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Review

Deciphering the Role of Ca^{2+} Signalling in Cancer Metastasis: From the Bench to the Bedside

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Simple Summary: Ca^{2+} dyshomeostasis is implicated in several key pathophysiological processes attributed to cancer metastasis biology. Here, we decipher the role of intracellular and extracellular Ca^{2+} signalling pathways in processes that contribute to metastasis at the local level (involving cell proliferation, adhesion, motility, invasion, migration and the epithelial-mesenchymal transition) and also their effects on cancer metastasis globally. Ca^{2+} proteins are potential candidates for cancer biomarkers and druggable targets for future metastatic cancer therapy.

Abstract: Metastatic cancer is one of the major causes of cancer-related mortalities. Metastasis is a complex, multi-process phenomenon, and a hallmark of cancer. Calcium (Ca^{2+}) is a ubiquitous secondary messenger, and it has become evident that Ca^{2+} signalling plays a vital role in cancer. Ca^{2+} homeostasis is dysregulated in physiological processes related to tumour metastasis and progression—including cellular adhesion, epithelial–mesenchymal transition, cell migration, motility, and invasion. In this review, we looked at the role of intracellular and extracellular Ca^{2+} signalling pathways in processes that contribute to metastasis at the local level and also their effects on cancer metastasis globally, as well as at underlying molecular mechanisms and clinical applications. Spatiotemporal Ca^{2+} homeostasis, in terms of oscillations or waves, is crucial for hindering tumour progression and metastasis. They are a limited number of clinical trials investigating treating patients with advanced stages of various cancer types. Ca^{2+} signalling may serve as a novel hallmark of cancer due to the versatility of Ca^{2+} signals in cells, which suggests that the modulation of specific upstream/downstream targets may be a therapeutic approach to treat cancer, particularly in patients with metastatic cancers.

Keywords: calcium; Ca^{2+} signals; metastasis; cancer

Citation: Alharbi, A.; Zhang, Y.; Parrington, J. Deciphering the Role of Ca^{2+} Signalling in Cancer Metastasis: From the Bench to the Bedside. *Cancers* **2021**, *13*, 179 . https://doi.org/10.3390/cancers13020179

Received: 15 December 2020
Accepted: 3 January 2021
Published: 7 January 2021

1. Introduction

Cancer is a serious public health condition globally. Metastasis is a significant hallmark of cancer, defined as the transition of cancer cells from their original site to another site, and accounts for ~90% of cancer-related mortalities [1]. Metastasis is a complex phenomenon that involves multiple phases (from the translocation from the primary site to the colonization of the secondary site) and several pathophysiological processes (including cell proliferation, adhesion and motility; tumour invasion and migration; angiogenesis; and the epithelial-mesenchymal transition) which interact with each other at a local level to develop metastatic cancer at a global level. It is a fundamental phenomenon in our understanding of the underlying molecular mechanisms related to cancer pathogenesis; hence, it is a viable target for cancer therapy and approaches to prevent and target metastatic cancer have drawn scientific attention for several decades and remain of great interest in decoding cancer biology. Ca^{2+} is a versatile second messenger, and its homeostasis is critical to hindering the development of metastatic cancer at both the intracellular and extracellular levels. Intracellular and

extracellular Ca^{2+} signalling is implicated in several key pathophysiological processes which are attributed to tumour metastasis and progression [2–9].

Importantly, dysregulation of spatiotemporal Ca^{2+} homeostasis at both intracellular and extracellular levels, in terms of spatiotemporal oscillations or waves, alters cellular physiological processes at the local level leading to metastatic cancer globally (shown in Figure 1). There are two main Ca^{2+} signalling pathways: intracellular (local) and extracellular (global). The implications of their communication and complementary interplay for the development of metastatic cancer are becoming extremely difficult to ignore. It has become evident that intracellular calcium channels, including inositol 1,4,5-trisphosphate (IP_3) receptors (IP_3Rs), transient receptor potential cation channels (TRPML, mucolipins), and two-pore channels (TPCs), play roles in the modulation of key processes that regulate tumour progression and migration [9–12]. Our recent review discussed briefly the role of two-pore channel 2 (TPC2) in tumour cell migration [9]. In addition, extracellular Ca^{2+} signalling pathways, via calcium-sensing receptor (CaSR)and store-operated calcium entry (SOCE), have been shown to contribute to pathophysiological processes that promote metastasis [13,14]. A growing quantity of experimental evidence and a limited number of clinical trials suggest a potential clinical application of Ca^{2+} modulators and their upstream/downstream targets as a therapeutic approach to treat metastatic cancer. Recently, a considerable amount of literature has been produced around the theme of Ca^{2+} signalling in cancer, particularly its pivotal role in pathophysiological processes towards cancer metastasis. Here, we look at the role of Ca^{2+} signalling at both the intracellular and extracellular levels in cancer metastasis, which will contribute to a deeper understanding of cancer pathogenesis and permit us to further investigate Ca^{2+} signalling as a regulator of tumour progression and metastasis.

