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Review

ER Ca^{2+} release and store-operated Ca^{2+} entry – partners in crime or independent actors in oncogenic transformation?

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ABSTRACT

Ca^{2+} is a pleiotropic messenger that controls life and death decisions from fertilisation until death. Cellular Ca^{2+} handling mechanisms show plasticity and are remodelled throughout life to meet the changing needs of the cell. In turn, as the demands on a cell alter, for example through a change in its niche environment or its functional requirements, Ca^{2+} handling systems may be targeted to sustain the remodelled cellular state. Nowhere is this more apparent than in cancer. Oncogenic transformation is a multi-stage process during which normal cells become progressively differentiated towards a cancerous state that is principally associated with enhanced proliferation and avoidance of death. Ca^{2+} signalling is intimately involved in almost all aspects of the life of a transformed cell and alterations in Ca^{2+} handling have been observed in cancer. Moreover, this remodelling of Ca^{2+} signalling pathways is also required in some cases to sustain the transformed phenotype. As such, Ca^{2+} handling is hijacked by oncogenic processes to deliver and maintain the transformed phenotype. Central to generation of intracellular Ca^{2+} signals is the release of Ca^{2+} from the endoplasmic reticulum intracellular (ER) Ca^{2+} store via inositol 1,4,5-trisphosphate receptors ($InsP_3Rs$). Upon depletion of ER Ca^{2+}, store-operated Ca^{2+} entry (SOCE) across the plasma membrane occurs via STIM-gated Orai channels. SOCE serves to both replenish stores but also sustain Ca^{2+} signalling events. Here, we will discuss the role and regulation of these two signalling pathways and their interplay in oncogenic transformation.

1. Overview of Ca^{2+} handling

Ca^{2+} is a multifunctional second messenger that participates in almost all aspects of cellular physiology, intervening in processes including fertilisation, cell division, muscle contraction, synaptic transmission, hormone release and immune responses [1]. To perform this signalling function, variations in its levels in the cytosol in the form of complex patterns that vary in space, time and location are generated. These changes in cytosolic Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$) are brought about and shaped through the concerted action of a toolkit of Ca^{2+} handling proteins comprising Ca^{2+} channels, binding proteins, pumps and exchangers. Specifically, through the gating of Ca^{2+} channels on the plasma membrane and on intracellular Ca^{2+} stores, Ca^{2+} flows down its concentration gradient, entering the cytosol where its concentration is increased. Ca^{2+} signals are then terminated by Ca^{2+} pumps and exchangers, which extrude Ca^{2+} from the cell or sequester it back into the internal stores.

Ca^{2+} is primarily stored in the endoplasmic reticulum (ER) and to a lesser extent in the Golgi apparatus and lysosomes. Ca^{2+} is released from ER stores predominantly via inositol 1,4,5-trisphosphate ($InsP_3$) receptor ($InsP_3R$) and ryanodine receptor (RyR) channels [2]. $InsP_3Rs$ open in response to $InsP_3$, produced following hydrolysis of phosphatidyl inositol 4,5-bisphosphate (PIP_2) in response to activation of phospholipase C by extracellular agonists [3]. Three $InsP_3R$ isoforms ($InsP_3R1$, 2 and 3) are expressed in mammalian systems that are assembled in tetramers or heterotetramers, which display subtly different sensitivities to $InsP_3$ and Ca^{2+} itself [4]. The relative proportion of these isoforms varies according to tissue type, cellular location and development stage, thereby allowing $InsP_3$ signalling to fulfil specific cellular needs. RyRs are also expressed as three isoforms, which in contrast to $InsP_3Rs$ generally form homotetrameric channels that only require Ca^{2+} for gating. Skeletal muscle RyRs (RyR1) can however be activated via a conformational change in their associated plasmalemmal dihydropyridine receptors (DHPRs, otherwise known as

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$Ca_V1.1$), which occurs following cellular depolarisation. The Ca^{2+} sensitivity of both $InsP_3Rs$ and RyR is bell-shaped, with a stimulatory effect of $[Ca^{2+}]_{cyt}$ in the physiological range (~100 nM – 1 μM) that is maximal at 1 μM, above which activity of these channels is inhibited. However, the $[Ca^{2+}]_{cyt}$ levels at which Ca^{2+}-dependent inhibition and activation occur show isoform-specific differences. $InsP_3Rs$ also underlie Ca^{2+} release from other intracellular Ca^{2+} storage organelles, including lysosomes and Golgi apparatus [5]. A further pathway involved in Ca^{2+} release from intracellular stores involves the second messenger NAADP (nicotinic acid-adenine dinucleotide phosphate), which stimulates Ca^{2+} release from lysosomes *via* two-pore channels (TPCs) [6]. In addition, members of the transient receptor potential family of channels (TRP), mediate Ca^{2+} release from the lysosomes, e.g. the mucolipins (TRPML), which are gated by PIP_2 [7]. Plasma membrane (PM) Ca^{2+} channels contributing to Ca^{2+} signals (the so-called 'ON-reactions') include voltage-gated Ca^{2+} channels (VGCCs; e.g. P, Q, L and N-type voltage Ca^{2+} channels primarily expressed in excitable cells), store-operated channels (SOC; OraiI1,2,3), TRP channels and ligand-gated Ca^{2+} channels (e.g.nicotinic acetylcholine nACh N-methyl-D-aspartate (NMDA) and purinergic receptors) [8]. Responsible for the termination of Ca^{2+} signals (the 'OFF-reactions') are plasma membrane Ca^{2+} ATPases (PMCAs), sarco-endoplasmic reticulum Ca^{2+} ATPases (SERCAs) on the ER, mitochondrial Ca^{2+} uptake mechanisms via the voltage dependent anion channel (VDAC1) and the mitochondrial Ca^{2+} uniporter (MCU) and Ca^{2+} pumps/exchangers on other organelles such as the Golgi apparatus (Secretory Pathway Calcium ATPases, SPCAs) and lysosomes [9,10]. Where rapid high capacity Ca^{2+} extrusion is required, as in electrically excitable cells, Sodium Calcium Exchangers (NCX), which extrude one Ca^{2+} for three Na^+, are expressed [11].

