31 Metabolic Disorders and Cancer: Store-Operated Ca^{2+} Entry in Cancer – Focus on IP_3R-Mediated Ca^{2+} Release from Intracellular Stores and Its Role in Migration and Invasion

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Abstract

Store-operated calcium entry (SOCE) plays important roles in a multitude of cellular processes, from muscle contraction to cellular proliferation and migration. Dysregulation of SOCE is responsible for the advancement of multiple diseases, ranging from immune diseases, myopathies, to terminal ones like cancer. Naturally, SOCE has been a focus of many studies and review papers which, however, primarily concentrated on the principal players localized to the plasma membrane and responsible for Ca^{2+} entry into the cell. Much less has been said about other players participating in the entire SOCE event. This review aims to address this shortcoming by discussing the accumulated scientific knowledge focused on the inositol trisphosphate receptors (IP_3Rs), principal player responsible for emptying intracellular Ca^{2+} stores in a majority of cells, and their involvement in regulation of cell migration and invasion in cancer.

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31.1 Introduction

Cancer is one of the most common terminal diseases in developed countries. It is among the main causes of death in the world with more than 100 different types of cancer identified at present, each represented by a specific genotype. Cancer progression development follows three typical steps: initiation, promotion, and progression. The initiation is the step when one or more errors appear in the original DNA sequence, so-called driver mutations, by lesions due to endogenous or exogenous factors. These driver mutations lead to the transformation of the cells which thus become abnormal. The promotion is the identical multiplication of transformed cells. These cells form an abnormal mass called neoplasm or tumor. We talk about cancer once transformed cells have acquired the capacity to trigger the formation of blood vessels (neo-angiogenesis) allowing, in particular, their feeding in nutrients and oxygen ensuring the tumor growth. The last stage is the progression during which cancer cells cross the blood vessel and lymphatic basal lamina in order to migrate to other tissues. Once the cells have arrived at the new tissue, they cross the vessels' basal lamina for the second time to insert themselves into the tissues. This process is called metastasis, and it is the main cause of death by cancer (Hanahan and Weinberg 2011; Jin et al. 2017).

Among the proteins of particular importance that can be targeted by genetic alterations, we find ion channels which are implicated in various carcinogenesis processes such as proliferation, migration, or cancer cell survival. This importance of ion channels stems from their role in maintaining the intracellular ion equilibrium which is crucial for most physiological functions. An imbalance in any of these processes, caused by modification of expression and/or functionality of an ion channel, is called a channelopathy and can be a root cause of a severe disease, such as cancer (Prevarskaya et al. 2010).

One of the more important ions in cellular homeostasis is Ca^{2+} which is a key second messenger, regulating numerous physiological and pathological processes ranging from muscle contraction to much more fatally important ones such as cell motility and death. While, classically, ion channels have been considered to be localized to the plasma membrane (PM), many ion channels have recently been found in the membranes of various intracellular organelles, such as the endoplasmic reticulum (ER), mitochondria, or the nuclear membrane (Leanza et al. 2013). Interestingly, while plasma membrane-localized ion channels are best known to participate in fast-paced cellular processes like muscle contraction or action potential propagation, the majority of intracellular ion channels are known to play important roles in regulating cellular function and fate. For instance, the IP_3Rs and the ryanodine receptors (RyRs), acting as Ca^{2+} release channels in the ER, were shown to regulate various important cellular functions, such as apoptosis,

contraction, cell motility, proliferation and migration (Prevarskaya et al. 2011; Vervloessem et al. 2014).

In general, increase of intracellular Ca^{2+} concentration happens by Ca^{2+} entering the cell via the Ca^{2+}-permeable ion channels of the plasma membrane or by the release of Ca^{2+} from internal stores, typically the endoplasmic or sarcoplasmic reticulum. The release of Ca^{2+} from the ER correspondingly requires the presence of Ca^{2+}-permeable ion channels with the two principal and best studied such protein classes being IP_3Rs and RyRs. The basal cytoplasmic Ca^{2+} concentration is regulated also by specialized transport proteins, such as PMCA (plasma membrane Ca^{2+} ATPase), responsible for the transport of excessive Ca^{2+} out of the cell through the plasma membrane, and SERCA, present in the ER membrane and responsible for Ca^{2+} reuptake by the internal stores. Additionally, store-operated channels (SOC) are known to be present in the plasma membrane, where they are responsible for Ca^{2+} entry into the cells when internal stores are exhausted, and implicate Orai and STIM (stromal interaction molecule) proteins (Yang et al. 2012). The mechanism of such replenishment of Ca^{2+} upon store depletion is called store-operated Ca^{2+} entry (SOCE). In the majority of studies, SOC response is stimulated by blocking SERCA chemically (Michelangeli and East 2011). A classical irreversible SERCA inhibitor is thapsigargin, which blocks Ca^{2+} reuptake into the ER and leads to gradual decrease of its Ca^{2+} content and eventual opening of SOCs.

Since their discovery at the beginning of the twenty-first century, a lot of studies have involved STIM and Orai in various cellular processes from immune cell activation, muscle contraction, and sperm chemotaxis to regulation of gene transcription and cell fate (Kahl and Means 2003; Yoshida et al. 2003). In these studies, Orai1 and STIM1 have been found to be important for cellular migration. For example, suppression of these proteins by siRNA or inhibition of SOC currents by SKF96365 inhibited the migration of the human breast adenocarcinoma cell line MDA-MB-231 and decreased the formation of metastases in mice (Yang et al. 2009). Thus, the importance of SOCE in various cellular processes, including such critical ones as migration and invasion, is well known. The role of STIM and ORAI proteins in hallmarks of cancer and in particular in tissue invasion or metastasis processes has also been extensively studied (Fiorio Pla et al. 2016). However, the majority of associated research focused on immediate players responsible for Ca^{2+} entry into the cells via the PM, with less evidence put forward on how other players, such as IP_3Rs, participate in this big picture. This review aims to close this gap by focusing on the recent findings of how IP_3R activity is regulated by different players and how changes of this activity affect the complex processes of migration and invasion of cancer cells.

