Tumor-Derived Exosomes Modulate Primary Site Tumor Metastasis

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Tumor-derived exosomes (TDEs) are actively produced and released by tumor cells and carry messages from tumor cells to healthy cells or abnormal cells, and they participate in tumor metastasis. In this review, we explore the underlying mechanism of action of TDEs in tumor metastasis. TDEs transport tumor-derived proteins and non-coding RNA to tumor cells and promote migration. Transport to normal cells, such as vascular endothelial cells and immune cells, promotes angiogenesis, inhibits immune cell activation, and improves chances of tumor implantation. Thus, TDEs contribute to tumor metastasis. We summarize the function of TDEs and their components in tumor metastasis and illuminate shortcomings for advancing research on TDEs in tumor metastasis.

Keywords: tumor-derived exosomes, metastasis, pre-metastatic niche, angiogenesis, immunosuppression

BACKGROUND

Exosomes are extracellular vesicles, approximately 30–150 nm in diameter, that contain functional biomolecules, such as proteins, RNA, DNA, and lipids, and can interact with recipient cells (Balaj et al., 2011; Choi et al., 2013; Peinado et al., 2012). Exosomes are present in various body fluids and are regarded as a key component of intercellular communication. Tumor cell-, stromal cell-, or even normal cell–derived exosomes play an important role in tumor progression and can induce angiogenesis and accelerate metastasis (Hood et al., 2011; Luga et al., 2012; Peinado et al., 2012). The components and functions of the exosomes depend on the cell types; some studies have shown many differences in the contents and release rate in different types of cells. But, the complete mechanism and process have not yet been elucidated and need to be further explored. Metastasis is the leading cause of tumor-induced death and is a complex process involving local invasion, survival, and evasion from immunosurveillance, invasion into circulation, and extravasation at secondary organs (Fidler and Kripke, 2015; Wan et al., 2013). Tumor-derived exosomes (TDEs) are a significant component of the tumor microenvironment and are involved in promoting tumor metastasis through several mechanisms, including acquiring primary tumor migration capacity, tumor angiogenesis, escaping immune system organotropic metastasis, forming the pre-metastatic niche, and metastatic tumor growth in the secondary site.

In this review, we summarize the function of exosomes in every aspect of cancer metastasis (Figure 1) to provide a better systematic comprehension of the role of exosomes in tumor metastasis and propose practical implications of early diagnosis, treatment, and prognostic methods for cancer.
TUMOR-DERIVED EXOSOMES ENHANCE THE MIGRATION ABILITY OF TUMOR CELLS

Tumor-Derived Exosomes Promote Epithelial–Mesenchymal Transition to Initiate Metastasis

Epithelial–mesenchymal transition (EMT) frequently initiates the metastatic process (Li et al., 2021). Epithelial tumor cells acquire mesenchymal characteristics under the influence of cancer-associated fibroblasts (CAFs) in the tumor stroma (Diepenbruck and Christofori, 2016). Epithelial markers, including E-cadherin, zona occludens 1 (ZO-1), cytokeratins, desmoplakin, and laminin, are downregulated, and mesenchymal markers, including N-cadherin, β-catenin, and vimentin, are upregulated (Sommers et al., 1994; Li Y. et al., 2019). During EMT, tumor cells lose their apical–basal polarity, basement anchoring, and cell–cell junctions and switch to a low proliferation state with enhanced migratory and invasion capabilities (Basil et al., 2020). Once the tumor cells reach a distant pre-metastatic niche, the reversed process takes place (Maren, 2016). This so-called mesenchymal–epithelial transition (MET) returns tumor cells to a high proliferative state and enables the formation of micrometastases (Bakir et al., 2019). TDEs play an important regulatory role in mediating the EMT and MET transformation (Bigagli et al., 2019). There has been increasing research showing the signaling pathway involved in inducing cancer-related EMT. We propose that the critical components in TDEs can serve to promote EMT.

The latest hypothesis is TDEs may be conduits for initiating signals for EMT. For example, TDEs carry EMT derivers, such as transforming growth factor-beta (TGF-β), tumor necrosis factor-alpha (TNF-α), hypoxia-inducible factor 1 alpha (HIF-1α), protein kinase B (AKT), caveolin-1, platelet-derived growth factors (PDGFs), and β-catenin Wnt pathway modulators, that directly enhance the process of EMT (Aga et al., 2014; Kucharzewska et al., 2013; Luga et al., 2012; Ramteke et al., 2015). TDEs transmit non-coding RNA, such as, miR-128-3p, miR-27, LINC00960, linc02470, circ-PVT1, and circ-CPA4, that upregulate EMT (Huang C.-S. et al., 2020; Liu et al., 2019; Wang J. et al., 2018). Therefore, many studies have shown that tumor

![FIGURE 1](image1.png)

**FIGURE 1** | Function of TDEs in tumor metastasis. TDEs are mainly involved in tumor metastasis through five aspects. Step 1: acquisition of tumor migration ability; Step 2: angiogenesis; Step 3: immunosuppression; Step 4: localization of metastatic sites; and Step 5: enhancement of proliferation ability of tumor cells after migration.

![FIGURE 2](image2.png)

**FIGURE 2** | TDEs enhance the migration ability of tumor cells by promoting EMT and degrading the ECM. (A): Exosomes carry proteins, miRNA, IncRNA, and circRNA to promote the occurrence and development of EMT. (B): TDEs carry proteins or non-coding RNA to initiate degradation of the ECM.
cells can secrete exosomes into the extracellular space and promote the EMT through their effectors: proteins, miRNAs, circRNAs, and IncRNAs (Figure 2A).

**Tumor-Derived Exosomes Promote Extracellular Matrix Degradation**

The extracellular matrix (ECM) is a scaffold for tissues and organs (Eble and Niland, 2019). The ECM is a complex network combined with proteins, proteoglycans, and glycoproteins that can regulate cell growth, survival, motility, and differentiation through specific receptors, such as integrin, syndecan, and discoidin receptors (Leitinger, 2011; Xian et al., 2010). Cancer-associated ECM is not only an integral feature of a tumor but also actively contributes to its histopathology and malignant behavior (Levental et al., 2009; Provenzano et al., 2008). From tumor initiation to metastasis, ECM molecules bind with cell surface receptors and activate intracellular signaling pathways. ECM adhesion–induced signals promote self-sufficient growth through mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) (Pylayeva et al., 2009). Focal adhesion kinase (FAK) signaling inhibits p15 and p21, which are growth suppressors, and p53 to limit the induction of apoptosis (Kim et al., 2008). TGF-β and RhoA/Rac signaling promote EMT induction and enhance promigratory pathways (Leight et al., 2012). The ECM can also enhance angiogenesis and strengthen vascular endothelial growth factor (VEGF) signaling in endothelial cells (Liu and Agarwal, 2010).

TDEs mediate tumor–tumor and tumor–host cell crosstalk (Kalluri, 2016). TDEs interact with and regulate the synthesis of ECM components and are involved in ECM remodeling (Rackov et al., 2018). The proteins on the surface of TDEs promote the activation of membrane-associated proteinases, such as Adamts1, Adamts4, and Adamts5, thus improving proteolytic activity (Ginestra et al., 1997; Lo Cicero et al., 2012). In addition, matrix metalloproteinases (MMPs) derived from TDEs participate in localized degradation and ECM proteolysis during cellular migration and metastasis (Ginestra et al., 1997; Atay et al., 2014). However, besides exosomal surface proteins, non-coding RNA also mediates ECM degradation. For example, breast cancer–derived exosomes carry miR-301 to regulate matrix modulation (Morad et al., 2020). Gastric cancer cell–derived exosomal miR-27a reshapes the ECM at adjacent sites and promotes tumor progression by downregulating CspR2 expression and upregulating α-SMA expression (Wang et al., 2018). Currently, there are no direct reports on other non-coding RNAs, such as IncRNA and circRNA, but TDE-derived IncRNA and circRNA can influence fibroblast, chondrocyte, and epithelial cell function, secreting ECM components into the extracellular space (Tan et al., 2020).

Some data suggested that the ECM is a prerequisite for tumor cell invasion and metastasis (Tan et al., 2020). When the tumor cells metastasize, they detach from the ECM. Furthermore, the exosomes participate in this process (Figure 2B).

**TUMOR-DERIVED EXOSOMES PROMOTE ANGIOGENESIS DIRECTLY OR INDIRECTLY**

Regardless of tumor size, metastasis may occur; however, in most cases, metastasis is associated with large primary neoplasms (Fidler and Kripke, 2015). If a tumor mass exceeds 1 mm in diameter, angiogenesis is bound to occur (Folkman, 1971; Nagy and Dvorak, 2012). Therefore, exploring tumor angiogenesis is an important way to understand tumor metastasis.

