



Review

Molecular Underpinnings of Brain Metastases

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Abstract: Brain metastases are the most commonly diagnosed type of central nervous system tumor, yet the mechanisms of their occurrence are still widely unknown. Lung cancer, breast cancer, and melanoma are the most common etiologies, but renal and colorectal cancers have also been described as metastasizing to the brain. Regardless of their origin, there are common mechanisms for progression to all types of brain metastases, such as the creation of a suitable tumor microenvironment in the brain, priming of tumor cells, adaptations to survive spreading in lymphatic and blood vessels, and development of mechanisms to penetrate the blood–brain barrier. However, there are complex genetic and molecular interactions that are specific to every type of primary tumor, making the understanding of the metastatic progression of tumors to the brain a challenging field of study. In this review, we aim to summarize current knowledge on the pathophysiology of brain metastases, from specific genetic characteristics of commonly metastatic tumors to the molecular and cellular mechanisms involved in progression to the central nervous system. We also briefly discuss current challenges in targeted therapies for brain metastases and how there is still a gap in knowledge that needs to be overcome to improve patient outcomes.

Keywords: brain metastases; molecular mechanisms; genetic features; central nervous system; breast cancer; lung cancer; melanoma



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1. Introduction

Brain metastases (BMs) are the most commonly diagnosed central nervous system (CNS) tumors in adults in the United States, estimated to occur up to ten times more frequently than primary brain tumors [1]. Advancements in treatments of primary tumors have led to prolonged survival of patients, increasing the pool of prevalent cancer patients at risk for BMs [2]. Coupled with advancements in neuroimaging and increased physician and patient awareness, diagnoses of BM can be made earlier, helping to improve patient outcomes. Lung cancer, breast cancer, and melanoma are widely recognized as the three most prevalent causes of BMs [3,4], with renal or gastrointestinal causes representing a good fraction of BMs in certain populations [1,5].

The challenge remains in characterizing the mechanisms under which BMs are initiated and how they progress. This encompasses exploring the molecular and genetic underpinnings of tumors linked to BMs, the factors influencing brain tropism, the dynamics between tumor cells and the brain's microenvironment, as well as the key mechanisms driving therapy resistance. Developments in molecular science in recent decades have

allowed researchers to obtain more information on the intrinsic metastatic progress of tumors but the brain remains an organ in which investigation of these fundamental molecular underpinnings has proved limited. In this review, we intend to compile the most up-to-date information and recent research made on metastatic mechanisms on the brain, focusing on the specifics of breast cancer, lung cancer, and melanoma in the hopes of uncovering research gaps that can be further investigated to improve targeted therapies and patient outcomes.

2. Brain Metastases Epidemiology

Despite their high frequency, there is a lack of systematic, nationwide reporting of BMs [2]. Although precise values of BMs are unknown, more than 100,000 people are diagnosed annually [2], and it has been estimated that around 20% of all patients with cancer will develop BMs [6]. However, only estimates can be made since incidence data of BMs from all cancer sites is not widely available, and most studies determine incidence, prevalence, and prognosis using data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) system [7], which takes the presence of synchronous BM at time of diagnosis of primary tumor as its only metric [3,7].

Breast cancer, lung cancer, and melanoma are among the most commonly associated tumors with BMs [1,5]. Autopsy studies report the incidence of BMs from lung tumors to be as high as 52%, but this varies depending on the histology of the tumor, the patient's sex, and the stage at the time of diagnosis [1]. For BMs from breast cancer, autopsy studies have reported an incidence of around 18–30%, while studies utilizing the SEER database usually report lower numbers [1,7,8]. This is largely due to the fact that BMs are rarely present at times of primary tumor diagnosis, excluding it from the database. Melanoma, ranked as the third leading cause of BMs, has shown incidence rates varying from 6% up to 28% in some population-based studies [3,8]. Research has demonstrated that BMs are more prevalent in melanomas located in the head and neck region compared to those on the extremities or trunk. This increased incidence is especially notable among male patients, younger individuals, and cases with greater Breslow thickness [9]. Further explorations about patient characteristics, such as age, sex, ethnicity, and their role in BM incidence, can be found in the work of Parker et al. [10].

The presence of synchronous BM at times of diagnosis of primary tumor is associated with poorer survival than finding extracranial metastases only, with median survival time being only 5 months [10]. A study comparing median overall survival (OS) in BMs patients from different solid tumors showed that breast cancer patients had the shorter OS, with 9.9 months in contrast to 10.3 and 13.7 months in melanoma and non-small cell lung cancer (NSCLC), respectively [11]. In contrast, another study suggested that with an OS of 10 months, breast cancer had longer survival than melanoma and NSCLC [3]. The molecular subtype of primary tumors significantly influences both the risk of BMs development and the associated prognosis [6]. In breast cancer, patients with human epidermal growth factor receptor 2 (HER2)-positive, hormone receptor-negative subtypes and those with triple-negative subtypes (negative for estrogen receptor (ER), progesterone receptor (PR), and normal HER2 expression) exhibit a higher incidence of BMs [12]. Notably, the triple-negative subgroup has the shortest median survival, at just 6.0 months [12]. In NSCLC, BMs are more frequently observed in cases with epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma receptor tyrosine kinase (ALK) rearrangements, with over 45% of patients developing CNS involvement within the first three years of survival [13]. Melanoma is the tumor with the strongest affinity for the CNS, with some autopsy studies reporting up to 75% of CNS involvement [14]. Jakob et al. found that CNS involvement was significantly higher in patients with mutations in the v-raf murine

sarcoma viral oncogene homolog B1 (*BRAF*) and neuroblastoma RAS viral (v-ras) oncogene homolog (*NRAS*), occurring in 24% and 23% of cases, respectively [15]. In comparison, patients with wild-type genes exhibited a CNS involvement prevalence of only 12% [15].

Knowledge of the epidemiology of BMs has improved screening, diagnostic, and treatment standards, and these data have been used to create prognostication tools such as the recursive partitioning analysis (RPA) score [16] and the newer Graded Prognostic Assessment (GPA) [17]. GPA, in particular, integrates patient data such as age, Karnofsky Performance Score (KPS), number of BMs, and presence of extracranial metastases with histologic and molecular data from the primary tumor in a diagnosis-specific index (DS-GPA) [18]. An updated, user-friendly GPA calculator can be accessed at BrainMetGPA.com.

There is an imperative need for improvement in the reporting of BMs to help identify patients at the highest risk for BMs. Moreover, this could promote research into the mechanisms that make these patients develop BMs in the first place and develop targeted therapies.

3. Genetic Predisposition for Brain Metastases

Metastatic lesions have a different molecular and genomic landscape than their primary tumors [19]. Phylogenetic analysis of tumor variations and migration histories have shown that clonal branching can occur within the primary tumor as often as it occurs after egressing the primary tumor [20], making circulating tumor cells (CTCs) and circulating tumor DNA better resources for capturing the tumor heterogeneity of metastatic progression [21]. Genome-wide sequencing analyses of CTCs have identified some mutations that can be considered crucial for determining organ tropism. Brastianos et al. sequenced matched BMs, primary tumors, and normal tissue of 86 patients and observed branched evolution from a common ancestor in the metastatic lesions [19]. They found that extracranial and lymph node metastases diverged from BMs but that even spatially and temporally separated BMs were genetically homogeneous to each other, indicating that the genetic alterations acquired by brain-tropic tumor cells are different from those in other metastatic sites and probably grant an advantage for survival in the brain [19]. To identify metastatic signatures, researchers developed a MetMap using 500 cell lines from 21 different solid tumor types in mouse xenograft models. This map revealed patterns of metastasis that are specific to certain organs and linked these patterns to various clinical and genomic characteristics [22]. The MetMap can help determine common molecular and genetic alterations that enhance metastasis to certain organs and potentially find new therapeutic approaches. The complex evolution tumor cells must endure to reach the brain and survive in it requires the cooperation of genetic, epigenetic, transcriptomic, metabolic, and immunologic factors and will only occur in brain-tropic cells, prepared to go through all those changes. Figure 1 offers a summary of specific mutations associated with brain tropism in different primary cancer types.

3.1. Genetic Features of Breast Cancer Brain Metastases

Advancements in gene expression profiling have greatly enhanced our understanding of breast cancer. The expression levels of three pivotal receptors in breast cancer—estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu)—help categorize it into four primary molecular subtypes. These include luminal A (ER-positive, PR variable, HER2-negative), luminal B (ER-positive, PR variable, HER2-positive or negative), HER2-enriched (ER-negative, PR-negative, HER2-positive), and basal-like (ER-negative, PR-negative, HER2-negative). Notably, the basal-like subtype constitutes the majority of “triple-negative” breast cancers [23,24].

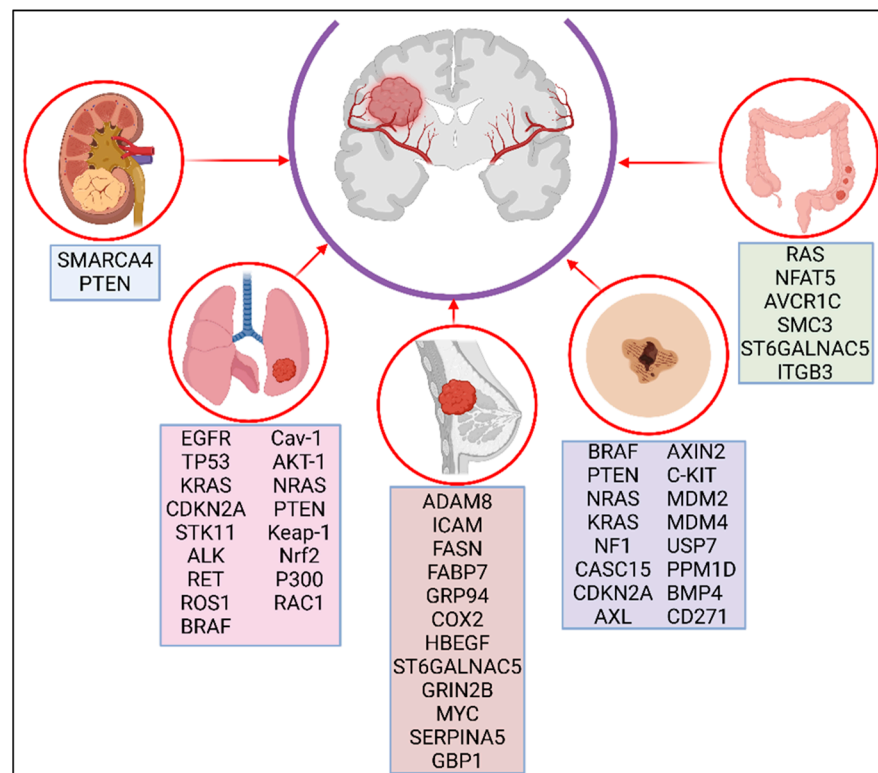


Figure 1. Genetic features of brain metastases in different cancer types.

Breast cancer molecular subtypes have preferential sites for metastases and possess a protein profile associated with homing of the metastatic site. A large, registry-based, single-institution study showed that patients with the HER2-positive and triple-negative subtypes had the highest incidence of BMs [25]. This follows the line of previous reports showing that basal-like/triple-negative tumors pose a higher risk for BMs, with HER2-enriched in second place [26,27]. However, HER2 and hormonal receptor statuses are hypothesized to shift upon reaching the brain [26]. Similarly, triple-negative brain-metastatic cells exhibit elevated β 2-adrenergic receptor mRNA and protein levels compared to their primary tumor counterparts, enhancing their proliferative capacity [28]. Triple-negative and basal-like breast cancer subtypes have been found to compromise the blood–brain barrier (BBB), whereas BMs from HER2/neu-positive breast cancers generally preserve BBB integrity [29]. This prompts the need for HER2/neu-positive cells to find alternative pathways to penetrate the BBB. HER2-HER3 dimers can form in breast cancer BMs and preferentially link to their ligand heregulin (also known as neuregulin-1) in the endothelial cells of the BBB [30]. Heregulin and HER2 signaling induces activation of extracellular cathepsin B and matrix metalloproteinase (MMP)-9, on which transmigration through the BBB is dependent [30]. MMP-9 enhances extracellular proteolysis and is upregulated by the metalloprotease-disintegrin *ADAM8*, which is highly expressed in all BMs but particularly breast cancer cells [31]. Cathepsins, on the other hand, are a family of proteases involved in protein degradation and processing, and their increased expression and activity could promote angiogenesis, invasion, and cell proliferation in some cancers [32,33]. In BMs, cathepsin S is produced by macrophages and breast cancer tumor cells, and it mediates BBB transmigration via proteolytic cleavage of the junctional adhesion molecule (JAM)-B [34]. Heregulin also upregulates intercellular adhesion molecule 1 (ICAM1), which is linked to increased invasion, motility, and metastasis in breast cancer [30]. Gene expression profiling of paired primary breast carcinomas and their corresponding BMs identified the upregulation of 1314 genes and the downregulation of 1702 genes in BMs relative to the

primary tumors [35]. This study also showed activation of the HER2 pathway and gains in transcript and protein expression of rearranged during transfection (*RET*) gene in BMs, both linked to disease progression [35]. Interestingly, there was no loss in *PTEN* expression in the analyzed specimens, which has been reported as a driver for BMs induced by astrocytes [36]. A nationwide cohort study in Finland determined that basal-like subtypes tended to first metastasize to the brain and had a protein profile with high expression of neural cell stemness-linked proteins nestin and prominin-1, which could potentially help breast tumor cells adapt to the brain [37].

Jin et al. trialed their MetMap with breast cancer cells that metastasized to the brain and demonstrated these cells present an altered lipid metabolism, which is necessary for tumor cell survival within the brain microenvironment [22]. Increased fatty acid synthase (*FASN*) gene expression in breast cancer cells has been identified as a way to overcome low lipid availability in the brain [38]. Enzymes associated with glycolysis, the tricarboxylic acid cycle, and oxidative phosphorylation pathways show elevated expression and could further promote efficient energy production via glucose oxidation. Furthermore, the pentose phosphate pathway and the glutathione system demonstrate heightened activity, contributing to the reduction in reactive oxygen species [39]. Whether reprogramming occurs before seeding the brain or is induced by the lipid-poor environment of the brain is not known, but it is suggested that high *FASN* expression increases cell propensity to colonize the brain [38]. Increased levels of fatty acid binding protein 7 (FABP7) are also seen in HER2-positive breast cancer BMs, and besides its role in metabolic reprogramming, FABP7 upregulates metastatic genes and pathways, such as Integrins-Src, MEK/ERK, Wnt/ β -catenin, and vascular endothelial growth factor (VEGF)-A [40,41]. Overexpression of proteins involved in fatty acid synthesis and degradation, as well as glucose-regulated protein 94 (GRP94), help cells compensate for the hypoglycemic stress they are subject to in the brain [42].

