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Solving Mitochondrial Mysteries

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Abstract

This is an exciting time in mitochondrial biology. The mitochondrion is finally beginning to reveal some of its long held secrets. The scientific community has started to identify at the molecular level some of the key channels and transporters that have been well studied biochemically, but which have escaped molecular identification. This special issue provides state-of-the art reviews and original articles on the mitochondrial permeability transition pore (mPTP), regulation of mitochondrial calcium homeostasis and regulation of mitochondrial dynamics.

The mitochondrial permeability transition pore (mPTP) was first described in the 1970s. Based on biochemical analysis several candidates have been proposed to form this pore, including the inner mitochondrial membrane proteins, adenine nucleotide translocator (ANT) and the phosphate carrier, possibility connecting via contact sites to the outer mitochondrial voltage dependent anion channel (VDAC). However the mPTP activity remained despite genetic ablation of these targets (although for ANT ablation its calcium sensitivity was altered), suggesting that they were not the pore forming unit. In 2013, three groups reported a role for the mitochondrial F1F0ATPase in forming the mPTP [1–3], although the subunits involved differed in these studies. Bernardi's group reported that dimers of the F1F0ATPase can form the mPTP; these findings are reviewed in this issue [4]. Morciano et al [5], review the data suggesting that the c-ring of the ATPase can form the mPTP. Halestrap and Richardson [6] provide a critical assessment of past and present candidates for the mPTP and suggest that perhaps a small fraction of the "ATP synthasome", which is composed of the F1F0ATPase, the phosphate carrier, ANT and VDAC, might form a conformation creating the mPTP. Although genetic deletion studies have eliminated many candidates for the pore forming unit, they have confirmed that mitochondrial cyclophilin activates the mPTP. Alam et al [7], focus on cyclophilin D and potential mechanisms by which it might regulate the mPTP, as well as on possible physiological roles for cyclophilin D. A recent paper has reported that loss of CypD can alter pyruvate and branch chain amino acid metabolism [8]. The role of hexokinase as a regulator of the mPTP is also reviewed [9]. Ong et al [10] round out the five review articles on the mPTP with a focus on the role of the mPTP in ischemia-reperfusion injury and cardioprotection.

Another important mitochondrial mystery was recently solved with simultaneous reports identifying the long sought after mitochondrial calcium uniporter (MCU). It was known for

over 60 years that the mitochondria were capable of accumulating large amounts of calcium. As well as being the driving force for ATP synthesis, mitochondrial membrane potential also drives calcium uptake into the mitochondria. In spite of extensive studies, the identity of the MCU eluded mitochondrial biologists until 2011 [11, 12]. Mice lacking MCU have recently been generated and have provided some expected as well as some surprising results which are reviewed [13]. The regulation of mitochondrial calcium homeostasis is reviewed here [14] and in a previous issue of the journal [15]. The mitochondrial Na dependent Ca efflux pathway (NCXL) was recently reviewed in this journal [16].

Mitochondrial dynamics recently have been recognized to play an important role in mitochondrial and cellular health and function. Indeed a recent paper has suggested a relationship between inner membrane topology and calcium transport mechanisms [17]. Changes in mitophagy and mitochondrial fission and fusion are linked to cell death, but the details are still unclear. The role of fission and fusion and mitophagy in the control of proteolytic pathways has been recently reviewed [18]. As mentioned by Gottlieb in her review “A key to mitochondrial homeostasis is the ability to remove and replace components throughout the network”. This special issue has several reviews on the current state of mitophagy which lay out key areas for future studies [19–21]. Hammerling and Gustafsson [22] also recently reviewed this topic. Chan et al [23] detail their elegant methods for measuring turnover rate of mitochondrial proteins and show that mitochondrial proteins turnover at different rates. A recent paper by Shekar et al [24] also obtained a similar finding. If mitophagy were the main mechanism of mitochondrial protein turnover, one would expect that all mitochondrial proteins would have a similar turnover rate. The differing rates of mitochondrial protein turnover do not diminish the importance of mitophagy (especially in disease processes), but they suggest that other protein turnover mechanisms predominate under basal, unstressed conditions.

There are two reviews that focus on mitochondrial fission and fusion or the proteins that regulate fission and fusion [21, 25]. Mitochondrial fission and fusion have been well documented in dividing cells, although as noted by Sadoshima and coworkers [21] “the continuous occurrence of mitochondrial fusion and fission has not been tracked in normal adult ventricular cardiomyocytes and, thus, their roles have been inferred based on pharmacological or genetic manipulation.” Although the levels of fission and fusion in a postmitotic cardiomyocyte appear to be low, there is clear evidence from genetic mouse models that the proteins involved in fission and fusion have important roles in cardiovascular physiology and pathology. Mitofusin 2 has been shown to be important in tethering the mitochondria to the SR [26]. The Dorn laboratory and the Walsh laboratory, have both made mice with ablation of mitofusin 2; they have contributed an insightful review on this topic highlighting the areas of agreement and those where the data differ and providing some possible explanations for the latter [25].

In addition to these state of the art review articles this special issue also contains several original research articles. [27–30]. Taken together this special issue provides up to date reviews as well as original research articles on some of the hottest topics in mitochondrial biology.

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Highlights:

Special issue provides reviews on mitochondria permeability transition pore

Special issue provides reviews on mitochondrial calcium homeostasis

Special issue provides reviews on mitochondrial dynamics

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