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Circulating Tumor Cells: Does Ion Transport Contribute to Intravascular Survival, Adhesion, Extravasation, and Metastatic Organotropism?

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Abstract Survival in the circulation, extravasation from vasculature, and colonizing new tissues represent major steps of the metastatic cascade and pose a big challenge for metastasizing tumor cells. Tumor cells circulating in blood and lymph vessels need to overcome anoikis, cope with mechanical stimuli including shear stress, and defeat attacks by the immune system. Once adhered to the vessel wall, a circulating tumor cell (CTC) can trick the endothelial cells into loosening their intercellular junctions so that the endothelium becomes penetrable for the tumor cell. Since tumor cells tend to metastasize to predestinated target organs and tissues, called organotropism, the distribution of metastases is anything but random. The molecular-physiological mechanisms underlying CTC survival, extravasation, and

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organotropism are very likely to include the presence and activity of ion channels/transporters due to the latter's key function in cytophysiological processes. To date, a very limited number of studies explicitly show the involvement of ion transport. This review describes the contribution of ion channels and transporters to CTC survival, extravasation, and organotropism where known and possible. In addition, supposed connections between ion transport and CTC behavior are demonstrated and imply the potential to be therapeutically taken advantage of.

Keywords Ca^{2+} · Homing · Intravascular milieu · Mechanosensitivity · Premetastatic niche

1 Introduction

The degree of malignancy of a tumor disease is determined by the tumor cells' propensity to invade surrounding tissue, to spread and metastasize. These steps of the metastatic cascade also include the cells' long-distance transport by blood and lymph flow as well as their ability to adhere to the vessel wall in order to extravasate at a distant organ site far away from the primary tumor (Valastyan and Weinberg 2011). During the course of these events blood cells play a double-edged role. While natural killer (NK) cells represent serious opponents of circulating tumor cells (CTCs), platelets, neutrophils and monocytes/macrophages may even help them to survive the intravascular milieu, extravasate and colonize a new tissue or organ.

In respect of rolling and adhesion to the vessel wall, CTCs quite often mimic or avail themselves of the mechanisms used by leukocytes (Strell and Entschladen 2008). The receptor-ligand pairs involved in rolling are mostly the same in leukocytes and tumor cells, with E- and P-selectins expressed on endothelia as well as (peritoneal) mesothelia being the major receptors (Gebauer et al. 2013; Köhler et al. 2010). In contrast, the receptor-ligand pairs that mediate tumor cell adhesion to the endothelium are quite different from those involved in leukocyte adhesion (Strell and Entschladen 2008). Specific interactions between structures on the tumor cell surface and tissue-/organ-specifically expressed proteins on the endo-/mesothelium, including locally released chemokines (please see Sect. 5.1), contribute significantly to the organ distribution of metastases which is anything but random (Langley and Fidler 2011; Paget 1989). The preference of tumor cells to metastasize to predestinated target-organs is called "organ-specific metastasis" or "metastatic organotropism."

The present review article describes the travel route of metastasizing tumor cells from the moment of intravasation through to the colonization of the target-organ, including indispensable survival mechanisms. There is hardly any direct evidence for the contribution of ion transport to these steps of the metastatic cascade. However, due to their pivotal role in regulating cellular functions, ion channels and transporters must be inevitably involved. Their involvement will be described

and explained where known and possible. In other cases, presumed links between ion transport and the survival of metastasizing cells are pointed up. Central modulators affecting, and being affected by, ion channels and transporters are pH and cytosolic Ca^{2+} concentrations together with signaling events.

2 Surviving the Intravascular Milieu

Being swept away by the blood flow represents a major challenge for tumor cells. From thousands up to millions of cells that come off the primary tumor every day (Butler and Gullino 1975; Swartz et al. 1999), less than one out of ten thousand circulating tumor cells (<0.01%) may eventually end up as a metastasis (Fidler 1970, 2003; Strilic and Offermanns 2017). In breast cancer patients, the half-life of circulating tumor cells (CTCs) was found to be 1–2.4 h (Meng et al. 2004). Most of these CTCs die due to hemodynamic shear stress in the circulation (Fan et al. 2016) or anoikis, i.e. the loss of cell–cell or cell–matrix contacts including the absence of extracellular matrix-derived survival signals (Kim et al. 2012). A third obstacle to be overcome by CTCs is the immune surveillance, particularly the clutches of natural killer (NK) cells of the innate immune system (Morvan and Lanier 2016).

To cope with all these challenges, CTCs use a number of (molecular) mechanisms (Strilic and Offermanns 2017).

2.1 Coping with Mechanical Stress

In order to resist mechanical destruction by hemodynamic forces, CTCs activate both the RhoA/actomyosin axis and actin-nucleating formins in response to fluid shear stress which, including the activity of myosin II, protects them from plasma membrane damage (Moose et al. 2020). Accordingly, short-term inhibition of myosin II delays metastasis of circulating prostate cancer cells in a mouse model (Moose et al. 2020). Since the CaM-dependent activity of myosin II needs Ca^{2+}, and the resistance to fluid shear stress requires the presence of extracellular Ca^{2+} (Barnes et al. 2012), CTC adaptation to mechanical stress definitely involves Ca^{2+} transport across the plasma membrane. In general, a number of mechanosensitive ion channels have a share in Ca^{2+} signaling of tumor cells: while direct Ca^{2+} influx can be mediated by Ca^{2+} conducting channels such as Piezo or TRP channels, K^+ outward currents carried by, inter alia, mechanosensitive members of the two-pore domain K^+ channel family keep up the electrochemical gradient essential for Ca^{2+} influx (Pethö et al. 2019). Albeit there is no study to date explicitly proving the nature of the Ca^{2+} channels and transport mechanisms that are involved in CTCs' shear stress resistance, exposure to fluid shear stress does trigger Ca^{2+} influx accompanied by an increase in cell stiffness. Transformed prostate cancer cells (PC-3) show a graduated increase in stiffness in response to the level of shear stress whereas non-transformed

prostate epithelial cells (PrEC LH) do not show a significant change (Chivukula et al. 2015). In addition to channels and transporters mediating Ca^{2+} influx provoked by fluid shear stress, the Na^+/H^+ exchanger NHE1 may contribute to the increase in stiffness and thus facilitate CTC survival. Its overexpression, typical of a multitude of tumor entities, leads to a reorganization of the cortical cytoskeleton accompanied by a significant increase in cortical stiffness of human melanoma (MV3) cells (Keurhorst et al. 2019). This effect is based on the mere presence of NHE1 as a structural element independently of its ion transport function.

An additional strategy by which single CTCs can protect themselves from mechanical stress-induced death is the recruitment of thrombocytes (platelets) and monocytes/macrophages in order to form a physical shield (Schlesinger 2018; Stegner et al. 2014). To this end, CTCs express tissue factor at their surface (Bourcy et al. 2016; Hisada and Mackman 2019). The tissue factor triggers the coagulation cascade including the activation of platelets which results in the formation of a protective platelet clot around the tumor cells. The clot then recruits monocytes/macrophages to the CTCs (Gil-Bernabé et al. 2012, 2013), and the accruing clusters or microaggregates not only protect the CTCs from mechanical stress but also help them adhere to the endothelium and extravasate at a distant site (Strilic and Offermanns 2017). According to this, an inhibition of mechanisms underlying tumor cell–platelet interaction causes a significant decrease in metastasis (Labelle and Hynes 2012; Mammadova-Bach et al. 2020; Takagi et al. 2013).