Other gene signatures expressed in breast cancer cells that metastasize to the brain include *COX2*, *HBEGF*, and *ST6GALNAC5*, which mediate BBB migration [43]; *PCDH7*, involved in linkage and interaction of tumor cells with astrocytes [44]; and *GRIN2B*, particularly increased in triple-negative breast cancers and involved in coding the GluN2 subunit of the NMDAR [45]. The glutamate-stimulated GluN2B-NMDAR signaling axis activation in cancer cells promotes colonization and metastatic tumor growth in the brain by forming pseudo-tripartite synapses in which tumor cells act as an astrocyte [45]. The *MYC* oncogene is highly expressed in CTCs from metastatic variants of breast cancer, and it regulates the adaptation of CTCs to the brain environment by reducing the oxidative stress produced by activated microglia via gene upregulation of glutathione peroxidase 1 (GPX1) [46]. A specific protein signature in CTCs consisting of HER2+/EGFR+/HPSE+/Notch1+ was termed “brain metastasis selected markers” by Zhang et al. and proved to increase CTC BMs compared with the parental CTC lines [47]. *SERPINA5* is significantly upregulated in breast cancer BMs, which induces the production of anti-PA serpins [46,48]. Also, the *GBP1* gene is upregulated in ER-negative breast cancer cells that develop BMs [49]. *GBP1* codes for the Guanylate-Binding Protein 1 (GBP1), binding activated T lymphocytes and enabling tumor cells to cross the BBB [49].

3.2. Genetic Features of Lung Cancer Brain Metastases

Lung cancer is primarily categorized into two major histological types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [50]. Within the NSCLC group, further classifications include adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, among other subtypes [50]. Whole exome sequencing of samples from NSCLC and SCLC patients showed that NSCLC had a higher percentage of seemingly metastases-

specific mutations, suggestive of branched evolution. In contrast, SCLC samples showed low heterogeneity, which suggests these tumors spread using a parallel and linear model of evolution [51]. In a systematic review of 72 studies comprising data from 2346 patients, the most common genetic alterations seen in BMs from NSCLC were *EGFR*, *TP53*, *KRAS* (Kirsten rat sarcoma viral oncogene), *CDKN2A* (cyclin-dependent kinase inhibitor 2A), and *STK11* [52]. Although not considered a driver gene, mutations in the tumor suppressor *TP53* are highly prevalent [53]. These mutations are linked to the development of new distant metastases [54] and exhibit strong concordance between primary NSCLC tumors and their corresponding BMs [55,56]. Mutations in the p53 protein disrupt cell cycle control, allowing the replication of damaged DNA and resulting in uncontrolled cell proliferation [57]. The *EGFR* family consists of four distinct members, all belonging to the ErbB/HER protein family: ErbB1, ErbB2, ErbB3, and ErbB4 [58]. Mutations in some tumors can continuously activate *EGFR*, enhancing tumor growth, invasion, and metastasis [59]. A meta-analysis of 26 studies demonstrated a positive association between *EGFR*-mutated NSCLC tumors and BMs, with an odds ratio (OR) of 1.58 (95% CI: 1.36–1.84), which confirms that *EGFR* mutation is a significant risk factor for BMs in NSCLC [60].

ALK gene fusion and *RET* gene fusion are also positive driver genes for NSCLC BMs [61]. *ALK* gene rearrangements frequently involve translocation or fusion with another partner gene, including echinoderm microtubule-associated protein-like 4 (*EML4*), the most prevalent in NSCLC [62,63]. *ALK* gene rearrangements result in the formation of an oncogenic *ALK* tyrosine kinase that persistently activates various downstream signaling pathways, including PI3K-AKT, MEK2/3-MEK5-ERK5, JAK-STAT, and MAPK. This continuous activation promotes increased proliferation and survival of tumor cells [64]. *ALK* fusions have been found to be constant between primary NSCLCs and their associated BMs [65]. Compared to *EGFR*-positive groups, *ALK*-positive patients have a higher incidence of BMs at the time of initial lung cancer diagnosis [66]. However, Rangachari et al. found a similar baseline incidence of BMs in *EGFR*-mutated and *ALK*-rearranged NSCLCs and an evolutionary increase in CNS involvement over time, with >45% of patients in both groups showing BMs after three years of survival [13]. Larger BM tumor size has also been reported in the *EML4-ALK* fusion groups compared to groups without fusion [67].

The *RET* protooncogene codes for a receptor tyrosine kinase and has been identified in NSCLC rearranged or fused with over a dozen partner genes, with the kinesin family member 5B gene (*KIF5B*) being the most common [68]. *RET* fusion-positive NSCLCs have BMs in 25% to 50% of cases [69–71]. Although the exact mechanism of how *RET* fusion promotes brain organotropism for tumor cells is not known, recent trial results in patients receiving the selective *RET* inhibitor selpercatinib demonstrated decreased CNS metastatic progression of *RET* fusion-positive NSCLC, with no CNS involvement at all in patients with no previous BMs [72]. These results suggest *RET* plays a fundamental role in promoting tumor cell growth and survival in the brain.

The C-ros oncogene 1 (*ROS1*) encodes a receptor tyrosine kinase that is structurally analogous to *ALK* [73]. NSCLC harboring *ROS1* rearrangements exhibits a cumulative incidence of CNS metastasis comparable to that of *ALK* fusion-positive tumors [74]. The incidence of BMs in *ROS1*-rearranged NSCLC patients at the time of diagnosis is approximately 20–30%, while it is as high as 50% in patients post-crizotinib therapy [75]. Crizotinib, an *ALK*/*MET* kinase inhibitor developed for *ALK*-rearranged NSCLC, is also effective in treating *ROS1*-rearranged tumors [76]. However, it has low BBB penetration, and even with therapy, *ROS1*-positive patients commonly progress to CNS metastasis [77]. Recent clinical trials have demonstrated the promising efficacy of novel tyrosine kinase inhibitors (TKIs) in overcoming crizotinib resistance in BMs of *ROS1*-rearranged NSCLC [78,79]. Additionally, *MET* amplification in NSCLC leads to the heightened expression and continuous activation

of the Met receptor, also known as the hepatocyte growth factor receptor (HGFR) [80]. This, in turn, promotes tumor cell migration and epithelial-to-mesenchymal transition phenotype [81]. Moreover, *MET* amplification has been found enriched in NSCLC BMs compared to paired primary tumors [82].

KRAS oncogene mutations are recognized as prevalent drivers in BMs from NSCLC, though their exact incidence varies across different studies [83,84]. The *RAS* genes encode a family of proteins that play critical roles in regulating cell growth, differentiation, and apoptosis [85], and *KRAS* mutation has been shown to upregulate PD-L1 expression in NSCLC through p-ERK signaling [86]. Activation of the PD-1/PD-L1 axis suppresses T-cell activity within the tumor microenvironment, allowing tumor cells to escape immune detection [87]. This immune regulation function of *KRAS*-mutations may improve tumor cell survival in the brain, but it also makes NSCLC BMs with *KRAS*-mutations more susceptible to treatment with immune checkpoint inhibitors (ICIs) [88].

Other less frequent mutations related to BMs from NSCLC include *BRAF* mutations [89], *Cav-1* [90], *AKT-1* [91], *NRAS*, and *PTEN* [92]. Gene expression signatures able to activate the WNT/TCF pathway are associated with lung adenocarcinoma metastases to the brain and lung [93]. The target genes *HOXB9* and *LEF1* within the WNT/TCF pathway play pivotal roles in facilitating chemotactic migration and promoting colony expansion in lung adenocarcinoma [93]. Furthermore, overexpression of the hyaluronan receptor by lung adenocarcinoma tumor cells increases inflammation and binding to hyaluronan-rich microenvironments such as the extracellular matrix of brain metastatic niches [94]. Aljohani et al. performed whole-genome sequencing on normal lung tissues, primary NSCLC tumors, their corresponding BMs, and CTCs. The study revealed that primary tumors contained mutations in genes associated with cell adhesion and motility. In contrast, BMs and CTCs exhibited mutations in genes responsible for adaptive and cytoprotective functions related to cellular stress responses, including *Keap-1*, *Nrf2*, and *P300* [95].

Several other adaptations can be seen in lung cancer CTCs. Analysis of tissue from lung adenocarcinoma and its matched CTCs and BMs using scRNA-seq have demonstrated that CTCs were in an intermediate place between BMs tumor cells, which leaned towards the epithelial phenotype and primary tumor cells, mostly found in a mesenchymal state [96]. Furthermore, *RAC1*, highly expressed in metastatic tumor tissue, was involved in adhesion, degradation, and VEGF signaling pathways [96]. CTCs overexpressing CD44v6 exhibited increased expression of the mesenchymal marker vimentin and reduced expression of the epithelial marker E-cadherin, thereby facilitating cell invasion and BMs through the activation of epithelial-to-mesenchymal transition [97].

3.3. Genetic Features of Melanoma Brain Metastases

The *BRAF* oncogene encodes a protein that is essential for the functioning of the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathway [98]. *BRAF* gene mutations cause MAPK/ERK continuous activation and signal transduction, increasing cell growth, migration, and proliferation [98]. Approximately half of advanced melanomas harbor mutations in the *BRAF* gene [99], which are linked to an increased frequency of BMs [100,101]. Moreover, the incidence of *BRAF* mutations is higher in BMs than in primary melanomas or metastases to other organs, suggesting there may be an independent evolution of subclones [102].

V600E is the most frequently occurring *BRAF* mutation in melanoma, and it also has the highest association with BMs [99,101]. The loss of the *PTEN* protein has been shown to decrease the time to melanoma BMs in patients with *BRAFV600* mutations [103]. However, *BRAF* mutations alone are not sufficient for BMs to occur, and there is proof that *PTEN* gene silencing cooperates with *BRAFV600E* mutations in melanoma progression via the

phosphoinositide 3-kinase (PI3K)/AKT pathway activation [104]. Although AKT1 activation can independently drive BM progression, it is augmented by *PTEN* silencing [105]. The bidirectional communication between the PI3K/AKT/mTOR and the MAPK/ERK pathways is critical for abnormal proliferation and therapy resistance in cancer [106].

BRAF-mutant melanomas have a significantly higher activation of AKT than *NRAS*-mutant melanomas [107]. However, *NRAS* mutations are also a significant risk factor for BMs, with a higher risk of developing BMs compared to patients with *NRAS* wildtype [15,108,109]. *NRAS* forms part of the Ras genes family, which also includes *HRAS* (Harvey Rat Sarcoma Virus) and *KRAS* (Kirsten Rat sarcoma virus) [110]. *NRAS* mutations are present in approximately 20% of human melanomas, whereas *HRAS* and *KRAS* mutations occur in only 1% and 2% of melanomas, respectively [111]. Both *NRAS* and *KRAS* mutations are enriched in melanoma BMs [112]. These mutated genes code for constitutively active Ras proteins that stimulate multiple signaling cascades, including the MAPK/ERK pathway and the PI3K/AKT pathway [110]. These are the same signaling cascades activated in tumors with *BRAF* mutations and *PTEN* silencing. However, *NRAS*-mutant melanomas exhibit normal *PTEN* levels, suggesting *BRAF*-mutant and *NRAS*-mutant tumors differ in their mechanisms of progression towards BMs [107,113]. Moreover, concurrent mutation of *NRAS* and *BRAF* is rare [113]. Evidence has also shown that the microenvironment in *NRAS*-mutant melanoma BMs is enriched in neutrophils in contrast to the primary melanoma [114]. In myeloproliferative neoplasms, a link between *NRAS* mutations and neutrophil hyperleukocytosis via activation of the granulocyte colony-stimulating factor (G-CSF) has been elucidated [115]. The exact mechanism of how neutrophils are seen in *NRAS*-mutated melanoma BMs remains to be exposed.

Other driver genes of melanoma are *NF1* inactivation and *C-KIT* mutations [116]. *NF1* functions as an inhibitor of Ras signaling, and its loss results in continuous activation of the MAPK and PI3K pathways. Likewise, mutations in *KIT*, a receptor tyrosine kinase, similarly initiate the activation of these pathways [117]. Patients with “quadruple negative” disease (no *BRAF*, *NRAS*, *NF1*, or *C-KIT* mutations) have the lowest risk of developing BMs [116]. This suggests the important implications of MAPK/ERK and PI3K/AKT activation in the metastatic progression of melanoma and their potential as therapeutic targets. Lessard et al. identified that metastatic melanoma cells exhibit elevated levels of the long intergenic non-coding RNA CASC15, which was associated with BMs in mouse xenograft models [118]. Additionally, increased expression of miR-301a in melanoma is linked to overall metastatic activity [119]. Although various other non-coding RNAs have been recognized as important regulators of melanoma progression and resistance to therapy, their specific roles in BMs remain unclear [120]. Alterations in the *CDKN2A* gene or the p16-cyclin D-CDK4/6-retinoblastoma protein pathway (CDK4 pathway) have been found in virtually all melanoma cell lines [121,122]. CDK4 activation inhibits the retinoblastoma protein, promoting cell cycle progression, and is usually associated with tumor suppressor *CDKN2A* (p16INK4A) deletion, furthering melanoma cell survival [121]. It has also been found that patients with deletions in *CDKN2A* genes also display *MDM2* and *MDM4* amplifications, which is associated with a higher risk for metastasis to the brain [123]. *MDM2* and *MDM4* are negative regulators of p53; therefore, amplifications in *MDM2/4* decrease p53 function. The ubiquitin-specific protease 7 (*USP7*), a protein that protects *MDM2/4* from proteasomal degradation, is increased in metastatic melanoma [124]. *PPM1D*, another negative regulator of p53, is overexpressed in metastatic melanoma, and gain-of-function mutations in immune cells promote immune escape and proliferation [125]. Even though *CDKN2A*, *MDM2/4*, *USP7*, or *PPM1D* are not considered driver mutations, their effect in the CDK4 and p53 pathways has a pro-metastatic effect.

The nerve growth factor (NGF) receptor CD271 is a low-affinity receptor for NGF, a member of the neurotrophin family proteins, highly expressed in melanoma cells even before BMs [126,127]. NGF and neurotrophin 3 (NT-3) are highly expressed in tumor-adjacent tissues in the brain, suggesting brain organotropism between the CD271-positive cells and the brain tumor niche [128]. CD271 has also been linked to SOX10, a specific marker of the neural crest, and it provides melanoma cells with neural crest stem cell signatures, a common ancestor between melanocytes, glial cells, and neurons [129]. It has been reported that aggressive melanoma cells hijack neural crest-related signaling pathways to increase plasticity and facilitate invasion in the brain [130]. *BMP4* and the Wnt target gene *AXIN2* are important for neural crest development and are also upregulated in BMs, suggesting melanoma acquires neuronal-like characteristics that make them highly efficient in metastasizing the brain [130]. Neurotrophins further stimulate invasion by producing extracellular matrix degradative enzymes such as heparinase, which destroys the basement membrane of the BBB [128]. AXL, a receptor tyrosine kinase, is involved in promoting epithelial-to-mesenchymal transition, treatment resistance, and metastasis in melanoma BMs [131]. AXL is typically upregulated in CD271-positive BMs and may actively contribute to immune escape. This occurs through mechanisms such as reduced HLA class I expression, increased production of immunosuppressive cytokines and PD-L1, and diminished infiltration of CD8⁺ lymphocytes [132]. The immune microenvironment of BMs has shown distinct characteristics when compared to their primary tumors or extracranial metastases, such as decreased IFN γ production and activated T-cells [114]. Moreover, there are fewer inflammatory cytokines, immune cell infiltrates, and maturation of dendritic cells, whereas there is enhanced oxidative phosphorylation [114]. Altogether, melanoma cells can invade and proliferate in the brain through a series of genetic, molecular, and immune mechanisms.