In contrast to the finite intracellular Ca^{2+} stores, the extracellular space represents an inexhaustible source of Ca^{2+}. The interplay between ER and PM Ca^{2+} channels is important for cytosolic Ca^{2+} dynamics. While short-lived Ca^{2+} transients in non-excitable cells primarily involve Ca^{2+} release from intracellular stores, sustained Ca^{2+}signalling events also require Ca^{2+} influx from the extracellular space. Ca^{2+} influx across the PM can be directly activated via PM-mediated mechanisms or through store-operated Ca^{2+} entry (SOCE). SOCE is mediated via the Orai-channel family (Orai1-3) of highly Ca^{2+}-selective, hexameric channels, which are gated by stromal interaction molecule 1 and 2 (STIM1 and STIM2) [12,13]. STIM proteins are ER-located Ca^{2+} sensors that detect ER Ca^{2+} content through their ER luminal N-terminal EF-hand and activate Orai channels through a physical interaction via specialised domains located in their cytosolic C-terminal tail [14]. Under resting conditions, STIM proteins are homogenously distributed across the ER membrane. Upon ER Ca^{2+} depletion, STIM proteins aggregate and cluster at ER-PM contact sites, where they recruit Orai channels and provoke their opening [15]. STIM2 has a lower affinity for Ca^{2+} than STIM1, enabling STIM2 to sense smaller decreases in ER Ca^{2+} content [16]. As such, STIM2 is defined as a regulator of basal $[Ca^{2+}]_{ER}$, in contrast to STIM1, which responds to more robust ER store depletion, for example following agonist stimulation [17]. Two splice variants of STIM2 have recently been described, which act to promote (STIM2.2) or inhibit (STIM2.1) SOCE [18,19]. As STIM1 and STIM2 co-localise at punctae, SOCE can thus be finely tuned on the basis of the STIM1/STIM2 ratio and the predominant STIM2 splice variant [20,21]. Recent studies confirm the role of STIM2 as an important modulator of STIM1/Orai1 coupling [22,23]. STIM proteins play roles independent of their gating of the Orai family of channels. They have also been reported to activate SOCE *via* TRP channels, including TRPC1, 3, 4 and 5 [24]. Interestingly, Orai1 is required for TRPC1 function *via* a dynamic signalling complex involving TRPC1, STIM1 and Orai1, localised in ER-PM junctions [25,26]. At rest, TRPC1 is docked in a trafficking vesicle at the PM. Following store depletion, Orai1 associates with and is activated by STIM1, leading to Ca^{2+} entry. This causes insertion of TRPC1 into the PM, where it is subsequently gated and activated by STIM1, allowing TRPC1-mediated Ca^{2+} influx. Furthermore, Ca^{2+} currents of Orai channels and TRPC channels seem to stimulate different cellular processes. For example, Orai1-mediated Ca^{2+} influx activates NFAT through a local $[Ca^{2+}]$ increase near the Orai1 channel, which in turn activates calcineurin, triggering dephosphorylation and nuclear translocation of NFAT [27,28]. Ca^{2+} entry *via* TRPC1, however, does not affect NFAT dephosphorylation but contributes to the activation of NFkB [29,30]. The Orai family is not only a key player in SOCE, it is also an equally essential component of an agonist-activated, store-independent Ca^{2+} entry pathway [31]. This pathway is mediated through the arachidonic acid-regulated Ca^{2+}-selective (ARC) channel, which is formed by a combination of Orai1 and Orai3 subunits and is regulated by a population of STIM1 molecules localised in the PM [32].

Changes in intracellular $[Ca^{2+}]$ are transduced into a cellular response via a number of Ca^{2+} binding/sensor proteins. Ca^{2+} binds to these proteins via specialised Ca^{2+} binding motifs including EF hands and C2 domains. Through variations in affinity of these domains and localisation of the proteins, these signal transducers contribute specificity in Ca^{2+} signalling mechanisms. Notable examples amongst these Ca^{2+} signal effectors are the archetypal EF hand-containing Ca^{2+}binding protein calmodulin (CaM) and C2 domain-containing protein kinase C (delta, PKCδ). Upon binding Ca^{2+}, CaM associates with and engages a number of downstream effectors including the protein phosphatase calcineurin and Ca^{2+}/CaM kinases (CaMK1-IV) (Fig. 1). Proteins once considered as Ca^{2+} buffers including calbindin-D28k and calretinin, also function as Ca^{2+} sensors, enabling them to modulate Ca^{2+} signalling outputs [33].

2. Ca^{2+} regulation of cell processes involved in cancer

Ca^{2+} plays a major role in the development, progression and maintenance of cancer [34,35]. Cells become cancerous through the progressive accumulation of mutations in their genome. Subsequent to transformation, the cell displays a series of defining traits or hallmarks [36,37]: self-sufficiency from growth signals, independency from anti-growth signals, escape from apoptosis, loss of differentiation potential, neoangiogenesis, metastasis, metabolic reprogramming, immune surveillance evasion, genome instability and exploitation of inflammatory responses. These features render the cancer cell autonomous from the physiological signals that would normally regulate its lifespan. As Ca^{2+} participates in the processes underlying nearly all of these cancer hallmarks [38–40], most notably in regulating the balance between cell proliferation and death, it is not surprising that changes in the abundance or activity of Ca^{2+} handling proteins impact oncogenesis. Indeed, a dramatic increase in research in this area over the last years has uncovered a critical role for Ca^{2+} in key control nodes in oncogenic transformation [34,35]. Not only have changes in expression levels of Ca^{2+} handling proteins in cancerous cells been identified, interfering in Ca^{2+} handling pathways has emerged as a promising target for therapy [41,42].

Altered expression of Ca^{2+} handling proteins has been reported in cancers from different tissue origins [34,43]. Changes in the activity of Ca^{2+} signalling pathways and regulated processes have also been observed [35,44]. A defining picture of how Ca^{2+} signalling is modified at each stage of oncogenesis and how in turn the initiating mutation and tissue of origin impacts or influences this alteration in Ca^{2+} signalling is only just emerging. Moreover, whether Ca^{2+} signalling remodelling is a driver or a passenger of oncogenesis is not clearly established [45]. Precluding this deeper understanding is that oncogenesis involves a series of phenotypic changes and that the mechanism by which oncogenes remodel Ca^{2+} signals to promote tumorigenesis are not fully resolved. Further, the same Ca^{2+}-handling proteins show both increases and decreases in expression depending on the cancer type or stage [46,47]. Here, we will attempt to summarise the involvement and interactions between Ca^{2+} signalling via $InsP_3$-induced Ca^{2+} release (IICR) and SOCE in cancer. Specifically, how these Ca^{2+} signalling

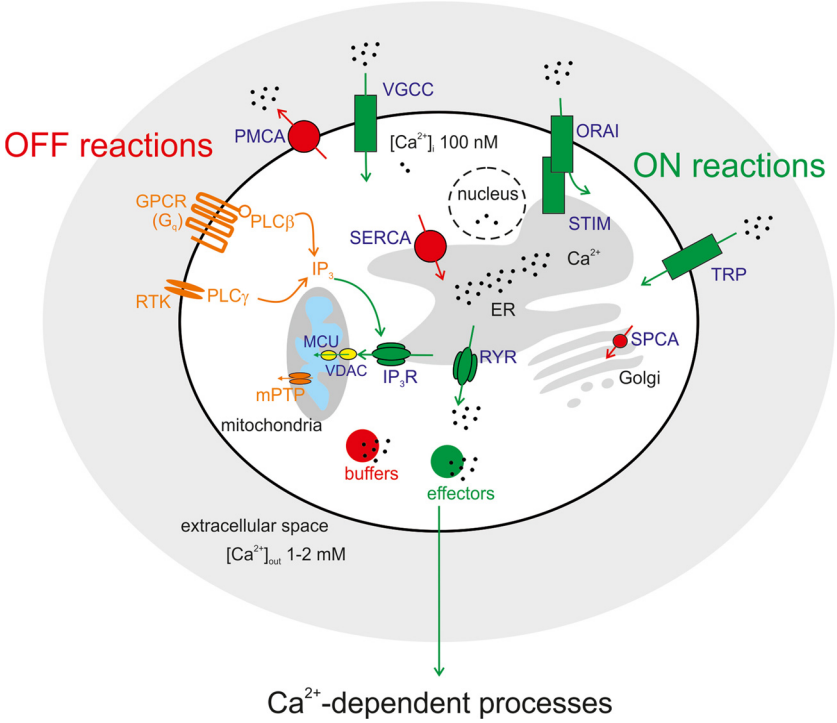

Fig. 1. An overview of Ca^{2+} signals. Ca^{2+} signals are created in the ON reactions (in green), where Ca^{2+} channels on the plasma membrane or on the membranes of intracellular stores open to increase the intracellular Ca^{2+} concentration. Ca^{2+} signals are terminated in the OFF reactions (in red), where Ca^{2+} pumps on the same membranes extrude Ca^{2+} outside the cytoplasm. Ca^{2+} effectors and buffers contribute to starting Ca^{2+} -dependent processes and to the modulation of Ca^{2+} signals. Mitochondrial channels (in yellow) contribute to the regulation of Ca^{2+} signals as well as the cellular bioenergetics.

pathways regulate different features of transformed cells, how Ca^{2+} signals generated are altered at the different stages of oncogenic transformation, and whether modifications in Ca^{2+} handling by these pathways drive and sustain the transformed phenotype. Prior to describing specific roles of SOCE and IICR in cancer, we will also attempt to provide a comprehensive picture of how cancer cells may employ or require different Ca^{2+} signals as they progress through the stages of tumorigenesis.