Another survival mechanism has been found in highly metastatic human breast cancer cells expressing significant amounts of a truncated form of the channel protein Pannexin 1 (PANX1) (Furlow et al. 2015). PANX1 is an ATP-permeable channel and, under normal cellular conditions, auto-inhibited because it is plugged by its C-terminal tail. During apoptosis, cleavage of the C-terminus by caspase 3 or 7 activates PANX1 and allows ATP release (Chekeni et al. 2010; Ruan et al. 2020; Sandilos et al. 2012). In highly metastatic breast cancer cells, however, co-expression of a truncated form of PANX1 with full-length wild-type PANX1 protects from apoptosis (Furlow et al. 2015). The presence of truncated PANX1 is accompanied by an elevated ATP release through mechanosensitive full-length PANX1 activated by membrane stretch during deformation in the microvasculature. By autocrine binding to purinergic P2Y receptors the released ATP induces a signaling cascade that suppresses deformation-induced apoptosis of the circulating breast cancer cell. Consequently, therapeutic inhibition of PANX1 by small-molecule inhibitors can reduce breast cancer metastasis (Furlow et al. 2015).

2.2 Resistance to Anoikis

A loss of integrin-mediated cell adhesion to extracellular matrix proteins normally induces anoikis, a special type of apoptosis (Tajbakhsh et al. 2019). CTCs utilize a variety of mechanisms to counteract anoikis (Buchheit et al. 2014). An efficient way to avoid anoikis is the retention of cell–cell or even fragmented cell–matrix

adhesions within the circulating tumor cell clusters, also termed circulating microemboli. These circulating microemboli can either originate from collectively migrating tumor cells that enter the blood stream via chaotically structured and leaky tumor vessels typical of highly angiogenic tumors (Hou et al. 2011) or they arise from the disintegration of the primary tumor into the vasculature (Liotta et al. 1976). Although circulating tumor cell clusters are rather rare compared to single CTCs, these clusters have a 23–50-fold increased metastatic potential (Aceto et al. 2014).

Since the focal adhesion kinase (FAK) is a central player in integrin-mediated adhesion signaling, single CTCs establish alternative ways of FAK phosphorylation or even bypass FAK signaling. Thus, FAK phosphorylation and signaling in non-adherent cells may be ensured by endosomes that carry integrin dimers while containing integrin-binding extracellular matrix components such as fibronectin (Alanko et al. 2015). Another way to maintain FAK signaling may be integrin-mediated self-stimulation by self-secreted fibronectin or collagen. Stimulation of β1 integrin by fibronectin or collagen causes activation of $K_v11.1$ (*human ether-a-go-go-related gene* potassium channel hERG, KCNH2), which is essential for direct FAK phosphorylation (Cherubini et al. 2005; Jehle et al. 2011). FAK phosphorylation in response to $K_v11.1$ activation may enable detached cells to resist anoikis. In fact, overexpression of both FAK and $K_v11.1$ has been shown to enhance dissemination and invasiveness of tumors (Kornberg 1998; Lastraioli et al. 2004).

Moreover, fibronectin can promote cell survival, mediate chemo- and radioresistance, and inhibit apoptosis in breast and lung cancer cells (Aoudjit and Vuori 2012; Naci et al. 2015). In pancreatic cancer cells, an increased *Wnt2* expression correlates with a TGFβ-activated kinase 1 (TAK1; MAP 3 K7)-dependent upregulation of fibronectin, suppresses anoikis, and facilitates adhesion-independent sphere formation (Yu et al. 2012).

Aside from fibronectin, CTCs could potentially also make use of serum vitronectin and other serum proteins, e.g. osteopontin, thrombospondin or reelin, as ligands in order to keep up integrin-mediated signaling and thus resist anoikis (Bera et al. 2020; Cooper et al. 2002; Lal et al. 2009; Rouanne et al. 2016).

Beyond that, FAK-mediated anoikis resistance has been found to correlate with the expression of carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6), also known as CD66c (Duxbury et al. 2004; Johnson and Mahadevan 2015; Lee et al. 2018). As a bypass or an alternative to missing FAK signaling, anti-apoptotic, pro-survival pathways are upregulated or tumor suppressors and suppressing pathways are downregulated. For instance, the PI3/Akt signaling pathway, which normally is inducible by FAK as well, or the MAPK/ERK pathway is stimulated by overexpressed receptor tyrosine kinases and downregulation of the tumor suppressor PTEN (Paoli et al. 2013). A moderately increased ROS production is often found in tumor cells (Perillo et al. 2020) and helps to counteract anoikis by modulating the activities of redox-sensitive proteins of the PI3/Akt and MAPK signaling pathways and prominent transcription factors such as p53, NF-κB, HIF, AP-1, and Nrf2 (Groeger et al. 2009).

Finally, although not shown explicitly in CTCs, the detachment from the extracellular matrix could induce autophagic and antioxidant effector pathways whose

concerted action might (i) enable increased survival in the bloodstream and (ii) facilitate the formation of metastases (Dey et al. 2015). In more detail, cells react to the loss of substrate adhesion by activating a cytoprotective ER stress response consisting of three pathways that are normally kept inactive by the ER-located chaperone GRP-78 (also known as "binding immunoglobulin protein" (BiP) or "heat shock 70 kDa protein 5" (HSPA5)) (Korennykh and Walter 2012): the ATF6 (transmembrane activating transcription factor *6*), the IRE1 (iron responsive element 1), and the PERK (transmembrane protein kinase RNA-like endoplasmic reticulum kinase; located in the ER membrane) pathway (Dey et al. 2015; Wakabayashi and Yoshida 2013). Activated PERK directly activates transcription factor Nrf2 and phosphorylates eIF2α (eukaryotic (translation) initiation factor 2α). peIF2α leads to upregulated translation of the cAMP-dependent transcription factor ATF4. ATF4 then triggers a cytoprotective program by upregulating key genes of autophagy, and, by cooperating with Nrf2, activates the antioxidant protein HO-1 (heme oxygenase 1) in order to antagonize the increasing oxidative stress induced by the loss of cell-matrix adhesion (Dey et al. 2015).

In breast cancer cells of the MCF-7 line, incorporation of the STAT3 (signal transducer and activator of transcription 3)-controlled zinc transporter ZIP6 (SLC39A6) into the plasma membrane induces EMT (epithelial-mesenchymal transition), cell detachment, resistance to anoikis and an ongoing proliferative activity of cells in suspension (Hogstrand et al. 2013). ZIP6-mediated Zn^{2+} influx inactivates the glycogen synthase kinase 3β (GSK-3β) leading to activation of the transcription factor Snail. Snail then oppresses the transcription of E-cadherin resulting in cell rounding and detachment (Hogstrand et al. 2013). Snail is generally considered to be one of the key players inducing EMT accompanied by resistance to anoikis (Paoli et al. 2013; Peyre et al. 2021; Smit et al. 2009).

The Ca^{2+} activated Cl^- channel regulators 1 and 2 (CLCA1, 2; also called Cl^- channel accessory 1, 2) are secretory, self-cleaving, Zn^{2+}-dependent metalloproteases that activate Ca^{2+}-dependent Cl^- currents (Liu and Shi 2019; Yurtsever et al. 2012). They are involved also in apoptosis (Hutchings et al. 2019; Winpenny et al. 2009). Their downregulation, however, results in resistance to anoikis (Elble and Pauli 2001). While CLCA2 overexpression leads to increased Cl^- currents accompanied by a decrease in intracellular pH, a reduced expression of CLCA2 is associated with increases in proliferation, migration, and invasion, and a higher risk of metastasis (Walia et al. 2009, 2012).

2.3 Defeating Attacks by the Immune System

Once in the circulation, tumor cells encounter a huge number of immunosurveilling cells such as natural killer (NK) cells. NK cells express NKG2D (NK group 2d) receptors on their surface in order to recognize and bind their ligands (NKG2DL) which are primarily the cell surface glycoproteins MICA, MICB (MHC class I chain-related molecules A and B), and ULBPs 1–6 (Duan et al. 2019; Ghadially

et al. 2017; Molfetta et al. 2017). Basically, the transcription factor Sp1 mediates an upregulation of NKG2DL-expression during EMT resulting in an increased immunogenicity (Huergo-Zapico et al. 2014). However, NKG2DL-expression decreases as the tumor cells continue to dedifferentiate and is completely absent in poorly differentiated human colorectal cancer samples (López-Soto et al. 2013). For camouflage purposes, i.e. in order to elude immune surveillance, CTCs can either shed their NKG2DLs to (1) remain undetected and (2) misdirect the immune system (Dhar and Wu 2018), or they even avoid surface expression of NKG2DLs (Liu et al. 2019a; Schmiedel and Mandelboim 2018) as shown for leukemic stem cells in patients with acute myeloid leukemia (Paczulla et al. 2019).