3.4. Genetic Signatures in Other Brain Metastases

The mechanisms for the metastatic spread of colorectal cancer to the brain are still not completely understood. There is an association between *RAS* mutations in colorectal tumors, especially *KRAS* mutations, and increased risk of BMs [133–135]. High expression of *NEAT5* (Nuclear Factor of Activated T Cells 5), *AVCR1C* (Activin A Receptor Type 1C), and/or *SMC3* (Structural Maintenance of Chromosomes 3) is associated with colorectal BMs [136]. Certain gene variants are also associated with increased risk for BMs and BBB penetration, such as *ST6GALNAC5*, which encodes for a sialyltransferase involved in cell–cell adhesion, and *ITGB3*, which encodes integrin β 3, stimulating adhesion, migration, and angiogenesis [137]. While colorectal cancer was once believed to be an extremely rare cause of BMs, some studies have found that colorectal cancer patients can have an incidence of up to 14.6% of BMs [138]. Most of those patients were asymptomatic at the time of diagnosis. Furthermore, synchronous lung metastases increase the risk of BMs [139]. This finding suggests that the genomic or molecular alterations needed to metastasize to the brain are common to other sites and acquired early during metastatic progression.

A genomic next-generation sequencing study in renal cell carcinoma BMs found an enrichment of the *SMARCA4* gene in BM tumors in contrast with primary tumor and extracranial lesions [140]. *SMARCA4* encodes a subunit of the SWI/SNF chromatin-remodeling complex, which functions as an epigenetic regulator of gene expression and plays a critical role in tumor suppression [141]. Renal cell carcinoma that metastasized to the brain also showed more PI3K pathway alterations, primarily *PTEN* inactivation, than cells that did not metastasize to the brain [142]. As previously discussed with melanoma BMs, the PI3K pathway plays an important role in metastatic progression. Wyler et al. demonstrated that the expression of chemokines and their receptors play a significant role

in the propensity of renal cell carcinoma to metastasize to the brain [143]. Specifically, the levels of the monocyte-specific chemokine CCL7 and its receptor CCR2 were found to be elevated in BMs compared to primary tumors [143]. This suggests that the recruitment of monocytes and macrophages is a key factor contributing to the establishment of BMs [143]. Of note, renal cell carcinoma is a highly immunogenic entity: Harter et al. demonstrated that they had the highest levels of CD3+ and CD8+ lymphocytes and the strongest PD-1 levels, which correlates to smaller brain tumor sizes [144].

4. Molecular Mechanisms of Metastatic Progression to the Central Nervous System

As early as 1889, Stephen Paget described the pattern in which breast cancers metastasized predominantly to certain organs more than others and compared it to seeds that can only grow on suitable soil [145]. Despite being over a hundred years old, this “Seed and Soil” theory continues to be valid today. The potential of tumor cells to metastasize depends on interactions between selected metastatic cells and mechanisms unique to some organ microenvironments in which chemotaxis and growth can occur [146]. Studies of multiphoton laser scanning microscopy have allowed us to follow individual tumor cells that metastasize to the brain and determine the multi-step process they go through for metastasis [147]. However, this metastatic cascade is an inherently inefficient process, prompting tumor cells to develop adaptations to increase their possibilities of survival. In this section, we focus on brain and CNS metastases and review the key steps and players involved in metastatic progression. Figure 2 offers a visual summary of this metastatic process and the primary elements playing a role in it.

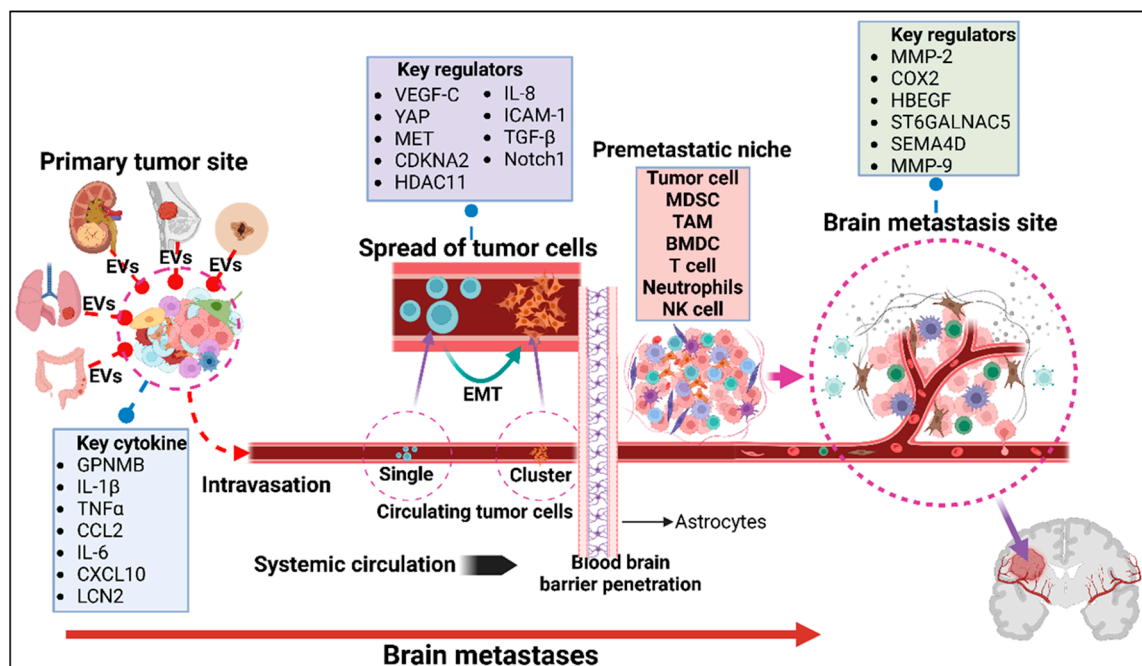


Figure 2. Molecular mechanisms of brain metastatic progression.

4.1. The Pre-Metastatic Niche

First of all, tumor cells confirm their destination and prepare it for their arrival before leaving the primary tumor [148]. This co-evolution of tumor and target-organ microenvironment forms the “pre-metastatic niche” (PMN) [149], and it involves the interaction between tumor-derived factors, tumor-recruited cells, and local stroma [150]. The specific

modifications that occur at the PMN are needed to favor the survival of tumor cells once they arrive, and a wide array of molecules and cells participate in this process.

Inflammation plays a crucial role in cancer progression and migration [151]. Studies have shown that hematopoietic progenitor cells from the bone marrow migrate to pre-metastatic sites and form clusters prior to tumor cell arrival, facilitated by receptor–ligand interactions [152]. At these sites, they establish an inflammatory chemokine gradient that attracts additional bone marrow-derived cells and tumor cells to the PMN [152], a process further supported by increased VEGF-induced vascular density [153]. Many inflammatory chemokines have been identified to help in the recruitment of bone marrow-derived myeloid cells to PMN and favor metastasis in several organs via suppression of host immunity, angiogenesis, and remodeling of tissue [154]. In the brain, granulocyte-derived molecules like lipocalin-2 (LCN2) trigger inflammatory activation of astrocytes, which in turn recruit myeloid cells to the brain [155]. Glycoprotein nonmetastatic melanoma B (GPNMB) expressed by macrophages and microglia is also linked to neuroinflammation, as it is upregulated in microglia, producing higher levels of inflammatory cytokines, including interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α) [156]. Increased expression of GPNMB reduces T-cell activation by interacting with syndecan-4, enabling melanoma cells to escape immune detection and destruction [157]. There is also a contrasting anti-inflammatory role for GPNMB when bound to CD44 in astrocytes, showing deduction of nitric oxide synthase, reactive oxygen species, nitric oxide, and IL-6, but its exact effect on BMs has not been elucidated [158].

Cells in the PMN can produce pro-inflammatory cytokines and other pro-tumoral factors, but these can also come from distant cells either in the primary tumor or the bone-marrow and reach their target organs through extracellular vesicles. Extracellular vesicles selectively fuse with resident cells at their intended destinations, displaying unique integrin expression profiles linked to their metastatic organotropism [159]. Extracellular vesicles, including exosomes, microvesicles, and oncosomes, are membrane-enclosed particles released by various cell types into the extracellular space [160]. Extracellular vesicles can cross the intact BBB via transcytosis, facilitated by the upregulation of the endocytic pathway in brain endothelial cells, making them efficient carriers for tumor-derived factors [161]. These extracellular vesicles-derived factors interact with the soluble matrix, influencing the formation of a PMN by activating and recruiting inflammatory and resident cells [162,163].

Ruan et al. demonstrated how brain cells are reprogrammed by breast cancer-derived extracellular vesicles carrying high levels of miR-199b-5p, which targets solute carrier transporters in astrocytes and neurons, leading to the retention of metabolites in the extracellular space for tumor cells to use [164]. Exosomes carrying miR-122 microRNA can suppress glucose uptake by non-tumor cells in the PMN, which increases nutrient availability for tumor cells [165]. Proteomic analysis of exosomes derived from brain metastatic cells showed increased expression of hyaluronan-binding protein (CEMIP) [166]. Endothelial and microglial cells internalizing CEMIP-positive exosomes triggered angiogenesis and inflammation in the perivascular niche, facilitating brain vascular remodeling and metastasis [166]. BMs and PMN formation primarily take place in the brain parenchyma, traditionally regarded as an immune-privileged site [167]. The metastatic brain tumor microenvironment exhibits a unique cellular and non-cellular composition even when compared with that of primary tumors such as glioblastoma [168]. The extracellular matrix, an integral component of the PMN, has distinct protein arrangements regulated both by tumor and stromal cells, with organ-specific features [169]. For example, the extracellular matrix in metastatic brain tumors shows a highly organized appearance, with thick, dense collagen bundles clustering the tumor cell regions inside well-defined borders [168]. A proteomic analysis of NSCLC BMs has also shown an increased expression of invasion-related

molecules such as integrin- α 7, integrin- β 1, and syndecan-4 in the extracellular matrix [170]. Expression of certain extracellular matrix proteins such as tenascin-C in the brain restricts T-cell migration, decreasing their concentration in the PMN and their ability to lyse tumor cells [171], promoting an immunosuppressive landscape.

Long non-coding (lnc) RNA increases the release of CCL2 to recruit macrophages in breast cancer BMs [172], while tumor cell-derived ANXA1 promotes microglial migration [173]. Later, both macrophages and microglia are activated via the PI3K signaling pathway to act as metastasis promoters [174]. The interaction between melanoma cells and microglia supports BM progression through melanoma-derived IL-6, which enhances STAT3 phosphorylation and SOCS3 expression in microglia, thereby aiding melanoma cell survival [175]. Moreover, increased expression of MMP-3 in microglia facilitated melanoma cell growth [176]. Both brain-resident microglia and bone marrow-derived macrophages are present in brain tumors and are actively recruited to the tumor microenvironment [177]. Microglia are regarded as the main contributors to CNS-resident tumor-associated macrophages (TAMs) [178]. TAMs represent the predominant type of immune cells detected in BMs, irrespective of primary tumor origin [168]. Karimi et al. used mass cytometry to analyze the tumor microenvironment of 139 high-grade gliomas and 46 BMs, achieving single-cell spatial resolution of immune lineages and activation states [179]. They found that monocyte-derived TAMs constituted about 30.5% of the tumor microenvironment, compared to 9.2% for resident microglia [179]. Collectively, TAMs in the microenvironment of BMs do not fall into the classic polarization of M1 (inflammatory, IFN γ -activated) and M2 (immune-modulating, IL4-activated) phenotypes [180,181], and their phenotype can remain highly plastic in response to different signals and interactions within the microenvironment [182,183].

Both TAMs and tumor cells can interact with lymphocytes in the tumor microenvironment of BMs to produce defective T cell states [181,184]. In an integrated analysis of brain tumor microenvironments, CD4⁺ T cells showed a hyporesponsive, anergic phenotype, while CD8⁺ T cells exhibited an exhaustion signature such as the one seen in chronic activation [181]. The chemokine interferon- γ inducible protein 10 (Cxcl10) is upregulated in myeloid-derived microglia, and despite its role as a chemotactic factor for lymphocytes, it also attracts more CNS-myeloid cells carrying immunosuppressive proteins that reduce T cell activation and promotes tumor growth [183]. Multiomics analyses have shown that in lung cancer BMs, the separation of myeloid and lymphoid cells into specific compartments is driven by unique cytokine networks [185]. Other cells, such as NK cells, neutrophils, and T cells, can also be found in BMs microenvironments, with distinct densities depending on the primary tumor type [179,184]. For example, in melanoma BMs there is higher neutrophil infiltration and increased CD8⁺ T cells in the margins of the tumor [179,181]. CD8⁺ T cells and other leukocytes have also been found in the CSF, matching the immune microenvironment of BMs and proving that cell exchange occurs between these compartments [186].

PMN formation in the brain, therefore, relies on intricate and diverse processes involving factors derived from tumor cells and brain-resident cells. The combination of inflammation, angiogenesis, immunosuppression, and selective brain-tropism help model the PMN, subsequently promoting tumor cell invasion and growth.

4.2. Lymphatic Spread of Tumor Cells

Given the genetic heterogeneity observed between primary tumor cells and their metastatic counterparts, it is suggested that tumor cells can arrive at their destination both through direct hematogenous spread from the primary tumor and sequential progression from lymph nodes [187]. In solid tumors, intravasation into lymphatic vessels and lymph

nodes is more common and usually precedes metastasis to the vascular system [188], while tumor cells reach the lymphatic vessels alone or form clusters [188,189]. It has been demonstrated that once in the lymph node parenchyma, tumor cells can directly invade the lymph node vessels to enter the blood circulation, bypassing the thoracic duct [190,191].

Initially, the release of inflammatory chemokines from tumor and inflammatory cells in the tumor microenvironment induces lymphangiogenesis and enhances lymphatic intravasation [187]. Tumor-derived cytokines, soluble factors, and extracellular vesicles can prime the stromal cells in lymph nodes to create a lymphatic metastatic niche similar to the PMN [192,193]. VEGF-C overexpression in tumor cells has been shown to induce hyperplasia of the peritumoral lymphatic vessels, enhancing flow rate and delivery to lymph nodes [194]. The transport to lymphatic lymph nodes is actively regulated by signaling pathways, including the SDF-1/CXCR4 axis [195], the CCL1–CCR8 interactions [196], and the VEGF-C-induced upregulation of CCR7–CCL21 signaling [197]. VEGF-C enhances immune tolerance in murine melanoma models by inducing the deletion of antigen-specific CD8(+) T cells through lymphatic endothelial cells [198]. Chronic IFN signaling during the initial anti-tumor response induces epigenetic rewiring of tumor cells in the lymph nodes, upregulating PD-L1 and promoting immune tolerance [199,200]. Together with increased MHC-I expression, tumor cells are able to evade NK cells and resist T cell-mediated cytotoxicity [199]. Cancer cells in the lymph nodes also exhibit elevated expression of MHC-II, increasing regulatory T cells while decreasing CD4(+) T cells [201].

