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Review

Intracellular Ca^{2+} signaling and Ca^{2+} microdomains in the control of cell survival, apoptosis and autophagy

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ABSTRACT

The endoplasmic reticulum (ER), mitochondria and lysosomes are physically and/or functionally linked, establishing close contact sites between these organelles. As a consequence, Ca^{2+} release events from the ER, the major intracellular Ca^{2+}-storage organelle, have an immediate effect on the physiological function of mitochondria and lysosomes. Also, the lysosomes can act as a Ca^{2+} source for Ca^{2+} release into the cytosol, thereby influencing ER-based Ca^{2+} signaling. Given the important role for mitochondria and lysosomes in cell survival, cell death and cell adaptation processes, it has become increasingly clear that Ca^{2+} signals from or towards these organelles impact these processes. In this review, we discuss the most recent insights in the emerging role of Ca^{2+} signaling in cellular survival by controlling basal mitochondrial bioenergetics and by regulating apoptosis, a mitochondrial process, and autophagy, a lysosomal process, in response to cell damage and cell stress.

Contents

Abbreviations: AMBRA1, autophagy/Beclin 1 regulator 1; AMPK, AMP-activated kinase; ATF4, activating transcription factor-4; Atg, autophagy-related; BIRD-2, Bcl-2/IP_3R disruptor-2; CREB, cAMP response element-binding protein; ER, endoplasmic reticulum; ERMES, ER mitochondria encounter structure; ETC, electron-transport chain; GRP75, glucose-regulated protein 75; GSK3β, glycogen synthase kinase-3β; IDH, isocitrate dehydrogenase; IP_3, inositol 1,4,5-trisphosphate; IP_3R, IP_3 receptor; αKGDH, α-ketoglutarate dehydrogenase; LC3, microtubule-associated protein light chain 3; LRRK2, leucine-rich repeat kinase 2; MAM, mitochondria-associated membrane; MCU, mitochondrial Ca^{2+} uniporter; MEF, mouse embryonic fibroblast; Mfn, mitofusin; mPTP, mitochondrial permeabilization transition pore; mTORC1, mammalian or mechanistic target of rapamycin complex 1; NAADP, nicotinic acid adenine dinucleotide phosphate; NFAT, nuclear factor of activated T cells; PDH, pyruvate dehydrogenase; PERK, protein kinase RNA-like ER kinase; PML, promyelocytic leukemia; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; RyR, ryanodine receptor; SDH, succinate dehydrogenase; SERCA, sarco-/endoplasmic Ca^{2+}-ATPase; TCA, tricarboxylic acid; TFEB, transcription factor EB; TMBIM, transmembrane Bax inhibitor motif; TPC2, two-pore channel 2; TRP, transient receptor potential; ULK1/2, Atg1/Unc-51-like kinase 1/2; UPR, unfolded protein response; VDAC, voltage-dependent anion channel.

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1. Introduction

Complex spatio-temporal Ca^{2+} signals regulate many fundamental cellular processes including fertilization, differentiation, proliferation, secretion, metabolism, gene expression, contraction, learning and memory, etc. [1–3]. Moreover, intracellular Ca^{2+} plays multiple roles in the induction or regulation of processes related to cell survival and cell death. Intracellular Ca^{2+} is since long recognized as a factor contributing in an important way to various cell death modalities as necrosis, apoptosis, and anoikis [4]. Recent results also propose a role of Ca^{2+} in necroptosis [5,6]. Finally, in the last years evidence is accumulating for a role of intracellular Ca^{2+} in autophagy [7–10]. Autophagy is essentially a survival process but can, under persistent stress conditions, lead to the demise of the cell.

The endoplasmic reticulum (ER) is the main Ca^{2+}-storage organelle and therefore plays a central role in intracellular Ca^{2+} signaling. Ca^{2+} handling by the ER essentially depends on the Ca^{2+}-uptake activity of the sarco-/endoplasmic Ca^{2+}-ATPases (SERCA) [11], the expression of luminal Ca^{2+}-binding proteins [12] and the nature and the activity of Ca^{2+}-release channels. Besides passive Ca^{2+} leak through basal ER Ca^{2+}-leak channels (see Section 2.3), Ca^{2+} release out of the ER predominantly occurs via the inositol 1,4,5-trisphosphate (IP_3) receptor (IP_3R) [3,13–15] and the ryanodine receptor (RyR) [16–18]. Especially the role of the IP_3R and of IP_3-induced Ca^{2+} release has been recognized in both apoptosis [19,20] and autophagy [21,22].

During the last years, it has become increasingly clear that Ca^{2+} handling by other organelles, and especially by the mitochondria and the lysosomes, plays an important role in the regulation of apoptosis and autophagy. It is well established that mitochondria exist in close apposition to the ER, allowing for a privileged Ca^{2+} transfer from the ER to the mitochondria via successively the IP_3R and the voltage-dependent anion channels (VDACs) [23,24]. Many proteins are expressed at the mitochondria-associated membranes (MAMs) (see Section 2.2), which are the part of the ER making close connections with the mitochondria, and that are therefore involved in the exchange of Ca^{2+}, reactive oxygen species (ROS) and lipids between ER and mitochondria. These locations also determine mitochondrial fission and inflammasome formation and provide membranes for autophagy [25–29]. The Ca^{2+} microdomain between ER and mitochondria and the amount of Ca^{2+} transferred to the mitochondria is critical for determining the occurrence of apoptosis or autophagy [7,29–31].

