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Fis1, Bap31 and the kiss of death between mitochondria and endoplasmic reticulum

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Dynamic structural and functional liaisons between mitochondria and the endoplasmic reticulum (ER) support a wide range of cell functions, including the ability of the cell to kill itself by apoptosis. A new study in this issue of *The EMBO Journal* sheds light on how these interactions regulate Bax/Bak-driven cell death within the complex milieu of the cell, suggesting that mitochondria–ER dynamics can involve an unanticipated two-way communication in cell death, from mitochondria to ER and back again.

Much of our knowledge on apoptosis induction in higher organisms, which revolves around mitochondria and pro-apoptotic Bcl-2 family members such as Bax or Bak, has derived from reconstitution studies using biochemical and genetically defined systems. These studies revealed step-wise activation of Bax/Bak in the mitochondrial outer membrane by activator BH3-only proteins, regulated by prosurvival Bcl-2 family proteins as well as by sensitizing BH3-only proteins. In the complex environment of the intact cell, however, where the potential for competing reactions is enormous, the question of efficiencies and specificities takes precedence. As a consequence, there exists a large array of supporting players to ensure rapid and orderly cell demise by the Bax/Bak mechanism. Not surprisingly, many of these supporting roles involve mitochondrial biology—in particular, mitochondrial fusion/fission dynamics as well as the close physical and functional relationship of the mitochondrion with the ER, where all three subgroups of the Bcl-2 family also reside (Suen *et al*, 2008; Rizzuto *et al*, 2009; de Brito and Scorrano, 2010). A major challenge is to understand how mitochondrial dynamics and privileged ER communication translate into optimal Bax/Bak-dependent mitochondrial outer membrane permeabilization, proapoptotic cytochrome c release, and subsequent activation of downstream executioner caspases. Stefan Grimm and colleagues now shed new light on the complex crosstalk between the two organelles during apoptosis, by documenting the interaction between ER-localized Bap31 and Fis1 at the mitochondrial outer membrane (Iwasawa *et al*, 2011) (see Figure 1).

In response to apoptosis-inducing physiological stress stimuli, multiple proteins are engaged to exploit the mitochondria–ER dynamics axis. Fas stimulation, for example, activates procaspase-8, which results in the cleavage of a limited number of target proteins. These targets include Bid, a potent direct activator of Bax/Bak, as well as the integral polytopic ER membrane protein Bap31, whose cytosolic tail is cleaved by caspase-8 to generate proapoptotic p20Bap31 (Ng *et al*, 1997). Bap31 is an ER protein sorting factor proposed to escort integral membrane client proteins from their biogenesis site at the Sec61 translocon to other ER complexes that determine their fate in the ER, such as retro-translocation via the Derlin1 complex for delivery to the proteasome (Wang *et al*, 2008). In addition to interfering with Bap31-mediated protein trafficking at various levels, p20 causes a rapid transmission of ER calcium signals to mitochondria via the IP3 receptor complex conduit at close ER–mitochondria junctions (Rizzuto *et al*, 2009); in mitochondria, these Ca^{2+} signals stimulate DRP1-dependent