31.2 Cellular Migration and Invasion

During metastasis formation, one of the six initial hallmarks of cancer, the migration of epithelial and endothelial cells is a key step leading to the propagation of the primary tumor and to the invasion of neighboring tissues (Hanahan and Weinberg

2000, 2011). However, cell migration is also a central mechanism in homeostasis of healthy tissues. Important physiological processes such as embryogenesis, immune defense, angiogenesis, and wound healing are closely linked to the capability of cells to migrate.

In general, cell migration is conceptualized as a cyclic process (Lauffenburger and Horwitz 1996). It consists of multiple steps, such as the formation of organized adhesive structures, or focal adhesion sites, containing receptors and integrins linked to the extremities of actin fibers (Westhoff et al. 2004) and membrane protrusions, such as lamellipodes or invadopodes, controlled by small GTPases, Rac and Cdc42, with a finely controlled balance between detachment and adhesion at the focal adhesion sites (Ridley et al. 2003). The lamellipodes are surface-attached structures that are found at the leading edge of migrating cells. In order to become invasive, tumor cells need to acquire abilities that allow increased migration through the extracellular matrix (ECM). In order to do this, tumor cells have specialized membrane protrusions, called invadopodia, that provide important functions for invasion. It should be noted that the term invadopodia is primarily used in conjunction with cancer cells, while the term podosome can often be found in the literature when talking about normal cells. Invadopodia are actin-rich plasma membrane protrusions at the ventral surface of the cell, often situated under the nucleus, that are proteolytically active and responsible for the focal degradation of ECM components through matrix metalloproteinases (MMP) (Nabeshima et al. 2002; Yoon et al. 2003).

Both, Ca^{2+} release and Ca^{2+} influx, have been linked to cell migration depending on cell types and stimuli (Agle et al. 2010; Tsai et al. 2014; Yang and Huang 2005). Thus, migrating cells are polarized and exhibit a transient and steady gradient of intracellular Ca^{2+}. That gradient increases from the front of the cell to the rear and is thought to be responsible for rear-end retraction (Brundage et al. 1991; Hahn et al. 1992). The increased cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) at the rear end is related among others to myosin II contraction and calpain-mediated release of focal adhesions leading to the retraction of the uropod (Eddy et al. 2000; Palecek et al. 1998). The retraction is accomplished via myosin II contraction, which is regulated by myosin light chain (MLC) phosphorylation through Ca^{2+}-dependent MLC kinase (MLCK) and by disassembly of adhesions at the rear of the cell owing to calpain-mediated cleavage of focal adhesion proteins such as integrins, talin, vinculin, and focal adhesion kinase (FAK) (Ridley et al. 2003). However, the cyclic morphological and adherence changes that are observed during cell migration are also supported by repetitive Ca^{2+} signals, which take the form of Ca^{2+} spikes or oscillations (Pettit and Fay 1998).

It is therefore natural that migration of the tumor, being strongly dependent on these Ca^{2+} signals, is accompanied by changes in expression and activity of ion channels. Below we discuss how IP_3Rs participate in these processes, regulate intracellular Ca^{2+}, and work in ensemble with SOCs.

31.3 Intracellular Ca^{2+} Release Channels: The IP_3Rs

31.3.1 The Discovery of the IP_3Rs

Involvement of IP_3R in intracellular Ca^{2+} regulation was observed for the first time over 30 years ago, when Streb et al. (1983) found a second messenger that was able to increase $[Ca^{2+}]_i$ from a non-mitochondrial store: inositol 1,4,5-trisphosphate (IP_3). This discovery was followed by concentrated efforts of many researchers to discover the target of this second messenger. This goal was achieved first by K. Mikoshiba's team, which was working on a P400 protein which was absent in Purkinje-neuron-degenerating mutant mice and found that this protein binds IP_3 (Furuichi et al. 1989a; Maeda et al. 1988), and established its complete primary sequence (Furuichi et al. 1989b; Maeda et al. 1990).

One year later the P400 protein was found to form a channel by incorporating it into a planar lipid bilayer and recording its activity and was renamed IP3R. Moreover, in the same paper, it was shown that this channel exhibited a Ca^{2+} conductance (Maeda et al. 1991). These findings were confirmed by the work of other teams that achieved similar results, establishing the identity of the IP_3R at the same time (Sudhof et al. 1991; Supattapone et al. 1988).

The IP_3R is one of the first ion channels that were discovered to be localized in the ER (Ross et al. 1989). The channel is a tetramer, formed from monomers of 260 kDa in size. Each monomer contains binding sites for IP_3 and Ca^{2+} in the N-terminal region, six transmembrane domains forming a pore region and the determinants for tetramer formation in the C-terminus (Fan et al. 2015; Taylor and Konieczny 2016).

The IP_3R is a principal Ca^{2+} release channel from the internal stores in the majority of cells, participating in the regulation of intracellular Ca^{2+} in the cytosol and in Ca^{2+} transfer between ER and mitochondria (Rizzuto et al. 2009). Over the years, a lot of different studies have implicated the IP_3R in plenty of physiological and pathological mechanisms. Indeed, an overexpression of the IP_3R is observed in numerous forms of cancer, typically in correlation with an increase in proliferation or migration (Ivanova et al. 2014).

