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Review Article

An Overview of Metastatic Organotropism: Mechanisms and Emerging Therapeutic Targets

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Abstract

The main cause of cancer-related mortality is metastasis, which is the spread of tumor cells from their initial location to distant sites in the body. The process is not random but follows a distinct pattern of organotropism, in which certain cancers preferentially colonize distant sites. For example, estrogen-positive breast cancer may metastasize to the bones or colorectal cancer to the liver. Understanding the molecular drivers of organotropism is critical for developing effective therapies. This work combines the traditional "seed and soil" theory with modern molecular discoveries to provide a thorough overview of the current mechanistic framework underlying metastatic organotropism. We describe the multistep journey of circulating tumor cells, emphasizing key determinants such as the intrinsic properties of cancer cells, the creation of a favorable pre-metastatic niche, the interactions between disseminated cells and the microenvironment, and the role of the immune system in metastasis. We discuss organ-specific strategies aimed at disrupting the metastatic cascade, including targeting niche-forming pathways, intercepting cancer cell adhesion and modulating the immune microenvironment. Finally, we outline future challenges and opportunities, emphasizing the need for advanced models and integrative multi-omics to underscore the shifting therapeutic paradigm from late-stage generalized treatment to early targeted prevention of metastasis.

Keywords: Dormancy, Metastasis, Organotropism, Pre-metastatic niche, Reawakening.

نظرة عامة على تربيولوجيا الأعضاء النقيلية: الآليات والأهداف العلاجية الناشئة

الخلاصة

السبب الرئيسي للوفيات المرتبطة بالسرطان هو النقائل، وهي انتشار خلايا الورم من موقعها الأصلي إلى مواقع بعيدة في الجسم. العملية ليست عشوائية بل تتبع نمطا مميزا من التربيولوجيا العضوية، حيث تستعمر بعض أنواع السرطان المواقع البعيدة بشكل أفضل. على سبيل المثال، قد ينتقل سرطان الثدي الإيجابي للهرتروجين إلى العظام أو سرطان القولون والمستقيم إلى الكبد. فهم المحركات الجزيئية للتربيولوجيا العضوية أمر بالغ الأهمية لتطوير علاجات فعالة. يجمع هذا العمل بين نظرية "البذور والتربة" التقليدية مع الاكتشافات الجزيئية الحديثة لتقديم نظرة شاملة على الإطار الميكانيكي الحالي الذي يقوم عليه النسيج العضوي النقلي. نوصف الرحلة متعددة الخطوات لخلايا الورم المتداولة، مع التركيز على المحددات الرئيسية مثل الخصائص الجوهرية لخلايا السرطان، وخلق محفظة مناسبة قبل الانتقال، والتفاعلات بين الخلايا المنتشرة والبيئة الدقيقة، ودور الجهاز المناعي في الانتشار. نناقش استراتيجيات خاصة بالأعضاء تهدف إلى تعطيل سلسلة الانتشار، بما في ذلك استهداف المسارات التي تشكل التخصص، واعتراض التصاق خلايا السرطان، وتعديل البيئة الدقيقة المناعية. وأخيرا، نحدد التحديات والفرص المستقبلية، مع التأكيد على الحاجة إلى نماذج متقدمة وتقنيات متعددة تكاملية لتأكيد النموذج العلاجي المتغير من العلاج المعمم في المراحل المتأخرة إلى الوقاية المستهدفة مبكرا من النقائل.

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INTRODUCTION

The dissemination of cancer cells from their original tumor to distant sites in the body is called metastasis and remains the ultimate cause of most deaths, accounting for over 90% of recorded mortalities [1]. Unlike the often-curable primary tumor, metastasis is a systemic disease affecting multiple organs, compromising their functions and eventually leading to death [2–5]. Metastasis involves a cascade of steps in which cells from the primary tumor progressively acquire new traits enabling them to disseminate through the vascular system, the lymphatic systems, or through the direct infiltration of an adjacent structure [6]. Transcellular migration, where the cancer cell is engulfed by another cell, or paracellular, where the cancer cell is transported in the space between cells, are other reported routes of migration [7]. The sequence of steps in the metastatic process, illustrated in Figure 1, involves the initial local invasion of the primary tumor cells into the surrounding tissues. Tumors can release millions of cells daily, and some tumors can initiate this step at a relatively early stage in their development [8]. Metastasis, in general, is an inefficient process, and fewer than one in 5000 primary tumor cells succeed in generating eventual macroscopic metastases. This is partly due to the attrition that cancer cells suffer in confronting various stresses in their journey to the distant site [8,9]. The main vehicle of metastasis is blood circulation, and it will be our focus in this narrative review (Figure 1) [10].

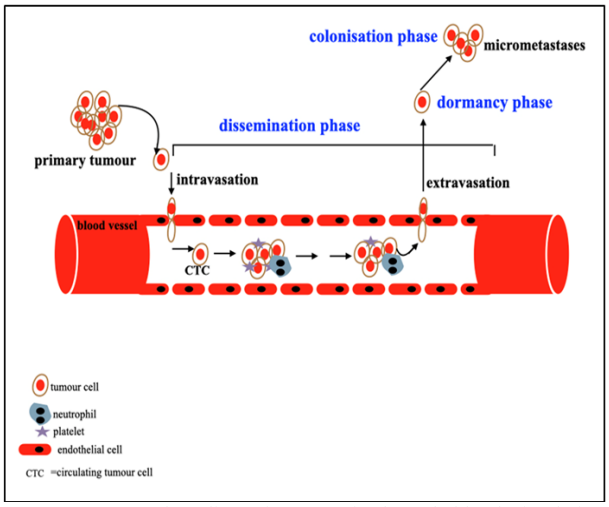

Figure 1: General outline of metastasis through blood circulation. Tumour cells undergo three distinct phases: dissemination, dormancy, and colonization before they grow into detectable micrometastases. Tumour cells often travel in clusters with other cells for support and protection