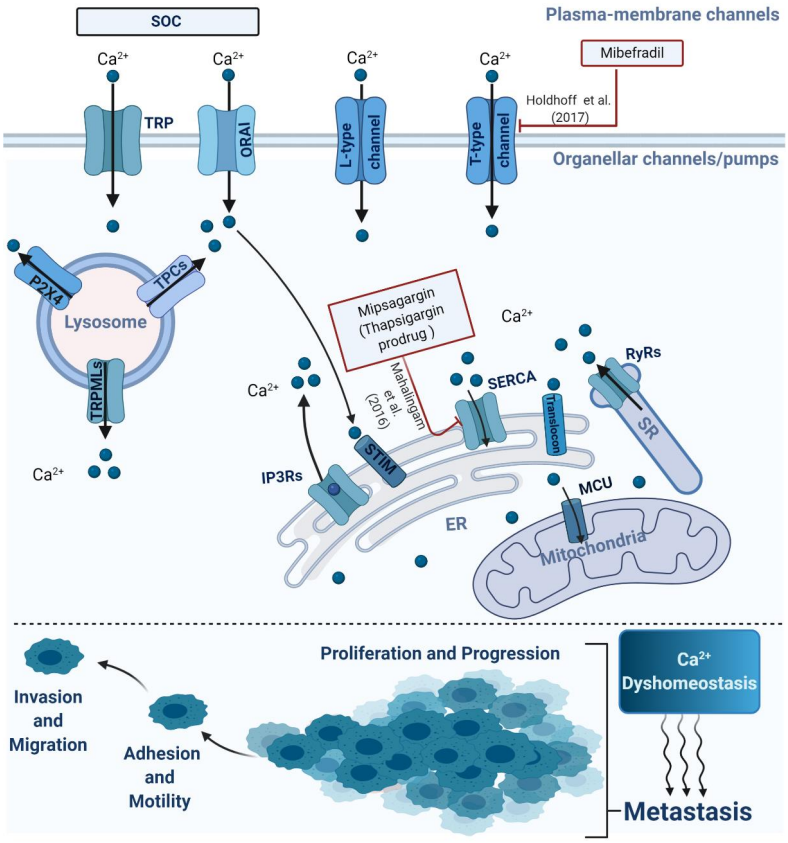

Figure 1. Schematic representation of the main intracellular or extracellular calcium channels involved in metastasis. The alterations of Ca^{2+} homeostasis via organellar or plasma channels/pumps were implicated in several processes attributed to cancer metastasis, involving cell proliferation, invasion, migration and progression.

2. Intracellular Calcium Signalling in Metastasis

2.1. Endoplasmic and Sarcoplasmic Reticulum Ca^{2+} Channels/Pumps

Endoplasmic and sarcoplasmic reticulum Ca^{2+} channels/pumps include inositol 1,4,5-trisphosphate (IP_3) receptors (IP_3Rs), ryanodine receptors (RyRs), the translocons, and sarco-endoplasmic reticulum Ca^{2+} reuptake pump (SERCA). SERCA acts as a mobiliser of Ca^{2+} from the cytosol into the ER to maintain cytoplasmic Ca^{2+} homeostasis. It consists of three major isoforms (SERCA1-3) [15]. Chung et al. (2006) found that high SERCA2 expression was correlated with lymph node metastasis, advanced stages of tumourigenesis, and significantly shorter survival compared to low SERCA2 expression in patients with colorectal cancer [16]. Unlike earlier findings, high SERCA3 expression was significantly associated with longer survival, negatively correlated tumour node metastasis (TNM) staging and distant metastases, but not with lymph node metastasis in patients with gastric carcinomas [17]. Shi et al. (2018) showed that SERCA is involved in Yap (Yes-activated protein)-mediated hepatocellular carcinoma metastasis [18].

The emerging role of intracellular Ca^{2+} signalling in cancer cell migration is not a recent discovery. Rondé et al. highlighted the intracellular Ca^{2+} oscillations which are linked to cell migration in U-87MG cells (an in vitro model of malignant glioma) via IP_3Rs, but not ryanodine receptors [19]. A previous study found that ryanodine receptor isoform-2 (RYR2) gene expression was upregulated by 45-fold in epidermal growth factor (EGF)-treated MDA-MB-468 cells (mesenchymal-like state) compared to MDA-MB-468 cells (epithelial-like state), suggesting that the involvement of the RYR2/Ca^{2+} signalling pathway in the EGF-induced epithelial-mesenchymal transition (EMT) in breast cancer, which is a critical process for cell adhesion, invasion and migration, ultimately leads to a metastatic state [20]. Recently, Fukushima et al. have uncovered the role of translocation associated membrane protein 2 (TRAM2), a component of the translocon, in metastasis [21]. They have shown that TRAM2 knockdown eliminated metastatic traits—including cell invasion and transendothelial migration in oral squamous cell carcinoma (OSCC) cells—by modulating the expression of matrix metalloproteinases. Their study found that Ca^{2+} permeability via translocon mediates cancer progression [21]. Ca^{2+} release in the intracellular compartment is mainly mediated by IP_3Rs, which are located on the ER [16]. There are three isoforms: IP_3R type 1 (IP_3R1), IP_3R type 2 (IP_3R2), and IP_3R type 3 (IP_3R3) [18]. The release of Ca^{2+} from the ER to the cytosol via IP_3Rs is mainly trigged by IP_3 and Ca^{2+} [22]. Whole-exome sequencing (WES) conducted by Hedberg et al. in patients with head and neck squamous cell carcinoma (HNSCC) underpinned the potential clinical utility of IP_3R3 as a prognostic biomarker. They discovered genetic mutations in IP_3R3 in metastatic or recurrent HNSCC cancers, but not in the primary tumour [23]. IP_3R3 overexpression is implicated in various types of cancer including breast, colorectal, cholangiocarcinoma, gastric and glioblastoma, and promotes cancer progression by enhancing metastatic phenotypes [24–28]. When siRNA was used to silence IP_3R3 in an in vitro model of breast cancer, this was shown to attenuate cell migrations induced by Ca^{2+} oscillations [24]. Recent data showed that IP_3R3 function was drastically impaired by epidermal growth factor receptor (EGFR) and tyrosine-protein kinase (MET) inhibitors in oncogene-driven non-small cell lung cancer (NSCLC), thus raising intriguing questions regarding the possibility of targeting upstream or downstream regulator or effector proteins of IP_3R3 to treat metastatic cancer patients, particularly those with NSCLC [29].

In contrast to the findings which demonstrated that the IP_3R3/Ca^{2+} signalling pathway is critical for cancer invasion and migration in vitro, IP_3R2 was found to be a key mediator of ER Ca^{2+} signals which mediate migration in human lung cancer cells (A549 cell line) [30].

Taken together, these findings emphasise the critical role of Ca^{2+} signalling from the ER, mainly via IP_3Rs, which acts as a key regulator of several pathophysiological processes related to tumour progression and migration. Despite substantial in vitro evidence that has led to the recognition of emerging roles of IP_3Rs as modulators of Ca^{2+} signalling and

enhanced metastatic traits, further studies utilizing in vivo IP_3R knockout mouse models will help to further reveal the molecular mechanisms of IP_3Rs as mediators of metastasis.

