Advances in the study of cancer metastasis and calcium signaling as potential therapeutic targets

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Abstract

Metastasis is still the primary cause of cancer-related mortality. However, the underlying mechanisms of cancer metastasis are not yet fully understood. Currently, the epithelial-mesenchymal transition, metabolic remodeling, cancer cell intercommunication and the tumor microenvironment including diverse stromal cells, are reported to affect the metastatic process of cancer cells. Calcium ions (Ca2+) are ubiquitous second messengers that manipulate cancer metastasis by affecting signaling pathways. Diverse transporter/pump/channel-mediated Ca2+ currents form Ca2+ oscillations that can be decoded by Ca2+-binding proteins, which are promising prognostic biomarkers and therapeutic targets of cancer metastasis. This paper presents a review of the advances in research on the mechanisms underlying cancer metastasis and the roles of Ca2+-related signals in these events.

Keywords

Calcium channel, cancer metastasis, epithelial-mesenchymal transition, tumor microenvironment, immunosurveillance, metastatic colonization

Introduction

Cancer metastasis is a process in which cancer cells spread from the primary site to secondary sites. Cancer metastasis is affected by chemoattractants [1], the tumor microenvironment (TME) [2], tissue topography [3], the epithelial-mesenchymal transition (EMT), metabolic remodeling [4, 5], communication between cancer cells [6], etc. Despite the significant achievements in the diagnosis of cancer and therapy interventions, cancer-related death remains an urgent problem worldwide, with cancer metastasis being the major challenge [7-9]. Firstly, metastatic cancer cells can seed new foci and grow into new tumors in target organs, even after
exclusion of the primary tumor due to early dissemination and seeded metastasis [10]. Secondly, metastatic cancer cells exhibit enhanced survival ability and resistance to most chemo- and radio-therapy that are highly efficient in certain primary nonmetastatic cancer cells [11, 12].

Ubiquitous calcium ions (Ca\(^{2+}\)) are major second messengers and are critical to diverse physiological cellular events. Remodeling Ca\(^{2+}\) signals have been demonstrated to be essential in numerous diseases, including cancer [13-15]. In addition to chemoresistance, Ca\(^{2+}\) is also of importance in cancer metastasis, as proven decades ago [16, 17]. For example, Ca\(^{2+}\) is essential for focal adhesion turnover by regulating tyrosine kinase focal adhesion kinase (FAK) [13]. Focal adhesion turnover is critical in cycles of adhesion and detachment. It forms the traction points through which a cell moves forward and retracts the rear [18]. The intracellular distribution of Ca\(^{2+}\) is delicately balanced by several channel/pump/transporter families, including dozens of proteins located on the plasma membrane, endoplasmic reticulum (ER), mitochondria, and lysosomes. The signals of regional Ca\(^{2+}\) oscillations are decoded by numerous Ca\(^{2+}\)-binding proteins with different distributions and affinities for Ca\(^{2+}\), further inducing a signaling cascade to regulate cell activity [17]. With the incessant discoveries of metastatic mechanisms, Ca\(^{2+}\)-binding proteins, and Ca\(^{2+}\) channels/pumps/transporters, the roles of Ca\(^{2+}\) signaling in cancer metastasis have been increasingly revealed, serving as promising biomarkers for the prognosis and therapeutic targets of cancer metastasis.

**Basic process of tumor metastasis**

Solid tumor metastasis is a complicated multistep and inefficient process. It includes separation and migration from primary tumors, invasion of local tissues, extravasation into blood or lymphatic vessels for transmission, extravasation into distant tissues and growth into macroscopic tumors [9]. Both cell-autonomous and noncell-autonomous mechanisms are crucial for successful cancer metastasis [19]. The plasticity of cancer cells, including their morphology and metabolism, is one major reason for successful cancer metastasis. For example, cells usually require the formation of lamellipodia at their leading edge, cycles of focal adhesion turnover, cell body contraction, and tail retraction [20-22]. Furthermore, intervention stresses, including radio- [23] and chemo-therapy [11], can also cause cancer metastasis.

The “amoeboid” form of invasion means that individual cancer cells with morphological plasticity can pass through existing interstices in the extracellular matrix (ECM). This movement differs from that of collective and mesenchymal invasion, both of which are dependent on the ability of the cancer cells to clear a path [24, 25]. Collective metastasis involves clusters of cancer cells invading adjacent tissues and spreading to distal organs [26]. Some studies demonstrate that multicellular tumor cell clusters, not single cell, present tumor invasive fronts, systemic circulation, and colonization of distant organs. Within these clusters, cancer cells may communicate and exchange signaling factors to promote metastasis [6, 27]. Mesenchymal invasion through the EMT program is the best characterized form of metastasis. In this process, cancer cells remodel the pattern of cytoskeletal proteins and adhesion molecules, and they further acquire stem features. E-cadherin, a classical and critical adhesion molecule, is lost in EMT. This loss favors cancer cells escape from endothelial cell (EC) sheets and promotes metastasis [20].

Tumor cells penetrating tissues through confining spaces must undergo extensive deformation, including its nucleus. However, this deformation can cause localized loss of nuclear envelope (NE) integrity and DNA damage, which may be a weakness of metastatic cancer cells [28]. Cancer cells exhibit increased chromatin accessibility during metastatic progression, which enhances prometastatic gene expression and promotes the metastatic ability of cancer cells [29]. Synonymous mutations may specifically regulate the expression of proteins that favor metastasis. Upregulation of tRNA\(^{Glu}\)UUC and tRNA\(^{Leu}\)CCG promotes breast cancer metastasis, with tRNA\(^{Glu}\)UUC promoting metastatic progression by directly enhancing exosome component exosome component 2 (EXOSC2) and glutamate receptor interacting protein 1 (GRIP1) associated protein 1 (GRIPAP1) protein expression [30]. The expression of genes coding ribosomal proteins (RPs) and regulators of translation is also increased in breast circulating tumor cells (CTCs). RPL15 (eL15), a component of the large ribosomal subunit, increases the translation rate of other RPs and cell cycle regulators, leading to breast cancer cells metastatic growth in multiple organs [31].
Mechanisms of cancer cells metastasis
Separation and migration from primary tumors

Dissemination and metastasis may occur at an early tumor stage or even precede primary tumor formation [10, 32, 33]. One force that drives cells disseminating from tumors is the repulsive effect, which is also called contact inhibition of locomotion (CIL). CIL suppresses forward locomotion during cell-cell contact and redirects cell motility, which can enhance cancer invasiveness by favoring redirection of cancer cells into the stromal environment [34].