2.1. Ca^{2+} in cell proliferation

It is classically considered that Ca^{2+} oscillations sustain cell survival and are important for regulation of cell processes, including cell proliferation and metabolism, while large elevations in $[Ca^{2+}]_i$ promote apoptosis [48]. Indeed, Ca^{2+} oscillations occur throughout the cell cycle, and play strategic roles at nodal cell cycle phases such as during the early G_1 phase and the G_1/S and G_2/M transitions, where they correspond to peaks of activity of CaM and CaMK [38,49,50]. At early G_1, Ca^{2+} regulates the transcription of immediate-early genes, such as FOS, JUN and MYC [51]. At the G_1/S transition, mitogen dependent signalling and Ca^{2+} increases activate Ras through guanine nucleotide exchange factors (GEFs) and GTPase acitivating proteins (GAPs) as well as CaM. Active Ras and Ca^{2+}/CaM complexes are responsible for the transcription of cyclin D1 and formation of cyclin D1/CDK4 complexes. At the same time, CaM inhibits p21 and p27 while calcineurin promotes NFATc1 dephosphorylation, which in turn translocates to the nucleus and transactivates Myc [50,52–54]. Myc and Ras activate cyclin E/CDK2. All these events coincide to determine the multistep phosphorylation of retinoblastoma protein (Rb), which then releases the inhibitory transcription factor E2F, allowing DNA synthesis and progression into S phase [55,56]. At S and G_2/M transition, activation of CaMKII is necessary for correct centrosome duplication [57].

The aforementioned Ca^{2+} signals that control these cell cycle checkpoints show requirements for both ER Ca^{2+} release and SOCE [50]. A particular role for SOCE in the control of the G_1/S transition has been however recently demonstrated [58–60]. In this regard, SOCE is upregulated during the G_1/S transition through mechanisms involving STIM phosphorylation and its increased trafficking to subplasmalemmal *punctae*, as well as through Orai1 upregulation. Subsequent to this cell cycle phase, SOCE is downregulated while $InsP_3$-mediated signalling is active. The mechanism of SOCE involvement in G_2/M and early G_1 is more elusive.

2.2. Ca^{2+} involvement in cell death and metabolism

Ca^{2+} is a key player in mitochondrial metabolism. Oscillating Ca^{2+} signals drive mitochondrial bioenergetics by boosting the activity of three key enzymes of the TCA cycle, i.e. pyruvate dehydrogenase, isocitrate dehydrogenase and alpha-ketoglutarate dehydrogenase, as well as two components of the electron transport chain (ETC), namely cytochrome c oxidase and F0-F1-ATPase [61]. While Ca^{2+} oscillations fuel mitochondrial bioenergetics, sustained and high amplitude intracellular Ca^{2+} transients result in mitochondrial Ca^{2+} overload and production of reactive oxygen species (ROS). ROS trigger the opening of the mitochondrial permeability transition pore (mPTP), evoking loss of inner mitochondrial membrane potential, mitochondrial swelling and rupture of the mitochondrial membrane. The molecular identity of the mPTP has been long sought but notably has recently been shown to be established by dimers of the F0-F1-ATPase [62]. Ca^{2+} can directly bind to these dimers and facilitate the formation of mitochondrial megachannels upon addition of the ATP synthase inhibitor Benzodiazepine 423 [63]. An elegant experiment showed the critical role for mitochondrial matrix Ca^{2+} in the opening of mPTP in conditions of phenylarsineoxide and *p*-hydroxyphenylglyoxal, whereby mPTP opening was blunted by BAPTA, a Ca^{2+} chelator [64]. The Ca^{2+}-trigger site for the mPTP was identified in the catalytic site of the F-ATP synthase β subunit, provoking a conformational change via oligomycin sensitivity-conferring protein (OSCP) and the lateral stalk to the inner membrane [65]. The actual pore-forming subunit of the mPTP complex remains a matter of debate, however. Recent evidence indicates that the mPTP is formed upon dissociation of the F0-F1-ATPase dimers, and the c subunit functions as the pore-forming subunit of the mPTP complex [66]. Besides the direct impact of Ca^{2+} on the proteins forming the mPTP, mitochondrial Ca^{2+} also provokes cardiolipin dissociation from complex II of the respiratory chain, resulting in its disassembly [67]. The catalytic subunits (SDHA and SDHB) produce excessive ROS in the

mitochondrial matrixtriggering mPTP opening. This leads to Ca^{2+}-induced mitochondrial outer membrane permeabilisation (MOMP), the release of cytochrome C and other apoptotic mediators [64,68].

Although mitochondria take up Ca^{2+} irrespective of its source, efficiency of Ca^{2+} uptake is greatest at the ER-mitochondrial interface. At this location, the $InsP_3R$ is connected to VDAC1 on the outer mitochondrial membrane through the chaperone GRP75 [69]. In this way, microdomains, known as mitochondria-associated ER membranes (MAMs) are created, allowing quasi-synaptic Ca^{2+} transfer from the ER to the mitochondria [70,71]. These contact sites are interesting targets for modulation of Ca^{2+}signalling, either to evade or to induce cell death [68,72,73]. Modulation of $InsP_3Rs$ at these sites are discussed below. As cancer cells are highly dependent on anabolic pathways for the production of substrates/products critical for cell division, maintenance of mitochondrial metabolism is essential. In several tumorigenic cell types, abrogating ER-mitochondrial Ca^{2+} fluxes leads to mitotic catastrophe, while in healthy cells, it results in autophagy and a slowdown of cell cycle progression. This indicates that constitutive intra-organellar Ca^{2+} fluxes are an indispensable factor for both cell growth and survival [74–76]. However, these findings have been challenged in other studies. For instance, $InsP_3R$ inhibition in tumorigenic MCF7 breast cancer cells provoked autophagy, and HEK293 cells remain viable even in the face of genetic knockout of all three $InsP_3R$ isoforms via CRISPR/Cas9 [77,78].

2.3. Ca^{2+} in angiogenesis, invasion and metastasis

After reaching a critical size, the growing tumour mass develops its own vasculature in order to maintain a supply of nutrients and an oxygen to the core of the tumour (tumour angiogenesis). Angiogenesis depends on, amongst other factors, a Ca^{2+}-dependent increase in expression of the hypoxia-inducible factor 1 (HIF-1α) transcription factor [79]. HIF-1α subsequently drives the transcription of vascular endothelial growth factor (VEGF), that in turn promotes endothelial cell (EC) proliferation, migration and formation of new vasculature (tubulogenesis). This potent pro-angiogenic effect of VEGF is elicited in part through activation of downstream Ca^{2+} signalling pathways [39,80], including of Ca^{2+} release from intracellular stores and Ca^{2+} entry across the plasma membrane [81–86]. Depending upon VEGF levels, different patterns of Ca^{2+} signals are observed in ECs, which have specific consequences for cell function. At low VEGF, oscillatory Ca^{2+} signals are observed, which induce NFAT nuclear translocation and EC proliferation, while at higher VEGF concentrations, sustained Ca^{2+} signals of a lower amplitude that promote EC migration via MLCK have been reported [87].

Cancer cell migration and matrix invasion show a strong dependence on Ca^{2+} signalling pathways. The MCU is a key player in these processes. Indeed, MCU silencing leads to a downregulation of HIF-1α, thereby impairing transcription of HIF-1α target genes involved in tumour progression [88]. Tumour cell invasion requires epithelial-mesenchymal transition (EMT), through which cancer cells lose cell-cell contacts, change in shape, loose the polarized organization, and downregulate epithelial markers (e.g. E-cadherin, claudins, occludins) in favour of mesenchymal markers (e.g. N-cadherin, vimentin, integrins) [89,90]. Enhanced Ca^{2+} signalling involving TRP channels and ligand-gated P2X channels is associated with EMT and plays a role in controlling the expression of certain mesenchymal markers [39,91].

