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Review

Cell death as a result of calcium signaling modulation: A cancer-centric prospective☆

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ABSTRACT

Calcium ions (Ca^{2+}) and the complex regulatory system governed by Ca^{2+} signaling have been described to be of crucial importance in numerous aspects related to cell life and death decisions, especially in recent years. The growing attention given to this second messenger is justified by the pleiotropic nature of Ca^{2+}-binding proteins and transporters and their consequent involvement in cell fate decisions. A growing number of works highlight that deregulation of Ca^{2+} signaling and homoeostasis is often deleterious and drives pathological conditions; in particular, a disruption of the main Ca^{2+}-mediated death mechanisms may lead to uncontrolled cell growth that results in cancer. In this work, we review the latest useful evidence to better understand the complex network of pathways by which Ca^{2+} regulates cell life and death decisions.

1. Introduction to Ca^{2+} involvement in life and death

There are four main fundamental, intimately related and interdependent processes of cellular life: survival, proliferation, differentiation and death. Calcium ions (Ca^{2+}) have been proven to be essential in each of these processes, but there is a particular interest in the study of Ca^{2+} homeostasis in cell death mechanisms [1–3]. Indeed, Ca^{2+} signaling has been highlighted/demonstrated to be critically involved in the initiation, implementation and propagation of cell death pathways [4]. Most cells undergo an ordered "physiological" type of death called programmed cell death, which is necessary for maintaining organized cell turnover during development. In other cases, cells can undergo processes that disrupt their integrity and trigger the release of harmful content in a less orderly manner; alternatively, cells can go through a predominantly cytoprotective process that, if exacerbated, becomes a prodeath pathway [2]. Ca^{2+} signaling represents a pathway shared by different death mechanisms, attesting to how these ions are indispensable for both life and death decisions, whether through programmed or nonprogrammed pathways [5–7].

Under resting conditions, the extracellular Ca^{2+} concentration is approximately 1 mM, while the cytosolic Ca^{2+} concentration ($[Ca^{2+}]_c$) is maintained at ~100 nM. Under stimulation, $[Ca^{2+}]_c$ may increase to the micromolar range and reach values that exceed 10 μM in microdomains such as the mitochondrion-associated membranes (MAMs). Increases in $[Ca^{2+}]_c$ can be evoked by both Ca^{2+} release from intracellular reservoirs, which store large amounts of Ca^{2+}, and Ca^{2+} influx through plasma membrane (PM) channels. Among the intracellular organelles that store Ca^{2+} are the sarco/endoplasmic reticulum (SR/ER), the Golgi and lysosomes, which have been recently demonstrated to act as Ca^{2+} stores that are able to respond to physiological second messengers and to bidirectionally communicate with the ER [8].

Whether extracellular Ca^{2+} influx prevails over intracellular Ca^{2+} mobilization or vice versa depends on the stimulus and the cell type.

Cell fate decisions are dependent on ER-mitochondrial Ca^{2+} transfer in a critical way, in fact while rapid Ca^{2+} release from the ER generates transient cytoplasmic and mitochondrial waves with a prosurvival function, stimuli that induce a prolonged increase in the mitochondrial $[Ca^{2+}]$ are responsible for apoptotic or necrotic cell death [9]. The characterization of the influence of many oncogenes on intracellular Ca^{2+} homeostasis, especially over the past decade, has helped to clarify this major role of Ca^{2+} ions in deciding cell fate. Ca^{2+} signaling is controlled by an assortment of Ca^{2+} channels, pumps and PM- or

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intracellular organelle membrane-localized exchangers; dysregulation of the expression or activity of some of these proteins is often associated with certain tumor pathologies [10]. In reference to the tumor microenvironment, the establishment and maintenance of marked multidrug resistance has been associated with specific Ca^{2+} signaling pathways [11].

In the following sections, we will report new findings concerning the consequences of Ca^{2+} signaling modulation on cell fate, with particular attention given to Ca^{2+}-driven cell death mechanisms; we will also focus on the role of Ca^{2+} homeostasis perturbation in the onset and progression of tumor pathologies.

2. Calcium signaling: pathways and proteins involved

Ca^{2+} ions are able to translate information delivered by extracellular and intracellular signals into an intracellular effect controlling a wide range of cellular processes, sometimes even opposing cellular processes. Indeed, cellular spatiotemporal Ca^{2+} signals are regulated by a plethora of specialized Ca^{2+} pumps, channels and Ca^{2+}-binding proteins referred to as the "molecular toolkit" for Ca^{2+} signaling; this toolkit is used by cells in a coordinated manner to both maintain cellular homeostasis and carry out specific cellular functions [12–14].

As discussed above, under resting conditions, the extracellular [Ca^{2+}] exceeds the intracellular [Ca^{2+}] ([Ca^{2+}]$_i$) on the order of 10^4 [15–17]; Ca^{2+} can enter the cell via various ways.

Ca^{2+}-permeable channels of the PM can be divided mainly into three categories: (i) voltage-operated Ca^{2+} channels (CaVs), whose opening is increased by loss of membrane potential; (ii) receptor-operated Ca^{2+} channels, which are modulated by ligand binding and (iii) second messenger-operated channels, whose opening is regulated by the binding of a second messenger on the inner surface of the membrane [18].

In addition, the transmembrane flux of Ca^{2+} ions may be mediated by the transient receptor potential (TRP) channel family, which has different gating mechanisms and is responsible for ER agonist-induced Ca^{2+} depletion-triggered Ca^{2+} entry [19].

Most often, cell Ca^{2+} mobilization is induced by the stimulation of G protein- or phosphotyrosine-coupled receptors in the PM, which activate different isoforms of phospholipase C, triggering the hydrolysis of the PM lipid phosphatidylinositol 4,5-bisphosphate into inositol 1,4,5-trisphosphate (IP3) and diacylglycerol. IP3 interacts with IP3 receptors (IP3Rs), Ca^{2+} channels located in the ER and Golgi apparatus, causing their opening and Ca^{2+} release into the cytosol [20–23].

The fast opening of IP3Rs, of which there are three isoforms (IP3R1–3), on ER membranes allows mitochondria (which have major roles as both regulators and decoders of Ca^{2+} inputs and localize to specific positions throughout the cell) to be exposed to microdomains with Ca^{2+} concentrations one order of magnitude higher than those of the bulk cytoplasm [24,25]. This large Ca^{2+} release, as discussed later, is necessary to induce Ca^{2+} accumulation through the inner mitochondrial membrane (IMM) which exploits its electrical polarization to create an electrochemical potential serving as driving force.

Ca^{2+} penetration into the highly permeable mitochondrial outer membrane (OMM) is mediated by voltage-dependent anion channels (VDACs), which form pores on the OMM. There are three subtypes of VDACs (VDAC1, VDAC2 and VDAC3) that generally ubiquitously expressed, with specific isoform ratios and submitochondrial distributions among tissues. However, VDAC channels mediate the permeability of the OMM not only to ions but also to nucleotides (ADP and/or ATP) and other metabolites [26,27].

Once in the mitochondrial intramembrane space, Ca^{2+} ions are moved across the IMM to the mitochondrial matrix through the mitochondrial Ca^{2+} uniporter (MCU) complex [28–30]. It is now well established that this uniporter is a macromolecular complex composed of the pore-forming subunit MCU, previously known as CCDC109a, and several regulatory proteins [31–35]. Among them is the MCU paralog MCUb, the intermembrane space (IMS)-resident protein mitochondrial calcium uptake protein 1 (MICU1) and MICU2 [36,37]. MICU1 forms a heterodimeric structure by binding to its paralog MICU2 [38–40] through the essential MCU regulator EMRE (also known as SMDT1) [41] and MCUR1 binds to MCU and EMRE functioning as a scaffold factor [42]. Each MICU1 and MICU2 subunit contains four EF-hands, of which two are capable of binding Ca^{2+} [43]. MICU3, a tissue-specific MCU modulator expressed at high levels in the brain, forms a dimer with MICU1, but not with MICU2, and acts as a MCU-dependent mitochondrial Ca^{2+} uptake enhancer [44]. Upon Ca^{2+} elevation MCU and EMRE dynamically accumulate at the IMM in a MICU1-dependent manner [45].