**Tumor-Derived Exosomes Promote Angiogenesis by Activating Macrophages**

Cancer-derived exosomes stimulate macrophage infiltration and polarization for establishing a pre-metastatic niche. For example, exosomes derived from CT-26, a colon cancer cell, can provoke macrophages to secrete significantly high levels of monocyte chemoattractant protein-1 (MCP-1) and TNF, thus promoting the growth and migration of colorectal cancer cells. Lung cancer cell–derived exosomes containing miRNA-103 upregulate angiogenic VEGF-A and angiopoietin-1 expression from M2 macrophages (Hsu et al., 2018; Wu et al., 2019). Therefore, TDEs can motivate the angiogenic property of macrophages such as secretion of VEGF (Wu et al., 2019). It can induce angiogenesis by tumor cells. In addition, other immune cells also contribute to tumor angiogenesis, such as neutrophils, myeloid precursor cells (MPCs), and dendritic cells (DCs) (Albini et al., 2018). But, there are no reports about TDE-educated neutrophils, MPCs, or DCs to promote angiogenesis in metastasis.
Tumor-Derived Exosomes Carry Non-coding RNA and Proteins to Promote Angiogenesis Directly

TDEs carry non-coding RNAs, including microRNA, IncRNA, and circRNA, that play an indispensable role in angiogenesis. TDEs carry miR-25-3p that regulates VEGFR2, ZO-1, occludin, and claudin5 expression in ECs by targeting KLF2 and KLF4 and eventually promotes vascular permeability and angiogenesis (Felcht et al., 2012; Wu et al., 2019). TDEs deliver miR-130a to vascular cells to promote angiogenesis by targeting c-MYB (Yang et al., 2018). Exosomal miR-155-5p can induce angiogenesis through the SOCS1/JAK2/STAT3 signaling pathway (Zhou X. et al., 2018). Exosomal miR-135b promotes angiogenesis by inhibiting FOXO1 expression. Exosomal miR-23a induces angiogenesis by targeting TSGA10, prolyl hydroxylase, tight junction protein ZO-1, and SIRT1 (Sruthi et al., 2018; Bai et al., 2019). Exosomal miR-1229 promotes angiogenesis by targeting HIPK2. Exosomal miR-21 promotes angiogenesis by targeting STAT3 (Liu and Cao et al., 2016). In addition, IncRNA containing IncCCAT2, IncMALAT1, IncRNA-p21, and IncPOU3F3 or circRNA, such as TDE-derived circRNA-100338, also promote angiogenesis (Castellano et al., 2020; Huang X.-Y. et al., 2020; Lang, Hu, & Chen et al., 2017; Lang, Hu, &; Zhang Z. et al., 2017; Qiu J.-J. et al., 2018). IncRNA and circRNA are often used as "sponges" to regulate miRNA expression in cells. Moreover, TDEs carry a variety of angiogenic proteins, such as VEGF, IGFpB3, MMP2, ICAM-1, and IL-8, thus enhancing angiogenesis through in vitro and in vivo ligand/receptor signaling (Ludwig and Whiteside, 2018). Therefore, a combination of multiple non-coding RNAs and exosomal proteins promotes tumor angiogenesis.

The importance of angiogenesis in tumor metastasis cannot be understated, TDEs can carry proteins and non-coding RNAs that directly promote angiogenesis or they can mediate angiogenesis indirectly by "educating" macrophages to release proangiogenic factors (Figure 3).

TUMOR-DERIVED EXOSOMES CAN PROTECT TUMOR CELLS DURING METASTASIS

Tumor cells shed from primary or secondary tumors are called circulating tumor cells (CTCs) (Paoletti and Hayes, 2016). CTCs invade the bloodstream and attach to the endothelium in the target organ. They then invade the surrounding parenchyma to form new tumors (Garcia et al., 2018). Blood is an unfavorable environment for CTCs, and they struggle with circulating immune cells (Agarwal et al., 2018). TDEs help CTCs metastasize smoothly by inhibiting immune cell activity and conferring a protective layer on them, thus maintaining cellular integrity (Figure 4).

Tumor-Derived Exosomes can Suppress Immune Cells to Protect CTCs

The immune system inhibits the progression of cancer cells. Many immune cells are found circulating in human blood, including T lymphocytes, natural killer (NK) cells, and B lymphocytes (de la Cruz-Merino et al., 2008; Grivennikov et al., 2010; McCarthy, 2001). These immune cells play crucial roles in immune surveillance, immunosuppression, and killing effects and mainly act on CTCs (Deepak and Acharya, 2010; Pahl and Cerwenka, 2017; Wernersson and Pejler, 2014; Ye et al., 2017). Immune cells can recognize and attack CTCs under normal circumstances; therefore, immunosuppression is necessary for the metastasis of CTCs (Guo et al., 2019). Many researchers have found that TDEs can suppress immune cells. Exosomes carry bioactive molecules that can impair immune cell function (Becker et al., 2016; Kalluri, 2016; Robbins and Morelli, 2014). Programmed cell death receptor ligand 1 (PD-L1) can bind to programmed cell death protein 1 (PD-1) to inactivate T cells through its extracellular domain (L. Chen and Han, 2015; Chen et al., 2015; Garcia-Diaz et al., 2019). TDEs carry PD-L1 on their surface and suppress CD8+ T cell function in metastatic melanoma (Chen et al., 2018). In addition to PD-1, TDEs can also carry other ligands to inhibit T cell function, and prolyl hydroxylase can inhibit CD4+ and CD8+ T cell functions by oxygen sensing (Clever et al., 2016). TDEs block T cell activation and enhance T cell apoptosis (Czernik and Dutcher, 2017; Ludwig et al., 2017). TDEs can also cause NK cell dysfunction. NK cells do not express PD-1; however, TDEs interfere with the TGFβ/TGFβR1/II pathway and other common molecular pathways, such as the adenosine pathway, eventually driving NK cell responses (Hong et al., 2017). In addition, TDEs can inhibit NK cell cytotoxicity by suppressing STAT5 activation (Zhang et al., 2007). B cells play a critical role in immunoglobulin, antigen, and proinflammatory cytokine secretion (Mauri and Bosma, 2012). TDE HMGB1 regulates the proliferation of T cell Ig and mucin domain-1+ (TIM-1+) B cells and fosters cancer cell immune evasion (Ye et al.,
### Table 1: Chart for organotropic metastasis with respect to cancer types.

| Cancer type                      | Organotropic metastasis | References |
|----------------------------------|-------------------------|------------|
| Acute myeloid leukemia           | Liver metastasis        | Wang H. et al. (2020); Wang N. et al. (2020) |
| Breast cancer                    | Yogeswaran et al. (2019); Tahara et al. (2019); Ma et al. (2020a) |
| Lung metastasis                  | Kim et al. (2016); Yousufi et al. (2016); Tyagi et al. (2021) |
| Brain metastasis                 | Pedrosa et al. (2018); Chiang et al. (2020); Hosono et al. (2020) |
| Lymph node metastasis            | Zhang H. et al. (2017); Qiu et al. (2020); Zhang Q. et al. (2017); Xu et al. (2021) |
| Liver metastasis                 | Ma et al. (2015); Yousufi et al. (2018); Bale et al. (2019); Ji et al. (2020) |
| Bladder cancer                   | Fan et al. (2020)       |
| Lymph node metastasis            | Doshi et al. (2013); Tuncer et al. (2014) |
| Lung metastasis                  |                         |
| Liver metastasis                 |                         |
| Mediastinum                      |                         |
| Colon cancer                     | Liver metastasis        | Yao et al. (2017); Tokoro et al. (2018); Li K. et al. (2019); Zhu et al. (2020) |
| Cervical cancer                  | Liver metastasis        | Ali et al. (2017); Chen et al. (2020); Hsieh et al. (2021) |
| Brain metastasis                 | Liver metastasis        | Hwang et al. (2013); Sato et al. (2015); Fenzl et al. (2017); Kim et al. (2019b); Sun et al. (2020) |
| Lymph node metastasis            | Wu et al. (2022); Zhang C. et al. (2020); Zhang Q. et al. (2020); Zhong et al. (2020) |
| Bone metastasis                  | Yoon et al. (2013); Dhar and Islam (2014); Makino et al. (2016) |
| Liver metastasis                 | Nance et al. (2020); Liu et al. (2021) |
| Gastrointestinal stromal tumor   | Liver metastasis        | Yoshida et al. (2012); Tokoro et al. (2018) |
| Bone metastasis                  | Liver metastasis        |                         |
| Lymph node metastasis            | Akhtar et al. (2015); Suzuki et al. (2015) |
| Brain metastasis                 | Canda et al. (2009); Gong et al. (2011); Kubo and Takeuchi (2017) |
| Liver metastasis                 | Naou et al. (2011)       |
| Gastric cancer                   | Liver metastasis        | Xu et al. (2020a); Carvalho et al. (2020) |
| Brain metastasis                 | Liver metastasis        | Qu et al. (2018a); Wang et al. (2019d); Abe et al. (2020) |
| Lymph node metastasis            | York et al. (1999); Peng et al. (2014); Yang et al. (2016); Qu et al. (2018b); Cavaney et al. (2018) |
| Bone metastasis                  | Liver metastasis        | Chen et al. (2019); Wang J. et al. (2020); Wang Y. et al. (2020); Kim et al. (2021) |
| Liver metastasis                 | Ubukata et al. (2011); Miki et al. (2017); Qu et al. (2018a); Fujita et al. (2020); Imura et al. (2020) |
| Lymph node metastasis            | Zhang G. et al. (2017); Qu et al. (2018b); Luo et al. (2019); Ohara et al. (2020) |
| Glioblastoma                     | Liver metastasis        | Hoffman et al. (2017) |
| Lymph node metastasis            | Liver metastasis        | Wojnarczyk et al. (1997); Datta et al. (1998); Alouabi et al. (2020) |
| Bone metastasis                  | Liver metastasis        | Richard et al. (2019); Nagata et al. (2020) |
| Liver metastasis                 | Liver metastasis        | Yung et al. (1983); Shuto et al. (1995) |
| Hepatocellular carcinoma         | Liver metastasis        | Zhang et al. (2019b); Park et al. (2019); Ma et al. (2020b); Hu et al. (2020) |
| Lymph node metastasis            | Liver metastasis        | Xu et al. (2016); Ikegami et al. (2017); Liu et al. (2018a) |
| Stomach and colon                | Liver metastasis        | Kim et al. (2020) |
| Brain metastasis                 | Liver metastasis        | Yamakawa et al. (2015); Lin et al. (2017); Nam et al. (2019) |
| Lung metastasis                  | Liver metastasis        | Zhang et al. (2019a); Kapoor et al. (2020) |
| Head and neck cancer             | Liver metastasis        | Nishino et al. (1986); AlShammari et al. (2020) |
| Brain metastasis                 | Liver metastasis        | Nishino et al. (1986); Kofler et al. (2017) |
| Lymph node metastasis            | Liver metastasis        | Zhou X. et al. (2018); Nienstedt et al. (2018); Zhou Z. et al. (2018); Mermod et al. (2019); Fang et al. (2020); Nishio et al. (2021) |
| Bone metastasis                  | Liver metastasis        | Bhandari and Jan. (2013); Chi et al. (2021) |
| Liver metastasis                 | Liver metastasis        | Chen et al. (2017) |
| Lung cancer                      | Liver metastasis        | Sridhar et al. (2019); Wang B. et al. (2020); Lu et al. (2020) |
| Brain metastasis                 | Liver metastasis        | Liu et al. (2017); Okabe et al. (2018); da Silva et al. (2019); Wang et al. (2019b); Ai et al. (2020) |
| Lymph node metastasis            | Liver metastasis        | Xia et al. (2015); Kong et al. (2017); Wang C.-F. et al. (2020); Wang L. et al. (2020) |
| Brain metastasis                 | Liver metastasis        | Ajishanai et al. (2018); Waqar et al. (2018); Wang et al. (2019a); Luo et al. (2020b); Fujimoto et al. (2020) |
| Lymph node metastasis            | Liver metastasis        | Merkow et al. (2016); Mo et al. (2017); Muhsin-Sharafalmi et al. (2017); Faries et al. (2018); Soler-Cardona et al. (2018) |
| Bone metastasis                  | Liver metastasis        | Kircher et al. (2016); Katona et al. (2017); Redmer, (2018); Schwarz et al. (2019) |
| Lung metastasis                  | Liver metastasis        | Zhu et al. (2016); Hyun et al. (2020); Park et al. (2020); Stansel et al. (2020) |
| Multiple myeloma (BM-MSC)         | Liver metastasis        |            |
| Mesothelioma                     | Liver metastasis        | Estelles Piera et al. (1993) |
| Liver metastasis                 | Liver metastasis        | Estch et al. (1997); Marzullo et al. (2020) |
| Lymph node metastasis            | Liver metastasis        | Laurin, (1974); Swayne et al. (1990); Roegel et al. (1993); Huang et al. (2019) |
| Bone metastasis                  | Liver metastasis        | Sussman and Rosai, (1990); Yan et al. (2006); Abdel Rahman et al. (2008); Takehara et al. (2014) |
| Brain metastasis                 | Liver metastasis        | Asoh et al. (1990); Kawai et al. (1997); Hirooka et al. (2016) |
| Ovarian cancer                   | Liver metastasis        | Ueda et al. (1973) |
| Brain metastasis                 | Liver metastasis        | Palneshan et al. (2014); Stassenko et al. (2019) |