The Ca^{2+} dependence of cell migration is widely reported, including in cancer. Transient Ca^{2+} microdomains, also referred to as 'calcium flickers', occur at the leading front of a migrating cell, thereby facilitating local cytoskeletal remodelling and orchestrating directional movement [92,93]. In this way, they act as a steering wheel to turn the cell in a new direction. These short elevations in local [Ca^{2+}] are brought about through several mechanisms, including $InsP_3R$ signalling, modulation of SERCA and activation of TRPM7. Importantly, the flicker activity responds to directional cues of chemoattractants without any central command. Finally, invasion (the ability of the cancer cell to degrade the extracellular matrix (ECM) in order to reach the bloodstream and colonise other tissues), is a Ca^{2+}-dependent process. Ca^{2+} oscillations and Ca^{2+} influx are necessary for the formation of invadopodia structures and the recruitment of degrading enzymes such as matrix metalloproteases (MMPs), mainly through SOCE, TRP channels and VGCCs [39].

3. Ca^{2+} release channel modifications in cancer

The importance of Ca^{2+} signalling in many aspects of cell physiology including cellular processes related to tumour development, places the $InsP_3Rs$ centre stage in cancer biology [76]. A number of observations underpin this proposed role of $InsP_3Rs$. For example, absence of $InsP_3R$-mediated Ca^{2+} signals in thymocytes leads to the development of malignancies in mice, which resemble T-cell acute lymphoblastic leukemia [94]. The maintenance of the ER-mitochondrial Ca^{2+} flux via $InsP_3Rs$ is important to sustain mitochondrial bioenergetics, which is required by cancer cells despite their dependence on glycolysis (Warburg effect) [95–97]. It is therefore not surprising that $InsP_3R$ expression levels are often altered in cancer. For instance, $InsP_3R3$ is overexpressed in glioblastoma cells and reducing its expression *via* siRNA resulted in impaired cell migration due to inhibition of cytosolic Ca^{2+} signalling [98]. Furthermore, in MCF-7 cells, $InsP_3R$ blockage resulted in growth inhibition and 17-β-estradiol seems to induce cell proliferation in the same cell line through elevation of $InsP_3R$ levels [99]. Interestingly, the different $InsP_3R$ isoforms exhibit different types of Ca^{2+} responses [100]; a feature presumably due to different regulation by Ca^{2+}, $InsP_3$ and cofactors. While $InsP_3R1$ produces regular Ca^{2+} oscillations, which in the context of cancer cells may sustain the cell cycle, $InsP_3R3$ produces larger transients, which are instrumental in signalling apoptosis [100–102]. Indeed, $InsP_3R3$ silencing (thereby increasing the contribution of $InsP_3R1$ to Ca^{2+} signalling) often reveals an oscillatory Ca^{2+} signalling pattern [103,104]. In line with this, we showed that $InsP_3R3$ is the prevalent subtype in a non-tumorigenic colon cancer cell line compared to the isogenic tumorigenic counterpart, which predominantly expresses $InsP_3R1$ and is protected from apoptosis [105].

The role of $InsP_3Rs$ in cancer, particularly that of $InsP_3R3$, has been the subject of a number of recent studies [45,46]. It appears that the expression level of this channel is finely tuned by the cancer cell to balance proliferation and apoptosis, which can be considered as early stages of tumourigenesis. $InsP_3R3$ levels are dynamically regulated through ubiquitylation, leading to proteasomal degradation of the channel. Several tumour suppressors, such as BAP1 and PTEN, are known to influence the ubiquitylation status of $InsP_3R3$ [106]. BAP1 possesses deubiquitylation enzyme activity, preventing its proteasomal degradation. PTEN, on the other hand, competes with the F-Box protein FBXL2 ubiquitylase for $InsP_3R3$ binding, thereby preventing FBXL2-mediated ubiquitylation of the channel. While healthy cells favour deubiquitylation of the $InsP_3R3$, cancer cells display defects in the expression of tumour suppressors, such as BAP1 and PTEN, resulting in decreased $InsP_3R3$ levels. Yet in contrast to the anti-cancer, pro-apoptotic function of $InsP_3Rs$, $InsP_3R3$ is upregulated in several malignant, migratory cancers and cancer cell lines (Table 1), e.g. gastric [107], small and non-small cell lung [108,109], colorectal (CRC) [110], glioblastoma [98] and breast cancer [111]. Moreover, $InsP_3R3$ inhibition reduces cell migration [98,103,104]. Very recently, silencing of $InsP_3R3$ in different cancer cell models, including colorectal cancer DLD1 cells, ovarian cancer A2780 cells, and clear cell renal cell carcinoma RCC4 cells augmented apoptosis sensitivity, whereas silencing of $InsP_3R1$ conferred apoptotic protection [112]. Excitingly, DLD1 cells deficient in $InsP_3R3$ displayed reduced in vivo tumour growth. Therefore, the latter study advocates that in some cancer cells, $InsP_3R3$ could fulfil an anti-apoptotic role, while $InsP_3R1$ acts as a pro-apoptotic channel. Thus, it might be possible that early downregulation of

Table 1
Summary of alterations in expression of different Ca^{2+} toolkit proteins in different cancers.

Ca^{2+} channel	Up/down regulation	Cancer type	Refs	notes
$INsP_3R1$	Up	colorectal cancer cell lines	[105]	low ER content
	Up/high phosphorylation	prostate cancer cell lines	[114]	low ER content
$INsP_3R2$	Up	breast cancer cell lines and patients	[111]	
	Up	diffuse large B-cell lymphoma cell lines (DLBCL)	[178]	
$INsP_3R3$	Down	colorectal cancer cell lines	[105]	
	Up	malignant gastric cancer cell lines	[107]	
	Up	small and non-small lung cancer cell lines	[108,109]	not in primary tumour-derived cells
	Up	colorectal cancer patients	[110]	
	Up	glioblastoma primary cells	[98]	
	Up	breast cancer cell lines and patients	[111]	
STIM1	Up	(advanced) hepatocellular carcinoma patients	[137]	
	Up	colorectal cancer patients	[134]	
	Up	colorectal cancer cell lines	[135]	
	Down	colorectal cancer cell lines (HCT116)	[156]	
	Up	colon cancer cell lines (DLD-1)	[156]	
	Same but SOCE diminished	invasive melanoma primary cells	[158]	PKC
	Up	metastatic colorectal cancer primary cells	[136]	
	Up in invasive front	cervical cancer cell lines	[138]	
	Up	Breast cancer patients (high STIM1/STIM2 ratio)	[139]	
	Down	Mammary epithelium during lactation	[139]	
STIM2	Up	Glioblastoma patients	[160]	
	Up	colorectal cancer patients	[161]	
	Down	colorectal cancer cells	[135]	
	Up	colorectal cancer cells (HCT116)	[156]	
	Down	colon cancer cells (DLD-1)	[156]	
	Up	Mammary epithelium during lactation	[139]	
Orai1	Up	Malignant glioblastoma primary cells	[140]	
	Up	Malignant oesophageal cancer primary cells	[141]	
	Up	colon cancer cell lines	[135]	
	Up	breast cancer primary cells	[139]	
Orai2	Up	colon cancer cell lines	[135]	
	Up	metastatic colorectal cancer primary cells	[136]	
Orai3	Up	colon cancer cell lines	[135]	
	Up	prostate cancer cell lines	[164]	
SERCA 2	Down	small/non-small lung cancer cell lines	[108]	lower ER content
	Down	colon cancer cell lines	[105]	
	Up	colon cancer cell lines and primary tumours	[179]	
SERCA 3	Down	Colon and gastric cell lines	[180]	
	Down	Colon cancer primary cells	[181]	
	Down	Leukemia cells (immortalization)	[182]	
	Down	Leukemia primary cells	[183]	
PMCA1	Down	oral cancer primary cells and cell lines	[184]	early epigenetic silencing
PMCA2	Up	breast cancer primary cells (normally decreased during weaning)	[185]	
	Up	breast cancer cell lines	[186]	
PMCA4	Up during differentiation	colon and gastric cancer cell lines	[187]	
	Up during differentiation	colon cancer cell lines	[188]	
SPCA1	Up	primary basal-like breast tumours	[189]	
SPCA2	Up	epithelial cancer cell lines vs mesenchymal cancer cell lines	[190]	EMT, metastasis

Table 2a
Effect of altered Ca^{2+} toolkit expression at early stages of tumourigenesis (uncontrolled growth).

