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Review

Interorganellar calcium signaling in the regulation of cell metabolism: A cancer perspective

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ABSTRACT

Organelles were originally considered to be individual cellular compartments with a defined organization and function. However, recent studies revealed that organelles deeply communicate within each other via Ca^{2+} exchange. This communication, mediated by specialized membrane regions in close apposition between two organelles, regulate cellular functions, including metabolism and cell fate decisions. Advances in microscopy techniques, molecular biology and biochemistry have increased our understanding of these interorganelle platforms. Research findings suggest that interorganellar Ca^{2+} signaling, which is altered in cancer, influences tumorigenesis and tumor progression by controlling cell death programs and metabolism.

Here, we summarize the available data on the existence and composition of interorganelle platforms connecting the endoplasmic reticulum with mitochondria, the plasma membrane, or endolysosomes. Finally, we provide a timely overview of the potential function of interorganellar Ca^{2+} signaling in maintaining cellular homeostasis.

1. Introduction

Intracellular communication among cellular compartments is carried out by specialized molecular hubs, which are frequently situated in specific membrane domains, to regulate important cellular processes, including metabolism. For example, Ca^{2+} communication between organelles is a widespread phenomenon that involves many, if not all, organelles [1].

Interorganellar Ca^{2+} signaling is a dynamic process used by cells to decode extracellular signals and respond to energy requirements or to adapt to stress in a spatiotemporal fashion. This precise process relies on different protein entities, some of which are unknown, depending on the organelles involved.

Under resting conditions, the cytosolic Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$) is maintained at approximately 100 nM; some organelles, such as the endoplasmic reticulum (ER) and Golgi apparatus, act as intracellular Ca^{2+} stores, accumulating cation concentrations on the order of hundreds of μM [2]. The extensive membranous network of the ER includes multiple sites in close proximity to the plasma membrane (PM) to facilitate luminal Ca^{2+} refilling through store-operated Ca^{2+} entry (SOCE) channels and the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA) pumps [3,4]. This process is regulated at the ER-PM platform by stromal interaction molecule 1 (STIM1), an ER transmembrane protein that senses the intraluminal Ca^{2+} level and recruits the PM Ca^{2+} channel protein ORAI1, leading to Ca^{2+} refilling in the ER [5] (Fig. 1). Additionally, Ca^{2+} signaling to endolysosomes may be generated by juxtaposition with the ER (Fig. 1). An intimate relationship exists between the ER and endosomal system to initiate Ca^{2+} signaling or to store and buffer the released Ca^{2+}. Endolysosomes are connected to other organelles, such as mitochondria, the PM and the Golgi apparatus. At these contact sites, not only Ca^{2+} is exchanged but also lipids (particularly cholesterol) and free radicals are transferred

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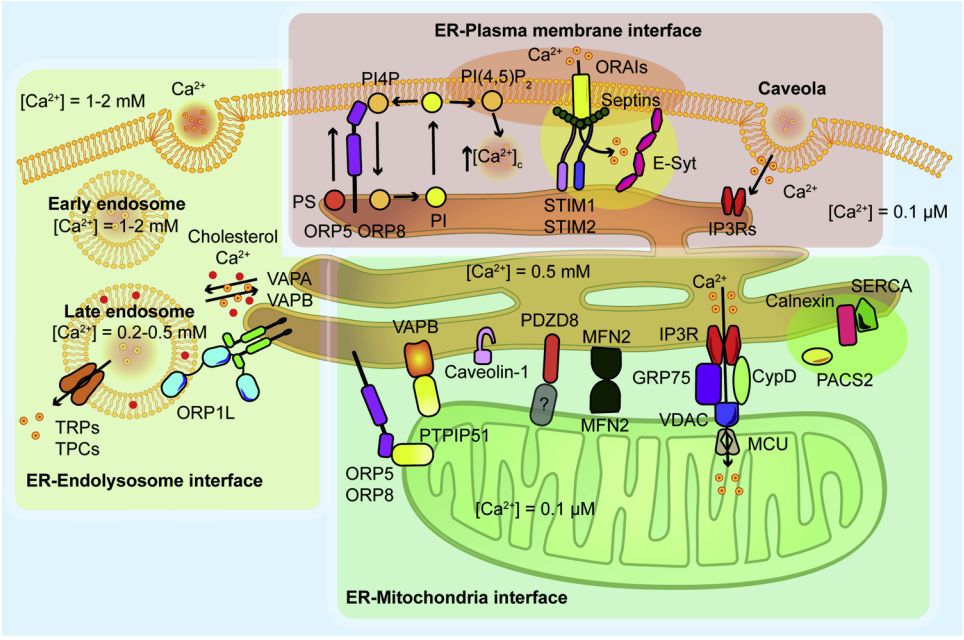

Fig. 1. Description of Ca^{2+} transfer between different organelles by different Ca^{2+} effectors and their interactors in the modulation of interorganelle tethering. The circled groups of proteins have mutual regulatory activity. CypD, cyclophilin D; E-Syt, extended-synaptotagmin; GRP75, mortalin; IP3R, inositol 1,4,5-trisphosphate receptor; MCU, mitochondrial Ca^{2+} uniporter; MFN2, mitofusin 2; ORAIs, Ca^{2+} release-activated Ca^{2+} channel proteins; ORP, oxysterol-binding protein; PACS-2, phosphofurin acidic cluster sorting protein 2; PDZD8, PDZ domain-containing protein 8; PI4P, phosphatidylinositol 4-phosphate; PS, phosphatidylserine; PI, phosphatidylinositol; PI(4,5)P2, phosphatidylinositol 4,5-bisphosphate; PTPIP51, phosphatase-interacting protein 51; SERCA, sarco/endoplasmatic reticulum Ca^{2+} ATPase; STIM1, stromal interaction molecule 1; STIM2, stromal interaction molecule 2; TPCs, two-pore channels; TRPs, transient receptor potential channels; VAPA, vesicle-associated membrane protein-associated protein A; VAPB, vesicle-associated membrane protein-associated protein B; VDAC, voltage-dependent anion channel.

between the organelles as messengers.

Adequate Ca^{2+} transfer between cellular compartments requires a proper tether; for the PM, transfer is supported by caveolar lipid rafts, which are cellular invaginations 50–100 nm deep that form a spatial link between two membranes to facilitate interactions between these two structures [4]. The importance of caveolae in Ca^{2+} signaling is confirmed by the strategic localization of pivotal Ca^{2+} effectors, such as SOCE channels, PM Ca^{2+} ATPase pumps and inositol 1,4,5-trisphosphate (IP_3) receptor (IP3R)-like proteins, and by the existence of specific Ca^{2+}microdomains in the lumina of caveolae, which provide a platform for the assembly of diverse Ca^{2+} signaling complexes [6–9]. Transient increases in the $[Ca^{2+}]_{cyt}$ occur through Ca^{2+} release from the ER via IP3Rs or ryanodine receptors and by the entry of Ca^{2+} from the extracellular space. The ER-mitochondria interface is a specialized membrane domain called the mitochondrial-associated membrane (MAM) and is the location of Ca^{2+} transfer from the ER to mitochondria [10] (Fig. 1). Ions released by IP3Rs cross the outer mitochondrial membrane (OMM) via the voltage-dependent anion channel (VDAC) to enter the mitochondrial matrix through the mitochondrial Ca^{2+} uniporter (MCU) complex. This selective Ca^{2+} channel in the inner mitochondrial membrane (IMM) and the mitochondrial membrane potential ($\Delta\Psi_m$), the driving force for Ca^{2+} accumulation, play a fundamental role in shaping mitochondrial Ca^{2+} signaling and in controlling aerobic metabolism as well as cell death [11,12].