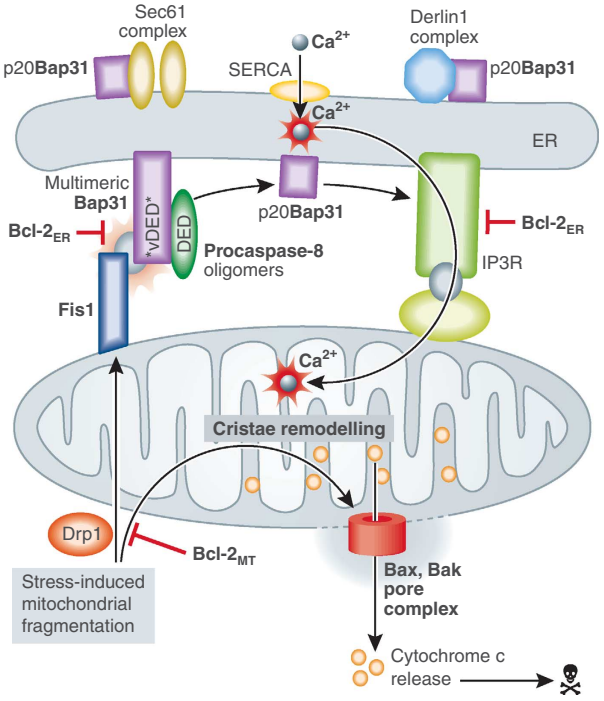

Figure 1 Model for the involvement of the Fis1/Bap31/procaspase-8 platform in Bax/Bak-mediated permeabilization of the mitochondrial outer membrane. Additional opportunities for regulation involve prosurvival members of the Bcl-2 family operating at the ER, as well as other targets of p20Bap31 that might influence the ER membrane protein trafficking machinery.

organelle fission and cytochrome c release (Breckenridge *et al*, 2003), the latter through an indirect influence on cristae remodelling, mobilizing intra-cristae cytochrome c stores (Germain *et al*, 2005; de Brito and Scorrano, 2010). The importance of this pathway is underscored by the fact that expression of a non-cleavable mutant of Bap31 at the ER prevents Fas-induced release of cytochrome c from mitochondria, despite activation of endogenous Bid (Nguyen *et al*, 2000; Breckenridge *et al*, 2003).

The involvement of the mitochondrial fission–fusion machinery also extends to the structural interactions between the ER and mitochondria. The outer membrane fusion protein mitofusin 2 (Mfn2) docks with ER derivatives of Mfn1 and Mfn2 at specialized ER–mitochondrion contact sites that harbour much of the machinery underlying the multiple biochemical transactions between these organelles (de Brito and Scorrano, 2010). Iwasawa *et al* (2011) now provide evidence that the outer membrane fission protein Fis1, which has also been implicated in apoptosis, can make physical contact with ER-localized Bap31, possibly through direct interaction or in the context of a larger complex. These findings are thus significant as they open the possibility for bi-directional communication between the two organelles to support cell death. In the case of Fas signalling, activated caspase-8 transmits parallel pathways to the ER and mitochondria, with Ca^{2+} transmission being the relevant ER output. But what about stress stimuli that largely impinge on mitochondria? Is there a way to elicit a feedback ER contribution? First evidence supporting this notion came from studies by Scorrano and colleagues, who showed that cell death induced by Fis1 over-expression required ER Ca^{2+} transmission; in the absence of Bax/Bak, this led to protracted and toxic mitochondrial Ca^{2+} overload (Alirol *et al*, 2006). Iwasawa *et al* (2011) now extend this finding by suggesting that the Fis1/Bap31 complex constitutes a platform for recruiting procaspase-8 in response to death stimuli such as etoposide or actinomycin D that depend on Fis1 for cytotoxicity. The cytosolic domain of Bap31 contains a variant of the death effector domain (DED) (Ng *et al*, 1997), known for its function in procaspase-8 recruitment to death receptor oligomers. Bap31 is also typically multimeric in the ER membrane, and has previously been shown to interact with both canonical procaspase-8 and the procaspase-8L isoform (Ng *et al*, 1997; Breckenridge *et al*, 2002). The new study finds pre-formed Fis1–Bap31 complexes to recruit procaspase-8 in response to both ectopic Fis1 expression or stress induced by etoposide or actinimycin D, dependent on the Bap31 variant DED domain. Subsequently, active caspase-8 is required to cleave Bap31, which then stimulates release of ER Ca^{2+}. Two scenarios can then be envisaged. If a parallel pathway is concurrently causing the activation of mitochondrial Bax and Bak, then the elevation of Ca^{2+} levels in the cytosol and within mitochondria may activate pathways that support cytochrome c release (such as mitochondrial cristae remodelling). In the absence of such parallel Bax/Bak-activating pathways, however, the protracted loss of Ca^{2+} homeostasis and stress caused by mitochondrial Ca^{2+} overload may itself activate Bax/Bak, or stimulate non-apoptotic death pathways. Furthermore, ER calcium homeostasis and Bap31/procaspase-8 complexes are targets of anti-apoptotic Bcl-2 at the ER. By uncovering the Fis1–Bap31 connection, mitochondria–ER dynamics just got a lot more intimate.

Conflict of interest

The authors declare that they have no conflict of interest.

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