Contacting the gut: Mitochondria-associated Endoplasmic Reticulum Membranes in the Enteric Nervous System

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Abstract

Changes in the connections between the endoplasmic reticulum (ER) and mitochondria, as well as alterations in mitochondria-associated ER membrane (MAM) signalling, have been documented in various neurodegenerative diseases affecting the brain. Despite the growing recognition of the significance of the gut-brain axis in neurodegenerative conditions, there has been no prior investigation into the biology of MAM within the enteric nervous system (ENS). Our recent research reveals, for the first time, the existence of connections between the ER and mitochondria within enteric neurons. Additionally, we observed alterations in the dynamics of these connections in the enteric neurons from a mouse model exhibiting age-related neurodegeneration. These findings provide the first detailed characterization of MAM in the ENS under physiological conditions and in a mouse model of age-associated neurodegeneration and shed new light on the potential role of enteric MAM in the context of neurodegenerative disorders.

Keywords

enteric nervous system, mitochondria-associated ER membranes, Parkinson's disease, Alzheimer's disease, ageing

Over the past decade, changes in both mitochondrial-associated membrane (MAM) dynamics and signalling have consistently been linked to age-related neurodegenerative disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD). Neuronal damage in these disorders often coincides with cellular functions regulated by contacts between the endoplasmic reticulum (ER) and mitochondria, as well as MAM signalling (Markovinovic et al., 2022).

A growing body of research indicates that the gut plays a significant role in neurodegeneration, as seen in PD, AD, and age-related neurodegeneration. The enteric nervous system (ENS), a key component of the gut-brain axis, governs major gastrointestinal functions (Markovinovic et al., 2022). Despite extensive research on MAM in the central nervous system (CNS), no data are available regarding MAM in the ENS, and this forms the focal point of the current study.

In our recently published study (Delfino et al., 2024), we have, for the first time, identified the presence of ER-mitochondria contacts in enteric neurons. Utilizing electron microscopy, we conducted a detailed characterization of these interactions. Our initial findings demonstrated that mitochondria naturally form MAM with ER membranes in enteric neurons of the myenteric plexus in young adult C57BL/6J mice. Approximately 14% of the total mitochondrial surface was found to be in contact with ER membranes. Notably, these connections exhibit similarities and are found in the same order of magnitude to what is found in the neurons in the CNS, where 10 to 15% percent of the total mitochondrial surface is occupied by ER (Stoica et al., 2014, 2016). We further characterized the length, spatial distribution, and surface occupation of ER on mitochondria, revealing the dynamic nature of MAM in enteric neurons. Key MAM proteins were expressed in the gut, such as Sigma1R and mitofusin 2 and tethers such as VAPB and PTPIP51 were actively interacting in enteric neurons.

These observations prompted an exploration of ER-mitochondria associations in enteric neurons in a pathological context, using SAMP8 mice — a non-transgenic model of age-related neurodegeneration displaying both

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CNS and GI dysfunctions. Our investigation revealed constipation in 8-month-old SAMP8 mice compared to control animals. Concurrently, SAMP8 enteric neurons exhibited an increased number of ER-mitochondria contacts compared to control mice, accompanied by, a reduction in PGP9.5 and in HuD positive cells by 75% and 53%, respectively, indicative of enteric neuronal loss. Interestingly, no difference in ER-mitochondria contacts was observed in longitudinal smooth muscle cells. We also found that calcium homeostasis we altered in SAMP8 mice enteric neurons. Because the non-transgenic SAMP8 model recapitulates some of the complexity found in patients, it is not easy to draw a direct link between MAM dysfunction and slow transit as symptoms cannot be solely attributed to MAM alteration. However, our findings are rather suggesting that the observed slow transit constipation in SAMP8 mice is the result of neuronal dysfunction leading to the loss of enteric neurons, rather than a functional defect in smooth muscle cells. This indicates that damage made to MAM in the enteric neurons could contribute to altered gut function.

There is now mounting evidence showing that slow transit is an enteric neuropathy rather than a functional disorder (Bassotti et al., 2013), with many studies showing that severely constipated patients exhibit abnormalities in the ENS, such as changes in the neurochemical coding (Wattchow et al., 2008). MAM plays a critical role in regulating keys cellular functions in neurons, which include calcium homeostasis, mitochondria biogenesis and oxidative phosphorylation needed for ATP production, neurite growth, synaptic activity and autophagy amongst others (Markovinovic et al., 2022). Therefore, a defect in MAM signalling could trigger neuronal dysfunctions in the ENS leading to gastrointestinal dysfunction. Despite current knowledge, whether and how MAM regulate digestives functions (e.g. intestinal motility and barrier permeability) remains unexamined until our work. One way to understand the direct role that MAM could play in regulating digestive functions through enteric neurons is to modulate (up or down) the amount of tethering between ER and mitochondria in a neuronal-specific manner. In a recent publication, Lu et al. have linked a reduction in ER-mitochondria associations with cardiac dysfunctions during ageing suggesting that damage made to MAM during ageing could affect other key organs like the heart (Lu et al., 2022).

From the literature (Markovinovic et al., 2022), both VAPB-PTPIP51 and mitofusin 2 seem to be the most reliable and interesting tethering proteins to modulate, since they seem to be involved in short and large contact spacing respectively which regulate different MAM functions. Moreover, knock-out animal models for VAPB, PTPIP51 and mitofusin 2 are already available but haven't been studied for gastrointestinal features yet.

Gastrointestinal disorders, in particular constipation, is now considered as a characteristic feature in neurodegenerative disorders such as PD or AD (Rao and Gershon, 2016); however, the mechanistic make up behind this is still poorly understood as no obvious neuronal loss seems to occur. In the case of PD, growing evidence show that the aggregation of alpha-synuclein, one of the major PD drivers, occurs early in enteric neurons and closely mirrors the synucleinopathy found in central neurons (de Guilhem de Lataillade et al., 2020). Our hypothesis is that pathological drivers like accumulation of alpha-synuclein or Aß triggers damage to MAM homeostasis in enteric neurons, which alters neuronal function even without any neuronal loss in a similar fashion to the CNS. In order to confirm this hypothesis, a first critical step would be to perform an in-depth characterization of MAM in the ENS of PD patients at different disease stages. To do so, submucosal biopsies from PD patients would be an ideal place to start as they offer fresh tissue without any post-mortem artefacts, and multiple samples could be taken from the same patient to perform a comprehensive study, as one biopsy could be used for electronic microscopy, one for proximity ligation assay, one for IHC and a last one for western blotting, giving a multiple range of assays to draw a reliable conclusion. Aiming in the same direction, more research is needed to characterize whether MAM biology is affected both in the CNS and the ENS during neurodegenerative disorders like PD, and if so in what time scale. Therefore restoring the MAM in neurodegenerative disorders seems to be a way forward in alleviating disease symptoms, and some clinical trials have even reached phase II for PD with this approach (Payne et al., 2020). However, because of the complexity of the damage to MAM in a given disease, it is often difficult to determine whether ER-mitochondria interactions would benefit from being tightened or loosened, making it important to understand the nature of the dysfunction in a particular patient. Using enteric biopsies to monitor MAM status and changes in tethering proteins in a patient could help to determine the individual requirements for a modulating treatment for MAM dysfunction.

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