



RESEARCH HIGHLIGHT OPEN

Janus-faced Mitofusin 2 (MFN2): mitochondria-endoplasmic reticulum shaping and tethering functions unveiled

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Signal Transduction and Targeted Therapy (2024)9:4

; <https://doi.org/10.1038/s41392-023-01730-y>

In a recently published study in *Science*, Naòn et al. report two uncharacterized splice variants of Mitofusin 2 (MFN2) that specifically shape and tether the endoplasmic reticulum (ER) to mitochondria.¹ This work sheds new light on the pleiotropic effects previously ascribed to MFN2 loss-of-function mutations, and has important implications for associated metabolic and neurological diseases.

Mitochondria are dynamic organelles undergoing extensive communication with the ER via so-called mitochondria-ER contact sites (MERCs).² As for other types of contact sites, MERCs play essential roles in transducing cellular stimuli into organelle-specific, compartmentalized signaling and metabolic functions. These functions include Ca²⁺ homeostasis, lipid metabolism, membrane dynamics (e.g., formation of autophagosomes), reactive oxygen species (ROS)-mediated signaling, apoptosis and inflammatory signals.² Assembly and maintenance of MERCs is believed to be mediated by several structural tethers that accumulate at the interface between mitochondria and the ER, thereby anchoring the two organelle membranes to ensure proximity of ~10–30 nm. The crucial role of MERCs in mammalian cells is emphasized by the growing evidence suggesting that MERC dysregulation is a common hallmark of several diseases, including neurodegeneration.

Being anchored to the mitochondrial outer membrane (OMM) by two transmembrane domains, the dynamin-like GTPase MFN2 plays a major role in regulating fusion dynamics. Consistent with this model, loss-of-function Mitofusin 2 mutations in various settings in vitro and in vivo lead to disrupted mitochondrial morphology and, in the long-term, ensuing mitochondrial dysfunction.³ However, on account of its presumptive dual localization on the ER, MFN2 has also been proposed to act as structural tether by forming homo- and heterotypic complexes with MFN2 and MFN1 situated on the OMM.⁴ Studies on models of Mitofusin 2 deletion have since then reported effects (often controversial) on MERC formation and/or stability, fueling debate about how MFN2 could simultaneously coordinate such diverse functions.³

Instead of pursuing the hypothesis of a promiscuous role of MFN2 itself, Naòn et al. explored the possibility that the MFN2 gene may give rise to functionally distinct splice variants. They identified two such variants in the human allele that are significantly shorter than the corresponding full-length MFN2 transcript, as they lack (fully or in part) the coiled-coil 1 and the GTPase domains (Fig. 1). Not only are these variants translated into proteins, but they exhibited a specific localization to the ER, hence

they were termed *ERMIN2* and *ERMIT2*. Topologically, both variants exhibit their N and C termini exposed to the cytosol, and none of them could rescue the morphological defects of the mitochondrial network which characterizes *Mfn2* knockout cells. However, *ERMIN2* appeared able to specifically rescue ER morphology, while *ERMIT2* was necessary to restore ER-mitochondria tethering in the presence of MFN1. MERC functionality following *ERMIT2* expression was validated in cells in vitro by monitoring mitochondrial Ca²⁺ uptake following ER release, and in liver-specific *Mfn2* knockout mice by tracing L-serine incorporation into phosphatidylserine and phosphatidylethanolamine (as a proxy to evaluate ER-to-mitochondria lipid transfer). Intriguingly, viral-mediated *ERMIT2* expression alone in liver-specific *Mfn2* knockout mice or in a model of diet-induced NASH (nonalcoholic steatohepatitis) improved hepatic inflammation and reduced the expression of ER stress markers,³ supporting the specific role of MERCs in liver metabolism.

This study provides fundamental insights into the biological function of MFN2 and associated splice variants, disentangling their specific roles in regulating mitochondrial and ER dynamics, but also tethering functions. It is of particular interest that in contrast to human MFN2, only one mouse *Mfn2* variant (MoV-*Mfn2*) was identified, which appears to be an analog of *ERMIT2*. This would argue that the ER-shaping function of *ERMIN2* might be taken over by MoV-*Mfn2* in mouse, suggesting that the emergence of an additional species-specific MFN2 variant (*ERMIN2*) may play important roles in e.g., disease or higher-order functions in humans. On the other hand, this work also raises several questions. For instance, given the similar structure and topology of the two splice variants, it remains unclear why MERCs are stabilized uniquely by *ERMIT2*, despite the ability of Mitofusins to bind both, *ERMIN2* and *ERMIT2*.³ Likewise, no mechanistic explanation was yet provided about how *ERMIN2* may carry out its proposed function on ER remodeling. Is this function required for both, ER tubules and sheets, or is rather specific for certain domains? And how exactly does *ERMIN2* exert this function? Is this role played via homotypic interactions or by interacting with other partners on the ER or on other organelles distinct from mitochondria? Given the pathophysiological role of MFN2 missense mutations in causing Charcot-Marie-Tooth 2A (CMT2A), a severe form of peripheral axonopathy, it will be important for future work to assess the relevance of these newly discovered variants for neuronal and axonal integrity, particularly in settings of loss- or gain-of-function mutations affecting *ERMIN2* or *ERMIT2*-related functions that may cause previously neglected