As mentioned earlier, the first identified physiological trigger for the activation of these channels is known to be IP_3. However, further studies elucidated the specific mechanism of IP_3R activation by IP_3 in a Ca^{2+}-sensitive manner. The IP_3R is regulated in a bimodal manner by Ca^{2+} itself—its activity increases with the increase of $[Ca^{2+}]_i$ to a certain level, a phenomenon that is known as Ca^{2+}-induced Ca^{2+} release (CICR). However, IP_3R activity is inhibited at higher $[Ca^{2+}]_i$, with IP_3 removing this inhibition of IP_3R activity at high $[Ca^{2+}]_i$ (Foskett et al. 2007). IP_3 itself is produced in the cells in response to stimulation of surface receptors such as receptor tyrosine kinases (RTK) and G-protein-coupled receptors (GPCR), leading to the activation of phospholipase C (PLC). The PLC is an enzyme that metabolizes phosphatidylinositol 4,5-biphosphate (PiP2) into IP_3 and diacylglycerol (DAG), both of which are second messengers, thus triggering various signaling cascades that can involve IP_3Rs and lead, for example, to cellular growth.

31.3.2 Role of the IP_3Rs in Regulating Migration and Invasion

While the identity of IP_3R channels and their role in Ca^{2+} release from internal stores have been known for a long time, the question of their involvement in regulating cellular migration and invasion has only recently became a topic of active studies. Publications covering this subject are few, but their number is steadily increasing in the last few years (see Table 31.1).

Treatment with caffeine was found to inhibit the IP_3R-mediated Ca^{2+} release by selectively targeting IP_3R3 in glioblastoma cell lines. Interestingly, the mRNA

Table 31.1 Implication of IP_3R in migration and invasion

Cell type	Mechanism and function	References
Swiss 3T3 fibroblasts	GPCR were stimulated (bombesin, bradykinin, vasopressin) resulting in IP_3-mediated Ca^{2+} release in fibroblasts. Released Ca^{2+} associates with calmodulin (CaM), modulating CaMKII (CaM-dependent protein kinase II). CaMKII, in turn, phosphorylates FAK at Ser-843. Once FAK is phosphorylated, it leads to increased formation of focal adhesion sites	Fan et al. (2005)
WI-38 (human embryonic lung fibroblasts)	Alterations in the membrane potential via transient receptor potential melastatin 7 (TRPM7) and chemoattractant signal transduction via IP_3R2 are responsible for Ca^{2+} flickers at the front of a migrating cell, controlling the direction of cell migration	Wei et al. (2009); for review Wei et al. (2010)
Melanoma cells (Mel-2 and SK-Mel-24)	The PLCε/IP_3/IP_3R1 pathway mediates EPAC (exchange protein activated by cyclic AMP)-induced Ca^{2+} elevation which increases melanoma cell migration through the interaction between S100A4 and MHCIIA (myosin heavy chain IIA) and the resultant actin assembly	Baljinnyam et al. (2010)
Glioblastoma cell lines (U178MG, U87MG, and T98G); mouse xenograft model of glioblastoma	Caffeine inhibits invasion and increases survival rate of subject animal (in mouse xenograft model of glioblastoma) by selectively targeting the IP_3R3	Kang et al. (2010)
Pancreatic ductal adenocarcinoma cells (PDAC; PANC-1 cell line)	The migration of PDAC cells was strongly suppressed by selective inhibition of IP_3Rs and SOCE (using xestospongin B and siRNA)	Okeke et al. (2016)

level of IP_3R3 was significantly increased in glioblastoma cells compared to normal cells (Kang et al. 2010). The inhibition of IP_3R3 by caffeine suppresses the migration and invasion of glioblastoma cell lines when assessed by scrape motility, matrigel invasion, soft agar, and mouse brain slice implantation. To show this, U87MG cells, a glioblastoma cell line known for its high tumorigenicity, were injected into the skin of nude mice, some of which were supplied with caffeine in drinking water. The supplementation with caffeine considerably increased the mean survival rate of mice, proposing IP_3R3 as a promising novel therapeutic target for glioblastoma treatment and showing that caffeine could be a useful adjunct therapy (Kang et al. 2010). Noteworthy, the final concentration of caffeine measured in the mice brain corresponded to levels of caffeine produced by drinking two to five cups of coffee per day by humans. Caffeine is a well-known activator of RyRs but has also been shown to inhibit IP_3R activity (Brown et al. 1992), although ryanodine, a known inhibitor of RyR activity, did not show any effect on migration and invasion of the transformed cells. The type 3 IP_3R was also implicated in peritoneal dissemination of gastric cancer (Sakakura et al. 2003).

IP_3R-mediated Ca^{2+} release has also been linked to metastatic melanoma. Interestingly, Ca^{2+} release from the stores promoted the migration of metastatic epithelial breast adenocarcinoma (MDA-MB-231) and cervical carcinoma (HeLa) cell lines via the activation of S100A4 protein by Ca^{2+} (Mueller et al. 1999). Indeed, the PLC/IP_3/IP_3R1 pathway has been shown to mediate EPAC (exchange protein activated by cyclic AMP)-induced Ca^{2+} elevation that in turn increases melanoma cell migration through the interaction between S100A4 and MHCIIA and the resultant actin assembly (Baljinnyam et al. 2010). This suggests that IP_3R can also be a potential target for the suppression of melanoma cell migration opening a perspective of treatments against the metastasis development (see Fig. 31.1).

In addition, the use of the PLC inhibitor U73122 significantly decreased the Ca^{2+} release from the ER and decreased the migration of melanoma cell through monolayers of human umbilical vein endothelial cells (HUVECs) (Peng et al. 2009).

A key constituent involved in the regulation of focal adhesion turnover is FAK. It is a non-receptor kinase that promotes cell migration by transferring signals between growth factor receptors and integrins. FAK is regulated by phosphorylation at tyrosine and serine residues. By using GPCR agonists such as bombesin, bradykinin, and vasopressin stimulates the PLC/IP_3/IP_3R pathway leading to Ca^{2+} mobilization from ER stores in Swiss 3T3 fibroblasts. This released Ca^{2+} associates with CaM, and, subsequentially, the Ca^{2+}/CaM complex regulates CaMKII (calmodulin-dependent protein kinase II) which then rapidly phosphorylates FAK at Ser-843. Once FAK is phosphorylated at this and three other locations (Ser-722, Ser-732 and Ser-910), it facilitates the formation of focal adhesion points (Fan et al. 2005) (see Fig. 31.1).