In this review, we focus on interorganelle platforms that operate Ca^{2+} transfer involving the ER. We review the mechanisms by which these platforms control the interorganellar Ca^{2+} distribution to regulate cell metabolism and the ways in which they are linked to the development of tumors.

2. Structural and functional features of interorganellar coupling

Advances in imaging technologies and/or isolate membrane contact sites in living cells have permitted partial identification of the molecular identity and activities of proteins residing within these intimate regions. In addition to the molecular determinants, pivotal structural features such as the frequency of organelle contact, the spacing between both organelles and the size of the contact region must be considered. These parameters, which differ among cells, are extremely variable and strictly dependent on the functional context.

The ER is the most interconnected cellular organelle, and mediating its resident proteins may allow them to contact their partners on other organelles to generate interorganellar coupling, through which Ca^{2+} can be exchanged. These interconnections are discussed individually in this section, and the principal features are highlighted.

2.1. ER-mitochondria interface

The first evidence of an interaction between the ER and mitochondria was obtained using electron microscopy in 1959, but this interaction was long considered an artifact [13]. The ER-mitochondria interface was isolated in 1990, and further experimental approaches have confirmed the physical proximity and functionality of ER-mitochondrial coupling [14–16].

The distance between these two membranes is 10–30 nm [17], and only approximately 10% of the mitochondrial surface is in direct contact with the ER [15]. The transfer of Ca^{2+} from the ER to mitochondria is optimal at a distance of 15 nm [18], although MAMs are dynamic structures, and the distance and the amount of mitochondria involved varies between cellular and functional contexts. Whether all ER-mitochondrial coupling connections have the same protein composition is unclear, but high-resolution electron tomography has shown the presence of physical linkers [19], and the protein interactions between ER and mitochondria can result in a tethering complex. To date, three proteomics studies have been performed to analyze the protein composition of MAM fraction [20–22]. Initially, in NG108/105 cells, the authors identified 250 proteins in MAMs but 991 proteins were modulated in MAMs in human fibroblasts after infection. In addition, Sala-Vila et al. reported that caveolin-1 (cav1), which enhances Ca^{2+} uptake into mitochondria to promote its tumor suppressor activity, is an important component of this domain [23]. These studies suggest that several proteins are involved in the formation and/or stabilization of ER-mitochondrial coupling; furthermore, modulating the expression of specific proteins in MAMs seems to be sufficient to destabilize this interaction.

The molecular identity of ER-mitochondrial tethering is well defined in yeast; an elegant genetic screen identified the ER-mitochondria encounter structure (ERMES) and, subsequently, the ER membrane complex (EMC) [24]. The ERMES complex tethers ER to mitochondria, forming approximately two to ten foci per yeast cell, while the EMC complex interacts with the mitochondrial protein Tom5, forming a tether between the two organelles [25].

The molecular identity of ER-mitochondrial tethering in mammalian cells is less clear. In mammalian cells, ERMES homologs have not been identified, but several proteins have been demonstrated to modulate the ER-mitochondria platform. Although all of these proteins may not abolish ER-mitochondrial coupling, only the identified PDZD8 seems necessary for the formation of ER-mitochondrial contacts in mammalian cells [26]. PDZD8 is an ER protein required for mitochondrial Ca^{2+} uptake in neurons; if PDZD8 is deleted, the average surface area of individual ER-mitochondria contacts decreases by approximately 80%. Indeed, PDZD8 contains an SMP domain that is functionally orthologous to the SMP domain (synaptotagmin-like mitochondrial-lipid binding protein domain) found in the ERMES component Mmm1. However, the respective mitochondrial partner of PDZD8 involved in ER-mitochondrial coupling is unidentified.

Another example of a protein regulating ER-mitochondrial coupling is the phosphofurin acidic cluster sorting 2 (PACS-2) protein. PACS-2 deletion causes mitochondrial fragmentation and reduced apposition to the ER, leading to the inhibition of interorganelle Ca^{2+} signal transmission [27], while PACS-2 overexpression enhances ER-mitochondrial interactions and Ca^{2+} exchange [28]. The precise role of PACS-2 in ER-mitochondrial coupling has not been completely elucidated; however, it plays a pivotal role in the trafficking of ion channels between secretory pathway compartments [29] and regulates the activity of calnexin, an ER chaperone enriched in MAMs that can modulate intraluminal Ca^{2+} signaling through SERCA activity [30].

The role of mitofusin 2 (MFN2) as an ER-mitochondria tether is debatable. This mitochondrial protein, which controls organelle fusion, is localized at both the OMM and at ER and forms tethers between the ER and mitochondria, thus influencing Ca^{2+} transfer [31]. Disruption of ER-mitochondrial interactions and Ca^{2+} transfer in *Mfn2-/-* mouse embryonic fibroblasts indicated that the distance between these two organelles increases when this protein is deleted [31]. Recently, this concept was debated because new experiments performed in the same *Mfn2* knockout cells showed increased ER-mitochondrial interactions and Ca^{2+} transfer, suggesting that further investigations are necessary to pinpoint the exact role of MFN2 [32,33].

Another well-known protein complex, which is strongly correlated with functional ER-mitochondria apposition, is the Ca^{2+} channeling complex formed by IP3R at the ER and the chaperone glucose-regulated protein 75 (GRP75) and VDAC at the OMM [34]. This complex has also been associated with cyclophilin D, enriched in the MAM fraction, as this new partner of the complex can regulate interorganellar Ca^{2+} flux in hepatocytes and cardiomyocytes [35–37]. However, this complex does not seem to have features of a physical tether; in DT40 cells, knocked out for all the isoforms of IP3R3, the ER-mitochondria contacts are unmodified [17].

Finally, both the ER-resident vesicle-associated membrane protein-associated protein B (VAPB) and the mitochondrial tyrosine phosphatase-interacting protein 51 (PTPIP51) are involved in physical and functional ER-mitochondrial coupling [38]. Genetic manipulation of these mediators induces alterations in ER-mitochondrial coupling and interorganellar Ca^{2+} transfer, with repercussions on autophagy [39,40]. In addition, VAPB participates in ER-Golgi coupling where the ER is located very close (approximately 10 nm) to the trans-Golgi network [41] through interaction with ceramide transport protein (CERT), which is relevant to ceramide transport via ER-Golgi contact sites [42]. Indeed, interaction between mitochondrial PTPIP51 and the ER-resident oxysterol-binding protein (OSBP)-related proteins ORP5 and ORP8 at MAMs has recently been demonstrated; these proteins are involved in the ER-PM interface and in phosphatidylserine (PS) transfer, suggesting an interconnection among these three structures [43,44].

