



# Editorial: Mitochondrial Remodeling and Dynamic Inter-Organelle Contacts in Cardiovascular Physiopathology

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## Editorial on the Research Topic

### Mitochondrial Remodeling and Dynamic Inter-Organelle Contacts in Cardiovascular Physiopathology

Emerging evidence has shown that membranes of many subcellular organelles are dynamic and engage in structural and functional communications, thereby creating new intracellular compartments by either sharing proteins or by owning a distinct pool (Rizzuto et al., 1998; Giorgi et al., 2018).

Membranes from different organelles do not fuse together, but preserve their integrity by approaching not more than a few nanometers (usually 10 nm); this distance is enough to create transient contacts which significantly impact physiological processes (e.g., lipid metabolism, material exchange) (Simmen and Tagaya, 2017; Vance, 2020) and human diseases (van Vliet and Agostinis, 2018; Simoes et al., 2020).

Growing advances in technologies, including cell fractionation (Wieckowski et al., 2009; Montesinos and Area-Gomez, 2020), confocal (Chung et al., 2015; Galmes et al., 2016), and transmission electron microscopy (Csordás et al., 2006), alongside new tools which combine biochemistry and online databases (e.g., Contact-ID) (Kwak et al., 2020), have allowed the study of contact sites in many types of living cells, in order to address new structural, functional, and modulatory properties.

Contact sites in cardiomyocytes, especially those established between sarcoplasmic reticulum (SR), and transverse tubules (TT) of the sarcolemma, and with mitochondrial membranes, are necessary for excitation-contraction coupling (ECC) efficiency (Gambardella et al., 2018) and suitable calcium signaling (Fearnley et al., 2011). The latter sustains cell survival by modulating mitochondrial ATP generation to match cardiac workload and also cell death (Jouaville et al., 1999; Traaseth et al., 2004; Bonora et al., 2019).

Among the intracellular organelles, mitochondria play an essential role in cardiomyocyte bioenergetics, because they constitute 35% of the total cell volume to satisfy the high-energy demand of heart (Elfering et al., 2004; Benard et al., 2007). As such, it is not surprising that mitochondrial dysfunction underlies several defects observed during heart development and differentiation, participating actively in the pathogenesis of a number of cardiovascular diseases (Santulli et al., 2015; Bravo-Sagua et al., 2020). Hence, maintaining a healthy mitochondrial population is an essential homeostatic requirement that the cell retains by controlling multiple checkpoints including a balanced ratio between mitophagy and biogenesis, including mitochondrial fission and fusion (Morciano et al., 2020).

The present collection includes 11 reports subdivided in the following categories: basic mechanisms, human diseases, and therapies.

## BASIC MECHANISMS

Five out of 11 reports belong to this category and are authored by Rossini and Filadi, Lin et al., Gilkerson et al., Lynch et al., and Piquereau et al.. The authors highlighted the importance of the cytoarchitecture, especially SR-mitochondria contact sites and spatio-temporal mitochondrial remodeling, in some molecular pathways essential for cardiomyocyte function. These include calcium signaling, one of the main players in mitochondrial bioenergetics and cardiac contractility; in this context, organelles and proteins involved in intracellular calcium fluxes have been analyzed both *in vitro* and *in vivo*. Moreover, new insights have been provided about reactive oxygen species (ROS) production, mitochondrial dynamics, and quality control in the adaptation of the heart to multiple stress conditions. Lastly, there is a report highlighting the ability of sex hormones as factors able to influence metabolism via mitochondrial remodeling.

## DISEASES

Four manuscripts authored by Gao et al., Salazar-Ramírez et al., Ramaccini et al., and Kumar et al. report compelling evidence of how mitochondrial dysfunction and alterations in organelle communication can impact cellular homeostasis in cardiovascular diseases. Indeed, the rewiring of calcium signaling at SR-mitochondria interface (but also at the sarcolemma), the imbalance in mitophagy, defects in fusion-fission machinery, lipid biosynthesis, ATP and ROS production are analyzed in a wide range of pathologies including dilated cardiomyopathy (DCM), heart failure, ischemia-reperfusion injury, and cardiac arrhythmia.