The MCU complex has a very low affinity (Kd ~ 15–20 μM [46]) but a very high selectivity for Ca^{2+} ions; these features allow it to open only at a relatively high [Ca^{2+}]; this limit value exceeds the [Ca^{2+}]$_c$ reached upon cell stimulation (1–3 μM). This apparent inconsistency is explained by the observation that MCU senses these [Ca^{2+}] elevations at subdomains, named MAMs, which are composed of mitochondrial membrane portions in close contact with the ER surface [47–49]. These interorganelle associations were assessed through the use of different techniques—mainly live imaging, electron microscopy and subcellular fractionation—to establish the presence of these interactions at both the protein and organelle levels [50] (Fig. 1).

The close association between these two organelles is possible thanks to different proteins, which play a bridging action between ER and mitochondria. Among these, we must mention IP3R–GRP75–VDAC1 complex, that is not just a channel alignment structure but acts as a physical MAMs linker and mitofusin protein Mfn2, an integral mitochondria membrane protein that is also required on adjacent mitochondria to mediate fusion [2].

The associations that mitochondria form with the ER are not exclusive, since these organelles can also associate with the PM, forming so-called PM-associated membranes (PAMs) [51] that are exposed to the increases in [Ca^{2+}] induced by the activation of voltage-gated Ca^{2+} channels in the PM [25]. Ca^{2+} accumulation in mitochondria results in enhanced energy production (e.g., stimulation of the Krebs cycle, NADH formation and fueling of respiratory chain activity, with increased ATP production) and reactive oxygen species (ROS) accumulation [30]; the contribution of LETM1 should also be mentioned in this context as LETM1-dependent mitochondrial Ca^{2+} flux plays an important role in shaping cellular bioenergetics (25077561).

Excessive Ca^{2+} accumulation can be effectively avoided by mitochondrial matrix-localized buffer systems [30,52]. Indeed, while changes in the physiological mitochondrial [Ca^{2+}] stimulate cellular metabolism, massive accumulation of this ion in the organelle matrix (a process known as Ca^{2+} overload) causes the opening of a Ca^{2+}-sensitive, highly conductive and voltage-dependent channel: the mitochondrial permeability transition pore (mPTP) [53]. This [Ca^{2+}]$_m$ overload leads to the mPT, the consequent irreversible increase in the permeability of the IMM to small molecules, mitochondrial depolarization, increased ROS production and OMM rupture, causing the release of IMS-resident proapoptotic factors into the cytosol [54], which activates the intrinsic apoptotic signaling pathway. The mPTP is a multimeric protein complex of unclear composition; the c-subunit of F0 ATP synthase appears to be a critical component of this complex that is regulated by the OMM protein VDAC and the IMM protein cyclophilin D [7,55–57]. Recently, Karch et al. made clear that the adenine nucleotide translocator (ANT) acts as the inner membrane pore-forming component and is an essential element of mPTP, with an unknown species requiring Cyclophilin D [58]. The mPT is an event associated with the loss of mitochondrial membrane potential and structural integrity, which promotes the release of IMS-resident proapoptotic factors, including cytochrome *c*, Smac/DIABLO and AIF, into the cytosol, triggering caspase-dependent and caspase-independent pathways [54,59].

ATP depletion and oxidative stress contribute to Ca^{2+}-dependent pore opening, which may be prevented using inhibitors of mitochondrial Ca^{2+} uptake, such as the selective MCU complex inhibitors ruthenium

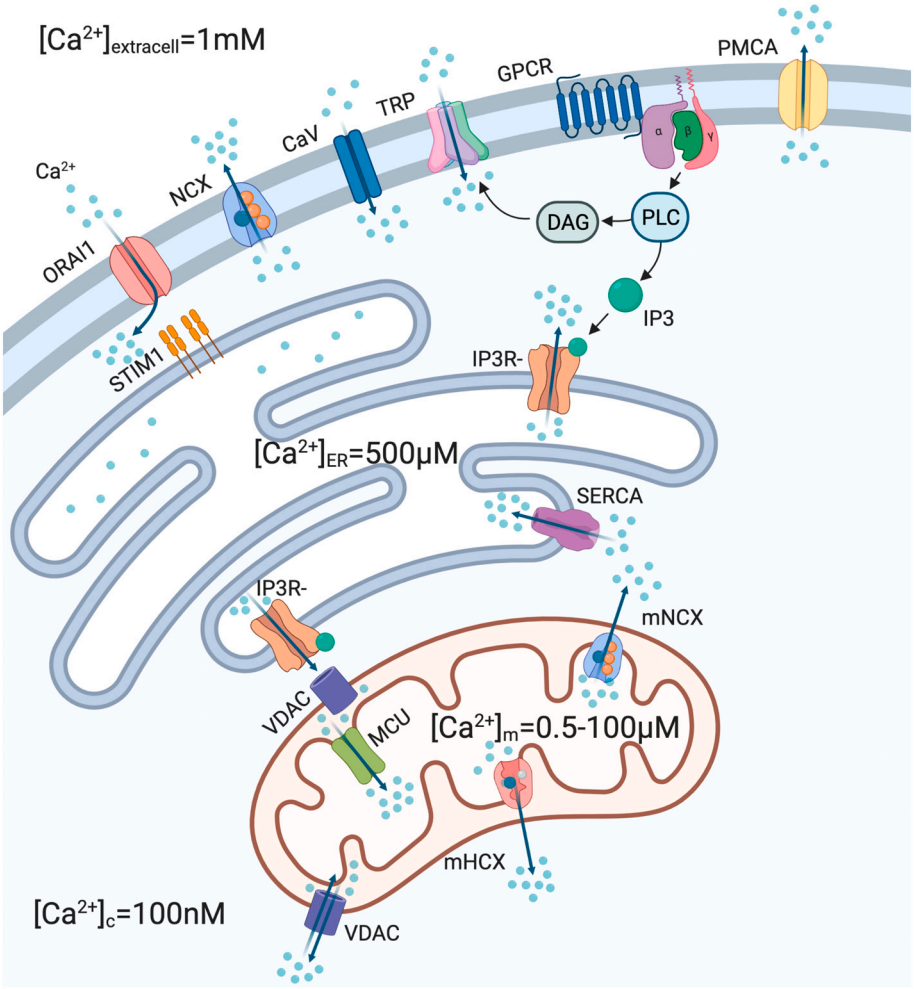

Fig. 1. Representation of Ca^{2+} signaling pathway. Signal transduction via Ca^{2+} represents a crucial signaling pathway that can transduce signals with diverse spatial and temporal dynamics in all eukaryotic cells. The importance of this process is well represented by the fact that a large portion of human genome encodes proteins used to assemble this signaling system. In Figure, $[Ca^{2+}]$ represents free Ca^{2+} concentrations.

red, DS16570511 and Ru265 [60–62]. Mitochondrial Ca^{2+} remodeling plays a fundamental role in shaping pathological signaling cascades required for clinical manifestations and disease pathogenesis, such as inflammation, cancer, neurodegenerative disease and cardiac disorders (as reviewed in [63–65]).

Under physiological conditions, a transient increase in mitochondrial $[Ca^{2+}]$ is followed by ion extrusion through VDAC channels in the OMM. At IMM level, the two main systems involved in this process are the mitochondrial Na^{+}/Ca^{2+} exchanger (mNCX), which is predominant in excitable tissues such as heart and brain, and the mitochondrial H^{+}/Ca^{2+} exchanger (mHCX), which is present mainly in nonexcitable tissues (the liver and kidney) [66]. Once in the cytoplasmic compartment, Ca^{2+} ions are cleared out of cells (through PMCA or NCX) or returned to the endoplasmic reticulum to reestablish basal intracellular ion levels via the ER-resident Ca^{2+} pump sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA). SERCA has different tissue-specific splice variants encoded by three SERCA genes (ATP2A1, ATPA2 and ATP2A3) and maintains the correct ER Ca^{2+} levels by actively pumping Ca^{2+} into the ER from the intracellular space [67].

In addition, the resting $[Ca^{2+}]_{ER}$ is restored through store-operated Ca^{2+} entry (SOCE), which activates extracellular Ca^{2+} influxes across membrane channels.

ER-inserted stromal interaction molecule-1 (STIM1) and the calcium release-activated calcium channel protein ORAI1 are the main proteins involved in this process and physically interact at ER–PM junctions in a functional Ca^{2+} release-activated Ca^{2+} (CRAC) channel complex [68]. Furthermore, stromal-interacting molecule proteins (STIM1 and STIM2), which are ER Ca^{2+} sensors that initiate SOCE, are required for Ca^{2+} store depletion-mediated Ca^{2+} influx which occurs through the interaction and activation of STIM1/2 with the PM Ca^{2+} channel ORAI [56] (Fig. 1).