Localized Ca^{2+} flickers at the leading lamella permit the decision-making for turning direction of the migrating cells: the cell turns in the direction of higher Ca^{2+} flicker activity. These flickering Ca^{2+} microdomains result in membrane tension via TRPM7 and chemoattractant signal transduction via IP_3R2. However, by

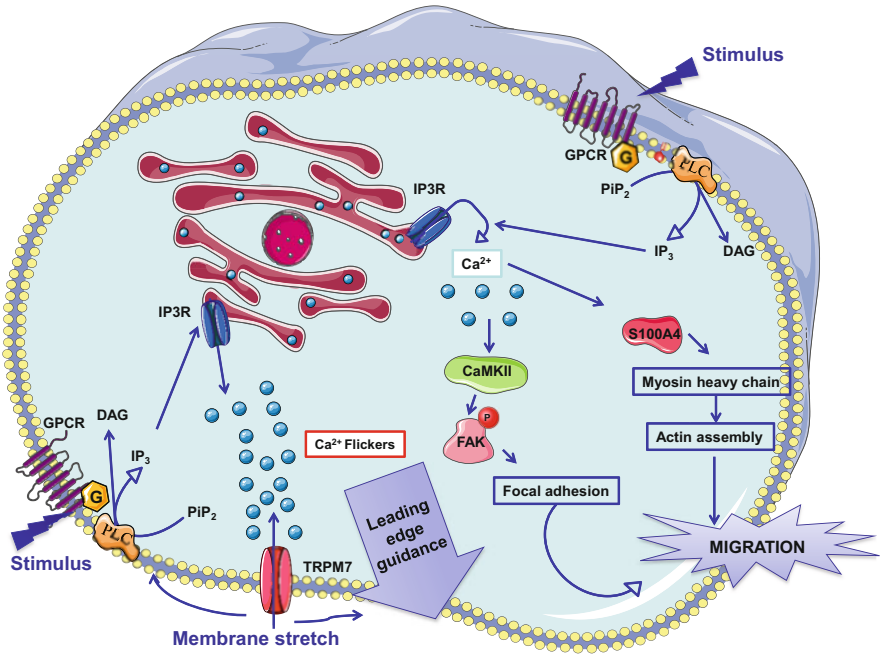

Fig. 31.1 This figure represents the cross section of a migrating cell at the leading edge. It demonstrates the known pathways by which the IP_3Rs participate in cell migration/invasion through controlling the release of Ca^{2+} from the ER. Activation of GPCRs by external stimuli is represented via lightning bolts and the activation of further pathways, as well as Ca^{2+} release and production of secondary messengers are indicated by the *arrows*. The membrane stretch-activated, transient receptor potential cation channel subfamily M member 7 (TRPM7)-mediated Ca^{2+} influx coupled to IP_3R-mediated Ca^{2+} release participates in the guidance of the leading edge toward a chemoattractant (Wei et al. 2010). Formation of focal adhesions is facilitated by IP_3R-mediated Ca^{2+} release that is stimulated through surface GPCRs or EPAC leading to CaMKII-dependent FAK phosphorylation (Fan et al. 2005). IP_3R-mediated Ca^{2+}mobilization from the endoplasmic reticulum (ER) stores also promotes cell migration in an S100A4-dependent manner (Baljinnyam et al. 2010)

themselves, these flickers only determine the turning direction but not the migration speed. Indeed, the use of EGTA to chelate intracellular Ca^{2+} slows the turning but not the migration speed in a dose-dependent manner, showing that spatiotemporal organization of Ca^{2+} microdomains is important in such convoluted cellular processes as cell migration (Wei et al. 2009, 2010) (see Fig. 31.1).

Recently, IP_3Rs have been shown to translocate from cell-cell contacts to the leading edge of migrating pancreatic ductal adenocarcinoma cells (PDAC) which was accompanied by the formation of ER-PM junctions and STIM1 puncta. Xestospongin B, a selective IP_3R inhibitor, and the STIM-Orai inhibitor GSK-79751 suppressed the migration of the cell line PANC-1. Taken together, these data emphasize that both, Ca^{2+} release and Ca^{2+} influx, are important for cell migration (Okeke et al. 2016).

31.3.3 Role of IP_3Rs in SOCE

The principal pathways by which ion channels regulate cellular migration are associated with their primary functions, such as regulation of cellular adhesion, volume or migration speed, maintenance of cellular potential, and regulation of intra- and extracellular pH. Unfortunately, the link between the expression and function of IP_3Rs and the mechanisms of their involvement in cancer cell migration, invasion, and metastasis is not yet well understood. Nonetheless, there is general consensus that Ca^{2+} signaling alterations play a major role in carcinogenesis (Parkash and Asotra 2011; Wei et al. 2012).