Tumour stage	Ca^{2+} channel	Event	Cancer type	Refs	Notes
Early: growth control independency	$INsP_3R1$	Promotes Ca^{2+} oscillations which sustain proliferation	hepatocellular carcinoma	[191]	
		Mediates wogonoside-induced differentiation	primary acute myeloid leukemia	[192]	
	$INsP_3R3$	2-APB Inhibition blocks proliferation	gastric cancer	[107]	
		Silencing reduces proliferation	breast cancer	[113]	
		2-APB/XestC inhibition reduces growth	breast cancer	[99]	
	STIM1	STIM1/Orai1 siRNA blocks in G1/S	cervical cancer	[58]	passive G2/M
		Silencing blocks in S and G2/M	cervical cancer	[59]	
		siRNA impairs proliferation	clear cell renal carcinoma	[143]	
	Orai1	Inhibition suppresses growth	oesophageal cancer	[141]	
	Orai3	Inhibition blocks proliferation	Breast cancer	[163]	
	SERCA2	Heterozygosity confers tumorigenicity	squamous cell tumours	[193]	
		Silencing inhibits proliferation	CRC cells	[179]	
		SERCA inhibition provokes G_0/G_1 arrest	leukemia (Notch +)	[194]	
	MCU/MICU1	MICU1 inhibitory phosphorylation by AKT sustains growth	Lung cancer	[195]	increased ROS

$InsP_3R3$ confers a survival advantage, while increasing its expression at later stages of tumorigenesis enables the cancer cell to proliferate and migrate, as seen in breast cancer [99,103,104,113], gastric cancer [107] and glioblastoma [98]. The reported roles of $InsP_3R3$ as an anti- versus a pro-apoptotic Ca^{2+}-release channel may also in part be related to differeces in the subcellular location of this channel between

Table 2b
Effect of altered $Ca2^{+}$ toolkit expression at early stages of tumourigenesis (apoptosis evasion).

Tumour stage	Ca^{2+} channel	Event	Cancer type	Refs	Notes
Early: apoptosis evasion	$InsP_3R1$	Mediates sulforaphane-dependent apoptosis	ovarian cancer cell lines	[196]	nuclear translocation
		Mediates androgen removal-derived apoptosis	prostate cancer cell lines	[114]	
		Downregulation protects from cisplatin-induced apoptosis	bladder cancer cell lines	[115]	
		Silencing reduces apoptosis	colorectal cancer	[112]	
	$InsP_3R2$	Mediates apoptosis at MAMs through interaction with Bcl-2	DLBCL cell lines	[119,178]	
	$InsP_3R3$	2-APB inhibition induces apoptosis	gastric cancer cell lines	[107]	
		2-APB inhibition enhances apoptosis	colorectal cancer patients	[110]	
		Silencing inhibits tumour growth and induces apoptosis	colorectal cancer ovarian cancer renal cancer	[112]	
	STIM1	Inhibits extrinsic apoptosis	leukemic cell lines	[153,154]	
		Increased SOCE improves survival	Malignant melanoma cell lines	[152]	
	Orai1	Downregulation confers apoptosis resistance	prostate cancer cell lines	[155]	
	Orai3	Inhibition induces proliferation	Breast cancer cell lines	[163]	
		Mediates SOCE	ER+ breast cancer cells	[162]	
		Promotes proliferation via AA channels	prostate cancer cell lines	[164]	NFAT
	SERCA2	p53 stimulates activity inducing mitochondrial pro-apoptotic uptake	Cervical, lung, breast, colorectal cancer cells, fibroblasts	[197]	
	PMCA1	Silencing enhances ionomycin-induced necrosis	breast cancer cell lines	[198]	
	PMCA2	Overexpression protects from apoptosis	breast cancer cell lines	[185]	
	PMCA4	Silencing enhances ABT-263-dependent apoptosis	breast cancer cell lines	[198]	
	SPCA1	Inhibition decreases IGFR production	basal-like breast tumours	[189]	
	MCU/MICU1	Increased mitochondrial Ca^{2+} flux improves survival Inhibition of Ca^{2+} flux induces apoptosis	Malignant melanoma cell lines Breast and prostate cancer cells, transformed fibroblasts	[152] [74]	

Table 2c
Effect of altered Ca^{2+} toolkit expression at early stages of tumourigenesis (metastasis).

Tumour stage	Ca^{2+} channel	Event	Cancer type	Refs	Notes
Late: Angiogenesis Migration	$InsP_3R2$	2-APB inhibition impairs migration	lung adenocarcinoma cell lines	[199]	
	$InsP_3R3$	Silencing favours rounded shape (non-migratory) and remodels cytoskeleton	breast cancer cell lines	[104]	EMT
Invasion metastasis		Caffeine inhibition reduces migration	primary glioblastoma cells	[98]	
		Silencing decreases migration	breast cancer cell lines	[103]	
	STIM1	siRNA blocks metastasis	breast cancer cell lines	[142]	
		siRNA reduces invasion	Glioblastoma primary cells	[140]	
		siRNA reduces focal adhesion turnover	hepatocellular carcinoma patients	[137]	
		siRNA impairs migration	primary clear cell renal carcinoma cells	[143]	
		shRNA inhibits migration	colorectal cancer patients	[134]	
		HIF-1 inhibition downregulates STIM1 and vice versa		[146]	
	STIM2	Inhibition reduces migration	Melanoma cell lines	[144]	
		Does not regulate migration	Cervical cancer cell lines	[138]	
	Orai1	Inhibition reduces migration	Melanoma cell lines	[144]	
	SERCA2	Silencing inhibits migration	Colorectal cancer cell lines	[179]	
	MCU	Silencing reduces migration	Cervical and breast cancer cell lines	[200]	
		Silencing reduces migration, overexpression enhances metastasis	breast cancer cell lines	[201]	miRNA-340

different cancer cell models. We can speculate that $InsP_3R3$ at MAMs serves as a pro-apoptotic channel, whereas $InsP_3R3$ outside MAMs serves as an anti-apoptotic channel. On the other hand, the involvement of the $InsP_3R1$ and 2 in tumour development is less straightforward. For instance, hormone refractory prostate cancer cells display elevated $InsP_3R1$ expression levels, which is thought to increase Ca^{2+} leakage from the ER making less Ca^{2+} available for induction of apoptosis through mitochondrial Ca^{2+} overload [114]. In bladder cancer cells resistant to cisplatin, however, $InsP_3R1$ levels are reduced and overexpression of $InsP_3R1$ induced apoptosis and restored sensitivity to cisplatin [115].