2.2. ER-plasma membrane interface

ER-PM coupling, described for the first time in 1957 in muscle, is a ubiquitous structural feature in all mammalian cells [45]. These membrane contact sites are involved in numerous functions, such as Ca^{2+} homeostasis regulation, lipid exchange, non-vesicular cholesterol transport and organelle dynamics [46]. Such specialized ER domains, preferentially associated with PM, are called the PM-associated membranes (PAM) fraction, containing many types of intracellular membranes (mainly ER but also mitochondria) that can be co-isolated with the PM. These membranes are not fused, the distance between the ER and PM is approximately 10–30 nm; this distance is regulated by the presence of molecular tethers [47–49]. Although ER-PM coupling has been previously observed, the molecular identity of this connection remains largely elusive. However, in 2012, Toulmay et al. identified the ER tricalbins as ER-PM tethering molecules in yeast [50]. The mammalian homologs of tricalbins are the three isoforms of extended synaptotagmins (E-Syt), ER proteins implicated in ER-PM coupling, lipid transfer and Ca^{2+} signaling [51]. The lipid composition of the PM is very important for intracellular signaling and is regulated by the local $[Ca^{2+}]_{cyt}$ at the ER-PM interface. ORP5 and ORP8, found at the ER-PM interface, are implicated in this process via transferring PS from the ER to the PM, which drives the countertransport of phosphatidylinositol 4-phosphate to the ER. At the ER membrane, phosphatidylinositol 4-phosphate is converted to phosphatidylinositol (PI), which is transported back to the PM and rapidly converted to phosphatidylinositol 4-phosphate and phosphatidylinositol 4,5-bisphosphate (PIP2), which mediating PLC is metabolized to diacylglycerol (DAG) and IP3. In turn, IP3 production leads to an increase in the cytoplasmic Ca^{2+} concentration via IP3Rs and SOCE response [12,52]. STIM1 and STIM2 in the ER and the three isoforms of the ORAI channel at the PM are the key determinants orchestrating the SOCE response at the ER-PM interface [53]. Under resting conditions, dimers of STIM proteins and hexamers of ORAI subunits are freely diffused along all ER and PM membranes. Intraluminal Ca^{2+} depletion from the store regulates the loss of Ca^{2+} ions from the luminal EF-hand motifs on STIM, which induces a conformational change in the structure favoring STIM oligomerization and translocation to the ER-PM interface. This clustering of STIM at the ER-PM interface blocks the free diffusion of ORAI hexamers, thus favoring ORAI oligomerization, which results in Ca^{2+} influx at the ER-PM interface [54]. The SOCE response is completed through the deoligomerization of the STIM-ORAI complex when the intraluminal Ca^{2+} level in the ER has been replenished. Caveolae are the preferred interorganelle platform for SOCE, and this domain can simultaneously release Ca^{2+} in an IP3R-dependent manner [55].

The depletion of E-Syt alters the Ca^{2+}-dependent activation of ORAI channels, indicating crosstalk between E-Syt in ER-PM tethering and STIM-ORAI signaling [56]. Indeed, ER Ca^{2+} store depletion induces rapid septin rearrangement and PIP2 redistribution at the ER-PM interface to favor a functional STIM-ORAI interaction [57]. These rearrangements are necessary for efficient STIM-ORAI interactions and SOCE channel gating. Septins are scaffold proteins redistributed at the PM; their participation in the formation of ORAI clusters control PIP2 redistribution in the lipid microdomain, which is necessary for STIM-ORAI complex stability [57]. These observations confirm that efficient ER-PM Ca^{2+} transfer occurs through the dynamic redistribution not only of proteins but also lipids to the ER-PM interface.

2.3. ER-endolysosome interface

An additional intimate coupling relationship of the ER is represented by its interaction with the endosomal system. This process is controlled by cholesterol levels in the endosome and occurs through the interaction of the endosomal cholesterol-sensing protein oxysterol-binding protein-related protein 1 L (ORP1 L) with the ER proteins VAPA and VAPB [58]. Coupling between these organelles favors the participation of the ER in endosomal processes such as transport and fusion events, vesicular body formation and receptor management. At these contact sites, messengers such as lipids and Ca^{2+} are exchanged between the coupled organelles.

Endosomes not only release extracellular Ca^{2+} to induce new intracellular Ca^{2+} signaling cascades but also store and buffer Ca^{2+} released from the ER upon stimulation. Early endosomes, which are derived from membrane endocytosis, may engulf extracellular Ca^{2+} at concentrations similar to those in the extracellular environment, on the order of 1–2 mM [59]. This internalized Ca^{2+} is released from endosomes through transient receptor potential (TRP) channels and two-pore channels [60–63], reducing the luminal Ca^{2+} concentration to approximately 3–40 μM [64,65]. Ca^{2+} release from endosomes may also induce ER Ca^{2+} mobilization and vice versa, indicating that the ER-endolysosome interface is a dynamic site for Ca^{2+} crosstalk between these organelles.

Late endosomes and lysosomes exhibit Ca^{2+} concentrations similar to ER (approximately 0.2-0.5 mM), suggesting that mature endosomes can absorb Ca^{2+} through unknown Ca^{2+} uptake channels [66,67] and, like the ER, store the ion [68–70]. The fact that endolysosomal Ca^{2+} concentrations are much higher than the $[Ca^{2+}]_{cyt}$ suggests that endolysosomal compartments actively participate in the induction of intracellular Ca^{2+} signaling, in turn suggesting that endolysosomes might generate a Ca^{2+} flux similar to that between the ER and mitochondria or the ER and the PM.

3. Interorganelle crosstalk in energy metabolism

Although organelles are functional units compartmentalized to perform specific metabolic tasks, they are interconnected by a system of Ca^{2+} communication to adapt to environmental changes.

3.1. ER-mitochondria interface

The ER participates in several anabolic and catabolic processes, such as protein synthesis and degradation, gluconeogenesis, glycogen synthesis and breakdown, membrane lipid synthesis and recycling [71]. The synthesis of most membrane phospholipids occurs on the ER membrane, and the products are subsequently sent through the interorganelle platform to other organelles by mechanisms that are partially unknown.

MAMs play an important role in lipid metabolism; in fact, these domains contain different enzymes linked to the biosynthesis and transfer of phospholipids, triacylglycerols, cholesterol, and cholesteryl esters [72]. The role of lipids at MAMs in the physical interaction between the ER and mitochondria has been thoroughly investigated, showing the impact of cholesterol and raft-like microdomains. In particular, cholesterol is an important substrate in regulating the association between the ER and mitochondria [73]. Increased ceramide level, an important mitochondrial sphingolipid, is associated with the initiation of apoptosis by OMM permeabilization. Interestingly, ceramide synthesis, occurs in the ER and partially in mitochondria and at the MAMs [74].

The ER hosts several enzymes involved in protein and lipid metabolism, and perturbations in the homeostasis of cellular energy production, redox state or Ca^{2+} concentration leads to ER stress and the activation of unfolded protein response (UPR) signaling. The UPR maintains protein homeostasis, but numerous later studies suggest that the UPR can also control lipid homeostasis. ER stress and proteins involved in UPR signaling have been found to control hepatic lipid metabolism, thus participating in hepatic steatosis and insulin resistance [75,76]. Furthermore, ER stress has been reported to induce autophagy and to exert a general effect on glucose metabolism [77]. Autophagy is a conserved and tightly regulated catabolic process that regulates metabolic homeostasis, permitting the degradation of organelles or cytoplasmic constituents to obtain energy [78]. Moreover, in 2013, Hamasaki et al. demonstrated that ER-mitochondria contact sites are important in autophagosome formation [79].

During the adaptive phases of ER stress, both the reticular and mitochondrial network redistribute towards the perinuclear area, augmenting the coupling of these organelles and the contact sites to potentiate interorganellar Ca^{2+} transfer to initiate metabolic adaptation that increases mitochondrial bioenergetics [80].