Tumor cells in the lymph nodes also undergo metabolic adaptations. Metastasis-initiating cells show elevated expression of the fatty acid receptor CD36 and lipid metabolism genes. Studies have shown that palmitic acid or a high-fat diet can enhance CD36 expression, increasing the metastatic potential of tumor cells [202,203]. Genes involved in the fatty acid oxidation pathway are upregulated in lymph node-metastatic tumor cells through bile acid-induced activation of the yes-associated protein (YAP) [204]. Moreover, lipid metabolism is also important for tumor cells to overcome ferroptosis in the lymphatic environment since the hallmark of ferroptosis is the lethal accumulation of lipid peroxidation products [205]. In the lymph, however, there are low iron levels and high levels of oleic acid, glutathione, and other antioxidants, decreasing exposure to oxidative stress and making tumor cells more resistant to ferroptosis when they enter the blood [206].

The reprogramming that occurs in the lymph nodes ultimately leads to a survival and metastatic advantage for tumor cells. Phylogenetic studies of metastatic breast cancer tumors have discerned that the genetic heterogeneity between primary tumors and their distant metastases comes from either a monoclonal metastatic precursor that evolves outside the primary tumor or polyclonal precursors originated from the primary tumor from the start [21]. Phylogenetic studies for other types of cancer have yielded similar results [207,208]. Mohammed et al. discovered that tumor cells reaching the lymphatic vessels exhibit a gene and protein profile indicative of a hybrid epithelial/mesenchymal phenotype and stem cell-like characteristics, which contribute to their high metastatic potential [188]. In mouse melanoma models, key driver mutations such as *BRAF* alterations and changes in genes like *MET* or *CDKNA2* (either gain or loss) are observed to occur within lymph nodes [209]. Cells with driver mutations combined with a loss of tumor suppressor genes that would normally help eliminate cells with mutations can, therefore, undergo transformation freely toward the development of melanoma [99]. Chromatin modifier histone deacetylase 11 (HDAC11) serves as a dynamic epigenetic regulator in the lymph nodes microenvironment as demonstrated in breast cancer cells models, in which increased HDAC11 expression inhibits cell cycle suppressors E2F7 and E2F8, promoting tumorigenesis and growth in the lymph nodes while downregulation of HDAC11

upregulates RRM2, promoting migration and egress from lymph nodes to distant sites predominantly through the draining blood vessels of lymph nodes [210].

4.3. Hematogenous Spread of Tumor Cells

Tumor cells can also enter directly from the primary tumor into the bloodstream. A clone subpopulation of breast cancer cells reprogrammed to overexpress the proteins Serpine2 and Slpi showed vascular mimicry and efficient blood intravasation [211]. However, only a small percentage of tumor cells that enter the circulation will survive the environmental pressures of the bloodstream to successfully metastasize [212]. CTCs, or tumor microemboli, initially enter the bloodstream as single cells but rapidly aggregate into clusters. This clustering, occurring after detachment from the primary tumor, is facilitated by the cancer stem cell marker CD44 through intercellular CD44-CD44 homophilic interactions [213]. Stemness of tumor cells is induced by epithelial-to-mesenchymal TRANSITION, and it supports migration [214]. Both mesenchymal and epithelial tumor cells enter the bloodstream and contribute to CTC clusters, with evidence indicating a dynamic plasticity between epithelial and mesenchymal states [214,215]. Hydrodynamic shear stress in the systemic circulation promotes epithelial-to-mesenchymal transition in CTCs. This process is driven by the generation of reactive oxygen species and nitric oxide and the suppression of extracellular signal-regulated kinase and glycogen synthase kinase β signaling pathways [215].

CTC clusters are more resistant to cell death than individual CTCs, increasing their potential to metastasize [216]. Their larger size allows them to overcome fluid shear stress and collisions with other cells in the circulation, promoting margination to the endothelium wall, which increases their probability of arrest and adhesion to wall receptors [217]. Despite their larger size, CTC clusters can navigate capillary-sized vessels by rearranging them into single-file chains [218], enabling them to reach distant organs. Additionally, capillary beds with slower flow rates promote CTC arrest and enhance active cell adhesion [219]. CTCs associated with neutrophils showed a transcriptomic profile that supported cell cycle progression and cell migration [220]. In later cancer stages, neutrophils show increased immunosuppressive functions, suggesting they have a dynamic role in metastatic progression [221]. Inflamed neutrophils form aggregates with CTC in the intraluminal space, but once CTC arrest occurs in a vessel, they lose contact with the tumor cells. However, they remain in close proximity to the clusters and endothelium due to chemokine signaling mediated by self-secreted IL-8, tumor-derived CXCL-1, and the endothelial cell glyco-calyx [222]. IL-8 also causes endothelial barrier disruption and extravasation of nearby tumor cells [222]. Neutrophil extracellular traps (NETs) are neutrophil-derived DNA webs released in inflammatory states to trap and kill pathogens, but they can also trap CTCs [223]. They capture CTCs via β 1-integrin, which is upregulated in inflammation both in CTCs and NETs [224]. Studies have shown that the interaction between β 2 integrin on neutrophils and ICAM-1 on melanoma cells facilitates the anchoring of melanoma cells to the vascular endothelium [225]. ICAM-1 on triple-negative breast cancer cells promotes tumor cell secretion of suPAR, a chemoattractant for neutrophils, and attaches to CD11b molecules on neutrophils to form CTC-neutrophil bonds [226].

Platelets also interact and travel along CTCs, and a bidirectional exchange of lipids, proteins, and RNA occurs between them [227]. Tumor cells can transfer mutant RNA into blood platelets to produce “tumor-educated platelets” [228]. Platelets efficiently transfer structural components to tumor cells through extracellular vesicles, internalization, or direct contact, effectively “educating” tumor cells in the process [229]. Platelet-derived TGF β and direct contact with CTCs activate the TGF β /Smad and NF- κ B pathways in tumor cells, driving their transition to a mesenchymal-like phenotype [230]. Platelet-derived RGS18

promotes the expression of the immune checkpoint molecule HLA-E in CTCs. As a result, CTCs can escape NK-mediated immune surveillance and killing [231]. Direct contact with platelets can upregulate the inhibitory checkpoint molecule CD155 in CTCs and inhibit NK-cell cytotoxicity when CD155 is engaged with immune receptor TIGIT [232]. The cross-talk between CTCs and platelets, therefore, creates highly dynamic and aggressive phenotypes that help preserve CTCs integrity during their transit in the bloodstream, enhance invasiveness and proliferation, perpetuate epithelial-to-mesenchymal transition and stem-like phenotypes, and evade death [229,233]. Platelets also stimulate YAP1 dephosphorylation and its nuclear translocation in CTCs, triggering a pro-survival gene expression profile that prevents anoikis in detached conditions [234].

CTC clusters are often accompanied by myeloid-derived suppressor cells (MDSCs), a group of immature myeloid cells that promote both systemic and local immunosuppression, forming a protective barrier around CTCs to aid in metastasis [235]. Aside from their immunosuppressive roles, CTC-MDSC interactions increase the production of reactive oxygen species in MDSC, which induces pro-tumorigenic differentiation and proliferation of tumor cells by upregulation of Notch1 receptor expression and activation in CTCs [236]. There have been attempts to oppose the immunosuppressive aspects of MDSC by targeting therapies against them. Some drugs have been approved by the FDA, some are undergoing clinical trials, and others are being investigated in preclinical models. However, there is still no consensus for their use [237].

Macrophages can have a dual role in regard to immunity against CTCs. On the one hand, CD24, a cancer stemness marker, can be expressed in tumor cells and play a suppressive role in tumor immunity as a phagocytic inhibitor when bound to macrophages via Siglec-10 [238]. On the other hand, Zhang et al. reported macrophages that engulf apoptotic tumor cells integrate tumor DNA into their nuclei, transforming into tumor stem cells while maintaining macrophage surface markers, enabling them to evade immune detection [239]. Therefore, some macrophages can promote metastasis while others interfere with it. More recently, Fu et al. [240] discovered that microbiota from the primary tumor can be carried by CTCs as intracellular bacteria capable of reorganizing the actin cytoskeleton of tumor cells and enhancing resistance to mechanical stress [240].

Tumor cells thrive in hypoxic conditions due to metabolic reprogramming [241], and CTC clusters offer protection against the toxic oxygen concentrations in the bloodstream [242]. Hypoxic CTC clusters promote a cancer stem-like phenotype in CTCs [243] and the acquisition of a reactive oxygen species-resistant phenotype that enhances CTC survival upon reoxygenation [244]. Oxidative stress and hypoxia favor CTCs to develop resistance mechanisms against anoikis, a form of apoptosis induced upon cell detachment from their native environment [245]. Several other adaptations have been linked to anoikis resistance, such as increased epithelial-to-mesenchymal transition, change in integrins' profiles, oncogene activation, and overexpression of key metabolic enzymes or receptors [245]. The inclusion of carcinoma-associated fibroblasts in CTC clusters provides a metastatic advantage to tumor cells [246], likely favoring anoikis resistance, transportation of nutrients, and epithelial-to-mesenchymal transition [247].

4.4. Vascular Cooption

Vascular cooption describes the mechanism by which metastatic cells preferentially grow alongside the outer surfaces of existing blood vessels. This strategy is present in more than 95% of early micrometastases within the CNS [248]. Adhesion to vessels depends upon tumor cell β 1 integrins adhesion to the vascular basement membrane and [248] the establishment of microcolonies [248].

In some organs, the presence of mesenchymal stem cells acting as pericytes at the perivascular space of the PMN mediate the extravasation of tumor cells [249]. It has been proposed that pericytic mimicry or angiotropism is a process closely related to vascular cooption and can be seen in melanoma cells that metastasize to the brain [250]. CTC from lung and breast cancers that metastasize to the brain utilize the cell adhesion molecule L1CAM to move along capillaries. This movement involves the activation of YAP through interactions with $\beta 1$ integrin and integrin-linked kinase (ILK) [251].

Plasmin suppresses vascular cooption by deactivating L1CAM, an axon guidance molecule utilized by metastatic cells to navigate along brain capillaries. However, serpins that inhibit plasminogen activators produced by cancer cells, including neuroserpin and serpin B2, prevent the generation of plasmin. This inhibition facilitates vascular cooption in BMs associated with lung cancer, breast cancer [48], and melanoma [250]. Serpins also protect cancer cells by inhibiting the plasmin-generated FasL death signal [48]. A lncRNA associated with breast cancer cells increased expression of ICAM1, which mediated vascular co-option by increasing tumor cells' ability to stretch over brain capillaries and extravasate into the brain parenchyma [172].

Intravascular cell arrest in brain microvessels before extravasation has been demonstrated to create a focal hypoxic microenvironment in the PMN, leading to ischemic changes that upregulate vascular remodeling factors such as Angiopoietin-2 (Ang-2) and VEGF [252]. Ang-2 facilitates tumor cell colonization and transmigration in the PMN and later supports stable oxygen and nutrient supply for metastatic growth [252].

4.5. Blood–Brain Barrier Penetration

There is evidence that the BBB, known as the tightest endothelial barrier, can be modified by soluble factors secreted by tumor cells or dysregulation of the normal brain microenvironment. Tumor-derived heparinase, for instance, can degrade the basement membrane of the BBB, facilitating tumor cell invasion into the brain [253,254]. Additionally, the absence of normal astrocytes leads to the downregulation of the DHA transporter Mfsd2a, expressed by endothelial cells, causing disruption of the BBB [255].

There are also tumor-derived extracellular vesicles that can be taken up by endothelial cells to increase the permeability of the BBB. Lung cancer cells secrete exosomes mediated by the action of TGF- β carrying lncRNA that increases the expression of MMP-2 in brain microvascular endothelial cells [256]. MMP-2 destroys tight junctions between endothelial cells both in the lung and the brain, increasing vascular permeability, tumor cell migration, and invasion [256,257]. Extracellular vesicles from breast cancer carrying miR-181c promote BBB disruption by altering actin dynamics [258], while extracellular vesicles containing miR-105 target the tight junction protein ZO-1 in endothelial barriers, compromising their integrity [259].

Tumor cells must acquire specialized adaptations before brain colonization, some of which involve specific mediators for BBB crossing. For example, breast cancer cells express COX2, the EGFR ligand HBEGF, and the $\alpha 2,6$ -sialyltransferase ST6GALNAC5, which facilitate their traversal across the BBB [43]. ST6GALNAC5, in particular, was found to be specifically expressed only in brain-tropic metastatic cells, enhancing cooption to endothelial cells [43]. COX2 has been linked to the upregulation of MMP-1, which can degrade components of the BBB such as Claudin and Occludin [260]. In metastatic breast cancer cells, Klotz et al. demonstrated that semaphorin 4D (SEMA4D) regulates tumor cells' transmigration through the BBB [46]. When SEMA4D binds to its receptor Plexin-B1 (PLXNB1) in endothelial cells, it makes them switch to a proangiogenic phenotype [261]. This effect may also be enhanced by TAMs [262]. Inactivating PLXNB1 has shown a shift

in the immune landscape of tumor microenvironments towards an antitumor response; however, angiogenesis is not affected since SEMA4D can bind to alternative receptors [263].

Endothelial cells in the tumor microenvironment of BMs exhibit elevated Ki67 levels and enhanced microvascular proliferation. In contrast, the proliferation is suppressed in the presence of CD8⁺ T cells. Additionally, the tight-junction protein claudin-5, essential for BBB integrity, is downregulated in cancer cells located near endothelial cells, especially within the cores of BMs. This supports the hypothesis that vascular co-option plays a role in BMs colonization in regions with compromised endothelial junctions [179]. Herrera et al. found that breast-to-brain metastasis cell lines were able to traverse an enhanced blood-cerebrospinal fluid barrier (BCSFB) while primary breast cancer cell lines could not [264]. These findings reflected two things: firstly, cells that have previously colonized the brain must have acquired critical mechanisms to allow them to traverse CNS barriers; secondly, the preferential migration of breast cancer cells through the BCSFB may indicate it is an often-overlooked potential point of entry for tumor cells [264]. Under normal conditions, the BCSFB in the choroid plexus exhibits greater permeability than the BBB due to its transport and secretory functions [265]. Chemotherapies such as paclitaxel and 5-Fluorouracil (5-FU), commonly used in breast cancer, have been demonstrated to increase brain-barrier permeability to tumor cells, especially through the BCSFB due to upregulation of MMP-9 leading to Claudin-6 downregulation in the choroid plexus cells [266]. MMP-9 activity in the choroid plexus cells also resulted in the release of Tau from breast cancer cells, which formed neurofibrillary tangles that further destabilized the BCSFB [266]. Studies also have revealed that patients with parenchymal brain metastatic lesions often exhibit tumor cells in the ipsilateral blood–cerebrospinal fluid barrier [266].