2.2. Endolysosomal Ca^{2+} Channels

TPCs, TRPML, and P2X(4) receptors are intracellular Ca^{2+} permeable channels and are located in the endolysosomal compartment, which consists of early, late, and recycling endosomes, lysosomes, and autophagosomes. While they have an evident role in the involvement of endolysosomal Ca^{2+} signalling pathways in cancer phenotypes from tumour initiation to cancer cell migration [11], the molecular mechanisms underlying endolysosomal Ca^{2+} signal-mediated metastasis remains speculative. Two-pore channel type 1 (TPC1) and two-pore channel type 2 (TPC2) are two isoforms of the two-pore channel superfamily, expressed in mammalian cells. Recently, the effects of TPCs and particularly TPC2 on pathophysiological processes related to metastatic cancer have been observed in in vitro and in vivo cancer models [9]. TPC1- or TPC2-deficient T24 cells (an in vitro model of bladder cancer) generated by siRNA showed a significant decrease in metastatic phenotypes cell adhesion and migration compared to control cells [31]. In the same study, diminished TPC function achieved either by silencing using siRNA or pharmacological inhibition by Ned-19 or tetrandrine in T24 cells was shown to alter β1-integrin recycling, which is involved in cell motility and invasion. This ultimately hinders tumour metastasis [31]. Notably, the inhibition of TPC2 function using siRNA or inhibitors in an in vivo mouse mammary cancer model has been shown to significantly reduce the formation of lung metastasis [31]. These results differ from recent evidence demonstrating that the downregulation of TPC2 expression or TPC2 knockout promotes tumour metastasis in melanoma cells generated from an advanced stage of tumourigenesis [32]. The controversy about whether TPC2/Ca^{2+}signaling in metastatic cancer promotes or hampers metastatic traits—such as tumour cell adhesion, motility, invasion and progression—might reflect TPC2 having differential roles in different types or stages of cancer. Three isoforms of transient receptor potential cation channels (TRPMLs) found in mammals are TRPML1, TRPML2, and TRPML3 [33]. TRPML1 knockdown conducted with siRNA in HepG2 cells (an in vitro human hepatocellular liver carcinoma model) impaired invasion and attenuated cell migration compared to WT HepG2 cells [34]. Additionally, this study identified for the first time the mechanism of action of tetrabromobisphenol A (TBBPA), a toxin that has been linked to hepatic cancer invasion and migration, finding that TBBPA evoked endolysosomal Ca^{2+} signals upon binding to TRPML1 [34]. An increased expression of transient receptor potential mucolipin1 (TRPML1) was also detected in advanced stages (III–IV) compared to early stages (I–II) of tumourigenesis in patients with non-small-cell lung cancer (NSCLC); TRPML1 silencing or inhibition in vitro impaired pathophysiological processes related to metastatic NSCLC cancer, indicating that enhanced expression of mucolipin 1 was involved in cancer progression and metastasis by promoting cell invasion, proliferation and migration in NSCLC [35]. TRPML-2 mRNA and protein levels were found to be elevated in brain cancer patients and correlated with advanced pathological grades (from astrocytoma (I) to glioblastoma (IV)) [36]. TRPML-2-deficient U251 and T98 cells (an in vitro model of glioblastoma) showed a reduction in cell proliferation involving the inhibition of AKT and ERK1/2 signalling [36], suggesting that TRPML-2 acts as a regulator of ERK1/2 and AKT signalling pathways in glioblastoma cell proliferation.

Recently, TRPML3 was discovered to be one of the nine gene signatures predicting overall survival in patients with pancreatic cancer [37]. Downregulation of TRPML3 expression acts as a protective factor in the prognostic nomogram established for pancreatic cancer [37]. The above findings suggest the possibility of the clinical utility of TRPML subtypes as a potential distinct prognostic marker for cancer progression and overall survival in various cancer subtypes. The P2X(4) receptor is expressed in the endolysosomal system and modulated by ATP and pH [38]. To our knowledge, no previous study has investigated the role of P2X(4) receptors in metastatic traits. Endolysosomal Ca^{2+} signals have attracted growing interest as a novel biomarkers or therapeutic targets for metastatic

carcinoma. Further studies to confirm these findings through in vivo mouse models or a prospective large cohort of cancer patients are required.

Despite the substantial literature that implicates the different roles of lysosomal Ca^{2+} release channels in cancer metastasis, there is a lack of evidence for how these lysosomal Ca^{2+} channels may interact to mediate development of metastatic cancer at a global level. We speculate that lysosomal Ca^{2+} dyshomeostasis contributes to metastatic phenotypes with distinctive roles for these channels and possible crosstalk that requires further investigation to expand our knowledge of the pathophysiology of cancer metastasis biology. The mobilisation of cytosolic Ca^{2+} into endolysosomal compartments is poorly understood and remains enigmatic. Garrity et al. found that the ER plays a role in the Ca^{2+} refilling of lysosomes [39], and we infer that it occurs via an unidentified Ca^{2+} transporter.

2.3. Intracellular Ca^{2+} Signalling and Ca^{2+}-Activated K^+ Channels (K_{Ca}) in Metastasis

Intracellular calcium oscillations activate Ca^{2+}-activated K^+ channels, involving intermediate ($K_{Ca3.1}$) and large conductance ($K_{Ca1.1}$), were found to promote tumour cell proliferation, migration and progression [40–43]. $K_{Ca3.1}$ and $K_{Ca1.1}$ differ in their Ca^{2+} sensitivities. $K_{Ca3.1}$ requires a small physiological alteration in Ca^{2+}, while $K_{Ca1.1}$ responds to a large change in Ca^{2+} [44]. Several studies have provided substantial evidence that $K_{Ca3.1}$ and $K_{Ca1.1}$ contribute to glioblastoma metastasis biology [45–48]. Growing evidence is linking $K_{Ca3.1}$ to glioma cell invasion and migration [46,49,50], and recent data has implicated that $K_{Ca3.1}$ is upregulated in high-radiation dose-induced glioblastoma cell invasion [51]. $K_{Ca1.1}$ was shown also to play a role in radiation-enhanced glioblastoma migration in in vitro and in vivo murine models [52]. Pharmacological inhibition of $K_{Ca1.1}$ diminished migratory capability of glioblastoma cells induced by hypoxia in U87-MG cells [47]. Overall, these findings indicate the indirect involvement of intracellular Ca^{2+} signalling-mediated cell invasion and migration via either $K_{Ca3.1}$ or $K_{Ca1.1}$ in glioblastoma. Further work is required to underscore the crosstalk between these channels and intracellular Ca^{2+} signalling at the molecular level to understand the pathophysiology behind the roles of these channels in glioblastoma metastasis biology. These channels might represent viable clinical tools that can enhance the efficiency of detection and guide the treatment of glioblastoma patients.