An interesting recent study has highlighted how the different heteromerization of ORAI channels leads to different Ca^{2+} signaling response. ORAI3 and ORAI2 relative to ORAI1 levels can alter the magnitude of SOCE and downstream Ca^{2+} signaling [69].

3. Main cell death mechanisms

Cell death is a crucial and essential aspect of life, and it has been demonstrated to be directly connected to cell survival and proliferation [12]. Cell death can occur through different mechanisms, and the preferred pathway and morphological changes observed can vary depending on the stimulus and the cell setting.

3.1. Apoptosis

Apoptosis is the most important and well-studied mechanism of programmed cell death. This death process, classified as type I cell death, is characterized by cell membrane blebbing, cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA

fragmentation. The apoptotic process is regulated by a plethora of stimuli, including Ca^{2+} signaling [1,35,70,71].

Specifically, upon death signaling activation, the cytoplasmic pro-apoptotic proteins Bax and Bak, which are part of the Bcl2 protein family [72], are translocated to the OMM and form oligomers contributing to mitochondrial permeabilization and the consequent release of mitochondrion-derived activator of caspase (Smac)/direct inhibitor of apoptosis-binding protein (DIABLO) and cytochrome C. Once in the cytosol, cytochrome C triggers the formation of the apoptosome consisting of caspase-9, cytochrome C and the cofactor apoptosis protease-activating factor (Apaf), which activates the effector proteins caspase-3, −6 and, −7 and also induces apoptosis [73,74]. Caspases, the executors od apoptosis, are endoproteases that hydrolyze peptide bonds in a reaction that depends on catalytic cysteine residues in the caspase active site [75]. Smac/DIABLO in turn contributes to the apoptotic pathway by impeding the function of IAP and XIAP, proteins that prevent the pro-apoptotic roles of caspase-3, −7 and -9 [76].

In addition, another apoptotic signaling pathway, termed the extrinsic pathway, can be activated. This is initiated by the binding of death ligands [e.g., Fas ligand (FasL), TNF-related apoptosis inducing ligand (TRAIL), and tumor necrosis factor-α (TNF-α)] to death receptors of the TNF receptor superfamily. Subsequently, the death-inducing signaling complex (DISC), which consists of the Fas-associated death domain (FADD) protein and procaspase-8/10, is assembled [77]. The DISC can both activate downstream effector caspases (caspase-3, −6 and − 7) and induce cell death or activate the mitochondrion-mediated intrinsic apoptotic pathway by cleaving the Bcl-2 family member Bid into truncated Bid (tBid). Subsequently, tBid activates Bak and Bax at the mitochondria, resulting in OMM permeabilization and release of proteins such as cytochrome *c* and Smac/DIABLO [78] (Fig. 2).

3.2. High autophagic activity levels and apoptosis

Autophagy, classified as type II cell death, is an evolutionarily conserved process with the main function of collecting, degrading and recycling intracellular material to enhance cell survival. It is mainly activated in response to nutrient deprivation and other stresses [79,80]. The connection between apoptosis and autophagy processes is complex since they are not mutually exclusive pathways and can cooperate with or counteract each other.

In general, as stated above, autophagy antagonizes apoptosis, supporting cell viability by creating a favorable environment that promotes cell survival [81,82]. However, excessive autophagy results in programmed cell death [83]. In this scenario, the autophagy and apoptosis pathways may occur in parallel-one pathway may be predominant or act as a backup mode if the other is blocked [84].

Finally, there is evidence that autophagy can support apoptosis, assisting this process in several ways (e.g., by supporting the formation of ATP, which is required for phosphatidylserine exposure, without leading to cell death itself); this evidence further reveals the complexity of the relationship between these two pathways [85].

Basal levels of autophagy are necessary to maintain homeostasis, as

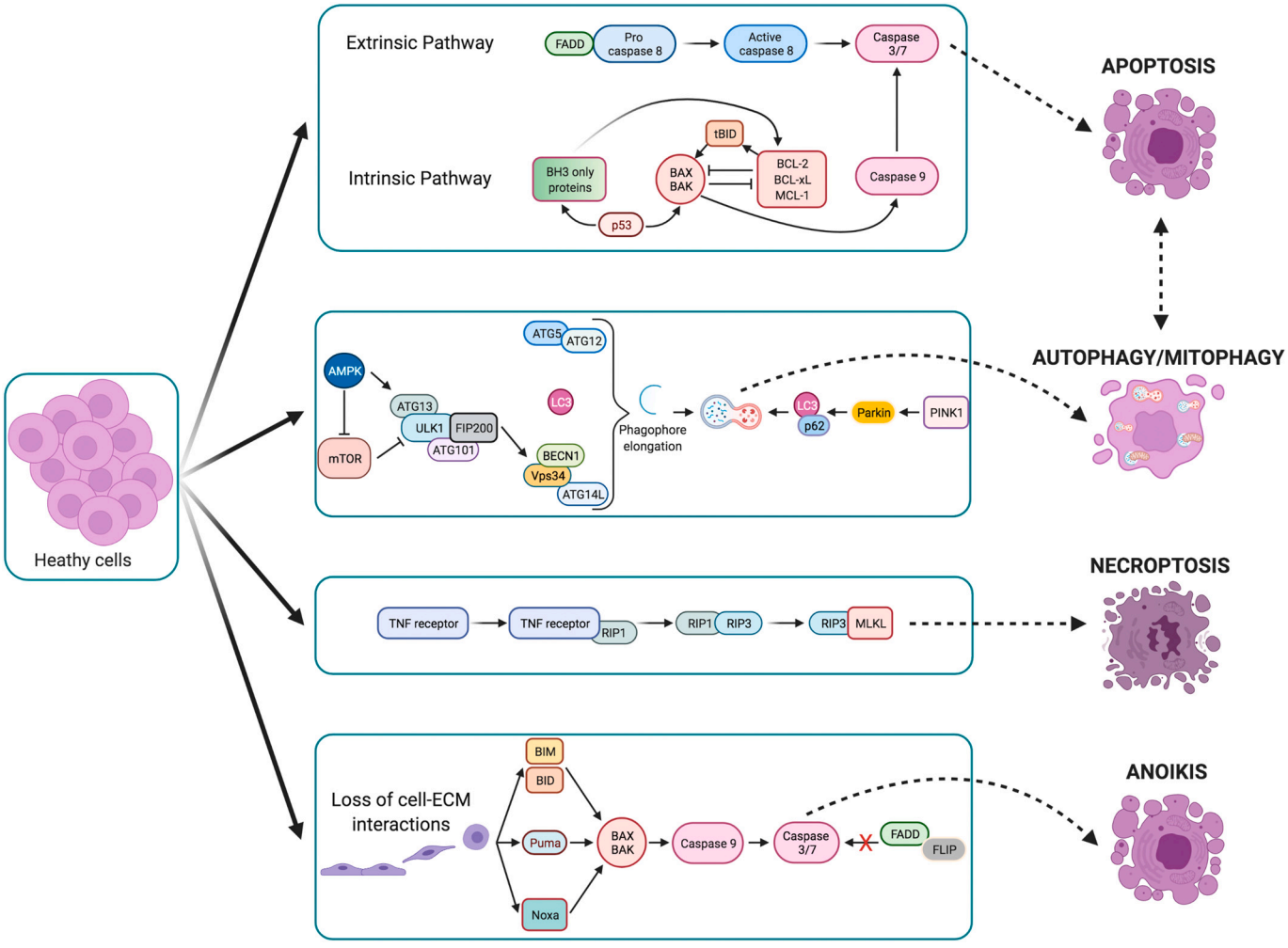

Fig. 2. Main cell death mechanisms and molecular pathways. Cells eliminate themselves through various dying mechanisms to reach the delicate balance necessary for the homeostatic well-being of eukaryotes.

this process removes damaged proteins and organelles and operates as an intracellular quality system. During the autophagic process, intracellular components are enclosed in eukaryotic bilayer membrane vesicles, named phagosomes, and transported to lysosomes to form autophagolysosomes for degradation [86–88].

The majority of proautophagic events converge on the mammalian target of rapamycin (mTOR) pathway [89,90] and activation of AMP-activated protein kinase (AMPK), which is able to sense changes in the AMP:ATP ratio resulting from energy starvation [91,92]. These kinases may modulate the activation of the unc-51-like autophagy-activating kinase 1 (ULK1) complex (known as the Atg1 complex in yeast), which consists of serine/threonine kinase ULK1, scaffolding subunit FAK family-interacting protein of 200 kDa (FIP200), and regulatory subunits ATG13 and ATG101 [93]. Under physiological conditions, mTORC1 inhibits the ULK1 complex by binding and phosphorylating both ULK1 and the ATG13 regulatory subunit [94,95]; under nutrient deficiency conditions, AMPK phosphorylates the ULK1 complex at multiple sites, inducing the activation of this complex [94] and the inactivation of mTORC1 [96].