In primary tumor sites, cancer cells recruit myeloid-derived suppressor cells (MDSCs) to induce the acquisition of the EMT/stemness phenotype in cancer cells at the invasive cancer edge [35]. Ephrin type-A receptor 2 (EphA2) promotes membrane-anchored membrane type-1 matrix metalloproteinase (MT1-MMP) expression in invasive breast cancer cells. MT1-MMP in turn cleaves EphA2 and activates the EphA2/Src/RhoA axis, which induces actomyosin contractility and cell junction disassembly. These changes ultimately induce cell transition to rounded morphology, cell-cell repulsion, dissemination, and single-cell invasion [36].

Crosstalk between cancer cells and circulatory systems

For seeding and growth at the secondary sites, cancer cells usually infiltrate into circulatory systems such as lymphatic and/or vascular vessels. CTCs are essential for distant metastasis of cancer, but only a small subset of CTCs can generate metastatic tumors [37-39]. This is because circulatory systems and distant organs are usually not hospitable to cancer cells, due to oxidative stress, anoikis, and the immunosurveillance system [40-42]. Melanoma cells with high metastatic ability preferentially upregulate monocarboxylate transporter 1 (MCT1) to consume more lactate, and cells with high MCT1 expression are more prominent in blood than in primary tumors. Selective inhibition of MCT1 does not affect the migration or invasion of melanoma cells or primary tumor growth, but it significantly reduces the frequency of circulating melanoma cells in the blood and cancer metastasis. This outcome is the result of MCT1 promoting cell survival during metastasis, partly by decreasing oxidative stress [37, 43]. Internalized β1-integrin localizes to autophagy-related endomembranes and triggers c-Met-sustained prosurvival in an adhesion-independent manner, preventing detached cancer cells from undergoing anoikis. This mechanism gives cancer cells sufficient time to land successfully [44].

Crosstalk between cancer cells and the lymphatic system

Lymphatic and vascular systems are the major access for cancer cells destined for distal metastasis by increased permeability [45], lymphoid hyperplasia [46], or angiogenesis [47]. Interestingly, cancer cells preferentially metastasize regionally through the lymphatic system before metastasizing to distant organs via blood. This outcome is partially the result of lymph fluid containing a high level of oleic acid, which protects cancer cells from ferroptosis in an acyl-coenzyme A synthetase long-chain family member 3 (ACSL3)-dependent manner [42]. Vascular endothelial growth factor-D (VEGF-D) produced by cancer cells inhibits prostaglandin degradation and results in the dilution of collecting lymphatic vessels, which ultimately promotes cancer metastasis [48]. Melanoma cells secrete midkine to induce distal premetastatic niches by driving lymphangiogenesis in a paracrine-dependent manner [46]. Cancer cells also produce interleukin-6 (IL-6) to activate signal transducer and activator of transcription 3 (STAT3) to induce hypoxia-inducible factor-1 alpha (HIF-1α), VEGF, and C-C motif ligand (CCL) 5 expression in lymphatic ECs (LECs) within premetastatic niches to promote metastasis [49]. IL-10 derived from tumor-associated macrophages (TAMs) increases the expression of specificity protein 1 (Sp1) in LECs in a hypoxic TME. This Sp1 expression in turn induces the production of CCL1 in activated LECs to recruit TAMs and cancer cells, resulting in lymphatic vessels encapsulated by TAMs (LVEM) to promote cancer metastasis [50].

Crosstalk between cancer cells and the vascular system

Patrolling monocytes in blood possess early interactions with metastatic cancer cells. They can scavenge cancer cells from the vasculature and promote natural killer (NK) cell recruitment and activation [41]. Platelet-secreted transforming growth factor β (TGFβ) is necessary but not sufficient for the extravasation and subsequent metastatic niche formation of CTCs. Furthermore, platelets directly interacting with CTCs
activate nuclear factor-kappa B (NF-κB) signals and induce the EMT in cancer cells, which in cooperation with TGFβ signaling facilitates metastasis [51, 52].

Cancer cells can recruit ECs and initiate angiogenesis to promote metastasis [47]. Chemotherapy can also enhance angiogenesis to promote metastasis [53]. In addition to recruiting myeloid cells, tumor cell-derived CCL2 activates C-C motif receptor (CCR) 2 on ECs, inducing vascular permeability and subsequent cancer cell extravasation [45]. In brain cancer metastasis, melanoma cells increase blood-brain barrier (BBB) permeability [54]. Amyloid precursor proteins from cancer cells induce endothelial necroptosis via death receptor 6 (DR6) on ECs to enhance extravasation [55]. The intracellular domain of Notch1 receptors (N1ICDs) are activated in ECs in both primary tumors and premetastatic niches. N1ICDs ultimately induce EC senescence, neutrophil infiltration, tumor cells adhesion to the endothelium, intravasation, and metastasis [56].

Some cancer cells preferentially attach to the vascular network and migrate through endothelial layers by adopting a spindle-shaped morphology. They invaginate into the endothelial network by forming nanoscale membrane bridges between metastatic cancer cells and ECs to transfer signaling factors. This signaling leads to a cancer cell-induced pathological endothelium and metastatic foci in vivo [57].

Metastatic cancer cells that intravasate into the vasculature secrete Serpin Family E Member 2 (SERPINE2) and secretory leukocyte protease inhibitor (SLPI) to promote metastasis. These factors are required to program cancer cells for vascular mimicry, a program in which cells differentiate into endothelial-like cells and form extracellular-matrix-rich tubular structures to carry blood from the vasculature to hypoxic regions of the tumor [58]. A novel theory explaining cancer spread is called angiotropic migration, which is derived from a program initially involved in embryogenesis. In cancer metastasis, cancer cells attach to the abluminal surfaces of blood vessels and spread via continuous migration, competing with pericytes and replacing them, i.e. pericyte mimicry. This manner of spreading has been demonstrated in several types of cancer, including melanoma, glioma, colon, and breast cancer [59].

Metastatic colonization

Metastatic cancer cells at secondary sites may die, be cleared, grow into macrometastases, or remain dormant only to grow into micrometastases decades after seeding [9, 32]. The reasons for the dormancy of cancer cells may be attributed to unfit proliferation conditions, such as nutrient starvation or inhibition by the immune system, or they may acquire suppressive factors from the primary tumor, or lack the ability to activate angiogenesis [60]. For example, breast cancer cells can directly engulf mesenchymal stem cells to enhance their prosurvival ability, but they then turn dormant [61].