The detachment step is then followed by intravasation, transit, arrest, and extravasation through the vascular walls into distant tissues. Those cells that have survived the stresses and the strange environment so far will participate in the formation of a micro-metastatic colony, which subsequently proliferates into clinically detectable metastases [3,11]. The interplay between cancer cells and the microenvironment of the target organ is at the core of the metastatic cascade, which involves numerous cytokines, growth factors, and signaling pathways [12]. These mediators bestow on cancer cells the ability to adopt different phenotypic states and co-opt their surrounding immune and stromal cells to support their growth and evade detection [2]. The varying degree of interactions between cancer cells and the microenvironment, in addition to tumor cell-intrinsic factors, can result in metastasis following a non-random distribution among distant organs, called organotropism or organ-specific metastasis [13]. This was recognized in the original theory of metastasis proposed by Stephen Paget in 1889 as the "seed and soil" hypothesis, where the seeds are the cancer cells and the soil is the metastatic organ. Different cancer types and subtypes show distinct organotropism, illustrated in Figure 2. For instance, prostate cancer often metastasizes to the bones, while uveal melanoma, cancer in the eye's uvea, typically colonizes the liver [14–16]. Breast cancer cells can colonize different organs such as bone, lung, liver, and brain, with certain subtypes having distinct preferences [17,18]. Stomach, pancreatic, gallbladder, and colorectal cancers frequently metastasise to the liver before moving to other secondary sites such as the lungs [19]. Bone, brain, liver, lung, and lymph nodes are the archetypal representative tissues for metastasis, with the liver and lungs being the first organs that circulating tumor cells (CTCs) encounter. Anatomical features can only provide partial support for organotropism, and a non-random pattern of metastasis may be due to a combination of intrinsic genetic differences in cancer cells and molecular/cellular factors in the microenvironment of the target organ. The consensus now is that organotropism is regulated by multiple factors, including tumor-intrinsic factors, circulation patterns, organ-specific niches, and the interactions between cancer cells and the host microenvironment [13]. In this narrative review, we will investigate the drivers of metastatic organotropism and the emerging therapeutic opportunities in targeting these events.

METHODS

Literature searches for this review were confined to the years September 2000–December 2025. Articles were initially examined using the keywords provided above and the search engines PubMed, Google Scholar, Web of Science, and ResearchGate. The initial collection of publications was screened by the author, considering the manuscript's citations and the journal's impact factor. Studies that were deemed to fall outside the scope of this basic narrative review were excluded. Publications before September 2000 were only considered if their content represented a significant and/or historic contribution to the topic.

General Mechanistic Determinants of Organotropism

The early theory of metastasis postulated that hemodynamic forces resulting from the abundant blood flow and the narrow blood vessels are behind the spread of cancer cells to distant organs [20]. However, we know now that the disseminating tumor cells (DTCs) assume a non-random distribution among various recipient organs, illustrated in Figure 2, suggesting the contribution of the receiver tissues to metastasis [13,21-25]. The migration of a primary tumor to distant organs involves many steps that are briefly summarized in the subsequent subsections.

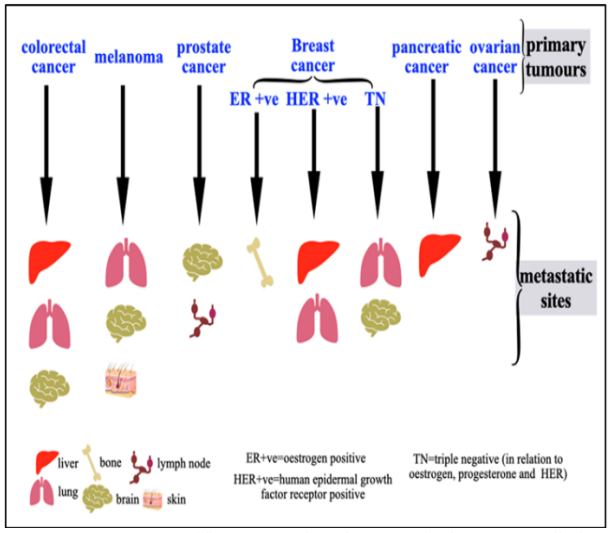

Figure 2: Organ-specific metastasis. The spread of cancer to distinct organs is non-random and influenced by tumour-intrinsic factors as well as interactions between cancer cells and the microenvironment.

Preparing a pre-metastatic niche (PMN)

Where tumor cells secrete extracellular vesicles (EVs) and soluble factors to influence the microenvironment of target tissue [26].

Detachment

Requiring the primary tumor cells to lose proteins that keep the epithelial cells stuck together, such as E-cadherin, and upregulate traits that help migratory mesenchymal cells, such as N-cadherin, vimentin, and fibronectin [27,28]. The disseminated cells must then force their way into a blood or lymphatic vessel through interactions with other constituents of TME [29-31].

Clustering and platelet coating

To enhance DTCs' survival compared to single cells [32]. DTCs' survival is also promoted through the downregulation of antigen presentation, hiding them from being identified as foreign by immune cells [33].

Extravasation

Where surface adhesion molecules, such as integrins and CD44, bind to their complementary molecules, such as selectins, ICAM-1, and VCAM1, on the endothelial cells, causing the DTCs to halt movement. This process is also aided by appropriate signaling between cancer cells and the endothelium [34-37].

Dormancy

Is the clinically silent non-proliferative state that is regulated by a complex interplay between tumor cells and TME. The overexpression of certain genes, such as *KISS1* and *DEC2,* was found to maintain the state of dormancy in melanoma and lung cells, respectively [38,39].

Reawakening

The critical event leads to the often-lethal metastatic disease and is triggered by a change in the balance of the dormancy signals [40]. The preceding mechanistic framework applies, in general, to metastasis from most primary tumors regardless of their type and origin, with organ-specific details given in the following sections.

Liver metastasis

Metastasis to the liver is commonly encountered with a range of primary cancers, including colorectal, breast, and prostate malignancies [41]. The journey of disseminated colorectal cancer cells to the liver is particularly important as it takes place through the portal vein in contrast to other gastrointestinal tract tumor cells, which enter the blood circulation through the hepatic artery [42,43]. Upon the arrival of the DTCs to the liver sinusoidal vessels, the specialized liver capillary network, they encounter resident Kupffer cells (KCs, the liver's primary macrophages) and natural killer cells (NKs), as depicted in Figure 3.