Ion channel activity can essentially be described as a series of transitions between open and closed states, with a particular probability of being open (P_{open}). The opening/closing of the IP_3Rs can be modulated by different factors such as Ca^{2+}, IP_3, and Mg^{2+}. For example, the IP_3R activity is regulated by Ca^{2+} in a bimodal manner. P_{open} of IP_3R, and thus Ca^{2+} release from ER, is very low at low Ca^{2+} levels, gradually increasing with the rise of $[Ca^{2+}]_i$, reaching a plateau at μM concentrations, and finally being again inhibited at higher $[Ca^{2+}]_i$, thus also leading to a decrease in Ca^{2+} release. In the majority of publications, involvement of the IP_3Rs in migration and invasion was found through the use of its major agonist, IP_3. Once the IP_3R is activated, Ca^{2+} is released from the ER and can either stimulate Ca^{2+}-dependent proteins such as calpain or Ca^{2+}-activated ion channels (Fig. 31.2). In that way, the mobilization of Ca^{2+} from the intracellular stores via IP_3Rs can magnify the Ca^{2+} entry signal via SOCs and result in a strong response capable of inducing cell migration and invasion or even stimulate metastasis formation. The release of Ca^{2+} from the ER via IP_3Rs has also been shown to induce the SOC opening. The Ca^{2+} release induces Ca^{2+} entry via STIM1/ORAI1 resulting in Ras and Rac protein (small GTPases) activation (Yang et al. 2009) which in turn accelerates the turnover of focal adhesions and further increases migration. In support of these observations, there is now considerable evidence that STIM1 activates both, Orai1 and TRPC1, via distinct domains at its C-terminus (Ong et al. 2016).

Concerning the invasion mechanism, there is no evidence that the IP_3Rs can directly affect the activation of metalloproteinases and, thus, the digestion of the extracellular matrix necessary for cell invasion. Otherwise, it has been shown that the induction of MMP2 and MMP9 can happen via Ca^{2+} flux through TRPV2 (Monet et al. 2010). Moreover, S100A4 has been found to control the invasive potential of human prostate cancer cells through the regulation of MMP9 expression, contributing to the proteolysis of ECM by invadopodia (Saleem et al. 2006). It has been suggested that the link between IP_3Rs and ECM degradation can be S100A4 (also known as mts1) which is a Ca^{2+}-binding protein associated with invasion and metastasis of cancer cells and can, therefore, be activated by Ca^{2+} release via the IP_3Rs (Baljinnyam et al. 2010). Further studies on this interesting topic are needed to confirm these hypotheses.

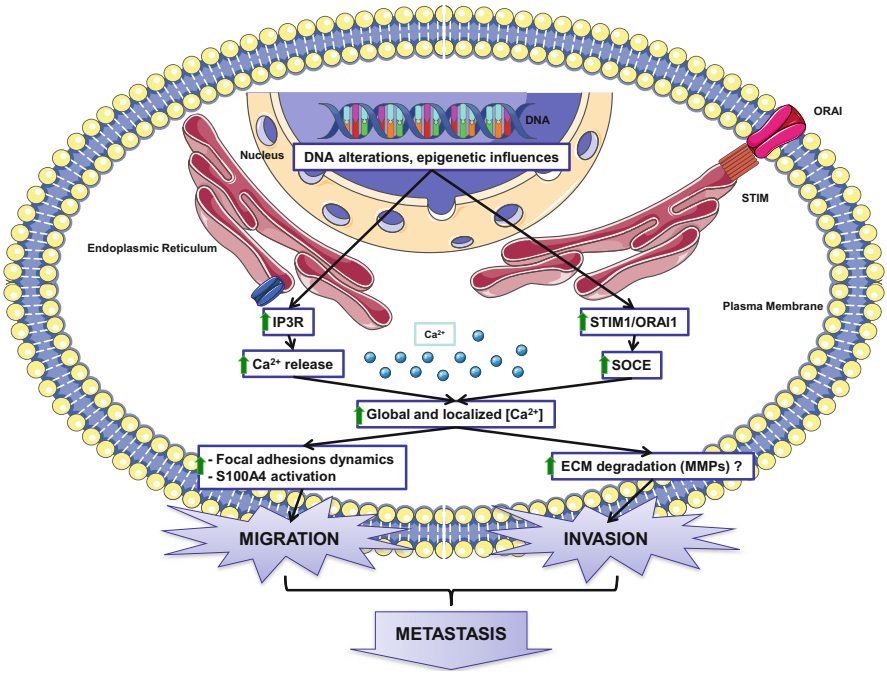

Fig. 31.2 This scheme illustrates the roles IP3Rs play in SOCE regulation for the promotion of cancer cell metastasis. The *black arrows* show the sequence of events; the *green upward arrows* indicate an increase in the expression and/or function of the corresponding protein(s) or augmentation of the corresponding process. The "?" indicates that the associated step has been recently hypothesized in literature (Baljinnyam et al. 2010) but requires further evidence

31.3.4 Role of IP_3Rs Protein Partners in SOCE

It is well known that IP_3R activity is heavily modulated by various partner proteins. Among them are in particular the proteins of the Bcl-2 family that modulate the activity of IP_3Rs directly or indirectly. Multiple studies, such as Rong et al. (2008), have shown that Bcl-2 is present in the ER where it can interact directly with all three IP_3R isoforms, inhibiting their activity via multiple binding sites proposed to explain this interaction (Fouque et al. 2016; Ivanova et al. 2016). Other proteins of the Bcl-2 family such as Bcl-xL or Mcl-1 are also known to interact with the IP_3Rs and modulate its activity (Eckenrode et al. 2010; Monaco et al. 2012).

Interestingly, Bcl-2 and Bcl-xL are found to be overexpressed in many cancers. Overexpression of Bcl-2 is observed in 30–60% of androgen-dependent and nearly 100% of androgen-independent prostate cancers, with similar results observed for Bcl-xL. Unfortunately, the studies carried out so far reported primarily on the changes in the expression levels, with little to no data on the possible impact of the modulation of IP_3R activity by Bcl-2/Bcl-xL on cancer cell migration/invasion. To find this likely link, it could be very interesting to test the effects of different

drugs already known to specifically disrupt the interaction between Bcl-2 protein family members and the IP_3Rs, such as ABT-199, a BH3 mimetic that specifically binds Bcl-2's hydrophobic cleft (Vervloessem et al. 2016), on cancer cell migration and invasion properties.