Bone marrow-derived myeloid cells can become central nervous system (CNS) myeloid-like cells once they translocate to the brain. CNS-native myeloid cells display downregulation of CX3CR1, which enhances C-X-C motif (CXC) chemokine ligand (CXCL)10 signaling to foster an immunosuppressive niche and promote brain metastasis of cancer cells [62]. In addition, astrogliosis and neuroinflammation are instigated in the early stage of metastasis to promote the initial growth of metastatic melanoma cells in the brain [54].

Hospitable destinations: the liver and lung

Thrombopoietin-mediated activation of lysine degradation reduces oxidative stress via the Lys-Glu pathway and induces c-myc to recruit chromatin modifiers to regulate gene expression in cancer cells. This process enhances the production of acetyl-CoA and is essential for thrombopoietin-binding receptor-positive colorectal cancer cells spread in liver metastasis. The liver is the major organ producing thrombopoietin, which is a niche component that is critical for cancer cell colonization. Thrombopoietin production is probably why the liver is a preferred target organ of metastatic cancer cells [63].

The lung with high oxygen is also a favored target of metastatic cancer cells. Prolyl hydroxylase (PHD), an oxygen sensor, is intrinsically and functionally redundant in lung T lymphocytes. PHD inhibits HIF accumulation to suppress glycolytic metabolism. This suppression leads to a pulmonary T helper (Th)-1 cell response, promotes CD4+ T cell effector function, and restrains CD8+ T cell activation, ultimately resulting in an immunosuppressive microenvironment that gives license to tumor colonization at the lung [64].
Adaptation to the target organ microenvironment

Efficiently taking advantage of the homing organ microenvironment is especially important for successful metastasis of cancer cells. In addition to sensing the level of Rac activity in adjacent cells to organize individual cells in cell clusters, Rab11b is necessary for metastatic breast cancer cells to adapt to the brain microenvironment, since Rab11b manipulates the expression of critical proteins at the cancer cell surface. For example, Rab11b regulates the recycling of integrin β1, which allows cancer cells to engage with the brain ECM efficiently to activate mechanotransduction signaling [65, 66]. To adapt to hepatic hypoxia, metastatic colon cancer cells (CRCs) import extracellular phosphocreatine, which is mediated by the creatine transporter SLC6A8, to generate intracellular ATP [67]. Ovarian cancer cells that metastasize to the omentum utilize fatty acids produced by adipocytes to meet their energetic requirement via upregulating fatty acid-binding protein (FABP) 4 [4].

Brain astrocytes secrete exosomes containing miRNAs that inhibit phosphatase and tensin homolog (PTEN) expression in metastatic cancer cells. This process is reversible since cancer cells restore PTEN expression after they leave the brain. Loss of PTEN in cancer cells leads to the upregulated secretion of the chemokine CCL2, which recruits ionized calcium binding adaptor molecule 1 (IBA1)-expressing myeloid cells. This process ultimately promotes the outgrowth of brain metastatic tumor cells via enhanced proliferation and attenuated apoptosis [68].

Preparation and inducing transformation of the soil

Most cancer cells are poorly adapted to the microenvironment of the premetastatic tissue where they land, at least initially. The transcriptional and proteomic diversity between micrometastatic and primary tumor cells is universal. Cancer cells that have undergone the EMT may undergo the mesenchymal-epithelial transition (MET) to restore efficient proliferation ability, which can be induced by granulocytic MDSCs (gMDSCs) that are recruited by cancer cells at metastatic sites [35, 69, 70]. Cancer cells can inhibit Th-1 polarization or decrease CD4+ T cell levels in the metastatic TME to favor cancer cells survival [7, 71].

Cancer cells may remodel the ECM to form a premetastatic niche by secreting extracellular vesicles (EVs) in advance to escape dormancy at metastatic sites [72-74]. Tumor cells can prepare the premetastatic niche by secreting exosomes, which can be taken up by specific resident cells at their predicted destination. For example, the secretome of hypoxic primary cancer contains lysyl oxidase, which facilitates osteolytic lesion formation to promote CTCs colonization and metastasis formation in bone [75]. Exosomes from lung-, liver- and brain-tropic tumor cells fuse preferentially with lung fibroblasts and epithelial cells, liver Kupffer cells, and brain ECs, respectively. These exosomes determine the target organ of cancer cells; for example, exosomes from lung-tropic model cells redirected the metastasis of bone-tropic tumor cells because they transport specific integrins to the distal organ, where they activate Src and upregulate the expression of promigratory and proinflammatory S100 molecules. In addition, α6β4 and α6β1 are associated with lung metastasis, while αvβ5 is linked to liver metastasis [76].

Once CTCs arrive at the target organ, they lodge in capillaries and shed microscale blebs with diameters of ~ 5 μm into the vasculature. Most of these microparticles preferentially attach to the vasculature or independently migrate along the inner walls of vessels instead of dispersing in the blood flow. These microparticles are ingested by they recruit waves of distinct myeloid cell subsets. The cells in the early waves facilitate the survival of CTCs, while a small population of resident conventional dendritic cells in the last waves interact with CTCs and exert antimetastatic effects [77].

Phosphorylation of adenosine monophosphate (AMP)-activated protein kinase (AMPK)α is upregulated in metastatic tumors. Deletion of AMPKα impairs lung metastasis without affecting primary tumor growth. This effect is due to the ability of AMPK to phosphorylate the catalytic α subunit of PDHc (PDHA) to drive the tricarboxylic acid (TCA) cycle, which renders cancer cells resistant to metabolic and oxidative stress [78]. Fructose can promote metastasis of colon and breast cancers [79, 80]. CRCs that metastasize to the liver display upregulation of aldolase B (ALDOB). ALDOB promotes fructose metabolism, which is essential for the growth of CRCs in the liver. More importantly, CRC cells that are directly injected into the liver also display
an increase in ALDOB. This finding directly demonstrates that reprogramming metabolism occurs both at the premetastatic stage and when cancer cells land on new organs [79].

**Crosstalk between cancer cells and the TME**

Communications between cancer cells and the TME are pivotal in cancer metastasis. The TME, including the ECM, bacteria, fibroblasts, mesenchymal stem cells, and macrophages, is essential for the phenotype of tumor [12, 81, 82]. Several types of cells derived from bone marrow, including macrophages, neutrophils, mast cells, and myeloid progenitors, are involved in pathological angiogenesis. In addition to reducing the effect of drugs targeting vasculature EC signals, they can facilitate local invasion [9, 83]. Cancer cells recruit gMDSCs and monocytic MDSCs (mMDSCs) for infiltration. The mMDSCs promote cancer cells dissemination by inducing EMT/stemness, while gMDSCs promote metastatic growth by reverting EMT/stemness [35]. Bacteria were firstly detected in human tumors more than 100 years ago. Intracellular bacteria are present in both cancer and immune cells [84]. Exosomes from those bacteria deliver factors such as IL-8 to noninfected cancer cells to increase the metastasis rate [1].

