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Cancer-Related Increases and Decreases in Calcium Signaling at the Endoplasmic Reticulum-Mitochondria Interface (MAMs)

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Abstract Endoplasmic reticulum (ER)-mitochondria regions are specialized subdomains called also mitochondria-associated membranes (MAMs). MAMs allow regulation of lipid synthesis and represent hubs for ion and metabolite signaling. As these two organelles can module both the amplitude and the spatiotemporal patterns of calcium (Ca^{2+}) signals, this particular interaction controls several Ca^{2+}-dependent pathways well known for their contribution to

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tumorigenesis, such as metabolism, survival, sensitivity to cell death, and metastasis. Mitochondria-mediated apoptosis arises from mitochondrial Ca^{2+} overload, permeabilization of the mitochondrial outer membrane, and the release of mitochondrial apoptotic factors into the cytosol. Decreases in Ca^{2+} signaling at the ER-mitochondria interface are being studied in depth as failure of apoptotic-dependent cell death is one of the predominant characteristics of cancer cells. However, some recent papers that linked MAMs Ca^{2+} crosstalk-related upregulation to tumor onset and progression have aroused the interest of the scientific community.

In this review, we will describe how different MAMs-localized proteins modulate the effectiveness of Ca^{2+}-dependent apoptotic stimuli by causing both increases and decreases in the ER-mitochondria interplay and, specifically, by modulating Ca^{2+} signaling.

Keywords Calcium · Calcium signaling · Cancer · Downregulation · MAMs · Upregulation

1 Introduction

Ca^{2+} is the third most abundant metal in nature, and it was adopted as a regulator in the early evolutionary stages in prokaryotes (Cai et al. 2015). Ca^{2+} ions play a crucial role in countless biological processes, and one of their most important contributions is undoubtedly represented by Ca^{2+} signaling, a complex network of extra- and intracellular messenger systems that mediates a wide range of pathways (Rimessi et al. 2020). The characterization of the complex network involving Ca^{2+} signaling has been in progress for approximately 140 years since the first experiments examining the contraction of isolated rat hearts (Ringer 1883). Since then, extensive progress has been made in understanding the numerous molecular pathways involved, although many aspects are still being debated and still need to be defined. Evolutionarily, cells have developed systems to constantly maintain Ca^{2+} concentrations at very low background levels to avoid the precipitation of phosphate salts, making this ion the logical choice for the exchange of signals (Carafoli and Krebs 2016). The crucial role of Ca^{2+} in cell biology results from the ability of cells to shape Ca^{2+} signals in the dimensions of space, time, and amplitude (Alonso et al. 2009).

Ca^{2+} enters cells through an assortment of Ca^{2+}-permeable channels that respond to different stimuli or acts as a second messenger, e.g., in the phosphoinositol signaling pathway, in which inositol trisphosphate (IP3) binds to Ca^{2+} channels on the endoplasmic reticulum (ER), transporting Ca^{2+} into the cytoplasm. Once in the cell, the effects of Ca^{2+} can be mediated by direct binding to its effectors, such as the phosphatase calcineurin, or indirectly by activating the ubiquitous Ca^{2+}-binding protein calmodulin, leading to the regulation of target molecules such as the Ca^{2+}/

calmodulin-dependent kinases CaMKII and CaMKIV (Kerkhofs et al. 2017). Temporally and spatially defined Ca^{2+} changes in the cytoplasm or in well-defined organelles represent a highly versatile intracellular signal capable of regulating many different processes, including depolarization, hormonal secretion, contraction of smooth and striated muscles, and cellular replication and activation of cytoplasmic, mitochondrial, and nuclear enzymes (Giorgi et al. 2018a).

Proteins that participate in Ca^{2+} signaling are mostly ubiquitous, but their distribution is highly tissue-specific (Berridge et al. 2003). Cells that need rapid Ca^{2+} signals, such as myocytes, express many voltage-activated calcium channels to allow quick Ca^{2+} entry through the plasma membrane, which then, via ryanodine receptors (RyRs) on the sarcoplasmic reticulum, triggers further calcium release. However, nonexcitable cells display calcium oscillations that last for tens of seconds and preferentially use the phosphoinositol signaling pathway to control gene expression and metabolism (Cui et al. 2017).

Therefore, a lack of Ca^{2+} ions can lead to various issues, and excess Ca^{2+} ions have harmful effects. Indeed, a sustained rise in intracellular Ca^{2+} is considered the initial step of irreversible cellular injury, mediated by the activation of the intracellular self-destructive lysosomal enzymes responsible for breakdown of subcellular organelle membranes and increases in oxidative stress and for the hyperactivation of phospholipases and endonucleases, which, through DNA damage, participate in apoptosis (Danese et al. 2017). Intracellular Ca^{2+} signals are controlled by Ca^{2+} influx through the plasma membrane (PM) and Ca^{2+} release from intracellular stores, mainly the ER and Golgi. Intracellular Ca^{2+} stores are constantly refilled while cytosolic Ca^{2+} is extruded from the cell by the plasma membrane Ca^{2+} ATPase (PMCA) pump, to maintain the optimal cytosolic Ca^{2+} concentration (Marchi et al. 2018).

In the cell, one of the organelles in which changes in $[Ca^{2+}]$ are particularly important is the mitochondrion (Giorgi et al. 2018b), which decodes Ca^{2+} signals in very sensitive and specific inputs that regulate metabolism, energy production, autophagy, and apoptosis (Giorgi et al. 2018a).

Membrane juxtaposition of both the mitochondria and the ER leads to the highly specialized MAMs compartment, which can be defined as areas of close organelle apposition but that are biochemically distinct from pure mitochondria and pure ER (Morciano et al. 2018). These contact sites are part of abundant heterotypic contacts, which, especially in recent years, have been well characterized and which include the ER-plasma membrane, ER-Golgi, lipid droplets–peroxisomes, mitochondria-lipid droplets, mitochondria–vacuoles/endosomes/lysosomes, ER-lipid droplets, mitochondria-plasma membrane, mitochondria–peroxisomes, ER-lipid droplets, and mitochondrial inner and outer membranes (Eisenberg-Bord et al. 2016).

To witness the strong tethering between the ER and mitochondria, an isolated MAM fraction contains membrane fragments of the outer mitochondrial membrane, the ER, and some plasma membrane proteins (Poston et al. 2013). Tomography analysis has revealed the morphology of these ER-mitochondria-connecting tethers (Csordas et al. 2006). The maintenance of this delicate structural juxtaposition results strategic for the regulation of a huge number of biological processes,

essentially through Ca^{2+} exchange. Poston et al. reported that there are around 1,000 molecular components of the MAMs fraction (Poston et al. 2013) and their study led to an elucidation of the multiple roles played by this particular subcellular compartment. In particular, MAMs co-regulate and influence Ca^{2+} signaling/dynamics, synthesis/transport of lipids and lipid intermediates, autophagy, apoptosis, and energy metabolism.

Noteworthy is the fact that MAM structures are sensitive to physiological cell conditions and this reflects in a transient and highly variable MAM composition. The length of ER-mitochondria tethers is a determining factor, critical for an efficient Ca^{2+} transfer, and an ER-mitochondria physical distance modulation is a condition found in different pathophysiological situations. About that, these two organelles' interplay is also involved in mitochondrial shape and size, and MAM-regulated mitochondrial fusion/fission process undoubtedly covers a crucial role in governing mitochondrial dynamics. Dynamin-related protein 1 (Drp1) is responsible for mitochondrial fission; following its activation, Drp1 translocates from the cytosol to the mitochondria and oligomerizes and constricts this organelle until its division is achieved. Focusing on mitochondrial fusion, mitofusin 1 (Mfn1) and mitofusin 2 (Mfn2) are responsible for the outer membrane fusion, while optic atrophy 1 (Opa1) mediates mitochondrial inner membrane fusion (Ponte et al. 2020).

MAMs are enriched in channels involved in calcium transfer, allowing perfect and synergistic signaling between the ER and mitochondria. Moreover, MAMs target many proteins with oncogenic/oncosuppressive functions that modulate cell signaling pathways involved in physiopathological processes (Danese et al. 2017).

As Ca^{2+} signaling-governed processes (such as energy production, metabolism, autophagy, and apoptosis) are dysregulated in cancer cells and play a key role in Ca^{2+} transfer and signaling in MAMs, the perturbation of these Ca^{2+} transport systems at the ER and the mitochondria in relation to tumor onset and progression has become a very hot topic, especially in recent times. In fact, the recent characterization of the many oncogenes and tumor suppressors residing at the MAMs has led many research groups to elucidate how these proteins mediate their functions by altering ER-mitochondrial Ca^{2+} transfer, thereby promoting or preventing cancer cell survival. Increases or decreases in calcium exchange through the MAMs interface can either exert protumorigenic effects (such as promoting metastatic transformations) or antitumorigenic effects (such as restoring sensitivity to apoptosis) in a cancer type- and cancer state-specific manner (Kerkhofs et al. 2018).