Class III phosphoinositide 3-kinase complex I (PI3KC3-C1) is another pivotal autophagy-initiating complex composed of phosphoinositide (PI) kinase vacuolar protein sorting 34 (VPS34), regulatory subunit Beclin-1 (Atg6 in yeast), scaffold protein VPS15, and ER-targeting protein ATG14L [93]. The phosphorylation of VPS34 and Beclin-1 [97] by ULK1 can activate the complex, triggering the nucleation of the phagophore, also known as the isolation membrane.

In mammals, autophagosomes can originate at ER-mitochondria contact sites [98]. Moreover, some of the key components of the autophagosome process (Atg5, Atg14, Beclin-1, Vps15, Vps34) move to the MAM under starvation conditions, and alterations in ER-mitochondria tethering lead to decreased autophagy [98]. This evidence highlights the interplay between the ER and mitochondria in the autophagic process.

After initiation, the phagophore starts to elongate into a cup-shaped structure and begins to engulf cellular material. This stage requires two ubiquitin-like protein (UBL) conjugation systems: the ATG12–ATG5 UBL and the microtubule-associated light-chain B (LC3B) phosphatidylethanolamine PE UBL [99]. Nascent pro-LC3 is cleaved by the cysteine protease ATG4B, and processed LC3 is then conjugated to membrane-associated PE [100]. LC3 lipidation is widely used as an autophagosome marker and has been shown to depend on ER-mitochondrial connections [101].

Mitophagy is a highly specialized process that ensures mitochondrial quality control, maintaining mitochondrial homeostasis by removing dysfunctional or damaged mitochondria, which are sources of genotoxic ROS, through the autophagic machinery [102].

The PINK1/Parkin pathway is the best-known mechanism of mitophagy regulation in most mammalian cells. PINK1, the key initiator of mitophagy, is a serine/threonine kinase that accumulates on the OMM of depolarized mitochondria, where it phosphorylates S65 of the E3 ubiquitin ligase Parkin, blocking its autoinhibitory activity and leading to its activation and further recruitment to the OMM of damaged mitochondria [103,104]. In turn, Parkin ubiquitinates one or more OMM proteins, which are then recognized by p62 and recruited to autophagosomes by LC3, which commits mitochondria to autophagic turnover [105]. The p62 protein serves as a bridge between Parkin on the OMM and the autophagosome since it binds to ubiquitinated proteins on the OMM using its ubiquitin-associated domain and binds to LC3 via another specific region [106] (Fig. 2). Parkin/PINK1 also cause MAMs disruption, catalyzing a rapid burst of Mfn2 phosphoubiquitination to trigger p97-dependent disassembly of Mfn2 complexes from the OMM, dissociating mitochondria from the ER [107].

An additional mechanism of Parkin activation involves mitophagy receptor autophagy and beclin 1 regulator 1 (AMBRA1), which is normally associated with the Bcl-2 protein at the OMM. Upon stimulation of mitophagy, AMBRA1 binds to Beclin1 and then to Parkin [108]. The interaction of Parkin and AMBRA1 is strongly increased during prolonged mitochondrial depolarization. Upon mitophagy induction, AMBRA1 can bind the autophagosome adaptor LC3, exploiting the LC3-interacting region (LIR) domain. This interaction is crucial for the promotion of Parkin-dependent and Parkin-independent mitochondrial clearance [109].

Similar to AMBRA1, other mitophagy receptors on the OMM, such as BNIP3, NIX and FUNDC, can also bind to the autophagosome via LIR fragments. Some of them are translocated from the cytoplasm to mitochondria upon induction of mitophagy; others are constitutively attached to the OMM via the transmembrane domain and can bind LC3 directly [110]. Ca^{2+} signaling can regulate the autophagic process, but the mechanism depends on cell conditions; Ca^{2+} signaling can even exert opposite roles under basal and stress conditions.

In terms of modulation of the autophagic process by Ca^{2+}, the role of autophagy in cancer is often complex and even controversial, as autophagy has an inhibitory effect on early tumor initiation and growth but promotes survival in the metastatic stage and maintains tumor dormancy until distant colonies are successfully established [111].

Increasing evidence indicates that defects in the mitophagy machinery, similar to the aforementioned defects in apoptosis and autophagy, may also have a role in cancer progression [112].

3.3. Necroptosis

Accumulating evidences has recently shown that necrosis could be finely adjusted by a set of catabolic mechanisms and signal transduction pathways [113]. Regulated necrosis is termed “programmed necrosis” or “necroptosis” [113].

Similar to apoptosis and autophagy, necroptosis plays a pivotal role during physiological development and is implicated in the onset of many human diseases, including cancer [114].

Necroptosis has typical morphological features of necrosis represented by organelles swelling, collapse, loss of cell membrane integrity and deficiency of nuclear chromatin [115].

As already described for apoptosis, during necroptosis, mPT occurs as a consequence of lipid peroxidation induced by ROS generation, and in turn, apoptosis-inducing factor (AIF) is released from mitochondria [116]. One of the principal hallmarks of this type of programmed cell death is the multistep formation of the “necrosome” by receptor-interacting protein kinase 1 (RIP1) and RIP3 after induction by different stimuli, such as the TNF receptor superfamily [117], T cell receptors [118], interferon receptors and Toll-like receptors (TLRs) [119]. At cytosolic level, an increase in Ca^{2+} accumulation triggered by RIP1/RIP3 complex formation results to be a critical mediator in MAM-induced necroptosis through a persistent c-Jun N-terminal kinase (JNK) activation and mitochondrial ROS production [120].

Upon death ligand binding, RIP1 binds with death receptors via their respective death domains (DDs) and forms the death complex with RIP3 through their homotypic interaction motif (RHIM) domains, activating their kinase activities [121]. RIP3 ultimately phosphorylates mixed lineage kinase domain-like protein (MLKL), leading to its translocation to the cell membrane and subsequent membrane integrity disruption [122] (Fig. 2).

RIPK3/RIPK1 is not a necroptosis-exclusive pathway; hence, carefully dissecting these pathways will offer better targets for therapeutic approaches in the future [123].

3.4. Anoikis

Anoikis was originally defined as a particular type of apoptotic cell death induced by the loss of attachment to the cell-extracellular matrix (ECM) [124]. The interaction of cells with the ECM is mediated by cell-specific integrin receptors that adhere to specific ECM counterparts. This interplay modulates the transduction of many different signals that span from gene expression, motility, proliferation and differentiation to cell

localization regulation, and as a consequence, this interplay regulates cellular survival and death. In 1994, Frisch and Francis noticed that loss of epithelial cell matrix attachment resulted in apoptosis [125,126].

Anoikis plays a pivotal role in physiological tissue homeostasis and development, and its dysregulation is a critical mechanism in cancer metastasis since it prevents detached epithelial cells from colonizing elsewhere. Indeed, the development of resistance to anoikis enables cells to survive after detachment from their primary site while traveling through the vascular system until they colonize a distal organ and establish metastatic lesions [127–131].

During anoikis, the mitochondrial pathway is activated, and proapoptotic Bcl-2 proteins play a critical role [132]. Bim and Bid, two members of the Bcl-2 protein family, are activated via the detachment of cells from the ECM and facilitate the oligomerization of Bax-Bak within the OMM. Usually, Bim is sequestered by dynein cytoskeletal complexes, but when cells detach from the ECM, the Bim protein is released from the complex and translocates to the mitochondria, where it interacts with Bcl-xL, neutralizing its antiapoptotic function [126,133,134] and promoting Bax-Bak oligomerization within the OMM [126,127]. Loss of cell-ECM interactions also triggers cytosolic Bim accumulation caused by the inhibition of its proteasomal degradation.

Bid and Bim are not the only members of the Bcl-2 family proteins to have been demonstrated to be involved in the anoikis pathway. Indeed, Noxa (Latin term for damage) and the p53 upregulated modulator of apoptosis (Puma) contribute to fibroblast anoikis, and Bmf induces anoikis in epithelial cells [135–137] (Fig. 2).

Moreover, the intrinsic apoptosis pathway is not the only pathway involved in anoikis induction.