**Cancer-associated fibroblasts**

Cancer-associated fibroblasts (CAFs) can produce exosomes that transfer bioactive factors such as miRNA to induce the EMT and stemness of cancer cells [12]. Cancer cells undergoing the EMT preferentially localize to the leading edge of primary tumors, resulting in their positioning adjacent to the stroma, which includes CAFs [85]. EphA-mediated CIL promotes the formation of disseminated tumor cells (DTCs) [36, 86]. Furthermore, EphB2-induced EphB3/EphB4/Cdc42 signaling tightens the interaction between DTCs and CAFs, allowing for invasiveness and metastasis [86]. CAFs generate tracks to facilitate collective invasion by remodeling protease- and force-mediated matrix [2]. CAFs produce ligands that correspond to receptors expressed by cancer cells to promote metastasis [85]. For example, TGFβ derived from cancer cells enhances the secretion of IL-11 in CAFs. IL-11 in turn activates GP130/STAT3 in cancer cells to initiate metastasis [85]. CAFs can act as damage-associated molecular pattern (DAMP) sensors. Activation of nucleotide-binding domain and leucine-rich repeat containing (NLR) family pyrin domain containing 3 (NLRP3) signaling in CAFs increases the production of IL-1β. IL-1β facilitates breast cancer cells metastasis in the lung by modulating the immune cell milieu at the metastatic site and the expression of adhesion molecules [87].

**TAMs**

TAMs secrete TGFβ1, EGF and matrix-degrading enzymes, including Ca²⁺-dependent MMPs [88, 89]. Metastatic double-negative prostate cancer (DNPC) cells express high level of CCL2 to recruit M2-like TAMs and Tregs, which enhances metastasis initiation in conjunction with immunosuppression and neoangiogenesis [39]. In addition to promoting angiogenesis, angiotensin (Ang) II-activated ECs also produce CCL2. This production recruits additional CCR2⁺ macrophages to infiltrate tumors, which ultimately promotes metastasis [90]. TAMs are negatively correlated with the survival of hepatocellular carcinoma (HCC) patients, since these TAMs secrete TGFβ1 to induce the EMT and confer higher invasiveness in cancer cells [91]. Interestingly, cancer cells can produce a series of factors, including IL-4, colony stimulating factor-1 (CSF-1) and platelet-derived growth factor-BB (PDGF-BB), directly or indirectly in a pericyte- and fibroblast-derived IL-33-dependent manner to recruit TAMs, and thus promote metastasis [9, 92].

**Mesenchymal stem cells**

Mesenchymal stem cells (MSCs) are usually involved in maintaining tissue architecture and mediating pathological stromal responses during injury repair. Interestingly, cancer cells produce soluble factors that recruit MSCs from the bone marrow to the primary tumor site. Intratumor MSCs secrete CCL5 to stimulate the invasive behavior of cancer cells [93, 94]. Moreover, CXCL16 produced by cancer cells binds to CXC receptor (CXCR) 6 on MSCs, leading to the transition of MSCs to CAFs and the production of CXCL12. CXCL12 further binds to CXCR4 on cancer cells, inducing EMT and promoting metastasis [95]. In addition to TAMs, a small population of breast cancer cells can engulf MSCs to promote self-renewal, mesenchyme-like and metastatic properties [94, 96].
Communications between cancer cells

Communications between cancer cells depend on direct interactions or EVs, including exosomes, to transfer biomolecules such as proteins and nucleic acids [97]. Cancer cells undergoing EMT can produce the EMT-inducing transcription factor Six1 to promote the metastasis of non-EMT cancer cells [98]. Collective metastasis is also dependent on the EMT. Clusters of cancer cells internalize N-cadherin, which induces the acquisition of only a partial mesenchymal phenotype characterized by an increase in tissue fluidity that is similar to a solid-like-to-fluid-like transitional state. This transitional state allows cells to migrate under physical constraints without abolishing the cell cooperation required for collectiveness [99]. This enhanced cell metastatic potential is associated with poorer prognosis in cancer patients [6, 27]. These tumor cell clusters preferentially display high level of the epithelial cytoskeletal protein keratin 14 (K14), desmosome and hemidesmosome adhesion complex genes but are depleted of major histocompatibility complex (MHC) class II genes [100].

Cancer cells within multicellular clusters can form nano alumina to construct their own internal microenvironment, from which they exchange and concentrate growth factors such as epigen to drive metastatic outgrowth [6]. Although E-cadherin has been widely demonstrated to inhibit cancer metastasis, E-cadherin is intriguingly required for the metastasis of invasive ductal carcinoma (IDC). This requirement is based on that E-cadherin enable cancer cells to form collective metastasis by reducing reactive oxygen species (ROS) and preventing cancer cells from apoptosis, which is especially critical during systemic dissemination and early seeding [39]. Clusters, usually containing as many as 20 cells, that are too large to pass through narrow vessels can reversibly reorganize into single-file chain-like geometries that reduce their hydrodynamic resistances, allowing them to successfully traverse 5–10 μm constrictions, even in whole blood [101]. Correspondingly, PEP06 polypeptide 30, a cluster-dissociating agent, inhibits cancer metastasis by manipulating the EMT, the αv integrin/FAK/Src axis, and E-cadherin-based intercellular junctions [102, 103].

Reprogramming metabolism

Antioxidants N-acetylcysteine and vitamin E reduce ROS, free heme level, and stabilize the transcription factor BACH1, resulting in glycolysis-dependent metastasis of lung cancer cells [104]. This finding suggests that oxidative stress may have an inhibitory effect on metastasis at the initial stage. Metastatic melanoma cells but not primary melanoma cells are capable of engulfing and digesting live autologous melanoma-specific CD8+ T cells to increase their survival, particularly under nutrient-stress conditions [105].

Some cancer stem cells (CSCs) do not display high levels of mesenchymal genes but express the high level of the fatty acid receptor CD36. These CSCs are critical for metastasis initiation and rely particularly on dietary lipids to promote metastasis [106]. Although the primary and lymph node metastases of melanoma cells display a similar level of cholesterol, metastatic cells in lymph nodes can probably produce or recruit more bile acids to activate vitamin D receptor/YAP, which promote metastatic cells adaptation to their new microenvironment [107].