The aim of this review is to clarify how the perturbation of Ca^{2+} signaling at the ER-mitochondria interface can play a double-sided role in tumor pathology and progression. Modulation of calcium signaling at the MAMs, highly dynamic signaling hubs, could therefore represent a good therapeutic strategy in the future.

2 MAM-Localized Ca^{2+} Signaling Modulators in Cancer: Channels and Receptors

Ca^{2+} signaling represents an important tool that regulates many physiological cellular events from proliferation to cell death. Given the pivotal role it plays in such events, it is understandable why, over the past decades, remodeling of its shape has been demonstrated to be involved in the onset of many pathological conditions, such as tumor progression (Monteith et al. 2012; Prevarskaya et al. 2014; Marchi et al. 2020). Proteins involved in the maintenance of Ca^{2+} homeostasis consist of pumps, exchangers, and channels and have been described as part of the Ca^{2+} signaling "toolkit" (Berridge et al. 2003).

In resting conditions, the free cytosolic Ca^{2+} concentration is much lower than that in most extracellular fluids, and an ion concentration gradient is generated. Thus, when Ca^{2+}-permeable ion channels in the plasma membrane are open, Ca^{2+} flux into the cell increases (Carafoli 2002). However, as already mentioned, Ca^{2+} signaling can be generated by both external and internal cellular sources.

In the cell, the main ion reservoir from which Ca^{2+} can be transferred is the endoplasmic reticulum. On the one hand, the ER is the primary cell Ca^{2+} store; on the other hand, the main cellular Ca^{2+} signaling translators are the mitochondria.

Indeed, depletion of luminal ER Ca^{2+} levels is followed by a rapid increase in ion mitochondrial concentration. To ensure this interaction is effective, the ER and the mitochondria are juxtaposed on the MAMs at a short distance of approximately 10–25 nm (Csordas et al. 2006; Rizzuto et al. 1998; Marchi et al. 2014) in the smooth ER and at approximately 50 nm in the rough ER (Wang et al. 2015; Giacomello and Pellegrini 2016).

2.1 ER Side

Many ER-resident proteins involved in Ca^{2+} transfer have been found at the MAMs: the sarco-/endoplasmic reticulum Ca^{2+} ATPase (SERCA) and inositol 1,4,5-trisphosphate receptors (IP3R), among others. SERCAs are members of the P-type ATPase superfamily of primary active transporters (a large family of membrane-embedded pumps (Wang et al. 2015)) and can maintain the correct cytosolic and reticular Ca^{2+} concentrations.

The 110 kDa SERCA protein has 10 helix intramembrane domains involved in the interaction with two Ca^{2+} ions transferred to the ER lumen at the expense of adenosine triphosphate (ATP). The Ca^{2+} flux is coupled to the exchange of two to three protons moved to the cytoplasm (Palmgren and Nissen 2011). In addition to transmembrane domains, SERCA has three cytoplasmic regions: the nucleotide-binding domain (N), designed for ATP binding; the phosphorylation (P) domain, which hosts the amino acid residue phosphorylated by ATP; and the actuator (A) domain at the N-terminus, which controls enzyme dephosphorylation. During

ATP hydrolysis, conformational changes in the protein domains occur, and as consequence, the intermembrane domains warp, enabling Ca^{2+} transport (Toyoshima et al. 2000; Moller et al. 2010).

To date, at least 12 isoforms of SERCA (SERCA1a-b, SERCA2a-d, SERCA3a-f) have been identified in vertebrates (Lipskaia et al. 2014), each characterized by tissue and developmental specificity. This diversity is because SERCAs are encoded by three different genes located on three chromosomes (ATP2A1, ATP2A2, and ATP2A3), each generating alternative splicing variants that differ mainly in the C-terminus of the protein.

The diversities in the coding sequencing of these proteins do not affect the protein tertiary structures, which are highly conserved among all isoforms, but instead lead to differences in Ca^{2+} affinity. Among all these proteins, ubiquitous SERCA2b is the isoform with the highest Ca^{2+} affinity and plays a crucial role in the regulation of ER Ca^{2+} uptake and Ca^{2+} homeostasis (Vandecaetsbeek et al. 2009). All SERCA isoforms are present along the entire ER membrane and are not particularly enriched in MAMs.

SERCA activity can be modulated by many proteins. Among them, the recently identified ER-luminal protein disulfide isomerase thioredoxin-related transmembrane protein 1 (TMX1) displays palmitoylation-dependent MAMs localization. TMX1 can directly interact with SERCA2b (Gutierrez and Simmen 2018; Lynes et al. 2012) and inhibit its activity, reducing Ca^{2+} transfer.

If SERCA activity is lowered by TMX1, its activity is enhanced by the redox active form of the redox-sensitive selenoprotein N (SEPN1) (Gutierrez and Simmen 2018). MAMs result particularly enriched in redox regulatory proteins, and TMX1 and SEPN1 are among them (Krols et al. 2016; Marino et al. 2015).

Calnexin is a chaperone protein that localizes at the ER-mitochondrial contact sites in a palmitoylation-dependent manner (Lynes et al. 2012). The primary function of this protein is to interact with misfolded proteins to improve the folding efficiency of ER proteins (Lamriben et al. 2016). Upon palmitoylation, calnexin moves to the MAMs, where it interacts with SERCA2b, increasing Ca^{2+} transfer from the cytosol to the ER (Lynes et al. 2013). Interestingly, the modulation of SERCA2b activity by calnexin is counteracted by TMX1 in a way that may suggest competition for the same binding site (Krols et al. 2016; Raturi et al. 2016).

IP3Rs are large-conductance nonselective cation channels that together with the RyRs, which is mainly expressed in sarcoplasmic reticulum, are major structures through which Ca^{2+} exits the ER (Ashby and Tepikin 2001).

IP3R channels are homo- or heterotetramers composed of four subunits of approximately 300 kDa each. The molecular structure of the IP3R monomer, determined by cryogenic electron microscopy, consists of three structural domains: an N-terminal ligand-binding domain, containing both the IP3-binding core and the suppressor region, a central modulatory domain, and a Ca^{2+} channel region at the C-terminus containing six intramembrane helices. The C-tails interact directly with the N-terminal domains of the other subunits (Fan et al. 2015).

In vertebrates, there are three different isoforms of IP3R (IP3R1, IP3R2, and IP3R3) encoded by three genes (ITPPR1, ITPR2, and ITPR3, in humans). Despite

the high homology in the amino acid sequences (60–80%), these isoforms have a different expression pattern, with IP3R1 mainly expressed in neuronal cells, IP3R2 in muscle and liver cells, and ubiquitous IP3R3 in most cultured cells (Mikoshiba 2007; Foskett et al. 2007). In addition, the different isoforms show differences in ligand-binding sensitivity and regulation by Ca^{2+} and ATP (Newton et al. 1994; Miyakawa et al. 1999; Tu et al. 2005; Khan et al. 2006; Betzenhauser et al. 2008; Wagner 2nd et al. 2008; Vervloessem et al. 2015).

IP3Rs are enriched at MAMs levels, where they also exert a structural role, being in close proximity with the mitochondrial voltage-dependent anion channel 1 (VDAC1) and by interacting with the chaperone glucose-regulated protein GRP75 which acts as a tether between the two proteins and organelles (Bernard-Marissal et al. 2018). It has also been recently highlighted that IP3R isoforms differently regulate ER-mitochondrial contacts and local calcium transfer, proving that IP3Rs structural role in MAM compartment is crucial (Bartok et al. 2019).

The activity of IP3R receptors is regulated primarily by inositol trisphosphate (IP3), released at the plasma membrane after the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) by phospholipase C (PLC).

However, IP3Rs can also be modulated by ATP, post-translational modification (Mak and Foskett 2015; Bansaghi et al. 2014; Yule et al. 2010; Prole and Taylor 2016; Ivanova et al. 2014; Ramos-Franco et al. 1998), and Ca^{2+} ions, which act both from the luminal ER side, increasing the sensitivity to its ligand, and from the cytoplasmatic sides from which Ca^{2+} plays a dual role as an activator at low concentrations and an inhibitor if its concentration is higher than 300 nM (Table 1).

As noted earlier, there is a juxtaposition between the two MAM-forming organelles, and Ca^{2+} release from the ER is followed by uptake at the mitochondrial interface.

2.2 *Mitochondrial Side*

After being released from the ER, Ca^{2+} ions can first cross the outer mitochondrial membrane through VDAC and, once in the mitochondrial intramembrane space, enter the matrix through the mitochondrial Ca^{2+} uniporter (MCU).