(Continued on following page)
CTCs Activate Platelets Directly or by Releasing Exosomes

Platelets play major roles in hemostasis and coagulation and regulate the efficiency of canceration, tumor angiogenesis, tumor metastasis, and chemotherapy (Sharma et al., 2014). Platelets and cancer cells interact, thus affecting tumor growth and metastasis (Sharma P. et al., 2018). During blood circulation, other nontumor help is essential, for example, platelets can protect CTCs from blood flow shear forces by providing a protective layer. CTCs release soluble mediators, such as adenosine diphosphate (ADP), thromboxane (TX) A2, or high-mobility group box 1 (HMGB1), that can ligate toll-like receptor 4 (TLR4) to instigate localized platelet activation and form thrombus encasing tumor cells, thus protecting them from cytolysis by NK cells (Aitokallio-Tallberg et al., 1985; Nieswandt et al., 1999; Yu et al., 2014; Zucchella et al., 1989).

The interaction between platelets and CTCs can lead to platelet activation, and platelets release cytokines conducive to the survival and proliferation of tumor cells. When platelets combine with circulating tumor cells, platelet-derived soluble factors (TGF β and PDGF) mediate and prevent NK cells from detecting and dissolving tumor cells (Lambert et al., 2017; Lee J.-K. et al., 2013).

Finally, platelets prevent tumor cells from being eliminated by the immune system. Platelet-derived TGF-β can downregulate NKG2D expression and inactivate NK cells (Y. Chen et al., 2015; Kopp et al., 2009). The platelet expression profile in tumor and nontumor patients varies substantially (Sanzarpia et al., 2018). The interaction between CTCs and platelets can protect CTCs from immune surveillance during circulation and help tumor cells adhere to the endothelial cells at the metastasis site (Sanzarpia et al., 2018). Kuznetsov et al. showed that luminal breast cancer cells carried platelets that loaded factors with the effect of pro-inflammatory and pro-angiogenic activities and confirmed that these factors were released at distant tumors sites (Kuznetsov et al., 2012). Platelets are essential for releasing proangiogenic cytokines and recruiting angiogenic vascular endothelial growth factor receptor 2+ (VEGFR2+) cells that promote malignant progression (Schlesinger, 2018). Moreover, studies have shown that platelets may not just have a secondary role but may also drive malignant progression (or metastasis) (Kuo et al., 2011).

In human blood, platelets are considered to be the major contributors of exosomes (Caby et al., 2005). Goetzl et al. showed that endothelial cells absorb platelet-derived exosomes and enhance their adhesion by increasing endothelial cell adhesion protein expression and anti-adhesion factor production, thereby promoting CTC adhesion in vascular endothelial cells (Goetzl et al., 2016). Platelet-derived exosomes also increase platelet adhesion to monocytes and consequently monocyte activation, thus promoting the formation of inflammatory phenotypes (Goetzl et al., 2016).

Therefore, many researchers believe that blood platelets may be a potential source of biomarkers to aid cancer diagnosis. Nonetheless, the mechanism using which CTC-educated platelets mediate CTCs to avoid damage in the circulatory system still needs further research. We firmly believe that these CTC-educated platelet-derived exosomes play an important role in preventing damage to CTCs.

INTEGRINS OF TUMOR-DERIVED EXOSOMES DETERMINE ORGANOTROPIC METASTASIS

That different types of cancer cells preferentially colonize and metastasize to different organs is the salient feature of metastasis (Nguyen et al., 2009). Current research shows that tumors mainly metastasize to lung, brain, lymph node, bone, and liver tissues. We have summarized organotropic metastasis with respect to cancer types (Table 1). Many studies focus on tumor cell

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### Table 1

| Cancer type          | Organotropic metastasis | References |
|----------------------|-------------------------|------------|
| Cancer type          |                         | References |
|                       | Lymph node metastasis   | Kleppe et al. (2011); Zhou et al. (2016); Hong et al. (2018); Longo et al. (2020) |
|                       | Bone metastasis         | Kumar et al. (1982); Tiwari et al. (2007); Zhang and Sun, (2013) |
|                       | Liver metastasis        | Xu et al. (2017); Wang et al. (2019a); Zhuo et al. (2020) |
|                       | Lung metastasis         | Park et al. (2017); Sakimura et al. (2019); Uesato et al. (2020) |
|                       | Brain metastasis        | Matsumura et al. (2009); Lemke et al. (2013); Matsumoto and Yoshida, (2019); Sasaki et al. (2019) |
|                       | Lymph node metastasis   | Kanda et al. (2011); Liu et al., 2018b; Ma et al., 2018; Seifert et al. (2020) |
|                       | Bone metastasis         | Saff et al. (2010a); Gauden et al. (2017); Outani et al. (2018) |
|                       | Liver metastasis        | Ho et al. (2020); Wang et al. (2021a) |
| Prostate cancer       | Lung metastasis         | Polistina et al. (2020) |
|                       | Brain metastasis        | Hernandez-Esquivel et al. (2018); Marchand Crety et al. (2020); Shida et al. (2023) |
|                       | Lymph node metastasis   | Li F. et al. (2019); Xu et al. (2020b); Zhao et al. (2020); Klingenberg et al. (2021) |
|                       | Bone metastasis         | Berish et al. (2018); Zhang, (2019); Wen et al. (2020) |
|                       | Liver metastasis        | Simons et al. (2020); Ma B. et al. (2021) |
adhesion function, and extracellular matrix molecules, such as integrins, have been determined to be related to the choice of organotrophic metastasis (Valastyan and Weinberg, 2011).

Integrins, a large family of adhesion molecules, can mediate cell–cell and cell–extracellular matrix interactions (Desgrosellier and Cheresh, 2010). Many integrins are associated with tumor angiogenesis, such as αvβ3, αvβ5, and α5β1 (Cascone et al., 2005; Lee et al., 2013a; Huang and Rofstad, 2018). β1 integrins bind to vascular cell adhesion molecule 1 (VCAM-1) on ECs and play an important role in trans-endothelial migration (Klemke et al., 2007). Integrins participate in tumor angiogenesis by interacting with the VEGF–VEGFR and ANG–TIE pathways (Klemke et al., 2007). αvβ3 integrin binds to the adhesion molecule L1 on ECs driving trans-endothelial migration (Voura et al., 2001). αvβ3 integrin is the most abundant and influential receptor among integrins on ECs and can regulate angiogenesis (De et al., 2005; Mahabeleshwar et al., 2008; Shattil and Ginsberg, 1997). It can be activated and colocalized with VEGF-R2 on ECs of proliferating blood vessels (Mahabeleshwar et al., 2008). VEGF-stimulated c-Src can be the phosphorylate β3 subunit on ECs, promoting VEGF-R2 phosphorylation and activation (De et al., 2005; Mahabeleshwar et al., 2008; Mahabeleshwar et al., 2007). In addition, αvβ3 is necessary for the survival and maturation of new blood vessels, and proliferative angiogenic EC apoptosis occurs after treatment with αvβ3 antagonists (Brooks et al., 1994). Briefly, integrin subunits α1, α2, α3, α4, α5, α6, α9, αv, β1, β3, and β5 are involved in physiological or pathological angiogenesis. Exosomes affect several steps of angiogenesis including motility, cytokine production, cell adhesion, and cell signaling (Taverna et al., 2012). These can improve the tumor environment before metastasis.

Although integrins are secreted by tumor cells, it is transported by exosomes to a distant organ (Peinado et al., 2017). Lyden et al. showed that tumor exosome integrins can determine organotropic metastasis. They suggested that tumor exosome integrins can fuse with organ-specific resident cells and activate Src phosphorylation and proinflammatory S100 expression to establish a pre-metastatic niche (Hoshino et al., 2015). In addition, more bodies of evidence identified that different integrins on the surface of exosomes play varied roles in metastasis to specific organs (Alderton, 2015; Hoshino et al., 2015; Paolillo and Schinelli, 2017). For instance, exosomal integrins α6β4 and α6β1 preferentially direct tumor cells to the lungs, and αvβ5 induces liver metastasis (Hoshino et al., 2015). Tumor exosomes can prepare pre-metastatic niches to facilitate organ-specific metastasis, even for cancer cells equipped to metastasize (Figure 5).