Leptomeningeal disease (LMD) occurs when tumor cells invade the leptomeningeal membrane and the CSF [267]. Intracranial tumor cells spread via three mechanisms: direct perivascular pathways from the brain parenchyma, hematogenous routes from the systemic circulation, or iatrogenic seeding [268]. Extracranial tumor cell dissemination to the CSF occurs via hematogenous spread from the systemic circulation, backward migration along cranial or spinal nerves, invasion from the bone marrow via vascular pathways in the dura or skull, dissemination through meningeal lymphatic vessels, or through iatrogenic implantation [268]. Tropism for the meninges involves specific histological, molecular, and genetic alterations in the primary tumor cells [269]. Once in the leptomeninges, tumor cells continue adapting to overcome the intrinsic microenvironmental challenges of the CSF, including inflammation and sparse micronutrients [270]. Cancer cells within the CSF increase their expression of LCN2 when stimulated by inflammatory cytokines produced by CSF macrophages [270]. Besides its role in activating astrocytes in the PMN [155], LCN2 can also function as an iron-binding molecule. TAMs in the tumor microenvironment can help deliver iron to tumor cells to promote growth [271]. The uptake of iron in the CSF by tumor cells outcompetes macrophages that need iron to generate reactive oxygen species, therefore impairing the respiratory burst and phagocytosis functions needed for tumor control [270]. Tumor cells located in the cerebrospinal fluid produce complement component 3 (C3), which activates the C3a receptors on the epithelial cells of the choroid plexus. This activation compromises the BCSFB, permitting plasma elements like amphiregulin to enter the CSF and support the growth of tumor cells [272].

4.6. Astrocytes in Progression of Brain Metastases

Astrocytes serve as important mediators of BMs, as they can promote neuroinflammation, immunosuppression, angiogenesis, chemotaxis, and tumor cell invasion. Metastatic lung cancer cells release factors, including macrophage migration inhibitory factor, IL-8, and plasminogen activator inhibitor-1 (PAI-1). These factors activate astrocytes, producing

inflammatory cytokines such as IL-6, TNF- α , and IL-1 β , promoting increased tumor cell proliferation [273]. Schwartz et al. demonstrated that melanoma-secreted factors activate astrocytes to upregulate the expression of inflammatory chemokines such as CCL2, CXCL10, and CCL7, instigating astrogliosis, neuroinflammation, and hyperpermeability of the BBB [274]. Astrocyte-secreted CXCL10 has been demonstrated to facilitate the migration of melanoma cells toward astrocytes. This effect is attributed to the elevated expression of CXCR3, the receptor for CXCL10, in melanoma cells with a propensity for brain tropism [275]. Similarly, CCL2 can promote transmigration and extravasation of cancer cells via the CCL2-CCR2 astrocyte–cancer cell axis [276]. COX2 expressed in breast cancer cells increases prostaglandins, activating astrocytes to secrete CCL7, promoting self-renewal of tumor-initiating cells [260]. Soluble factors from triple-negative breast cancer cells induced upregulation and activation of the NLRP3 inflammasome in peritumoral astrocytes, consequently increasing IL-1 β release, inflammation, and proliferation of metastatic cells [277]. There is evidence that in metastatic triple-negative breast tumors, IL-1 β enhances the adhesion of cancer and immune cells to the brain endothelium via upregulation of cell adhesion molecules such as ICAM-1, VCAM-1, and E-selectin [278]. Lung cancer cells produce protocadherin 7 (PCDH7), which facilitates the creation of connexin 43 (Cx43) gap junctions with astrocytes. These connections enable the transfer of the second messenger cGAMP from tumor cells to astrocytes, thereby activating the STING pathway. Activation of this pathway leads to the secretion of inflammatory chemokines such as IFN α and TNF α . These chemokines act as paracrine signals for tumor cells to activate pathways such as the STAT1 and NF- κ B signaling pathways, promoting their own growth and chemoresistance [44].

Astrocytes promote immunosuppression by significantly increasing the levels of neuronal-specific cyclin-dependent kinase 5 (Cdk5). This elevated Cdk5 reduces both the expression and functionality of class I major histocompatibility complexes, thereby disrupting the antigen presentation pathway [279]. Furthermore, reactive astrocytes with a signal transducer and activator of transcription 3 (STAT3) activation modify the innate and acquired immune system responses in the metastatic microenvironment [280].

Following early infiltration of tumor cells to the brain, activated astrocytes produce factors such as MMP-9, which promotes angiogenesis and release of growth factors from the extracellular matrix [281]. These signals persist as long as the astrocyte–tumor cell mutual association remains. Astrocytes also epigenetically upregulate Reelin expression in Her2+ breast cancer cells that migrate to the neural niche, conferring them a survival advantage in the brain microenvironment [282]. Peroxisome proliferator-activated receptor γ (PPAR γ) in metastatic tumor cells activates astrocytes in the lipid-rich environment around the glial cells, enhancing cell proliferation in advanced BMs but not during early steps [283]. Astrocytes-derived exosomes containing *PTEN*-targeting microRNAs downregulate *PTEN* mRNA and protein expression in brain-tropic metastatic tumor cells [36]. *PTEN* loss in tumor cells facilitates perivascular brain colonization and invasion [284] and later increases secretion of the chemokine CCL2, which attracts myeloid cells, furthering metastatic proliferation [36].

5. Challenges Targeting Brain Metastases and Future Therapeutic Implications

Treatment for BMs includes neurosurgical resection, radiotherapy (i.e., either stereotactic radiosurgery, or whole-brain radiotherapy), and tumor-specific chemotherapy and targeted therapies [285]. The optimal therapeutic approach for each etiology of BMs will depend on the specific molecular and genetic landscape of the primary tumor. For example, HER2-positive patients can be treated with monoclonal antibodies such as trastuzumab or pertuzumab, whereas triple-negative breast cancer BMs treatment relies on BBB-permeable

chemotherapeutics, such as capecitabine, cisplatin, and temozolomide [285,286]. In NSCLC BMs, tyrosine kinase inhibitors (erlotinib, gefitinib) have demonstrated good BBB penetration, and ALK inhibitors and ICIs are also available options for treatment [287]. In melanoma, chemotherapeutic agents have limited efficacy, which has started the investigation of a combination of immunotherapy and targeted therapy [288].

However, the development of resistance mechanisms limits the success of targeted therapies. Traditionally, resistance mechanisms were classified as intrinsic or acquired, but evidence has shown that the pattern of “acquired” resistance might be intra-tumor heterogeneity present from the start and expanded under selective pressures from targeted therapies [289]. Metastases and BMs, in particular, pose an extra challenge in determining targetable patterns and elucidating the development of resistance mechanisms. Over half of BMs harbor genomic alterations not found in primary tumors [19], prompting the need for direct BMs biopsies, which are not always accessible or feasible due to poor patient conditions [290]. Liquid biopsies have emerged as alternatives to analyzing tumor tissue. CTCs, cell-free tumor DNA (ctDNA), and extracellular vesicles from plasma and CSF can be collected and processed. However, most published research has been retrospective and performed in small, heterogeneous patient cohorts, and methodologic techniques for processing are diverse [291–293]. Translation into clinical practice must first overcome several technical barriers, including assay optimization and standardization, incorporation of liquid biopsies in more clinical trials, and creation of data biobanks to facilitate translational research [294].

The BBB represents a physical obstacle for chemotherapeutic agents to enter the brain. The integrity of the BBB varies in brain tumors and selectively excludes molecules based on factors such as electric charge, lipid solubility, and molecular weight. Disruption of the BBB using hyperosmolar mannitol has been investigated as a method to improve the delivery of large molecules, including proteins, antibodies, immunoconjugates, and viral vectors [295]. Low-intensity pulsed ultrasound with systemic microbubbles can increase BBB permeability as demonstrated with several agents in primary brain tumors [296]. Enhanced drug delivery with nanotechnology and nanocarriers has also been extensively researched [297]. Unfortunately, none of these methods has reached clinical feasibility yet.

Resistance in melanoma BMs with BRAFV600 mutations is primarily mediated by drug efflux transporters, including P-glycoprotein (P-gp; ABCB1) and breast cancer resistance protein (BCRP; ABCG2), located at the BBB and impeding penetration into BMs [298]. Moreover, the brain microenvironment may also exert an effect on resistance mechanisms that have not yet been fully elucidated.

Immunotherapies have become a pillar of cancer therapies, and ICIs targeting the PD-1/PD-L1 pathway, such as pembrolizumab (Keytruda), nivolumab (Opdivo), and atezolizumab (Tecentriq), have been approved by the FDA to treat different primary tumors presenting with BMs [299]. However, some patients exhibit resistance primarily due to the tumor microenvironment mechanisms such as defects in antigen presentation, cytokines signaling, presence of immune inhibitory molecules, and T cell exclusion [300].

There is an urgent need to advance BMs therapies and improve outcomes for patients. The gap in knowledge about mechanisms for metastases to the brain is still wide, and researchers must account for tumor heterogeneity and fast evolution when developing new therapies. Identifying more patients at risk or in the early stages of metastasis could further help researchers understand how different BMs develop and how to block their progression.

6. Conclusions

Brain metastases continue to be frequent causes of central nervous system tumors, and research has actively tried to determine the mechanisms that promote their formation. Advances in genetic and molecular sciences have allowed us to define models of the complex interactions between tumor cells, brain microenvironment, and host adaptations. However, there is still a gap in our knowledge about the molecular underpinnings of these tumors, what makes certain cells brain-tropic, and what makes them more equipped for survival in the hostile brain microenvironment. The heterogeneity of the tumors of origin and the infinite numbers of adaptations tumor cells can go through under different environmental pressures make this a highly dynamic field of study, which hinders the clinical applicability of study results for patients in a real-life setting.

We are reaching an era in which molecular studies in medicine require the intervention of other fields of research, such as artificial intelligence, machine learning, and computational simulation systems, which would allow for the processing of greater loads of information and hopefully create predictive models that help to determine tumor behavior, patient prognosis, and response to therapy using easily accessible samples (i.e., tumor circulating cells in the blood and primary tumor tissue), which remains a challenge for brain tumors.

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Abbreviations

ALK	Anaplastic lymphoma kinase
BBB	Blood–brain barrier
BCSFB	Blood cerebrospinal fluid barrier
BM	Brain metastases
BRAF	V-raf murine sarcoma viral oncogene homolog B1
CDKN2A	Cyclin-dependent kinase inhibitor 2A
CNS	Central nervous system
CTCs	Circulating tumor cells
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
FABP7	Fatty acid binding protein 7
FASN	Fatty acid synthase
GBP1	Guanylate-binding protein 1
GPNMB	Glycoprotein nonmetastatic melanoma B
GPX1	Glutathione peroxidase 1
HDAC11	Histone deacetylase

HER2	Human epidermal growth factor 2
ICAM	Intercellular adhesion molecule
ICIs	Immune checkpoint inhibitors
KRAS	Kirsten rat sarcoma viral oncogene
LCN2	Lipocalin-2
lncRNA	Long non-coding RNA
MDSC	Myeloid-derived suppressor cells
MMP	Matrix metalloproteinase
NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog
NSCLC	Non-small-cell lung cancer
PMN	Pre-metastatic niche
PR	Progesterone receptor
RET	Rearranged during transfection
ROS1	C-ros oncogene 1
SCLC	Small-cell lung cancer
TAMs	Tumor-associated macrophages
TNF- α	Tumor necrosis factor- α
VEGF	Vascular endothelial growth factor
YAP	Yes-associated protein

References

- Ostrom, Q.T.; Wright, C.H.; Barnholtz-Sloan, J.S. Brain Metastases: Epidemiology. In *Handbook of Clinical Neurology*; Elsevier: Amsterdam, The Netherlands, 2018; pp. 27–42.
- Sacks, P.; Rahman, M. Epidemiology of Brain Metastases. *Neurosurg. Clin. N. Am.* **2020**, *31*, 481–488. [[CrossRef](#)] [[PubMed](#)]
- Cagney, D.N.; Martin, A.M.; Catalano, P.J.; Redig, A.J.; Lin, N.U.; Lee, E.Q.; Wen, P.Y.; Dunn, I.F.; Bi, W.L.; Weiss, S.E.; et al. Incidence and Prognosis of Patients with Brain Metastases at Diagnosis of Systemic Malignancy: A Population-Based Study. *Neuro Oncol.* **2017**, *19*, 1511–1521. [[CrossRef](#)] [[PubMed](#)]
- Davis, F.G.; Dolecek, T.A.; McCarthy, B.J.; Villano, J.L. Toward Determining the Lifetime Occurrence of Metastatic Brain Tumors Estimated from 2007 United States Cancer Incidence Data. *Neuro Oncol.* **2012**, *14*, 1171–1177. [[CrossRef](#)] [[PubMed](#)]
- Fox, B.D.; Cheung, V.J.; Patel, A.J.; Suki, D.; Rao, G. Epidemiology of Metastatic Brain Tumors. *Neurosurg. Clin. N. Am.* **2011**, *22*, 1–6. [[CrossRef](#)]
- Achrol, A.S.; Rennert, R.C.; Anders, C.; Soffietti, R.; Ahluwalia, M.S.; Nayak, L.; Peters, S.; Arvold, N.D.; Harsh, G.R.; Steeg, P.S.; et al. Brain Metastases. *Nat. Rev. Dis. Primers* **2019**, *5*, 5. [[CrossRef](#)]
- Kromer, C.; Xu, J.; Ostrom, Q.T.; Gittleman, H.; Kruchko, C.; Sawaya, R.; Barnholtz-Sloan, J.S. Estimating the Annual Frequency of Synchronous Brain Metastasis in the United States 2010–2013: A Population-Based Study. *J. Neurooncol.* **2017**, *134*, 55–64. [[CrossRef](#)]
- Barnholtz-Sloan, J.S.; Sloan, A.E.; Davis, F.G.; Vigneau, F.D.; Lai, P.; Sawaya, R.E. Incidence Proportions of Brain Metastases in Patients Diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J. Clin. Oncol.* **2004**, *22*, 2865–2872. [[CrossRef](#)]
- Daryanani, D.; Plukker, J.T.; de Jong, M.A.; Haaxma-Reiche, H.; Nap, R.; Kuiper, H.; Hoekstra, H.J. Increased Incidence of Brain Metastases in Cutaneous Head and Neck Melanoma. *Melanoma Res.* **2005**, *15*, 119–124. [[CrossRef](#)]
- Parker, M.; Jiang, K.; Rincon-Torroella, J.; Materi, J.; Azad, T.D.; Kamson, D.O.; Kleinberg, L.R.; Bettgowda, C. Epidemiological Trends, Prognostic Factors, and Survival Outcomes of Synchronous Brain Metastases from 2015 to 2019: A Population-Based Study. *Neurooncol. Adv.* **2023**, *5*, vdad015. [[CrossRef](#)]
- Mills, M.N.; Potluri, T.K.; Kawahara, Y.; Fahey, M.; Figura, N.B.; Soyano, A.E.; Washington, I.R.; Diaz, R.; Oliver, D.E.; Yu, H.-H.M.; et al. The Presentation of Brain Metastases in Melanoma, Non-Small Cell Lung Cancer, and Breast Cancer and Potential Implications for Screening Brain MRIs. *Breast Cancer Res. Treat.* **2022**, *191*, 209–217. [[CrossRef](#)]
- Avila, J.; Leone, J.; Vallejo, C.T.; Lin, N.U.; Leone, J.P. Survival Analysis of Patients with Brain Metastases at Initial Breast Cancer Diagnosis over the Last Decade. *Breast Cancer Res. Treat.* **2024**, *205*, 579–587. [[CrossRef](#)] [[PubMed](#)]
- Rangachari, D.; Yamaguchi, N.; VanderLaan, P.A.; Folch, E.; Mahadevan, A.; Floyd, S.R.; Uhlmann, E.J.; Wong, E.T.; Dahlberg, S.E.; Huberman, M.S.; et al. Brain Metastases in Patients with EGFR -Mutated or ALK -Rearranged Non-Small-Cell Lung Cancers. *Lung Cancer* **2015**, *88*, 108–111. [[CrossRef](#)] [[PubMed](#)]
- Glitz, I.C.; Heimberger, A.B.; Sulman, E.P.; Davies, M.A. Prognostic Factors for Survival in Melanoma Patients with Brain Metastases. In *Brain Metastases from Primary Tumors*; Elsevier: Amsterdam, The Netherlands, 2016; Volume 3, pp. 267–297.