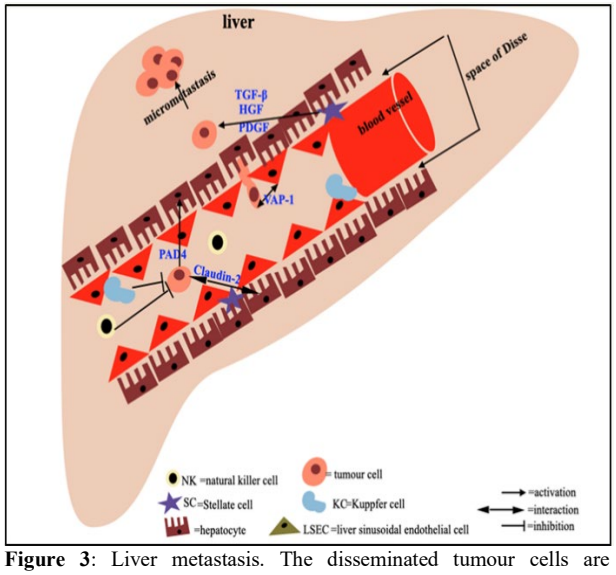

Figure 3: Liver metastasis. The disseminated tumour cells are confronted and attacked by Natural killer cells (NKs) and Kupffer cells (KCs). The enzyme PAD4 appears to be essential for the post-translational modifications of proteins of the extracellular matrix, and metastasis to the liver. Claudin-2, a crucial tight-junction protein, also facilitates interactions between cancer cells and hepatocytes. The docking and extravasation of tumour cells are enhanced by the expression of VAP-1 by the liver sinusoidal endothelial cells. The creation of a suitable niche in the liver is promoted by stellate cells secreting factors such as PDGF, HGF, and TGF-β.

Kupffer cells comprise around 10% of all liver cells and could eliminate tumor cells via phagocytosis. Additionally, the NKs, being also an important part of the immune system, could attack and kill cancer cells that threaten the immune tolerance of the liver. High expression of the receptors CXCR4 by cancer cells and the binding of these receptors to their cognate ligands, CXCL12, expressed by the liver cells, facilitate their recruitment to the liver [44]. Moreover, CD44 V.6 expressed by cancer cells can bind to E-selectin on liver sinusoidal endothelial cells (LSECs), and the common tumor marker carcinoembryonic antigen (CEA) can help cancer cells to stick to Kupffer cells and LSECs [45,46]. Those DTCs that make it through the liver sinusoidal endothelial layer will extravasate into the space of Disse to encounter stellate cells. Several genes are implicated in driving the ability of cancer cells to home in on and colonize the liver. The MET pathway is essential for extravasation and proliferation of DTCs [47]. The MET receptor is activated by the hepatocyte growth factor (HGF), which is produced in large quantities by liver stromal cells. The HGF/MET signaling promotes invasion of cancer cells through matrix degradation. The *MET* gene is frequently overexpressed or amplified in cancers with a high propensity for liver metastasis [48]. The aberrant activation of Wnt/β-catenin is often a hallmark of metastasizing colorectal cancer and hepatocellular carcinoma. Mutations in KRAS and p53 enhancing cancer cells' survival, proliferation, and

invasiveness are strongly associated with aggressive disease and a higher incidence of liver metastases [49,50]. Through transcriptional profiling of breast metastases, Kimbung and colleagues were able to identify 17 tumor-intrinsic factors, mostly involved in cadherin and integrin signaling, favoring liver metastasis [51]. The post-translational modification of the extracellular matrix proteins, where arginine is converted to citrulline, appears to be essential for the growth of liver metastasis [52]. Such citrullination can occur with the help of an enzyme called peptidylarginine deiminase 4 (PAD4), derived from various malignancies. This underpins the DTCs' interactions with the hepatocytes, forming the bulk of the liver and playing an important role in liver tropism [41]. Tabaries and colleagues found that claudin-2 is abundant in liver metastases from breast cancer and not from lung cancer, pointing to the significance of DTC/hepatocyte interactions [53]. Once established in the liver, DTCs will find this organ to be a fertile ground for metastases. Key cellular players include stellate cells, Kupffer cells, and LSECs, as seen in Figure 3.

The stellate cells are normally dormant but are activated by signals from tumor cells to release HGF and collagen, creating a fibrotic niche that protects and nourishes the disseminated cancer cells. Kupffer cells act as a double-edged sword in phagocytosing cancer cells early on, but the malignancy programs them later to secrete factors such as TGF-β and VEGF that promote immunosuppression and angiogenesis [54]. The porous structure of LSECs makes it relatively easy for cancer cells to arrest and extravasate. They also express adhesion molecules such as VAP-1 that facilitate docking. This soil, the liver, is also an immunologically active organ, and DTCs often hijack inflammatory signals, e.g., IL-6/STAT3, to promote their own survival and proliferation while shutting down antitumor immune responses. Prior to the development of liver metastases, the formation of a niche is pivotal in promoting the spread of cancer. Tumor cells secrete EVs carrying factors such as integrins, microRNAs, VEGF, TGF-β, and TNFα. Specific integrins like avβ5 on exosomes determine their organotropism, as in the case of CRC-derived exosomes containing avβ5, helping to home in on Kupffer cells in the liver [55]. Also, miR-21 and miR-122 can prime the liver by promoting inflammation and altering metabolic pathways in hepatocytes [56,57]. Exosomes from pancreatic ductal adenocarcinoma (PDAC) cells can activate Kupffer cells to release TGF-β [58]. The latter triggers stellate cells to produce fibronectin, which in turn stimulates the recruitment of bone marrow-derived macrophages that induce liver metastasis [58]. Liver resident cells can also help the establishment of niches, e.g., stellate cells can secrete growth factors and cytokines such as PDGF, HGF, and TGF-β to degrade the extracellular matrix and establish a suitable microenvironment for the survival and growth of tumor cells [59].