**TUMOR CELL GROWTH AT THE METASTASIS SITE**

Once tumor cells migrate to tissues and organs, TDEs provide them with a good growth environment and the ability to promote their growth.

**Tumor-Derived Exosomes Promote Pre-metastatic Niche Formation**

A pre-metastasis niche is a primary tumor in secondary organs and tissues that creates a favorable microenvironment for subsequent metastasis. Tumor-derived molecules secreted by primary tumors play a key role in preparing distant sites for the formation of new pre-metastasis niches, promoting metastasis and even determining the orientation of metastatic organs. These major tumor-derived molecules are usually tumor-derived secretory factors, extracellular vesicles (EVs), and other molecular components (Minciacchi et al., 2015). Exosomes containing protein, mRNA, or DNA fragments promote the pre-metastasis niche formation by mediating the communication between tumor cells and surrounding components or transferring their contents to recipient cells (Chin and Wang, 2016; Zhou et al., 2014).

Tumor cells are “seeds”. With tumor-secreting factors, tumor cell–secreting vesicles, and exosomes acting as catalysts, tumor...
| Cancer type | Exosome component | Target cells | Potential regulation | Roles in metastasis steps | References |
|-------------|-------------------|--------------|----------------------|---------------------------|------------|
| AML         | TGF-β             | NK cells     | NKG2D                | Step 3: immunosuppressive | Szczepanski et al. (2011) |
|             | DPP4              | Bone         | -                    | Step 5                    | Namburi et al. (2021)    |
|             | TGFβ/TGFβRI/II    | Mammary epithelial cells | HOXD10 and KLF4  | Step 1: enhance invasion ability | Singh et al. (2014) |
| Breast cancer | miR-10b          | Lung fibroblast | PKM                | Step 2: non-coding RNA influence angiogenesis | Fong et al. (2015) |
|             | miR-222           | Breast cancer cells | PRR RIG-I        | Step 5                    | Namburi et al. (2021)    |
|             | miRNA-503         | Microglia    | -                    | Step 3: immunosuppressive | Xing et al. (2018)       |
|             | Caveolin-1        | Breast cancer cells | -                 | Enhance metastases         | Campos et al. (2018)     |
|             | miR-193b          | Breast cancer cells | RAB22A            | Step 1: enhance invasion ability | Sun et al. (2018)        |
|             | CEMIP             | Brain endothelial and microglial cells | - | Step 2: angiogenesis | Rodrigues et al. (2019) |
|             | hsa-miR-940       | Osteoblastic | ARHGAP1 and FAM134A | Step 5                    | Hashimoto et al. (2018)  |
|             | miR-126a          | Lung         | S100AB/A9            | Step 2                    | Deng et al. (2017)        |
|             | miR-222           | Breast cancer cells | NF-xB             | Step 1                    | Ding et al. (2018)       |
|             | miR-130a-3p       | Breast cancer cells | RAB5B            | Step 1                    | Kong et al. (2018)       |
|             | miR-939           | Breast cancer cells | VE-cadherin       | Step 2: non-coding RNA influence angiogenesis | Di Modica et al. (2017) |
| Bladder Cancer | miR-770           | TNBCs        | STIMP                | Decrease metastases       | Li Y. et al. (2018)      |
|             | miR-4443          | Breast cancer cells | TIMP2              | Step 4                    | Wang H. et al. (2020)    |
|             | miR-210           | Endothelial cells | -                  | Step 2: non-coding RNA influence angiogenesis | Kosaka et al. (2013)     |
| CML         | miR-1910-3p       | Breast cancer cells | MTMR3             | Step 1: enhance invasion ability | Wang B. et al. (2020)    |
|             | miR-146a          | CAFs         | TXNIP                | Step 5                    | Yang et al. (2020b)      |
|             | miR-4443          | Liver        | -                    | Step 1: enhances invasion ability | Wang J. et al. (2020)    |
| Colon cancer | hsp 70            | MDSC         | STAT3                | Step 3: immunosuppressive | Chalmin et al. (2010)    |
|             | KRAS mutation     | Colon CA cells | -                  | Step 5: tumor growth       | Demory Beckler et al. (2013)    |
|             | TF                | EC           | -                    | Step 3: platelet activation | Garnier et al. (2012)    |
|             | miR-193a          | Colon cancer cells | Caprin1          | Step 5: decrease the growth of cells | Teng et al. (2017)       |
| Gastrointestinal | miR-92a-3p      | Colon cancer cells | -                  | Step 1: EMT               | Hu J. L. et al. (2019)   |
|             | lncRNA H19        | Colon cancer cells | miR-141            | Step 5: MET               | Ren et al. (2018)        |
|             | miR-21-5p; miR-155-5p | Colon cancer cells | BRG1          | Step 5                    | Lan et al. (2019)        |
|             | miR-182-3p        | Colon cancer cells | FOXO4             | Step 1: EMT               | Liu et al. (2019)        |
|             | GDF15             | HUVECs       | Smad                 | Step 2                    | Zheng et al. (2020)      |
|             | MCP-1; TGF-β      | Macrophages  | VEGF, ZO-1, occludin, and Claudin5 | Step 2: activating macrophages | Chen et al. (2016)    |
|             | miR-25-3p         | ECs          | -                    | Step 2: angiogenesis       | Zeng et al. (2018)       |
| Cervical cancer | miR-1229         | Cervical cancer cells | -                  | Step 2: angiogenesis       | Hu H.-Y. et al. (2019)   |
|             | Survivin          | Cervical cancer cells | - | Step 5: tumor growth | Khan et al., 2009; Khan et al., 2011 |
| GIST        | Ccr-PVT1          | Cervical cancer cells | MIR-1286     | Step 1: EMT               | Wang H. et al. (2020)    |
|             | miR-221-3p        | HLEC         | VASH1                | Step 2: Lymphatic vessel formation | Zhou et al. (2019) |
|             | miR-663b          | Cervical cancer cells | MGAT3          | Step 1: EMT               | You et al. (2021b)       |
|             | KIT               | Progenitor muscle cells | MMP1          | Step 1: Influence the relationship between tumor cells and cell matrix | You et al. (2021b) |
| Gastric cancer | miR-27a          | CAFs         | -                    | Step 1: EMT               | Wang J. et al. (2018)    |
|             | miR-130a          | ECs          | C-MYB                | Step 2: angiogenesis       | Yang et al. (2018)       |
|             | miR-135b          | ECs          | FOX1                 | Step 2: angiogenesis       | Bai et al. (2019)        |
| Glioblastoma | EGFR vIII         | Glioblastoma cells | VEGF, Bcl-x (L), p27 | Step 5: tumor growth         | Al-Nedawi et al. (2008) |
|             | matrix metalloproteinases, IL-8, PDGFs, and caveolin 1 | Glioblastoma cells | PI3K/PI2AKT   | Step 1: EMT               | Kucharzewska et al. (2013) |
|             | L1CAM             | Glioblastoma cells | FAK, FGFR         | Enhance metastases         | Pace et al. (2019)       |
|             | miR-148a          | Glioblastoma cells | CADM1          | Step 1                    | Cai et al. (2018)        |
|             | MDA-9/Syntenin    | Glioblastoma cells | CD83-AP-2       | Step 1                    | Das et al. (2018)        |