At transcriptional level, aberrant methylation of the genes encoding NKG2DLs or low acetylation of histones can lead to NKG2DL silencing in tumor cells of different origin (Li et al. 2011a; Ritter et al. 2016). In glioma cells with mutations of the isocitrate dehydrogenase (IDH), loss-of-function mutations induce 2-hydroyglutaric acid-mediated epigenetic and metabolic reprogramming, eventually silencing ULBPs 1 and 3 (Zhang et al. 2016a). In other malignant glioma cells, TGF-β suppresses the transcription of *MICA*, *ULBP2*, and *ULBP4* without affecting the mRNA levels of *MICB*, *ULBP1,* and *ULBP3* (Eisele et al. 2006). *MICA* mRNA expression can be decreased also by IFN-γ as shown for both solid (cervical) and hematological (erythroleukemia and lymphoma) cell lines (Zhang et al. 2008).

At translational level, miR-10b, miR-20a, mir-34a, miR-93, or miR-106 either destabilize the NKG2DLs' mRNAs or inhibit their translation in a number of tumor cell lines such as melanoma, breast, prostate, or colorectal cancer (Codo et al. 2014; Heinemann et al. 2012; Stern-Ginossar et al. 2008; Tsukerman et al. 2012; Yang et al. 2018). In contrast, miR-889-overexpression protects hepatocellular carcinoma cells from NK cell-mediated lysis, because it significantly inhibits MICB expression (Xie et al. 2018).

At post-translational level, proteolytic enzymes, shedding and secretion help to reduce NKG2DL surface expression in tumor cells (Duan et al. 2019). Thus, IFN-γ not only regulates MICA expression at the transcriptional level but also promotes its hydrolysis by matrix metalloproteinases (MMPs) (Zhang et al. 2008). "A disintegrin and metalloproteases" (ADAMs) 10 and 17 mediate shedding of MICA and MICB from human mammary, pancreatic, and prostate carcinoma cells (Chitadze et al. 2013). A significant amount of soluble NKG2DL is found in sera of leukemia patients where it impairs antileukemia reactivity of NK cells by downregulating their NKG2D (receptor) expression (Hilpert et al. 2012). Similarly, glioblastoma cells secrete lactate dehydrogenase 5 (LDH5) to trigger NKG2DL expression in myeloid cells including monocytes, which then results in the downregulation of NKG2D in NK cells (Crane et al. 2014).

NK cells' effective antitumor activity requires direct, physical contact. Consequently, physical shielding does not only protect tumor cells from mechanical stress (please see Sect. 2.1) but also helps them to escape from NK cell attacks as coating with tumor cell-activated platelets impedes lysis of tumor cells by NK cells (Nieswandt et al. 1999) and facilitates metastasis (Palumbo et al. 2005). The formation of stable platelet/tumor cell aggregates needs fibrinogen or fibrin

crosslinking factor FXIII. Loss of these coagulation factors causes a strong decrease in metastasis in an NK-cell dependent manner (Palumbo et al. 2005, 2008). The adhesion molecule P-selectin is expressed on platelets and mediates platelet/tumor cell adhesion by binding to sialylated, fucosylated glycans on the tumor cell surface (Borsig et al. 2002; Mannori et al. 1995), mostly in a Ca^{2+}-dependent way (Erpenbeck and Schön 2010). Furthermore, by releasing TGFβ, also the platelets cause a reduction of NKG2D receptors on NK cells (Kopp et al. 2009). Finally, platelets can furnish tumor cells with both platelet-derived GITRL (glucocorticoid-induced TNF-related ligand; TNFSF18) which inhibits NK cells' antitumor reactivity (Placke et al. 2012b) and with normal MHC class I molecules which help the tumor cells to hide from immunosurveillance (Placke et al. 2012a).

While CTC clusters and CTCs surrounded by platelets or leukocytes can easily travel through the macrovasculature as silent emboli, these virtually conglomerate structures need to regroup before entering microvessels and capillaries with diameters of $\leq$10 μm, so that the single cells can pass through sequentially (Au et al. 2016). In capillary beds, even single CTCs can be halted within <30 min after entering the blood stream (Aceto et al. 2014; Micalizzi et al. 2017). Hence, it seems plausible that extracellular vesicles, exosomes or microparticles released from platelets/leukocytes rather than the actual, intact cells would confer the above-mentioned ligands/receptors to CTCs and thus enable them to camouflage and remain undetected by the immune system.

3 Adhesion to the Vessel Wall

In addition to simply being physically stuck inside small capillaries at the secondary site, CTCs need to adhere to and interact with the endothelium in order to eventually extravasate (Azevedo et al. 2015; Foss et al. 2020; Osmani et al. 2019). While the attachment of CTCs to endothelial cells can be mediated by a variety of ligands and receptors such as selectins, cadherins, integrins, CD44 and immunoglobulin superfamily receptors (Bendas and Borsig 2012; Reymond et al. 2013), CD44 and β1 integrin have been identified as key mediators of CTC adhesion. They counteract the shear forces that otherwise would cause the detachment of CTCs from the endothelial cell layer (Follain et al. 2018, 2020; Osmani et al. 2019). In addition to mediating CTC adhesion to the endothelial cell layer or being a biomarker for cancer cells with stem-like properties (Mani et al. 2008) CD44 may enhance metastatic potential by effectuating homophilic CTC interactions, possibly resulting in the formation of CTC clusters even post-intravasation (Chaffer and Goetz 2018; Liu et al. 2019b; Rodrigues and Vanharanta 2019).

Melanoma cell adhesion molecule (MCAM; also known as MUC18 or CD146) is expressed on both melanoma and endothelial cells, and it is believed that homophilic interactions promote tumor cell extravasation and metastasis because antibodies against MCAM inhibit human melanoma growth and metastasis (Mills et al. 2002), and B16 wild-type cell metastasis to the lungs is drastically reduced in

MCAM knockout mice (Jouve et al. 2015). In human melanoma cells of the MV3 cell line, MCAM expression correlates with the expression of the Na^+/H^+ exchanger NHE1 (SLC9A1), and MV3 cell–cell adhesion is pH-sensitive and depends on NHE1 expression (Hofschröer et al. 2017). This observation together with the aforementioned homophilic interaction of MCAM expressed on melanoma and endothelial cells (Mills et al. 2002) points to a potential contribution of NHE1 to the adhesion of tumor cells to the vessel wall.

4 Extravasation

Specific ligand-mediated interactions between tumor and endothelial cells do not necessarily result in adhesion but are nonetheless required for extravasation. Thus, the homophilic interaction between junctional adhesion molecules C (JAM-C) expressed on melanoma and endothelial cells does not impact adhesion but clearly abets lung metastasis (Langer et al. 2011). Also soluble ligands secreted by endothelial cells, e.g. CXCL12, mediate tumor extravasation by binding to chemokine receptors such as CXCR4 expressed particularly on gastrointestinal tumor cells which then stimulates the small GTPases Rho, Rac, and Cdc42 required for cell migration (Gassmann et al. 2009). The latter is consistent with the observations that (1) Cdc42 depletion in various tumor cells leads to a significant decrease in both β1 integrin-dependent interaction with endothelial cells and experimental lung metastasis (Reymond et al. 2012), and (2) that transient RhoC depletion in prostate cancer (PC3) cells reduces early PC3 cell retention in the lungs and in vivo metastasis formation (Reymond et al. 2015).