VDAC is a 30-kDa protein existing in all eukaryotic cells in three different isoforms: VDAC1 and VDAC2 are expressed in most mammals, and VDAC3 is the isoform with the lowest expression (De Pinto et al. 2010; Huang et al. 2014; Maldonado et al. 2013). VDAC is the most abundant outer mitochondrial membrane protein, and due to its permeability not only to anions but also to respiratory substrates, ATP, reactive oxygen species (ROS), and cytochrome C can be considered master regulators of mitochondrial bioenergetics (Shoshan-Barmatz et al. 2010; Weisthal et al. 2014). The permeability of this channel is highly impacted by its two conformational states, opened and closed, since in the closed state, the channel is permeable only to small ions but not to anionic metabolites (Shoshan-Barmatz et al. 2010; Gincel et al. 2000; Schein et al. 1976). The switch between the

t1.1 **Table 1** Summary of Ca^{2+} signaling modulators founded at MAMs and implicated in cancer onset and progression

t1.2			Modulator	Ca^{2+}-related mechanism	Tumor
t1.3	Downregulation of MAMs Ca^{2+} crosstalk	Low ER-Ca^{2+} release	*Akt*	IP3R3 phosphorylation	Thyroid, breast, cervical, ovarian, non-small cell lung, pancreatic, prostate, gastric, brain, and colon cancer; renal and hepatocellular carcinoma (Revathidevi and Munirajan 2019)
t1.4			*BAP1*	IP3R3 deubiquitylation and stabilization	Mesothelioma (Bononi et al. 2017), uveal and cutaneous melanoma, renal carcinoma (Rai et al. 2016)
t1.5			*Bcl-2*	Decreases ER Ca^{2+} efflux by targeting IP3R3	Lymphoma, small cell lung cancer (Bittremieux et al. 2019)
t1.6			*Bcl-XL*	Enhance IP3R-mediated Ca^{2+} signals	Multiple myeloma, melanoma, glioblastoma, and prostate, colorectal, non-small-cell lung, and pancreatic cancer (Trisciuoglio et al. 2017; Scherr et al. 2016; Zhang et al. 2014; Yoshimine et al. 2013)
t1.7			*ERO1-α*	Oxidizes IP3R1 promoting ER Ca^{2+} release	Breast and colon cancer (Takei et al. 2017; Tanaka et al. 2017)
t1.8			*H-Ras*	Decreases IP3R3 expression	Pancreatic carcinoma; colorectal and head and neck cancer; lung, hematopoietic, and dermatological cancers (Munoz-Maldonado et al. 2019)
t1.9			*Mcl-1*	Stimulates non-MAM-localized IP3R3 Ca^{2+} release increasing ER Ca^{2+} leak	Lung, breast, and cervical cancer (Chen et al. 2019; Campbell et al. 2018; Zhang et al. 2012)
t1.10			*p53*	Binds to SERCA pump	Almost all
t1.11			*PACS-2*	Player in MAMs integrity regulation	Colorectal cancer (Kveiborg and Thomas 2018)

(continued)

Table 1 (continued) t1.13

		Modulator	Ca^{2+}-related mechanism	Tumor	t1.14
		PERK	Acts as MAMs structural tethering	Breast cancer (Feng et al. 2017)	t1.12
		PML	Regulates the phosphorylation of IP3R3	Almost all	t1.13
		PTEN	Antagonizes IP3R3 Akt-mediated phosphorylation	Lung, prostate, head, stomach, breast, and pancreatic cancer (Salmena et al. 2008)	t1.14
		RyR2	ER Ca^{2+} release	Melanoma, breast cancer, lymphoma, prostate cancer, thyroid carcinoma (Xu et al. 2019; Carpi et al. 2018; Lu et al. 2017; McCarthy et al. 2003; Mariot et al. 2000)	t1.15
		STAT3	Promotes IP3R3 degradation	Breast cancer (Yu et al. 2014)	t1.16
	Low mitochondrial uptake	*Bcl-2*	Regulates mitochondrial Ca^{2+} uptake targeting VDAC1	Hematopoietic, lung, gastric, breast, and prostate cancer (Frenzel et al. 2009)	t1.17
		Bcl-XL	Regulates mitochondrial Ca^{2+} uptake targeting VDAC1	Multiple myeloma, melanoma, glioblastoma, and prostate, colorectal, non-small-cell lung, and pancreatic cancer (Trisciuoglio et al. 2017; Scherr et al. 2016; Zhang et al. 2014; Yoshimine et al. 2013)	t1.18
		EZH2	Its inhibition inactivates MICU1	Breast, prostate, and endometrial cancers; melanoma and head and neck squamous cell carcinoma (Kim and Roberts 2016)	t1.19
		FATE1	Acts as a MAMs anti-tether agent	Hepatocellular carcinoma; colon and gastric cancer (Dong et al. 2003)	t1.20
		Fhit	Increases mitochondrial Ca^{2+} hotspots number	Silenced in >50% of cancers (Kiss et al. 2017)	t1.21

(continued)

t1.23 **Table 1** (continued)

t1.24			Modulator	Ca^{2+}-related mechanism	Tumor
t1.22			*miR-25*	Downregulates MCU	Prostate and in colon cancer (Marchi et al. 2013)
t1.23			*miR-7*	Reduce VDAC1 expression	Hepatocarcinoma and neuroblastoma (Chaudhuri et al. 2016a; Bargaje et al. 2012)
t1.24			*TRPC3*	Affects mitochondrial membrane potential	Breast cancer (Wang et al. 2019)
t1.25	Upregulation of MAMs Ca^{2+} crosstalk	High ER-Ca^{2+} release	*ERO1-α*	Regulates Ca^{2+} efflux from the ER	Breast and colon (Takei et al. 2017; Tanaka et al. 2017)
t1.26			*GRP78*	Store ER Ca^{2+}	Epithelial ovarian and prostate cancer; diffuse large B cell lymphoma; renal cell, colorectal, endometrial gastric, and squamous cell carcinoma (Niu et al. 2015)
t1.27			*IP3R3*	Ca^{2+} release from the ER	Hepatocellular and kidney carcinoma; cholangiocarcinoma (Guerra et al. 2019; Ueasilamongkol et al. 2020; Rezuchova et al. 2019)
t1.28			*Sig1R*	Binds and activate IP3R3	Glioma and melanoma; prostate, lung, colon, and breast cancer (Crottes et al. 2013)
t1.29		High mitochondrial Ca^{2+} uptake	*MCU*	Mitochondrial Ca^{2+} uptake	Breast cancer; hepatocellular carcinoma (Vultur et al. 2018)
t1.30			*MCUR1*	Positive regulator of MCU	Hepatocellular carcinoma (Jin et al. 2019; Ren et al. 2018)
t1.31			*MICU1*	Regulates MCU gating	Renal, ovarian, breast, and lung cancer (Marchi et al. 2019a)
t1.32			*RIPK1*	Binds MCU to promote Ca^{2+} entry	Colorectal cancer (Zeng et al. 2018)

opened and closed states is regulated by many factors, including Bcl2 family members (Tsujimoto and Shimizu 2000), Ca^{2+} ions (Bathori et al. 2006), and voltage. Indeed, high mitochondrial voltages induce VDAC to close (Gincel et al. 2000) in a N-terminus-mediated manner (Abu-Hamad et al. 2009).

Among VDAC channels, the most frequently expressed and consequently studied isoform is VDAC1 (Messina et al. 2012), which has been shown to be targeted to the MAMs (Hajnoczky et al. 2002; Shoshan-Barmatz and Gincel 2003; Colombini 2012) and to regulate the Ca^{2+} flux through the mitochondria outer membrane (Rapizzi et al. 2002). If regulation of mitochondrial Ca^{2+} signaling is not a unique feature of VDAC1, the ability to transmit proapoptotic stimuli to the mitochondria seems to be an exclusive characteristic of this isoform (De Stefani et al. 2012).

To reach the mitochondrial matrix and regulate all the previously mentioned processes, Ca^{2+} entering the outer mitochondrial membrane has to permeate the inner mitochondrial membrane that, unlike the outer membrane, is not permeable to ions. The accumulation of Ca^{2+} inside the mitochondrial matrix follows an electrogenic gradient and is driven by the low Ca^{2+} affinity uniporter complex MCU. Due to the low Ca^{2+} affinity of this MCU complex, the rapid mitochondrial ion accumulation is difficult to explain without considering the presence of close contacts between the ER and the mitochondria, which create microdomains with a high Ca^{2+} concentration (Rizzuto et al. 1998).

MCU is a complex of approximately 480 kDa composed of the channel-forming subunits MCUa and MCUb, organized mainly in pentamers. MCUa and MCUb have opposite effects on Ca^{2+} ion transfer (allowing and inhibiting permeation, respectively), and their relative quantities in the complex regulate the Ca^{2+} transport capability of MCU itself. In addition to the channel-forming subunits, mitochondrial calcium uptake 1 and 2 (MICU1 and MICU2) and the essential MICU regulator (EMRE) are part of the uniporter complex and play a pivotal role in regulating the integrity of the complex itself (De Stefani et al. 2015; Oxenoid et al. 2016; Raffaello et al. 2013; Sancak et al. 2013). MCU complexes were enriched in MAMs, positioned more to the mitochondrial periphery, indicating high accessibility to cytoplasm-derived Ca^{2+} inputs (Marchi et al. 2017).