## REFERENCES

- Benard, G., Bellance, N., James, D., Parrone, P., Fernandez, H., Letellier, T., et al. (2007). Mitochondrial bioenergetics and structural network organization. *J. Cell Sci.* 120, 838–848. doi: 10.1242/jcs.03381
- Bonora, M., Wieckowski, M. R., Sinclair, D. A., Kroemer, G., Pinton, P., and Galluzzi, L. (2019). Targeting mitochondria for cardiovascular

## THERAPIES

In CVD, the altered mitochondrial remodeling and impaired inter-organelle communications of cardiomyocytes may be amenable to therapeutic interventions, especially considering the dynamic and reversible nature of these interactions (Ferrandi et al., 2013; Sabbah, 2016; Siasos et al., 2018; Kerkhofs et al., 2019). In this sense, the last 2 reports authored by Elorza et al. and Angebault et al. summarize the currently available therapies targeting mitochondrial fitness (e.g., maintaining the correct balance of biogenesis and the control of mitochondrial heteroplasmy to prevent age-related diseases) and report the beneficial effects of metformin in mice affected by Duchenne muscular dystrophy (DMD)-associated cardiomyopathy. In this preclinical model, metformin was able to normalize SR-mitochondria interactions, and restore the function of the electron transport chain (ETC) Complex I and the expression of mitochondrial calcium-handling protein complexes.

## AUTHOR CONTRIBUTIONS

GS and GMor conceived, wrote, and finalized the Editorial. GMon and VP wrote the Editorial.

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disorders: therapeutic potential and obstacles. *Nat. Rev. Cardiol.* 16, 33–55. doi: 10.1038/s41569-018-0074-0

- Bravo-Sagua, R., Parra, V., Muñoz-Cordova, F., Sanchez-Aguilera, P., Garrido, V., Contreras-Ferrat, A., et al. (2020). Sarcoplasmic reticulum and calcium signaling in muscle cells: homeostasis and disease. *Int. Rev. Cell Mol. Biol.* 350, 197–264. doi: 10.1016/bs.ircmb.2019.12.007