Aerobic glycolysis (the Warburg effect) has been widely used as a marker of cancer [9, 108]. FABP7 is increased in patients with breast cancer metastases in the brain. It inhibits fatty acid oxidative phosphorylation (OXPHOS) and enhances the formation of lipid droplets, which facilitates HER2+ breast cancer metastasis to the brain [109]. Moreover, DTCs may reprogram their metabolism to survive and colonize at metastatic sites. Micrometastatic triple-negative breast cancer (TNBC) cells in the lungs and lymph nodes upregulate mitochondrial OXPHOS, the pharmacological inhibition of which profoundly reduces lung metastasis [38]. CTCs display high expression of peroxisome proliferator-activated receptor-gamma 1α (PGC-1α), which is regulated by Ca2+ and is necessary for intravasation of cancer cells into the circulatory systems. PGC-1α enhances mitochondrial biogenesis and respiration coupled with the remodeling of actin cytoskeleton signals. Silencing of PGC-1α ultimately decreases the aggressive properties of cancer cells, such as metastatic lung colonization and nodule formation [38, 110].
Escape from immunosurveillance

Leukocyte immunoglobulin-like receptor B4 (LILRB4) is exclusively expressed on monocytic cells. It inhibits T cell proliferation and T cell-mediated antitumor immunity meanwhile promoting acute myeloid leukemia (AML) cell migration and tumor infiltration [111]. Metastatic castration-resistant prostate cancer (mCRPC) cells induce an increase in the population of osteoclasts in bone marrow. Osteoclasts produce TGFβ, which inhibits Th-1 polarization in the metastatic TME and is the cause of the poor response of metastatic cancer to immune checkpoint therapy [71]. Cancer cells that have metastasized to the liver can recruit macrophages and siphon-activated antigen-specific T cells. These macrophages display high expression of FasL, which diminishes CD4+ T cells through their direct contact, which induces FasL/Fas-dependent apoptosis, resulting in systemic immunosuppression [7]. PHD restrains CDB+ T cell effector function, also leading to an immunosuppressive microenvironment that favors cancer cell colonization at the lung [64].

Roles of calcium signaling in cancer metastasis

Ca2+, a ubiquitous second messenger, is critical to cancer development, including metastasis and therapy resistance [17]. Ca2+ has been widely demonstrated to manipulate events critical to metastasis, including the EMT [112], invadosome formation, ECM degradation [113] and angiogenesis [114]. Serum Ca2+ level is positively associated with the risk of node metastasis in endometrial and breast cancer [115, 116], but low serum calcium level indicates poor distant metastasis-free survival of patients with nasopharyngeal carcinoma [117].

Cancer cells contacting with ECs induces oscillatory intracellular and intercellular Ca2+ waves in ECs that generated from the contact site. It coupled with ECs retraction that may be responsible for cancer metastasis [118]. Direct current electric field (dcEF)-mediated epidermal growth factor receptor (EGFR) polarization and Ca2+ influx promote cancer cell electrotaxis [119]. β2-adrenoceptor initiates a cAMP-Ca2+ feedforward loop that enhances the invasion of breast cancer cells [120]. Metformin inhibits fibrosarcoma invasion and migration by reducing MMP9 activity in a Ca2+-dependent manner [121]. Several Ca2+ channel blockers have been demonstrated to inhibit cancer cell metastasis in diverse ways. Nifedipine and diltiazem reduce cancer cells adhesion to ECs and the metastasis rate by remodeling the tumor cell cytoskeleton, affecting cell mobility and inhibiting tumor cell-induced platelet aggregation [122].

Ca2+-dependent proteins

Numerous Ca2+-dependent proteins containing Ca2+-binding sites, such as calmodulin (CaM) [123, 124], Ca2+/CaM-dependent kinase (CaMK) [125], calreticulin [126], Ca2+ sensor [127], Ca2+-sensing receptor (CaSR) [128], calpain [129], calcineurin [130], myosin light-chain kinase (MLCK) [131] and phospholipase S100 family proteins [132], have been widely known to be vital to cancer metastasis. CaM, with four EF-hands, is one of the most important Ca2+ signal-decoding proteins. It can rapidly redistribute to subcellular compartments in response to various signals. Migration signals trigger a spatiotemporal redistribution of CaM to the leading edge of the migrating cell; for example, EGF induced CaM redistribution from the nucleus to the cytoplasm to activate invadopodia-associated proteins [123, 133]. Calreticulin can inhibit ER stress to inhibit EMT, which promotes cancer cells liver metastasis [126]. CaSR located on the plasma membrane senses extracellular Ca2+. CaSR induces activation of AKT/β-catenin, leading to cancer metastasis [128, 134]. Calpain cleaves talin, resulting in more rapid adhesion disassembly rates [129]. Neuronal Ca2+ sensor 1 (NCS1) promotes the motility of cancer cells by localizing to the cell leading edge [135].

S100A4 reduces the expression of E-cadherin and β-catenin in cancer cells, while S100A4+ stromal cells enhance the stem cell-like phenotype of tumor cells [136, 137]. S100A9 can be secreted by TAMs, which is increased in HCC-related TAMs and HCC cells. It enhances the stem cell-like and metastatic properties of HCC cells by activating NF-κB and recruiting more macrophages to infiltrate tumors [138, 139]. Ca2+-activated potassium channels promote the proliferation and migration of endometrial and breast cancer cells, while they also mediate blood-brain tumor barrier opening to promote brain metastasis [140-142].
Limited by the scope of this brief review to cover all Ca\textsuperscript{2+}-dependent proteins and protein-mediated Ca\textsuperscript{2+} currents, we mainly focus on the proteins critical for Ca\textsuperscript{2+} currents that have also been reported to be involved in cancer metastasis (Table 1).