Among the mitochondrial Ca^{2+} uptake family of regulator proteins MICU1 and MICU2, the best characterized is MICU1, which functions as a gatekeeper that can sense the Ca^{2+} levels of the intermembrane space. Indeed, at low concentrations, the gate is closed, but as soon as the Ca^{2+} levels pass the [Ca^{2+}] threshold of 700 nM for MICU1-MICU2 heterodimers and 300 nM for MICU1 homodimers, the Ca^{2+}-binding EF hands of MICU1 bind the ion and undergo a conformational change that opens the channel (Csordas et al. 2013; Mallilankaraman et al. 2012a; Perocchi et al. 2010; Petrungaro et al. 2015; Park et al. 2020) (Table 1).

3 Decrease in ER-Mitochondria Ca^{2+} Crosstalk

3.1 Dysfunctional ER-Ca^{2+} Release

As described in the introductory section, in recent years, increasing evidence has shown that organelles communicate with each other through Ca^{2+} signaling. In particular, at the MAMs level, interorganellar Ca^{2+} signaling is profoundly spatiotemporally regulated. Interestingly, in the tumor setting, an alteration of Ca^{2+} signaling has been shown to affect malignant transformation and tumor progression through the control of cell death programs and metabolism (Rimessi et al. 2020; Monteith et al. 2007).

In this context, the ER not only plays a decisive role in Ca^{2+} signaling but also guarantees a control system for correct protein folding and stress sensing. Alterations in ER homeostasis, including substantial Ca^{2+} depletion, are associated with the pathophysiology of many diseases, including cancer (Mekahli et al. 2011).

The normal Ca^{2+} exchange between the ER and the mitochondria requires adequate filling of the ER Ca^{2+} stores. Thus, decreasing the ER Ca^{2+} levels will compromise ER-mitochondrial Ca^{2+} transfer. As a consequence, changes in the ER Ca^{2+} store content affect the Ca^{2+} efflux from the ER to the mitochondria and ultimately cell survival (Ivanova et al. 2017).

The maintenance of physiological low levels of mitochondrial Ca^{2+} uptake by IP3R is crucial to preserve cellular bioenergetics in normal and cancer cells by enabling the dehydrogenase activation of the tricarboxylic acid (TCA) cycle, strong ATP production and metabolic intermediates for the generation of building blocks, allowing the cells to enter the cell cycle and proliferate. In breast cancer cells but not in normal cells, Ca^{2+} release suppression mediated by the inhibition of IP3R activity caused cell death through a deregulated autophagic mechanism (Singh et al. 2017a) and mitotic disruption, as reported by Cárdenas C. et al. (2016).

Regarding type 3 IP3R, the depletion of IP3R3 or its pharmacological blocking increased the level of the autophagic marker microtubule-associated protein 1A/1B-light chain 3 (LC3)-II through the upregulation of autophagic protein 5 (Atg5) and ROS generation, leading to the blockage of tumor growth in a mouse model of breast cancer (Singh et al. 2017a). This finding is correlated with the high expression of IP3R3 in human malignant tissues and high concentrations of metabolites in the serum of patients (Singh et al. 2017b).

Moreover, it has been reported that the inhibition of IP3R with caffeine, a nonspecific inhibitor of these receptors, leads to a decreased migration of glioblastoma cells and a substantially increased mean survival in a mouse glioblastoma xenograft model (Kang et al. 2010). In the Caco-2 colon cancer cell line, IP3R3 silencing, or nonspecific pharmacological inhibition by 2-APB in gastric cancer cells, induced apoptosis, while overexpression protected cells from staurosporine-induced apoptotic death (Shibao et al. 2010).

Interestingly, various MAM-located oncosuppressors and oncogenes have been reported to interact with IP3Rs, including the oncogene protein kinase B (PKB), also

known as Akt, promyelocytic leukemia protein (PML), BRCA1 associated protein 1 (BAP1), phosphatase and tensin homolog deleted on chromosome 10 (PTEN) and B-cell lymphoma 2 (Bcl-2) family proteins, modifying the Ca^{2+} release patterns and cell fate (Bononi et al. 2017; Akl and Bultynck 2013; Missiroli et al. 2017; Kuchay et al. 2017; Giorgi et al. 2010). Although the aforementioned proteins are all present at the ER-mitochondria interface, only PTEN and PML are particularly enriched on MAMs (Missiroli et al. 2016; Bononi et al. 2013).

Akt, as well as protein kinase C (PKC) isozymes (Pinton et al. 2004), is a key player in regulating multiple signaling pathways through calcium signaling tuning, such as cell metabolism, cell proliferation, and survival (Szado et al. 2008). Notably, in human breast cancers, the phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway is frequently dysregulated (Gonzalez-Angulo et al. 2011; Stemke-Hale et al. 2008).

On the ER side, IP3R Akt-mediated phosphorylation results in a decreased magnitude of Ca^{2+} release and, as a result, reduced mitochondrial Ca^{2+} uptake. Moreover, this decrease in Ca^{2+} flux protected glioblastoma cell lines from the effects of apoptotic stimuli (Szado et al. 2008).

In 2012, our group demonstrated that Akt specifically phosphorylates type 3 IP3R, leading to diminished mitochondrial Ca^{2+} influx and, consequently, protecting cells from apoptosis (Marchi et al. 2012).

PML tumor suppressor protein has been implicated in diverse cellular processes ranging from tumor suppression to defense against virus infection (Bernardi and Pandolfi 2007; Everett and Chelbi-Alix 2007; Hsu and Kao 2018; Pinton et al. 2011). An extranuclear fraction of PML has been demonstrated to be targeted to the MAMs in a p53-dependent manner (Missiroli et al. 2016) and to form a multicomplex with type 3 IP3R, the serine threonine kinase Akt and protein phosphatase 2A (PP2A) (Giorgi et al. 2010).

It has been shown that PML regulates the phosphorylation of IP3R by controlling the activity of Akt through the recruitment of the PP2A phosphatase at the MAMs interface. Hence, PML can coordinate Ca^{2+} mobilization into the mitochondria, which then triggers the cell death program. Conversely, in the absence of PML, PP2A does not assemble with IP3R and Akt, resulting in a higher activation of Akt (phospho-Akt). Once activated, Akt can hyperphosphorylate IP3R, thereby suppressing ER Ca^{2+} release to the mitochondria (Giorgi et al. 2011).

BAP1 is a member of the ubiquitin C-terminal hydrolase (UCH) subfamily of deubiquitylating enzymes and has tumor suppressor activity, which has been mainly correlated with its nuclear localization (Lee et al. 2014; Ismail et al. 2014). When BAP1 localizes to the ER, it binds, deubiquitylates, and stabilizes the activity of the IP3R3 channel, modulating Ca^{2+} release from the ER to the cytosol and then to the mitochondria, promoting apoptosis. In $BAP1^{+/-}$ carriers, the reduced level of BAP1 resulted in a diminished IP3R3 quote with a subsequent Ca^{2+} transfer decrease from the ER to the mitochondria. This event caused a reduced propensity of $BAP1^{+/-}$ cells to undergo apoptosis following DNA damage induced by asbestos or UV light (Bononi et al. 2017).

PTEN is another Ca^{2+}-related tumor suppressor that has been shown to be mutated or suppressed in many tumors (Salmena et al. 2008). Bononi et al.

demonstrated that a fraction of cellular PTEN is localized at the MAMs, where it interacts with IP3R3, antagonizing its Akt-mediated phosphorylation and enhancing Ca^{2+} transfer from the ER to mitochondria. In this way, it reestablishes cellular sensitivity to Ca^{2+}-mediated proapoptotic stimuli. Conversely, PTEN knockdown reduced the Ca^{2+} release from the ER and decreased mitochondrial Ca^{2+} transients, thus preventing cell death activation (Bononi et al. 2013). Moreover, a novel role for PTEN has been proposed; it can compete with F-box and leucine-rich repeat protein 2 (FBXL2), an E3-ubiquitin ligase F-box protein, for binding to IP3R3 to prevent its degradation. It has been demonstrated that FBXL2 degradation of IP3R3 is enhanced in cancer cells in which PTEN expression is lowered, thereby resulting in the inhibition of apoptosis (Kuchay et al. 2017).

The Bcl-2 family of anti- and proapoptotic proteins is predominantly localized to the mitochondria, ER, and MAMs, and their activities strongly reflect their intracellular localization (Morciano et al. 2018). Bcl-2 is a proto-oncogene known for its involvement in inhibition of apoptosis through its interaction with the proapoptotic proteins BCL2 associated X protein (Bax) and Bcl-2 homologous antagonist/killer (Bak) (Rimessi et al. 2020). Indeed, at the ER, Bcl-2 prevents excessive Ca^{2+} flux by directly targeting all three IP3R receptor isoforms, which would lead to mitochondrial Ca^{2+} overload and opening of the permeability transition pore (mPTP) (Chen et al. 2015; Bonora et al. 2017). Dysregulation of Bcl-2 expression has been highlighted in various cancers, including hematopoietic, lung, breast, and prostate tumors (Morciano et al. 2018).