Ca^{2+} release by lysosomes has also been implicated in the autophagy process [32–36]. As recent evidence indicates a close apposition of ER and lysosomes [37] and their functional interaction at the level of Ca^{2+} handling [37–40], the concept of a Ca^{2+} microdomain at the ER-lysosome interface that can drive and/or shape complex Ca^{2+} signals was proposed [41]. Moreover, such microdomains would be ideally localized to control the autophagy process, which in most cases exactly occur at the interface between ER and lysosomes [22].

Importantly, recent research has led to the identification of several Ca^{2+} transporters in those organelles, advancing our understanding of the regulation by Ca^{2+} of key steps in apoptosis and autophagy. Hence, the mitochondrial Ca^{2+} uniporter (MCU) has been identified as the key transporter responsible for the rate-limiting transfer of Ca^{2+} across the inner mitochondrial membrane [42,43] as well as several of its regulators [44]. Moreover, the mitochondrial permeabilization transition pore (mPTP) has been identified as dimers of the F-ATP synthase [45–48]. Finally, although the lysosomal Ca^{2+}-uptake mechanism still remains unknown, the two-pore channel 2 (TPC2) emerged as the main lysosomal nicotinic acid adenine dinucleotide phosphate (NAADP)-sensitive Ca^{2+}-release channel [49–52].

This review will therefore focus on the newest findings explaining how intracellular Ca^{2+}, and especially the Ca^{2+} ions at the ER-mitochondrial and the ER-lysosomal interface, regulate cell survival and cell death.

2. Ca^{2+} signaling from the ER impacts mitochondrial function, controlling cell death and survival

Ca^{2+} signaling from the ER critically controls cell death and survival by impacting the mitochondria [30,53]. The ER-located IP_3Rs and the outer mitochondrial membrane-localized VDAC1 can be physically linked through chaperones like glucose-regulated protein 75 (GRP75) [54]. As such, these tethers establish an efficient Ca^{2+}-signaling domain between ER and mitochondria, enabling "quasi-synaptic" Ca^{2+} transfer between both compartments [24]. This structural organization overcomes the inherent low-affinity properties of the MCU, the Ca^{2+}-transport system located at the inner mitochondrial membrane [53]. In part, this is the consequence of the high local [Ca^{2+}] (in the range of 10–20 μM) that is observed in the ER-mitochondrial interspace compared to the bulk cytosolic [Ca^{2+}], which after cell stimulation typically does not exceed a few μM [23,55–57]. Thus, through these microdomains, even low-level Ca^{2+} signals could affect mitochondrial processes. Moreover, intracellular Ca^{2+} can impact the mitochondria in a dichotomous manner, thereby favoring both cell survival and cell death, dependently on the characteristics of the Ca^{2+} signals involved.

2.1. Basal Ca^{2+} -signaling events controlling cell survival

Basal Ca^{2+}-signaling events occurring along the ER-mitochondrial axis mostly via IP_3R-mediated oscillatory patterns drive mitochondrial bioenergetics, in particular by enhancing the activity of key enzymes involved in the tricarboxylic acid (TCA) cycle, pyruvate dehydrogenase (PDH), isocitrate dehydrogenase (IDH) and α-ketoglutarate dehydrogenase (αKGDH) [53]. Recent evidence indicates a high robustness of the mitochondrial metabolism towards its regulation by Ca^{2+} oscillations [58]. Adequate TCA-cycle progression will result in enhanced production of NADH, which is used by the electron-transport chain (ETC) complexes to build up H^+ gradients across the inner mitochondrial membrane that are used to drive ATP production via the F-ATP synthase (Fig. 1A). A comparison of the metabolism between wild-type DT40 cells and DT40 cells devoid of IP_3Rs (the so-called triple knockout cells) indicated that the latter had a very different basic energy metabolism, with an increased Warburg effect and an increased ROS production that appears to account for their reduced proliferation [59]. In non-tumor cells, interfering with the constitutive Ca^{2+} transfer to the mitochondria by inhibiting IP_3Rs impairs ATP production, leading to the activation of AMP-activated kinase (AMPK) and a subsequent increase in basal autophagic flux as a compensatory pro-survival response [60] (see Section 3.3). However, this effect might be strongly dependent on growth conditions as ablation of IP_3Rs in DT40 cells did increase AMPK activity in one study [60] but not in another [59]. In tumor cells, however, IP_3Rs are essential for cell survival by delivering an adequate Ca^{2+} supply to the mitochondrial matrix to sustain its metabolism [61,62]. The mitochondrial TCA cycle is used to produce mitochondrial substrates that serve for anabolic processes, like nucleotide production, underlying cell growth and proliferation. Non-tumorigenic cells slow down their proliferation when mitochondrial metabolism becomes compromised, like upon IP_3R inhibition. However, tumor cells appear to proliferate in an uncontrolled manner irrespective of the energy status of the mitochondria. Therefore in those cells, although IP_3R inhibition

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