Table 1. Representative studies about Ca\textsuperscript{2+} channels/pumps/uniporters in cancer metastasis

| Channels/Pumps/Uniporters | Alteration | Events/Mechanisms | Cancer type | Reference |
|---------------------------|------------|-------------------|-------------|-----------|
| VGCC                      | Cav1.2 ↑   | -                 | CRC         | [143]     |
|                           | Cav1.3 ↑   | -                 | Breast cancer, endometrial carcinoma | [144, 145] |
|                           | Cav2.2 ↑   | EMT               | Breast cancer | [146]     |
|                           | Cav3.1/3.2 - | -                 | Glioblastoma, RAF\textsuperscript{V600E} melanoma | [147, 148] |
| CRAC                      | -          | -                 | Ovarian cancer | [149]     |
| Orai1                     | ↑          | Focal adhesion turnover, invadopodium formation, EMT and extracellular matrix degradation | Glioma, melanoma and breast cancer | [13, 150-153] |
| Orai2                     | ↑          | Focal adhesion disassembly | GC | [154]     |
| Orai3                     | -          | Neuroendocrine-to-mesenchymal transition | Gastro-enteropancreatic neuroendocrine tumor | [151]     |
| STIM1                     | ↑          | Focal adhesion turnover and invadopodium formation | Melanoma, gastric and breast cancer | [13, 153, 155] |
| STIM2                     | ↑          | EMT               | Breast cancer | [8]       |
| MS4A12                    | ↑          | -                 | Colon cancer | [156]     |
| TRPV channel              | TRPC1 ↑    | EMT               | Breast cancer | [157]     |
|                           | TRPC3 ↑    | -                 | Melanoma     | [158]     |
|                           | TRPC4 -    | -                 | Medulloblastoma | [159]     |
|                           | TRPC5 ↑    | EMT               | Colon cancer | [160]     |
|                           | TRPC6 ↑    | EMT               | Breast and gastric cancer | [161-163] |
|                           | TRPM2 -    | EMT               | Gastric cancer | [164]     |
|                           | TRPM3 ↑    | EMT               | Renal cell carcinoma | [165]     |
|                           | TRMP4 ↑    | EMT               | Prostate cancer | [166, 167] |
|                           | TRMP5 -    | MMP9              | Melanoma     | [168]     |
|                           | TRPM7 ↑    | EMT               | Nasopharyngeal carcinoma, ovarian and breast cancer | [169-171] |
|                           | TRPM8 ↑    | EMT               | Colon cancer | [172]     |
|                           | TRPML1 -   | Lysosomal exocytosis | Hepatocellular carcinoma | [173]     |
|                           | TRPP2 ↑    | EMT               | Laryngeal squamous cell carcinoma | [174]     |
|                           | TRPV1 ↓    | Peritoneal dissemination | GC | [175]     |
|                           | TRPV2 ↑    | -                 | Prostate and esophageal cancer | [176]     |
|                           | TRPV4 ↑    | Matrix stiffness and EMT | Endometrial and breast cancer | [177, 178] |
|                           | ↓          | Tumor vessel integrity | Prostate cancer | [179]     |
|                           | TRPV5 ↓    | -                 | Renal cell carcinoma | [180]     |
|                           | TRPV6 ↑    | -                 | Prostate cancer | [181]     |
VGCCs comprise five subtypes and ten members. Endostatin, a commercial agent targeting angiogenesis, reduces glioblastoma cells migration by directly inhibiting T-type VGCCs [147]. Cav1.3 expression is increased in breast cancer, atypical hyperplasia, and endometrial carcinoma tissues. It partially mediates estrogen-induced Ca$^{2+}$ influx and endometrial carcinoma cells migration [144, 145]. Ca$^{2+}$ is increased at filopodia tips and correlated with filopodia stabilization. Filopodia stabilization leads to focal adhesion formation, which is critical to the migration of cells. L-type Ca$^{2+}$ channel blockers, such as amlodipine, besylate, felodipine, manidipine, and cilnidipine, potently inhibit L-type Ca$^{2+}$ channel/calpain-1-mediated filopodia formation, which efficiently reduces the cancer cells migration and invasion rates [145]. The Cav1.2 level is increased in CRCs. Nifedipine, another L-type Ca$^{2+}$ channel blocker, inhibits CRC migration and PD-1 via Cav1.2/Ca$^{2+}$-mediated activation of nuclear factor of activated T cell 2 (NFAT2). The combination of nifedipine with an anti-PD-1 antibody significantly reduces cancer cell liver metastasis and the PD-1$^+$ CD8$^+$ T cells level among tumor-infiltrating lymphocytes [143].

### Ca$^{2+}$ release-activated Ca$^{2+}$ channels

Orai proteins located on the cell membrane are the core components of Ca$^{2+}$ release-activated Ca$^{2+}$ channels (CRACs) that mediate SOCE. Upon ER Ca$^{2+}$ depletion, STIM activates Orai to mediate Ca$^{2+}$ influx. CRACs play critical roles not only in immune cells but also in cancer cells [13, 14, 201]. Chemoresistant ovarian cancer cells acquire enhanced migratory ability by increasing SOCE-mediated focal adhesion turnover [11]. ACE2 promotes metastasis of breast cancer by activating the PAK1/NF-κB/Snail1 axis via SOCE [202]. MFAP5

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**Table 1. Representative studies about Ca$^{2+}$ channels/pumps/uniorpers in cancer metastasis (continued)**

| Channels/Pumps/Uniporters | Alteration | Events/Mechanisms | Cancer type | Reference |
|---------------------------|------------|--------------------|-------------|-----------|
| ATP dependent pumps       |            |                    |             |           |
| PMCA4                     | ↓          | EMT                | GC          | [182]     |
| SERCA                     | -          | Focal adhesions    | Glioblastoma| [183]     |
| SERCA2                    | ↑          | -                  | Colorectal cancer| [184] |
| SERCA3                    | ↓          | -                  | Colorectal adenoma-adenocarcinoma| [185] |
| P2X7                      | ↑          | EMT and formation of filopodia | Melanoma and colon cancer| [186-188] |
| P2Y                      | -          | -                  | Colon cancer| [187]   |
| P2Y2                      | -          | EMT                | Prostate cancer| [189, 190] |
| P2Y6                      | -          | Filopodia and focal adhesions | Lung cancer| [191] |
| P2Y12                     | -          | Positive regulation of Akt in platelets | -| [192] |
| MCU complex               |            |                    |             |           |
| EMRE                      | ↓          | -                  | TNBC        | [193]     |
| MCU                       | ↑          | ROS, MVD, tube formation and sprouting capacity | Hepatocellular carcinoma and TNBC| [194-196] |
| MCUb                      | ↓          | ROS                | TNBC        | [196]     |
| MICU1                     | ↑          | ROS                | TNBC        | [193]     |
| MICU2                     | ↓          | ROS                | Hepatocellular carcinoma| [194] |
| MCUR1                     | ↑          | EMT                | HCC         | [197]     |
| TPCs                      |            |                    |             |           |
| Tpc2                      | ↓          | EMT                | Melanoma    | [198]     |
| IP$_3$R                   | ↑          | -                  | Colorectal cancer| [199] |
| RyR                       | RyR2       | ↓                  | Thyroid carcinoma| [200] |