In tumour cells, not only do differences in $InsP_3R$ expression levels affect cell survival, changes in Ca^{2+} release properties can also influence crucial cellular processes. First, phosphorylation of the $InsP_3R$ can alter its function dramatically, for example through the PKB/AKT pathway, thereby reducing pro-apoptotic Ca^{2+} transfer to the mitochondria and conferring a survival advantage [116,117]. Conversely, tumour suppressor PML [23] impacts phosphorylation of the $InsP_3R3$ at the MAMs to promote ER-to-mitochondria pro-apoptotic Ca^{2+} fluxes [63] Furthermore, $InsP_3R$ activity can be greatly influenced by an array of oncogenes. For instance, cancer cells promote cell survival through activity of the Bcl-2 family at the ER. On the one hand, anti-apoptotic Bcl-2-family members are able to prevent pro-apoptotic Ca^{2+} signalling [56]. For instance, Bcl-2 can directly interact with the modulatory domain of the $InsP_3R$ via its BH4 domain, thus inhibiting aberrant Ca^{2+} release [57–59]. On the other hand, Bcl-2-family members, such as Bcl-2, Bcl-XL and Mcl-1, can also increase pro-survival Ca^{2+} oscillations through sensitisation of $InsP_3Rs$, which in turn drives mitochondrial metabolism and provides the cancer cell with ATP [60]. In certain Bcl-2-dependent cancer cell models, including diffuse large B-cell lymphoma (DLBCL), Bcl-2 is found in complex with $InsP_3R2$, whereby Bcl-2 displacement from the $InsP_3R$ channel results in Ca^{2+}-

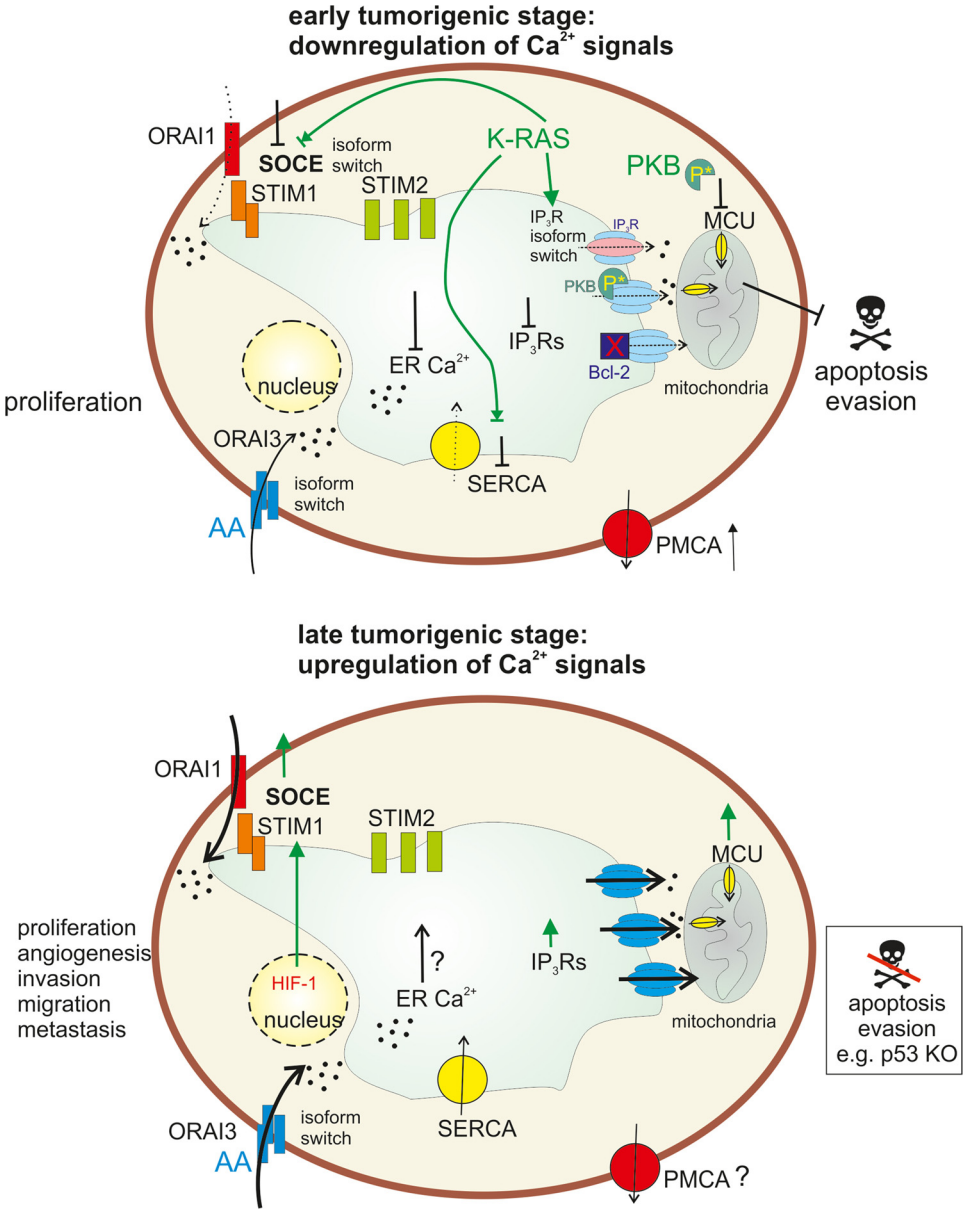

Fig. 2. Modifications of Ca^{2+} signals at early and late stages of tumour development. An initial downregulation (top panel) of the ER Ca^{2+} content and mitochondrial Ca^{2+} uptake could protect from apoptosis and encourage proliferation. Lowering ER Ca^{2+} could be obtained through an $InsP_3R$ isoform switch, increased $InsP_3R$ phosphorylation by overactive PKB, a decrease in SERCA pumps expression or activity, an increase in PMCA expression or a decrease in MCU activity. SOCE could also be decreased through a switch in the STIM1/STIM2 ratio. Increased expression of Orai isoforms other than Orai1 could favour the upregulation of AA-mediated, non-capacitative Ca^{2+} entry.
At later stages (bottom panel), on the background of compromised apoptotic mechanisms (e.g. by KO mutations in p53), turning up Ca^{2+} signals through upregulation of $INsP_3Rs$, SOCE mediators, non-SOCE Ca^{2+} entry or mitochondrial fluxes sustains angiogenesis and the proliferating, invading and migrating cancer cell.

driven cell death [118–120]. In DLBCL cancer cells, the high $InsP_3R2$ expression in combination with constitutively active B-cell receptor signalling and thus $InsP_3$ signalling leads to an addiction to Bcl-2 mediated suppression of pro-apoptotic $InsP_3R$-dependent Ca^{2+} release events [119,120]. Peptides targeting the BH4 domain of Bcl-2 (such as BIRD-2 [121]), which is responsible for $InsP_3R$ interaction and inhibition, disrupt $InsP_3R$/Bcl-2 complexes and provoke apoptosis through intracellular Ca^{2+} overload, further exacerbated through Ca^{2+} influx from the extracellular environment [120,122]. Recently, a screen (using > 25,000 compounds) to identify small molecules that target $InsP_3R$/Bcl-2 complexes in cancer has yielded a lead compound that is able to provoke Ca^{2+} increases in Jurkat and CLL cells and to provoke cell death in Bcl-2-dependent cancer cell models [123]. This compound killed Bcl-2-dependent myeloma cells with an IC50 of ~5 μM without affecting the viability of normal human lymphocytes. BH4-domain-antagonizing tools can also be combined with BH3 mimetics (such as venetoclax/ABT-199) to target cancer cells poorly responding to venetoclax/ABT-199 or to sensitise cancer cells to venetoclax/ABT-199 [124–126]. The latter observation seems to involve the Ca^{2+} dependent upregulation of Bim, a pro-apoptotic BH3-only protein, in response to low [BIRD-2]. Also, the recently identified lead compound could promote venetoclax-induced cell death [123]. As such, peptide tools/small molecules targeting Bcl-2's BH4 domain may therefore represent interesting lead compounds to tackle several diseases by promoting ER-mitochondrial Ca^{2+} fluxes [127]. Unlike that for $InsP_3Rs$, much less is known about the role of RyRs in cancer, possibly because these channels are mainly studied in excitable cells, where the onset of cancer itself is rarer. RyRs are known to be expressed in breast cancer [128] and prostate cancer cells, where they may have a role in regulating apoptosis [129,130]. In a breast cancer cell line, for instance, EGF-induced EMT was associated with elevated mRNA levels of several ER Ca^{2+} pumps and channels, of which RyR2 displayed the most prominent change in gene expression levels [89]. These findings might suggest that RyRs also play a significant role in tumour onset and progression.