3. Extracellular Components of Ca^{2+} Signalling in Metastasis

Apart from providing structural supports for cells to form organs and tissues, the extracellular matrix (ECM) and extracellular proteins play other vital roles in various cell functions. Proteins in the extracellular space and on the cell membranes form a complicated network which initiates signalling cascades in the intracellular space; such signalling cascades regulate multiple aspects of cell behaviour including determination, differentiation, proliferation, and migration [53]. Although extracellular proteins have been less studied in relation to cell signalling than intracellular components, abundant evidence of their critical functions has been revealed in the past decade. Here we review some extracellular proteins related to Ca^{2+} signalling with particular emphasis on their mechanisms of action and functional roles in processes linked to cancer, especially metastasis.

3.1. Calcium-Sensing Receptor (CaSR)

As the ECM is the largest Ca^{2+} reservoir in multicellular organisms, macromolecules in the extracellular space directly bind to receptors on the cell surface resulting in Ca^{2+} entering the cell [54]. One such receptor is the calcium-sensing receptor (CaSR), a ubiquitously expressed G protein-coupled receptor sensing extracellular Ca^{2+} levels and controlling Ca^{2+} homeostasis by regulating parathyroid hormone release in the parathyroid gland and inhibiting Ca^{2+} reabsorption in the kidney [55,56]. The functions of the CaSR in the parathyroid gland and kidney have long been well recognized but a recent study reported that the CaSR has played pivotal roles in diverse processes such as inflammation, apoptosis, migration and proliferation. In particular, its paradoxical role in cancer has aroused a lot of

interest [57]. The CaSR suppresses cell proliferation and induces terminal differentiation in parathyroid and colon tumors, as shown by recent studies which provided abundant evidence that overexpressing the CaSR suppressed the proliferation of colorectal cancer cell both in vivo and in vitro [58,59], while inversely, it acts as an oncogene in prostate, testicular, ovarian, and breast cancer, especially bone metastasis in breast and prostate cancer [60,61]. As early as 2006, Liao et al. demonstrated that elevated extracellular Ca^{2+} facilitated skeletal metastasis of prostate cell lines and that this effect was associated with an up-regulated CaSR which mediated the influx of extracellular Ca^{2+} triggering the AKT signalling pathway, but extracellular Ca^{2+} influx had no effect in prostate cancer cells derived from a lymph node metastasis [57]. Around the same time, Mihai et al. provided clinical evidence that CaSR-positive tumors were more likely to develop bone metastasis in breast cancer, by assessing the intensity of CaSR expression in the primary tumor histological sections [62]. This effect was later shown to have involved extracellular-signal-regulated kinase (ERK1/2) and phospholipase C beta (PLCβ) as downstream effectors [63]. Using similar methods as Mihai et al., Feng et al. identified a promotion function for the CaSR in metastatic prostate cancer; thus by pathological and statistical analysis, they found that compared to non-metastatic prostate cancer tissue, metastatic cancer tissue specifically expressed a higher level of the CaSR [61]. In 2014, Joeckel et al. demonstrated in renal cell carcinoma (RCC) cells that the CaSR mediated the promotion function of extracellular Ca^{2+} on tumor cell proliferation and bone metastasis via activation of the PI3K (phosphatidylinositol 3-kinase)/AKT pathway, the PLCγ-1 pathway, and the mitogen activated protein kinase (MAPK) cascades [64,65].

Taken together, the findings show that binding of these proteins to the CaSR initiates intracellular Ca^{2+} signaling cascades which lead specifically to the bone metastasis of multiple cancers, indicating that the CaSR can be a treatment target and also a diagnostic indicator of metastasis to bone.

3.2. Store-Operated Calcium Entry (SOCE)

One of the major mechanisms that regulate and remodel Ca^{2+} influx pathways in tumour progression is store-operated calcium entry (SOCE), the process in which Ca^{2+} passes through the cell membrane upon the depletion of intracellular Ca^{2+} stored in the endoplasmic reticulum (ER) [66,67]. Growing evidence has shown that SOCE and its molecular determinants are involved in various cell behaviours including proliferation, angiogenesis, invasion, and migration in some types of cancers [68–70].

3.2.1. ORAI

As an important determinant of SOCE, ORAI proteins, which form a store-operated calcium selective ion channel, have been linked to roles in the development of cancer cells. ORAI forms calcium release-activated channels (CRAC) on the cell surface and interacts with stromal interaction molecule 1 (STIM1) which senses the Ca^{2+} concentration inside the ER and regulates SOCE [71]. In 2014, Umemura et al. reported that melanoma cell proliferation and metastasis were significantly suppressed by either genetically down-regulating ORAI or pharmacologically inhibiting SOCE [68], and since it has long been recognized that in melanoma cells, proliferation is regulated via ERK signalling, and migration is regulated via calpain-dependent actin dynamics [72], Umemura et al. proved that both these regulatory mechanisms were initiated by SOCE [68]. In hepatocarcinoma tissues, Tang et al. reported that genetic downregulation of ORAI1 or pharmacological inhibition of SOCE using SKF96365 improves 5-FU-induced autophagy and cell death in HepG2 cells (an in vitro model of hepatocarcinoma) [73]. ORAI mediated SOCE also leads to metastasis in acute myeloid leukemia, as reported by Diez-Bello et al. Genetic knockdown of ORAI1 and ORAI2 in the promyeloblastic cell line HL60, attenuated cell proliferation and metastasis via promotion of the phosphorylation of the focal adhesion kinase (FAK), which was shown to be essential for cell migration and invasion [66,74]. The link between FAK and another ORAI isoform, ORAI3, and their roles in tumorigenesis, was also reported

by Motiani et al. in breast cancer cells [75]. Of all the ORAI isoforms, ORAI1 is the most ubiquitously expressed and the most well studied, however, future studies may focus on determining whether different ORAI isoforms have varying roles in different cancer types or at different stages of tumourigenesis.

3.2.2. Stromal-Interaction Molecule (STIM)

Stromal-interaction molecule (STIM) is a Ca^{2+} sensor in the ER that triggers SOCE activation. How STIM regulates cancer progress is controversial. Chen et al. revealed, through in vitro studies, mouse models, and clinical analyses, that STIM1-dependent signalling regulates proliferation, migration, and angiogenesis in cervical cancer cells [76]. STIM1 also affects invasion and migration of gastric cancer cells, possibly through an unknown pathway independent of the MEK/ERK signaling, as reported by Xu et al. [77].