In mitochondria, Ca^{2+} is a fundamental metabolic messenger essential to the control of mitochondrial metabolic activity in support of oxidative phosphorylation (OXPHOS): specifically, Ca^{2+} regulates the activity of pyruvate, NAD-isocitrate dehydrogenase and oxoglutarate dehydrogenase and the consequent production of ATP by the respiratory chain [81,82]. Recently, an alteration in mitochondrial bioenergetics has been found in cancer cell metabolism; this alteration is linked to mutations in enzymes of the TCA cycle, including succinate dehydrogenase, fumarate hydratase and isocitrate dehydrogenase [83,84] and arises due to metabolic reprogramming that is required to support uncontrolled growth and proliferation in the tumor environment. In particular, the loss of function of fumarate hydratase has been linked to a subset of cancers in which cells are respiratory-deficient and accumulate high levels of fumarate with a general impairment of energy metabolism [85].

The role of Ca^{2+} in cardiac mitochondria isolated from pigs has been studied; Ca^{2+} was demonstrated to activate cardiac aerobic respiration at the level of both the Ca^{2+}-sensitive dehydrogenases and the F_oF_1ATPases [86]. These observations have also been reported in isolated skeletal muscle mitochondria, where Ca^{2+} increases the conductance of complexes I, III and IV and the consequent ATP production [87]. Mitochondria control metabolic flexibility because their biogenesis and function are adapted to conditions of nutrient limitation or caloric excess to restore energy homeostasis, which is why some metabolic pathologies, such as type 2 diabetes mellitus and obesity, are also linked to mitochondrial dysfunction [88].

Indeed, in the ER, one role of Ca^{2+} is to control the calreticulin/calnexin cycle, which is responsible for overseeing the folding of newly synthesized proteins. In particular, studies in calreticulin knockout mice have highlighted a role of this protein in controlling cellular differentiation and organ development via a Ca^{2+}-dependent mechanism [89]. In 2019, Brandt et al. found a novel involvement of calnexin in triacylglycerol synthesis, showing that calnexin interacts with acyl CoA-diacylglycerol acyltransferase-2 (DGAT2), an integral membrane protein of the ER and that calnexin-deficient mouse embryonic fibroblasts exhibited lower intracellular triacylglycerol levels and produced smaller lipid droplets than their wild-type counterparts [90].

In the last year, different studies have correlated the spatial organization of IP3Rs in clusters in the ER membrane with the propagation of Ca^{2+} signals in the regulation of cellular homeostasis. All three IP3R isoforms cluster to generate local Ca^{2+} puffs with largely similar mean amplitudes, temporal characteristics, and spatial extents in intact cells [91]; most of these clusters move via linkage to microtubules, but a small subset are immobile and involved in Ca^{2+} signaling. These IP3Rs have an optimal localization: near ER-PM junctions where STIM1 accumulates after Ca^{2+} store depletion [92].

IP3Rs modulate several Ca^{2+}-mediated processes and participate in cellular metabolism; in particular, studies in IP3R knockout cells have revealed significant perturbations in the energy charge and reduced glutathione and NADPH ratios, along with a decreased cellular growth rate, linked to higher reactive oxygen species (ROS) levels [93]. The absence of basal constitutive low-level Ca^{2+} signaling by IP3Rs has been demonstrated to lead to metabolic impairment resulting from diminished Ca^{2+} uptake by mitochondria: this condition enhances the phosphorylation and inhibition of pyruvate dehydrogenase and the activation of AMPK, which in turn activates prosurvival autophagy by a mTOR-independent mechanism [82].

In addition, downregulation of IP3R1 has been demonstrated to result in improved mitochondrial respiration, decreased cellular stress and enhanced glucose tolerance in obese animals [28], suggesting an important role of this receptor in mitochondrial metabolism.

Metabolic homeostasis is dependent on both the energy and redox statuses. Mitochondria producing ATP for the cellular energy supply are

also the primary source of intracellular ROS generation due to electron leakage from the respiratory chain. Complex I and complex III are the main sources of ROS production, although complex II also contributes [94]. Excessive ROS can lead to cell death by oxidative stress; however, recent studies reveal a new role of mitochondrial ROS as signaling molecules: these molecules act to improve metabolic homeostasis and signal transduction [95,96]. Diverse enzymes involved in ER redox homeostasis are located at MAMs: for example, glutathione peroxidase 8 (GPX8) is enriched in ER-mitochondria interface to regulate ER Ca^{2+} storage and fluxes [97]. Localization of Ero1α at MAMs depends on oxidizing conditions within the ER; this localization requires normoxic conditions and is linked to the role of Ero1< in the regulation of ER Ca^{2+} release by IP3Rs during ER stress [98,99]. In addition, GRP75 plays a role in mitochondrial functionality and redox homeostasis in neuronal cells: GRP75 silencing counteracts both cytosolic and mitochondrial Ca^{2+} overload under conditions of oxidative stress, blocking the production of ROS and preserving mitochondrial respiration through the maintenance of ER-mitochondrial coupling [100].

VDAC1 plays an important role in the energy metabolism of mitochondria because it controls the electron transport chain and metabolite exchange across mitochondrial membranes [101]; in fact, downregulation of VDAC1 expression decreases metabolite flux between mitochondria and the cytosol and inhibits cell growth [102].

Furthermore, MCU mediates mitochondrial Ca^{2+} uptake in pancreatic β-cells, and this Ca^{2+} accumulation is fundamental for the sensing of normal glucose levels [103]. In fact, a relationship between changes in the Ca^{2+} concentration in the mitochondrial matrix and consequent increases in the cytosolic ATP/ADP ratio that induces glucose-stimulated insulin secretion [104] has been demonstrated.

In the liver, altered insulin signaling is often associated with impaired mitochondria or ER stress; in fact, disruption of MAM integrity leads to altered insulin signaling in both mouse and human primary hepatocytes and in vivo [36]. These data demonstrate that MAM integrity controls hepatic insulin action and resistance. Similar alterations in insulin signaling have been found in cardiac hypertrophy, where insulin stimulates Ca^{2+} release from the ER and increases mitochondrial Ca^{2+} levels [105]. Arruda et al. showed that in the liver of obese mice, there is a profound reorganization of MAMs that establishes excessive ER-mitochondrial coupling, resulting in mitochondrial Ca^{2+} overload, impaired metabolic homeostasis, compromised mitochondrial oxidative capacity and augmented oxidative stress that can be correlated with the progression of insulin resistance and diabetes [28].

The expression of PTPIP51, which, in adipose tissue, acts as an effector in insulin signaling, has been correlated with insulin resistance [106]. Recent evidence has identified a role for this protein in adipocyte metabolism as a mediator between lipogenesis and lipolysis by switching between the lipogenic insulin pathway and the lipolytic PKA pathway via physical interaction with the insulin receptor and PKA [107]. VAPB-PTPIP51 tethers regulate autophagy by controlling Ca^{2+} influx to mitochondria from the ER [40]. In *C. elegans,* loss of the ER-resident VAP homolog VPR-1 causes triacylglycerol accumulation in muscular compartments; similar data have been obtained in VAPB knockout mice, indicating the presence of mitochondrial dysfunction that affects energy metabolism [108]. Mutations in VAPB/ALS8 are also associated with amyotrophic lateral sclerosis and spinal muscular atrophy [109,110].