Lung metastasis

The lung is highly prone to metastasis and represents a common target for several primary cancer types, accounting for up to 54% of spreading from primary tumors and the cause of around 30% of metastasis deaths [29]. Although the thin blood/air barrier is advantageous for respiration, its fragility facilitates DTC infiltration [60]. Alveolar type II lung cells, which produce surfactants, can express CXCL12 and CCL2 directly, attracting CXCR4+ and CCR2+ producing cancer cells. The lung fibroblasts are key responders to tumor-derived signals, and once activated, they proliferate and release extracellular matrix proteins and growth factors that support metastatic growth. Minn *et al*. identified a set of genes mediating breast cancer metastasis to the lungs by providing growth advantages to the primary tumor and to its "seeds" in the lung [61]. *KRAS* and *PIK3CA* mutations were also found to be associated with a higher incidence of colorectal cancer metastasis to the lungs [62]. Furthermore, the deletion of *PTEN* led to lung macrometastasis with 100% penetrance in prostate cancer [63]. The ErbB receptors play an important role as a genetic driver of lung metastasis [64]. Breast cancer cells with high levels of these receptors are more likely to metastasize to the lung due to increased motility and proliferation, which are advantageous in the lung microenvironment. Among the homing chemokine drivers that work as the primary navigation system guiding DTCs to the lung, the CXCR4/CXCL12 axis is important, and the ligand, CXCL12, was found to be highly expressed in lung fibroblasts and pneumocytes [65,66]. Lung-associated surface molecules, including endothelial cell adhesion molecules (ECAMs), selectins, and integrins, critically mediate DTCs' trapping in lung tissue (Figure 4).

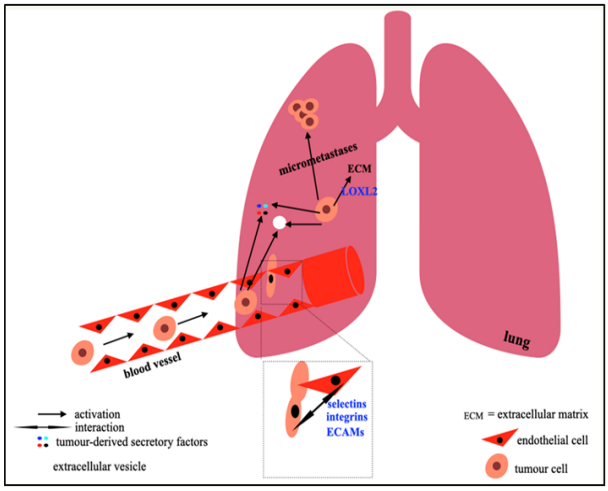

Figure 4: Lung metastasis. Selectins, integrins, and ECAMs mediate disseminated tumour cells (DTCs) trapping and extravasation in lung tissues. Tumour-derived secretory factors and extracellular vesicles play an important part in preparing the lungs for the arrival of DTCs. One of these factors, LOXL2, drives the rearrangement of the extracellular matrix (ECM) and the recruitment of immune cells for further support of the pre-metastatic niche.

The lung endothelial ECAM1 (LU-ECAM1) was identified as a melanoma-specific lung homing factor, and a monoclonal antibody against it led to a 90% reduction in lung colonies with no effect on lung metastasis originating from other primary cancers [67]. E-selectin, a member of the selectin family that also mediates cell adhesion, is expressed in the lung pre-metastatic niche and can preferentially facilitate adhesion and transendothelial migration of breast cancer cells through CD44 binding [68]. Integrins, another group of cell adhesion proteins, can mediate cell/cell or cell/ECM interactions, and melanoma cells expressing integrin β3 are more likely to spread to the lungs [69]. Lysyl oxidase-like 2 (LOXL2), as part of the tumor-derived secretory factors (TDSFs) secreted by hepatocellular carcinoma, forms lung PMN through synergistic mechanisms (Figure 4) [70]. TGF-β produced by macrophages and fibroblasts in the lung promotes EMT and drives fibrosis, creating a stiff, supportive stroma, and exerts potent immunosuppressive effects [71].

Lymph node metastasis

Lymph nodes (LNs) are an important part of the immune system, functioning as a barrier against pathogens while helping the induction and maturation of immune responses. Cancer cells can hijack the lymphatic system and subserve it to their advantage in spreading to various sites in the body, thus making metastasis to this system key in evaluating cancer patients. For DTCs to spread to other organs, they are faced with two main choices, as depicted in Figure 5. Either to take the vascular route or disseminate using the lymphatic vessels. Lymph angiogenesis, the growth of lymphatic vessels, and the release of VEGF-C/VEGF-D play a central role in the effective dissemination of tumor cells into the lymph nodes [72]. Interleukin-6 (IL-6) has been shown to promote lymph angiogenesis via VEGF-C in gastric cancer, and IL-7 can promote the development of lymph vessels through VEGF-D in lung and breast cancers [73]. The acquisition of EMT will help cancer cells to lose adhesion and become more mobile to invade local lymphatic vessels [74]. Cases exhibiting LN metastasis in hepatocellular carcinoma, for example, often feature significantly elevated rates of EMT [75]. As discussed earlier, even before cancer cells arrive at a distant lymph node (LN), the primary tumor sends out signals, in the form of VEGF, TNFα, and exosomes, to create a welcoming environment. For example, these signals can make the lymph node's lymphatic vessels leakier and easier for DTCs to enter. The blood vessels in and around LNs are, in general, abnormally permeable such that the plasma persistently accumulates in the extracellular sites [76]. Drainage of this accumulated plasma becomes impeded owing to the compression of the local lymphatic vessels by the growing tumor, resulting in an increase in intratumoral interstitial fluid pressure [77]. The fluid dynamics and the increased pressure favor the flow of DTCs and tumor-derived PMN molecules to access the LNs [78]. The expression of specific chemokines and their corresponding receptors, such as CCL21 (ligand highly expressed in LNs) and CCR7 (receptor), is a fundamental driver of LN-tropism (see Figure 5) [79].