Paracellular diapedesis, i.e. squeezing through the endothelial cell layer by moving between endothelial cells, is the prevalent mode of extravasation and requires loosening of inter-endothelial cell junctions (Leong et al. 2014; Schumacher et al. 2013). Transcellular diapedesis, i.e. crossing the endothelium by penetrating individual cell bodies, has been shown in vitro, but seems rather rare and most likely requires both endothelial myosin II activity and E-selectin mediated activation of ERK and p38 MAPKs in endothelial cells (Khuon et al. 2010; Tremblay et al. 2008; Wettschureck et al. 2019). A recent study confirms that the microvascular endothelium reorganizes its membranes and cytoskeletal structures in order to directly contribute to the extravasation of tumor cells into the brain, and that melanoma cells primarily migrate paracellularly while breast cancer cells are able to migrate transcellularly (Herman et al. 2019). However, it needs to be stressed that up to now transcellular extravasation in vivo has been found only in microvascular endothelia, possibly because they are typically characterized by a lack of smooth muscle cells.

Endothelial reorganization is usually induced by the CTCs themselves. Breast cancer cells secrete angiopoietin-like 4 (ANGPTL4) or its C-terminal fibrinogen-like domain (cANGPTL4). cANGPTL4 weakens endothelial cell–cell contacts by activating an α5β1 integrin-mediated Rac1/PAK/β-catenin pathway. In a subsequent step, cANGPTL4 directly interacts with VE-cadherin and claudin-5 which causes

disruption of intercellular adhesion, thus allowing for transendothelial tumor cell migration (Huang et al. 2011; Padua et al. 2008). Melanoma cells secrete osteonectin (SPARC). SPARC binds to VCAM1 which triggers actin remodeling and loosening of endothelial junctions, mediated by a ROS-MKK3/6-p38MAPK-MLC2 signaling pathway and promoting extravasation and metastasis (Tichet et al. 2015). Other soluble factors that are secreted by metastatic cells and increase vascular permeability by modulating endothelial tight and adherens junctions include lipid 12(S)-hydroxyeicosatetranoic acid (12(S)-HETE), angiopoietin 2 (Ang-2), the chemokine CCL2 (C-C motif chemokine ligand 2, monocyte chemotactic protein 1), CXCL12 (stromal cell-derived factor 1α, SDF-1α), fibrinogen, HGF/SF, VEGF, PCB 104 (2,2′,4,6,6′-pentachlorobiphenyl), and a group of heat-stable, trypsin-sensitive, O-glycosylated glycoproteins ranging from 10 to 50 kD (García-Román and Zentella-Dehesa 2013).

Instead of gently loosening endothelial cell–cell junctions, a variety of human and murine tumor cells act more ruthlessly by inducing necroptosis in endothelial cells in order to locally perforate the endothelium and hence facilitate extravasation and metastasis (Strilic et al. 2016). To this end, CTCs express amyloid precursor protein (Pandey et al. 2016; Tsang et al. 2018) which binds to its receptor, death receptor 6 (DR6), on endothelial cells to induce necroptotic signaling pathways (Strilic et al. 2016). Additionally, necroptotic endothelial cells could possibly reinforce the opening of the endothelial barrier by releasing damage-associated molecular patterns (DAMPs) such as high-mobility group protein 1 (HMGB1) or ATP (Kaczmarek et al. 2013; Pilzweger and Holdenrieder 2015; Strilic and Offermanns 2017).

4.1 With the Assistance of Blood Cells

4.1.1 Platelets

Also blood cells contribute to CTCs' extravasation. For instance, platelets normally assist immune cells with their extravasation (Gros et al. 2015). They – like the metastatic CTCs (see above) – release HGF, fibrinogen, VEGF, and 12(S)-HETE, and, in addition, platelet-derived activating factor (PAF), thrombin, ATP and serotonin in order to increase vascular permeability. Indeed, there is evidence that platelets recruited by CTCs occasionally promote CTC extravasation (Foss et al. 2020; Labelle et al. 2014; Schumacher et al. 2013). Dense granule-derived ATP released from tumor cell-activated platelets acts on endothelial junctions and the cytoskeleton, mediated by $P2Y_2$ receptors and with the objective of opening the endothelial barrier to facilitate transendothelial migration and metastasis (Schumacher et al. 2013). Upon activation by ATP, the G-protein coupled $P2Y_2$ receptor leads to (1) Ca^{2+} release from intracellular stores via stimulation of phospholipase Cβ including the generation of IP3 (Raqeeb et al. 2011) and (2) activation of the PKC/Src pathway (Bilbao et al. 2010). The activated $P2Y_2$ transiently associates with VEGFR-2 and VE-cadherin at endothelial cell–cell adhesions

while Src phosphorylates VEGFR-2, VE-cadherin, VE-cadherin-bound p120-catenin, and probably also β- and γ-catenins in order to ensure a coordinated release of endothelial adherens junctions (Liao et al. 2014; Liu et al. 2004; Seye et al. 2004; Zou et al. 2015). Subsequent binding of p120-catenin to the guanine nucleotide exchange factor Vav2 activates Rac1 (Valls et al. 2012) which may induce cytoskeletal rearrangements to further facilitate the passage of CTCs through the newly formed intercellular space (Liao et al. 2014; Spindler et al. 2010). At the same time, the $P2Y_2$ mediated Ca^{2+} release from intracellular stores results in the activation of SK_{Ca} and IK_{Ca} channels. The concomitant membrane hyperpolarization causes additional Ca^{2+} influx via store-operated channels (SOCs, consisting mainly of TRPC1 & 4 and requiring TRPC4 subunits (Cioffi et al. 2005)) further promoting K_{Ca} channel activity (Raqeeb et al. 2011; Sheng and Braun 2007). The elevated cytosolic Ca^{2+} concentration also stimulates the activities of CaM (calmodulin) and eNOS (endothelial nitric oxide synthase) which considerably contributes to the increase in endothelial permeability (Sheng and Braun 2007; Thibeault et al. 2010). On the whole, CTCs usurp the physiological mechanism by which platelets assist neutrophils in extravasating at inflamed sites. Although a number of ion channels and transporters passing Ca^{2+} and K^+ are involved, they just fulfill their regular functions. In this context, their expression and activity cannot be considered to be pathophysiological so that they are barely usable as therapeutic targets. The actual pathological step is the platelet activation by CTCs via either direct physical interaction between mucin-like glycoprotein podoplanin or galectin on the CTC cell surface and CLEC-2 or glycoprotein VI on the platelet surface, respectively, or via ADP, thromboxane A2 or high-mobility group box 1 (HMGB1) released by the CTC to bind to the toll-like receptor 4 (TLR4) on the platelet (Schlesinger 2018).

In addition, the podoplanin, expressed on tumor cell surfaces, stimulates the release of TGFβ from platelets (Takemoto et al. 2017). The TGFβ then activates Smad and NF-κB signaling pathways in the tumor cells leading to a more mesenchymal and invasive phenotype which may contribute to extravasation (Labelle et al. 2011).

4.1.2 Neutrophils

Although neutrophils are known to play pro-metastatic roles, their short half-life makes it difficult to precisely analyze the underlying mechanisms. Nevertheless, it has been shown that granulocyte-colony stimulating factor (G-CSF) mediates conversion of neutrophils into immunosuppressive cells that block the antitumor functions of $CD8^+$ T (Coffelt et al. 2015, 2016) and NK cells (Spiegel et al. 2016). Furthermore, platelets promote tumor cell extravasation indirectly by recruiting granulocytes specifically to the vicinity of platelet/tumor cell aggregates. To this end, tumor cell-activated platelets release CXCL5 and CXCL7 both of which bind to CXCR2 chemokine receptors on granulocytes co-expressing granulocyte marker Ly6G, integrin α-M (=CD11b), and matrix metalloproteinase 9 (MMP9) (Labelle et al. 2014). Releasing MMPs 8 and 9, neutrophils facilitate extravasation by

disintegrating the extracellular matrix such as the basement membrane (Cools-Lartigue et al. 2014; Spiegel et al. 2016). The tumor-activated platelets can also trigger neutrophil degranulation including the formation of neutrophil extracellular traps (NETs) (Cedervall et al. 2018). NETs are netlike structures that (1) consist of expelled neutrophil DNA with associated proteolytic enzymes, (2) function as a pathogen trap, and (3) can also sequester circulating tumor cells and thus promote local adhesion and metastasis (Cools-Lartigue et al. 2013; Demkow 2021; Park et al. 2016). The capture of CTCs in NETs can be mediated by NET-associated β1-integrin or CEACAM1 (carcinoembryonic Ag cell adhesion molecule 1) as shown for lung (A549; Najmeh et al. 2017) and colorectal cancer (HT-29, MC38; Rayes et al. 2020) cells. Accordingly, preventing the formation of NETs or disintegrating them by application of DNase I-coated nanoparticles reduces lung metastases in mice (Park et al. 2016), and impeding NET formation with the peptidylarginine deiminase 4 (PAD4) inhibitor BMS-P5 can slow down the progression of multiple myeloma in mice and humans (Li et al. 2020).