Bcl-XL is another antiapoptotic member of the same family that is frequently overexpressed in many tumors, such as multiple myeloma, melanoma, glioblastoma, prostate cancer, colorectal cancer, non-small cell lung cancer, and pancreatic cancers (Trisciuoglio et al. 2017; Scherr et al. 2016; Zhang et al. 2014; Yoshimine et al. 2013). This protein is localized at the MAMs (Monaco et al. 2015), where it directly binds the IP3R channels, regulating IP3R-related Ca^{2+} release. Bcl-XL caused a strong sensitization of IP3R, promoting prosurvival Ca^{2+} oscillations (White et al. 2005).

Among the antiapoptotic proteins of the Bcl-2 family, myeloid cell leukemia 1 (Mcl-1) also lowers the calcium ER store content by stimulating IP3Rs outside of the MAMs, thereby increasing Ca^{2+} leakage from the ER, resulting in a decline in the basal ER Ca^{2+} levels (Eckenrode et al. 2010). In the presence of low [IP3], in Mcl-1-expressing cells, store depletion becomes more prominent, indicating that the sensitivity of IP3-dependent Ca^{2+} release is enhanced by Mcl-1. Mcl-1-mediated IP3R sensitization also contributes to low-level IP3R-mediated Ca^{2+} signaling from the ER to the mitochondria and thereby stimulates mitochondrial bioenergetics (Bittremieux et al. 2016).

At the MAMs, oncogenic H-Ras also affects Ca^{2+} transfer to the mitochondria to promote evasion from the apoptotic cascade (Rimessi et al. 2014). In colorectal cancer cells, oncogenic K-Ras modified the expression of IP3Rs, weakening the Ca^{2+} release from the ER to allow cells to escape Ca^{2+}-mediated apoptosis (Pierro et al. 2014). Indeed, Ras-driven mitochondrial dysfunction causes metabolic and redox changes that favor tumorigenesis (Hu et al. 2012). Hence, proper maintenance

of IP3R3 protein levels is crucial for preventing oncogenesis by strengthening tumor-suppressive ER-mitochondrial Ca^{2+} transfer.

Furthermore, MAMs are a molecular platform for the regulation of many oxidoreductases. In this context, endoplasmic reticulum oxidoreductin 1-α (ERO1-α) activity is broadly investigated for its enrichment at ER-mitochondria contact sites (Anelli et al. 2012) and its high expression in different tumor types (Kakihana et al. 2012). This oxidase impacts ER-Ca^{2+} storage and IP3-dependent fluxes. During ER stress, ERO1-α oxidizes type 1 IP3R, promoting the release of Ca^{2+} from the ER (Anelli et al. 2012). Furthermore, endoplasmic reticulum resident protein 44 (ERp44) (an ER luminal chaperone protein) binds to IP3R1 and inhibits its channel activity under reducing conditions, resulting in the blockade of Ca^{2+} transfer to the mitochondria (Higo et al. 2005). Oxidation of IP3R1 by ERO1-α causes the dissociation of ERp44, thus leading to the activation of Ca^{2+} release via IP3R1 (Li et al. 2009). ERO1-α silencing has been demonstrated to profoundly affect mitochondrial Ca^{2+} uptake, likely modifying MCU activity. Thus, ERO1-α links redox and Ca^{2+} homeostasis in MAMs (Anelli et al. 2012).

Recently, the oncogenic transcription factor signal transducer and activator of transcription 3 (STAT3), which mediates the signaling of cytokines, growth factors, and oncogenes (Yu et al. 2014), has been shown to localize only to MAMs (Su et al. 2020). At this location, it modulates ER-mitochondria Ca^{2+} release by interacting with the IP3R3 channel and promoting its degradation, resulting in greater cellular resistance to apoptotic stimuli (Avalle et al. 2019). In breast cancer cell lines, silencing STAT3 enhances the ER Ca^{2+} release and sensitivity to apoptosis following oxidative stress, correlating with increased IP3R3 levels. This evidence suggests that STAT3-mediated IP3R3 downregulation in the ER crucially contributes to its antiapoptotic functions via Ca^{2+} flux modulation.

Together with the IP3R receptors, RyRs and SERCA are the major Ca^{2+} players in the ER (Berridge 2012). In general, RyRs regulate melanocyte and T cell proliferation (Hakamata et al. 1994; Kang et al. 2000) and astrocyte migration (Matyash et al. 2002). Ryanodine receptor type 2 (RyR2), a member of the RyR family, controls the Ca^{2+} release from the sarcoplasmic reticulum into the cytosol (Ding et al. 2017). Different studies have confirmed the association of RyR2 with several cancer types, including melanoma (Carpi et al. 2018), breast cancer (Lu et al. 2017), lymphoma (McCarthy et al. 2003), and prostate cancer (Mariot et al. 2000). Recently, it has been reported that RyR2 is downregulated in thyroid carcinoma tissues and that low expression levels of RyR2 are closely associated with poor prognosis in thyroid carcinoma patients (Xu et al. 2019).

Over the past years, the tumor suppressor p53 has been shown to be altered in many human cancer tissues, including colon, breast, lung, brain, bladder, pancreatic, stomach, and esophageal cancer (Vogelstein et al. 2000). Some of p53 fraction is located at the MAMs, where it directly binds to the SERCA pump, changing its oxidative state and thus leading to an increased Ca^{2+} load, followed by an enhanced flux to the mitochondria. Consequently, during apoptotic stimulation, more Ca^{2+} can be released from the ER into the mitochondria, enhancing mitochondrial Ca^{2+} overload, opening of the mitochondrial mPTP, release of caspase cofactors, and

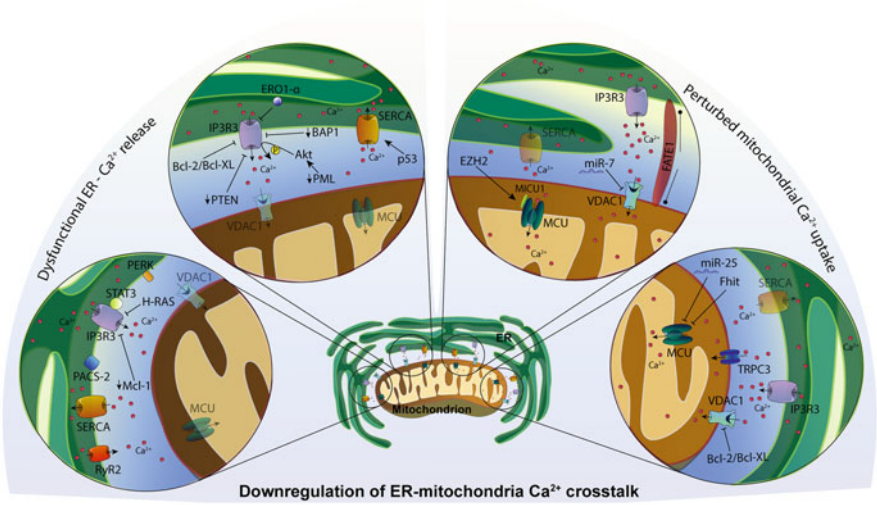

Fig. 1 Downregulation of MAMs Ca^{2+} crosstalk in cancer: graphical representation of the calcium signaling regulators involved in a cancer-related decreased Ca^{2+} crosstalk state. See text for further details. Ca^{2+}, calcium; ER, endoplasmic reticulum

ultimately induction of the intrinsic apoptosis pathway (Morciano et al. 2018). Dysregulation of p53-dependent Ca^{2+} homeostasis led to reduced ER Ca^{2+} release, resulting in a low responsiveness to apoptotic stimulation (Giorgi et al. 2015).

We must also note the phosphofurin acid cluster sorting 2 protein (PACS-2) and PKR-like ER kinase (PERK). PACS-2 is a multifunctional protein involved in retrograde ER-Golgi trafficking of multiple proteins (Youker et al. 2009). Although it is unclear whether a direct interaction of PACS-2 at the MAMs occurs, it was demonstrated that depletion of PACS-2 reduces mitochondrial-ER contact sites and mediates apoptosis (Simmen et al. 2005). PACS-2 was also demonstrated to be a fundamental player in rapamycin complex 2 (mTORC2)-dependent regulation of MAMs integrity (Betz et al. 2013). PERK is a protein kinase that, together with inositol-requiring enzyme 1 (IRE1) and transcription factor 6 (ATF6), acts as an ER stress sensor from the ER membrane, controlling UPR functioning. The function of this protein in the MAMs is independent of its role as an ER stress sensor and transcriptional regulator of redox homeostasis. Indeed, PERK maintains, through its cytoplasmic domains, the juxtaposition of the ER and the mitochondria, acting as a structural tether and permitting the transmission of ROS-mediated signals (Verfaillie et al. 2012).

In conclusion, changes in the ER Ca^{2+}-store content would perturb Ca^{2+} transfer from the ER to the mitochondria and ultimately influence cell death or survival. A reduction in intracellular store Ca^{2+} release is certainly the main mechanism adopted by cancer cells to escape mitochondria-mediated apoptosis (Fig. 1).

3.2 Perturbed Mitochondrial Ca^{2+} Uptake

Cancer-derived modifications in cellular physiology could be related to impairment of the Ca^{2+} signaling network, which is frequently associated with the dysregulation of several Ca^{2+} channels and pumps (Prevarskaya et al. 2014; Hanahan and Weinberg 2000).

