Not just the powerhouse of the cell: emerging roles for mitochondria in the heart

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This editorial refers to the following articles in this issue which are part of the Review Focus on Mitochondria in Cardiac Disease: Emerging Concepts and Novel Therapeutic Targets: T. Miura et al.1, pp. 7–15; D. Hausenloy et al.4, pp. 67–74; S.-B. Ong and D. Hausenloy6, pp. 16–29; M. Ruiz-Meana et al.7, pp. 30–39; S.L. Hänninen et al.8, pp. 75–82; M.G. Rosca and C.L. Hoppel10, pp. 40–50; C.-H. Chen et al.12, pp. 51–57; S.M. Davidson14, pp. 58–66. It also refers to the following articles in the next issue (Vol. 88, Issue 2): M. Gucek and E. Murphy2; S. Cadenas et al.5; H. Bugger and E.D. Abel9; D.A. Brown and B. O’Rourke11; V.B. Pillai et al.12

Mitochondria make up 30% of the volume of a single cardiomyocyte, underlining the importance of their conventional role as the ATP-producing ‘powerhouse’ of the cell. However, it is clear that this complex organelle plays a variety of roles within the cardiomyocyte that extend beyond its established function as the cellular powerhouse. In this regard, the most significant discovery was its critical role as an arbitrator of cell death1 in addition to its function in cellular survival. This review focuses on several novel and emerging roles for mitochondria in the heart that may provide an opportunity for the identification and development and of new therapeutic strategies for the treatment of cardiac disease.

Several of the reviews contained in this spotlight issue explore the role of mitochondria as targets for cardioprotection, i.e. protecting the heart against the detrimental effects of acute ischaemia–reperfusion injury (IRI). It is well established that mitochondrial dysfunction lies at the heart of cardiomyocyte death induced by IRI. However, recent evidence indicates that the contribution of mitochondria to cell injury goes well beyond their role as death executors through the opening of mitochondrial permeability transition pore (mPTP), as they contain several specific and highly regulated intrinsic signalling pathways and molecular complexes that may be determinants for cell death or survival under stressful conditions. Several novel strategies for preserving mitochondrial function during acute IRI are explored in this issue. To begin with, changes in mitochondrial proteins (in terms of expression and post-translational modification, termed the mitochondrial ‘proteome’) may provide valuable information in a variety of cardiac diseases. In this regard, Gucek and Murphy2 review the changes in the mitochondrial proteome which occur in a cardioprotective phenotype as a strategy for identifying novel mediators of cardioprotection.

The convergence of a diverse variety of signal transduction pathways originating from the cell surface to the mitochondria has been reported to underlie the endogenous cardioprotective phenomena of ischaemic preconditioning (IPC) and post-conditioning. However, the actual signalling pathway linking the cytosol to the mitochondrial matrix has eluded investigators. In this respect, Miura et al.1 review the current evidence supporting a role for pro-survival protein kinase signalling to the mitochondria in the context of myocardial protection. Whether these protein kinases are able to interact directly with components of the mitochondria such as the mPTP, a critical determinant of IRI, or whether they can influence mitochondrial function indirectly has attracted vigorous debate. The paradoxical role of the mPTP as a potential mediator of IPC is suggested in an original article by Hausenloy et al.4 who have demonstrated that reactive oxygen species (ROS)-induced activation of the pro-survival kinase Akt requires the presence of the cyclophilin-D component of the mPTP. The authors propose that non-pathological opening of the mPTP in response to the IPC stimulus may be required prior to the index ischaemic event to mediate IPC cardioprotection. In the context of adaptation to myocardial ischaemia, evidence on the role of hypoxia-inducible factor as a potential mediator of mitochondrial metabolic reprogramming is provided and discussed in the review by Cadenas et al.5

Mitochondrial morphology is a topic that has only very recently been investigated in the heart. Mitochondria are dynamic organelles that are able to undergo changes in morphology, generating either elongated, interconnected networks by the process of mitochondrial fusion or forming discrete, fragmented mitochondria by the process of mitochondrial fission. Whether these phenomena are relevant to the adult heart in which interfibrillar cardiac mitochondria have a unique arrangement is discussed in a contribution by Ong and Hausenloy.6 Specifically, these authors explore the potential for...
modulating mitochondrial morphology as a novel strategy for protecting against acute IRI, thereby providing new therapeutic targets for cardioprotection.

Loss of calcium homeostasis is one of the main determinants of cardiomyocyte hypercontracture and cell death during reperfusion injury. Interestingly, its role in cell death is not circumscribed to pathological hyperactivation of contractile machinery but also involves induction of mPTP opening in high-calcium microanatomical domains. Functional units between mitochondria and sarcoplasmic reticulum (SR) provide the basis for an efficient energy-demand coupling between SR and mitochondria but they may trigger pathological mPTP opening under conditions in which calcium and ROS production are pathologically dysregulated. The consequences of the interaction between SR and mitochondria in the setting of myocardial reperfusion and other cardiovascular pathologies are highlighted in the review by Ruiz-Meana et al. The tight molecular regulation of this interplay is also exemplified in the original article by Hänninen et al. who report that mitochondrial uncoupling results in a reduction in SR calcium through down-regulation of the SR calcium buffer calsequestrin (CASQ2).

Defects in mitochondrial bioenergetics are believed to underlie the cardiac dysfunction in both diabetic patients and patients with cardiac failure, topics that are reviewed by Bugger and Abel and Rosca and Hoppel, respectively. The molecular mechanisms underlying this mitochondrial dysfunction are described in detail for both diabetic animal models and diabetic patients. Remarkably, efficient mitochondrial oxidative phosphorylation does not exclusively rely on the activities of individual electron transport chain complexes but also on their appropriate supramolecular assembly into functional units or respirasomes. Insufficient respirasome formation, as well as changes in mitochondrial biogenesis and morphology and mitochondrial metabolic remodelling that follows the development of cardiac failure, may play an important pathophysiological role in failing myocardium.

Several novel functions for cardiac mitochondria are introduced by three other reviews. To begin with, an intriguing, new role for cardiac mitochondria is in modulating the origin and propagation of arrhythmias within the heart. Brown and O’Rourke review the current evidence that implicates a number of mitochondrial ion channels as well as mitochondrial proteome in the development and progression of cardiac disease, highlighting the importance of the endothelium as a potential therapeutic target for the treatment of cardiac disease.

Therefore, the field of cardiac mitochondrial biology continues to impress with the variety of emerging novel concepts highlighted in this spotlight issue. We await with great anticipation the exciting developments in this field of research which should result in the identification of novel mitochondria-targeted therapeutic strategies for treating cardiac disease.

Conflict of interest: none declared.

References
11. Chen C-H, Sun L, Mochly-Rosen D. Mitochondrial aldehyde dehydrogenase-2 may represent an intrinsic protective mechanism with great therapeutic potential for treating acute IRI, as reviewed in detail by Mochly-Rosen and colleagues.