4. Ca^{2+} entry channels in cancer

Increasing evidence for the role of SOCE in cancer has emerged over the last decade [131], and also Ca^{2+} entry via VGCCs and TRPs is important in the evolution of cancer [132,133]. The intimate relationship between SOCE and ER Ca^{2+} release places this pathway

centre stage in the regulation of cell physiology and likely the process of oncogenic transformation. STIM1 and Orai1 are considered the main mediators of SOCE in several different cancer cell types, and their role has been particularly recognised in the metastatic stage. Both STIM1 and Orai1 are frequently upregulated in invasive, malignant and metastatic tumours or cell lines (Table 1), such as advanced colorectal cancers [134–136], hepatocellular carcinoma [137], cervical cancer [138], breast cancer [139], glioblastoma [140] and oesophageal cancer [141]. Consistently, their pharmacological or genetic inhibition reduces migration and invasion, as seen in breast cancer cells [142], glioblastoma [140], hepatocellular carcinoma [137], clear cell renal carcinoma [143], colorectal cancer [134] and melanoma [144]. In colorectal cancer, high STIM1 activity is also reported to be mediated by Heat shock protein 27 (HSP27) [145], which is involved in STIM1 stabilisation at *punctae*. To maintain their viability and allow growth, metastatic cancers also need to form new vasculature in the mass. Indeed, the low O_2 tension associated with tumour environment promotes STIM1 expression via HIF-1α, which in turn upregulates HIF-1α expression in a feed-forward fashion [146]. VEGF expression is also associated with increased expression of SOCE components (e.g. STIM1) [59]. VEGF in turn stimulates Ca^{2+} signalling via amongst other pathways a complex interplay between SOCE, the PLCγ-IP_3R Ca^{2+} release, and TRPC1 [81–86]. Indeed, STIM1, Orai1 and TRPC1 are critical mediators of SOCE in ECs [147,148]. Altered expression of SOCE components as well as some TRP channels such as TRPC6 [149], TRPA1 [150] or TRPV4 [151] in cancer leads to the proliferation, migration and tubulogenesis of tumour-derived endothelial cells (TECs), which then allow vascularisation of the tumour mass. SOCE and non-SOCE components as well as ER-Ca^{2+} release in TECs therefore represent an important target for therapy [86]

Less is clear regarding the modulation of SOCE and its mediators at the early stages of tumorigenesis. A direct involvement of STIM1 and SOCE in the G1/S transition of the cell cycle in SiHa cervical cancer cells has been described [58]. Furthermore, proliferation is repressed through inhibition of STIM1/Orai1 or SOCE in esophageal squamous cell carcinoma [141] and clear cell renal cell carcinoma [143]. In malignant melanoma, enhanced SOCE is responsible for improved survival through the maintenance of PKB activity, which is known to protect from apoptosis [152]. Studies conducted in leukemic cell lines have also shown that SOCE activation can temporarily inhibit extrinsic apoptotic pathways to prevent accidental cell death [153,154]. On the other hand, Orai1 downregulation confers apoptotic resistance [155], consistent with the hypothesis that SOCE activation stimulates proliferation by simultaneously increasing ER Ca^{2+} content and mitochondrial uptake. Physiologically, upregulation of SOCE actors is important in mediating apoptosis in a number of cell types including neurons, endothelial cells and lymphocytes (for refs. see [131]). Thus, it is possible that SOCE activation has a general pro-proliferative and pro-migratory effect but will support tumorigenesis only when apoptotic mechanisms have been hijacked in other ways (e.g. increase in PKB-dependent $InsP_3$R phosphorylation). Alternatively, SOCE may be reduced as a strategy to lower ER Ca^{2+} content and protect from apoptosis, as seen for example by our group [156], where SOCE was equally diminished in two different $KRAS^{wt/G13D}$ colorectal cancer cell lines bearing a different abundance of STIM1 (and STIM2, see later). This might seem counterintuitive but the demand for Ca^{2+} signals during tumorigenic transformation presumably differs according to the stage of differentiation and functional requirements of the cell [34,49,157]. Indeed, in line with our analysis, others have described an impairment of SOCE, even in invasive compared to non-invasive tumours, e.g. in melanoma [158]. In a comparison of primary CRC cells with metastatic cells, the expression levels of STIM1 and Orai1 were found not to vary however, at least at the transcript level, and blockade of these proteins did not affect proliferation and migration in either cell type, despite the fact that SOCE was inhibited [136]. In this latter study, even though STIM1 and Orai3 are upregulated in metastatic CRC cells, SOCE was larger in primary cells because ER Ca^{2+} content was lower. A similar anti-correlation between ER store load and SOCE was reported in KRAS mutated colorectal cell lines by our group [105]. To complicate this scenario, different SOCE inhibitors might exert different effects [159]. The contribution of SOCE to the onset and maintenance of the cancer phenotype is therefore incompletely defined.

An understanding of the role of SOCE in cancer is further complicated by the different patterns of expression of the other STIM and Orai isoforms (relative to STIM1 and Orai1) in cancer. Moreover, how the various STIM and Orai isoforms combine to affect SOCE remains to be fully clarified, and changes in the relative abundance of these isoforms may indeed participate in the tumorigenic process [156]. Insights into the role of STIM2 in the context of cancer and its role in tumourigenesis is now emerging. STIM2 was originally reported to be upregulated in glioblastoma [160]. In CRC however, STIM2 has been shown to be both upregulated [161] and downregulated [135], with an inverse correlation between expression and invasiveness [161]. In contrast, Orai1/STIM2 expression in melanoma directly correlates with invasiveness [144]. As mentioned, our group observed a different STIM1/2 ratio, even between CRC cell lines harbouring the same KRAS mutation, with SOCE being reduced in both [156]. It is not clear whether some of these controversies are due to the analysis of different STIM2 splice variants. In a study of 295 breast tumours, the poorer prognosis was associated with those displaying a high STIM1/STIM2 ratio [139]. More recently, different roles for STIM1 and STIM2 in cervical cancer cells have been proposed. While both control proliferation, only STIM1 would also regulate migration [138].

Moreover, changes in Orai2 and Orai3 have been described in oncogenesis. In breast cancer, a specific role for Orai3 in mediating SOCE was reported in oestrogen receptor-positive (ER + ve) but not in ER-negative (ER-ve) cells, where STIM1 and Orai1 are the main SOCE actors [162,163]. In prostate cancer cells, Orai3 is overexpressed, forms AA-gated channels and its overexpression correlates with proliferation and apoptosis resistance [164]. Orai2 and Orai3 were also overexpressed in CRC but their role remained elusive [135] (and Roderick group-unpublished data). Further studies are indeed needed to confirm whether Orai2 and Orai3 play a role in cancer and could be used as tumour biomarkers, as it has been proposed for breast cancer [139,162,163].