(Continued on following page)
| Cancer type | Exosome component | Target cells | Potential regulation | Roles in metastasis steps | References |
|-------------|------------------|-------------|----------------------|--------------------------|------------|
| HCC         | LncRNA CCAT2     | ECs         | -                    | Step 2: angiogenesis     | Lang et al. (2017a) |
|             | LncRNA POUSF3    | ECs         | -                    | Step 2: angiogenesis     | Lang et al. (2017b) |
|             | miR-584, 517c, 378 | HCC cells   | TAK1                 | Step 5: tumor growth     | Kogure et al. (2011) |
|             | miR-1247-3p      | Fibroblasts  | B4GALT3              | Step 5: TASCs            | Fang T. et al. (2019) |
|             | miR-122          | HCC cells   | IGF1R                | Step 5: tumor growth     | Qian and Pollard, (2010) |
|             | miR-27b-3p/miR-92a-3p | HCC cells | VE-cadherin          | Step 2: non-coding RNA   | Basu and Bhattacharyya et al. (2014) |
|             | miR-103          | ECs         | -                    | Step 5: TASCs            | Basu and Bhattacharyya et al. (2014), Fang J. H. et al. (2018) |
|             | miR-21, miR-10b  | HCC cells   | -                    | Step 1                  | Tian et al. (2019) |
|             | SMAD3            | HCC cells   | ROS                  | Step 4: attach           | Fu et al. (2018) |
|             | LOXL4            | HUVECs      | FAK/Src              | Step 6: tumor growth     | Li R. et al. (2020) |
|             | Vps4A            | HCC cells   | β-catenin            | Step 1: EMT             | Han et al. (2019) |
|             | miR-320a         | HCC cells   | CDK2, MMP2           | Step 1: EMT             | Zhang Z. et al. (2017) |
|             | incRNA FAL1      | HCC cells   | miR-1236             | Enhance metastases       | Li B. et al. (2018) |
|             | p120-catenin     | HCC cells   | STAT3                | Enhance metastases       | Cheng et al. (2019) |
|             | miR-372-3p       | HCC cells   | Rab11a               | Enhance metastases       | Cao et al. (2019) |
|             | Alpha-enolase    | HCC cells   | Integrin αβγ4        | Enhance metastases       | Jiang et al. (2020) |
|             | circ_MMP2        | HCC cells   | MMP2                 | Enhance metastases       | Liu et al. (2020) |
|             | miR-92a-3p       | HCC cells   | PTEN/Akt             | Step 1: EMT             | Liu et al. (2020) |
|             | LOX141           | HUVECs      | miR-590-3p/ROCK      | Step 2: angiogenesis     | You et al. (2021a) |
|             | miR-30a; miR-222 | HCC cells   | MIAP                 | Enhance metastases       | Du et al. (2021) |
|             | S100A4           | HCC cells   | STAP1                | Enhance metastases       | Sun et al. (2021) |
|             | miR-1290         | HCC cells   | SREK1                | -                       | Wang et al. (2021b) |
|             | circRNA-100338   | HUVECs      | -                    | Step 2: angiogenesis     | Huang et al. (2020b) |
|             | TIM11            | B cells     | TLR/MAPK             | Step 3: immunosuppressive| Ye et al. (2018) |
| HNC         | FasL             | T cells     | Jurkat               | Step 3: immunosuppressive| Kim et al. (2005) |
|             | miR-23a          | HUVECs      | TSGA10               | Step 2: angiogenesis     | Bao et al. (2018) |
|             | miR-103          | M2 macrophages | VEGF-A             | Step 2: angiogenesis     | Ludwig et al. (2017) |
|             | miR-23a         | HCC cells   | ZO-1                 | Step 2: angiogenesis     | Hsu et al. (2017) |
|             | miR-21           | HUVECs      | -                    | Step 2: angiogenesis     | Liu et al. (2016a) |
|             | LncRNA-p21       | HUVECs      | -                    | Step 2: angiogenesis     | Castellano et al. (2020) |
| Melanoma    | MET              | BM progenitor cells | -                  | Step 5: tumor growth     | Peinado et al. (2012) |
|             | PD-L1            | T cells     | PD-1                 | Step 3: immunosuppressive| Chen et al. (2018) |
|             | snRNA            | Lung epithelial cells | TLR3             | Step 5: TASCs            | Liu et al. (2016b) |
|             | CD151            | Lung, lymph node and stromal cells | -           | Step 4: location         | Malla et al. (2018) |
|             | Fas              | T cells     | MMP9                 | Step 3: immunosuppressive| Cai et al. (2012) |
|             | miR-191; let-7a  | Melanoma cells | -                   | Step 1: EMT             | Xiao et al. (2016) |
|             | Immunomodulatory, proangiogenic factors | Melanoma cells | -             | Step 2: angiogenesis     | Elostrom et al. (2014) |
|             | HSP70            | NK cells    | -                    | Step 3: immunosuppressive| Eilsner et al. (2007) |
|             | uPAR             | HMVECs; ECFCs | ERK1,2               | Step 2: angiogenesis     | Biagioni et al. (2021) |
|             | miR-106b-5p      | Melanoma cells | EphA4               | Step 5: MET              | Luan et al. (2021) |
|             | miR-155-5p       | CAFs        | SOCS1/JAK2/STAT3     | Step 2: angiogenesis     | Zhou X. et al. (2018) |
| Multiple myeloma (MM-MSC) | miR-15a       | MM cells     | FAK                  | Step 1: EMT             | Roccaro et al. (2013) |
|             | miR-let-7c       | ECs         | -                    | Step 2: TDEs promote angiogenesis by activating macrophages | Tian et al. (2021) |
| Mesothelioma | miR-135b        | EC          | HIF-FIH              | Step 2                   | Umezuz et al. (2014) |
|             | TGF-β            | Fibroblasts  | SMAD                 | Step 1: influence the relationship between tumor cells and cell matrix | Webber et al. (2010) |
| NPC         | HIF1α            | NPC cells   | LMP1                 | Step 1                  | Aga et al. (2014) |
|             | miR-23a          | EC          | TSGA10               | Step 2: angiogenesis     | Bao et al. (2018) |
|             | MMP13            | NPC cells   | -                    | Step 1                  | You et al. (2015) |
|             | circMYC          | NPC cells   | -                    | Step 2: angiogenesis     | Luo et al. (2020a) |

(Continued on following page)
cells can promote the formation of the “soil” (host microenvironment) in a distant metastasis site and promote the growth of cancer cells. Cancer metastasis is preceded by the interaction between the seed and soil (Y. Chen et al., 2015; Lambert et al., 2017; Liu and Cao, 2016; Minciacchi et al., 2015). Primary tumor cells influence and change the microenvironment at secondary organs by promoting pre-metastasis niche factor before tumor cells arrive (Chin and Wang, 2016; He et al., 2017).

The characteristics of a pre-metastasis niche include the following six aspects. First, pre-metastasis niche formation is accompanied by the recruitment of bone marrow–derived cells (BMDC) (Y. Chen et al., 2015; Minciacchi et al., 2015). Literature suggests that extracellular matrix metalloproteinase inducer (EMMPRIN) in cancer cells can induce the secretion and expression of many factors, such as SDF and VEGF, which mediate the recruitment of BMDC to the liver and lungs (Y. Chen et al., 2015; Minciacchi et al., 2015). Second, the immune cells involved in the pre-transfer niche formation are heterogenous. Pre-metastasis niche formation involves not only the recruitment of foreign cells but also the reprogramming of resident stromal cells, promoting metastasis. Pre-metastasis niche formation also involves the change of the ECM. Niche formation before transfer is accompanied by a change in the vascular system. Metastatic breast cancer cells reduce tight junctions between endothelial cells by secreting exosomes containing mir-105, thus inducing systemic vascular leakage and promoting metastasis (Kong et al., 2019). Breast cancer cells secrete exosomes containing mir-122, which are absorbed by niche cells, and reduce glucose consumption by targeting pyruvate kinase, thus increasing the proliferation rate and survival rate of cancer cells and promoting metastasis (Fong et al., 2015). Pancreatic cancer–derived exosomes, rich in macrophage migration inhibitory factors, recruit macrophages and induce pre-metastasis niche formation in the liver (Costa-Silva et al., 2015). Modulation of the pre-metastatic niche formation by controlling TDEs is a new area for future chemotherapy research.

**Tumor-Derived Exosomes Promote the Growth of Metastasis Tumor**

The growth of metastatic tumors requires suitable “soil”. MET returns the cancer cells to a highly proliferative state but with the
loss of their migration characteristics, enabling tumor growth at the metastasis site (Li K. et al., 2019). The characteristics of MET are increased expression of mesenchymal markers, such as vimentin, and decreased expression of epithelial markers, such as E-cadherin, compared with that of EMT (Wells et al., 2008). MET supports the reacquisition of epithelial features to promote metastasis (Brabletz et al., 2001). Several signaling pathways are involved in regulating MET, including transforming growth factor (TGF), fibroblast growth factors (FGFs), bone morphogenetic protein (BMP), epidermal growth factor receptor (EGFR), hepatocyte growth factor (HGF), Wnt/β-catenin, and Notch pathways (Said and Williams, 2011). TDEs can support tumor progression and remodel surrounding parenchymal tissues at the metastatic site (Greening et al., 2015). TDEs play an important regulatory role mediating EMT and transforming MET (Bigagli et al., 2019). Gastric cancer cell-derived exosomes can mediate the stimulation of proinflammatory cytokine IL-1β secretion and activate the Akt and MAPK pathways to promote proliferation ability of tumor cells (Bussard et al., 2016). In addition, TDEs can transform stromal cells into tumor-associated stromal cells (TASCs) that can secrete many pro-tumorigenic factors, including IL-6 and IL-8. These factors can enhance the proliferation ability of tumor cells (Bussard et al., 2016). Hence, TDEs can enable tumor cells to acquire proliferation capacity directly through the MET process or promote tumor proliferation by inducing TASC formation and releasing related factors (Figure 6). Nevertheless, there is still a dearth of research on exosomes and their contribution to MET.

CONCLUSION

Exosomes play an important role in every step leading to tumor metastasis. Although there are many reports on the role of exosomes in metastasis, much is left to be explored of the potential mechanisms underlying metastasis. Although a few studies still have unclear results, we have summarized the published literature on the substances that exosomes carry, their main functions in different tumors, the target cells affected, and steps involved in metastasis. (Table 2). Exploring these underlying mechanisms will enlighten us about cancer biology and contribute to the prevention of and therapeutic strategies for malignancies. We can manipulate TDEs to impede not just metastasis formation but even established metastases.

AUTHOR CONTRIBUTIONS

SB and ZW developed the first draft of the manuscript. All authors contributed to the planning, organization, data collection, and writing of the manuscript. JD completed all figures and provided critical edits. The final version of the manuscript was approved by all authors.

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REFERENCES

Abdelrahman, A. R. M., Gaafar, R. M., Baki, H. A., El Hosieny, H. M., Aboulkasem, F., Faraht, E. G., et al. (2008). Prevalence and Pattern of Lymph Node Metastasis in Malignant Pleural Mesothelioma. Ann. Thorac. Surg. 86 (2), 391–395. doi:10.1016/j.thorsurg.2008.04.012

Abe, Y., Suzuki, M., Tsuji, K., Sato, M., Kimura, H., Kimura, H., et al. (2020). Lung Metastasis from Gastric Cancer Presenting as Diffuse Ground-Glass Opacities. Respir. Med. Case Rep. 30, 101104. doi:10.1016/j.rmcrr.2020.101104

Agaya, M., Bentz, G. L., Raffa, S., Torrisi, M. R., Kondo, S., Wakisaka, N., et al. (2014). Exosomal HIF1α Signaling Promotes Invasive Potential of Nasopharyngeal Carcinoma-Associated LMP1-Positive Exosomes. Oncogene 33 (37), 4613–4622. doi:10.1038/onc.2014.66

Agarwal, A., Bulic, M., El-Ashty, D., and Cote, R. J. (2018). Circulating Tumor Cells. Cancer J. 24 (2), 70–77. doi:10.1097/PPO.0000000000000310

Ali, C., Ma, G., Deng, Y., Zheng, Q., Gen, Y., Li, W., et al. (2020). Nnn23-H1 Inhibits Lung Cancer Bone-specific Metastasis by Upregulating mitr-660-Sp Targeted SMARCA5. Thorac. Cancer 11 (3), 640–650. doi:10.1111/tc.14308

Aitokallio-Tallberg, A., Kärkkäinen, J., Pantzar, P., Wahlström, T., and Ylikorkala, O. (1985). Prostacyclin and Thromboxane in Breast Cancer: Relationship to Impedance. J. Thromb. Thrombolysis 2 (3), 199–206. doi:10.1007/bf012055-01886-63