- Chung, J., Torta, F., Masai, K., Lucast, L., Czaplá, H., Tanner, L. B., et al. (2015). Intracellular transport. PI4P/phosphatidylserine countertransport at ORP5- and ORP8-mediated ER-plasma membrane contacts. *Science* 349, 428–432. doi: 10.1126/science.aab1370
- Csordás, G., Renken, C., Várnai, P., Walter, L., Weaver, D., Buttle, K. F., et al. (2006). Structural and functional features and significance of the physical linkage between ER and mitochondria. *J. Cell Biol.* 174, 915–921. doi: 10.1083/jcb.200604016
- Elfering, S. L., Haynes, V. L., Traaseth, N. J., Ettl, A., and Giulivi, C. (2004). Aspects, mechanism, and biological relevance of mitochondrial protein nitration sustained by mitochondrial nitric oxide synthase. *Am. J. Physiol. Heart Circ. Physiol.* 286, H22–H29. doi: 10.1152/ajpheart.00766.2003
- Fearnley, C. J., Roderick, H. L., and Bootman, M. D. (2011). Calcium signaling in cardiac myocytes. *Cold Spring Harb. Perspect. Biol.* 3:a004242. doi: 10.1101/cshperspect.a004242
- Ferrandi, M., Barassi, P., Tadini-Buoninsegni, F., Bartolommei, G., Molinari, I., Tripodi, M. G., et al. (2013). Istaroxime stimulates SERCA2a and accelerates calcium cycling in heart failure by relieving phospholamban inhibition. *Br. J. Pharmacol.* 169, 1849–1861. doi: 10.1111/bph.12278
- Galmes, R., Houcine, A., van Vliet, A. R., Agostinis, P., Jackson, C. L., and Giordano, F. (2016). ORP5/ORP8 localize to endoplasmic reticulum-mitochondria contacts and are involved in mitochondrial function. *EMBO Rep.* 17, 800–810. doi: 10.15252/embr.201541108
- Gambardella, J., Trimarco, B., Iaccarino, G., and Santulli, G. (2018). New insights in cardiac calcium handling and excitation-contraction coupling. *Adv. Exp. Med. Biol.* 1067, 373–385. doi: 10.1007/5584\_2017\_106
- Giorgi, C., Danese, A., Missiroli, S., Patergnani, S., and Pinton, P. (2018). Calcium dynamics as a machine for decoding signals. *Trends Cell Biol.* 28, 258–273. doi: 10.1016/j.tcb.2018.01.002
- Jouaville, L. S., Pinton, P., Bastianutto, C., Rutter, G. A., and Rizzuto, R. (1999). Regulation of mitochondrial ATP synthesis by calcium: evidence for a long-term metabolic priming. *Proc. Natl. Acad. Sci. U.S.A.* 96, 13807–13812. doi: 10.1073/pnas.96.24.13807
- Kerkhofs, M., Bultynck, G., Vervliet, T., and Monaco, G. (2019). Therapeutic implications of novel peptides targeting ER-mitochondria Ca<sup>2+</sup>-flux systems. *Drug Discov. Today* 24, 1092–1103. doi: 10.1016/j.drudis.2019.03.020
- Kwak, C., Shin, S., Park, J.-S., Jung, M., Nhung, T. T. M., Kang, M.-G., et al. (2020). Contact-ID, a tool for profiling organelle contact sites, reveals regulatory proteins of mitochondrial-associated membrane formation. *Proc. Natl. Acad. Sci. U.S.A.* 117, 12109–12120. doi: 10.1073/pnas.1916584117
- Montesinos, J., and Area-Gomez, E. (2020). Isolation of mitochondria-associated ER membranes. *Methods Cell Biol.* 155, 33–44. doi: 10.1016/bs.mcb.2019.12.001
- Morciano, G., Patergnani, S., Bonora, M., Pedriali, G., Tarocco, A., Bouhamida, E., et al. (2020). Mitophagy in cardiovascular diseases. *J. Clin. Med.* 9:892. doi: 10.3390/jcm9030892
- Rizzuto, R., Pinton, P., Carrington, W., Fay, F. S., Fogarty, K. E., Lifshitz, L. M., et al. (1998). Close contacts with the endoplasmic reticulum as determinants of mitochondrial Ca<sup>2+</sup> responses. *Science* 280, 1763–1766. doi: 10.1126/science.280.5370.1763
- Sabbah, H. N. (2016). Targeting mitochondrial dysfunction in the treatment of heart failure. *Expert Rev. Cardiovasc. Ther.* 14, 1305–1313. doi: 10.1080/14779072.2016.1249466
- Santulli, G., Xie, W., Reiken, S. R., and Marks, A. R. (2015). Mitochondrial calcium overload is a key determinant in heart failure. *Proc. Natl. Acad. Sci. U.S.A.* 112, 11389–11394. doi: 10.1073/pnas.1513047112
- Siasos, G., Tsigkou, V., Kosmopoulos, M., Theodosiadis, D., Simantiris, S., Tagkou, N. M., et al. (2018). Mitochondria and cardiovascular diseases—from pathophysiology to treatment. *Ann. Transl. Med.* 6:256. doi: 10.21037/atm.2018.06.21
- Simmen, T., and Tagaya, M. (2017). Organelle communication at Membrane Contact Sites (MCS): from curiosity to center stage in cell biology and biomedical research. *Adv. Exp. Med. Biol.* 997, 1–12. doi: 10.1007/978-981-10-4567-7\_1
- Simoes, I. C. M., Morciano, G., Lebedzinska-Arciszewska, M., Aguiari, G., Pinton, P., Potes, Y., et al. (2020). The mystery of mitochondria-ER contact sites in physiology and pathology: a cancer perspective. *Biochim. Biophys. Acta Mol. Basis Dis.* 1866:165834. doi: 10.1016/j.bbadis.2020.165834
- Traaseth, N., Elfering, S., Solien, J., Haynes, V., and Giulivi, C. (2004). Role of calcium signaling in the activation of mitochondrial nitric oxide synthase and citric acid cycle. *Biochim. Biophys. Acta* 1658, 64–71. doi: 10.1016/j.bbabi.2004.04.015
- van Vliet, A. R., and Agostinis, P. (2018). Mitochondria-associated membranes and ER stress. *Curr. Top. Microbiol. Immunol.* 414, 73–102. doi: 10.1007/82\_2017\_2
- Vance, J. E. (2020). Inter-organelle membrane contact sites: implications for lipid metabolism. *Biol. Direct.* 15:24. doi: 10.1186/s13062-020-00279-y
- Wieckowski, M. R., Giorgi, C., Lebedzinska, M., Duszyński, J., and Pinton, P. (2009). Isolation of mitochondria-associated membranes and mitochondria from animal tissues and cells. *Nat. Protoc.* 4, 1582–1590. doi: 10.1038/nprot.2009.151

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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