4.1.3 Monocytes/Macrophages

In addition to neutrophils and platelets, monocytes/macrophages contribute to CTC extravasation as well. Metastatic CTCs recruit monocytes/macrophages to the site of extravasation by releasing the CC-chemokine ligand 2 (CCL2) which attracts circulating monocytes expressing CC-receptor 2 (CCR2) and 6C2 (LY6C; in mice) or $CD14^{high}CD16^{negative}$ (in humans) (Cassetta and Pollard 2018; Qian et al. 2011), or indirectly by inducing local endothelial activation which results in E-selectin expression (Häuselmann et al. 2016). The endothelial E-selectin mediates the adhesion of the attracted monocytes to the endothelium, and the bond between E-selectin and its ligand triggers signaling in both the monocytes and the endothelial cells, eventually leading to (1) a stronger, integrin-mediated adhesion, (2) the retraction of endothelial cells, and (3) a subsequent loosening of the endothelial tight junctions through de-phosphorylation of VE-cadherin (Häuselmann et al. 2016). Beyond that, extravasated monocytes in the underlying tissue can differentiate into metastasis-associated macrophages, which then release VEGF to increase vascular permeability and thus promote tumor cell extravasation (Cassetta and Pollard 2018; Qian et al. 2009, 2011).

5 Organotropism

Already in 1889, Stephen Paget postulated that metastasis formation requires both cancer cell-intrinsic properties (“seed”) and a congenial microenvironment (“soil”) (Paget 1989). Accordingly, different cancers show different preferences with regard to the organs they metastasize to (Gao et al. 2019). Renal, thyroid, and liver cancer cells metastasize preferentially to the lungs; ovarian, colon, and gastric cancer cells

to liver and peritoneum; pancreatic cancer cells to lungs and liver; lung cancer cells to bone and brain. Breast and prostate cancer share the same preferences with the highest incidence of metastases in bone and lungs. In addition, breast cancer often metastasizes to liver and brain. Melanoma can be considered an all-rounder because it spreads nearly everywhere with the highest incidences of metastases in lungs, liver, brain, bone, and peritoneum (Gao et al. 2019). CTCs can also colonize the primary tumor, i.e. their tumor or origin. This process, called "tumor self-seeding," may select for cancer cells that are more aggressive than those originally in the primary tumor, and may – at least partly – explain local recurrence after tumor excision (Kim et al. 2009). However, it needs to be stated that so far there is not sufficient clinical evidence to substantially support this concept.

Independently of different cancer types' preferences including the unique characteristics of each target organ, they share a number of general principles underlying organotropism (Gao et al. 2019). At first, a premetastatic environment is formed. Both soluble factors and exosomes containing (mi)RNA are released from the primary tumor. They interact directly with cells residing at a prospective metastatic site. At the same time, they trigger the release of progenitor cells from bone marrow and conduct their target-oriented travel to a prospective metastatic site. Thus, the soluble factors and exosomes released by the primary tumor in combination with bone marrow-derived cells are significantly involved in arranging the premetastatic niche for later colonization (Fig. 1a; Izraely and Witz 2021; Wang et al. 2021).

In a second step, CTCs are then decoyed into this premetastatic niche by inflammatory chemokines released from local cells (Moore 2001; Zlotnik et al. 2011).

5.1 Locally Released Chemokines Lure CTCs

The involved chemokine receptor-ligand pairs include, among others, CXCR1/2-CXCL8 (Ha et al. 2017; Li et al. 2014), CXCR4-CXCL12 (Guo et al. 2016; Iwasa et al. 2009; Müller et al. 2001), CCR6-CCL20 (Ghadjar et al. 2006; Kadomoto et al. 2020), and CCR7-CCL21 (Mashino et al. 2002; Rizeq and Malki 2020). Thus, in patients with axillary node positive primary breast cancer, the expression of chemokine receptors determines the target organ of metastasis. CXCR4 expression increases the risk of metastasis to the liver, CX3CR1 expression favors metastasis to the brain, CCR6 expression causes metastasis to the pleura, and CCR7 expression can be associated with the occurrence of skin metastases (André et al. 2006).

Lung tropism of osteosarcoma is mediated primarily by CXCL8 and IL-6 (Gross et al. 2018). CXCL8 triggers the release of Ca^{2+} from intracellular stores (Joseph et al. 2010) and causes phosphorylation of Akt and Erk1/2 (Hosono et al. 2017), i.e. two signaling pathways known to drive cell migration and invasion. To date, ion channels and transporters potentially involved in this CXCR1/2-CXCL8-dependent organotropic process, such as K^+ or Ca^{2+} channels, have not been identified.