The contribution of excessive SOCE to cell death also seems to underlie increased cell death susceptibility of cells expressing a Bcl-2 mutant carrying a three-amino acid mutation within the Bcl-2 BH1 domain [165]. It is proposed that ER Ca^{2+} depletion caused by this mutant version of Bcl-2 leads to activation of SOCE and increased expression levels of SOCE-activating molecules. As a consequence of this excessive SOCE-mediated Ca^{2+} influx, caspases are activated, and apoptosis induced. The protection from apoptosis in this model by inactivation of SOCE or chelating intra- or extracellular Ca^{2+} supports the role of SOCE.

5. Interdependence of ER Ca^{2+} release and SOCE

While we and others discuss apparently distinct contributions of ER Ca^{2+} release via $InsP_3$R and Ca^{2+} entry via SOCE to oncogenic transformation, these two pathways are highly interdependent and cannot be readily dissociated. In its simplest terms, ER Ca^{2+} release induces SOCE, and SOCE is needed to replenish/maintain ER Ca^{2+} levels – required for further release. Thus, with greater Ca^{2+} release, Ca^{2+} entry is likely to be more highly activated and increased SOCE could modify Ca^{2+} release. How can these two pathways act independently in cell physiology and pathology? For example, and at odds with the requirement of maintenance of ER Ca^{2+} levels to allow the ER to perform its many cellular functions [138], a substantial loss of ER Ca^{2+} has been considered to be required for SOCE activation [166]. The question then arises as how physiological stimuli induce SOCE while sustaining other ER functions related to Ca^{2+} signalling. Notably, unlike the substantial

depletion in ER Ca^{2+} observed when SOCE is experimentally induced by thapsigargin, ER [Ca^{2+}] remains relatively stable in cells stimulated with physiologically relevant levels of agonist [167]. This could suggest that SOCE is preferentially activated by a sub-compartment of the ER store that is more depleted by agonist than the bulk ER. The preferential activation of I_{CRAC} by agonist in type II or type III $InsP_3Rs$ expressing DT40 B lymphocytes compared to type 1 $InsP_3R$ expressing cells may support such a model [168]. A model for SOCE activation involving a direct role for $InsP_3Rs$ in gating Ca^{2+} entry, which could thus contribute to selective SOCE activation at Ca^{2+} release sites, has also been considered. This model is analogous to the conformational coupling of the L-type voltage gated Ca^{2+} channel ($Ca_V1.2$ a.k.a DHPR) and RyR1 in skeletal muscle – albeit signalling from the ER to the plasmalemma rather than the reverse [169]. A proximal localisation of the $InsP_3Rs$ and the SOCE machinery at ER-PM junctions would lend support to such a model [170]. Indeed, $InsP_3$ has been demonstrated to activate a PM current in excised patches that was similar to I_{CRAC} [171]. $InsP_3Rs$ have also been shown to directly interact with Orai channels [172]. This model may however be restricted to certain cell types and is not consistently supported. The identification of STIM proteins also circumvents the need for an interaction between $InsP_3Rs$ and Orai to bring about SOCE. Recent findings now indicate that $InsP_3Rs$ immobilised alongside ER-PM junctions, play an important role in stimulating SOCE [170]. Activation of these $InsP_3Rs$ provokes a substantial drop in ER [Ca^{2+}] in these junctions, thereby triggering SOCE. Due to the rapid diffusion of Ca^{2+} within the ER, however, luminal [Ca^{2+}] in the ER will be minimally affected. This model gives rise to the idea that every ER-PM junction forms an autonomous SOCE unit which is regulated by its own immobilised $InsP_3Rs$. Significantly, only $InsP_3Rs$ at these junctions, termed 'licensed' $InsP_3Rs$, contribute to the elementary Ca^{2+} puffs generated in cells stimulated with agonist or $InsP_3$. This paradigm would thus allow SOCE activation without compromising other ER functions. Ca^{2+} entering at these junctions not only has local effects, regulating signalling effectors such as calcineurin/NFAT, it is also resequestered back into the ER and 'tunnelled' to the remote ER, where it may regulate other cell functions [173,174]. Additionally, by ensuring ER refilling, Ca^{2+} remains available for Ca^{2+} release and for maintenance of $InsP_3R$ activity. This latter function may indeed contribute to the change in pattern of the Ca^{2+} signal from Ca^{2+} oscillations to a tonic elevation in $[Ca^{2+}]_i$ brought about by Ca^{2+} influx occuring during cell stimulation with $InsP_3$ [175].

A direct role of $InsP_3Rs$ in promoting Ca^{2+} influx via SOCE, independent of their role in bringing about store depletion and subsequent activation of STIM has also been suggested. Recent findings suggest that $InsP_3Rs$ may trigger SOCE through an additional pathway where $InsP_3Rs$ facilitates the coupling of STIM to Orai [176]. Following their activation, $InsP_3Rs$ translocate to STIM punctae, thereby increasing STIM oligomerisation and ultimately enhancing SOCE. Notably,SOCE is strongly suppressed during mitosis through uncoupling of ER-Ca^{2+} store depletion and activation of Ca^{2+} influx [177]. STIM1 is reported to be phosphorylated in mitotic cells, thereby disabling its rearrangement into PM punctae and inhibiting SOCE activation. This latter mechanism of regulation of STIM is likely to be of greater importance in highly proliferative cells than in cancer. The consequences of this co-regulation of Ca^{2+} release mechanism and SOCE are not fully resolved. Given that both ER Ca^{2+} release and SOCE are initially lowered, then enhanced over the course of oncogenic development, we may hypothesise that an initial downregulation of the ER Ca^{2+} content (be it through an $InsP_3$ isoform switch, or a change in SERCA expression or activity) may lead to impaired SOCE and impaired mitochondrial uptake, an event which would protect from apoptosis while ensuring cancer cell viability through enhanced glycolysis. Lowered ER content would then stimulate higher SOCE, progressively upregulating Ca^{2+} leak, mitochondrial uptake and activity, and even more SOCE, in a feed-forward mechanism, which sustains invasion and metastasis.

6. Concluding remarks and model

The remodelling of the Ca^{2+} toolkit during the stages of oncogenic transformation is complex and designed to meet the needs of the cell during these stages – for example, to promote proliferation, invasiveness, metabolism and avoid death. Ca^{2+} signalling mechanisms show substantial co-regulation in activity and expression. As such, care should be taken in overinterpreting findings of studies in which a full detailed analysis of the Ca^{2+} signalling-ome has not been carried out. Moreover, and not covered in this review of SOCE and ER Ca^{2+} release, is the array of the growing list of regulators/protein partners of the pathways described.

The alterations in the expression of Ca^{2+} toolkit proteins occurring in cancer are summarised in Table 1. Table 2a 2b 2c summarises the studies discussed here in relation to early or late tumorigenic stages. As previously mentioned, we have attempted to build a general model of Ca^{2+} signalling modifications occurring in cancer (Fig. 2). In this model, a downregulation of Ca^{2+} signals and of the ER Ca^{2+} content (obtained through an $InsP_3R$ isoform switch and/or increased phosphorylation by overactive PKB and interaction with Bcl-2 family members, a decrease in SERCA pumps expression or activity, an increase in PMCA expression and a decrease in MCU activity, together with a decrease in SOCE or a switch in the STIM1/STIM2 ratio) would initially protect from apoptosis and encourage proliferation. At later stages, on the background of compromised apoptotic mechanisms (e.g. by KO mutations in p53), augmentation of Ca^{2+} signals through upregulation of $InsP_3Rs$, SOCE mediators, non-SOCE Ca^{2+} entry or mitochondrial fluxes sustains the proliferating, invading and migrating cancer cell. It is envisaged that a detailed knowledge of the Ca^{2+} signalling signature of cancers at different tumorigenic stages in a patient-specific manner may help in their more effective therapeutic targeting.

Declaration of Competing Interest

None.

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