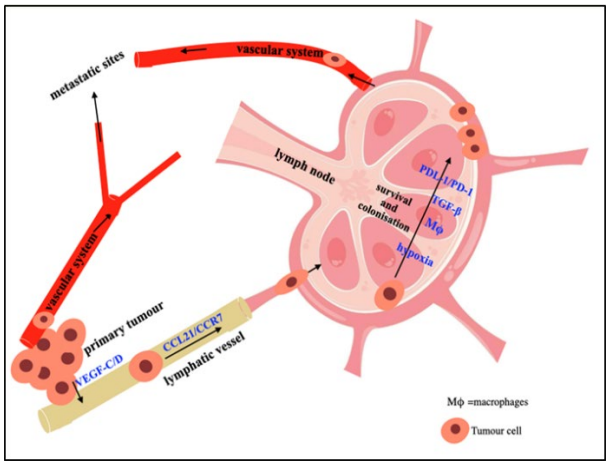

Figure 5: Lymph node metastasis. Primary tumour cells choosing the lymphatic system for dissemination are facilitated by the CCL21/CCR7 signalling axis. Survival and colonization in the LN are driven by signals such as PDL-1/PD-1 and TGF-β. Additionally, resident macrophages help to eliminate natural killer cells and cytotoxic T cells to promote cancer cell survival. Hypoxia also plays an important part in inducing genetic alterations in DTCs to make them more adaptable to the new microenvironment.

This creates a chemical gradient that actively attracts CCR7-expressing cancer cells towards the lymph nodes. There is also strong evidence for the role of the CXCR4/CXCL12 axis in enhancing glioma cell invasion of LNs [80]. Once residing in the LN environment, cancer cells must evade immune attack by T cells and NK cells. DTCs express proteins like PD-L1 that directly inhibit attacking T cells and adapt their metabolism to thrive in the lymph node conditions. The role of TGF-β in inhibiting natural killer cells, cytotoxic T cells, macrophages, and hypoxia is vital to induce genetic changes that enhance the survival of DTCs in the lymphatic system. Anatomical LN drainage patterns, the specific routes that lymph fluid travels, are typically encountered with head and neck cancer and melanoma primaries. Sentinel LN mapping is a standard procedure with melanoma, where a dye is injected at the tumor site, and the first node it drains to, the sentinel LN, is biopsied [81].

Bone metastasis

Several primary cancers can metastasize to the bone; amongst them are breast and prostate cancers [15]. ER+ breast cancer cells exhibit a stronger bone tropism compared to ER- cells, and androgen receptor-driven prostate cancer cells are linked to bone metastasis [82]. In preparing the bone for the arrival of DTCs, the primary tumor cells secrete factors like VEGF and PTHrP (parathyroid hormone-related protein, which functions in bone development and remodeling) and exosomes; refer to Figure 6 [82,84].

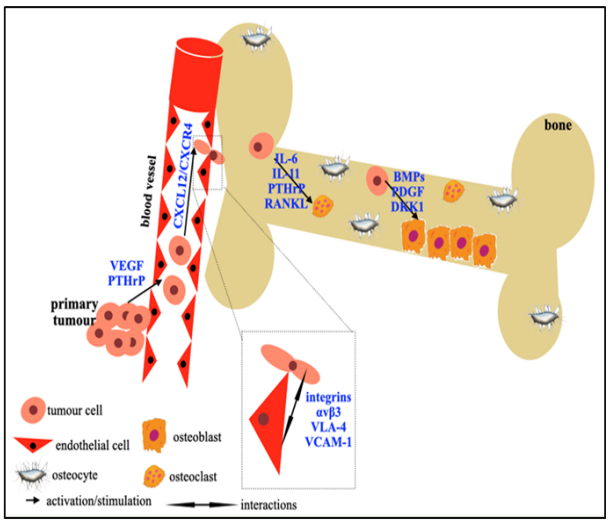

Figure 6: Bone metastasis. Factors released by primary tumour cells, like VEGF and PTHrP to recruit bone marrow-derived cells maintain an immunosuppressive bone environment. Chemokine and adhesion molecules e.g. CXCL12/CXCR4, are crucial for the homing of DTCs to bones. The arrest and exit of DTCs from the blood to the bones are aided by factors such as integrins, αvβ3, VLA-4, and VCAM-1. Cancer cells secrete primary mediators of osteoclasts, such as PTHrP, IL-6, IL-11, and RANKL and factors like BMPs, PDGF, and DKK1 to stimulate osteoblasts. The release of these mediators maintains the vicious cycle between bone formation and destruction.

These recruit bone marrow-derived cells to create immunosuppressive and pro-growth environments and make the blood vessels in and around the bone marrow stickier by upregulating adhesion molecules such as E-selectin to facilitate the arrest of DTCs [82]. The released factors can also activate the bone-resorbing cells, the osteoclasts, bone-breaking cells, to produce growth factors that will later fuel cancer proliferation. Following their journey in circulation, DTCs must exit the blood vessels and enter the bone marrow space. The process of homing and arrest is driven by specific chemokine/receptor pairs and adhesion molecules. The CXCR4/CXCL12 is the most critical homing mechanism for bone metastasis [83]. The ligand CXCL12 is abundantly produced by bone marrow stromal cells (like the osteoblasts). A powerful chemical gradient draws CXCR4-expressing cancer cells directly to the bone. Cancer cells also express integrins (e.g., αvβ3 and VLA-4) that bind to adhesion molecules (e.g., VCAM-1) on the bone marrow endothelial cells, allowing them to stop and extravasate into the bone marrow, as illustrated in Figure 6. Once residing in the bone marrow, cancer cells face a critical decision of either lying dormant or proliferating. If they undergo dormancy, they can reside in the bone for years or even decades, avoiding chemotherapy that targets rapidly dividing cells. The bone microenvironment, through signals like TGF-β, actively maintains this dormant state. For reasons not fully understood, some cells escape dormancy and begin to proliferate, initiating a state of ”vicious cycle” between bone formation and bone destruction involving the bone native cells of osteoclasts and osteoblasts. This leads to the formation of two main types of bone metastases: a destructive type (osteolytic {osteoclast-driven} metastasis) and a bone-forming type (osteoblastic metastasis), but many tumors exhibit mixed phenotypes and could be present in any skeletal site of metastases [84]. Accordingly, bone metastases typically exhibit "lytic," "sclerotic," or “mixed” phenotypes. Moreover, another type of bone cell called "osteocytes" also plays a major role in the regulation of bone modeling and remodeling by acting as sensors of mechanical stress on bone [82]. In osteolytic metastasis (bone destruction), which is common in breast cancer, lung cancer, melanoma, and renal cell carcinoma, the neoplastic cells secrete osteoclastogenic factors like PTHrP, IL-6, IL-11, and RANKL. The latter is the primary physiologic mediator of osteoclast formation and function, and when binding to its receptor, it promotes the activation of the osteoclastogenic factors to break down the bone matrix [85]. The resorbed bone releases stored calcium and other important growth factors to fuel the vicious cycle of bone formation and resorption. Osteoblastic metastasis is common in prostate cancer and some breast cancers where tumor cells secrete factors that stimulate osteoblasts, such as endothelin-1, bone morphogenic proteins (BMPs), PDGF, and Wnt inhibitors such as DKK1 [82,84]. These factors lead to the deposition of new, disorganized bones that are poorly structured and dense (sclerotic) but mechanically weak, leading to fractures. The osteoblastic response could be considered a physiological attempt by the body to activate bone repair. The active osteoblasts themselves also release growth factors that feed back to support the tumor cells and maintain the vicious cycle. The extracellular pH in the bone is also associated with the degree of acidification, with lower pH being linked to enhanced osteoclast resorption [86].