An important signaling protein at the ER-mitochondria interface is mammalian target of rapamycin complex 2 (mTORC2): its localization to MAMs is stimulated by growth factors and insulin, and its interaction with the IP3R-Grp75-VDAC1 complex via Akt leads to the phosphorylation of the MAM-associated proteins IP3R, hexokinase 2 and PACS-2, with an effect on growth and metabolism [111]. In addition, Akt is involved in mediating insulin resistance; the phosphatidylinositol-3 kinase (PI_3K)-Akt pathway is an important effector of insulin induction and induces the translocation of glucose transporters (GLUTs) to the cell membrane in order to increase glucose uptake [112].

Another tether protein, PACS-2, has been demonstrated to be involved in lipid metabolism. In fact, this MAM-regulating protein mediates the levels of the MAM-associated FACL4 protein, which converts fatty acids to the fatty acyl-CoA esters used in the formation of complex lipids, and PSS-1, which exchanges the head group of phosphatidylcholine with serine [27]. Recent evidence shows that PACS-2 mediates metabolism, interfering with SIRT1-dependent PGC-1α deacetylation. PACS-2 knockout mice were protected from diet-induced insulin resistance and obesity [28]. Additionally, MFN2 deficiency has been linked to impaired insulin signaling and glucose homeostasis in vivo, which is associated with ER stress and altered ROS handling [113]. MFN2 depletion modifies the cellular metabolic profile in different cell models, leading to reduced $\Delta\Psi_m$; cellular oxygen consumption; and decreased oxidation of glucose, pyruvate, and fatty acids [114–117]. In particular, MFN2 depletion represses the expression of nuclear encoded subunits of OXPHOS complexes I (p39), II (p70), III (p49), and V (α subunit), leading to decreased metabolic activity [115,118]. However, the way in which MFN2 can alter OXPHOS subunit expression is unclear.

3.2. ER-plasma membrane interface

The most thoroughly documented functions of the ER-PM platform are maintaining intracellular Ca^{2+} homeostasis and mediating lipid metabolism [119].

ER-PM platforms are hubs for lipid metabolism and the transport of phospholipids and sterols; these domains have a high capacity for PI and PS synthesis [120]. At the ER-PM interface, the SMP domain-containing ER membrane protein TMEM24 contributes to insulin secretion in brain, neuronal and insulinoma cells [121].

By contributing to intracellular Ca^{2+} signaling, ER-PM platforms support the regulation of cytosolic Ca^{2+} signaling involved in several metabolic processes. In the liver, for example, oscillations in the $[Ca^{2+}]_{cyt}$ act as signals for circulating hormones to regulate glycogenolysis, gluconeogenesis and mitochondrial metabolism; therefore, Ca^{2+} dysregulation leads to pathologies such as metabolic syndrome and nonalcoholic fatty liver disease [122].

ORP5 and ORP8 localize to both ER-PM and ER-mitochondria appositions to facilitate organelle interaction and to transport PIP2 in order to modulate mitochondrial morphology and respiration [123]. In fact, overexpression of ORP5/8 favored mitochondrial function, augmenting cell proliferation through increasing the Ca^{2+} concentration in caveolae on the PM and mitochondrial matrix [124].

Cav1, a fundamental constituent of caveolae, is the core component of the Ca^{2+}-dependent apoptotic pathway and participates in the regulation of critical mitochondrial functions during tumor development: impairment of the cav1/Ca^{2+} axis leads to mitochondrial metabolic failure and apoptosis [23].

E-Syt are directly implicated in the mobilization of ER-PM platforms for autophagosome biogenesis. Autophagy is enhanced in cells overexpressing E-Syt, while inhibition of E-Syt significantly reduced autophagosome biogenesis [125]. Specifically, Nascimbeni et al. demonstrated that VMP1 interacts with E-Syt and that stress-induced mobilization of Beclin1 leads to the formation of a Beclin1-VMP1-E-Syt complex at ER-PM junctions to ensure the spatiotemporal regulation of phosphatidylinositol 3-phosphate synthesis required for autophagosome biogenesis.

3.3. ER-endolysosome interface

Lysosomes are involved in both catabolic and metabolic processes and control cell functionality. The core machinery that oversees the fusion of the endosome and autophagosome with the lysosome represents the terminal degradative compartment of the cellular endocytic and autophagic pathways. In addition to this fundamental role, lysosomes mediate various cellular mechanisms (reviewed in [126]),

one of which is Ca^{2+} storage and, therefore, Ca^{2+} signaling. In fact, because of the different Ca^{2+} channels present on their membrane, lysosomes can both store and release Ca^{2+}, directly communicating with the ER [61].

Lysosomal Ca^{2+} signaling, mainly involved in fusion/fission events, is strongly amplified by the subsequent stimulation of ER Ca^{2+} release, connecting lysosomes to different cellular processes (reviewed in [127]). Mucolipin 1 (MCOLN1)-mediated endolysosomal Ca^{2+} release results in calcineurin activation, which in turn dephosphorylates TFEB and up-regulates genes involved in lysosomal biogenesis via the expression of coordinated lysosomal expression and regulation (CLEAR) elements [128]. The ER is the primary source of Ca^{2+} for the lysosome [129], in agreement with the close physical proximity and formation of contact sites between these organelles. ER-lysosome platforms were first observed in mammalian cells, revealing the mechanism behind the interaction of PTP1B, an ER-localized protein phosphatase, and the endosomal EGF receptor [130]. In the endolysosomal system, Ca^{2+} is released through two-pore channels that can be activated by the pyridine nucleotide metabolite NAADP, an important intracellular second messenger in mammalian cells [131,132]. Interestingly, two-pore channel-mediated Ca^{2+} release is influenced by lysosomal pH, and vice versa [133]. An example of the precise crosstalk between the ER and lysosomes occurs in cardiac myocytes, where NAADP induces the formation of microdomains with high Ca^{2+} concentrations between lysosomes and the sarcoplasmic reticulum in response to β-adrenoceptor activation [134].

4. Dysregulation of interorganellar communication in cancer

Ca^{2+} communication between organelles, either indirectly or directly through membrane contact, is fundamental for proper cell function and for the maintenance of tissue homeostasis. Disruption of this extensive Ca^{2+} signaling network is detrimental for the entire organism, leading to the development of pathological conditions, including cancer. Ca^{2+} impairment is frequently associated with the dysregulation of several Ca^{2+} channels and pumps [135,136]. Alterations in cellular physiology acquired by cancer cells include cell sufficiency in growth signals, insensitivity to growth inhibitory cues and the ability to evade programmed cell death; in turn, these processes are affected by communication between organelles [137]. Moreover, many oncogenic pathways supporting tumor cell growth and survival converge on cellular metabolism, which mainly relies on energy production and thus mitochondrial function [138].

4.1. ER-mitochondria interface

ER and mitochondria use Ca^{2+} to communicate in response to physiological and pathological stimuli. The main biological processes involving contact between the ER and mitochondria are the control of lipid biosynthesis, Ca^{2+} transfer, mitochondrial division and biogenesis [139]. These fine-tuned ER-mitochondrial dynamics control several aspects of cell survival, such as metabolism and sensitivity to cell death. Impaired Ca^{2+} handling can prevent mitochondrial Ca^{2+} overload and the dissociation of F_oF_1ATP synthase dimers at the base of permeability transition pore (PTP) openings [140], sustaining tumorigenesis through apoptosis evasion.

During the past decades, an increasing number of oncogenes and tumor suppressor genes have been shown to exert a function at the ER-mitochondria interface through the regulation of Ca^{2+} signaling (Fig. 2) [141].

