role of lysosomal calcium store as a hub of neuroprotection. Neural Regen Res 17(6):1259-1260.*

References

Deardorff AS, Romer SH, Fyffe REW (2021) Location, location, location: the organization and roles of potassium channels in mammalian motoneurons. J Physiol 599:1391-1420.

Dunlop RA, Banack SA, Bishop SL, Metcalf JS, Murch SJ, Davis DA, Stommel EW, Karlsson O, Brittebo EB, Chatziefthimiou AD, Tan VX, Guillemin GG, Cox PA, Mash DC, Bradley WG (2021) Is exposure to BMAA a risk factor for neurodegenerative diseases? A response to a critical review of the BMAA hypothesis. Neurotox Res 39:81-106.

Medina DL, Di Paola S, Peluso I, Armani A, De Stefani D, Venditti R, Montefusco S, Scotto-Rosato A, Prezioso C, Forrester A, Settembre C, Wang W, Gao Q, Xu H, Sandri M, Rizzuto R, De Matteis MA, Ballabio A (2015) Lysosomal calcium signalling regulates autophagy through calcineurin and TFEB. Nat Cell Biol 17:288-299.

Patel S, Muallem S (2011) Acidic Ca(2+) stores come to the fore. Cell Calcium 50:109-112.

Secondo A, Petrozziello T, Tedeschi V, Boscia F, Vinciguerra A, Ciccone R, Pannaccione A, Molinaro P, Pignataro G, Annunziato L (2019) ORAI1/STIM1 interaction intervenes in stroke and in neuroprotection induced by ischemic preconditioning through store-operated calcium entry. Stroke 50:1240-1249.

Settembre C, Fraldi A, Medina DL, Ballabio A (2013) Signals from the lysosome: a control centre for cellular clearance and energy metabolism. Nat Rev Mol Cell Biol 14:283-296.

Tedeschi V, Petrozziello T, Secondo A (2019a) Calcium dyshomeostasis and lysosomal Ca^{2+} dysfunction in amyotrophic lateral sclerosis. Cells 8:1216.

Tedeschi V, Petrozziello T, Sisalli MJ, Boscia F, Canzoniero LMT, Secondo A (2019b) The activation of Mucolipin TRP channel 1 (TRPML1) protects motor neurons from L-BMAA neurotoxicity by promoting autophagic clearance. Sci Rep 9:10743.

Tedeschi V, Sisalli MJ, Petrozziello T, Canzoniero LMT, Secondo A (2021) Lysosomal calcium is modulated by STIM1/TRPML1 interaction which participates to neuronal survival during ischemic preconditioning. FASEB J 35:e21277.

Xu H, Ren D (2015) Lysosomal physiology. Annu Rev Physiol 77:57-80.

Yu L, McPhee CK, Zheng L, Mardones GA, Rong Y, Peng J, Mi N, Zhao Y, Liu Z, Wan F, Hailey DW, Oorschot V, Klumperman J, Baehrecke EH, Lenardo MJ (2010) Termination of autophagy and reformation of lysosomes regulated by mTOR. Nature 465:942-946.

C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y