$\uparrow$: indicates increased; $\downarrow$: indicates decreased; -: indicates not available; VGCC: voltage-gated Ca$^{2+}$ channel; MFAP5: microfibrillar-associated protein 5; SOCE: store-operated Ca$^{2+}$ entry; STIM: stromal interaction molecule; TRP: transient receptor potential; TRPC: TRP canonical; TRPM: TRP melastatin; TRPML1: Mucolipin TRP channel 1; TRPP2: TRP polycystin 2; TRPV: TRP vaniloid; PMCA: plasma membrane Ca$^{2+}$ ATPase; GC: gastric cancer; SERCA: (Sarco)-ER Ca$^{2+}$ ATPase; MCU: mitochondrial calcium uniporter; EMRE: essential MCU regulator; MCUB: MCU dominant negative beta subunit; MICU: mitochondrial calcium uptake; MCUR1: MCU regulator 1; TPC: two-pore channel; IP$_3$R: inositol 1,4,5-trisphosphate receptor; RyR: ryanodine receptor; MVD: microvessel density.
secreted by CAFs activates FAK/cAMP response element-binding protein (CREB)/troponin C type 1 (TNNC1) via SOCE to enhance cancer metastasis [149].

CRAC-mediated Ca\(^{2+}\) regulates invadopodium formation and ECM degradation [155, 203]. Orai1-mediated SOCE promotes phosphorylation of proline-rich tyrosine kinase 2 (Pyk2), which regulates focal adhesion turnover and the EMT of glioma cells [150]. Elevation of Orai2 is positively correlated with lymph node metastasis of gastric cancer (GC). Orai2 induces FAK-mediated mitogen-activated protein kinases (MAPK)/extracellular signal-regulated kinase (ERK) activation and enhances focal adhesion disassembly at the rear edge of metastatic cancer cells [154]. The hEag1 K\(^{+}\) channels are essential for breast cancer cell migration because they promote Orai1-mediated Ca\(^{2+}\) current [204]. Inhibition of Orai or STIM decreases GTPase Ras- and Rac-mediated formation of new focal complexes at cell protrusions and disassembly of focal adhesions. This action ultimately inhibits breast cancer metastasis to the lung [13]. Orai3 and STIM2 also promote gastroenteropancreatic neuroendocrine and breast cancer metastasis, respectively [8, 151].

**TRP channels**

The TRP channel superfamily comprises seven subtypes with approximately thirty members, most of which can mediate Ca\(^{2+}\) currents. TRP channels are activated by diverse stimuli, including intra- and extra-cellular messengers, temperature, pH, chemical, mechanical and osmotic stress, ROS, and intracellular Ca\(^{2+}\) stores [17]. The expression of phospholipid phosphatase 4 (PLPP4) protein is increased, and it promotes cancer cells metastasis probably by activating TRPC channels-mediated Ca\(^{2+}\) influx [205]. TRPC1 inhibits the PI3K/AKT pathway and EMT, leading to reduced migration and invasion rates of cancer cells [157]. TRPC5 is elevated in colon cancer, which promotes cancer cell EMT and metastasis via the HIF-1α/Twist axis. In addition to promoting the migration and invasiveness of renal cancer cells, the upregulated expression of TRPC6 is also required for translocation of Orai1 and Orai3 to the plasma membrane of metastatic breast cancer cells [161, 162]. *Helicobacter pylori*, a well-known major risk factor for GC, increases TRPC6 transcription and Ca\(^{2+}\) influx via the Wnt/β-catenin pathway to enhance GC cells migration and invasion [163].

Cancer cells with high level of TRPM2 channels are more susceptible to neutrophil cytotoxicity. A reduction in TRPM2 expression leads to decreased tumor growth but increased DTC seeding potential in the premetastatic lung [206]. Upregulation of TRPM7 expression is correlated with the EMT and metastasis of ovarian cancer via the Ca\(^{2+}\)-related PI3K/AKT axis [171]. The level of TRPV1 channels is reduced in human GC tissues. This reduction leads to decreased Ca\(^{2+}\)/calmodulin-dependent protein kinase kinase beta (CaMKKβ) activity and contributes to GC peritoneal dissemination [175]. TRPV4 or TRPV6 is increased in endometrial, breast or prostate cancer, which promotes cancer cells metastasis [177, 178, 181]. Deletion of TRPV4 increases p-VEGFR2Y1175 level and ECs migration [207]. However, deficiency of TRPV4 causes reduced vascular E-cadherin level and destabilizes tumor vessel integrity, leading to cancer cells lung metastasis [179].

**Adenine/uridine nucleotide-dependent proteins that mediate Ca\(^{2+}\) current**

** Plasma membrane Ca\(^{2+}\) ATPase**

Reduction in PMCA4 level increases zinc finger E-box binding homeobox 1 (ZEB1) expression and the nuclear accumulation of NFAT isoform c1 (NFATc1). PMCA4 ultimately lead to advanced tumor-node-metastasis (TNM) stage and poor prognosis of GC patients. It also induces cancer cells transformation with elongated fibroblastoid morphology, reduced E-cadherin level and increased vimentin level, which can be inhibited by cyclosporine A [182].

**SERCA**

The miR-708 level is decreased in both lymph node and distal metastases, suggesting a cancer metastasis-suppressive role of miR-708. Neuronatin is a membrane protein in the ER with the ability to inhibit SERCA. Reduction in miR-708 level increases the expression of neuronatin, which further induces the elevation of intracellular Ca\(^{2+}\) level to promote cell migration and metastasis formation by activating the ERK/FAK axis [183]. Upregulation of SERCA2 in CRCs is positively related to serosal invasion and lymph node metastasis [184]. In contrast, the SERCA3 level is negatively related to lymphatic invasion of colorectal adenoma-adenocarcinoma [185].
Purinergic receptors

P2*7 (X indicates X or Y) receptors are highly expressed on LoVo and SW480 CRCs. Activation of P2*7 by ATP promotes CRCs metastasis by STAT3-dependent EMT [187]. P2X7 promotes cancer invasiveness by sustaining the activity of cell division cycle 42 (Cdc42) and promoting the acquisition of a mesenchymal phenotype [186]. P2Y mediates prostate cancer invasion via ERK1/2 and p38 or EMT/invasion-related genes [189, 190]. Activation of P2Y6 increases filopodia and the number of focal adhesions via Gαq/Ca²⁺/PKC and Gα₁₃/Rho-associated protein kinase-dependent pathways to promote lung cancer cell migration [191]. Depletion of apoptosis signal-regulating kinase 1 (ASK1) reduces the phosphorylation of P2Y12 in platelets, which leads to defects in platelet aggregation and a reduction in tumor metastasis [192].