Brain metastasis

Examples of cancers that can metastasize to the brain include lung cancer (particularly non-small cell lung cancer with EGFR mutations), breast cancer (especially HER2-positive and triple negative), and melanoma [87,88]. Metastasis to the brain represents one of the most complex and formidable challenges in oncology. The brain is a uniquely protected environment, and for cancer cells to successfully colonize it, they must overcome a series of barriers. Before cancer cells even arrive at the brain, the primary tumor can remotely prepare the brain for their arrival (Figure 7). To do that, cancer cells secrete extracellular vesicles (exosomes) and soluble factors into the circulation to function in guiding the cells to the brain and making their residence there conducive to survival and proliferation [89]. High among the functions of these released factors is compromising the blood-brain barrier (BBB), primarily composed of endothelial cells connected by tight junctions and the presence of basement membranes, pericytes, and astrocytes (Figure 7).

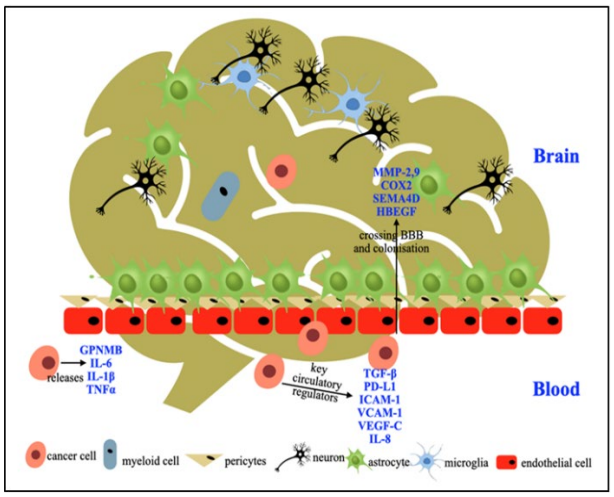

Figure 7: Brain metastasis. In preparing the brain for metastasis, the DTCs release factors such as GPNMB, IL-6, IL-1β, and TNFα, as well as extracellular vesicles. Tumour cells can survive the attacks by immune cells and the stresses of the circulatory journey through modulation of various proteins such as TGF-β, PD-L1, ICAM-1, VCAM-1, VEGF-C, and IL-8. Following that, various other signals and proteins, including MMP-2 and 9, COX2, SEMA4D, and HBEGF, will assist DTCs to cross the BBB and promote their survival in the new immunosuppressive brain environment.

Factors such as VEGF and exosomes carrying miR-181c can disrupt the tight junctions between brain endothelial cells, making the BBB more permeable [90]. Exosomes can be taken up by astrocytes, the brain's supporting cells, and microglia, the brain's immune cells, inducing them to become pro-inflammatory and pro-tumorigenic, thus creating a better supportive soil. Granulocyte-derived molecules like lipocalin-2 (LCN-2) trigger inflammatory activation of astrocytes, which in turn recruit myeloid cells to the brain [91,92]. Tumor-released factors can also mobilize immune cells from the bone marrow to travel to the brain and create an immunosuppressive environment. To cross the BBB, specific adhesion molecules like ICAM-1 and VCAM-1 on the brain endothelium bind to integrins on the DTCs, as illustrated in Figure 7. Factors like VEGF, MMPs, and prostaglandins secreted by cancer cells can degrade the tight junctions and the basement membrane of the BBB [87]. The brain environment is rich in specific growth factors, and successful metastatic cells often upregulate receptors for these molecules, e.g., HER2 in breast cancer can respond to brain-derived growth factors. High expression of GPNMB (glycoprotein nonmetastatic protein B) in macrophages and microglia is also linked to inflammation, making the brain a better niche for cancer cell survival [92]. The metastatic malignant cells can form gap junctions with astrocytes, allowing the transfer of cGAMP and activating the pro-survival STING pathway in cancer cells [93]. The brain-resident macrophages, microglia, can be polarized into a tumor-promoting M2 phenotype secreting immunosuppressive cytokines and growth factors. Brain-metastatic cells show a remarkable ability to use different energy sources like lactate and acetate and not just glucose, which is particularly important in the hypoglycemic tumor core.

Organotropism as a Therapeutic Target

The emerging therapeutic targets for organotropism are moving beyond the traditional cytotoxic drugs towards strategies that disrupt specific steps of the metastatic cascade. Disrupting organ-specific dissemination of cancer cells could significantly improve long-term survival of cancer patients since most cancer deaths result from the metastases rather than the primary tumors [94]. Below is a breakdown of the different targeting strategies.