FLICE-inhibitory protein (FLIP) is the primary endogenous inhibitor of the death receptor pathway and shows a higher affinity for the DISC than for caspase-8 and, as a consequence, inhibits caspase-8 recruitment and activation [129,138]. In human umbilical vein cells (HUVECs), cell detachment triggers FasL and Fas upregulation and FLIP downregulation, which leads to caspase-8 activation [139,140] (Fig. 2).

4. The Ca^{2+} connection: ion involvement in cell fate decisions

The involvement and contribution of Ca^{2+} ions in cell death have been well known for a long time. The first evidence showed that the triggering of necrotic cell death was a consequence of excessive Ca^{2+} entry into cardiomyocytes after ischemia [141]. This observation has since been confirmed in other cell types, where many cytotoxic agents have been found induce an increase in Ca^{2+} influx across the PM, causing collapse of the proton gradient and bioenergetic catastrophe, thus leading to necrotic cell death (as reviewed in [142]). Excessive Ca^{2+} entry also plays a leading role in apoptosis, where intracellular Ca^{2+} overload stimulates different Ca^{2+}-sensitive catabolic enzymes, such as proteases, endonucleases and phospholipases. Among the Ca^{2+}-dependent proteases, the Ca^{2+}-sensitive cysteine protease calpains play a key role in cell death (as reviewed in [143]). Two calpain isoforms (μ-calpain and m-calpain) require different intracellular Ca^{2+} concentrations for their activation (μM and mM, respectively). Their activation is regulated by an endogenous inhibitor, calpastatin, which is cleaved by caspase-3 during the apoptotic response, indicating that calpains participate in apoptosis [144]. In some cell types, such as neurons, cardiomyocytes and immune cells, the contribution of calpains to the apoptotic pathway is similar to that of caspases [145].

4.1. Ca^{2+} in apoptosis and necrosis

Several studies have demonstrated that apoptosis is regulated not only by the mitochondria through VDAC channels but also by Ca^{2+} dynamics at the ER, which is a main regulation mode for this type of cell death [28,53]. It is well known that adverse changes in Ca^{2+} signaling involve different intracellular organelles, such as the ER and mitochondria, where alterations in the Ca^{2+} levels of different cell compartments can induce a stress response to trigger apoptosis [53]. The initiation of the intrinsic apoptotic pathway leads to early ceramide-induced structural and functional alterations of the ER and mitochondria which commit cells to the apoptosis pathway [146]. Csorda's et al. demonstrated that ER-mitochondrial distance plays a pivotal role in modulating cell functions and survival, suppressing the propagation of Ca^{2+} signals to mitochondria when these organelles are at a distance greater than 25–30 nm and inducing mitochondrial Ca^{2+} overload and apoptosis when they are in close contact. Furthermore, a pool of the tumor protein p53 has been demonstrated to be localized at the ER–MAM interface, where it acts as a cell death inducer by regulating SERCA oxidation state and therefore activity under stress conditions [124].

Numerous studies, which we will discuss later, have also identified several oncogenes and tumor suppressors that act as specific regulators of IP3R3-mediated Ca^{2+} flux to mitochondria.

Typically, necrosis is an inflammatory response-associated event, and the activation of Ca^{2+}-dependent phospholipase A2 (PLA2) by intracellular Ca^{2+} confirms this. Indeed, the activation of PLA2 by Ca^{2+} ions triggers the production of arachidonic acid and the consequent generation of proinflammatory mediators and ROS induced by lipoxygenase and cyclooxygenase activation (as reviewed in [147]). In addition, the recruitment of PLA2 during the necrotic process is responsible for the production of lysophosphatides that induce membrane alterations [148], affecting the mPT, the release of proapoptotic factors and the activation of caspases [149].

Caspases are not directly modulated by Ca^{2+} ions, but once activated, they might in turn affect the $[Ca^{2+}]_i$. In particular, caspase or calpain may cleave IP3Rs resulting in a transient alteration of receptor-mediated Ca^{2+} signals, which can rapidly switch on alternative signaling pathways [150–153]. Similarly, during programmed cell death, the Na^+/Ca^{2+} exchanger is cleaved by caspase-3, indicating that loss of function associated with cleaved PM Ca^{2+} extrusions is a pivotal step in maintaining intracellular Ca^{2+} overload in apoptotic cells [154].

4.2. Ca^{2+} in autophagy

CaMKK is also recruited to regulate the autophagic process: an increase in $[Ca^{2+}]_i$ induces the activation of CaMKK, which promotes autophagy by regulating the AMPK/mTOR pathway [155]. Ca^{2+} function in the autophagic process is debated. It is not clear if the observed Ca^{2+} alterations are the cause or consequence of the process [156]. To date, a high number of works have shown that impaired ER-mitochondria Ca^{2+} transfer stimulates the autophagic process. The experimental manipulation of ER-mitochondria interplay has demonstrated that increasing or decreasing interorganelle Ca^{2+} transfer significantly impacts basal and chemically induced (rapamycin and torin-1) autophagy [157]. An increase in the closeness of the ER-mitochondria physical association, promoted by the overexpression of the ER protein VAPB and mitochondrial protein RMDN3 or PTPIP51, augments Ca^{2+} delivery from IP3Rs to mitochondria, which in turn inhibits autophagosome formation. In contrast, if ER-mitochondria coupling is lost, reduced Ca^{2+} transfer stimulates autophagosome formation, which has important repercussions on the pathophysiology of different diseases, such as cystic fibrosis and Parkinson's disease [158,159]. These findings are in line with a large number of publications that show that altered Ca^{2+} delivery from the ER to mitochondria and the cytosol stimulates autophagy [160–162]. Consistent with this, the effects of ER-mitochondria tethering on autophagosome formation and autophagy are neutralized by silencing MCU expression or by treating cells with specific MCU inhibitors, confirming that mitochondrial Ca^{2+} is a limiting factor in autophagy induction [158,163]. However, the nature of the autophagic stimulus plays a very important role in regulating this degradation process, as demonstrated by the fact that starvation-induced autophagy is not sensitive to ER-mitochondria tethering perturbations. Rapamycin and torin-1 pharmacological agents

induce autophagy by inhibiting mTOR activation and nutrient deprivation. Numerous upstream nutrient-sensing proteins, such as CaMKK and AMPK, are conditioned by the disruption of the Bcl-2-beclin1 complex [164,165]. Although, as stated above, numerous studies show that interrupting ER Ca^{2+} delivery to mitochondria is important in autophagy stimulation; paradoxically, starvation-induced autophagy seems to be mediated by an increase in ER Ca^{2+} content triggered by an increase in the level of ER Ca^{2+}-binding proteins and a reduction in the ER Ca^{2+} leak rate mediated by beclin1-dependent and IP3R-dependent Ca^{2+} release sensitization [166].

4.3. Ca^{2+} in necroptosis

Necroptosis is a relatively newly unveiled necrotic cell death pathway. Necrosis has always been described as an uncontrolled cell death mechanism, but recent evidence has shown that necrosis may actually be mediated by specific signal transduction pathways and degradative mechanisms [167]. RIP1 is phosphorylated by Ca^{2+}-sensitive calcium-calmodulin kinase II (CaMKK), which is activated by intracellular Ca^{2+} overload [168]. Excessive Ca^{2+} influx is mediated by non-voltage-sensitive transient receptor potential cation channel subfamily M member 7 (TRPM7), which is in turn regulated by the relocalization of MLKL to the PM [169]. These findings have been confirmed in caspase-8-deficient neuroblastoma cells, in which temporal increase in cytoplasmic Ca^{2+} can trigger CaMKII autophosphorylation, thereby causing necroptosis via RIP1 phosphorylation [168].

4.4. Ca^{2+} in anoikis

Ca^{2+} signaling has also been demonstrated to be involved in anoikis regulation [170]. Ca^{2+}-sensitive calpain proteases participate in the detachment of cancer cells from the matrix following antitumor drug treatment [171]. In addition, Ca^{2+}-activated chloride channel expression may impact anoikis in tumor cells; for example, the downregulation of these channels reduces anoikis in breast cancer [172]. Another example of a Ca^{2+}-sensitive protein involved in anoikis is the double C2-like domain β gene; ectopic expression of this gene induces anoikis-mediated cell death, promoting an increase in $[Ca^{2+}]_i$ and cytoskeletal remodeling [173]. In colonic epithelial cells, intracellular Ca^{2+} depletion is associated with anoikis-resistant behavior [174].