While the interaction between Bcl-2 family members and IP_3Rs has been known for a while, in the past few years scientists have shown that the IP_3Rs also interact with many other proteins, including the Sigma1 receptor which has also been found to modulate SOCE (Rosado 2016). Additionally, IP_3Rs have been suggested to interact with some of the channels belonging to the family of the TRP channels (Fiorio Pla and Gkika 2013). Thus, for example, TRPC3 was successfully co-immunoprecipitated with the IP_3Rs by glutathione S-transferase (GST) pulldown experiments (Boulay et al. 1999). Moreover, TRPC3 has been shown to be activated by IP_3, whereby the N-terminal IP_3-binding domain of IP_3R was essential (Kiselyov et al. 1999). Similar experiment permits allowed the identification of biochemical interactions between IP_3Rs and TRPC1 (Mehta et al. 2003). It is also interesting to note that there is now considerable evidence that STIM1 activates both, Orai1 and TRPC1, via distinct domains in its C-terminus (Ong et al. 2016).

31.4 Conclusion and Perspectives

Ca^{2+} plays many important roles in regulating cellular health and migration properties with SOCE being one of the primary mechanisms regulating intracellular Ca^{2+} homeostasis. It is therefore natural that SOCE is at the core of many diseases, including such important ones as cancer, with many publications focusing on the mechanisms and dysregulations of SOCE. This review has focused in particular on a less well-covered area of store-operated Ca^{2+}—the IP_3R channels responsible for the depletion of internal stores in a majority of cells and their various roles in modifying SOCE and affecting cellular motility and invasion.

The role of IP_3Rs in SOCE and associated diseases is a relatively novel topic. Recent publications only start to address the question of how IP3Rs modulate cancer progression in particular concerning the questions of migration and invasion. However, IP3R activity is known to be modulated by numerous protein partners. While multitude of studies have been devoted of the topics of this regulation itself, its involvement in SOCE regulation where cancer progression is concerned has not yet been properly addressed in scientific literature. Considering the increasing number of IP_3R protein partners discovered regularly in recent years, the importance of this angle should not be underestimated. However, as one can easily see, there is still a lot of research to be carried out in order to comprehensively understand the mechanisms by which these channels and SOCE regulate migration and invasion of cancer cells. Further research on any of these topics provides a great promise to develop treatments that could counteract or at least arrest progression of various forms of cancer toward metastatic stages.

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References

Agle KA, Vongsa RA, Dwinell MB (2010) Calcium mobilization triggered by the chemokine CXCL12 regulates migration in wounded intestinal epithelial monolayers. J Biol Chem 285:16066–16075

Baljinnyam E, De Lorenzo MS, Xie L, Iwatsubo M, Chen S, Goydos JS, Nowycky MC, Iwatsubo K (2010) Exchange protein directly activated by cyclic AMP increases melanoma cell migration by a Ca2+-dependent mechanism. Cancer Res 70:5607–5617

Boulay G, Brown DM, Qin N, Jiang M, Dietrich A, Zhu MX, Chen Z, Birnbaumer M, Mikoshiba K, Birnbaumer L (1999) Modulation of Ca(2+) entry by polypeptides of the inositol 1,4, 5-trisphosphate receptor (IP3R) that bind transient receptor potential (TRP): evidence for roles of TRP and IP3R in store depletion-activated Ca(2+) entry. Proc Natl Acad Sci USA 96:14955–14960

Brown GR, Sayers LG, Kirk CJ, Michell RH, Michelangeli F (1992) The opening of the inositol 1, 4, 5-trisphosphate-sensitive Ca2+ channel in rat cerebellum is inhibited by caffeine. Biochem J 282:309–312

Brundage RA, Fogarty KE, Tuft RA, Fay FS (1991) Calcium gradients underlying polarization and chemotaxis of eosinophils. Science 254:703–706

Eckenrode EF, Yang J, Velmurugan GV, Foskett JK, White C (2010) Apoptosis protection by Mcl-1 and Bcl-2 modulation of inositol 1,4,5-trisphosphate receptor-dependent Ca2+ signaling. J Biol Chem 285:13678–13684

Eddy RJ, Pierini LM, Matsumura F, Maxfield FR (2000) Ca2+-dependent myosin II activation is required for uropod retraction during neutrophil migration. J Cell Sci 1298:1287–1298

Fan RS, Jacoma RO, Jiang X, Sinnett-Smith J, Rozengurt E (2005) G protein-coupled receptor activation rapidly stimulates focal adhesion kinase phosphorylation at Ser-843. Mediation by Ca2+, calmodulin, and Ca2+/calmodulin-dependent kinase II. J Biol Chem 280:24212–24220

Fan G, Baker ML, Wang Z, Baker MR, Sinyagovskiy PA, Chiu W, Ludtke SJ, Serysheva II (2015) Gating machinery of InsP3R channels revealed by electron cryomicroscopy. Nature 527:336–341

Fiorio Pla A, Gkika D (2013) Emerging role of TRP channels in cell migration: from tumor vascularization to metastasis. Front Physiol 4:311

Fiorio Pla A, Kondratska K, Prevarskaya N (2016) STIM and ORAI proteins: crucial roles in hallmarks of cancer. Am J Physiol Cell Physiol 310:C509–C519

Foskett JK, White C, Cheung KH, Mak DO (2007) Inositol trisphosphate receptor Ca2+ release channels. Physiol Rev 87:593–658

Fouque A, Lepvrier E, Debure L, Gouriou Y, Malleter M, Delcroix V, Ovize M, Ducret T, Li C, Hammadi M, Vacher P, Legembre P (2016) The apoptotic members CD95, BclxL, and Bcl-2 cooperate to promote cell migration by inducing Ca(2+) flux from the endoplasmic reticulum to mitochondria. Cell Death Differ 23:1702–1716

Furuichi T, Yoshikawa S, Miyawaki A, Wada K, Maeda N, Mikoshiba K (1989a) Primary structure and functional expression of the inositol 1,4,5-trisphosphate-binding protein P400. Nature 342:32–38