3.2.3. TRP Channels

Alterations of Ca^{2+} homeostasis via transient receptor potential (TRP) channels were implicated in several processes attributed to cancer metastasis, practically cell proliferation and migration, which are two of cancer's hallmarks. TRP is a superfamily of cation channels localised in the plasma membrane and composed of subfamilies, such as transient receptor potential canonical (TRPC), transient receptor potential vanilloid (TPRPV) and transient receptor potential melastatin (TRPM) [78]. Although previous studies have provided evidence of the involvement of various isoforms of TRPC, such as TRPC1, TRPC4, TRPC5 and TRPC6, in regulating pathophysiological processes related to tumour metastasis [79–83], and several reviews [84–87] have also discussed it, current studies focus mainly on the role of TRPC6/Ca^{2+} signalling in cancer metastasis at the global level in various types of cancers and revealed the emerging roles of TRPC3 in melanoma metastasis at the local level. Oda et al. (2017) found that TRPC3 acts as a modulator of melanoma cell proliferation and migration in in vitro and in vivo models (using the C8161 human melanoma cell line) in a mechanism involving (matrix metallopeptidase 9) MMP9 activation [88]. Inhibition of TRPC6/Ca^{2+} signalling either pharmacologically (using SKF-96365) or by genetic downregulation using siRNA showed a significant reduction in A549 cell (an in vitro model of NSCLC) proliferation by arresting the cell cycle at the S-G2/M phase and invasion [89]. Therefore, inhibiting the effects of TRPC6/Ca^{2+} signalling may serve as a viable therapeutic target for patients with NSCLC metastatic cancer, and it warrants further investigation in an in vivo model. Recently, the novel roles of the Na^{+}/Ca^{2+} exchanger 1 (NCX1) and TRPC6 were deciphered in modulating transforming growth factor-beta (TGFβ), which plays a vital role in various aspects of human hepatocellular carcinoma metastasis, involving hepatic cell invasion and migration [90]. Recent evidence has shown that Ca^{2+} signalling via TRPC6 acts as a regulator of *Helicobacter pylori*-mediated gastric cancer invasion and migration involving activation of the Wnt/β-catenin signalling pathway in AGS and MKN45 cells [91]. A growing body of evidence highlights the contribution of various TRPM isoforms, including TRPM2, TRPM4, TRPM5, TRPM7 and TRPM8, in cancer metastasis biology [92–100]. Recent scientific attention was given to TRPM8 in bladder cancer metastasis. Wang et al. demonstrated that TRPM8 modulates cell proliferation and migration, ultimately leading to the development of bladder cancer metastatic phenotypes [101]. Knockdown of TRPM8 attenuates bladder cancer proliferation and progression in T24 cells and slows down tumour growth and progression in a murine model of human urinary bladder cancer [101]. The availability of a TRPM8 antagonist (PF-05105679), which has been tested in humans (phase 1 trial, NCT01393652) [102], raises a translational question regarding the possibility of modulating TRPM8 as a therapeutic approach and giving it as adjuvant therapy for patients with metastatic cancer after adequate data for its safety and tolerability (I.e. through clinical validation) have been obtained and an analogue to overcome one potential therapeutic limitation (causing a hot feeling in patients) has been developed that might greatly help the development of an anti-neoplastic agent to treat metastatic cancer.TRPV1, TRPV2 and TRPV4 are reported to regulate pathophysiological

processes related to metastatic traits [103–107]. Recently, growing evidence has shown that TRPV4 modulates epithelial-mesenchymal transition and cytoskeleton promoting cancer metastasis [108,109]. TRPV4/Ca^{2+} signalling enhances gastric cancer progression in an in vitro model of gastric cancer (HGC-27 and MGC-803 cells) and is significantly correlated with aggressive features (involving depth of tumour invasion and lymph node metastasis) in gastric cancer patients, which suggests its clinical utility as a biomarker to predict the prognosis in patients with gastric cancer [108]. Li et al. underpinned the role of TRPV4/Ca^{2+} signalling-promoted endometrial cancer metastasis through the modulation of the cytoskeleton in a mechanism involving the activation of the RhoA (Ras homolog gene family member A)/ROCK1(Rho-associated protein kinase 1) signalling pathway [109]. Further studies are required to expand our cancer biology knowledge of the molecular mechanisms underlying the TRP modulation of metastasis and the identification of novel targets/biomarkers to treat metastatic cancer.

3.2.4. Mitochondrial Ca^{2+} Uniporter and SOCE Crosstalk

The mitochondrial Ca^{2+} uniporter (MCU) mobilizes mitochondrial Ca^{2+} signalling from the cytosol into mitochondria. The cellular mechanisms underlying the regulation of Ca^{2+} signalling via MCU in pathophysiological processes that are related to metastatic cancer [110,111] and its links to store-operated Ca^{2+} entry-mediated tumour metastasis have been investigated [112]. Several studies have shown that MCU plays a pivotal role in breast cancer progression and metastasis and that it is a candidate therapeutic target and biomarker for breast cancer [112–114]. Tang et al. demonstrated that Ca^{2+} release via MCU is critical for SOCE-promoted metastasis in MDA-MB-231 breast cancer cells [112]. By contrast, Tosatto et al. suggested that the distinctive role of MCU enhances breast migration progression via a mechanism involving hypoxia-inducible factor-1α (HIF-1α) signalling, and they attributed the indirect effects of MCU on Ca^{2+} signalling via SOCE that was observed by Tan et al. to the cell line-dependent effect [113]. Similarly, recent evidence by Wang et al. is consistent with Tosatto et al.'s finding that MCU-mediated mitochondrial Ca^{2+} signals enhance metastatic phenotypes (involving the epithelial-mesenchymal transition process) through a distinctive mechanism via HIF-1α and VEGF (Vascular endothelial growth factor) signalling pathways in gastric cancer [115]. What remains unanswered is how MCU acts at the molecular level and what the possible complex interplay is between mitochondrial Ca^{2+} signalling, SOCE and metastatic cancer. These factors warrant further investigation in various cancer subtypes utilising in vitro and in vivo models.

3.3. Voltage-Gated Ca^{2+} Channels in Metastasis

Recently, voltage-gated Ca^{2+} channels (VGCCs), particularly L and T subtypes, have been implicated in the pathophysiological processes that drive cancer metastasis [116–121]. Grasset et al. demonstrated that pharmacological inhibition of the L-type calcium channel via verapamil or diltiazem decreases the EGF signalling mediated collective cancer cell invasion in in vitro and in vivo models of squamous cell carcinoma [120]. Recent evidence provided by Phiwchai et al. (2020) revealed the involvement of L-type calcium channel/Ca^{2+} signalling pathway in labile iron-driving hepatic cancer cell proliferation [121]. Knocked down or pharmacologically inhibited T-type calcium channels showed reduced migration and invasion of BRAFV600E cells, which provides evidence that T-type calcium channels play a role in melanoma metastasis [118]. These data highlight the potential of these channels to serve as promising therapeutic targets to treat patients with metastatic carcinomas due to the long-term medical use of these channel.