Bcl-2, the primary member of the Bcl-2 family, is a protooncogene known for its roles in inhibiting apoptosis (via interaction with the proapoptotic proteins Bax and Bak) and in promoting oncogenesis. Bcl-2 localizes in the ER and on the OMM [142] and directly inhibits the function of IP3Rs via the interaction of its N-terminal BH4 domain with the three isoforms of the channel [143]. These complex interactions

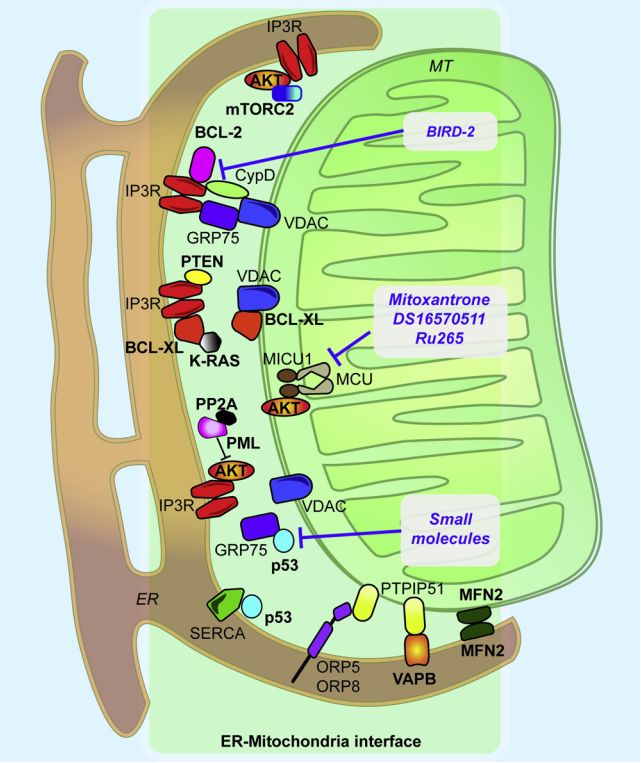

Fig. 2. Main ER-mitochondria Ca^{2+} transfer pathways dysregulated in tumorigenesis. Proteins up- or downregulated in cancer are shown in bold font. Drugs or compounds acting on Ca^{2+} at the ER-mitochondria interface are indicated in the squares. Akt, protein kinase B; Bcl-2, B-cell CLL/lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; CypD, cyclophilin D; ER, endoplasmic reticulum; GRP75, mortalin; IP3R, inositol 1,4,5-trisphosphate receptor; MICU1, mitochondrial Ca^{2+} uptake 1; MCU, mitochondrial Ca^{2+} uniporter; MFN2, mitofusin 2; MT, mitochondrion; ORP, oxysterol-binding protein; PML, promyelocytic leukemia protein; PP2a, protein phosphatase 2a; PTEN, phosphatase and tensin homolog deleted on chromosome 10; PTPIP51, phosphatase-interacting protein 51; SERCA, sarco/endoplasmatic reticulum Ca^{2+} ATPase; VAPB, vesicle-associated membrane protein-associated protein B; VDAC, voltage-dependent anion channel.

between Bcl-2 and IP3Rs suggest that the role of Bcl-2 in controlling Ca^{2+} signaling is to suppress excessive proapoptotic Ca^{2+} cues but to support prosurvival Ca^{2+} oscillations (Fig. 2) [141]. Therefore, dysregulation of Bcl-2 expression is a triggering event in various cancers, including chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DL-BCL), non-small cell lung carcinoma, multiple myeloma, follicular lymphoma and small cell lung cancer [144–148]. Selective treatment with a Bcl-2/IP3R inhibitor (BIRD-2) has shown promising results in the treatment of B-cell cancer [149], small cell lung cancer [150], chronic lymphocytic leukemia [151], multiple myeloma and follicular lymphoma [152]. Bcl-XL is another important antiapoptotic protein belonging to the Bcl-2 family and frequently overexpressed in tumors. Bcl-XL at the OMM has been proposed to modulate apoptosis by controlling mitochondrial membrane permeability (via VDAC) and regulating the release of cytochrome c [153,154]. Increased levels of Bcl-XL have been detected in tumors where cell survival is promoted at the expense of apoptosis, such as multiple myeloma; melanoma; glioblastoma; and prostate, colorectal, non-small-cell lung and pancreatic cancers [155–158]. Similar to Bcl-2, Bcl-XL directly binds the IP3R channel, regulating IP3R Ca^{2+} flux characteristics (Fig. 2) [159]. Accordingly, Bcl-XL inhibitors (WEHI-539; A-1155463; A-1331852) are used in therapies for B-cell lymphomas and various solid tumors [160,161].

Phosphorylated K-Ras interacts with IP3R1 along with Bcl-XL,

preventing the sensitization of channels, thus decreasing mitochondrial Ca^{2+} uptake and, in turn, inducing autophagy (Fig. 2) [162]. Ras is a small GTPase that translocates from the PM to internal membranes, including the ER and mitochondria, in response to stimuli [163]. At MAMs, oncogenic H-Ras affects Ca^{2+} transfer from the ER to mitochondria in order to induce apoptosis evasion [23]. In colorectal cancer cells, oncogenic K-Ras alters the expression of IP3Rs, reducing Ca^{2+} release to mitochondria from the ER in order to allow cells to evade Ca^{2+}-mediated proapoptotic signals [164]. Indeed, Ras-driven mitochondrial dysfunction causes metabolic and redox changes that sustain tumorigenesis [165].

The protooncogene Akt phosphorylates all isoforms of IP3R at a conserved consensus sequence, blocking IP_3R-mediated Ca^{2+} efflux from the ER to mitochondria, thus allowing cells to evade cell death [166,167]. The main Akt pathway, the phosphatidylinositol-3 kinase (PI_3K)-Akt pathway, is one of the most commonly dysregulated pathways in tumorigenesis, exhibiting somatic mutations, copy number alterations, aberrant epigenetic regulation and increased expression at the expense of *Akt* [168]. In mitochondria, Akt is responsible for phosphorylating the MCU regulatory subunit MICU1, which impairs MICU1 processing and stability, culminating in aberrant mitochondrial Ca^{2+} levels, ROS production and tumor progression [169]. Additionally, the Akt activator mTORC2 is localized at the ER/mitochondria compartment, where, with Akt, it is responsible for the maintenance of mitochondrial homeostasis along with the regulation of IP_3R phosphorylation and thus Ca^{2+} flux (Fig. 2) [111]. Interestingly, melatonin, the hormone known to regulate sleep-wake cycle, exhibits anticancer effects, reducing cancer cell proliferation by modulating the phosphorylation of Akt [170]. Thus, due to its safety, nontoxicity, and effectiveness represent a promising adjuvant therapy for cancer treatment [171,172].