Asoh, Y., Nakamura, M., Maeda, T., Shigai, T., Ogashiwa, M., Takeuchi, K., et al. (1990). Brain Metastasis from Primary Pericardial Mesothelioma. Neurol. Med. Chir. (Tokyo) 30 (11 Spec No), 884–887. doi:10.2176/nmc.30.884

Atay, S., Banskota, S., Crow, J., Sethi, G., Rink, L., and Godwin, A. K. (2014). Oncogenic KIT-Containing Exosomes Increase Gastrointestinal Stromal Tumor Cell Invasion. Proc. Natl. Acad. Sci. 111 (2), 711–716. doi:10.1073/pnas.1310501111

Bai, M., Li, J., Yang, H., Zhang, H., Zhou, Z., Deng, T., et al. (2019). miR-135b Delivered by Gastric Tumor Exosomes Inhibits FOXO1 Expression in Endothelial Cells and Promotes Angiogenesis. Mol. Ther. 27 (10), 1772–1783. doi:10.1016/j.ymthe.2019.06.018

Bakir, B., Chiarella, A. M., Pitaresi, J. R., and Rustgi, A. K. (2020). EMT, MET, Plasticity, and Tumor Metastasis. Trends Cell Biol. 30 (10), 764–776. doi:10.1016/j.tcb.2020.07.003
Bai, L., Lesnard, R., Dai, L., Cho, Y.-J., Pomeroy, S. L., Breakefield, X. O., et al. (2011). Tumour Microvesicles Contain Retrotransposon Elements and Amplified Oncogene Sequences. Nat. Commun. 2, 180. doi:10.1038/ncomms1380

Bale, R., Putzer, D., and Schullian, P. (2019). Local Treatment of Breast Cancer Liver Metastasis. Cancers 11 (9), 1341. doi:10.3390/cancers11091341

Bao, L., You, B., Shi, S., Shan, Y., Zhang, Q., Yue, H., et al. (2018). Metastasis-associated miR-23a from Nasopharyngeal Carcinoma-Derived Exosomes Mediates Angiogenesis by Repressing a Novel Target Gene TSGA10. Oncogene 37 (21), 2873–2889. doi:10.1038/s41388-018-0183-6

Basu, S., and Bhattacharyya, S. N. (2014). Insulin-like Growth Factor-1 Prevents miR-122 Production in Neighbouring Cells to Curtail its Intercellular Transfer to Ensure Proliferation of Human Hepatoma Cells. Nucleic Acids Res. 42 (11), 7170–7185. doi:10.1093/nar/gku346

Becker, A., Thakur, B. K., Weiss, J. M., Kim, H. S., Peinado, H., and Lyden, D. (2016). Extracellular Vesicles in Cancer: Cell-To-Cell Mediators of Metastasis. Cancer Cell 30 (6), 836–848. doi:10.1016/j.ccell.2016.10.009

Berish, R. B., Ali, A. N., Telmer, P. G., Ronald, J. A., and Leong, H. S. (2018). Gastric Cancer with Brain Metastasis and the Role of Human Epidermal Growth Factor 2 Status. Oncol. Lett. 15 (4), 5787–5791. doi:10.3892/ol.2018.3054

Bhagirath, D., Yang, T. L., Bucay, N., Sekhon, K., Majid, S., Shahryari, V., et al. (2018). Extracellular Vesicles IncRNA-P21 Expression in Tumor-Draining Lymph Node Mesenchymal Stromal Cells as a Prognostic Marker for Limited-stage Small Cell Lung Cancer. Cancer Res. 80 (14), 3860–3870. doi:10.1158/0008-5472.CAN-18-0743

Bhandari, V., and Jain, R. (2013). A Retrospective Study of Incidence of Bone Metastasis in Breast Cancer Patients. J. Clin. Diagn. Res. 7 (8), 2380–2383. doi:10.7860/jcdr/2013/jcdr13721

Biagioni, A., Laurenzana, A., Menicacci, B., Peppicelli, S., Andreucci, E., Bianchini, E., et al. (2021). uPAR-Expressing Melanoma Exosomes Promote Angiogenesis by VE-Cadherin, EGFR and uPAR Overexpression and Rise of ERK1,2 Activities. Mol. Cancer 20 (6), 1–13. doi:10.1186/s12943-020-0173-0

Bhandari, V., and Jain, R. (2013). A Prospective Study of Incidence of Bone Metastasis in Breast Cancer Patients. J. Clin. Diagn. Res. 7 (8), 2380–2383. doi:10.7860/jcdr/2013/jcdr13721

Bhandari, V., and Jain, R. (2013). A Prospective Study of Incidence of Bone Metastasis in Breast Cancer Patients. J. Clin. Diagn. Res. 7 (8), 2380–2383. doi:10.7860/jcdr/2013/jcdr13721

Bhandari, V., and Jain, R. (2013). A Prospective Study of Incidence of Bone Metastasis in Breast Cancer Patients. J. Clin. Diagn. Res. 7 (8), 2380–2383. doi:10.7860/jcdr/2013/jcdr13721

Brooks, P. C., Montgomery, A. M. P., Rosenfeld, M., Reisfeld, R. A., Hu, T., Klier, A. F., et al. (2001). Membrane-associated Hsp72 from Tumor-Derived Exosomes Inducing Apoptosis of Angiogenic Blood Vessels. J. Cell. Physiol. 188 (12), 537–547. doi:10.1002/jcp.10552

Bussard, K. M., Mutkus, L., Stumpf, K., Gomez-Manzano, C., and Marini, F. C. (2016). Tumor-associated Stromal Cells as Key Contributors to the Tumor Microenvironment. Breast Cancer Res. Treat. 15 (1), 10356–10361. doi:10.1007/s10537-015-0740-2

Bustamante, P., Piquet, L., Landreville, S., and Burnier, J. V. (2011). Uveal Melanoma Pathobiology: Metastasis to the Liver. Semin. Cancer Biol. 21, 65–85. doi:10.1016/j.semcancer.2010.05.003

Cai, Q., Zhu, A., and Gong, L. (2018). Exosomes of Glioma Cells Deliver miR-148a to Promote Proliferation and Metastasis of Glioblastoma via Targeting CADM1. Bull. of Cancer 105 (7–8), 643–651. doi:10.1016/j.bulcan.2018.05.003

Cai, Z., Yang, F., Yu, L., Yu, Z., Jiang, L., Wang, Q., et al. (2012). Activated T Cell Exosomes Promote Tumor Invasion via Fas Signaling Pathway. J. Cell. Physiol. 227 (12), 5954–5961. doi:10.1002/jcp.23046

Caldería, A., Giuffrida, R., di Meo, N., Massari, L., Dianzani, C., Cannavò, S. P., et al. (2020). Diagnosis and Treatment of Melanoma Bone Metastasis: A Multidisciplinary Approach. Dermatol. Ther. 33 (6), e14193. doi:10.1111/dth.14193

Campos, A., Salomon, C., Busto, R., Díaz, J., Martínez, S., Silva, V., et al. (2018). Carotenoid-Containing Extracellular Vesicles Transport Adhesion Proteins and Promote Migration in Breast Cancer Cell Lines. Nanomedicine 13 (20), 2597–2609. doi:10.2217/nmn-2018-0994

Candela, A. E., Ossoy, Y., Nalbant, O. A., and Sagol, O. (2008). Gastrointestinal Stromal Tumor of the Stomach with Lynch Node Metastasis. World J. Surg. Onc. 6, 97. doi:10.1007/s11717-006-9152-7

Cao, S.-Q., Zheng, H., Sun, B.-C., Wang, Z.-L., Liu, T., Guo, D.-H., et al. (2019). Long Non-coding RNA Highly Up-regulated in Liver Cancer Promotes Exosome Secretion. Wg (25), 3528–3529. doi:10.3748/wg.v25s13.5283

Carvalho, J., Teixeira, M., Silva, F. T., Esteves, A., Ribeiro, C., and Guerra, D. (2020). Esophageal Gastrointestinal Stromal Tumor with Rare Intracranial Metastasis. Case Rep. Gastrointest. Med. 2020, 1–4. doi:10.1155/2020/8842006

Cascone, I., Nappione, L., Maniero, F., Serini, G., and Bussolino, F. (2005). Stable Expression of TGFβ2 in Primary Human Myeloid-Derived Suppressor Cells. J. Immunol. 174 (11), 6719–6724. doi:10.4049/jimmunol.174.11.6719

Chalmr, F., Ladoire, S., Bussolino, F., and Marini, F. C. (2016). Gastric Cancer with Brain Metastasis and the Role of the Human Epidermal Growth Factor 2 Status. J. Clin. Med. 5 (4), 1387–1396. doi:10.3390/jcm.5041387

Cheng, Z., Lei, Z., Yang, P., Si, A., Xiang, D., Tang, X., et al. (2019). Exosome-transmitted P120-catenin Suppresses Hepatocellular Carcinoma Progression via STAS3 Pathways. Mol. Cancer 58 (8), 1389–1399. doi:10.1152/cancer.2012.23022
through the Release of Exosomes that Contain Long Non-coding RNA CCAAT2. *Oncol. Rep.* 38 (2), 785–798. doi:10.3892/or.2017.5742

Lazzari, H. L., Hu, G. W., Chen, Y., Liu, Y., Yu, W., Lu, Y. M., et al. (2017a). Glioma Cells Promote Angiogenesis through the Release of Exosomes Containing Long Non-coding RNA POU5F3. *Eur. Rev. Med. Pharmacol. Sci.* 21 (5), 959–972.