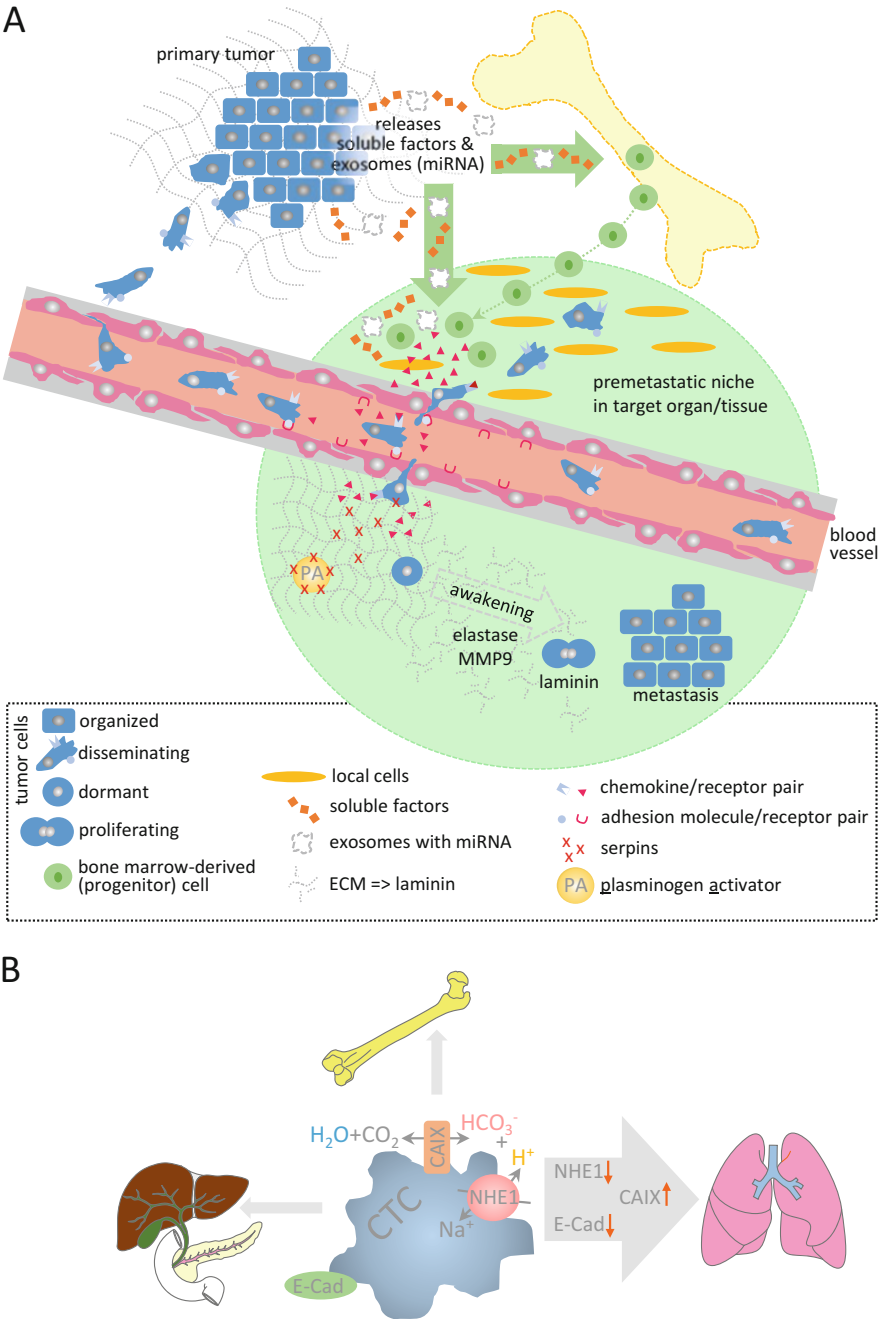

Fig. 1 Major steps and known factors in organotropism. (**A**) The primary tumor releases soluble factors and miRNA-containing extracellular vesicles and exosomes that arrive at prospective target organs/tissues and at the same trigger the release of progenitor cells from bone marrow. A premetastatic niche is established by a concerted action of the bone marrow-derived cells, exosomes, and soluble factors from the primary tumor, and, not shown for the sake of clarity,

5.1.1 CXCL12/CXCR4

Another example is CXCL12 (= stromal cell-derived factor 1 (SDF-1)) which is preferentially expressed in lung and liver and thus attracts CXCR4-carrying melanoma, breast cancer (Minn et al. 2005; Müller et al. 2001), and pancreatic cancer cells (Saur et al. 2005). Interestingly, the water/glycerol channel aquaporin-3 (AQP3) is required for CXCL12/CXCR4-dependent, directional breast cancer cell migration, including spontaneous metastasis of orthotopic xenografts to the lungs (Satooka and Hara-Chikuma 2016). CXCL12 induces the membrane NADPH oxidase 2 (Nox2) to generate H_2O_2. H_2O_2 then enters the breast cancer cell through AQP3. It oxidizes the phosphatases PTEN (phosphatase and tensin homolog) and PTP1B (protein tyrosine phosphatase 1B), resulting in the activation of the Akt pathway which drives directional cell migration (Satooka and Hara-Chikuma 2016). Similarly, CXCL12-activated Akt and Erk1/2 pathways propel endothelial colony-forming cell (ECFC) migration, homing and incorporation into neovessels, thus re-establishing perfusion in ischemic tissues and promoting tumor vascularization and metastasis (Zuccolo et al. 2018). The activation of the Akt and Erk1/2 pathways requires a CXCL12-induced increase in the intracellular Ca^{2+} concentration which is initiated by an $InsP_3$-mediated Ca^{2+} release from the ER and maintained by subsequent store-operated Ca^{2+} entry across the plasma membrane (SOCE) (Zuccolo et al. 2018).

In invasive glioblastoma, CXCL12 causes the activation of $K_{Ca}3.1$ (IK_{Ca}; KCNN4) channels including their long-term functional upregulation. $K_{Ca}3.1$ channel activity mediates glioblastoma cell migration and chemotaxis depending on CXCR4 expression (Sciaccaluga et al. 2010). Accordingly, a combined, simultaneous use of the anti-fungal $K_{Ca}3.1$ blocker clotrimazole, the CXCR4 inhibitor plerixafor (AMD3100), and the histamine 1 (H1) receptor antagonist mirtazapine has been suggested for cytotoxic glioblastoma treatment. The H1 receptor needs to be inhibited because it also can mediate $K_{Ca}3.1$ activation and thus represents a potential bypass of CXCR4 inhibition (Kast 2010).

$K_v11.1$ (hERG) channels mediate CXCL12/CXCR4-stimulated migration and invasion in leukemia cells (Li et al. 2009). In their plasma membranes, $K_v11.1$, CXCR4 and β1 integrin assemble to form a multiprotein complex (Pillozzi et al.

Fig. 1 (continued) local fibroblasts, mesenchymal stem cells, neutrophils, and macrophages. Chemokines released by local cells decoy the circulating tumor cells into the premetastatic niche, supported by specific, local adhesion events at the endothelial surface often mediated by selectins or integrins. Once in the target tissue, single tumor cells can fall dormant and eventually be woken up by the presence of extracellular matrix components such as laminin emerging from locally induced extracellular matrix digestion events. Metastasizing tumor cells can also repulse local attacks, for instance by releasing serpins to prevent the plasminogen activator (PA) from generating plasmin which otherwise would lead to the release of apoptosis-inducing soluble Fas Ligand. (**B**) Circulating tumor cells (CTCs) such as metastasizing melanoma, breast or pancreatic cancer cells are directed predominantly to the lungs when their NHE1 activity is reduced, their CAIX expression is high, or when E-cadherin expression is low. Please see text for additional, more detailed information

2011). Targeting CXCL12 or the CXCL12/CXCR4 axis with peptides and small molecules induces pro-apoptotic effects and may thus help to overcome chemoresistance in leukemia that is induced by CXCL12-releasing bone marrow mesenchymal stromal cells (Pillozzi et al. 2019).

5.1.2 CCL20/CCR6

In general, the CCL20 chemokine/CCR6 chemokine receptor pair contributes to cancer cell motility and metastasis (Korbecki et al. 2020). This has been shown for breast cancer (Muscella et al. 2017), prostate cancer (Ghadjar et al. 2008), ovarian cancer (Liu et al. 2020), lung cancer (Wang et al. 2016), esophageal squamous cell carcinoma (Liu et al. 2017), gastric cancer (Han et al. 2015), pancreatic cancer (Campbell et al. 2005; Kimsey et al. 2004), hepatocellular carcinoma (Huang and Geng 2010), colorectal cancer (Frick et al. 2016), and renal cell carcinoma (Kadomoto et al. 2019).

In patients with primary lung cancer, the production of CCL20 in adrenal glands is most likely to recruit CCR6-expressing lung cancer cells which then leads to the development of adrenal metastases (Raynaud et al. 2010).

Multiple myeloma cells trigger the upregulation of both CCL20 and CCR6 in the bone microenvironment and thus contribute to osteoclast formation and eventually to osteolytic bone lesions (Giuliani et al. 2008).

The expression of CCL20 within the periportal area of the liver is likely to attract CCR6 expressing colorectal cancer (CRC) cells (Dellacasagrande et al. 2003; Frick et al. 2016). Accordingly, liver metastases can be found in approximately 50% of CRC patients (Jemal et al. 2008). Here, too, as described above for the CXCR1/2-CXCL8 and the CXCR4-CXCL12 pairs, Erk1/2 and Akt signaling pathways are activated and promote proliferation and motility of CRC cells (Brand et al. 2006). Furthermore, CCL20 stimulation of CCR6 expressing human colon carcinoma cells causes phosphorylation of BCAR1/p130^{Cas} (Yang et al. 2005), a scaffolding protein overexpressed also in breast, ovarian, prostate, lung, and colorectal cancers as well as in hepatocellular carcinoma, glioma, melanoma, anaplastic large cell lymphoma, and chronic myelogenous leukemia (Barrett et al. 2013). BCAR1/p130^{Cas} is a key component of the pathway by which the focal adhesion kinase (FAK) can drive cell migration (Tikhmyanova et al. 2010). In a monolayer of polarized human colon adenocarcinoma cells, CCR6 stimulation has been associated with cAMP-stimulated electrogenic chloride secretion as CCL20 inhibits forskolin-stimulated cAMP production (Yang et al. 2005). The nature of ion transporters and channels possibly involved has not yet been identified. A potential candidate would be the cAMP-dependent CFTR (cystic fibrosis transmembrane conductance regulator). NKCC1 (Na^+, K^+, $2Cl^-$ cotransporter 1) could also be involved. NKCC1 activity is sensitive to cytoskeletal dynamics (Hecht and Koutsouris 1999; Matthews et al. 1994), and the BCAR1/p130^{Cas}, phosphorylated in response to CCL20 stimulation, associates with cytoskeletal complexes (Sawada et al. 2006; Defilippi et al. 2006) and could thus be an integrative module linking NKCC1 activity with cytoskeletal dynamics.