15. Jakob, J.A.; Bassett, R.L.; Ng, C.S.; Curry, J.L.; Joseph, R.W.; Alvarado, G.C.; Rohlf, M.L.; Richard, J.; Gershenwald, J.E.; Kim, K.B.; et al. NRAS Mutation Status Is an Independent Prognostic Factor in Metastatic Melanoma. *Cancer* **2012**, *118*, 4014–4023. [[CrossRef](#)] [[PubMed](#)]
16. Gaspar, L.E.; Scott, C.; Murray, K.; Curran, W. Validation of the RTOG Recursive Partitioning Analysis (RPA) Classification for Brain Metastases. *Int. J. Radiat. Oncol. Biol. Phys.* **2000**, *47*, 1001–1006. [[CrossRef](#)]
17. Sperduto, P.W.; Berkey, B.; Gaspar, L.E.; Mehta, M.; Curran, W. A New Prognostic Index and Comparison to Three Other Indices for Patients with Brain Metastases: An Analysis of 1960 Patients in the RTOG Database. *Int. J. Radiat. Oncol. Biol. Phys.* **2008**, *70*, 510–514. [[CrossRef](#)]
18. Sperduto, P.W.; Mesko, S.; Li, J.; Cagney, D.; Aizer, A.; Lin, N.U.; Nesbit, E.; Kruser, T.J.; Chan, J.; Braunstein, S.; et al. Beyond an Updated Graded Prognostic Assessment (Breast GPA): A Prognostic Index and Trends in Treatment and Survival in Breast Cancer Brain Metastases From 1985 to Today. *Int. J. Radiat. Oncol. Biol. Phys.* **2020**, *107*, 334–343. [[CrossRef](#)]
19. Brastianos, P.K.; Carter, S.L.; Santagata, S.; Cahill, D.P.; Taylor-Weiner, A.; Jones, R.T.; Van Allen, E.M.; Lawrence, M.S.; Horowitz, P.M.; Cibulskis, K.; et al. Genomic Characterization of Brain Metastases Reveals Branched Evolution and Potential Therapeutic Targets. *Cancer Discov.* **2015**, *5*, 1164–1177. [[CrossRef](#)]
20. Chroni, A.; Miura, S.; Hamilton, L.; Vu, T.; Gaffney, S.G.; Aly, V.; Karim, S.; Sanderford, M.; Townsend, J.P.; Kumar, S. Clone Phylogenetics Reveals Metastatic Tumor Migrations, Maps, and Models. *Cancers* **2022**, *14*, 4326. [[CrossRef](#)]
21. Brown, D.; Smeets, D.; Székely, B.; Larsimont, D.; Szász, A.M.; Adnet, P.-Y.; Rothé, F.; Rouas, G.; Nagy, Z.I.; Faragó, Z.; et al. Phylogenetic Analysis of Metastatic Progression in Breast Cancer Using Somatic Mutations and Copy Number Aberrations. *Nat. Commun.* **2017**, *8*, 14944. [[CrossRef](#)]
22. Jin, X.; Demere, Z.; Nair, K.; Ali, A.; Ferraro, G.B.; Natoli, T.; Deik, A.; Petronio, L.; Tang, A.A.; Zhu, C.; et al. A Metastasis Map of Human Cancer Cell Lines. *Nature* **2020**, *588*, 331–336. [[CrossRef](#)]
23. Goldhirsch, A.; Wood, W.C.; Coates, A.S.; Gelber, R.D.; Thürlimann, B.; Senn, H.-J. Strategies for Subtypes—Dealing with the Diversity of Breast Cancer: Highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann. Oncol.* **2011**, *22*, 1736–1747. [[CrossRef](#)] [[PubMed](#)]
24. Johnson, K.S.; Conant, E.F.; Soo, M.S. Molecular Subtypes of Breast Cancer: A Review for Breast Radiologists. *J. Breast Imaging* **2021**, *3*, 12–24. [[CrossRef](#)]
25. Poletes, C.; Amanirad, B.; Santiago, A.T.; Yan, M.; Conrad, T.; Jerzak, K.J.; Shultz, D.B. The Incidence of Brain Metastases in Breast Cancer According to Molecular Subtype and Stage: A 10-Year Single Institution Analysis. *J. Neurooncol.* **2024**, *169*, 119–127. [[CrossRef](#)] [[PubMed](#)]
26. Shao, M.; Liu, J.; Vong, J.S.; Niu, Y.; Germin, B.; Tang, P.; Chan, A.W.H.; Lui, P.C.W.; Law, B.K.B.; Tan, P.-H.; et al. A Subset of Breast Cancer Predisposes to Brain Metastasis. *Med. Mol. Morphol.* **2011**, *44*, 15–20. [[CrossRef](#)] [[PubMed](#)]
27. Ignatov, A.; Eggemann, H.; Burger, E.; Ignatov, T. Patterns of Breast Cancer Relapse in Accordance to Biological Subtype. *J. Cancer Res. Clin. Oncol.* **2018**, *144*, 1347–1355. [[CrossRef](#)]
28. Choy, C.; Raytis, J.L.; Smith, D.D.; Duenas, M.; Neman, J.; Jandial, R.; Lew, M.W. Inhibition of B2-Adrenergic Receptor Reduces Triple-Negative Breast Cancer Brain Metastases: The Potential Benefit of Perioperative β -Blockade. *Oncol. Rep.* **2016**, *35*, 3135–3142. [[CrossRef](#)]
29. Yonemori, K.; Tsuta, K.; Ono, M.; Shimizu, C.; Hirakawa, A.; Hasegawa, T.; Hatanaka, Y.; Narita, Y.; Shibui, S.; Fujiwara, Y. Disruption of the Blood Brain Barrier by Brain Metastases of Triple-negative and Basal-type Breast Cancer but Not HER2/Neu-positive Breast Cancer. *Cancer* **2010**, *116*, 302–308. [[CrossRef](#)]
30. Momeny, M.; Saunus, J.M.; Marturana, F.; McCart Reed, A.E.; Black, D.; Sala, G.; Iacobelli, S.; Holland, J.D.; Yu, D.; Da Silva, L.; et al. Heregulin-HER3-HER2 Signaling Promotes Matrix Metalloproteinase-Dependent Blood-Brain-Barrier Transendothelial Migration of Human Breast Cancer Cell Lines. *Oncotarget* **2015**, *6*, 3932–3946. [[CrossRef](#)]
31. Conrad, C.; Götte, M.; Schlomann, U.; Roessler, M.; Pagenstecher, A.; Anderson, P.; Preston, J.; Pruessmeyer, J.; Ludwig, A.; Li, R.; et al. ADAM8 Expression in Breast Cancer Derived Brain Metastases: Functional Implications on MMP-9 Expression and Transendothelial Migration in Breast Cancer Cells. *Int. J. Cancer* **2018**, *142*, 779–791. [[CrossRef](#)]
32. Joyce, J.A.; Hanahan, D. Multiple Roles for Cysteine Cathepsins in Cancer. *Cell Cycle* **2004**, *3*, 1516–1519. [[CrossRef](#)]
33. Linders, D.G.J.; Bijlstra, O.D.; Fallert, L.C.; Hilling, D.E.; Walker, E.; Straight, B.; March, T.L.; Valentijn, A.R.P.M.; Pool, M.; Burggraaf, J.; et al. Cysteine Cathepsins in Breast Cancer: Promising Targets for Fluorescence-Guided Surgery. *Mol. Imaging Biol.* **2023**, *25*, 58–73. [[CrossRef](#)] [[PubMed](#)]
34. Sevenich, L.; Bowman, R.L.; Mason, S.D.; Quail, D.F.; Rapaport, F.; Elie, B.T.; Brogi, E.; Brastianos, P.K.; Hahn, W.C.; Holsinger, L.J.; et al. Analysis of Tumour- and Stroma-Supplied Proteolytic Networks Reveals a Brain-Metastasis-Promoting Role for Cathepsin S. *Nat. Cell Biol.* **2014**, *16*, 876–888. [[CrossRef](#)] [[PubMed](#)]
35. Varešlija, D.; Priedigkeit, N.; Fagan, A.; Purcell, S.; Cosgrove, N.; O'Halloran, P.J.; Ward, E.; Cocchiglia, S.; Hartmaier, R.; Castro, C.A.; et al. Transcriptome Characterization of Matched Primary Breast and Brain Metastatic Tumors to Detect Novel Actionable Targets. *J. Natl. Cancer Inst.* **2019**, *111*, 388–398. [[CrossRef](#)] [[PubMed](#)]

36. Zhang, L.; Zhang, S.; Yao, J.; Lowery, F.J.; Zhang, Q.; Huang, W.-C.; Li, P.; Li, M.; Wang, X.; Zhang, C.; et al. Microenvironment-Induced PTEN Loss by Exosomal MicroRNA Primes Brain Metastasis Outgrowth. *Nature* **2015**, *527*, 100–104. [\[CrossRef\]](#)
37. Sihto, H.; Lundin, J.; Lundin, M.; Lehtimäki, T.; Ristimäki, A.; Holli, K.; Sailas, L.; Kataja, V.; Turpeenniemi-Hujanen, T.; Isola, J.; et al. Breast Cancer Biological Subtypes and Protein Expression Predict for the Preferential Distant Metastasis Sites: A Nationwide Cohort Study. *Breast Cancer Res.* **2011**, *13*, R87. [\[CrossRef\]](#)
38. Ferraro, G.B.; Ali, A.; Luengo, A.; Kodack, D.P.; Deik, A.; Abbott, K.L.; Bezwada, D.; Blanc, L.; Prideaux, B.; Jin, X.; et al. Fatty Acid Synthesis Is Required for Breast Cancer Brain Metastasis. *Nat. Cancer* **2021**, *2*, 414–428. [\[CrossRef\]](#)
39. Chen, E.I.; Hewel, J.; Krueger, J.S.; Tiraby, C.; Weber, M.R.; Kralli, A.; Becker, K.; Yates, J.R.; Felding-Habermann, B. Adaptation of Energy Metabolism in Breast Cancer Brain Metastases. *Cancer Res.* **2007**, *67*, 1472–1486. [\[CrossRef\]](#)
40. Cordero, A.; Kanojia, D.; Miska, J.; Panek, W.K.; Xiao, A.; Han, Y.; Bonamici, N.; Zhou, W.; Xiao, T.; Wu, M.; et al. FABP7 Is a Key Metabolic Regulator in HER2+ Breast Cancer Brain Metastasis. *Oncogene* **2019**, *38*, 6445–6460. [\[CrossRef\]](#)
41. George Warren, W.; Osborn, M.; Yates, A.; O'Sullivan, S.E. The Emerging Role of Fatty Acid Binding Protein 7 (FABP7) in Cancers. *Drug Discov. Today* **2024**, *29*, 103980. [\[CrossRef\]](#)
42. Santana-Codina, N.; Marcé-Grau, A.; Muixí, L.; Nieva, C.; Marro, M.; Sebastián, D.; Muñoz, J.P.; Zorzano, A.; Sierra, A. GRP94 Is Involved in the Lipid Phenotype of Brain Metastatic Cells. *Int. J. Mol. Sci.* **2019**, *20*, 3883. [\[CrossRef\]](#)
43. Bos, P.D.; Zhang, X.H.-F.; Nadal, C.; Shu, W.; Gomis, R.R.; Nguyen, D.X.; Minn, A.J.; van de Vijver, M.J.; Gerald, W.L.; Foekens, J.A.; et al. Genes That Mediate Breast Cancer Metastasis to the Brain. *Nature* **2009**, *459*, 1005–1009. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Chen, Q.; Boire, A.; Jin, X.; Valiente, M.; Er, E.E.; Lopez-Soto, A.; Jacob, L.S.; Patwa, R.; Shah, H.; Xu, K.; et al. Carcinoma–Astrocyte Gap Junctions Promote Brain Metastasis by CGAMP Transfer. *Nature* **2016**, *533*, 493–498. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Zeng, Q.; Michael, I.P.; Zhang, P.; Saghafeinia, S.; Knott, G.; Jiao, W.; McCabe, B.D.; Galván, J.A.; Robinson, H.P.C.; Zlobec, I.; et al. Synaptic Proximity Enables NMDAR Signalling to Promote Brain Metastasis. *Nature* **2019**, *573*, 526–531. [\[CrossRef\]](#) [\[PubMed\]](#)
46. Klotz, R.; Thomas, A.; Teng, T.; Han, S.M.; Iriando, O.; Li, L.; Restrepo-Vassalli, S.; Wang, A.; Izadian, N.; MacKay, M.; et al. Circulating Tumor Cells Exhibit Metastatic Tropism and Reveal Brain Metastasis Drivers. *Cancer Discov.* **2020**, *10*, 86–103. [\[CrossRef\]](#)
47. Zhang, L.; Ridgway, L.D.; Wetzel, M.D.; Ngo, J.; Yin, W.; Kumar, D.; Goodman, J.C.; Groves, M.D.; Marchetti, D. The Identification and Characterization of Breast Cancer CTCs Competent for Brain Metastasis. *Sci. Transl. Med.* **2013**, *5*, 180ra48. [\[CrossRef\]](#)
48. Valiente, M.; Obenaus, A.C.; Jin, X.; Chen, Q.; Zhang, X.H.-F.; Lee, D.J.; Chaft, J.E.; Kris, M.G.; Huse, J.T.; Brogi, E.; et al. Serpins Promote Cancer Cell Survival and Vascular Co-Option in Brain Metastasis. *Cell* **2014**, *156*, 1002–1016. [\[CrossRef\]](#)
49. Mustafa, D.A.M.; Pedrosa, R.M.S.M.; Smid, M.; van der Weiden, M.; de Weerd, V.; Nigg, A.L.; Berrevoets, C.; Zeneyedpour, L.; Priego, N.; Valiente, M.; et al. T Lymphocytes Facilitate Brain Metastasis of Breast Cancer by Inducing Guanylate-Binding Protein 1 Expression. *Acta Neuropathol.* **2018**, *135*, 581–599. [\[CrossRef\]](#)
50. Karimpour, M.; Ravanbakhsh, R.; Maydanchi, M.; Rajabi, A.; Azizi, F.; Saber, A. Cancer Driver Gene and Non-Coding RNA Alterations as Biomarkers of Brain Metastasis in Lung Cancer: A Review of the Literature. *Biomed. Pharmacother.* **2021**, *143*, 112190. [\[CrossRef\]](#)
51. Saber, A.; Hiltermann, T.J.N.; Kok, K.; Terpstra, M.M.; de Lange, K.; Timens, W.; Groen, H.J.M.; van den Berg, A. Mutation Patterns in Small Cell and Non-Small Cell Lung Cancer Patients Suggest a Different Level of Heterogeneity between Primary and Metastatic Tumors. *Carcinogenesis* **2016**, *38*, 144–151. [\[CrossRef\]](#)
52. Andrews, L.J.; Thornton, Z.A.; Saleh, R.; Dawson, S.; Short, S.C.; Daly, R.; Higgins, J.P.T.; Davies, P.; Kurian, K.M. Genomic Landscape and Actionable Mutations of Brain Metastases Derived from Non-Small Cell Lung Cancer: A Systematic Review. *Neuro-Oncol. Adv.* **2023**, *5*, vdad145. [\[CrossRef\]](#)
53. Kam, T.Y.; Wong, C.H.L.; Fong, J.K.S.; Lee, V.H.F.; Chiu, M.K.L.; Cheung, K.M.; Nyaw, S.F.; Lim, M.Y.; Kwan, C.K.; Mok, S.T.F.; et al. 169P Genomic Landscape of NSCLC Brain Metastases and Its Potential Association with TP53 and Tumor Mutation Burden: A Territory-Wide Program in Hong Kong. *ESMO Open* **2024**, *9*, 102744. [\[CrossRef\]](#)
54. Van Egeren, D.; Kohli, K.; Warner, J.L.; Bedard, P.L.; Riely, G.; Lepisto, E.; Schrag, D.; LeNoue-Newton, M.; Catalano, P.; Kehl, K.L.; et al. Genomic Analysis of Early-Stage Lung Cancer Reveals a Role for TP53 Mutations in Distant Metastasis. *Sci. Rep.* **2022**, *12*, 19055. [\[CrossRef\]](#) [\[PubMed\]](#)
55. Liao, L.; Ji, X.; Ge, M.; Zhan, Q.; Huang, R.; Liang, X.; Zhou, X. Characterization of Genetic Alterations in Brain Metastases from Non-small Cell Lung Cancer. *FEBS Open Bio* **2018**, *8*, 1544–1552. [\[CrossRef\]](#) [\[PubMed\]](#)
56. Wang, H.; Ou, Q.; Li, D.; Qin, T.; Bao, H.; Hou, X.; Wang, K.; Wang, F.; Deng, Q.; Liang, J.; et al. Genes Associated with Increased Brain Metastasis Risk in Non-Small Cell Lung Cancer: Comprehensive Genomic Profiling of 61 Resected Brain Metastases versus Primary Non-Small Cell Lung Cancer (Guangdong Association Study of Thoracic Oncology 1036). *Cancer* **2019**, *125*, 3535–3544. [\[CrossRef\]](#)
57. Marei, H.E.; Althani, A.; Afifi, N.; Hasan, A.; Caceci, T.; Pozzoli, G.; Morrione, A.; Giordano, A.; Cenciarelli, C. P53 Signaling in Cancer Progression and Therapy. *Cancer Cell Int.* **2021**, *21*, 703. [\[CrossRef\]](#)