4. Proteins Involved in Ca^{2+} Signalling Cascades and Their Roles in Metastasis

The crosstalk between calcium effector proteins such as calpain and calmodulin (CaM), and endolysosomal proteins such as the lysosome-associated membrane proteins (LAMPs), and cancer metastasis has begun to be unravelled. There are 15 isoforms of the calpain family of calcium-dependent cysteine proteases in mammals [122] and of those isoforms,

calpain-1, calpain-2 and calpain-9 have received considerable scientific attention for their roles in metastatic traits [123]. An increased expression of calpain-1 was detected in colorectal cancer and correlated with poor overall survival (OS), advanced pathological grade, and metastasis [124]. Calpain-1 deficient SW480 and HT29 cells (an in vitro model of colorectal cancer achieved by siRNA) exhibited significantly reduced of cell invasion and migration processes, which ultimately promoted tumour progression and metastasis compared to controlled cells [124]. Similarly, Yu et al. found that upregulation of calpain-1 protein levels were significantly associated with tumour progression and shorter OS in patients with pancreatic cancer [125]. When calpain-1 expression in pancreatic cancer cells was downregulated by siRNA in AsPC-1 and BxPC-3 cell lines, the invasion and migration abilities of pancreatic cancer cells were significantly attenuated [38]. Previously, calpain-1 overexpression was significantly associated with gallbladder carcinoma compared to cholecystitis, indicating that calpain-1 might act as a key mediator shifting gallbladder cells towards a tumour progression state that would make it a clinical tool for gallbladder carcinoma prognosis [126].

In 2003, Mamone, et al. discovered the emerging roles of calpain-2 at epigenetic levels, using in vitro and in vivo prostate cancer models as potential therapeutic targets to hinder metastatic prostate cancer [127]. These findings are consistent with a recent study conducted by Gao et al. that identified elevated levels of calpain-2 proteins in metastatic prostate cancer compared to primary tumours [128]. They also deciphered the underlying molecular mechanism of epigenetic activation for calpain-2-evoked cancer metastasis via the nuclear factor- κB (NF-κB)/ DNA (cytosine-5)-methyltransferase 1(DNMT1) signalling pathway [128].

In contrast to calpain-1 and calpain-2 isoforms, the downregulation of calpain-9 expression was associated with metastasis in patients with gastric cancer, suggesting the protective effect of calpain-9 expression and its roles in hampering gastric cancer progression [129]. Calpain small subunit 1 (Capn4) acts as a maintainer of calpain function and belongs to the calpain family. A growing body of evidence has demonstrated its promising prognostic biomarker potential and the crucial roles of Capn4 in metastatic phenotypes, from tumour invasion to progression, in various types of cancer that include nasopharyngeal carcinoma, gastric cancer, ovarian carcinoma, breast cancer, glioma and oesophageal squamous cell carcinoma [130–135]. Capn4 exhibited distinct underlying mechanisms depending on the cancer subtype context. The precise mechanisms underlying the actions of Capn4 and its complex interplay between Epstein-Barr virus latent membrane protein 1 (LMP1) and nasopharyngeal carcinoma metastasis, was uncovered via enhanced actin rearrangement-mediated ERK/JNK/AP-1 pathway signalling [130]. In addition, Zhao, et al. found that Capn4 promoted-cell invasion and gastric cancer metastasis involving Wnt/β-catenin/MMP9 signalling [134].

Calmodulin (CaM) is a multifunctional Ca^{2+} binding protein. Its role in metastatic traits was recently reviewed by Villalobo, and Martin, providing valuable insight into the roles of calmodulin in metastasis, from invasiveness to tumour cell migration [136]. It was shown that calcium/calmodulin-dependent protein kinase II (CaMKII) triggered gastric cancer cell metastasis by activating nuclear factor-κB (NF-κB) signalling involving AKT, which ultimately enhanced MMP-9production in BGC-803 cells (an in vitro model of human gastric cancer) [137]; this is a metastatic prompting protein present in various cancer subtypes. Pharmacological modulation of CaM by KN93, a specific inhibitor, in HCT116 cells (an in vitro model of human colon cancer) was found to drastically decrease colon cancer cell invasion and migration via ERK1/2 or p38 signalling [138]. Acetyl-CoA-activates cytosolic CaMKII-mediated metastasis in in vitro and in vivo models of prostate cancer [139].

The lysosome-associated membrane protein (LAMP) family consists of five members expressed mainly in the lysosome [140]. LAMP proteins are involved in various aspects of cancer metastasis biology. They maintain lysosomal homeostasis, where much endolysosomal Ca^{+2} signalling occurs. Although it has become clear that lysosome-associated membrane proteins play significant roles in autophagy [141], which contributes to cancer

metastasis [142], the complex interplay between LAMPs, Ca^{2+} signals, and autophagy-mediated metastasis remains elusive. LAMP1, LAMP2, and LAMP3 are the key LAMP isoforms emerging as important potential players in cancer biology [140]. Upregulation of LAMP1 expression has been reported to predict poor prognosis in various cancer subtypes including large B-cell lymphoma, epithelial ovarian cancer, breast cancer, and laryngeal squamous cell carcinoma [143–146]. The underlying mechanism of the role that ubiquitin-like protein 4A (UBL4A) plays in autophagy-mediated metastasis by suppressing autophagy and disturbing lysosomal functions through targeting LAMP1 in pancreatic ductal adenocarcinoma was unveiled recently [147]. Overexpression of LAMP2 has been associated with worse OS in oesophageal squamous cell carcinoma patients [148]. Upregulation of LAMP3 expression acts as a biomarker for poor prognosis in oesophageal squamous cell carcinoma (ESCC) and ovarian cancer [149,150], whereas downregulation of LAMP3 expression has been associated with poor prognosis in hepatocellular carcinoma [151]. A recent study conducted by Huang et al. provides a possible explanation for LAMP3 overexpression contributing to poor prognosis in ESCC [152]. The authors found that LAMP3-deficient ESCC cells had drastically reduced metastatic traits (invasive and metastatic capability) compared to non-deficient ESCC cells via activation of the cAMP-dependent protein kinase A (PKA)-mediated VASP phosphorylation pathway [152]. In addition, the authors showed that the number of lung metastases were attenuated after LAMP3 knockdown in an in vivo mouse model used for investigating LAMP3-mediated ESCC cell metastasis [152]. These findings imply that the proteins involved in Ca^{2+} signalling or lysosomal function fulfil functions far beyond their roles in maintaining Ca^{2+} or lysosomal homeostasis. Study of the interaction of these proteins in the context of metastasis might form the basis of a fruitful therapeutic approach for metastatic cancer. Further work is required to uncover the communication between LAMPs and Ca^{2+} signalling in lysosomes at a dynamic level.