Targeting the underlying molecular drivers of organotropism

This therapeutic approach is based on targeting specific mutations that predispose a tumor to spread to a particular organ. Certain driver mutations confer a preference to specific organs, e.g., EGFR-mutant lung cancer cells prefer to spread to the brain, and BRCA-mutant breast cancer cells prefer the ovaries [95]. Targeted therapy using osimertinib for EGFR-mutant non-small cell lung cancer is not only effective against the primary tumor but is also a potent strategy for preventing and treating associated organotropic metastases.

Dismantling the pre-metastatic niche

The goal here is to prevent the primary tumor from preparing a suitable environment in distant organs before cancer cells arrive. The key targets include:

Tumor-derived exosomes

The biogenesis of the exosomes could be targeted with drugs to block their formation and/or release, e.g., targeting neutral sphingomyelinase 2 (nSMase 2) [96]. The exosomes could also be depleted using dialysis-like apheresis devices to filter them out from the bloodstream. Alternatively, the uptake of tumor-derived exosomes by recipient cells could be inhibited using compounds such as heparin, wortmannin, and dynasore [97,98].

Educated bone marrow-derived cells

These cells include myeloid-derived suppressor cells (MDSCs) and hematopoietic progenitor cells expressing VEGFR1 (HPCsVEGFR1+) [99] travelling to the target organ and creating an immunosuppressive pro-angiogenic environment. Targeting these cells represents an opportunity to reduce metastasis, as in the case of employing antibodies such as anti-VEGFA to block their recruitment signals [100].

Inhibiting intravasation, circulation, & extravasation

The focus of this therapeutic modality is on the cancer cell's journey as it enters the bloodstream, travels through the blood vessels, and exits into the target organ.

Clusters of DTCs are significantly more metastatic than a single cancer cell, and targeting adhesion molecules, such as plakoglobin, disrupts cluster integrity, making them more vulnerable to destruction [101]. Targeting the BBB is another option to halt metastasis to the brain, and using BBB stabilizers, such as the repurposed angiotensin receptor blocker losartan, to prevent extravasation has been investigated [102].

Controlling proliferation in metastatic organs

DTCs and resident cells in metastatic organs can establish a crosstalk and a self-perpetuating feedback loop in the form of a “vicious cycle". Specific therapies can disrupt this proliferative phase depending on the nature of the metastatic organ. Denosumab is the prime example of disrupting RANKL/RANK interactions in bone metastasis [103]. Additionally, a neutralizing antibody against PTHrP, a key driver of osteoclast activation, is currently under investigation for bone metastasis [104]. For brain metastasis, disrupting the gap junctions that promote signal transfer between cancer cells and astrocytes can sensitize tumor cells to chemotherapy [93]. Another avenue for therapeutic intervention in brain metastasis is to employ the BBB’s own nutrient transporters to deliver drugs. Analogues of L-DOPA have been designed to act as substrates for influx transporters to be carried into the brain [105]. For liver metastasis, the usual target is the hepatic stellate cell, which, when activated by tumor cells, creates a dense fibrotic microenvironment that protects metastases and impedes drug delivery. Drugs like losartan can also reduce fibrosis and improve drug penetration [106].

Targeting the immune microenvironment of the metastatic site

The immune context of a metastatic site could be very different from the primary tumor. Microglia in the brain and Kupffer cells in the liver are often polarized into a pro-tumor immunosuppressive state. Blocking the survival of these pro-tumour macrophages using CSF1R inhibitors, for example, is being tested in combination with other therapies [107]. CD47 signal inhibitors can block these phagocytic signals on cancer cells, thus allowing organ-specific macrophages to eliminate them.

Maintaining dormancy and controlling reawakening

Dormancy is a reversible state in which the DTCs continue to survive in the distant organ as non-proliferative cells, sometimes for years or even decades. Dormancy is controlled by complex factors, including intrinsic cues arising from within the cells or as dictated by the surrounding microenvironment; for instance, hematopoietic stem cells were found to survive in a dormant state within the specific microenvironment of bone [108]. Dormancy can be controlled in two ways, either by preventing the reactivation or by eliminating the metastasized cancer cells. To achieve that, manipulating the tumor microenvironment or targeting cell-intrinsic survival mechanisms, as well as using immunotherapy, are a few of the advocated approaches. Ghajar argues for directing therapies towards targeting the tumor microenvironment to render the cancer cells more susceptible to chemotherapies [109]. The STING signaling pathway, a critical part of the innate immune system that triggers responses to infections and cancer, has been investigated in this regard. Hu et al. found that STING agonists help suppress the reawakening of dormant mouse cancer cells that would have become aggressive metastatic tumors [110]. Table 1 provides further details on therapeutic strategies for organotropic metastasis.

Future challenges and opportunities

An oncology shift from treating established metastases to preventing their formation requires overcoming the profound complexity of the metastatic cascade. For instance, the mechanisms critical for the initiation of a pre-metastatic niche through exosome signaling could be different from those required for colonization and outgrowth [94]. Targeting the early phase before metastases are even detectable poses a major clinical hurdle. Designing drugs that specifically block a particular organ's metastasis without affecting the function of that organ and overcoming biological barriers such as the BBB in brain metastasis remains a major challenge for drug delivery. Lack of reliable predictive biomarkers and animal models that fully recapitulate the human metastatic process are further obstacles. In the future, substantial strides will continue to be made in understanding the complexity of metastasis and improving the sensitivity of detection. Artificial intelligence and patient avatars derived from modeling the metastatic process will become more sophisticated and central to precision medicine [117], enabling more accurate predictions of treatment responses and personalized therapeutic strategies for patients with metastatic cancer.

Conclusions

Metastatic organotropism has evolved from descriptive clinical observation to a sophisticated molecular science. As this overview article has shown, the preferential colonization of organs is not a chance event but the result of a complex, multi-step interaction between disseminated tumor cells and the microenvironment of the distant tissue. The process is orchestrated by genetic and epigenetic programming of cancer cells, the formation of a pre-metastatic niche, and subsequent reciprocal signaling to ensure outgrowth of surviving cancer cells in a permissive, immune-suppressed environment. This review highlights preclinical/early

clinical attempts in translating this mechanistic knowledge into therapeutic strategies. Targeting key vulnerabilities such as the pre-metastatic niche or the circulating/extravasating tumor cells represents just some of these avenues. Manipulating the immunosuppressive landscapes at the metastatic site is yet another approach at minimizing the possibility of metastasis. Moreover, attempts at targeting organ-specific metastasis, such as the vicious cycle of bone remodeling, have also been receiving considerable research interest.