5.1.3 CCL19 and 21/CCR7

The CCL21/CCR7 chemokine axis contributes to a metastatic phenotype in a wide variety of cancer types (Rizeq and Malki 2020), including breast (Müller et al. 2001; Weitzenfeld et al. 2016), prostate (Maolake et al. 2018), urinary bladder (Xiong et al. 2017), cervical (Kodama et al. 2007), esophageal (Shi et al. 2015; Goto and Liu 2020), gastric (Ma et al. 2015; Ryu et al. 2018), pancreatic (Hirth et al. 2020; Zhang et al. 2016b), colorectal (Li et al. 2011b), and lung cancer (Zhong et al. 2017), as well as melanoma (Cristiani et al. 2019; Takeuchi et al. 2004), lymphoma (Fleige et al. 2018; Li et al. 2018; Yang et al. 2011), and oral, head, and neck squamous cell carcinoma (Chen et al. 2020; González-Arriagada et al. 2018).

Generally, the binding of CCL19 and CCL21 to the GPCR CCR7 induces the activation of a G_{α}-subunit and a $Gi_{\beta\gamma}$ heterodimer which then triggers downstream signaling effectors and signaling cascades. As a result, the activation of ERK1/2, PI3K/Akt, Rho GTPases, MAPK, and JAK/STAT can lead to the transcription and expression of different genes including MMPs and thus promote chemotaxis, cytoskeletal remodeling, extracellular matrix degradation, cell adhesion, migration, invasion, angiogenesis, and proliferation (Rizeq and Malki 2020). To date, it has not been shown explicitly that CCL19, 21/CCR7 mediated changes in tumor cell behavior involve ion channels and transporters. However, the signaling pathways sparked by CCR7 stimulation most likely address ion transport mechanisms as well, also in tumor cells. In CCR7 expressing mature dendritic cells, CCL19 and CCL21 trigger Ca^{2+} influx from the extracellular space. This Ca^{2+} influx is accompanied by KCa3.1 mediated K^+ efflux and, in presence of a yet undefined Cl^- conductance, propels cell migration (Shao et al. 2015).

5.2 *Given Factors at the Premetastatic Niche*

In addition to being attracted by chemokines CTCs can be retained at the premetastatic niche by specific, local adhesion events. E-selectin, for instance, supports hematogenous metastasis of estrogen-receptor negative (ER^-) $CD44^+$ breast cancer cells (Kang et al. 2015). Furthermore, characteristic vascular structures in target organs are associated with special requirements for cancer cell extravasation (Gao et al. 2019; Minami et al. 2019; Nguyen et al. 2009; Weidle et al. 2016), so that the particular architecture of a blood barrier, typical of an organ or a tissue, may select for cancer cells that are able to break down the local endothelial junctions and the appendant basement membrane. This interplay between metastasizing cell and local environment is continued by the cancer cells' interaction with the unique resident cells and their secretome including the extracellular matrix. However, the initiation of proliferation and growth in the secondary organ appears to be another obstacle for disseminating tumor cells (Chambers et al. 1995).

5.2.1 Falling Asleep and Awakening

Some of the disseminating tumor cells enter a dormant phase, induced by a lack of a sufficient, integrin-mediated adhesion to the extracellular matrix in the secondary organ (Barkan et al. 2010). In order to survive without proper anchorage, detached breast cancer cells autocrinally secrete laminin-5, a component of the basement membrane, which induces their own survival through α6β4-mediated NFκB activation (Zahir et al. 2003). As soon as the biomolecular composition of the surrounding microenvironment changes, for example by the release of membrane receptor-ligands from a locally degrading extracellular matrix or by inflammatory events, dormant cancer cells can be awakened by induction of various signaling pathways leading to the revival of proliferative activity (Park and Nam 2020). Sustained lung inflammation, for instance, can provoke the formation of neutrophil extracellular traps (NETs). Two NET-associated proteases, neutrophil elastase and MMP9, then successively fragment laminin, and the proteolytically remodeled laminin awakens dormant breast cancer cells (Fig. 1a), i.e. induces their proliferation, by activating α3β1 signaling (Albrengues et al. 2018).

5.2.2 Local Nutrient Supply

Furthermore, the nutrient composition in the target organ may differ considerably from that around the primary tumor and thus force the disseminating tumor cells to adapt their metabolic pathways to the new environment (Elia et al. 2018). Accordingly, brain metastases originating from various tissues drive their oxidative TCA cycle utilizing acetate rather than glucose or glutamine (Maher et al. 2012; Mashimo et al. 2014), and breast cancer-derived lung metastases change over to a pyruvate carboxylase-dependent replenishment of the TCA cycle (anaplerosis) due to an elevated bioavailability of pyruvate in the lung environment (Christen et al. 2016).

5.2.3 Defeating the Local Defense System

On the other hand, tumor cells are capable of repulsing attacks by the tissues that they are going to populate. Normally, plasmin from the reactive brain stroma represents a defense against metastatic invasion. Plasmin is generated from plasminogen by plasminogen activator (PA) which in brain is released mainly by astrocytes. Plasmin cleaves off soluble Fas Ligand (sFasL) from the membrane-bound FasL, also expressed on astrocytes. The sFasL then induces apoptosis in metastatic cells and inactivates the axon pathfinding molecule L1CAM, a cell adhesion molecule expressed by metastatic cells for spreading along brain capillaries and for metastatic outgrowth. However, metastasizing breast and lung adenocarcinoma cells express high levels of PA inhibitory serpins (serin-protease inhibitors) to

prevent plasmin generation and thus its metastasis-suppressive effects (Valiente et al. 2014).

5.3 *Lack of E-Cadherin, Reduced NHE1 Activity, and the Presence of CAIX Each Contribute to Lung Tropism*

The epithelial-mesenchymal transition (EMT) does not only confer on epithelial cells the abilities to detach from the cell layer/tissue, migrate, invade the surrounding tissue and degrade components of the extracellular matrix (Lambert et al. 2017), but it can also play a considerable role in metastatic organotropism as shown for pancreatic cancer (Reichert et al. 2018). One characteristic of EMT is a decreased expression of E-cadherin, the main component of adherens junctions. Adherens junction protein p120 (P120CTN) stabilizes E-cadherin at the adherens junctions (Ishiyama et al. 2010; Thoreson et al. 2000). A complete loss of *p120ctn* in metastatic pancreatic ductal adenocarcinoma (PDAC) cells shifts their organotropic preference from the liver to the lungs. Rescue with a p120ctn isoform restores liver organotropism (Reichert et al. 2018). According to this, and independently of the presence of P120CTN, E-cadherin-expressing PDAC cells prefer to metastasize to the liver while E-cadherin-negative metastases are found predominantly in the lungs (Fig. 1b; Reichert et al. 2018). Analogously, the inhibition of NHE1 by cariporide seems to direct the metastatic spread of murine melanoma (B16V) cells to the lungs (Vahle et al. 2014). NHE1 activity is affected by the NHE regulatory factor (NHERF1), and NHERF1 expression is upregulated in a variety of cancers where its expression level correlates with malignancy (Georgescu et al. 2008; Greco et al. 2019; Ma et al. 2016; Saponaro et al. 2014; Vaquero et al. 2017). The phosphorylation state of NHERF1 on serines S279 and S301 differentially controls NHE1 activity and metastatic organotropism of breast cancer (MDA-MB-231) cells (Greco et al. 2019). Replacing both S279 and S301 by alanine results in a significantly increased NHE1 activity and, in a xenograft mouse model, drives a shift from the predominantly lung colonization to a predominantly bone colonization. This led the authors (Greco et al. 2019) to conclude that NHERF1 phosphorylation can act as a signaling switch in metastatic organotropism.