In addition to limiting the excessive release of Ca^{2+} from the ER, cancer cells can effectively prevent mitochondrial Ca^{2+} overload by limiting mitochondrial Ca^{2+} uptake.

Among the proteins responsible for limitation of mitochondrial calcium influx are Bcl-2 and Bcl-XL, the antiapoptotic Bcl-2-family proteins discussed in the previous paragraph; Bcl-2 and Bcl-XL are partially localized at the mitochondrial outer membrane and, similar to other antiapoptotic proteins, are frequently upregulated in cancer; these proteins can regulate mitochondrial Ca^{2+} uptake through VDAC1 (Shoshan-Barmatz et al. 2010).

Considering that VDAC1 is involved in death and cell survival, it is not surprising that this channel could be a target for Bcl-2 family proteins (De Stefani et al. 2012). These proteins target the N-terminal region of VDAC1 (Abu-Hamad et al. 2009; Arbel and Shoshan-Barmatz 2010), and it has been demonstrated that only the Bcl-XL BH4 domain is essential to bind VDAC1 and inhibit cell death (Monaco et al. 2015). Several studies demonstrated that the interaction between Bcl-XL and VDAC1 suppresses proapoptotic Ca^{2+} uptake, preventing the dissipation of the mitochondrial potential and the release of cytochrome c and apoptosis-inducing factor (AIF) through the outer membrane.

Indeed, studies concerning mitochondrial Ca^{2+} uptake that compare Bcl-XL-overexpressing versus Bcl-XL-deficient cells have demonstrated that this protein may be involved in MAMs microdomain reorganization and results in an alteration of the capacity of mitochondrial Ca^{2+} uptake, proving that Bcl-XL inhibits VDAC1 (Monaco et al. 2015; Bittremieux et al. 2016; Shimizu et al. 2000; Li et al. 2008).

Nevertheless, VDAC1 in hepatocarcinoma tissues can be downregulated by the small noncoding RNA miR-7, influencing tumor proliferation and metastasis (Chaudhuri et al. 2016a; Bargaje et al. 2012). Chaudhuri et al. showed that in human neuroblastoma cells and in mouse primary cortical neurons, miR-7 can reduce VDAC1 expression, with consequent inhibition of mitochondrial Ca^{2+} uptake, membrane depolarization, mitochondrial fragmentation, cytochrome c release, and ROS production, promoting cancer cell survival (Chaudhuri et al. 2016a).

MCU allows calcium ion permeation into the mitochondrial matrix, and its overexpression leads to an increase in mitochondrial Ca^{2+} entry and ROS production, influencing the migration, invasion, and size of different tumor types (Yu et al. 2017; Tang et al. 2015; Wang et al. 2007). However, a reduction in MCU expression decreases mitochondrial Ca^{2+} uptake, the opening of the mPTP and the release of proapoptotic factors, thus having a protective effect on apoptosis (Marchi

et al. 2019b; Sebag et al. 2018; Oropeza-Almazan et al. 2017; Yuan et al. 2017; Liao et al. 2015; Qiu et al. 2013; Penston and Wormsley 1986).

Marchi et al. showed that, through MCU downregulation, the miR-25 MCU-targeting microRNA could perturb Ca^{2+} homeostasis, reducing the concentration of mitochondrial Ca^{2+} levels in HeLa cells. However, high levels of miR-25 have been observed both in prostate and colon cancer. The miR-25-dependent reduction in mitochondrial Ca^{2+} uptake correlates with resistance to proapoptotic stimuli and can be reversed by anti-miR-25 overexpression. Treatment with anti-miR-25 can restore the MCU expression levels and reverse the pathophysiology, thus suggesting a novel therapeutic target for prostate and colon cancer (Marchi et al. 2013).

One gene that is frequently deleted in many human cancers, principally in those caused by environmental carcinogens, is fragile histidine triad (FHIT). Consequently, its product, the Fhit protein, is absent or reduced in most cancers (Huebner and Croce 2003). The Fhit protein is localized in the mitochondria and the cytosol and acts as a tumor suppressor, increasing susceptibility to apoptosis (Siprashvili et al. 1997). Reintroduction of Fhit to the highly carcinogen-susceptible $Fhit^{-/-}$ mouse model reduced tumor sizes by activating apoptotic cell death (Zanesi et al. 2005). The Fhit protein generates ROS and enhances mitochondrial Ca^{2+} uptake by increasing mitochondrial Ca^{2+} hotspots. Therefore, Fhit acts as a tumor suppressor by modulating MCU opening and enhancing the susceptibility of cells to apoptosis, thus potentiating the effect of apoptotic agents (Rimessi et al. 2009).

Transient receptor potential cation channel subfamily C member 3 (TRPC3) belongs to a group of nonselective cation channels that are involved in different cellular mechanisms. TRPC3 channels can influence the mitochondrial membrane potential following their up- and downregulation. The activation of Ca^{2+}-sensitive downstream pathways occurs through the influx of calcium from transient receptor potential channels (TRP channels), which act as apoptotic regulators (Wang et al. 2019; Takahashi et al. 2018; Raphael et al. 2014; Monet et al. 2010). However, Shengjie Feng et al. have shown that a fraction of the TRPC3 protein is localized to the mitochondria and mediates mitochondrial Ca^{2+} uptake when the cytosolic calcium concentration is elevated. Since, as we previously noted, mitochondrial membrane potential seems to be affected by TRPC3 channels and because mitochondrial Ca^{2+} uptake is not abolished when MCU expression is downregulated (De Stefani et al. 2011), TRPC3 might be another channel that allows the entry of calcium into the mitochondria, in addition to MCU (Kirichok et al. 2004). In particular, resistance to apoptosis and the proliferation of some tumors could be related to its downregulation, which results in reduced mitochondrial calcium uptake (Feng et al. 2013).

Fetal and adult testis-expressed 1 protein (FATE1) is a 21-kDa protein that belongs to the cancer-testis antigen proteins that are mainly expressed in the testis under physiological conditions and are upregulated in different cancer types (Dong et al. 2003; Whitehurst 2014; Simpson et al. 2005). This molecule, being a member of the mitochondrial fission factor (Miff) protein family, shares some structural

similarities with Mff (Gandre-Babbe and van der Bliek 2008). The oncoprotein FATE1, which is located on the mitochondrial outer membrane preferentially in the MAMs compartment, is implicated in the regulation of Ca^{2+}-dependent apoptosis in cancer cells, acting as an anti-tether agent through the modulation of the distance between the ER and the mitochondria (Doghman-Bouguerra et al. 2016), being a direct connection between its increased expression and MAMs morphology in adrenocortical carcinoma (AAC) patients with a poor prognosis (Doghman-Bouguerra et al. 2016). Overexpression of FATE1 in adenoid cystic carcinoma (ACC) was related to a decrease in mitochondrial Ca^{2+} uptake that confers resistance to proapoptotic stimuli and chemotherapeutic drugs (Doghman-Bouguerra et al. 2016).

In most human cancer types, including head and neck squamous cell carcinoma (HNSCC), high levels of enhancer of zeste homolog 2 (EZH2) have been detected. EZH2 is the enzymatic subunit of the PRC2 complex (polycomb repressive complex 2), which methylates lysine 9 and lysine 27 of histone H3, and is fundamental for transcriptional repression (Kim and Roberts 2016; Schuettengruber et al. 2007; Boyer et al. 2006). EZH2 acts as an oncogene, and its high expression levels are associated with tumor cell proliferation and migration (Zhou et al. 2015a; Ning et al. 2015). Furthermore, it has been shown that inhibition of EZH2 in HNSCC cells in vitro and in vivo induces loss of mitochondrial membrane potential ($\Delta\Psi_m$) with consequent activation of cell death pathways. Inhibition of EZH2 involves accumulation of Ca^{2+} into the mitochondria, induced by inactivation of MICU1 (Zhou et al. 2015b; Cosentino and Garcia-Saez 2014) (Fig. 1).

4 Upregulation of ER-Mitochondria Ca^{2+} Crosstalk

4.1 New Insights into Ca^{2+} Signaling Perturbation in the MAMs

The numerous molecular pathways described thus far all involve a decreased uptake of Ca^{2+} to the mitochondria, resulting from decreased ER release or mitochondrial defects. Historically, reports that have assessed the remodeling of MAMs Ca^{2+} signaling associated with tumorigenesis, invasion, and metastasis all led to the conclusion that cancer cells undergo minor mitochondria-dependent apoptosis because of decreases in the Ca^{2+} release from the ER. Recently, the characterization of new MAM-localized proteins and the finding of new mechanisms of action led the scientific community to consider that even an upregulation of Ca^{2+} signaling at the MAMs level could be harmful and drive tumor onset and progression. In the following paragraphs, we will describe how this condition, hitherto described as the cause of apoptotic cell death, can lead to the onset and development of tumor diseases.