Mitochondrial calcium uniporter

Mitochondria, major intracellular Ca²⁺ stores, are primary sources of ROS, which promote tumor metastasis. MCU located on the inner mitochondrial membrane, is a Ca²⁺-selective channel and critical for major Ca²⁺ influx into mitochondria [208]. MCU-mediated ATP production regulates profibrotic macrophage polarization [209]. cl-CD95L enhances the metastatic dissemination of TNBC cells by enhancing MCU-mediated Ca²⁺ current [210]. However, reduction in histidine triad nucleotide-binding 2 (HINT2) enhances pancreatic cancer lymph node metastasis, probably by increasing MICU1/2 and decreasing EMRE levels to inhibit MCU activity [193, 211].

MCU is significantly associated with cancer aggressiveness and is increased in diverse cancers, including TNBC, HCC, and GC [88, 194-196]. Elevation of MCU level enhances metastatic colonization and MVD in breast cancer. MCU also inhibits the selective sorting of miR-4488 to extracellular vesicles by manipulating Ca²⁺-dependent RNA-binding proteins (RBPs). This process leads to relief of CX3-C motif chemokine ligand 1 (CX3CL1) repression to enhance tube formation capacity and sprouting capacity [195]. MCUb expression is decreased while that of MCU is increased in invasive TNBC and lymph node metastasis. Silencing MCU increases SOCE and the NADPH/NADH ratio while decreases ROS and HIF-1α levels [196]. MICU1 is decreased in metastatic HCC tissues, and MCU-mediated mitochondrial Ca²⁺ influx induces ROS/c-Jun N-terminal kinase (JNK) activation. This chain of events ultimately facilitates HCC intrahepatic and lung metastasis [194]. MCUR1 is significantly upregulated in metastatic HCC cells, which promote EMT and metastasis via the mitochondrial Ca²⁺-dependent ROS/Nrf2/Notch pathway [197].

TPC

TPC family proteins are nicotinic acid adenine dinucleotide phosphate (NAADP)-gated Ca²⁺ release channels located on endosomes, lysosomes, and melanosomes. Reduction in TPC2 expression activates the YAP/TAZ axis to inhibit the expression levels of ORAI1 and PKC-βII, which is found in the metastatic tumors but not in the primary melanoma cells in patients [198].

IP₃R and RyR

The EGF-induced EMT is coupled with specific alterations in the mRNA level of ER-related Ca²⁺ channels/pumps, including SERCAs, IP₃R, and RyR [212]. Trifluoperazine, an antipsychotic drug, can reduce glioblastoma invasion by binding with CaM to activate IP₃R-mediated Ca²⁺ release from the ER [213]. Furthermore, IP₃R-3 is increased in colon cancer, while RyR2 is decreased in thyroid carcinoma tissues, both of which are related to aggressiveness [199, 200].

Conclusions

Metastasis is still a great challenge for improving cancer therapy, in which Ca²⁺-manipulated signals have been proven to be critical. Currently, although great progress has been made, the mechanisms underlying the metastatic cascade and functions of Ca²⁺ have not yet been fully elucidated. Most previous studies have focused mainly on Ca²⁺-dependent proteins or Ca²⁺ channels/pumps in cancer cells, while only a few studies have investigated their functions in cancer stoma cells and the metastatic niche. There are still limited available drugs targeting Ca²⁺-mediated signals in the clinic or undergoing clinical trials for cancer.
metastasis therapy. Therefore, the development of drugs specifically targeting proteins that decoding calcium oscillation signals or mediating Ca\(^{2+}\) currents is highly desirable.

**Abbreviations**

ALDOB: aldolase B  
AMP: adenosine monophosphate  
AMPK: AMP-activated protein kinase  
Ca\(^{2+}\): calcium ions  
CAFs: cancer-associated fibroblasts  
CaM: calmodulin  
CaSR: Ca\(^{2+}\) sensing receptor  
CCL: C-C motif ligand  
CIL: contact inhibition of locomotion  
CRACs: Ca\(^{2+}\) release-activated Ca\(^{2+}\) channels  
CRCs: colon cancer cells  
CTCs: circulating tumor cells  
CXC: C-X-C motif  
CXCL: CXC chemokine ligand  
DTCs: disseminated tumor cells  
ECM: extracellular matrix  
ECs: endothelial cells  
EGF: epidermal growth factor  
EMRE: essential MCU regulator  
EMT: epithelial-to-mesenchymal transition  
EphA2: Ephrin type-A receptor 2  
ER: endoplasmic reticulum  
ERK: extracellular signal-regulated kinase  
FAK: focal adhesion kinase  
GC: gastric cancer  
gMDSCs: granulocytic MDSCs  
HCC: hepatocellular carcinoma  
HIF-1α: hypoxia-inducible factor-1alpha  
IL-6: interleukin-6  
IP\(_3\)R: inositol 1,4,5-trisphosphate receptor  
LECs: lymphatic ECs  
MCT1: monocarboxylate transporter 1  
MCU: mitochondrial calcium uniporter  
MDSCs: myeloid derived suppressor cells  
MET: mesenchymal-epithelial transition  
MICU: mitochondrial calcium uptake  
MMPs: matrix metalloproteinases  
NF-κB: nuclear factor-kappa B
NK: natural killer
PGC-1α: peroxisome proliferator-activated receptor-gamma coactivator 1α
PHD: prolyl-hydroxylase
PMCA: plasma membrane Ca\(^{2+}\) ATPase
PTEN: phosphatase and tensin homolog
ROS: reactive oxygen species
RPs: ribosomal proteins
RyR: ryanodine receptor
SERCA: (sarco)-endoplasmic reticulum Ca\(^{2+}\) ATPase
SOCE: store-operated Ca\(^{2+}\) entry
STAT3: signal transducer and activator of transcription 3
TAMs: tumor-associated macrophages
TGFβ: transforming growth factor β
tnbc: triple negative breast cancer
TPCs: two-pore channels
TRP: transient receptor potential
TRPC: TRP canonical
TRPM: TRP melastatin
TRPV: TRPV vanilloid
VGCCs: voltage-gated Ca\(^{2+}\) channels

**Declarations**

**Author contributions**
CCC, ZYX and WXW contributed to the conception and design of the review. CCC, ZYX, LG, ZSH and ZJH collected the related reports and drafted the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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