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Review

Mitochondrial alterations in apoptosis

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ABSTRACT

Besides their conventional role as energy suppliers for the cell, mitochondria in vertebrates are active regulators of apoptosis. They release apoptotic factors from the intermembrane space into the cytosol through a mechanism that involves the Bcl-2 protein family, mediating permeabilization of the outer mitochondrial membrane. Associated with this event, a number of additional changes affect mitochondria during apoptosis. They include loss of important mitochondrial functions, such as the ability to maintain calcium homeostasis and to generate ATP, as well as mitochondrial fragmentation and cristae remodeling. Moreover, the lipidic component of mitochondrial membranes undergoes important alterations in composition and distribution, which have turned out to be relevant regulatory events for the proteins involved in apoptotic mitochondrial damage.

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Abbreviations: CL, cardiolipin; Drp1, dynamin-related protein 1; ER, endoplasmic reticulum; GTPase, guanosine triphosphatases; Mfn, mitofusin; MIM, mitochondrial inner membrane; MOM, mitochondrial outer membrane; MOMP, mitochondrial outer membrane permeabilization; MPTP, mitochondrial permeability transition pores; mtDNA, mitochondrial DNA; NAO, 10-N-nonyl acridine orange; PA, phosphatidic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; ROS, reactive oxygen species; VDAC, voltage-dependent anion channel.

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1. Introduction: mitochondrial regulation of apoptosis

Mitochondria are organelles that play an essential role in the life and death of the cell. Their importance is mainly attributed to energy production in the form of ATP, but they are also involved in pathogenetic mechanisms leading to neurodegenerative diseases (e.g. autosomal dominant optic atrophy, Parkinson, Charcot-Marie-Tooth, Alzheimer (Green, 2004; Knott et al., 2008) and cancer (Green, 2004; Juin et al., 2013)).

Mitochondria are believed to originate from prokaryotic cells that invaded mammalian cells resulting in symbiosis. They are located in the cytosol and have different shapes, tubular or vesicular, with sizes ranging between 1 and 10 μm in length, depending on the cell type. These organelles are surrounded by a double membrane system, the mitochondrial outer and inner membranes (MOM and MIM, respectively), which differ in morphology and lipid composition (reviewed in Horvath and Daum, 2013). The MIM is folded into invaginations called cristae, which contain proteins involved in important mitochondrial functions, such as cytochrome c (Ow et al., 2008), and is rich in the anionic phospholipid cardiolipin (CL), which in eukaryotic cells is exclusively found in mitochondria. The MOM, instead, is smooth and the CL content is reduced compared to the MIM (Ardail et al., 1990). On the other hand, the MOM is fluid and permeable to small polar molecules (up to 3–5 KDa) due to the presence of protein transmembrane channels, while the MIM has restricted metabolite permeability.

In healthy conditions, mitochondria participate in important metabolic pathways, the most prominent being the production of energy by generating an electrochemical potential used to drive oxidative phosphorylation of ADP to ATP. Another key aspect of healthy mitochondria is their dynamic morphology. The regulated combination of mitochondrial fission and fusion determine the shape and number of mitochondria in the cell. In addition, these processes are important to preserve the health of the mitochondrial network by segregating damaged mitochondria (fission) or sharing and distributing damaged components (fusion) (Youle and van der Bliek, 2012). A dysfunction in the mechanisms that controls mitochondrial networks is an early step in neurodegeneration (Knott et al., 2008).

Under apoptotic stimuli, mitochondria undergo dramatic changes in their structure and function (Suen et al., 2008; Martinou and Youle, 2011; Ugarte-Uribe and Garcia-Saez, 2013). While this aspect is valid for both invertebrates and vertebrates, only in the latter mitochondria actively contribute to cell death by taking part in the so-called intrinsic pathway of apoptosis. The mitochondrial pathway of apoptosis is regulated by the Bcl-2 family of proteins by inducing mitochondrial outer membrane permeabilization (MOMP) (García-Sáez et al., 2010; Shamas-Din et al., 2013a,b). Pore formation in the membrane allows the release of cytochrome c and other apoptotic factors from the inter-membrane space into the cytosol, which activate caspases and induce cell death (Wei, 2001). The dysregulation of this mitochondrial function has an important role in tumorigenesis and in the cellular responses to anti-cancer therapies (Juin et al., 2013; Czabotar et al., 2014).