Laurini, R. N. (1974). Diffuse Pleural Mesothelioma with Distant Bone Metastasis. *Acta Pathol. Microbiol. Scand. A.* 82A (2), 296–298. doi:10.1111/j.1699-0643.1974.tb03854.x

Lázaro-Ibáñez, E., Sanz-Garcia, A., Visakorpi, T., Escobedo-Lucea, C., Siljander, P., Ayuso-Sacido, Á., et al. (2014). Different gDNA Content in the Subpopulations of Prostate Cancer Extracellular Vesicles: Apoptotic Bodies, Microvesicles, and Exosomes. *Prostate* 74 (14), 1379–1390. doi:10.1002/pros.22853

Lee, J.-K., Park, S.-R., Jung, B.-K., Jeon, Y.-K., Lee, Y.-S., Kim, M.-K., et al. (2013b). Exosomes Derived from Mesenchymal Stem Cells Suppress Angiogenesis by Down-Regulating VEGF Expression in Breast Cancer Cells. *PloS One* 8 (12), e84256. doi:10.1371/journal.pone.0084256

Lee, J., Kim, K. E., Choi, D.-K., Jung, J. Y., Jung, J.-J., Kiyonari, H., et al. (2013a). Angiopoietin-1 Guides Directional Angiogenesis through Integrin α V β 5 Signaling for Recovery of Ischemic Retinopathy. *Sci. Transl. Med.* 5 (203), 203ra127. doi:10.1126/scitranslmed.3006666

Leighton, J. L., Wozniak, M. A., Chen, S., Lynch, M. L., and Chen, C. S. (2012). Matrix R rigidity Regulates a Switch between TGF-Bi-Induced Apoptosis and Epithelial-Mesenchymal Transition. *MboC* 23 (5), 781–791. doi:10.1093/mboct/eim063

Leitinger, B. (2010). Transmembrane Collagen Receptors. *Cell
timeless* 1038/s41419-017-0030-7

Lee, J., Li, Z., Jiang, P., Peng, M., Zhang, X., Chen, K., et al. (2018). Circular RNA Lnc-Sox2ot Promotes EMT and Stemness by Acting as a ceRNA in Colorectal Cancer. *Mol. Cancer* 17 (1), 10078. doi:10.1038/s41598-019-45245-5

Liu, Y., Cao, X. (2016). Characteristics and Significance of the Pre-metastatic Niche. *Cell
timeless* 1038/s41388-018-0237-9

Liu, J., Agarwal, S. (2010). Mechanical Signals A ctivate Vascular Endothelial Growth Factor Receptor-2 to U pgrade Endothelial Cell Proliferation during Inflammation. *J. Biol. Chem.* 185 (2), 1215–1221. doi:10.4049/jimmunol.0903660

Liu, T., Zhang, X., Du, L., Wang, Y., Liu, X., Tian, H., et al. (2019). Exosome-transmitted miR-128-3p Increase Chemosensitivity of Oxaliplatin-Resistant Colon colorectal Cancer. *Mol. Cancer* 18 (1), 43. doi:10.1186/s12943-019-0981-7

Liu, Y., and Cao, X. (2016). Characteristics and Significance of the Pre-metastatic Niche. *Cell
timeless* 1038/s41388-019-0981-7

Liu, Y., Gu, Y., Han, Y., Zhang, Q., Jiang, Z., Zhang, X., et al. (2016a). Tumor Exosomal RNAs Promote Lung Pre-metastatic Niche Formation by Activating Alveolar Epithelial TLR3 to Recruit Neutrophils. *Cancer Cell* 30 (2), 243–256. doi:10.1016/j.ccell.2016.06.027

Liu, Y., Luo, F., Wang, B., Li, H., Xu, Y., Liu, X., et al. (2016b). STATH-regulated Exosomal miR-21 Promotes Angiogenesis and Is Involved in Neoplastic Processes of Transformed Human Bronchial Epithelial Cells. *Cancer Lett.* 370 (1), 125–135. doi:10.1016/j.canlet.2015.10.011

Liu, Y., Ren, W., Bai, Y., Wan, L., Sun, X., Liu, Y., et al. (2018a). Oxysrevertor Prevents Murine H22 Hepatocellular Carcinoma Growth and Lymph Node metastasis via Inhibiting Tumor angiogenesis and Lymphangiogenesis. *J. Nat. Med.* 72 (2), 481–492. doi:10.1007/s11418-018-1173-2

Liu, Y., Wu, T., Lu, D., Zhen, J., and Zhang, L. (2018b). CD44 Overexpression Related to Lymph Node Metastasis and Poor Prognosis of Pancreatic Cancer. *Int. J. Biol. Markers* 33 (3), 308–313. doi:10.1177/1774684717746951

Liu, Z.-L., Wang, C., Chen, H.-J., Li, X., Dai, L.-J., and Ding, Z.-Y. (2017). Bone Metastasis from Lung Cancer Identified by Genetic Profiling. *Oncol. Lett.* 13 (2), 847–850. doi:10.3892/ol.2016.5458

Lo Cicero, A., Majkowska, I., Nagase, H., Di Liegro, I., and Troeberg, L. (2012). Different gDNA Content in the Subpopulations of Prostate Cancer Extracellular Vesicles: Apoptotic Bodies, Microvesicles, and Exosomes. *Matrix Biol.* 313 (5), 107. doi:10.1016/j.matbio.2012.02.005

Longo, R., Bastien, C., Campitelli, M., Plastino, F., and Rozzi, A. (2020). Breast and Axillary Lymph Node metastasis from ovarian cancer: A case report. *Am. J. Case Rep.* 21, e925089. doi:10.12659/ajcr.925089

Lu, Y.-J., Yang, Y., Yuan, Y.-H., Wang, W.-J., Cui, M.-T., Tang, H.-Y., et al. (2020). A Novel Nomogram Based on SEER Database for the Prediction of Liver metastasis in Patients with Small-cell Lung cancer. *Ann. Palliat. Med.* 9 (5), 3123–3137. doi:10.21037/apm-20-886

Luan, W., Ding, Y., Xi, H., Ruan, H., Lu, F., Ma, S., et al. (2021). Exosomal miR-106b-5p Derived from Melanoma Cell Promotes Primary Melanocytes Epithelial-Mesenchymal Transition through Targeting EphA4. *J. Exp. Clin. Cancer Res.* 40 (1), 107. doi:10.1186/s13046-021-01906-w

Ludwig, N., and Whiteside, T. L. (2018). Potential Roles of Tumor-Derived Exosomes in Angiogenesis. *Expert Opin. Ther. Targets* 22 (5), 409–417. doi:10.1080/17422216.2018.1461411

Ludwig, S., Flors, T., Theodoraki, M.-N., Hong, C.-S., Jackson, E. K., Lang, S., et al. (2017). Suppression of Lymphocyte Functions by Plasma Exosomes Correlates with Disease Activity in Patients with Head and neck cancer. *Clin. Cancer Res.* 23 (16), 4843–4854. doi:10.1158/1078-0433.CCR-16-2819

Luga, V., Zhang, L., Viloria-Petit, A. M., Inanlou, M. R., Chiu, E., et al. (2016). Exosomal miR-21 Promotes Angiogenesis and Is Involved in Neoplastic Processes of Transformed Human Bronchial Epithelial Cells. *Cancer Lett.* 370 (1), 125–135. doi:10.1016/j.canlet.2015.10.011

Luo, K.-J., Chen, C.-X., Yang, J.-P., Huang, Y.-C., Cardenas, E. R., and Jiang, J. X. (2020a). Connexins in Lung cancer and Brain metastasis. *Front. Oncol.* 10, 599383. doi:10.3389/fonc.2020.599383

Luo, Y., Ma, J., Liu, F., Guo, J., and Gru, R. (2020b). Diagnostic Value of Exosomal circMyc in Radioresistant Nasopharyngeal Carcinoma. *Head & Neck* 42 (12), 3702–3711. doi:10.1002/hed.26441
Ubukata, H., Motohashi, G., Tabuchi, T., Nagata, H., Konishi, S., and Tabuchi, T. (2011). Overt Bone Metastasis and Bone Marrow Micrometastasis of Early Gastric Cancer. Surg. Today 41 (2), 169–174. doi:10.1007/s00595-010-4349-7

Ueda, S., Ooka, H., Yamashita, M., Hayashi, H., and Okayasu, T. (1973). Case of Pulmonary Metastasis of Ovarian Cancer erroneously Diagnosed and Treated as Pulmonary Tuberculosis for a Long Time. Nihon Kyubu Shikkan Gakkai Zasshi 11 (11), 684–687.

Usato, Y., Tamashiro, K., and Takatsuki, M. (2020). Long-term Survival after Repeated Resection for Lung Metastasis Originating from Pancreatic Cancer: a Case Report. Surg. Case Rep. 6 (1), 66. doi:10.1186/s40792-020-00832-x

Uluçkan, Ö. (2019). Mouse Models of Melanoma Bone Metastasis. Methods Mol. Biol. 1914, 343–348. doi:10.1007/978-1-4939-8997-3_19

Umezato, T., Tadokoro, H., Azuma, K., Yoshizawa, S., Ohyashiki, K., and Ohyashiki, H. (2014). Exosomal miR-135b Shed from Hypoxic Multiple Myeloma Cells Enhances Angiogenesis by Targeting Factor-Inhibiting HIF-1. Blood 124 (5), 3748–3757. doi:10.1182/blood-2014-05-576116

Valadi, H., Ekström, K., Bossios, A., Sjöstrand, M., Lee, J. J., and Lötvall, J. O. (2007). Exosome-Mediated Transfer of mRNAs and microRNAs Is a Novel Mechanism of Genetic Exchange between Cells. Nat. Cell Biol. 9 (6), 654–659. doi:10.1038/ncll01596

Valastyan, S., and Weinberg, R. A. (2011). Tumor Metastasis: Molecular Insights and Evolving Paradigms. Cell 147 (2), 275–292. doi:10.1016/j.cell.2011.09.024

Voura, E. B., Ramjeesingh, R. A., Montgomery, A. M. P., and Siu, C.-H. (2001). Tumor-Derived Exosomes Regulate Metastasis. Cancer Res. 61 (5), 1532–1536. doi:10.1158/0008-5472.CAN-00-1870

Wang, B., Mao, J.-h., Wang, B.-y., Wang, L.-x., Wu, H.-y., Xu, L.-j., et al. (2020). MiR-103a-5p Regulates Tumor Angiogenesis and Promotes Lung Cancer Metastasis. J. Cell Mol. Med. 24 (2), 1126–1135. doi:10.1111/jcmm.15025

Wang, X., Hu, L.-P., Qin, W.-T., Yang, Q., Chen, D.-Y., Li, Q., et al. (2021b). Identification of a Subset of Immunosuppressive P2RX1-Negative Neutrophils in Pancreatic Cancer Liver Metastasis. Nat. Commun. 12 (1), 174. doi:10.1038/s41467-020-20447-y