Furuichi T, Yoshikawa S, Mikoshiba K (1989b) Nucleotide sequence of cDNA encoding P400 protein in the mouse cerebellum. Nucleic Acids Res 17:5385–5386

Hahn K, DeBiasio R, Taylor DL (1992) Patterns of elevated free calcium and calmodulin activation in living cells. Nature 359:736–738

Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell 100:57–70

Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144:646–674
Ivanova H, Vervliet T, Missiaen L, Parys JB, De Smedt H, Bultynck G (2014) IP3R-isoform diversity in cell death and survival. Biochim Biophys Acta 1843:2164–2183
Ivanova H, Ritaine A, Wagner L, Luyten T, Shapovalov G, Welkenhuyzen K, Seitaj B, Monaco G, De Smedt H, Prevarskaya N, Yule DI, Parys JB, Bultynck G (2016) The trans-membrane domain of Bcl-2α, but not its hydrophobic cleft, is a critical determinant for efficient IP3 receptor inhibition. Oncotarget 7:55704–55720
Jin K, Li T, van Dam H, Zhou F, Zhang L (2017) Molecular insights into tumour metastasis: tracing the dominant events. J Pathol 241(5):567–577
Kahl CR, Means AR (2003) Regulation of cell cycle progression by calcium/calmodulin-dependent pathways. Endocr Rev 24:719–736
Kang SS, Han KS, Ku BM, Lee YK, Hong J, Shin HY, Almonte AG, Woo DH, Brat DJ, Hwang EM, Yoo SH, Chung CK, Park SH, Paek SH, Roh EJ, Lee SJ, Park JY, Traynelis SF, Lee CJ (2010) Caffeine-mediated inhibition of calcium release channel inositol 1,4,5-trisphosphate receptor subtype 3 blocks glioblastoma invasion and extends survival. Cancer Res 70:1173–1183
Kiselyov K, Mignery GA, Zhu MX, Muallem S (1999) The N-terminal domain of the IP3 receptor gates store-operated hTrp3 channels. Mol Cell 4:423–429
Lauffenburger DA, Horwitz AF (1996) Cell migration: a physically integrated molecular process. Cell 84:359–369
Leanza L, Biasutto L, Manago A, Gulbins E, Zoratti M, Szabo I (2013) Intracellular ion channels and cancer. Front Physiol 4:227
Maeda N, Niinobe M, Nakahira K (1988) Purification and characterization of P400 protein, a glycoprotein characteristic of Purkinje cell, from mouse cerebellum. J Neurochem 51:1724–1730
Maeda N, Niinobe M, Mikoshiba K (1990) A cerebellar Purkinje cell marker P400 is an inositol 1,4,5-trisphosphate (InsP3) receptor protein. Purification and characterization of InsP3 receptor complex. EMBO J 9:61–67
Maeda N, Kawasaki T, Nakade S, Yokota N, Taguchi T, Kasaiq M, Mikoshiba K (1991) Structural and functional characterization of inositol 1,4,5-trisphosphate receptor channel from mouse cerebellum. J Biol Chem 266:1109–1116
Mehta D, Ahmmed GU, Paria BC, Holinstat M, Voyno-Yasenetskaya T, Tiruppathi C, Minshall RD, Malik AB (2003) RhoA interaction with inositol 1,4,5-trisphosphate receptor and transient receptor potential channel-1 regulates Ca2+ entry. Role in signaling increased endothelial permeability. J Biol Chem 278:33492–33500
Michelangeli F, East JM (2011) A diversity of SERCA Ca2+ pump inhibitors. Biochem Soc Trans 39:789–797
Monaco G, Beckers M, Ivanova H, Missiaen L, Parys JB, De Smedt H, Bultynck G (2012) Profiling of the Bcl-2/Bcl-X(L)-binding sites on type 1 IP(3) receptor. Biochem Biophys Res Commun 428:31–35
Monet M, Lehen'kyi V, Gackiere F, Firlej V, Vandenberghe M, Roudbaraki M, Gkika D, Pourtier A, Bidaux G, Slomianny C, Delcourt P, Rassendren F, Bergerat JP, Ceraline J, Cabon F, Humez S, Prevarskaya N (2010) Role of cationic channel TRPV2 in promoting prostate cancer migration and progression to androgen resistance. Cancer Res 70:1225–1235
Mueller A, Bächi T, Höchli M, Schäfer BW, Heizmann CW (1999) Subcellular distribution of S100 proteins in tumor cells and their relocation in response to calcium activation. Histochem Cell Biol 111:453–459
Nabeshima K, Inoue T, Shimao Y, Sameshima T (2002) Matrix metalloproteinases in tumor invasion: role for cell migration. Pathol Int 52:255–264
Okeke E, Parker T, Dingsdale H, Concannon M, Awais M, Voronina S, Molgo J, Begg M, Metcalf D, Knight AE, Sutton R, Haynes L, Tepikin AV (2016) Epithelial-mesenchymal transition, IP3 receptors and ER-PM junctions: translocation of Ca2+ signalling complexes and regulation of migration. Biochem J 473:757–767