On the other hand, it has been observed that treatment with Ca^{2+} chelators and/or E-cadherin inhibitors induces anoikis in hepatocytes, where the Ca^{2+}-dependent cell adhesion protein E-cadherin plays a key role in spheroid formation and maintenance; this mechanism prevents cell death when extracellular matrices are absent [175].

In recent years, the contribution of Ca^{2+} signaling to the regulation of death in different cell types has been indicated to have increasing value, and these studies have shed light on the complexity of the intracellular Ca^{2+} signaling machinery.

5. Ca^{2+}-related proteins that are involved in tumor onset and progression

Especially in recent decades, the scientific literature has been enriched with evidence that illustrates how Ca^{2+} signaling-governed pathways have a clear overlap with a consistent number of processes that are crucial to cancer cell progression [176]. Among these processes, resistance to cell death inducers and sustained cell growth deserve mention. However, these are not the only aspects of cancer onset in which Ca^{2+} signaling plays a pivotal role. Indeed, it has been

Table 1
Ca^{2+} signaling-related proteins effects on cell death mechanisms.

Protein	Action	Through	Result	Reference
Bcl-2	Anti-apoptotic	IP3R biding	Decreases ER Ca^{2+} release /prevent mitochondrial Ca^{2+} transfer/ ER Ca^{2+} leak	[28,204,205,243–247]
Nix	Apoptotic	mPTP	ER Ca^{2+} content increase	[214]
BAD	Apoptotic	Heterodimerization with Bcl-xL	Increases in $[Ca^{2+}]$ change its phosphorylation state through calcineurin	[215,248,249]
SERCAs	Apoptotic / Anti-apoptotic	Deficiency	ER Ca $^{2+}$ depletion, CRAC channels activation, mitochondrial Ca $^{2+}$ uptake and ROS production	[250–254]
TMX1	Antiapoptotic	SERCA2b binding	Reduce ER Ca^{2+} uptake compromising MAMs	[232]
BRCA1	Apoptotic	IP3R direct binding	Increased IP3R-mediated calcium release	[221]
PTEN	Apoptotic	IP3R3 stabilization	Increase Ca^{2+} transfer from ER to mitochondria	[222,255]
PML	Inhibition of autophagy; Apoptotic	MAM localization	Increase Ca^{2+} transfer from ER to mitochondria	[223,256]
BAP1	Apoptotic	IP3R3 stabilization	Increase Ca^{2+} transfer from ER to mitochondria	[224]
Akt/PKB	Antiapoptotic	IP3R3 phosphorylation	Reduced ER Ca^{2+} release	[226,257]
p53	Apoptotic	SERCA binding and activation	Increasing ER Ca^{2+} loading / favoring Ca^{2+} transfer from the ER to the mitochondria	[28,124]
IP3R3	Apoptotic and Autophagic	ER Ca^{2+} release, ATP synthesis, AMP/ATP ratio and AMPK modulation	Regulation of Ca^{2+} transfer from ER to mitochondria	[258]
MCUR1 (Hepatocellular carcinoma, HCC)	Antiapoptotic	MCU interaction	Enhanced mitochondrial Ca^{2+} uptake ➔ increased mROS production ➔ P53 degradation	[259]
MCU silencing (Human colon cancer)	Resistance to apoptosis	Mitochondrial Ca^{2+} influx	Reduce mitochondrial Ca^{2+} uptake	[241]
MICU1 and MICU2 downregulation and EMRE upregulation (pancreatic cancer cells)	Apoptosis	Mitochondrial Ca^{2+} influx	Mitochondrial Ca^{2+} Uptake regulation	[260]
MICU1 (ovarian cancer cells)	Antiapoptotic	Mitochondrial Ca^{2+} influx	Increased mitochondrial Ca^{2+} uptake	[261]
Pfkfb3 (breast cancer stem cells, BCSCs)	Inhibition of autophagy	Physically interaction with the UBA domain of p62/sequestosome-1	PMCA function maintenance	[200]
MICU1 knockdown	Apoptosis	Mitochondrial Ca^{2+} influx	Ca^{2+} overload	[201]
TRPM3 (renal cell carcinoma)	Autophagy stimulation	Activation of CAMKK2, AMPK, and ULK1, and phagophore formation	Increased Ca^{2+} influx	[202]

demonstrated that cellular Ca^{2+} homeostasis is also involved in resistance to anticancer therapies and events in the tumor microenvironment. It is therefore logical that modifications of essential Ca^{2+} signaling proteins may be linked to cancer cell proliferation and invasiveness and anticancer drug sensitivity (Table 1).

The characterization of these proteins and their effect on Ca^{2+} homeostasis is possible thanks to the development of Ca^{2+}-sensitive fluorescent dyes [177] and genetically encoded Ca^{2+} indicators [178]. These tools have been fundamental in the characterization of intracellular Ca^{2+} signaling as they facilitate the quantitative analysis of Ca^{2+} in the cytoplasm and in important subcellular organelles including mitochondria and ER [179–182].

5.1. Ca^{2+} homeostasis perturbations across the PM

SOCE is the process by which the exhaustion of ER Ca^{2+} stores causes the influx of this ion across the PM. The expression of STIM1 and Orai1, the key molecular components of SOCE, is altered in various cancer types, including breast [183], esophageal [184] and cervical [185] cancers. SOCE mediated by STIM1 and ORAI1 seems to play a dual role during carcinogenesis. On one hand, increased SOCE has been described to promote tumor growth and metastasis in many cancer types; on the other hand, STIM1 causes growth arrest in human rhabdomyosarcoma, ORAI1 facilitates the apoptosis of prostate cancer (PCa) cells, and knockdown of ORAI1 leads to drug resistance [186]. In addition to isoform 1, also ORAI3 expression modulation lead to PCa cells enhanced growth and increased resistance to apoptosis. In particular, ORAI3 determines the oncogenic switch between arachidonic acid-regulated and store-operated Ca^{2+}-channels by disrupting normal homomultimerization of ORAI1 and favoring ORAI3 and ORAI1 heteromultimerization [187] (Fig. 3).

Especially in breast and lung tumor forms, TRP proteins, another family of proteins that mediate Ca^{2+} influx across the PM, are ectopically upregulated. In detail, in breast and lung tumors, where the master antioxidant regulator nuclear factor erythroid 2-like 2 (NRF2) is hyperactive, subfamily A1 (TRPA1) orchestrates ROS resistance [188]. Increased levels of TRPV6, the major member of the TRP superfamily, have been reported in a great number of cancers, including PCa, colon cancer, thyroid cancer, and parathyroid cancer [189–191], and in estrogen receptor-negative breast cancers, TRPV6 overexpression is testified by an increase in TRPV6 copy number [192] (Fig. 3).

Altered CaV channel gene expression profiles are related to different cancer types, and it has been shown that several CaV channel blockers prevent cancer invasion [193]. In particular, the CaV1.2 and CaV1.3 channels are usually localized to skeletal and smooth muscle cells, cardiac cells, pancreatic cells, neurons and fibroblasts and are overexpressed in most cancer types [194] (Fig. 3).