Associated to MOMP, many other alterations of mitochondria occur during apoptosis. These include lipid transfer between mitochondria and other organelles (Hoppins and Nunnari, 2012) as well as between the MIM and the MOM (Kagan et al., 2005), loss of mitochondrial functions, such as loss of the transmembrane potential required to drive oxidative phosphorylation, and loss of the ability to maintain calcium homeostasis (Wang, 2001; Green, 2004). In addition, fragmentation of mitochondria and cristae remodeling constantly coincide with MOMP (Suen et al., 2008; Wasilewski and Scorrano, 2009; Martinou and Youle, 2011; Ugarte-Uribe and Garcia-Saez, 2013). Here, we present an overview of the different alterations in mitochondria morphology and functionality during apoptosis (Fig. 1 and Table 1). We review the recent understanding of the mechanisms that induce mitochondrial damages and discuss the relevance of lipids in executing these processes, which finally lead to cell death. In addition we discuss the influence of each process on the others, providing a network (Fig. 2) which reports some links so far never reviewed in the literature.

2. Lipids and apoptosis: changes in the mitochondrial membrane composition and lipid distribution

Mitochondria have a complex membrane structure, due to the presence of two distinct bilayers. The lipid composition in each membrane is highly characteristic and differs between the outer and the inner membranes. The smooth mitochondrial outer membrane of most mammalian cells is mainly rich in phosphatidylcholine (PC), phosphatidylethanolamine (PE) and phosphatidylinositol (PI) and presents relatively small amounts of phosphatidylserine (PS) and CL (<1–10 mol%) (Colbeau et al., 1971; Hovius et al., 1993; de Kroon et al., 1997). In contrast, the highly folded MIM, is enriched in non-bilayer forming lipids, like CL (14–23 mol%) and PE (Colbeau et al., 1971; de Kroon et al., 1997).

MIM and MOM communicate with each other by formation of contact sites. It has been speculated that these contact sites enhance the exchange of lipids and proteins between the two mitochondrial membranes (Reichert and Neupert, 2002). In addition, these sites, being particularly rich in non-lamellar lipids CL and PE, may form hexagonal H_{II} structures (van Venetië and Verkleij, 1982; Aguilar et al., 1999; Unsay et al., 2013) and may provide a suitable place for the targeting of Bcl-2 proteins to the mitochondrial membrane (Lutter et al., 2000; Gonzalvez et al., 2005). Although the existence of contact sites has been debated for a long time, new evidence implicates the presence of specific proteins, or complexes of proteins, in their formation (Maniti et al., 2009; Harner et al., 2011). Nevertheless, the exact mechanisms involved in such process are not yet understood.

The lipid distribution within the two membranes is not arbitrary but rather organized for supporting specific mitochondrial functions (Claypool and Koehler, 2012; Horvath and Daum, 2013; Tatsuta et al., 2013). PE and CL, for example, associate with the TOM and SAM protein complexes to promote the insertion of proteins in a particular orientation into the MOM (Gebert et al., 2009; Becker et al., 2013). In addition, CL in the outer and inner membranes associates with several proteins of the apoptotic machinery (Schug and Gottlieb, 2009; Crimi and Esposti, 2011): it promotes caspase-8 translocation (Gonzalvez et al., 2008) and the targeting of Bcl2 proteins (Lutter et al., 2000; Kuwana et al., 2002) to the MOM. Also, reduced levels of CL affect the binding of cytocrome c to the MIM and its oxidation promotes the release of this protein from the inter-membrane space (Ott et al., 2002; Kagan et al., 2005).