Ong HL, de Souza LB, Ambudkar IS (2016) Role of TRPC channels in store-operated calcium entry. In: Rosado JA (ed) Calcium entry pathways in non-excitable cells, Advances in experimental medicine and biology. Springer, Cham, pp 87–109
Palecek SP, Huttenlocher A, Horwitz AF, Lauffenburger DA (1998) Physical and biochemical regulation of integrin release during rear detachment of migrating cells. J Cell Sci 940:929–940
Parkash J, Asotra K (2011) Calcium wave signaling in cancer cells. Life Sci 87:587–595
Peng H, Hodgson L, Henderson AJ, Dong C (2009) Involvement of phospholipase C signaling in melanoma cell-induced endothelial junction disassembly. Front Biosci 1:1597–1606
Pettit EJ, Fay FS (1998) Cytosolic free calcium and the cytoskeleton in the control of leukocyte chemotaxis. Physiol Rev 78:949–967
Prevarskaya N, Skryma R, Shuba Y (2010) Ion channels and the hallmarks of cancer. Trends Mol Med 16:107–121
Prevarskaya N, Skryma R, Shuba Y (2011) Calcium in tumour metastasis: new roles for known actors. Nat Rev Cancer 11:609–618
Ridley A, Schwartz M, Burridge K, Firtel R, Ginsberg M, Borisy G, Parsons J, Horwitz A (2003) Cell migration: integrating signals from front to back. Science 302:1704–1710
Rizzuto R, Marchi S, Bonora M, Aguiari P, Bononi A, De Stefani D, Giorgi C, Leo S, Rimessi A, Siviero R, Zecchini E, Pinton P (2009) Ca(2+) transfer from the ER to mitochondria: when, how and why. Biochim Biophys Acta 1787:1342–1351
Rong YP, Aromolaran AS, Bultynck G, Zhong F, Li X, McColl K, Matsuyama S, Herlitze S, Roderick HL, Bootman MD, Mignery GA, Parys JB, De Smedt H, Distelhorst CW (2008) Targeting Bcl-2-IP3 receptor interaction to reverse Bcl-2's inhibition of apoptotic calcium signals. Mol Cell 31:255–265
Rosado JA (2016) Sigma-1 receptors: a new pathway for the modulation of store-operated calcium entry. Biochem J 473:e9–e10
Ross CA, Meldolesi J, Milner TA, Satoh T, Supattapone S, Snyder SH (1989) Inositol 1,4,5-trisphosphate receptor localized to endoplasmic reticulum in cerebellar Purkinje neurons. Nature 339:468–470
Sakakura C, Hagiwara A, Fukuda K, Shimomura K, Takagi T, Kin S, Nakase Y, Fujiyama J, Mikoshiba K, Okazaki Y, Yamagishi H (2003) Possible involvement of inositol 1,4,5-trisphosphate receptor type 3 (IP3R3) in the peritoneal dissemination of gastric cancers. Anticancer Res 23:3691–3697
Saleem M, Kweon MH, Johnson JJ, Adhami VM, Elcheva I, Khan N, Bin Hafeez B, Bhat KM, Sarfaraz S, Reagan-Shaw S, Spiegelman VS, Setaluri V, Mukhtar H (2006) S100A4 accelerates tumorigenesis and invasion of human prostate cancer through the transcriptional regulation of matrix metalloproteinase 9. Proc Natl Acad Sci USA 103:14825–14830
Streb H, Irvine RF, Berridge MJ, Schulz I (1983) Release of Ca2+ from a nonmitochondrial intracellular store in pancreatic acinar cells by inositol-1,4,5-trisphosphate. Nature 306:67–69
Sudhof TC, Newton CL, Archer BT, Ushkaryov YA, Mignery GA (1991) Structure of novel InsP3 receptor. EMBO J 1:3199–3206
Supattapone S, Worley PF, Baraban JM, Snyder SH (1988) Solubilization, purification, and characterization of an inositol trisphosphate receptor. J Biol Chem 263:1530–1534
Taylor CW, Konieczny V (2016) IP 3 receptors: take four IP 3 to open. Sci Signal 9:1–9
Tsai F, Seki A, Yang HW, Hayer A, Carrasco S, Meyer T (2014) A polarized Ca2+, diacylglycerol, and STIM1 signaling system regulates directed cell migration. Nat Cell Biol 16:133–144
Vervloessem T, Yule DI, Bultynck G, Parys JB (2014) The type 2 inositol 1,4,5-trisphosphate receptor, emerging functions for an intriguing Ca^{2+}-release channel. Biochim Biophys Acta 1853:1992–2005
Vervloessem T, Ivanova H, Luyten T, Parys JB, Bultynck G (2016) The selective Bcl-2 inhibitor venetoclax, a BH3 mimetic, does not dysregulate intracellular Ca2+ signaling. Biochim Biophys Acta 1864:968–976
Wei C, Wang X, Chen M, Ouyang K, Song LS, Cheng H (2009) Calcium flickers steer cell migration. Nature 457:901–905

Wei C, Wang X, Chen M, Ouyang K, Zheng M, Cheng H (2010) Flickering calcium microdomains signal turning of migrating cells. Can J Physiol Pharmacol 88:105–110

Wei C, Wang X, Zheng M, Cheng H (2012) Calcium gradients underlying cell migration. Curr Opin Cell Biol 24:254–261

Westhoff MA, Serrels B, Fincham VJ, Frame MC, Carragher NO (2004) SRC-mediated phosphorylation of focal adhesion kinase couples actin and adhesion dynamics to survival signaling. Mol Cell Biol 24:8113–8133

Yang S, Huang XY (2005) Ca2+ influx through L-type Ca2+ channels controls the trailing tail contraction in growth factor-induced fibroblast cell migration. J Biol Chem 280:27130–27137

Yang S, Zhang JJ, Huang XY (2009) Orai1 and STIM1 are critical for breast tumor cell migration and metastasis. Cancer Cell 15:124–134

Yang X, Jin H, Cai X, Li S, Shen Y (2012) Structural and mechanistic insights into the activation of Stromal interaction molecule 1 (STIM1). Proc Natl Acad Sci USA 109:5657–5662

Yoon S, Park S, Yun C, Chung A (2003) Roles of matrix metalloproteinases in tumor metastasis and angiogenesis. J Biochem Mol Biol 36:128–137

Yoshida M, Ishikawa M, Izumi H, De Santis R, Morisawa M (2003) Store-operated calcium channel regulates the chemotactic behavior of ascidian sperm. Proc Natl Acad Sci USA 100:149–154