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Immune synapses: mitochondrial morphology matters

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Proper positioning of mitochondria is critical for cellular function. Mitochondria localization close to synapses regulates signalling at neuronal and immune synapses (ISs). Vice versa, synapses influence activity, motility and the fusion/fission balance of close-by mitochondria. In this issue of *The EMBO Journal*, Baixauli *et al* (2011) identify a role for the mitochondrial fission factor dynamin-related protein 1 (DRP1) at the IS. DRP1 not only controls mitochondrial fission but also mitochondrial positioning to the IS, thereby modulating IS formation and downstream signalling.

Main functions of mitochondria are energy supply, Ca^{2+} buffering, supply of metabolites and the sequestration of apoptotic factors (Hollenbeck and Saxton, 2005; Chan, 2006). It is not surprising that mitochondria thereby regulate a majority of cellular processes. In a simple model,

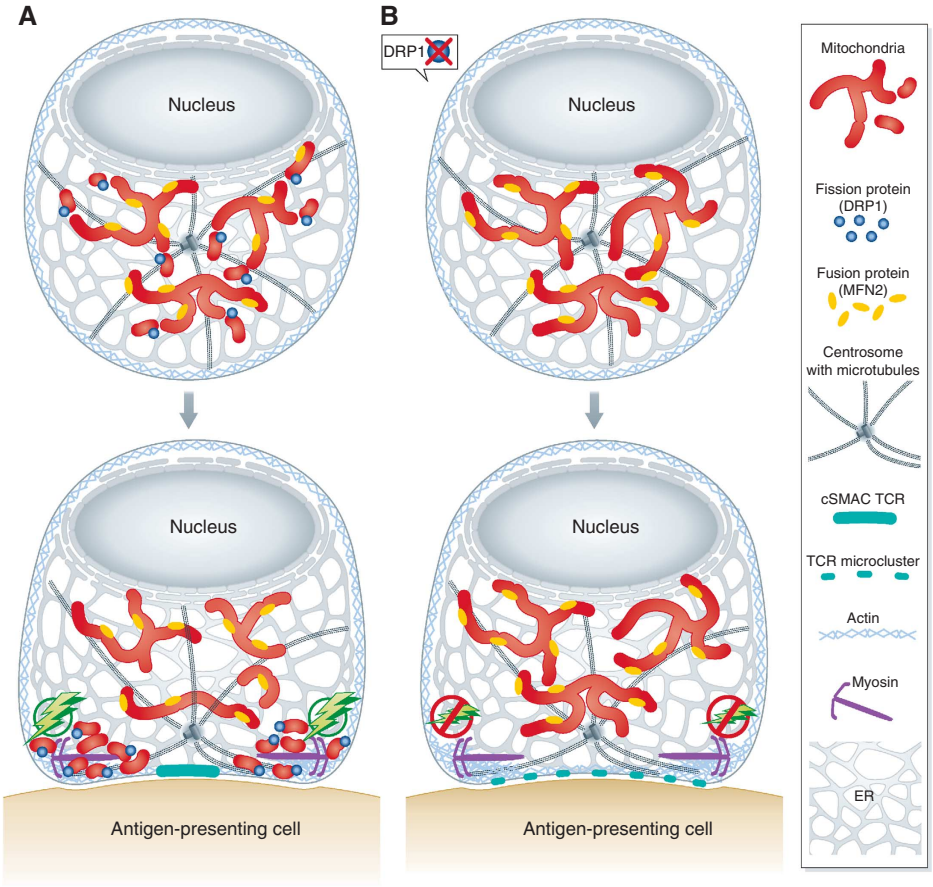

Figure 1 DRP1, mitochondrial localization and IS formation. (**A**) Balanced fusion/fission of mitochondria (red) by fusion (yellow, mitofusions, OPA1) and fission (blue, DRP1) proteins lead to a partly interconnected, partly single organelle structure. After IS formation with an antigen-presenting cell, mitochondria are transported towards the IS, probably passively by centrosome movement and actively along tubulin and actin filaments. They accumulate with actin at the pSMAC, where they provide proper energy supply for synaptic signalling including centripetal flux of TCR microclusters towards the cSMAC by myosin motors. (**B**) Inhibition of DRP1 induces unopposed fusion of mitochondria, which appear as interconnected network, partly tethered to the ER by mitofusins, and they cannot be transported as well to the pSMAC.

mitochondria constantly provide a sufficient amount of ATP for cellular processes. Considering diffusion of ATP, mitochondrial positioning within a spherical cell may be inconsequential. Such a simple model immediately fails in neuronal cells where soma and synaptic structures can be far from each other. It is obvious that, in the case that ATP is needed to fuel synaptic transmission, mitochondrial positioning must matter. Within the last 10 years, a tremendous amount of information about how mitochondrial morphology and positioning matter for cellular signal transduction has been obtained.

