DISPATCH

Organelles: The Emerging Signalling Chart of Mitochondrial Dynamics

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Many molecular and functional details of single events in mitochondrial dynamics have been reported, but little is known about their coordination *(AU:OK?)*. A recent study describes how cellular Ca^{2+} signals, via remodelling the actin cytoskeleton, synchronise the formation of endoplasmic reticulum–mitochondria contacts with inner and outer mitochondrial membrane fission.

Our understanding of individual functional modules of mitochondrial dynamics, such as mitochondrial movement, mitochondrial shape and size (fusion and fission), and mitochondria–organelle interactions (i.e., with the endoplasmic reticulum, plasma membrane and lysosome), has increased massively during the last decade (Figure 1; for recent reviews see [1–3]). The overall picture is complex, but homeostasis in these modules is clearly an absolute requirement for normal cellular function, since perturbation of the system leads to altered cellular phenotypes, loss of function ***(AU: please clarify what you mean here by 'loss of function')*** and often results in cell death [3]. Intriguingly, recent discoveries have also led to the suggestion that the distinct modules are coordinated, so it has been anticipated that cellular signals co-regulate the individual functional elements underpinning mitochondrial dynamics.

The role of contacts between the endoplasmic reticulum (ER) and mitochondria in marking the sites of mitochondrial fission and in triggering the process was recently established, with these two modules thus co-regulating downstream events, such as the segregation and maintenance of mitochondrial DNA, which are required for long-term cellular energetic homeostasis [4]. Moreover, it has been proposed that the dynamics of ER–mitochondria contacts depend on mitochondrial motility, a process possibly involving the metazoan Miro GTPases and their yeast orthologue Gem1, which shows a genetic interaction with components of the ER–mitochondria encounter structure (ERMES) ***(AU:OK?)*** [5]. Importantly, Ca^{2+} transfer is a central component of ER–mitochondria interactions, and Ca^{2+} has been suggested to regulate the extent of the interaction surface, at least under stress conditions [6]. Similarly, Ca^{2+} also triggers fission of both the outer and inner mitochondrial membranes [3,7].

In addition, the role of the cytoskeleton as modulator of mitochondrial dynamics has been extensively mapped. The key functions of the microtubule network in metazoans and the actin cytoskeleton in yeast for mitochondrial movement and positioning are well documented [1,8]. Moreover, actin and myosin in mammalian cells have been repeatedly shown to participate in the fission process [9,10]. The role of Ca^{2+} in the mitochondrial matrix and in metabolism ***(AU: please clarify how the role of Ca^{2+} in metabolism relates to fission as it is not mentioned in the part of the sentence that follows the colon)*** has also been highlighted in this interaction: Ca^{2+} mediated constrictions of the inner mitochondrial membrane were shown to precede the completion of fission by the outer mitochondrial membrane]. However, how these complex interactions are coordinated by cellular signalling has not yet been shown.

Now, in a recent study, Chakrabarti *et al.* [11] have connected the dots, describing a signalling network by which Ca^{2+}, a global cellular signal, triggers a coordinated response involving all the functional modules of mitochondrial dynamics. Their key observation is that Ca^{2+} and the formin INF2 mediate actin polymerization on the ER surface that then expands the ER–mitochondria contact site ***(AU:OK?)***. Ca^{2+} mobilization from the ER was previously shown to trigger actin redistribution around mitochondria [12]. Strikingly, however, in the new work ***(AU:OK?)*** this mobilization is shown to be sufficiently fast to promote efficient Ca^{2+} transfer between the ER and mitochondria during Ca^{2+} transients, ensuring the activation of mitochondrial Ca^{2+} uptake through the mitochondrial Ca^{2+} uniporter complex. So far, a few examples of *in situ* dynamic regulation of ER–mitochondria contacts have been described [2,6], but such a coordinated regulation of different modules in mitochondrial dynamics has not been previously demonstrated. From the work by Chakrabarti *et al.* [11] ***(AU:OK?)***, actin nucleation on the ER emerges as a highly dynamic regulator of the contact sites, promoting fast Ca^{2+} accumulation in the mitochondria. To close the Ca^{2+}-mediated circuit, these authors also confirm that increased levels of Ca^{2+} in the matrix trigger inner mitochondrial membrane constrictions [7]. These precede and induce Drp1-dependent fission, which is also promoted by actin- and Ca^{2+}-dependent recruitment of Drp1 to the outer mitochondrial membrane from the cytoplasm (Figure 1) [10]. This view unveils actin and Ca^{2+} as central players in integrating mitochondrial fission and ER–mitochondria contact formation, through an intra-mitochondrial Ca^{2+}-mediated loop, to ensure complete fission of both mitochondrial membranes. This intriguing mechanism aligns well with the previously known roles of Ca^{2+} in the individual functional modules (Figure 1), but also raises a series of outstanding questions.

First, how does acute actin redistribution affect mitochondrial movement and overall positioning, and via what mechanism? ***(AU:OK?)*** Mitochondrial distribution in mammalian cells so far has been attributed to microtubule-associated motor activity, and inhibition of mitochondrial movement along microtubules by Ca^{2+} and reactive oxygen species has been shown to contribute to the positioning of these organelles [13]. On the other hand, the role of the actin network in mitochondrial distribution is critical in yeast [8,14] and is starting to be recognized also in metazoans [15], but the effect of Ca^{2+}-mediated actin redistribution on mitochondrial positioning remains to be established.

Second, actin redistribution, according to Chakrabarti *et al.* [11], is a critical factor regulating mitochondrial Ca^{2+} uptake. While mitochondrial shape has been previously proposed to affect Ca^{2+} uptake [16,17], the question now arises as to whether cell shape and the cytoskeleton also have a role in regulating the mitochondrial Ca^{2+} signal.

Finally, how actin dynamics contribute to stress-mediated expansion of ER–mitochondria contacts [6], increased Ca^{2+} transfer to mitochondria, and mitochondrial fission [18] remains to be determined. ER–mitochondrial Ca^{2+} transfer can result in either metabolic adaptation to stress [19] or cell death due to mitochondrial Ca^{2+} overload ***(AU:OK?)*** [6]. Thus, remodelling of the actin cytoskeleton can affect cell fate decisions, signalling either survival or death. Metabolic activity is required for Ca^{2+}- and actin-induced mitochondrial fragmentation [11], suggesting cooperation with the adaptive response to stress. However, fragmentation of the mitochondrial network and Drp1 recruitment have also often been associated with cell death [18], and changes in the fusion–fission balance interfere with metabolic function [20]. Most likely, answers to these unresolved issues are not too far away.

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Figure 1. Regulation of functional mitochondrial dynamics modules by the Ca^{2+}- and actin-mediated signalling pathway described by Chakrabarti *et al.* [11].

1, Ca^{2+}-mediated actin nucleation on the ER surface [9,11,12]; 1a, Ca^{2+}-mediated arrest of mitochondrial movements [13]; 2, actin-mediated extension of ER–mitochondria contacts and outer mitochondrial membrane fission [9–11]; 3, enhanced ER–mitochondrial Ca^{2+} transfer via the mitochondrial calcium uniporter [6,11]; 4, inner mitochondrial membrane fission mediated by mitochondrial matrix Ca^{2+} [7,11]; 5, coupling of inner and outer mitochondrial membrane fission [7,11]. ***J: what is the difference between the grey and black arrows? Please clarify what is denoted by the question marks.***