The tumor suppressors PTEN and PML have been shown to be localized at MAMs. Mutations in phosphatase and tensin homolog deleted on chromosome 10 (*PTEN)* are present in many primary human tumors [173], resulting in the constitutive activation of the PI_3K-Akt pathway due to loss of PTEN function [174]. In addition, the role of PTEN in tumorigenesis has been associated with its ability to increase Ca^{2+} release from the ER via IP3Rs, thus restoring cellular sensitivity to Ca^{2+}-mediated proapoptotic stimuli through IP3R phosphorylation [175]. Furthermore, PTEN competes with F-box/LRR-repeat protein 2 (FBXL-2), a mediator of protein ubiquitination and degradation, for IP3R3 binding, decreasing proteasomal degradation of IP3R3 (Fig. 2) [176]. This antagonistic action of PTEN is responsible for maintaining IP3R3-mediated Ca^{2+} influx to mitochondria, thus preserving cellular responsiveness to proapoptotic stimuli. PML, a tumor suppressor mainly known for its role as a transcription factor at the nuclear level, is another protein that interacts with Akt. The presence of PML at MAMs regulates apoptosis through Akt dephosphorylation by protein phosphatase 2a (PP2A), inhibiting IP3R3 phosphorylation (Fig. 2) [177]. The distribution of PML at MAMs may be controlled by the tumor suppressor p53 [178]. p53 is one of the most extensively studied transcription factor proteins in cancer research and is normally localized in the cytosol and at mitochondria in response to stressors, such as chemotherapy or oxidative stress [179]. However, p53 may accumulate in the ER, affecting Ca^{2+} transfer via SERCA activity [180]. GRP75 is a cytosolic inactivator of p53 [181] that affects the functionality of p53 by retaining it in the cytoplasm, leading to the downregulation of p53 target genes [182]. Accordingly, GRP75 overexpression has been associated with liver cancer metastasis and has been linked with cisplatin resistance in ovarian cancer [183,184]. These findings indicate that GRP75 is a novel protein target for tumor therapies. Administration of anti-GRP75 molecules leads to tumor growth suppression, and small molecule inhibitors (MKT-077 and CAPE) that can prevent p53-GRP75 complex formation have recently been discovered [185].

VDAC interacts with different cytosolic proteins, including Bcl-2 family members, to mediate metabolic communication and signaling between the cytosol and mitochondria [186]. The interaction of VDAC1 with apoptosis-regulating proteins highlights the possible role of this protein in tumor progression. Indeed, VDAC1 has been shown to modulate mitochondrial metabolism in cancer cells, and its expression levels are different in tumor cells and normal tissues (reviewed in [186]). Silencing VDAC1 expression in cancer cell lines reduces the ATP level and the $\Delta\Psi_m$ value, suggesting a limited exchange of metabolites between mitochondria and the cytosol that results in decreased migration and the inhibition of cancer cell proliferation [187]. Therefore, VDAC1 is a novel target for cancer therapies via apoptosis regulation [188].

The final player in mitochondrial Ca^{2+} uptake is MCU, the overexpression of which has been associated with several different tumor types, such as colorectal, ovarian, prostate and breast, and correlated with tumor size, migration ability and invasion ability [189]. Interestingly, miR-25, the first microRNA identified to target MCU, is overexpressed in colon cancer. In this scenario, MCU is silenced and mitochondrial Ca^{2+} uptake is reduced, leading to resistance to proapoptotic stimuli that can be reversed by anti-miR-25 expression [190]. MCU is also a downstream target of miR-340, which inhibits motility and the switch from OXPHOS to glycolysis (the Warburg effect) in breast cancer cells [191]. The MCU inhibitor mitoxantrone, an anthracenedione-derived agent, has been used to treat hematological malignancies, but its antineoplastic effect is independent of MCU inhibition [192]. Recently, new compounds, including DS16570511 and Ru265, have been identified as specific, freely PM-permeable MCU inhibitors, but to date, no evidence for their utility in cancer treatment has been reported [193,194]. Fhit is a tumor suppressor that controls the affinity of MCU to physiological and proapoptotic Ca^{2+}-dependent stimuli [195]. Fhit acts as a tumor suppressor by increasing the number of mitochondrial Ca^{2+} hotspots —the initial sites of Ca^{2+} uptake in the mitochondrial matrix— to enhance the susceptibility of cells to apoptosis.

Importantly, the Ca^{2+} transfer between the ER and mitochondria is also affected by aberrant coupling of these two membranes. For instance, alterations in PACS-2 expression have been found in non-small cell lung cancer (NSCLC) [196]. Furthermore, changes in mitochondrial morphology, such as mitochondrial fragmentation, have been reported to protect against Ca^{2+}-dependent apoptosis, limiting mitochondrial Ca^{2+} overload by preventing the propagation of Ca^{2+} waves within the matrix. This dysregulation results in metabolic changes in cancer cells, inducing the Warburg effect [197]. Moreover, MFN2 has also been proven to mediate mTORC2-Akt signaling, indicating another critical contribution of MFN2 in suppressing tumor progression through direct inhibition of this pathway [198]. Accordingly, decreased expression of MFN2 has been reported in several tumors, such as liver, colorectal, lung and breast [198–201]. Genome-wide analysis of different human breast cancer cell lines and clinical specimens revealed that in the context of this tumor, not only is MFN2 expression downregulated but also the expression of the ER resident VAPB is often amplified or overexpressed [202]. VAPB, as stated before, is involved in the coupling of the ER with different cellular organelles, such as mitochondria, the Golgi apparatus or endolysosomes, thus regulating protein secretion and vesicle trafficking. Alterations in these processes may underlie the receptor localization and growth factor secretion that allow tumor growth [203]. PTPIP51 is another protein responsible for ER-mitochondrial coupling and was found to be overexpressed in glioblastoma, prostate cancer, breast cancer and keratinocyte carcinoma [204–207]. The involvement of PTPIP51 in tumorigenesis is mainly due to its multiple roles in cellular physiology, which involve the regulation of not only ER-mitochondria contact sites and consequently apoptosis and autophagy but also cellular differentiation, cell motility and cytoskeleton formation. Interestingly, PTPIP51 has been shown to interact with ORP5 and ORP8 at MAMs, regulating mitochondrial morphology and respiratory function [44]. ORPs play a role in the regulation of different cell signaling pathways through the mediation of membrane

contacts (ER-PM and ER-mitochondria), mainly controlling the transport of lipids and PS. Therefore, it is unsurprising that alterations in ORPs expression are linked to cancer development [208]. Specifically, ORP5 upregulation is related to increased invasion and poor prognosis in pancreatic cancer patients [209], while ORP8 downregulation has been observed in hepatocellular carcinoma cell lines [210]. Whether the involvement of ORPs in cancer development is strictly linked to lipid and PS transport and not to dysregulated Ca^{2+} transfer between compartments remains to be investigated. Notably, ORP dysregulation affects both the Akt and mTOR pathways in cells, suggesting the possible involvement of Ca^{2+} modulation.

4.2. ER-plasma membrane interface

PM-ER junctions are critically implicated in controlling the $[Ca^{2+}]_{cyt}$ via the regulation of Ca^{2+} channels in either the PM or the ER membrane.

In different types of tumors, the expression levels of SOCE components are altered. The resulting dysregulated Ca^{2+} influx affects tumorigenesis by increasing angiogenesis, promoting cell cycle progression and metastasis and affecting apoptosis [211]. Since the first reported mutation of STIM1 in human rhabdomyosarcoma, an increasing number of SOCE component alterations specific to cancer types and stages have been reported [212–214]. For instance, STIM1 levels are upregulated in colorectal cancer, clear cell renal cell carcinoma (ccRCC), and early-stage cervical cancer and are positively correlated with poor prognosis due to increased tumor size, invasion and metastasis [215–217]. Overexpression of STIM1 and Orai1 affects cell cycle progression by altering the expression of cell cycle regulatory proteins [211]. Moreover, SOCE regulates cell migration by generating Ca^{2+} pulses at the leading edge of cells, thus promoting myosin II-mediated directional movements via the activation of focal adhesion kinases [218]. Accordingly, downregulation of STIM1 and Orai1, either pharmacologically (e.g., by the SOCE inhibitor SKF-96365) or with siRNA, blocks cellular proliferation and invasion in several types of cancer [215,219–221].