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Received: 18 October 2023 Revised: 21 November 2023 Accepted: 11 December 2023

Published online: 01 January 2024

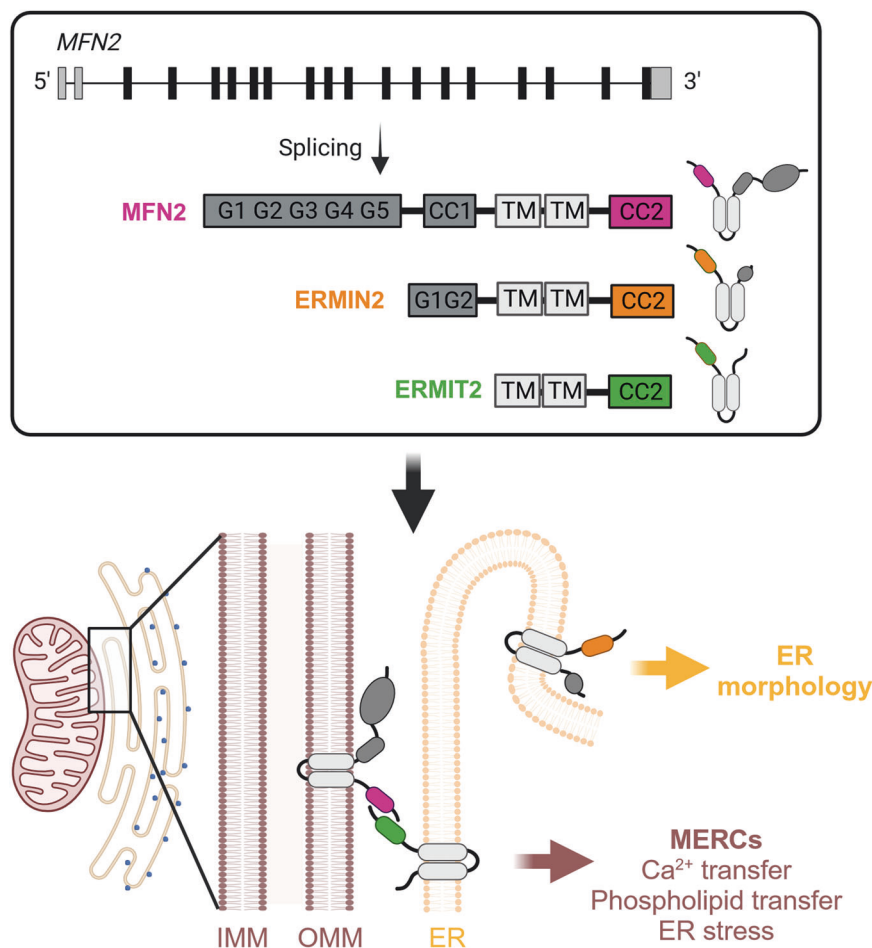


Fig. 1 ER-specific functions of spliced MFN2 variants. Alternative splicing of *MFN2* produces ERMIN2 and ERMIT2 variants, who lack in full or in part the GTPase and coiled-coil 1 domains and localize to the ER. While ERMIT2 specifically stabilizes MERCs and associated functions via interaction with MFN2 or MFN1, ERMIN2 shapes ER architecture. Created with Biorender.com

ER-specific phenotypes.⁵ In view of the often-conflicting evidence obtained from available genetic mouse models of CMT2A, which poorly reflect the clinical traits affecting CMT2A patients, the findings presented in this study thus pave the way for the generation of new pre-clinical models that may more faithfully reveal species-specific effects linked to dysregulated *MFN2* splice-variants during disease.

ACKNOWLEDGEMENTS

We apologize to colleagues whose work could not be cited here for editorial reasons. This work was supported by the Deutsche Forschungsgemeinschaft (SFB1218 – Grant No. 269925409 and CECAD EXC 2030 – Grant No. 390661388 to E.M. and M.B.; SFB1451 – Grant No. 431549029 to M.B.).

AUTHOR CONTRIBUTIONS

C.A.F., E.M., and M.B. wrote the manuscript. C.A.F. drafted the figure. All authors have read and approved the article.

FUNDING

Open Access funding enabled and organized by Projekt DEAL.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

REFERENCES

1. Naon, D. et al. Splice variants of mitofusin 2 shape the endoplasmic reticulum and tether it to mitochondria. *Science* **380**, eadh9351 (2023).
2. Csordas, G., Weaver, D. & Hajnoczky, G. Endoplasmic reticulum-mitochondrial contactology: structure and signaling functions. *Trends Cell Biol.* **28**, 523–540 (2018).
3. Zaman, M. & Shutt, T. E. The role of impaired mitochondrial dynamics in MFN2-mediated pathology. *Front. Cell Dev. Biol.* **10**, 858286 (2022).
4. de Brito, O. M. & Scorrano, L. Mitofusin 2 tethers endoplasmic reticulum to mitochondria. *Nature* **456**, 605–610 (2008).
5. Bernard-Marissal, N. et al. Altered interplay between endoplasmic reticulum and mitochondria in Charcot-Marie-Tooth type 2A neuropathy. *Proc. Natl Acad. Sci. USA* **116**, 2328–2337 (2019).



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