5. Challenges and Potential Clinical Utilities of Calcium Signalling as a Diagnostic and Therapeutic Target in Metastatic Cancer

Despite significant advances in the current approaches to diagnosing and treating metastatic cancer in clinical settings, some patients still have low successful response rates to therapy or experience delay in the detection of metastatic sites; hence identifying innovative biomarkers and therapeutic targets for metastatic cancer detection or therapy is required. Molecular characterization of Ca^{2+} signalling's role in cell invasion and motility, tumour progression, and metastasis is an evolving field receiving increased scientific attention, raising important questions regarding the possibility of translating these findings into potential clinical tools to optimize metastatic cancer diagnosis and therapy. While navigating clinicaltrials.gov, we found a paucity of clinical studies using changes in Ca^{2+} signalling pathways as a detection approach for metastatic cancer or targeting Ca^{2+} proteins as an adjuvant therapeutic approach for patients with metastatic cancer. Calcium electroporation (CaEP), characterized by introducing supraphysiological calcium concentrations into cells by applying electrical pulses [153], is a promising novel adjuvant therapeutic approach for cancer patients. This strategy is currently under investigation in phase 2 clinical trials (such as NCT01941901, NCT04259658, and NCT03628417), mainly in skin cancers in the metastatic state, in which it is administered intratumourally. A phase 1 clinical trial (NCT01056029) was conducted to investigate mipsagargin, which is a thapsigargin (noncompetitive inhibitor of the sarco-/endoplasmic reticulum Ca^{2+} ATPase) pro-drug, in locally advanced or metastatic solid tumours. Generally, mipsagargin has been shown to have acceptable safety and tolerability profiles, with prolonged disease stabilisation in some patients with solid tumours [154]. Mipsagargin has moved into phase 2, and its investigation has been completed in various cancer subtypes including hepatocellular carcinoma (NCT01777594), glioblastoma (NCT02067156), clear cell renal cell carcinoma (NCT02607553), and prostatic neoplasms (NCT02381236). In a phase 1 clinical trial (NCT01480050), combination therapy of mibefradil dihydrochloride (a T-type calcium channel blocker) and temozolomide (an alkylating agent) in patients with recurrent advanced stages of gliomas was found to be well-tolerated, with encouraging clinical responses in a subset of patients [155], warranting

further investigation in phase 2 trials. Despite Ca^{2+} being a ubiquitous second messenger, defining distinct downstream/upstream regulators of Ca^{2+} signalling pathways could be used to provide potential translation of preclinical evidence into clinical studies, in order to ultimately develop more effective and less toxic chemotherapeutic agents.

6. Conclusions

In summary, a growing body of evidence reveals the substantial effects of Ca^{2+} signalling-mediated cancer metastasis, raising important questions regarding the clinical utility of proteins involved in Ca^{2+} signalling cascades as cancer biomarkers or hallmarks. Several studies have detected dysregulated expression of intracellular or extracellular calcium channels or proteins related to Ca^{2+} signalling-triggered metastasis at the mRNA or protein levels in various cancer subtypes (see Table 1). These are attributed to pathophysiological processes, including cellular adhesion, motility, invasion, the epithelial-mesenchymal transition, and cell progression and migration at a local level, as well as the development of metastasis at a systemic level. Accumulating evidence points to an association between calcium channel proteins or Ca^{2+} signalling-related proteins at the mRNA or protein levels and the prognosis of patients with different types of cancers, suggesting possible clinical applications of Ca^{2+} signalling proteins as prognostic biomarkers. However, large prospective clinical studies with diverse patient populations are required to validate these findings and sufficiently establish the specificity and sensitivity of these biomarkers for cancer at a global level or among different cancers for them to be employed in our daily clinical practice.

Table 1. Some experimental evidence supporting Ca^{+2} signalling-mediated cancer metastasis.

Target				Expression		Type of Cancer	Process Related to Metastasis	Mechanism (If Applicable)	In Vitro (Cell Line)/In Vivo	Ref.
IP3R3	Intracellular calcium signalling in metastasis	Endoplasmic and sarcoplasmic reticulum Ca^{2+} channels/pumps	IP_3 receptors (IP_3Rs)	↑	Increased mRNA and protein levels	Breast cancer	Migration	Ca^{2+} signalling via IP_3R3 mediated cancer cell metastasis	MDA-MB-231 and MDA-MB-435S cells	[24]
				↑	Increased protein levels	Cholangiocarcinoma (CCA)	Migration		Patients with hilar/intrahepatic CCA and CCA cell lines	[25]
				↑	Increased protein levels	Colorectal carcinoma	Aggressiveness		Patients with advanced/metasatic colorectal carcinoma	[27]
				↑	Increased mRNA levels	Glioblastoma	Invasion and migration		Patients with glioblastoma	[28]
RYR2			Ryanodine receptors (RyRs)	↑	Increased mRNA levels	Breast cancer	Epithelial-mesenchymal transition (EMT)	RYR2/Ca^{2+} signals activate EGF-mediated EMT	MDA-MB-468 cells	[20]
TRAM2			Translocons	↑	Increased mRNA levels	Oral squamous cell carcinoma (OSCC)	Cellular invasion, and migration	Overexpression of TRAM2-mediated matrix metalloproteinase activation	OSCC-derived cell lines and primary OSCC tissues	[21]
SERCA2			Sarco-endoplasmic reticulum Ca^{2+} reuptake pump (SERCA)	↑	Increased protein levels	Colorectal Cancer (CRC)	Progression	Calcium signalling via SERCA2 mediation CRC progression	Patients with advanced stages of colorectal cancer	[16]