But how is positioning and morphology controlled? Motor-based transport of mitochondria along microtubules and actin filaments guides and controls their positioning in cells (Hollenbeck and Saxton, 2005). In addition, mitochondrial morphology constantly changes through balanced fusion and fission. These processes are regulated by GTPases influencing either fusion (mitofusins, OPA1) or fission (DRP1 with its receptor Fis1). Studies in *Drosophila melanogaster* and *Saccheromyces cerevisiae* have been instrumental in the identification of these GTPases and their functions: The role of DRP1 for fission was first discovered in the yeast mutant Dnm1 (Bleazard *et al*, 1999). Mitochondrial morphology changes are associated with developmental or neurodegenerative problems (Chan, 2006) and fusion/fission-dependent mitochondrial positioning is required for proper synapse functioning in neurons (Li *et al*, 2004) and muscle (Romanello *et al*, 2010).

In agreement with previous studies (Quintana *et al*, 2007; Contento *et al*, 2010), Baixauli *et al* (2011) report that mitochondria accumulate at the IS following T-cell stimulation. They advance this model further and show that the fission factor DRP1 regulates mitochondria positioning close to the peripheral supramolecular activation cluster (pSMAC; Figure 1A), which together with the central SMAC form the IS in T cells. Impairing DRP1 function leads to a decreased mitochondria distribution at the IS (Figure 1B), which impairs (local) ATP production. The associated mitochondria depolarization further limits energy supply. The consequences for the IS and its downstream signalling are drastic: the number of scattered CD3 microclusters outside of the central SMAC is increased because the ATP-dependent centripetal flux of these microclusters to the cSMAC by acto-myosin-dependent transport is decreased (Figure 1B). Because the microcluster flux to the cSMAC is required for downregulation of TCR at the IS (Lee *et al*, 2003), proximal TCR signalling and IL-2 production are increased, probably due to persistent TCR activity within the microclusters. In summary, the authors conclude that DRP1 modulates TCR signal strength at the IS.

Whereas the mechanism of how mitochondria influence neuronal and ISs is relatively straightforward (by local ATP production, local Ca^{2+} buffering and Ca^{2+} redistribution), the mechanisms of translocation and anchoring mitochondria at synapses appear to be complex. Baixauli *et al* (2011) speculate on how DRP1-mediated mitochondrial fission may facilitate mitochondrial redistribution and propose two possible explanations: (1) DRP1–mitochondria interaction exposes a dynein-binding site on DRP1. The dynein–DRP1 interaction enhances mitochondrial transport. (2) Dyneins (and potentially other motors) transport fragmented mitochondria more efficiently than larger networks.

Here, we explore the second hypothesis, which is in our opinion less speculative. From a physical point of view it is obvious that much more force is needed to move a larger mitochondrial network along microtubules or actin filaments compared with smaller fragmented mitochondrial organelles. In fact, to be efficiently moved, the mitochondria network appears to be separated into smaller organelles (Hollenbeck and Saxton, 2005). Tethering of mitochondria to the endoplasmic reticulum through mitofusin 2 (de Brito and Scorrano, 2008) further inhibits movement of a larger mitochondrial network. Balancing mitochondrial fusion by DRP1-dependent fission is thus necessary for sufficient mitochondrial fragmentation to secure transport and proper positioning at the IS (Figure 1). Repositioning of mitochondria to the IS is also dependent on LFA1-mediated adhesion as recently shown by Contento *et al* (2010), mostly due to actin accumulation at the pSMAC and centrosome reorientation towards the cSMAC.

TCR microclusters at the IS activate different signals including a large Ca^{2+} influx through the interaction of the ER Ca^{2+} sensor protein STIM1 and the Ca^{2+} channel ORAI1. Mitochondria buffer Ca^{2+} at the IS thereby avoiding premature inactivation of the Ca^{2+} channels (Quintana *et al*, 2007). Baixauli *et al* (2011) report increased global Ca^{2+} signals following DRP1 impairment. This phenotype may be caused by increased TCR signalling, an unopposedly fused mitochondrial network (which may enhance Ca^{2+} redistribution away from ORAI1 channels) or an increased apposition of mitochondria at the plasma membrane outside of the IS where they also control ORAI1 activity.

Ca^{2+} influx immobilizes mitochondria at the plasma membrane, potentially through interaction with the mitochondrial protein Miro, which is needed for kinesin-1-dependent mitochondrial transport through the adaptor protein milton (Wang and Schwarz, 2009). Considering the importance of the ER to activate Ca^{2+} influx and mitochondria to buffer Ca^{2+} influx, it is very interesting that mitofusin-2-dependent mitochondria–ER tethering also modulates trafficking of STIM1 to activate ORAI1 (Singaravelu *et al*, 2011). This finding further stresses the importance of the synapse–ER–mitochondria triangle to control Ca^{2+}-dependent T-cell activation (Kummerow *et al*, 2009).

Ca^{2+} import through the mitochondrial uniporter not only prevents ORAI1 inactivation but also helps to increase ATP production by activating mitochondrial dehydrogenases. The increased ATP levels at the IS are needed for energy-consuming signalling at the IS but they are also needed for the centripetal flux of TCR to the cSMAC, which is important for the termination of TCR signals by internalization and degradation (Lee *et al*, 2003). Thus, mitochondria strengthen but also terminate IS signalling. In this way they conform to a general principle of biology that the activation of a signal often also produces a delayed negative feedback mechanism to inhibit the very same signal.

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Conflict of interest

The authors declare that they have no conflict of interest.

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