Cav1, localized at the caveolar microdomain of the PM and normally dysregulated in cancer cells, is another protein involved in the regulation of Ca^{2+} flux. Cav1 has both antitumorigenic and protumorigenic effects. For example, the gene encoding cav1 is localized in a known tumor suppressor locus and is deleted in different types of cancer [222]. However, cav1 has been demonstrated to influence tumor development in bladder, colon, liver, stomach, breast and lung cancer by regulating Ca^{2+} homeostasis and migration [223–226]. Interestingly, cav1-mediated variations in intracellular Ca^{2+} levels are induced by the oncogene Ras, leading to mitochondrial alterations [23]. Cav1 antagonists such as nitrendipine, nifedipine and verapamil are routinely included in therapies for different disorders [227], indicating their potential use as cancer therapies.

The translocation and activity of sphingosine kinase 1 (SK1) are controlled by Ca^{2+} in caveolae [228]. Oncogenic SK1 expression induces an increase in the Ca^{2+} concentration in caveolae, which dysregulates cytoskeletal and focal adhesion assembly, leading to altered cellular migratory capacity [9].

ER/PM contact sites, and therefore Ca^{2+} exchange, are also modulated by E-Syt. Notably, E-Syt1 is a target of the oncogenic lung cancer fusion kinase CD74-ROS, which is commonly expressed in NSCLC [229]. Phosphorylation of E-Syt1 on tyrosine 993 (Y993) by CD74-ROS leads to increased tumor invasiveness. This site in E-Syt1, conserved in E-Syt2 and E-Syt3, is also phosphorylated in other cancer cell lines and in human NSCLC biopsies [230]. Therefore, E-Syts and their posttranslational regulation might represent a possible target for cancer therapy [51].

4.3. ER-endolysosome interface

Another important platform for Ca^{2+} signaling is the ER-endolysosome platform. At this interface, multiple cellular functions, such as endocytic trafficking, autophagy, and lysosomal function, are strictly regulated. Alterations in this interface influence cell metabolism and fate. Accordingly, lysosomes are widely acknowledged to be involved in maintaining the tumorigenic process and sustaining cell proliferation, metastasis and angiogenesis by providing cancer cells with energy and metabolic precursors [231]. In addition, lysosomes and endolysosomes are responsible for extracellular matrix remodeling, which is essential for angiogenetic processes, and are involved in mediating drug resistance (i.e., to chemotherapies) [232]. Studies aimed at assessing whether the endolysosome-associated Ca^{2+} machinery is involved in tumorigenesis have revealed that altered expression of the two-pore channels or the transient receptor potential channels is associated with malignant transformation [233]. For instance, increased expression of both TPC1 and TPC2 is associated with increased migration and metastasis in different cancer cell lines, and selective targeting of both genes reduces cell adhesion and migration in vitro [234]. TRPML2 is the only member of the transient receptor potential channel family to have been associated with tumor progression [235]. TRPML2 mRNA and protein are expressed in glioma tissues, and their levels are positively correlated with the malignant transformation from pilocytic astrocytoma (grade I) to glioblastoma (grade IV). In addition, TRPML2 overexpression results in cellular resistance to apoptosis through the phosphorylation of Akt and ERK 1/2 and blockade of caspase-3 [236]. Accordingly, TRPML-2 silencing restored apoptotic cell death in glioblastoma cells [236]. These findings suggest that endolysosomal Ca^{2+} signals could effectively be modulated, acting at both at the TPC and TRPM levels, and may be a promising target for cancer therapies [235].

5. Conclusion

Intracellular organelles are not independent but are structurally and functionally interconnected to allow reciprocal regulation of Ca^{2+}. Interorganelle platforms shelter various proteins with different functions, and several play a pivotal role in Ca^{2+} signaling and lipid transfer. The structure and function of these connections are dynamically regulated by nutritional and environmental cues, influencing cellular metabolism and thus allowing cells to adapt according to physiological and pathological requirements. Alterations in the interorganellar Ca^{2+} signaling directly affect cellular metabolism and, as expected, are associated with pathologies [237,238], including cancer. The importance of interorganelle platforms in regulating spatiotemporal Ca^{2+} signaling in cancer is further strengthened by multiple lines of evidence indicating that different oncogenes and tumor suppressors actively shape interorganelle platforms to alter Ca^{2+} communication between the organelles.

These interorganelle platforms are quickly becoming recognized as hotspots for metabolic decision-making and as possible targets for future antitumor approaches.

Interorganellar Ca^{2+} communication between cellular organelles is a new concept in biomedicine. The expanding roles of interorganelle Ca^{2+} signaling in cell physiology have encouraged researchers to return to apparently “easy” questions: What proteins reside in interorganelle platforms? How are these platforms organized to transfer Ca^{2+} between organelles?

To date, few studies have analyzed the protein content in interorganelle fractions or the interorganellar Ca^{2+} flux, providing few answers to these questions. Currently, researchers realize that the understanding of the form and function of interorganelle domains is limited.

Pioneering studies have developed tools to measure ER-mitochondrial coupling by mediating dimerization-dependent fluorescent proteins and the Ca^{2+} concentrations at the interorganelle interface

[18,239]; however, these tools require further refinement. The extension of these approaches to other interorganelle platforms has generated new tools for Ca^{2+} measurement that allow the investigation of intracellular Ca^{2+} microdomains in caveolae on the PM and the extent of Ca^{2+}filling of the lysosomal lumen [9,67]. The ER-mitochondria interface is the most extensively studied interorganelle platform, but to date, only three proteomics studies have been performed, with puzzling results [20–22].

The principal difficulty in such studies is related to the dynamic nature of these interorganelle platforms; current evidence shows the ways in which the protein and lipid composition of these structures change in response to different stimuli and cellular requirements.

The character of the lipid components in interorganelle platforms is crucial not only for the membrane stability and fluidity but also for Ca^{2+} transfer between organelles. Binding of Ca^{2+} to lipid membranes significantly alters the membranes by reducing their hydration, lipid mobility, and lateral interlipid distance. This local conformational membrane remodeling plays a significant role in the modulation of lipid-protein interactions as well as membrane-membrane associations [240]. Conversely, proteins may be lipidated; for example, IP3R is palmitoylated by the ZDHHC-SELENOK complex [241]. Reducing the palmitoylation of IP3R decreases IP3-stimulated Ca^{2+} release from the ER, leading to destabilization of the IP3R protein. This posttranslational modification is essential for the oncogenic function of approximately eighty cancer-associated proteins (both oncogenes and tumor suppressors); palmitoylation increases the affinity of these proteins for membranes (e.g., the Ras family) [242].

Another difficulty in this research area is the isolation of a pure interorganelle fraction; specific and effective protocols exist but do not guarantee a high level of purity. A contaminated fraction may generate spurious, difficult-to-interpret results.

However, further studies are needed to better understand the purpose and regulatory mechanisms of interorganellar Ca^{2+} signaling. Many fluorescent protein-based applications, engineered tools and new biochemical approaches are available for use in a wide variety of live-cell molecular imaging and biochemical applications to determine fusion protein localization, image dynamic changes in membrane proteins and visualize interorganellar Ca^{2+} dynamics.

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