Table 1. *Cont.*

Target				Expression		Type of Cancer	Process Related to Metastasis	Mechanism (If Applicable)	In Vitro (Cell Line)/In Vivo	Ref.
TPCs		Endolysosomal Ca^{2+} Channels	Two-pore channels (TPCs)	↑	Increased TPC1/TPC2 mRNA levels	Bladder cancer	Cell adhesion and migration	Endolysosomal Ca^{2+} signaling via TPC evoked β 1-integrin recycling	T24 cells	[31]
TPC2				↓	Decreased TPC2 mRNA levels	Melanoma	Cell adhesion and invasion	Reduction in TPC2 expression enhanced metastasis via YAP/TAZ activation	Patients with metastatic skin cutaneous melanoma (SKCM)	[32]
TRPML1			Transient receptor potential cation channels (TRPMLs)	↑	Increased mRNA levels	Non-small-cell lung cancer (NSCLC)	Invasion and migration	Ca^{2+} signals via TRPML1-mediated autophagy promoting tumor progression	Patients with advanced-stage (III–IV) NSCLC	[35]
TRPML2				↑	Increased mRNA and protein levels	Glioma	Cell proliferation and progression	Ca^{2+} signalling via TRPML2 promoting Glioma progression	Patients with advanced-stage (III–IV) glioma	[36]
CaSR	Extracellular components of Ca^{2+} signaling in metastasis	Calcium-sensing receptor (CaSR)		↓	Decreased mRNA level	Colorectal cancer (CRC)	Cell proliferation, differentiation and apoptosis	/	HT29/Caco2-15/colorectal cancer patients	[58]
				↓	Decreased mRNA and protein level	Parathyroid cancer	Cell proliferation	CaSR activation increases ERK phosphorylation	Patients with parathyroid adenomas	[59]
				↑	Increased mRNA and protein level	Breast cancer	Cell proliferation and migration	ERK1/2 MAPK or phospholipase C β (PLC β) pathway	Patients with breast cancer/breast cancer cell lines MDA-MB-231, MCF7, T47D, and BT474	[62,63]
				↑	Increased protein level	Prostate cancer	Cell proliferation and migration	CaSR mediated cell attachmentvia the AKT signaling pathway	Human prostate cancer tissue sections/prostate celllines PC-3, C4-2B and LNCaP	[57,61]
				↑	Increased mRNA and protein level	renal cell carcinoma (RCC)	Cell proliferation and migration	CaSR activated the PI3K (phospatidyl-inositol 3-kinase)/AKT, PLCγ-1, and MAPK pathway	Primary cells derived from RCC patients	[65]
ORAI1		Store-operated calcium entry (SOCE)	ORAI	↑	Increased protein level	Melanoma	Cell proliferation and migration	SOCE increases phosphorylation of ERK and calpain-dependent actin dynamics	Human metastatic melanoma cell lines	[68]
				↑	Increased mRNA and protein levels	Hepatocarcinoma (HCC)	Autophagic cell death	Orai1 blocks autophagy through AKT/mTOR signalling pathway	Tissues from HCC patients and human hepatocarcinoma cell line HepG2	[73]
ORAI 1 & ORAI 2				↑	Increased mRNA and protein levels	Acute myeloid leukemia	Cell proliferation and migration	Promoting phosphorylation of the focal adhesion kinase (FAK)	HL60 cell line	[66]
ORAI 3				↑	Increased mRNA and protein levels	Breast cancer	Cell proliferation and migration	SOCE-dependent NFAT activity and ERK1/2 and FAK kinase phosphorylation	MCF7 and MDA-MB231 cell lines/in vivo	[75]

Table 1. *Cont.*

Target		Expression		Type of Cancer	Process Related to Metastasis	Mechanism (If Applicable)	In Vitro (Cell Line)/In Vivo	Ref.
STIM1	Stromal-interaction molecule (STIM)	↑	Increased protein level	Cervical cancer	Cell growth, migration, and angiogenesis	STIM1 activate calpain and Pyk2, which regulate FAK	Human cervical cancer cell lines SiHa and CaSki/in vivo	[76]
STIM1		↑	Increased mRNA and protein levels	Gastric cancer	Cell migration and invasion	/	Human gastric cancer cells/gastric tumor tissues	[77]
TRPM8	TRP channels	↑	Increased mRNA	Bladder cancer	Cell proliferation and migration	Ca^{2+} signalling via TRPM8 mediated bladder cancer cell metastasis	Human bladder cancer tissue	[101]
TRPV4		↑	Increased protein level	Gastric cancer	Cell proliferation and invasion	TRPV4/Ca^{2+} signalling-mediated EMT	Human gastric cancer tissues	[108]

↑ Increased; ↓ Decreased.

To date, a few clinical trials have investigated the pharmacological modulation of Ca^{2+} signalling as a therapeutic strategy to treat patients with metastatic cancer. Calcium electroporation, mipsagargin and mibefradil in combination with temozolomide showed promising results in the early stages of clinical trials, warranting further investigation. This supports the possibility of translating these therapeutic strategies into the clinic as novel alternative approaches to be given alone or as adjuvants with other chemotherapeutic agents if they pass the development stages and are approved for clinical use by federal agencies, such as the Food and Drug Administration (FDA) or the European Medicines Agency (EMA). Despite the emerging roles of Ca^{2+} signalling in tumour progression and metastasis and its potential as a clinical tool that can enhance the detection rate and guide the treatment of metastatic cancer patients, several questions still remain to be answered, such as those relating to the precise mechanisms underlying Ca^{2+} signalling-mediated cancer metastasis. A key diagnostic or therapeutic challenge is discovering specific downstream or upstream regulators of Ca^{2+} signalling that are involved in metastatic cascades given the ubiquity of Ca^{2+} signals in our cells. Ca^{2+} signalling pathways are involved in diverse aspects of tumour progression and metastasis, and this further research will open up the possibility of using Ca^{2+} proteins as clinical biomarkers and utilising pharmacological modulators to optimise metastatic cancer therapy.

Author Contributions: A.A. contributed to the review-research question and design of the study, the literature review and interpretation, writing the manuscript, and creating the table and figure. Y.Z. wrote the section on extracellular calcium signalling in metastasis and contributed to the part of the table on extracellular calcium signalling. J.P. revised the manuscript. A.A. addressed the reviewers' comments. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: The Saudi Ministry of Education is supporting AA's graduate studies. The figure was created using BioRender. We thank Xuhui Jin for his suggestions after reading the review draft.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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