Wang, X., Luo, G., Zhang, K., Cao, J., Huang, C., Jiang, T., et al. (2018). Hypoxic Tumor-Derived Exosomal miR-301a Mediates M2 Macrophage Polarization via PTEN/P13K to Promote Pancreatic Cancer Metastasis. Cancer Res. 78 (16), 4586–4598. doi:10.1158/0008-5472.CAN-17-3841

Wang, X., Wang, B., Zhan, W., Kang, L., Zhang, S., Chen, C., et al. (2019e). Melatonin Inhibits Lung Metastasis of Gastric Cancer In Vivo. Biomed. Pharmacother. 117, 109019. doi:10.1016/j.biopha.2019.109018

Wang, X., Wang, X., Zhu, Z., Li, W., Yu, G., Jia, Z., et al. (2019). Prostate Carcinoma Cell-Derived Exosomal MicroRNA-26a Modulates the Metastasis and Tumor Growth of Prostate Carcinoma. Biomed. Pharmacother. 117, 109109. doi:10.1016/j.biopha.2019.109109

Wang, Y., Liu, W., Yu, Y., Liu, J.-j., Xue, H.-d., Qi, Y.-f., et al. (2020). CT Radiomics Nomogram for the Preoperative Prediction of Lymph Node Metastasis in Gastric Cancer. Eur. Radiol. 30 (5), 976–986. doi:10.1007/s00330-019-06398-z

Wang, S. N., Samson, P. P., Robinson, C. G., Bradley, J., Devarakonda, S., Du, L., et al. (2018). Non-small-cell Lung Cancer with Brain Metastasis at Presentation. Clin. Lung Cancer 19 (4), e373–e379. doi:10.1016/j.clcancer.2018.01.007

Weber, J., Steadman, R., Mason, M. D., Tabi, Z., and Clayton, A. (2010). Cancer Exosomes Trigger Fibroblast to Myofibroblast Differentiation. Cancer Res. 70 (23), 9621–9630. doi:10.1158/0008-5472.CAN-10-1722

Wells, A., Yates, C., and Shepard, C. R. (2008). E-cadherin as an Indicator of Mesenchymal to Epithelial Reversing Transitions during the Metastatic Seeding of Disseminated Carcinomas. Clin. Exp. Metastasis 25 (6), 621–628. doi:10.1007/s10510-007-9167-1

Wen, S., Wei, Y., Zen, C., Xiong, W., Niu, Y., and Zhao, Y. (2020). Long Non-coding RNA NEAT1 Promotes Bone Metastasis of Prostate Cancer through N6-Methyladenosine. Mol. Cancer (19), 171. doi:10.1186/s12957-020-01929-4

Xia, Y., Gopal, S., and Couchman, J. R. (2010). Syndecans as Receptors and Organizers of the Extracellular Matrix. Cell Tissue Res. 339 (1), 31–46. doi:10.1007/s00441-009-0829-3

Xiao, D., Barry, S., Kmetz, D., Egger, M., Pan, J., Rai, S. N., et al. (2016). Melanoma Cell-Derived Exosomes Promote Epithelial-Mesenchymal Transition in Primary Melanocytes through Paracrine/autocrine Signaling in the Tumor Microenvironment. Cancer Lett. 376 (2), 318–327. doi:10.1016/j.canlet.2016.03.050

Xie, Y., Zhang, B., Zhang, H., Li, W., Wang, K. P., and Shen, H. (2015). Evaluation of Lymph Node Metastasis in Lung Cancer: Who is the Chief Justice? J. Thorac. Dis. 7 (Suppl. 4), S231–S237. doi:10.3978/j.issn.2072-1439.2015.11.63

Xian, X., Gopal, S., and Couchman, J. R. (2010). Syndecans as Receptors and Organizers of the Extracellular Matrix. Cell Tissue Res. 339 (1), 31–46. doi:10.1007/s00441-009-0829-3

Xiao, D., Barry, S., Kmetz, D., Egger, M., Pan, J., Rai, S. N., et al. (2016). Melanoma Cell-Derived Exosomes Promote Epithelial-Mesenchymal Transition in Primary Melanocytes through Paracrine/autocrine Signaling in the Tumor Microenvironment. Cancer Lett. 376 (2), 318–327. doi:10.1016/j.canlet.2016.03.050

Xie, Z., Gao, Y., Ho, C., Li, L., Jin, C., Wang, X., et al. (2021). Exosome-delivered CD44v6/C1QBP Complex Drives Pancreatic Cancer Liver Metastasis by Promoting Fibrotic Liver Microenvironment. Gut 71, 568–579. doi:10.1136/gutjnl-2020-323014

Xing, F., Liu, Y., Wu, S.-y., Wu, K., Sharma, S., Mo, Y.-y., et al. (2018). Loss of XIST in Breast Cancer Activates MSN-C-Met and Reprograms Microglia via Exosomal miRNA to Promote Brain Metastasis. Cancer Res. 78 (15), 4316–4330. doi:10.1158/0008-5472.CAN-18-1102

Xu, D., Lin, X., and Qiu, X. (2020a). The Epithelial Gastrointestinal Stromal Tumor with Pulmonary Metastasis. Medicine (Baltimore) 99 (9), e19346. doi:10.1097/MD.0000000000019346

Xu, H., Xu, G. L., Li, X. D., Su, Q. H., and Dong, C. Z. (2021). Correlation between the Contrast-Enhanced Ultrasound Image Features and Axillary Lymph Node Metastasis of Primary Breast Cancer and its Diagnostic Value. Clin. Transl. Oncol. 23 (1), 155–163. doi:10.1007/s12094-020-02407-6
Zhang, X. (2019). Interactions between Cancer Cells and Bone Microenvironment Promote Bone Metastasis in Prostate Cancer. Cancer Commun. 39 (1), 76. doi:10.1186/s13046-019-0425-1

Zhang, Y.-F., Zhou, Y.-Z., Zhang, B., Huang, S.-F., Li, P.-P., He, X.-M., et al. (2019c). Pancreatic Cancer-Derived Exosomes Promoted Pancreatic Stellate Cells Recruitment by Pancreatic Cancer. J. Cancer 10 (18), 4397–4407. doi:10.7150/jca.27590

Zhang, Z., Li, X., Sun, W., Yue, S., Yang, J., Li, J., et al. (2017). Loss of Exosomal miR-320a from Cancer-Associated Fibroblasts Contributes to HCC Proliferation and Metastasis. Cancer Lett. 397, 33–42. doi:10.1016/j.canlet.2017.03.004

Zhao, Z., Liang, S., and Sun, F. (2020). LncRNA DLX6-AS1 Promotes Malignant Phenotype and Lymph Node Metastasis in Prostate Cancer by Inducing LARGE Methylation. Front. Oncol. 10, 1172. doi:10.3389/fonc.2020.01172

Zheng, X., Ma, N., Wang, X., Hu, J., Ma, X., Wang, J., et al. (2020). Exosomes Derived from 5-Fluorouracil-Resistant colon Cancer Cells Are Enriched in GDF15 and Can Promote Angiogenesis. J. Cancer 11 (24), 7116–7126. doi:10.7150/jca.49224

Zhong, Y., Lu, Q., Qiu, W., and Luo, Y. (2020). LINC00636 Promotes Lymph Node Metastasis and Cervical Cancer through Targeting NM23. Biosci. Rep. 40 (10). doi:10.1042/BSR20200367

Zhou, C.-F., Ma, J., Huang, L., Yi, H.-Y., Zhang, Y.-M., Wu, X.-G., et al. (2019). Cervical Squamous Cell Carcinoma-Secreted Exosomal miR-221-3p Promotes Lymphangiogenesis and Lymphatic Metastasis by Targeting VASH1. Oncogene 38 (8), 1256–1268. doi:10.1038/s41388-018-0151-x

Zhou, J., Sun, J.-Y., Wu, S.-G., Wang, X., He, Z.-Y., Chen, Q.-H., et al. (2016). Risk Factors for Lymph Node Metastasis in Ovarian Cancer: Implications for Systematic Lymphadenectomy. Int. J. Surg. 29, 123–127. doi:10.1016/j.ijsu.2016.03.039

Zhong, Y., Wu, K., Yang, J., Li, J., Li, J., He, Y., et al. (2018). Predicting Lymph Node Metastasis in Head and Neck Cancer by Combining Many-objective Radiomics and 3-dimensional Convolutional Neural Network through Evidential Reasoning*. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc., 1–4. doi:10.1109/EMBC.2018.8513070

Zhu, H., Jia, Z., Trush, M. A., and Li, Y. R. (2016). Nr2f2 Deficiency Promotes Melanoma Growth and Lung Metastasis. Ros 2 (4), 308–314. doi:10.20455/ros.2016.853

Zhu, Y.-J., Chen, Y., Hu, H.-Y., Zhou, Y.-W., Zhu, Y.-T., and Liu, J.-Y. (2020). Predictive Risk Factors and Online Nomograms for Synchronous Colon Cancer with Liver Metastasis. Front. Oncol. 10, 1681. doi:10.3389/fonc.2020.01681

Zhuo, S., Zhou, J., Ruan, G., Zeng, S., Ma, H., Xie, C., et al. (2020). Percutaneous Microwave Ablation versus Surgical Resection for Ovarian Cancer Liver Metastasis. Int. J. Hyperthermia 37 (1), 28–36. doi:10.1080/02656736.2019.1706767

Zong, Z.-H., Du, Y.-P., Guan, X., Chen, S., and Zhao, Y. (2019). CircWHSC1 Promotes Ovarian Cancer Progression by Regulating MUC1 and hTERT through Sponging miR-145 and miR-1182. J. Exp. Clin. Cancer Res. 38 (1), 437. doi:10.1186/s13046-019-1437-z

Zucchella, M., Dezza, L., Pacchiarini, L., Meloni, F., Tacconi, F., Bonomi, E., et al. (1989). Human Tumor Cells Cultured "In Vitro" Activate Platelet Function by Producing ADP or Thrombin. Haematologica 74 (6), 541–545.

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