Table 1: Main therapeutic strategies in targeting metastatic organotropism

Therapeutic strategy	Target/mechanism of action	Cancer type	Stage of development	Reference
Targeting pre-metastatic niche	-Tumour exosomes (nSMase2) -Educated BMDCs (VEGF-A)	Metastatic cancers	Preclinical/early clinical	[111,112,26]
Targeting circulating and extravasating DTCs	Targeting the gene, plakoglobin, associated with circulating tumour clusters	Breast cancer	Preclinical	[113]
Targeting bone "vicious cycle"	Targeting PTHrP When PTHrP is released by cancer cells, it binds to its receptor on neighboring bone cells, causing destruction of the bone.	Bone metastases of breast cancer	Preclinical	[104,114]
Targeting brain ME	AS602801 inhibiting connexin43, the gap junction between astrocytes and cancer cells to receive signals crucial for colonization.	Breast cancers	Preclinical, mouse models	[115]
Targeting liver ME	Losartan can inhibit hepatic stellate cells to create dense fibrotic and metastasis-protective ME	Hepatocellular carcinoma	Preclinical, murine models	[106]
Targeting the immune function	Blocking the CSF1R function using the FDA- approved Pexidaritinib	Metastatic renal cell carcinoma	Pexidaritinib is licensed for giant cell tumours of tendon sheath being assessed for metastatic renal cell carcinoma	[107]
Targeting the underlying molecular drivers	Targeting EGFR-mutant lung cancer metastasis to brain using Osimertinib (Tagrisso)	Brain metastasis	Osimertinib is licensed against NSCLC and being assessed for its effectiveness for brain metastasis	[116]

nSMase2: neural sphingomyelinase 2; BMDCs: bone marrow derived dendritic cells; VEGF-A: vascular endothelial growth factor A; DTCs: disseminated tumour cells; PTHrP: parathyroid hormone-related protein, ME-microenvironment; CSF1R: colony stimulating factor 1 receptor; FDA: food and drug administration; EGFR: epithelial growth factor receptor; and NSCLC: non-small cell lung cancer.

Abbreviations

avβ5: a type of integrin; BBB: blood-brain barrier; BMDCs: bone marrow-derived dendritic cells; BMPs: bone morphogenic proteins; BRCA: breast cancer; CCL2: chemokine attracting immune cells to sites of inflammation; CCR2: receptor for CCl2; CCR7/CCL21: chemokine receptor and ligand involved in directing cell movement to lymph nodes and inflammatory tissue; CD44 V.6: specific variants CD44, cell surface protein implicated in metastasis; CEA: carcinoembryonic antigen; cGAMP: cyclic GMP-AMP, a vital second messenger in the innate immune system; COX2: cyclooxygenase 2 enzyme; CRC: colorectal cancer; CSF1R: colony stimulating factor 1 receptor; CTCs: circulating tumour cells; CXCL12: chemokine involved in immune responses, development, survival and adhesion of cells; CXCR4: surface protein directing movement, development, and immune responses of cells; DEC2: transcriptional repressor protein; DKK1: secreted proteins acting as key inhibitors of Ant signalling; DTCs: disseminating tumour cells; ECAMS: endothelial cell adhesion molecules; ECM: extracellular matrix; EGFR: epidermal growth factor receptor; EMT: epithelial-mesenchymal transition; ER: estrogen receptor; ErbB: family of receptor tyrosine kinases, important for cell growth, differentiation, and survival; EVs: extracellular vesicles; FDA: the American food and drug administration; GPNMB: glycoprotein nonmetastatic protein B; HBEGF: heparin-binding epidermal growth factor; HER2: human epidermal growth factor receptor 2; HPC: hematopoietic progenitor cells; ICAM1: intercellular adhesion molecule-1, also known as CD54; IL: interleukin; KCs: Kupffer cells, liver's primary macrophages; KISS1: metastasis suppressor protein; KRAS: part of the RAS family cell signalling; L-DOPA: levodopa, a vital neurotransmitter; LCN-2: lipocalin-2; LN: lymph node; LOXL2: lysyl oxidase like 2; LSECs: liver sinusoidal endothelial cells; MDSCs: myeloid-derived suppressor cells; ME: microenvironment; MET: protooncogene for cell growth, survival, and tissue repair; HGF: hepatocyte growth factor; miR: microRNA; MMPs: matrix metalloproteinases; NF-κB: nuclear factor kappa enhancer of activated B cells; NKs: natural killer cells; NSCLC: non-small

cell lung cancer; nSMase2: neutral sphingomyelinase 2; p53: guardian of the genome tumour suppressor protein; PAD4: peptidylarginine deiminase 4; PD-1/PD-L1: programmed death receptor and ligand; PDAC: pancreatic ductal adenocarcinoma; PDGF: platelet-derived growth factor; PI3K/Akt: phosphoinositide 3-kinase/protein kinase B. Crucial signalling cascade many cell functions; PMN: pre-metastatic niche; PTEN: phosphatase and tensin homologue, tumour suppressor protein; PTHrP: parathyroid hormone-related protein; RANKL: receptor activator of nuclear factor kappa-B ligand; SEMA4D: semaphorin-4D; STAT3: signal transducer and activator of transcription 3; STING: stimulator of interferon genes, important in the innate immune system; TDSFs: tumour-derived secretory factors; TGF-β: transforming growth factor beta, regulator of cell growth, differentiation, development, tissue repair, and immune responses; TME: tumour microenvironment; TNFα: tumour necrosis factor alpha, inflammatory cytokine; VAP-1: vascular adhesion protein-1; VCAM1: vascular cell adhesion molecule 1; VEGF: vascular endothelial growth factor, stimulates growth of new blood vessels; VLA-4: very late antigen 4, a type of integrin; Wnt/β-catenin: fundamental cell signalling regulator of growth, differentiations and stemness.

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Conflict of interests

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Supplementary data can be shared with the corresponding author upon reasonable request.

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