Orphaned mitochondria in heart failure

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This editorial refers to ‘Impaired mitochondrial network excitability in failing guinea-pig cardiomyocytes’ by K.Y. Goh et al., pp. 79–89.

The heart is a highly efficient engine that relies on perfect tuning of all processes that support excitation–contraction (EC) coupling to pump blood to the body’s organs. Since this engine must adapt its pumping capacity to any evolving variations in the metabolic demand of the organism, it possesses efficient control mechanisms on the cellular level to match ATP supply to the constantly varying cellular demand. In the heart, ATP is produced primarily in mitochondria, and the ATP pool is turned over in less than a minute. Due to this high energetic demand, 30% of the cellular volume is partitioned to mitochondria, which are aligned in a highly organized fashion in areas with the highest energetic demand, i.e. underneath the plasma membrane with its ATP-consuming ion transporters, and along the myofilaments, where myosin ATPase is the dominant consumer of cellular ATP.

Two major factors that control mitochondrial respiration during workload transitions are Ca2+ and ADP. While ADP accelerates respiration and oxidizes the redox state of the energetic precursor NADH, Ca2+ activates the Krebs cycle to regenerate oxidized NAD+ to NADH. The close spatial alignment of mitochondria along the myofilaments and the sarcoplasmic reticulum (SR), the major cellular Ca2+ store, constitutes so-called microdomains in which privileged transfer of ADP and Ca2+ between myofilaments, the SR, and mitochondria is facilitated.

An important role for the spatial organization of mitochondria in this three-dimensional lattice within cardiac myocytes is played by mitofusin (Mfn) 1 and Mfn2. Both are located on the outer mitochondrial membrane where they can interact with Mfn1 and Mfn2 of neighbouring mitochondria, inducing mitochondrial fusion, a process which together with fission is critical for mitochondrial self-renewal and functional integrity. Furthermore, Mfn2 (but not Mfn1) tethers the SR to mitochondria to facilitate privileged Ca2+ transmission between both organelles. Finally, Mfn2 (but not Mfn1) is a regulator of mitochondrial autophagy (mitophagy) by mediating translocation of Parkin to mitochondria, which initiates ubiquitination of damaged mitochondrial proteins.

Goh et al.6 reveal that in a guinea pig model of systolic heart failure, Mfn1 and Mfn2 mRNA and protein are down-regulated, respectively, and that the spatial distribution of Mfn1 within the mitochondrial network becomes heterogeneous (Figure 1). This was associated with structural alterations of mitochondria consistent with a shift in the mitochondrial fission/fusion balance towards fission, with mitochondria becoming smaller and less well spatially organized (Figure 1). This observation is in line with the phenotype of mice with cardiomyocyte-restricted deletion of both Mfn1 and Mfn2, where mitochondrial fragmentation and respiratory dysfunction developed, which was associated with a rapidly progressive and lethal dilated cardiomyopathy. Therefore, the data of Goh et al.6 suggest that down-regulation of Mfn1 and Mfn2 in failing cardiac myocytes may indeed contribute to the development of heart failure.

In the heart, mitochondria are a dominant source of reactive oxygen species (ROS), which under physiological conditions are largely eliminated by Mn2+-dependent superoxide dismutase and NADPH-dependent antioxidant enzymes. In heart failure, mitochondrial ROS production and emission are substantially increased (‘oxidative stress’) and thought to play a causal role in the progression of the disease. On the other hand, lower levels of ROS can function as signalling molecules, for instance, by activating mitochondrial quality control mechanisms associated with mitophagy or inducing protection from cell death during ischaemia/reperfusion (in the context of ‘ischaemic preconditioning’). In their study, Goh et al.6 confirm previous results since the antioxidant capacity of failing cardiac myocytes was depleted and mitochondrial ROS emission increased compared with non-failing myocytes (Figure 1). Moreover, the susceptibility of mitochondria to undergo ROS-induced dissipation of their membrane potential (Δψm) was slightly increased in failing compared with non-failing myocytes, a property that per se may predispose to apoptotic and/or necrotic cell death.