PMCA4 and especially PMCA2 mRNA was found to be highly

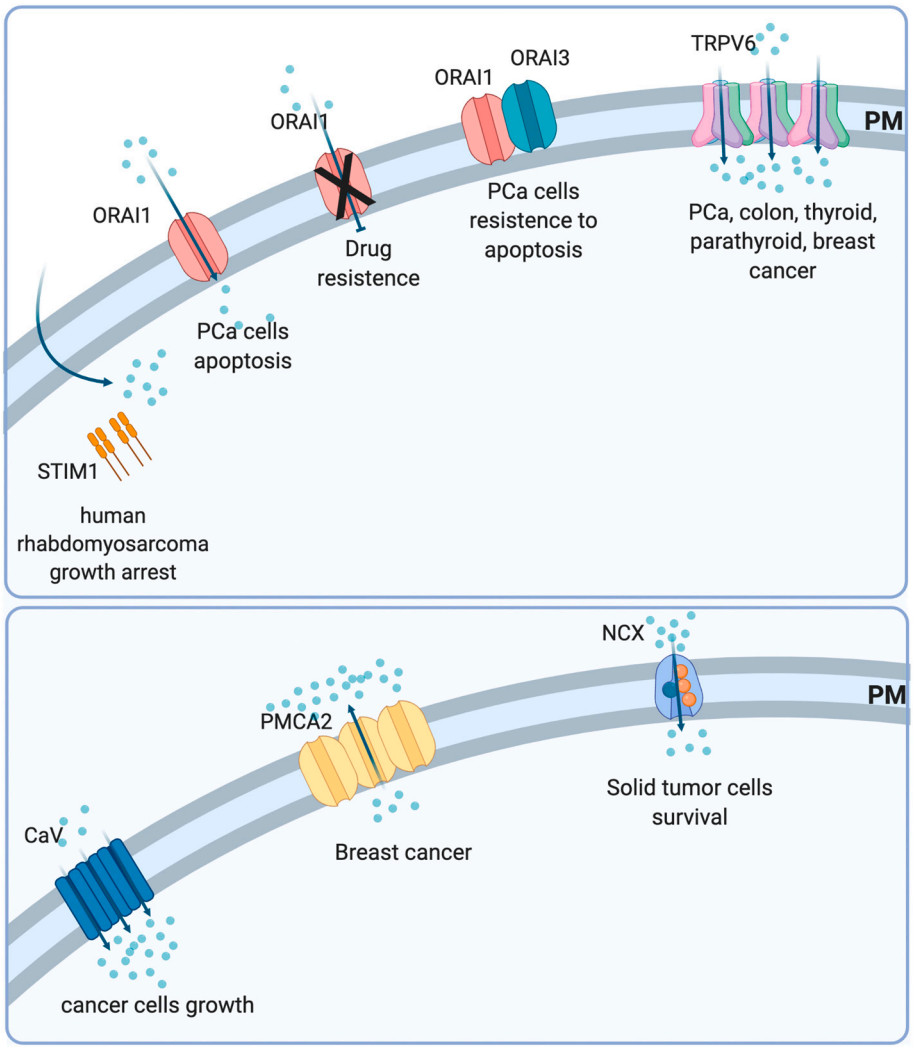

Fig. 3. Proteins located on / near to the PM that play an important role in tumor progression thanks to their ability to modify Ca^{2+} homeostasis. PM = plasma membrane.

overexpressed in some breast cancer cells [195]; in various solid tumors, the NCX1 exchanger exerts a reverse function (uptake of extracellular Ca^{2+}) and has a prosurvival role [196], indicating that the contributions of Ca^{2+} channels, pumps and exchangers are essential for tumor onset and progression (Fig. 3). miR-34 is a microRNA involved in Ca^{2+} signaling regulation and exerts its function by controlling the activities of pro- and antiapoptotic genes and regulating SOCE by targeting IP3R2, STIM1, and ORAI3 in immune cells [197].

The contribution of lysosomes to Ca^{2+} signaling is not directly proportional to the small size of these organelles since the their $[Ca^{2+}]$ is comparable to the $[Ca^{2+}]_{ER}$ (500 μM) [198]. Nguyen et al. revealed that impaired functionality of two-pore channels (TPCs), the Ca^{2+}-permeable cation channels located in the membrane of lysosomes that are involved in Ca^{2+} efflux, is responsible for the reduced adhesion and migration of cancer cells in vitro and the diminished formation of metastasis in vivo [199].

Recent evidence has revealed the correlation of the Ca^{2+}-mediated autophagic process with tumor pathologies. In breast cancer stem cells (BCSCs), a cell type very prone to unlimited self-renewal, autophagy activation contributes to metastatic dormancy by facilitating the autophagic degradation of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (Pfkfb3), a protein required for PMCA function [200]. Moreover, autophagy protects glioma cells against the stress caused by Ca^{2+} mobilization, and the administration of compounds that promote Ca^{2+} mobilization in combination with autophagy inhibitors, such as chloroquine, could represent a novel therapy for glioma patients [201]. TRPM3 has been shown to promote the progression of renal cell carcinomas by stimulating autophagy via calcium/calmodulin-dependent protein kinase kinase 2 (CAMMK2) [202].

5.2. Ca^{2+} homeostasis perturbations at the ER-mitochondria interface

MAMs, the above-described specialized regions of the ER that are preferentially juxtaposed to mitochondria, are strategic Ca^{2+} signaling microdomains essential for correct interorganelle communication; modulation of the composition, expression or activation of proteins in the MAM results frequently in several pathologies, including cancer [2]. Mitochondrial Ca^{2+} overload is strongly conditioned by Ca^{2+} release from the ER, which initiates the apoptotic signal cascade with the cooperation of Bcl-2 family proteins, including BAX, a protein that increases ER Ca^{2+} loading, thereby enhancing ER-mitochondria Ca^{2+} transfer, which leads to an increase in apoptosis [203].

Bcl-2 family proteins are divided into two groups: Bcl-2-like survival proteins (Bcl-2 or Bcl-xL) and proapoptotic Bcl-2 proteins (BAX or BAD). These proteins can localize to the ER and/or mitochondria, influencing ER-mitochondria Ca^{2+} crosstalk. The oncogene Bcl-2 exerts its antiapoptotic effect by controlling, through direct binding, the main ER Ca^{2+}-releasing channel IP3R, ultimately leading to suppression of the mitochondrial apoptosis pathway [204,205]. Disrupting the Bcl-2-IP3R complex with cell-permeable IP3R-derived peptides that target Bcl-2 can reverse the prosurvival effects of Bcl2, stimulating the apoptotic process in B-cell [206–209] and ovarian [210] cancers. IP3R-mediated Ca^{2+} release from the ER to mitochondria appears to be a key sensitizing step in numerous apoptotic models, although clarification is needed regarding the precise molecular mechanism and which IP3R isoform is involved, as there may be significant differences in this process in different cell types and under different physiological conditions [207,211–213].

Other Bcl-2 family members, such as Nix, can regulate ER Ca^{2+} loading to control ER-to-mitochondria Ca^{2+} transfer and induce programmed cell death. Nix localizes to the ER, where it increases ER Ca^{2+} content, leading to mitochondrial Ca^{2+} overload that confers cardiac myocyte apoptotic sensitivity [214]. While Bcl-2 family members may control intracellular Ca2+ signaling, Ca^{2+} ions themselves can modulate protein localization and modulation. BAD, which is usually associated with adaptor protein 14–3-3 in the cytosol, induces apoptosis after mitochondrial translocation and subsequent dephosphorylation by the Ca^{2+}-sensitive phosphatase calcineurin, which is in turn activated by pathological cytosolic Ca^{2+} elevations. Thus, BAD promotes mitochondrial permeabilization, enhancing heterodimerization with the antiapoptotic member Bcl-XL [215]. Talking about Bcl-XL, Monaco et al. highlighted that Bcl-XL, but not Bcl-2, through its BH4 domain, selectively targets VDAC1 and inhibits apoptosis by decreasing VDAC1-mediated Ca^{2+} uptake into the mitochondria [216]. Even BCL-2 member Mcl-1 interacts with VDAC and it has been shown how its sustained action on this channel in non-small lung carcinoma cells increase mitochondrial Ca^{2+} uptake, resulting in increased ROS production and cell migration [217,218] (Fig. 4).

In addition to BCL-2 members, the oncogene RAS regulates apoptosis and cell proliferation by modulating ER-Ca^{2+} release into mitochondria, playing a crucial role in cancer growth and maintenance of the tumor environment. RAS deregulates ER Ca^{2+} depletion, resulting in apoptosis inhibition, mitochondrial metabolism impairment and malignant cell survival [219] (Fig. 4).

The IP3R protein family is responsible for Ca^{2+} efflux from the ER and has been proven to be enriched in MAMs [50]. In addition to representing one of the most important and studied protagonists of calcium signaling, IP3Rs cooperate in maintaining microdomain structure and physiology through interacting with the chaperone glucose-regulated protein GRP75 and maintaining close proximity to mitochondrial VDAC1. Several Ca^{2+}-related oncogenes and tumor suppressors have been consistently identified as direct regulators of IP3Rs that act by impacting their gating and consequently their Ca^{2+} permeability [220]. Among the proteins that promote IP3R channel activity and are considered tumor suppressors are breast cancer gene 1 (BRCA1), which is recruited to IP3Rs during apoptosis and is responsible for apoptotic Ca^{2+} release and cell death [221]; phosphatase and tensin homolog (PTEN), which competes with F-box/LRR-repeat protein 2 (FBXL2) for IP3R3 binding, preventing its degradation [222]; promyelocytic leukemia protein (PML), which supports efficient ER-mitochondrial Ca^{2+} transfer in a p53-dependent manner [223]; and BRCA1-associated protein-1 (BAP1), which binds to, deubiquitylates and stabilizes IP3R3, thus regulating ER Ca^{2+} release and promoting apoptosis [224] (Fig. 4).