58. Roskoski, R. ErbB/HER Protein-Tyrosine Kinases: Structures and Small Molecule Inhibitors. *Pharmacol. Res.* **2014**, *87*, 42–59. [\[CrossRef\]](#)
59. Sasaki, T.; Hiroki, K.; Yamashita, Y. The Role of Epidermal Growth Factor Receptor in Cancer Metastasis and Microenvironment. *Biomed. Res. Int.* **2013**, *2013*, 8. [\[CrossRef\]](#)
60. Tan, L.; Wu, Y.; Ma, X.; Yan, Y.; Shao, S.; Liu, J.; Ma, H.; Liu, R.; Chai, L.; Ren, J. A Comprehensive Meta-Analysis of Association between EGFR Mutation Status and Brain Metastases in NSCLC. *Pathol. Oncol. Res.* **2019**, *25*, 791–799. [\[CrossRef\]](#)
61. Wang, H.; Wang, Z.; Zhang, G.; Zhang, M.; Zhang, X.; Li, H.; Zheng, X.; Ma, Z. Driver Genes as Predictive Indicators of Brain Metastasis in Patients with Advanced NSCLC: EGFR, ALK, and RET Gene Mutations. *Cancer Med.* **2020**, *9*, 487–495. [\[CrossRef\]](#)
62. Du, X.; Shao, Y.; Qin, H.; Tai, Y.; Gao, H. ALK-rearrangement in Non-small-cell Lung Cancer (NSCLC). *Thorac. Cancer* **2018**, *9*, 423–430. [\[CrossRef\]](#)
63. Soda, M.; Choi, Y.L.; Enomoto, M.; Takada, S.; Yamashita, Y.; Ishikawa, S.; Fujiwara, S.; Watanabe, H.; Kurashina, K.; Hatanaka, H.; et al. Identification of the Transforming EML4–ALK Fusion Gene in Non-Small-Cell Lung Cancer. *Nature* **2007**, *448*, 561–566. [\[CrossRef\]](#) [\[PubMed\]](#)
64. Hallberg, B.; Palmer, R.H. The Role of the ALK Receptor in Cancer Biology. *Ann. Oncol.* **2016**, *27*, iii4–iii15. [\[CrossRef\]](#) [\[PubMed\]](#)
65. Preusser, M.; Berghoff, A.S.; Ilhan-Mutlu, A.; Magerle, M.; Dinhof, C.; Widhalm, G.; Dieckmann, K.; Marosi, C.; Wöhrer, A.; Hackl, M.; et al. ALK Gene Translocations and Amplifications in Brain Metastases of Non-Small Cell Lung Cancer. *Lung Cancer* **2013**, *80*, 278–283. [\[CrossRef\]](#) [\[PubMed\]](#)
66. Kang, H.J.; Lim, H.-J.; Park, J.S.; Cho, Y.-J.; Yoon, H.-I.; Chung, J.-H.; Lee, J.H.; Lee, C.-T. Comparison of Clinical Characteristics between Patients with ALK-Positive and EGFR-Positive Lung Adenocarcinoma. *Respir. Med.* **2014**, *108*, 388–394. [\[CrossRef\]](#)
67. Qiao, M.; Zhao, C.; Liu, Q.; Wang, Y.; Shi, J.; Ng, T.L.; Zhou, F.; Li, X.; Jiang, T.; Yang, S.; et al. Impact of ALK Variants on Brain Metastasis and Treatment Response in Advanced NSCLC Patients with Oncogenic ALK Fusion. *Transl. Lung Cancer Res.* **2020**, *9*, 1452–1463. [\[CrossRef\]](#)
68. Ferrara, R.; Auger, N.; Auclin, E.; Besse, B. Clinical and Translational Implications of RET Rearrangements in Non-Small Cell Lung Cancer. *J. Thorac. Oncol.* **2018**, *13*, 27–45. [\[CrossRef\]](#)
69. Digumarthy, S.R.; Mendoza, D.P.; Lin, J.J.; Rooney, M.; Do, A.; Chin, E.; Yeap, B.Y.; Shaw, A.T.; Gainor, J.F. Imaging Features and Patterns of Metastasis in Non-Small Cell Lung Cancer with RET Rearrangements. *Cancers* **2020**, *12*, 693. [\[CrossRef\]](#)
70. Drilon, A.; Lin, J.J.; Filleron, T.; Ni, A.; Milia, J.; Bergagnini, I.; Hatzoglou, V.; Velcheti, V.; Offin, M.; Li, B.; et al. Frequency of Brain Metastases and Multikinase Inhibitor Outcomes in Patients with RET–Rearranged Lung Cancers. *J. Thorac. Oncol.* **2018**, *13*, 1595–1601. [\[CrossRef\]](#)
71. Gainor, J.F.; Lee, D.H.; Curigliano, G.; Doebele, R.C.; Kim, D.-W.; Baik, C.S.; Tan, D.S.-W.; Lopes, G.; Gadgeel, S.M.; Cassier, P.A.; et al. Clinical Activity and Tolerability of BLU-667, a Highly Potent and Selective RET Inhibitor, in Patients (Pts) with Advanced RET-Fusion+ Non-Small Cell Lung Cancer (NSCLC). *J. Clin. Oncol.* **2019**, *37*, 9008. [\[CrossRef\]](#)
72. Murciano-Goroff, Y.R.; Falcon, C.J.; Lin, S.T.; Chacko, C.; Grimaldi, G.; Liu, D.; Wilhelm, C.; Iasonos, A.; Drilon, A. Central Nervous System Disease in Patients with RET Fusion-Positive NSCLC Treated with Selpercatinib. *J. Thorac. Oncol.* **2023**, *18*, 620–627. [\[CrossRef\]](#)
73. Ou, S.-H.I.; Tan, J.; Yen, Y.; Soo, R.A. ROS1 as a ‘Druggable’ Receptor Tyrosine Kinase: Lessons Learned from Inhibiting the ALK Pathway. *Expert. Rev. Anticancer Ther.* **2012**, *12*, 447–456. [\[CrossRef\]](#)
74. Nakamura, T.; Yoshida, T.; Takeyasu, Y.; Masuda, K.; Sinno, Y.; Matsumoto, Y.; Okuma, Y.; Goto, Y.; Horinouchi, H.; Yamamoto, N.; et al. Distinct Metastatic Spread and Progression Patterns in Patients Treated with Crizotinib for ROS1- and ALK-Rearranged Non-Small Cell Lung Cancer: A Single-Center Retrospective Study. *Transl. Lung Cancer Res.* **2023**, *12*, 1436–1444. [\[CrossRef\]](#) [\[PubMed\]](#)
75. Ou, S.-H.I.; Zhu, V.W. CNS Metastasis in ROS1+ NSCLC: An Urgent Call to Action, to Understand, and to Overcome. *Lung Cancer* **2019**, *130*, 201–207. [\[CrossRef\]](#) [\[PubMed\]](#)
76. Yang, X.; Tang, Z.; Li, J.; Jiang, J.; Liu, Y. Progress of Non-Small-Cell Lung Cancer with ROS1 Rearrangement. *Front. Mol. Biosci.* **2023**, *10*, 1238093. [\[CrossRef\]](#) [\[PubMed\]](#)
77. Patil, T.; Smith, D.E.; Bunn, P.A.; Aisner, D.L.; Le, A.T.; Hancock, M.; Purcell, W.T.; Bowles, D.W.; Camidge, D.R.; Doebele, R.C. The Incidence of Brain Metastases in Stage IV ROS1-Rearranged Non-Small Cell Lung Cancer and Rate of Central Nervous System Progression on Crizotinib. *J. Thorac. Oncol.* **2018**, *13*, 1717–1726. [\[CrossRef\]](#)
78. Yang, J.-J.; Zhou, J.; Liu, S.-Y.M.; Li, M.; Zhang, Z.; Cheng, Y.; Fan, Y.; Pan, H.; Wang, B.; Chen, G.; et al. Foritinib in Advanced ROS1-Rearranged Non-Small-Cell Lung Cancer in China: A Multicentre, Open-Label, Single-Arm, Phase 2 Study. *Lancet Respir. Med.* **2024**, *12*, 671–680. [\[CrossRef\]](#)
79. Lin, J.J.; Drilon, A.E.; Cho, B.C.; Felip, E.; De Langen, A.; Yang, N.; Kim, S.-W.; Lu, S.; Kao, S.C.-H.; Velcheti, V.; et al. Intracranial and Systemic Efficacy of Repotrectinib in Advanced ROS1 Fusion-Positive (ROS1 +) Non-Small Cell Lung Cancer (NSCLC) and Central Nervous System Metastases (CNS Mets) in the Phase 1/2 TRIDENT-1. *J. Clin. Oncol.* **2023**, *41*, 9017. [\[CrossRef\]](#)