4.2 Increased ER-Ca^{2+} Release

The endoplasmic reticulum is an organelle that contains a network of tubules and flattened sacs and is mainly known for its major role in the production, processing, and transport of proteins and lipids. The ER also represents the major intracellular store of Ca^{2+}, an ion that is necessary on its lumen for second-messenger-induced Ca^{2+} release, the control of capacitative Ca^{2+} influx, and intra-ER chaperone activities such as polypeptide translocation, protein folding, and ER-associated degradation (Buck et al. 2007). In normal tissue cells, a sustained Ca^{2+} flux from the ER to the mitochondria can enhance the sensitivity of mitochondria to apoptotic stimuli; however, in some cases, an increase in Ca^{2+} ion leakage from the ER to the MAMs can promote tumor formation, especially in specific tissues and organs. For ER-mitochondria interorganellar Ca^{2+} signaling and, in particular, increased ER Ca^{2+} release, the recent revelation of the mechanisms by which IP3R3 upregulation drives oncogenesis via ER-mitochondrial Ca^{2+} crosstalk is particularly important. This statement is particularly strong because until last year, IP3R3 was well characterized as a Ca^{2+}-related proapoptotic protein. In fact, the tumor suppressors BAP1 and PTEN have a stabilizing effect on IP3R3 in the ER, promoting susceptibility to cell death (Bononi et al. 2017; Kuchay et al. 2017), and in contrast, the oncogene K-Ras^{G13D} downregulates IP3R3, preventing the apoptotic death of cancer cells (Pierro et al. 2014). Three recent works by Guerra et al. (2019), Rezuchova et al. (2019), and Ueasilamongkol et al. (2020), for the first time, have deviated from the idea that IP3Rs only have an anti-oncogenic potential by driving proapoptotic Ca^{2+} signals to mitochondria but attributed an oncogenic potential to ER-mitochondria Ca^{2+} crosstalk. In an analysis of tumor tissues, the IP3R3-protein levels were elevated in hepatocellular carcinoma biopsies compared to healthy liver biopsies (Guerra et al. 2019), in clear cell renal cell carcinoma kidney biopsies compared to healthy regions (Rezuchova et al. 2019) and in cholangiocarcinoma cancer biopsies and cancer cell lines compared to normal tissues and normal cholangiocyte cell models (Ueasilamongkol et al. 2020). In all cases, only type 3 IP3Rs were found to be overexpressed in tumor tissues, with no changes or slight downregulation of type 1 and type 2. In particular, IP3R3 seems to be completely absent in normal human hepatocytes but is clearly present in biopsies from individuals with hepatitis B virus, hepatitis C virus (HCV), non-alcoholic fatty liver disease (NAFLD), and alcoholic liver disease (ALD), which are the four most common predisposing factors to the development of hepatocellular carcinoma (Guerra et al. 2019). This increase was more pronounced in the late stages of hepatocellular carcinoma.

Notably, in cholangiocarcinoma cells, most IP3R3 is localized to the MAMs, while in normal cholangiocytes, it resides in the ER subapical pole. In these cells, MAM localization promotes basal respiration by increasing mitochondrial Ca^{2+} signaling, and thus, depletion of this channel in these cells is deleterious for nuclear and mitochondrial functionality (Ueasilamongkol et al. 2020). In HepG2 cells, IP3R3 upregulation promotes cell death, but its chronic overexpression can increase

the resistance of these cells to cell death inducers, enhancing malignant cell survival (Guerra et al. 2019).

The common key in all these cases is the extreme adaptation ability that drives oncogenesis and malignant cell transformation. These cancer cells became addicted to high IP3R3 levels at the MAM compartment for their survival, to maintain sustained cell metabolism and to obtain malignant features such as increased motility, migration, and invasion.

We want to include in this section the already mentioned ERO1-α, an extensively studied protein due to its ability to regulate many processes. ERO1-α is particularly enriched at the ER-mitochondria interface, controlling ER redox homeostasis and oxidative folding and regulating Ca^{2+} efflux from the ER and, consequently, mitochondrial Ca^{2+} accumulation (Anelli et al. 2012). ERO1-α is highly expressed in different tumor types and is associated with a poor prognosis in breast cancer (Kutomi et al. 2013). In fact, the expression of ERO1-α in triple-negative breast cancer cells is correlated with that of programmed cell death-ligand 1 (PD-L1), both at the protein and mRNA levels, via hypoxia-inducible factor 1-α (HIF-1α). Depletion of ERO1-α led to a significant reduction in PD-L1-mediated T-cell apoptosis, suggesting that ERO1-α has a key role in tumor-mediated immunosuppression (Tanaka et al. 2017).

Another MAMs Ca^{2+}- and tumor-related protein that acts at the ER level is the receptor chaperone stress-activated chaperone sigma-1 receptor (Sig1R), which senses ER Ca^{2+} concentrations and regulates cell survival. This protein could be considered "borderline" in this section considering its mechanism of action; in fact, Sig1R is an ER-localized protein that favors the efflux of calcium ions from the endoplasmic reticulum and has been described as being overexpressed in breast cancer, especially in cancer cells with metastatic potential (Gueguinou et al. 2017). ER chaperones are important in maintaining proper intracellular Ca^{2+} levels, protein folding, and the unfolded protein response (UPR) under ER stress conditions (Bartoszewska and Collawn 2020).

Two MAM-localized chaperones that belong to the heat shock 70 kDa (HSP70) protein family are of considerable importance in Ca^{2+} signaling: chaperone glucose-regulated protein GRP75 and glucose-regulated protein 78 (GRP78, also known as immunoglobulin heavy-chain-binding protein BiP) (Brocchieri et al. 2008; Wadhwa et al. 2002).

GRP75 ensures the juxtaposition between IP3R and VDAC1 in the mitochondrial outer membrane (Szabadkai et al. 2006). Its localization is mainly mitochondrial, but it is also present at low levels in the cytoplasm, nucleus, ER, and Golgi apparatus (Ran et al. 2000; Wadhwa et al. 1995), where it exerts many different functions from the import of unfolded proteins into the mitochondrial matrix to modulation of exocytosis and endocytosis (Flachbartova and Kovacech 2013; Voos and Rottgers 2002; Schneider et al. 1996; Kronidou et al. 1994; Scherer et al. 1992). Sig1Rs are particularly enriched at the MAMs and in normal tissues form a complex with GRP78, another MAM-localized chaperone. GRP78 can bind to misfolded proteins and to unassembled complexes and modulates ER-associated degradation (ERAD), which regulates the UPR (Pfaffenbach and Lee 2011; Wang et al. 2009; Little et al.

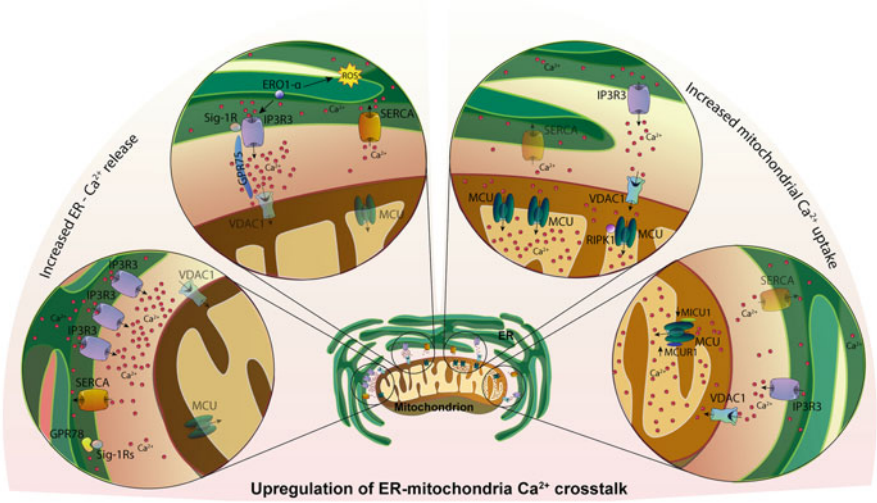

Fig. 2 Upregulation of MAMs Ca^{2+} crosstalk in cancer: graphical representation of the calcium signaling regulators involved in a cancer-related increased Ca^{2+} crosstalk state. See text for further details. Ca^{2+}, calcium; ER, endoplasmic reticulum

1994). Its molecular structure displays two domains: the substrate-binding domain (SBD), involved in binding unfolded peptides, and the nucleotide-binding domain (NBD), which binds ATP to be hydrolyzed to obtain energy to prevent unfolded protein aggregation at the N-terminus (Luo et al. 2006; Lindquist and Craig 1988). GRP78, like almost all other chaperones, is useful for storing ER Ca^{2+} as a high-capacity Ca^{2+}-binding protein under physiological conditions (Hendershot 2004).