In addition to the Bcl-2 protein family (whose BH4 domains bind to IP3Rs, preventing Ca^{2+} signals that mediate cell death [225]), the most well-known oncogene that performs its function by acting on IP3Rs is protein kinase B (PKB), also known as Akt; Akt protects cells from apoptosis by phosphorylating IP3R3 [226,227]. Depletion or pharmacological inhibition of IP3R3 increases the levels of the autophagic marker LC3-II through the upregulation of autophagic protein 5 (Atg5) and the generation of ROS. These events led to the inhibition of cancer growth in a mouse model of breast cancer and were correlate with high IP3R3 expression levels in human malignant tissues [228,229].

The SERCA protein family is responsible for ER Ca^{2+} uptake, and its contribution to the onset and progression of different tumors varies.

As an example, SERCA3 expression is considerably decreased while the $[Ca^{2+}]$ is unaffected due to a compensatory action of SERCA2 in colorectal cancer cells [230]. Mutations in the SERCA2-coding gene predispose mice to gastric carcinogenesis, and modifications to genes encoding other SERCA variants have been documented in many tumors, including head and neck cancer [231]. These SERCA defects protect cancer cells from proapoptotic Ca^{2+} overload, promoting tumor growth and progression. On the other hand, Raturi et al. highlight that ER-localized thioredoxin-related transmembrane protein 1 (TMX1) act as a SERCA2b inhibitor, reducing the import of cytosolic Ca^{2+} into the ER and that TMX1 KD phenotype have increased SERCA activity accompanied with compromised MAM and increased xenograft growth [232] (Fig. 4).

On the mitochondrial side of MAMs, the MCU complex is responsible for mitochondrial matrix Ca^{2+} uptake and is able to effectively act as a cell fate decision-controlling gate, preventing or promoting the mPT death pathway. Modifications in the composition or activity of the pore-

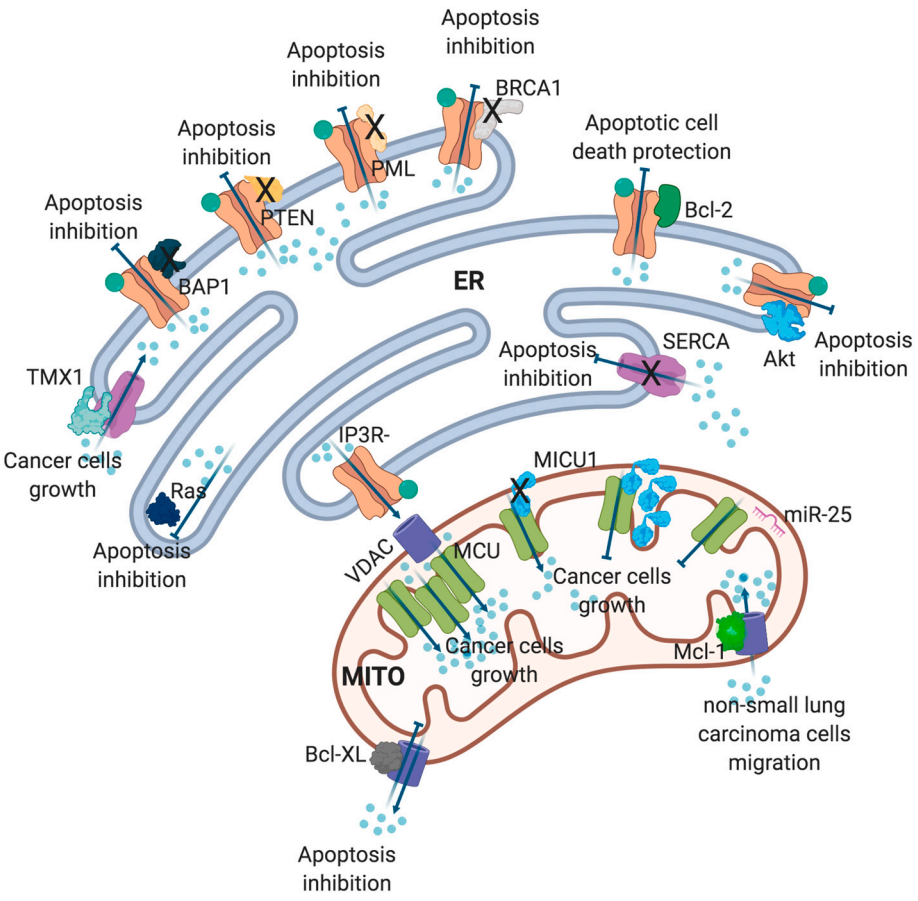

Fig. 4. Proteins on the mitochondria/ER interface that play an important role in tumor progression thanks to their ability to modify Ca^{2+} homeostasis. ER = endoplasmic reticulum; MITO = mitochondrion.

forming or regulatory subunits lead to mitochondrial and intracellular Ca^{2+} homeostasis perturbations, which often result in pathologies, including cancers [233]. An increase in MCU complex expression and activity leads to mitochondrial Ca^{2+} overload, which enhances mitochondrial respiration by favoring the activity of multiple dehydrogenases involved in the tricarboxylic acid cycle (TCA) and results in enhanced ROS and ATP production [234]. As ROS-driven activation of hypoxia inducible factor 1 subunit alpha (HIF1α) [235] and metallopeptidase 2 (MMP2) ROS-dependent secretion [236], along with improved ATP availability, are key events in tumor onset and progression, it is not surprising that increased MCU complex activity can be found in several cancer contexts [237,238]. MCU complex regulatory subunits are also involved in tumors. In particular, the contribution of regulatory subunits, especially MICU1, has been highlighted by works that describe how MICU1 downregulation is associated with poor disease outcomes in patients with breast cancer [239] and hepatocellular carcinoma [240]. In this scenario, MICU1 does not exercise its gatekeeper function, allowing the passage of a very large quantity of Ca^{2+} ions into the mitochondrial matrix in resting conditions. In contrast, in some other cancer cell types, reduced mitochondrial Ca^{2+} uptake promotes cancer growth and progression, conferring chemoresistance. MCU is downregulated by miR-25 in different cancer cell lines and in human colonic adenocarcinoma [241], and high MICU1 expression in ovarian cancer cells confers resistance to cisplatin [242] (Fig. 4).

6. Concluding remarks

Tumor pathologies are caused by deficiencies in the mechanisms underlying cell proliferation and cell death, and both of these phenomena are regulated by Ca^{2+} signaling. As reviewed herein, all Ca^{2+}-associated compartments (cytoplasm, lysosomes, ER and mitochondria) and extracellular space participate in cellular Ca^{2+} circulation and trafficking. This exchange generates signals with different spatial localizations, magnitudes and temporal characteristics that ultimately determine cell fate. The membranes delimiting the abovementioned compartments are rich in Ca^{2+}-handling proteins, and oftentimes, the rearrangement of these Ca^{2+} pumps, channels and Na^{2+}/Ca^{2+} exchangers leads to impaired cell death, which can transform a normal into a cancer cell.

Thus, in recent years, possible therapies aimed at Ca^{2+} signaling remodeling have become increasingly popular. For example, the TRPA1 inhibitor AM-0902 mediated a strong antineoplastic effect in mice without significant toxicity when used alone or in combination with chemotherapeutics [188]. A similar effect was achieved with the TRPV6-antagonistic peptides SOR-C13 and SOR-C27 [262], and the TRPV4 activator GSK1016790A prevented TRPV4+ human breast carcinoma growth in an immunodeficient mouse model [263].

IP3Rs represent a good target for the development of anticancer therapies. Several molecules have been evaluated for their ability to limit MAMs Ca^{2+} transfer or to support Ca^{2+} overload, thereby blocking cancer cell proliferation or sensitizing cancer cells to Ca^{2+}-mediated cell death, respectively [264].

The influence that Ca^{2+} ion flux exerts on malignant transformation, tumor progression, and response to therapy is now well established and proven. Although numerous therapies that aim to restore proper Ca^{2+} signaling have been found and are under development, a better understanding of this delicate and complex process is required.

CRediT authorship contribution statement

Alberto Danese: conceived the article, wrote the first version of the manuscript, prepared display items; Sara Leo wrote the first version of the manuscript; Alessandro Rimessi wrote the first version of the manuscript; Mariusz R. Wieckowski wrote the first version of the manuscript, Francesco Fiorica wrote the first version of the manuscript; Carlotta Giorgi conceived the article and supervise the first version of the manuscript drafting and display items preparation; Paolo Pinton conceived the article and supervise the first version of the manuscript drafting and display items preparation.

Declaration of competing interest

The authors declare no conflict of interests.

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