The major advance made by Goh et al.6 is that the aforementioned disturbance of Mfn-controlled mitochondrial morphology and ensuing spatial disorganization is associated with an impairment of the mitochondrial network behaviour in failing cardiac myocytes (Figure 1). This network behaviour plays an important role for a phenomenon termed ‘ROS-induced ROS release’, where the close vicinity of mitochondria to each other in the three-dimensional network within cardiac myocytes enables ROS released from one mitochondrion to induce ROS release from several neighbouring mitochondria through the activation of inner membrane anion channels and/or permeability transition pores (Figure 1). This ROS-induced ROS release is mechanistically coupled with synchronized Δψm oscillations of the mitochondrial network which account for periodic variations in the cellular ATP/ADP ratio. Through activation of sarcolemmal ATP-
pulse of ROS (induced by laser flash) to the onset of coordinated release are more prominent in heart failure with left bundle branch block since orphaned ryanodine receptors and dyssynchronous SR Ca\(^{2+}\) level apparently scales even to the whole-organ level (and/or oxidative) stress, such as during ischaemia/reperfusion and possibly, also heart failure.

Here, Goh et al.\(^6\) have elegantly elaborated that in failing cardiac myocytes, this coordinated mitochondrial network behaviour is substantially deteriorated (Figure 1). First, the time lag between an initiating pulse of ROS (induced by laser flash) to the onset of coordinated \(\Delta \Psi_m\) oscillations was nearly doubled, and when oscillations eventually occurred, they were much less homogeneous throughout the cell, both indicating that mitochondria in failing cardiac myocytes become ‘orphaned’ from mitochondrial clusters, presumably related to the aforementioned down-regulation of Mfn1 and Mfn2 and the ensuing spatial disorganization (Figure 1). The potential causality is supported by the observations that in mice with cardiomyocyte-specific deletion of either Mfn1\(^{19}\) or Mfn2,\(^{20}\) the propagation of \(\Delta \Psi_m\) depolarization within the cell in response to ROS was also substantially slowed.

These novel observations add another piece of evidence to the concept that in heart failure, ultrastructural disorganization of the otherwise highly organized intracellular lattice plays an important role in the pathophysiology of the disease in general. For instance, remodelling of the transverse (t)-tubular network in failing cardiac myocytes disconnects ryanodine receptors of the SR from their trigger, the Ca\(^{2+}\) influx through voltage-gated L-type Ca\(^{2+}\) channels,\(^{17}\) this translates into oscillations of contractile force\(^{16}\) and ventricular arrhythmias\(^{16}\) at times of metabolic (and/or oxidative) stress, such as during ischaemia/reperfusion and possibly, also heart failure. Since due to (Mfn2-mediated\(^5\)) privileged Ca\(^{2+}\) communication between the SR and mitochondria, the kinetic and spatial aspects of SR Ca\(^{2+}\) release are also key for the bioenergetic feedback response\(^{26}\) and the prevention of excessive mitochondrial ROS emission,\(^{27}\) the current study brings up the question whether spatial disorganization of mitochondria together with t-tubular remodeling\(^{21,22}\) also impairs the tight interplay between mitochondrial energetics and redox signal- ing with the processes of EC coupling. Furthermore, since mitochondrial network behaviour (involving synchronized \(\Delta \Psi_m\) oscillations and ROS-induced ROS release) not only mediates pathological processes such as arrhythmias, contractile dysfunction, and cell death,\(^{15–18}\) but can also be observed under physiological conditions in healthy un- stressed cells (albeit at higher frequencies but lower amplitudes),\(^{28}\) future work should address in how far orphaned mitochondria in failing cardiac myocytes impair ‘physiological’ ROS signalling required for mitochondrial quality control, protection from cell death, and other protective signalling events in the cell\(^{11–13}\).

**Figure 1** In the normal heart, the mitochondrial network is established by the close vicinity of mitochondria to each other, which is facilitated by interaction of the outer mitochondrial membrane fusion proteins mitofusin-1 and -2 (Mfn1/2). The network allows propagation of mitochondrial signals, such as ROS-induced ROS release in heart failure, and the mitochondrial network is impaired by decreased expression of Mfn1 and Mfn2, respectively, which results in disorganized, disconnected mitochondria that become partly orphaned from ROS-induced ROS signalling. At the same time, overall ROS levels are elevated as a sign of oxidative stress.

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**Editorial**

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