Szabadkai et al. highlighted the mechanism by which Sig1R, dissociating from BiP, binds IP3R3 following the activation of IP3Rs. This event leads to IP3R3 stabilization at the MAMs and to an enhancement of IP3R3-mediated Ca^{2+} fluxes to the mitochondria (Szabadkai et al. 2006). Although BiP is an excellent target to consider for neuroprotective therapeutic strategies (Enogieru et al. 2019), it also influences how tumor cells survive, proliferate, and develop chemoresistance. During chronic ER stress conditions that involve prolonged ER Ca^{2+} depletion, Sig1R localization changes from the MAMs to the peripheral ER, reducing cellular damage and thus preventing cell death. Another mechanism of Ca^{2+} homeostasis perturbation implemented by Sig1R that has direct consequences on cell invasiveness in breast cancer has been described by Gueguinou et al. (2017). Sig1R favors the migration of cancer cells by forming a functional molecular platform with the calcium-activated K^+ channels SK3 and ORAI calcium release-activated calcium modulator 1 (Orai1) (Gueguinou et al. 2017) (Fig. 2).

4.3 Increased Mitochondrial Ca^{2+} Uptake

Before the identification of the molecular players forming the MCU complex, the role of mitochondrial Ca^{2+} in cancer progression was simply confined to receiving Ca^{2+} from the ER, thereby regulating the apoptotic response. Low ER Ca^{2+} release results in reduced mitochondrial [Ca^{2+}], mPTP inhibition, and resistance to chemotherapeutic-induced cell death. Consistent with this view, many oncogenic factors act at the MAMs to limit ER-mitochondria Ca^{2+} transfer (see the "Downregulation of ER-mitochondria calcium crosstalk" section). However, many mitochondrial Ca^{2+} channels that are responsible for favoring Ca^{2+} accumulation, such as VDACs, are overexpressed, rather than reduced, in cancer (Mazure 2017). These observations suggest that an increased intrinsic capacity of the mitochondrial compartment to accumulate Ca^{2+} could contribute to sustained malignant progression, although, at least theoretically, it predisposes cells to Ca^{2+}-induced cell death. The oncogenic mechanisms regulated by mitochondrial Ca^{2+} mainly rely on the association between Ca^{2+} and the formation of mitogenic ROS, as well as pure stimulation of mitochondrial metabolism. Ca^{2+} accumulation activates four mitochondrial dehydrogenases, which in turn stimulate the respiratory chain and hence ATP production (Denton 2009). Thus, as a consequence of increased metabolic activity, ROS are generated inside the matrix, but they fail to trigger cell death, probably due to the superior antioxidant defense that often distinguishes the malignant phenotype (Gorrini et al. 2013).

The correlation between augmented mitochondrial Ca^{2+} entry, ROS production, and cancer growth appears evident for tumors overexpressing the uniporter complex pore-forming subunit MCU. Indeed, increased levels of MCU have been reported in different tumors, including breast and hepatocellular carcinomas (Vultur et al. 2018). In breast cancer, MCU-dependent mitochondrial Ca^{2+} entry is associated with ROS overproduction and higher metastatic potential through a mechanism that involves the downstream activation of HIF1-α transcriptional activity (Tosatto et al. 2016). Consistent with these observations, upregulation of MCU in triple-negative breast cancer cells promoted metastasis in an in vivo mouse model by enhancing glycolysis, a series of neoplastic events that is counteracted by the tumor-suppressor activity of miRNA-340 (Yu et al. 2017). Moreover, receptor-interacting protein kinase 1 (RIPK1) binds MCU to promote Ca^{2+} entry and colorectal cancer progression through stimulation of mitochondrial bioenergetics (Zeng et al. 2018). In hepatocellular carcinomas, the Ca^{2+}-ROS axis orchestrated by MCU resulted in activation of metalloproteinase-2 (MMP2) (Ren et al. 2017), a zinc-dependent endopeptidase associated with extracellular matrix degradation and metastasis (Shay et al. 2015).

The link between Ca^{2+} and ROS overproduction is also relevant for the cancer-related functions of MICU1, the principal member of the MCU complex that regulates the gating of the channel (Kamer and Mootha 2015). Our group recently showed that MICU1 downregulation, as a result of higher AKT activity, could sustain cancer progression through Ca^{2+}-dependent ROS generation (Marchi et al.

2019a). Indeed, loss of MICU1 disinhibits MCU, leading to Ca^{2+} permeation under resting (nonstimulated) conditions and increased mitochondrial ROS levels (Csordas et al. 2013), which could ultimately result in cell death (Mallilankaraman et al. 2012a; Liu et al. 2016). This finding implies that malignant cells showing low MICU1 levels predispose concomitant mechanisms to minimize the detrimental effects induced by ROS. Consistent with this view, MICU1 depletion in normal hepatocytes triggered extensive cell death, but upon pharmacological inhibition of mPTP opening, the loss of MICU1 conferred a strong proliferative advantage (Antony et al. 2016). Moreover, a combination of high mitochondrial Ca^{2+} entry through genetic manipulation of the MCU complex and mPTP closure exacerbated the tumorigenic potential of different cancer cells (Marchi et al. 2019b). Taken together, these observations suggest that variations in the composition of the MCU complex are a key event that cooperates with other oncogenic pathways to favor cancer growth.

Further evidence that supports this scenario derives from the protumorigenic role of MCU regulator 1 (MCUR1), which has been described as a matrix-located, positive regulator of the uniporter complex (Mallilankaraman et al. 2012b). In hepatocellular carcinomas, MCUR1 was strongly upregulated, and ROS production was augmented, leading to ROS-dependent degradation of p53 and consequent resistance to apoptosis (Ren et al. 2018). Notably, the cancer cell detoxification capacity was also increased due to activation of nuclear factor erythroid 2-related factor 2 (NRF2) (Jin et al. 2019), a master gene in the orchestration of the cellular antioxidant response (Cuadrado et al. 2019). Thus, MCUR1 can regulate two cancer hallmarks at once: Ca^{2+}-mediated metastatic potential and resistance to apoptosis. However, the expression of MCUR1 correlates with the permeability transition and reduced cell survival (Chaudhuri et al. 2016b), indicating that MCUR1 oncogenic activities might be solely due to the concomitant inhibition of the functions of the mPTP through a superior mechanism. Nevertheless, it has been proposed that MCUR1 could act as a complex IV assembly factor rather than as an MCU interactor (Paupe et al. 2015). In this context, variations in mitochondrial Ca^{2+} uptake and ROS levels are side products of respiratory chain defects; therefore, the active role of Ca^{2+} in MCUR1-mediated oncogenesis should be completely reevaluated.

Overall, these observations indicate that increased mitochondrial Ca^{2+} uptake acts with other oncogenic mechanisms (e.g., mPTP inhibition or activation of antioxidant systems) to sustain cancer growth and dissemination. The protumorigenic role of mitochondrial Ca^{2+} signaling involves other pathways in addition to ROS production and excess malignant cell bioenergetics, including the MCU-dependent control of cytosolic Ca^{2+} through store-operated Ca^{2+} entry (SOCE). The activity of the MCU complex sustains cytosolic Ca^{2+} fluxes through SOCE, which in turn regulates cytoskeletal dynamics and cellular migration (Prudent et al. 2016). Moreover, recent findings suggest that spontaneous mitochondrial Ca^{2+} oscillations through the MCU complex are essential for mitotic entry and cell cycle progression (Koval et al. 2019; Zhao et al. 2019), thus revealing another mechanism that could account for the aberrant proliferation of cancer cells with an altered composition of the MCU complex (Fig. 2).

5 Conclusions

The importance of the multiple and complex signaling pathways generated by the displacement of Ca^{2+} ions and, specifically, the Ca^{2+}-dependent communication between structurally and functionally interconnected intracellular organelles has been increasingly highlighted and described, especially in recent years. Evidence of this phenomenon is the dramatic effects on cell health that derive from perturbation of the MAMs morphology and modification of the ER-mitochondria tethering distance. Moreover, alterations in the MAMs protein pool and functionality have been connected with several pathological conditions, including diabetes, neurodegeneration, infection, and antiviral response and cancer (Pinton 2018). Tumor cells, in fact, could modify the systems that maintain cellular Ca^{2+} homeostasis to promote their survival and metastasis. The crucial role of the regulation of spatiotemporal Ca^{2+} signaling in the MAMs in cancer is confirmed by evidence that different oncogenes and tumor suppressors reside at the ER-mitochondria interface.

As shown previously, both an increase and a decrease of calcium ion exchange between these two organelles can, in a nonexclusive way, lead to the promotion or suppression of tumor behaviors in many tissues. This phenomenon is an indication of how the equilibrium that rules calcium homeostasis in this subcellular compartment is delicate, complex, and intimate. Specifically, although Ca^{2+} oscillations are essential at MAMs to feed mitochondrial metabolism, a persistent increase in mitochondrial $[Ca^{2+}]$ can lead to cell death. In this scenario, by limiting mitochondrial calcium uptake, many cancer cells develop resistance to death. On the other hand, it was also highlighted that an increased mitochondrial ability to accumulate Ca^{2+} supports malignant progression, by boosting mitochondrial metabolism and sustaining mitogenic ROS production. Thus, depending on the tumor context, MAM-localized Ca^{2+} signaling can exert different functions, also according to the different oncogenic paths involved.

Several questions have yet to be answered, many aspects remain to be clarified, and molecular pathways must be described to reach a good understanding of the complex mechanisms that stem from calcium signaling at the MAMs, knowledge that will be very useful in the development of novel therapeutic strategies for several tumors.

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