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

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Keywords: cardiovascular disease, mitochondria, sarcoplasmic reticulum, contact sites, signal transduction

Editorial on the Research Topic

Mitochondrial Remodeling and Dynamic Inter-Organellar 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.

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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/bse.ircmb.2019.12.007

**THERAPIES**

In CVD, the altered mitochondrial remodeling and impaired inter-organellar 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.

**FUNDING**

The Santulli Lab was supported in part by the National Institutes of Health (NIH: R01-DK123259, R01-1HL146691, R01-DK033823, R01-HL159062, R00-DK107895, R56-AG066431, T32-HL144456 to GS), and by the Irma T. Hirschl and Monique Weill-Caulier Trusts (to GS). VP was supported by grants from the Fondo Nacional de Desarrollo Científico y Tecnológico, FONDECYT, Chile (1190743), Fondo de Financiamiento de Centros de Investigación en Áreas Prioritarias, FONDAP, Chile (15130011), International Centre for Genetic Engineering and Biotechnology, ICGEB, Italy (CRP-ICGEB Research Grant CRP/CHL18-04), and U-Redes Generación, Vicerrectoría de Investigación y Desarrollo, Universidad de Chile, Chile (15130011), International Centre for Genetic Engineering and Biotechnology, ICGEB, Italy (CRP-ICGEB Research Grant CRP/CHL18-04), and U-Redes Generación, Vicerrectoría de Investigación y Desarrollo, Universidad de Chile, Chile (G_2018-35). GM was supported by the Italian Ministry of Health Grant (GR-2019-12369862).

**ACKNOWLEDGMENTS**

We thank Ana María Avalos for proofreading and revising our manuscript.
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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.