Also the carbonic anhydrase IX (CAIX) contributes indirectly to organotropism (Fig. 1b). Bone marrow-derived cells (BMDCs), including myeloid-derived suppressor cells (MDSC), macrophages, dendritic cells, and hematopoietic progenitor cells are recruited to potential metastatic sites where they act in concert to establish the premetastatic niche prior to the arrival of metastasizing tumor cells (Gabrilovich et al. 2012; Kaplan et al. 2005; Psaila and Lyden 2009; Quail and Joyce 2013). The production of chemokines and cytokines that mobilize granulocytic MDSCs to a potential (pre)metastatic niche requires the hypoxia-induced expression of CAIX by cancer cells in the (primary) tumor (Chafe et al. 2015). Hypoxic breast cancer cells

express significant amounts of CXCL10, CCL5, and the granulocyte colony stimulating factor G-CSF when, and only when, CAIX is expressed. Hypoxia-induced CAIX is needed for the activation of the NF-κB pathway which then results in the generation of G-CSF and eventually promotes breast cancer metastasis to the lungs (Chafe et al. 2015).

6 Conclusion and Outlook

Even though there is hardly any direct evidence proving it, the literature suggests that ion channels and transporters do contribute to both extravasation and organotropism of metastasizing tumor cells. Table 1 summarizes the channels and transporters potentially involved in (1) surviving the intravascular milieu, (2) adhesion to the vessel wall, (3) extravasation, and (4) metastatic organotropism.

NHE1 may be considered as a kind of "all-rounder" due to its dual function. (1) In its role as a structural element contributing to the organization of the cortical actin cytoskeleton and tying it to the plasma membrane, NHE1 possibly protects CTCs from mechanical stress. (2) In its role as H^+ extruder, NHE1 may promote both CTC adhesion to the vessel wall and subsequent, organ-specific extravasation by generating pH-nanodomains that modulate not only pH-dependent cell–substrate and MCAM-mediated cell–cell (melanoma-endothelium) adhesions but also the activity of matrix metalloproteases. Finally, there is evidence to suggest that NHE1 activity, regulated by NHERF1, has a hand in organotropism.

Regulation of the intracellular Ca^{2+} concentration $[Ca^{2+}]_i$ is interwoven with the modulation of K^+ conductances. K^+ channels including mechanosensitive K2P channels stabilize the membrane potential required for Ca^{2+} influx, e.g. through mechanosensitive channels (TRPs, Piezo), while increases in $[Ca^{2+}]_i$ activate Ca^{2+} sensitive K^+ channels (K_{Ca}s). This interplay, especially the controlled Ca^{2+} influx, may strengthen the actin cortex of CTCs, accompanied by an increase in cortical stiffness, and thus protect them from shear forces in the blood vessels. In endothelial cells, an elevation of $[Ca^{2+}]_i$ (1) can be induced by binding of ATP released from tumor cell-activated platelets to endothelial $P2Y_2$, (2) is mediated by SOC channels, and (3) results in an increased endothelial permeability which facilitates extravasation (Table 1).

In addition to pH and Ca^{2+} including the affected signaling pathways (e.g., Ca^{2+}/CaM signaling), the FAK signaling and the Akt pathway are major variables being modulated by ion channels/transporters and involved in organotropism and surviving the intravascular milieu. Permanent activation of FAK can prevent anoikis. Some CTCs secrete fibronectin or collagen and thus "autostimulate" their β1 integrin leading to activation of $K_v11.1$ concomitant with FAK phosphorylation. Another mechanism by which CTCs avoid anoikis is the adoption and perpetuation of mesenchymal features with the help of the Zn^{2+} transporter ZIP6.

AQP3 in cooperation with the Akt pathway is likely to play a role in organotropism by directing CXCR4 expressing breast cancer cells to the lungs

Table 1 Involvement of ion channels/transporters in CTC survival, extravasation, and organotropism

		Ion channel/transporter	Function/mechanism
Surviving intravascular milieu	Mechanical stress	TRPs & PIEZO (mechanosensitive)	Ca^{2+} influx => cell stiffness↑ => strengthens cell cortex => protects plasma membrane from shear stress damage
		Mechanosensitive two-pore K^+ channels (K2P)	Stabilize the electro-chemical gradient required for Ca^{2+} influx
		NHE1	Expression↑ => cortical stiffness↑
	Anoikis	$K_v11.1$ (hERG, KCN2)	β1 integrin, stimulated by self-secreted fibronectin or collagen, activates $K_v11.1$ which is essential for FAK-phosphorylation
		ZIP6 (Zn^{2+} transporter, SLC 39A6)	$[Zn^{2+}]_i$ ↑=> GSK-3β↓ => E-cadherin↓ => EMT↑ => anoikis↓
		CLCA2 (Cl^- channel *accessory*)	↓Expression => proliferation↑, motility↑, metastasis↑
Adhesion to vessel wall		NHE1	Regulation of cell surface pH => pH affects cell-cell adhesion => homophilic interaction between MCAM expressed on melanoma *and* endothelial cells↑
Extravasation		SOC (TRPC1 & 4) channels and K_{Ca}s *of endothelial* cells	ATP released from tumor cell-activated platelets binds to endothelial $P2Y_2$ => $[Ca^{2+}]_i$↑ => K_{Ca} activity↑, CaM activity↑, eNOS activity↑ => endothelial permeability↑
Organotropism		AQP3	CXCL12 activates Nox2, Nox2-generated H_2O_2 enters via AQP3 & oxidizes PTEN & PTP1B => Akt pathway ↑ => cell migration => CXCR4 carrying breast cancer cells directed to the lungs
		? CFTR and/or NKCC1 ?	CCL20 in periportal area attracts CCR6 expressing CRC cells to the liver 1. CCL20/CCR6 affects cAMP-stimulated electrogenic Cl^- secretion => CFTR? 2. CCL20/CCR6 => phosphorylation of BCAR1/$p130^{Cas}$ => affects FAK pathway & cytoskeleton => NKCC1 activity sensitive to cytoskeletal dynamics
		NHERF1/NHE1 axis	• NHE1 inhibition with cariporide directs metastasizing melanoma to the lungs • NHE1 activation by modified NHERF1-phosphorylation state shifts metastatic breast cancer spread from lungs to bone

Please bear in mind that several of these interrelations have not been shown directly and, therefore, are partially hypothetical. Please see text for more details
↑ = stimulation; ↓ = inhibition; => = causal connection

where local CXCL12 stimulates H_2O_2 production via membrane-bound Nox2. H_2O_2 crosses the plasma membrane through AQP3 in order to activate the Akt pathway by oxidizing PTEN and PTP1B which eventually stimulates directional cell migration.

Altogether the literature strongly suggests that several ion channels and transporters have a hand in CTC survival, extravasation, and organotropism, which points to their potential usefulness as therapeutic target(s) during and after resection of the primary tumor. Given the great potential to be exploited as therapeutic targets on the one hand, yet the insufficient hitherto existing knowledge and unsatisfying data availability on the other, it becomes apparent that far more efforts need to be made in order to identify and characterize the mechanistic roles of ion channels and transporters in the behavior of CTCs including extravasation and organotropism. Provided that an experimental setting includes chemokines, extracellular matrix (proteins and structure), and preferably also immune cells typically found in the organ of interest, advanced microfluidic models of cancer cell extravasation (Mondadori et al. 2020; Offeddu et al. 2021) may be a suitable tool to validate the involvement of ion channels/transporters in extravasation and organotropism, e.g. by using genetically modified tumor cell lines, and to test their responsiveness to antimetastatic drugs.

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