80. Zhang, Y.; Xia, M.; Jin, K.; Wang, S.; Wei, H.; Fan, C.; Wu, Y.; Li, X.; Li, X.; Li, G.; et al. Function of the C-Met Receptor Tyrosine Kinase in Carcinogenesis and Associated Therapeutic Opportunities. *Mol. Cancer* **2018**, *17*, 45. [\[CrossRef\]](#)
81. Baldacci, S.; Kherrouche, Z.; Cockenpot, V.; Stoven, L.; Copin, M.C.; Werkmeister, E.; Marchand, N.; Kyheng, M.; Tulasne, D.; Cortot, A.B. MET Amplification Increases the Metastatic Spread of EGFR-Mutated NSCLC. *Lung Cancer* **2018**, *125*, 57–67. [\[CrossRef\]](#)
82. Preusser, M.; Streubel, B.; Berghoff, A.S.; Hainfellner, J.A.; von Deimling, A.; Widhalm, G.; Dieckmann, K.; Wöhrer, A.; Hackl, M.; Zielinski, C.; et al. Amplification and Overexpression of CMET Is a Common Event in Brain Metastases of Non-small Cell Lung Cancer. *Histopathology* **2014**, *65*, 684–692. [\[CrossRef\]](#)
83. Isaksson, J.; Berglund, A.; Louie, K.; Willén, L.; Hamidian, A.; Edsjö, A.; Enlund, F.; Planck, M.; Vikström, A.; Johansson, M.; et al. KRAS G12C Mutant Non-Small Cell Lung Cancer Linked to Female Sex and High Risk of CNS Metastasis: Population-Based Demographics and Survival Data From the National Swedish Lung Cancer Registry. *Clin. Lung Cancer* **2023**, *24*, 507–518. [\[CrossRef\]](#) [\[PubMed\]](#)
84. Werner, R.S.; Rechsteiner, M.; Moch, H.; Curioni-Fontecedro, A.; Weller, M.; Weiss, T.; Regli, L.; Le Rhun, E.; Mairinger, F.; Opitz, I.; et al. Genetic Profiles of Oligometastatic Non-Small-Cell Lung Cancer and Corresponding Brain Metastases. *Eur. J. Cardio Thorac. Surg.* **2024**, *65*, ezae217. [\[CrossRef\]](#) [\[PubMed\]](#)
85. Califano, R.; Landi, L.; Cappuzzo, F. Prognostic and Predictive Value of K-RAS Mutations in Non-Small Cell Lung Cancer. *Drugs* **2012**, *72*, 28–36. [\[CrossRef\]](#) [\[PubMed\]](#)
86. Chen, N.; Fang, W.; Lin, Z.; Peng, P.; Wang, J.; Zhan, J.; Hong, S.; Huang, J.; Liu, L.; Sheng, J.; et al. KRAS Mutation-Induced Upregulation of PD-L1 Mediates Immune Escape in Human Lung Adenocarcinoma. *Cancer Immunol. Immunother.* **2017**, *66*, 1175–1187. [\[CrossRef\]](#)
87. He, J.; Hu, Y.; Hu, M.; Li, B. Development of PD-1/PD-L1 Pathway in Tumor Immune Microenvironment and Treatment for Non-Small Cell Lung Cancer. *Sci. Rep.* **2015**, *5*, 13110. [\[CrossRef\]](#)
88. Vassella, E.; Kashani, E.; Zens, P.; Kündig, A.; Fung, C.; Scherz, A.; Herrmann, E.; Ermis, E.; Schmid, R.A.; Berezowska, S. Mutational Profiles of Primary Pulmonary Adenocarcinoma and Paired Brain Metastases Disclose the Importance of KRAS Mutations. *Eur. J. Cancer* **2021**, *159*, 227–236. [\[CrossRef\]](#)
89. Tsakonas, G.; Grozman, V.; Ekman, S. Primary CNS Metastatic BRAF-Mutated Lung Adenocarcinoma with Complete Intracranial Response to BRAF/MEK Inhibition. *Clin. Lung Cancer* **2020**, *21*, e544–e546. [\[CrossRef\]](#)
90. Kim, Y.-J.; Kim, J.-H.; Kim, O.; Ahn, E.-J.; Oh, S.-J.; Akanda, M.R.; Oh, I.-J.; Jung, S.; Kim, K.-K.; Lee, J.-H.; et al. Caveolin-1 Enhances Brain Metastasis of Non-Small Cell Lung Cancer, Potentially in Association with the Epithelial-Mesenchymal Transition Marker SNAIL. *Cancer Cell Int.* **2019**, *19*, 171. [\[CrossRef\]](#)
91. Jin, Y.; Yuan, Y.; Yi, M.; Han, H.; Liu, B.; Li, Q. Phosphorylated-Akt Overexpression Is Associated with a Higher Risk of Brain Metastasis in Patients with Non-Small Cell Lung Cancer. *Biochem. Biophys. Res.* **2019**, *18*, 100625. [\[CrossRef\]](#)
92. Nicoś, M.; Krawczyk, P.; Jarosz, B.; Sawicki, M.; Trojanowski, T.; Milanowski, J. Prevalence of NRAS, PTEN and AKT1 Gene Mutations in the Central Nervous System Metastases of Non-Small Cell Lung Cancer. *Brain Tumor Pathol.* **2017**, *34*, 36–41. [\[CrossRef\]](#)
93. Nguyen, D.X.; Chiang, A.C.; Zhang, X.H.-F.; Kim, J.Y.; Kris, M.G.; Ladanyi, M.; Gerald, W.L.; Massagué, J. WNT/TCF Signaling through LEF1 and HOXB9 Mediates Lung Adenocarcinoma Metastasis. *Cell* **2009**, *138*, 51–62. [\[CrossRef\]](#) [\[PubMed\]](#)
94. Stevens, L.E.; Cheung, W.K.C.; Adua, S.J.; Arnal-Estapé, A.; Zhao, M.; Liu, Z.; Brewer, K.; Herbst, R.S.; Nguyen, D.X. Extracellular Matrix Receptor Expression in Subtypes of Lung Adenocarcinoma Potentiates Outgrowth of Micrometastases. *Cancer Res.* **2017**, *77*, 1905–1917. [\[CrossRef\]](#) [\[PubMed\]](#)
95. Aljohani, H.M.; Aittaleb, M.; Furgason, J.M.; Amaya, P.; Deeb, A.; Chalmers, J.J.; Bahassi, E.M. Genetic Mutations Associated with Lung Cancer Metastasis to the Brain. *Mutagenesis* **2018**, *33*, 137–145. [\[CrossRef\]](#) [\[PubMed\]](#)
96. Chen, M.; Li, H.; Xu, X.; Bao, X.; Xue, L.; Ai, X.; Xu, J.; Xu, M.; Shi, Y.; Zhen, T.; et al. Identification of RAC1 in Promoting Brain Metastasis of Lung Adenocarcinoma Using Single-Cell Transcriptome Sequencing. *Cell Death Dis.* **2023**, *14*, 330. [\[CrossRef\]](#)
97. Wang, Y.; Zhang, L.; Tan, J.; Zhang, Z.; Liu, Y.; Hu, X.; Lu, B.; Gao, Y.; Tong, L.; Liu, Z.; et al. Longitudinal Detection of Subcategorized CD44v6+ CTCs and Circulating Tumor Endothelial Cells (CTECs) Enables Novel Clinical Stratification and Improves Prognostic Prediction of Small Cell Lung Cancer: A Prospective, Multi-Center Study. *Cancer Lett.* **2023**, *571*, 216337. [\[CrossRef\]](#)
98. Śmiech, M.; Leszczyński, P.; Kono, H.; Wardell, C.; Taniguchi, H. Emerging BRAF Mutations in Cancer Progression and Their Possible Effects on Transcriptional Networks. *Genes* **2020**, *11*, 1342. [\[CrossRef\]](#)
99. Cheng, L.; Lopez-Beltran, A.; Massari, F.; MacLennan, G.T.; Montironi, R. Molecular Testing for BRAF Mutations to Inform Melanoma Treatment Decisions: A Move toward Precision Medicine. *Mod. Pathol.* **2018**, *31*, 24–38. [\[CrossRef\]](#)
100. Sandhu, M.R.S.; Chiang, V.L.; Tran, T.; Yu, J.B.; Weiss, S.A.; Goldberg, S.B.; Aboian, M.S.; Kluger, H.M.; Mahajan, A. Incidence and Characteristics of Metastatic Intracranial Lesions in Stage III and IV Melanoma: A Single Institute Retrospective Analysis. *J. Neurooncol.* **2021**, *154*, 197–203. [\[CrossRef\]](#)

101. El-Osta, H.; Falchook, G.; Tsimberidou, A.; Hong, D.; Naing, A.; Kim, K.; Wen, S.; Janku, F.; Kurzrock, R. BRAF Mutations in Advanced Cancers: Clinical Characteristics and Outcomes. *PLoS ONE* **2011**, *6*, e25806. [\[CrossRef\]](#)
102. Colombino, M.; Capone, M.; Lissia, A.; Cossu, A.; Rubino, C.; De Giorgi, V.; Massi, D.; Fonsatti, E.; Staibano, S.; Nappi, O.; et al. BRAF/NRAS Mutation Frequencies Among Primary Tumors and Metastases in Patients with Melanoma. *J. Clin. Oncol.* **2012**, *30*, 2522–2529. [\[CrossRef\]](#)
103. Bucheit, A.D.; Chen, G.; Siroy, A.; Tetzlaff, M.; Broaddus, R.; Milton, D.; Fox, P.; Bassett, R.; Hwu, P.; Gershenwald, J.E.; et al. Complete Loss of PTEN Protein Expression Correlates with Shorter Time to Brain Metastasis and Survival in Stage IIIB/C Melanoma Patients with BRAF V600 Mutations. *Clin. Cancer Res.* **2014**, *20*, 5527–5536. [\[CrossRef\]](#) [\[PubMed\]](#)
104. Dankort, D.; Curley, D.P.; Cartlidge, R.A.; Nelson, B.; Karnezis, A.N.; Damsky, W.E., Jr.; You, M.J.; DePinho, R.A.; McMahon, M.; Bosenberg, M. BrafV600E Cooperates with Pten Loss to Induce Metastatic Melanoma. *Nat. Genet.* **2009**, *41*, 544–552. [\[CrossRef\]](#) [\[PubMed\]](#)
105. Cho, J.H.; Robinson, J.P.; Arave, R.A.; Burnett, W.J.; Kircher, D.A.; Chen, G.; Davies, M.A.; Grossmann, A.H.; VanBrocklin, M.W.; McMahon, M.; et al. AKT1 Activation Promotes Development of Melanoma Metastases. *Cell Rep.* **2015**, *13*, 898–905. [\[CrossRef\]](#) [\[PubMed\]](#)
106. Burotto, M.; Chiou, V.L.; Lee, J.; Kohn, E.C. The MAPK Pathway across Different Malignancies: A New Perspective. *Cancer* **2014**, *120*, 3446–3456. [\[CrossRef\]](#)
107. Davies, M.A.; Stemke-Hale, K.; Lin, E.; Tellez, C.; Deng, W.; Gopal, Y.N.; Woodman, S.E.; Calderone, T.C.; Ju, Z.; Lazar, A.J.; et al. Integrated Molecular and Clinical Analysis of AKT Activation in Metastatic Melanoma. *Clin. Cancer Res.* **2009**, *15*, 7538–7546. [\[CrossRef\]](#)
108. Wang, Y.; Lian, B.; Si, L.; Mao, L.; Chi, Z.; Sheng, X.; Kong, Y.; Wang, X.; Bai, X.; Yan, X.; et al. Cumulative Incidence and Risk Factors of Brain Metastasis for Acral and Mucosal Melanoma Patients with Stages I–III. *Eur. J. Cancer* **2022**, *175*, 196–203. [\[CrossRef\]](#)
109. Adler, N.R.; Wolfe, R.; Kelly, J.W.; Haydon, A.; McArthur, G.A.; McLean, C.A.; Mar, V.J. Tumour Mutation Status and Sites of Metastasis in Patients with Cutaneous Melanoma. *Br. J. Cancer* **2017**, *117*, 1026–1035. [\[CrossRef\]](#)
110. Fedorenko, I.V.; Gibney, G.T.; Smalley, K.S.M. NRAS Mutant Melanoma: Biological Behavior and Future Strategies for Therapeutic Management. *Oncogene* **2013**, *32*, 3009–3018. [\[CrossRef\]](#)
111. Milagre, C.; Dhomen, N.; Geyer, F.C.; Hayward, R.; Lambros, M.; Reis-Filho, J.S.; Marais, R. A Mouse Model of Melanoma Driven by Oncogenic KRAS. *Cancer Res.* **2010**, *70*, 5549–5557. [\[CrossRef\]](#)
112. Rabbie, R.; Ferguson, P.; Wong, K.; Couturier, D.-L.; Moran, U.; Turner, C.; Emanuel, P.; Haas, K.; Saunus, J.M.; Davidson, M.R.; et al. The Mutational Landscape of Melanoma Brain Metastases Presenting as the First Visceral Site of Recurrence. *Br. J. Cancer* **2021**, *124*, 156–160. [\[CrossRef\]](#)
113. Goel, V.K.; Lazar, A.J.F.; Warneke, C.L.; Redston, M.S.; Haluska, F.G. Examination of Mutations in BRAF, NRAS, and PTEN in Primary Cutaneous Melanoma. *J. Investig. Dermatol.* **2006**, *126*, 154–160. [\[CrossRef\]](#)
114. In, G.K.; Ribeiro, J.R.; Yin, J.; Xiu, J.; Bustos, M.A.; Ito, F.; Chow, F.; Zada, G.; Hwang, L.; Salama, A.K.S.; et al. Multi-Omic Profiling Reveals Discrepant Immunogenic Properties and a Unique Tumor Microenvironment among Melanoma Brain Metastases. *NPJ Precis. Oncol.* **2023**, *7*, 120. [\[CrossRef\]](#)
115. Langabeer, S.E.; Haslam, K.; Groarke, E.; Conneally, E. An Acquired NRAS Mutation Contributes to Neutrophilic Progression in a Patient with Primary Myelofibrosis. *Br. J. Haematol.* **2018**, *183*, 308–310. [\[CrossRef\]](#) [\[PubMed\]](#)
116. Samlowski, W. The Effect of Non-Overlapping Somatic Mutations in BRAF, NRAS, NF1, or KIT on the Incidence and Outcome of Brain Metastases during Immune Checkpoint Inhibitor Therapy of Metastatic Melanoma. *Cancers* **2024**, *16*, 594. [\[CrossRef\]](#) [\[PubMed\]](#)
117. Reddy, B.Y.; Miller, D.M.; Tsao, H. Somatic Driver Mutations in Melanoma. *Cancer* **2017**, *123*, 2104–2117. [\[CrossRef\]](#) [\[PubMed\]](#)
118. Lessard, L.; Liu, M.; Marzese, D.M.; Wang, H.; Chong, K.; Kawas, N.; Donovan, N.C.; Kiyohara, E.; Hsu, S.; Nelson, N.; et al. The CASC15 Long Intergenic Noncoding RNA Locus Is Involved in Melanoma Progression and Phenotype Switching. *J. Investig. Dermatol.* **2015**, *135*, 2464–2474. [\[CrossRef\]](#)
119. Cui, L.; Li, Y.; Lv, X.; Li, J.; Wang, X.; Lei, Z.; Li, X. Expression of MicroRNA-301a and Its Functional Roles in Malignant Melanoma. *Cell. Physiol. Biochem.* **2016**, *40*, 230–244. [\[CrossRef\]](#)
120. Afsar, S.; Syed, R.U.; Khojali, W.M.A.; Masood, N.; Osman, M.E.; Jyothi, J.S.; Hadi, M.A.; Khalifa, A.A.S.; Aboshouk, N.A.M.; Alsaikhan, H.A.; et al. Non-Coding RNAs in BRAF-Mutant Melanoma: Targets, Indicators, and Therapeutic Potential. *Naunyn Schmiedeberg's Arch. Pharmacol.* **2024**, *398*, 297–317. [\[CrossRef\]](#)
121. Sheppard, K.E.; McArthur, G.A. The Cell-Cycle Regulator CDK4: An Emerging Therapeutic Target in Melanoma. *Clin. Cancer Res.* **2013**, *19*, 5320–5328. [\[CrossRef\]](#)
122. Walker, G.J.; Flores, J.F.; Glendening, J.M.; Lin, A.; Markl, I.D.C.; Fountain, J.W. Virtually 100% of Melanoma Cell Lines Harbor Alterations at the DNA Level Within CDKN2A, CDKN2B, or One of Their Downstream Targets. *Genes. Chromosomes Cancer* **1998**, *22*, 157–163. [\[CrossRef\]](#)

123. Arnoff, T.E.; El-Deiry, W.S. MDM2/MDM4 Amplification and CDKN2A Deletion in Metastatic Melanoma and Glioblastoma Multiforme May Have Implications for Targeted Therapeutics and Immunotherapy. *Am. J. Cancer Res.* **2022**, *12*, 2102–2117. [\[PubMed\]](#)
124. Qi, S.-M.; Cheng, G.; Cheng, X.-D.; Xu, Z.; Xu, B.; Zhang, W.-D.; Qin, J.-J. Targeting USP7-Mediated Deubiquitination of MDM2/MDMX-P53 Pathway for Cancer Therapy: Are We There Yet? *Front. Cell Dev. Biol.* **2020**, *8*, 233. [\[CrossRef\]](#) [\[PubMed\]](#)
125. Uyanik, B.; Goloudina, A.R.; Akbarali, A.; Grigorash, B.B.; Petukhov, A.V.; Singhal, S.; Eruslanov, E.; Chaloyard, J.; Lagorgette, L.; Hadi, T.; et al. Inhibition of the DNA Damage Response Phosphatase PPM1D Reprograms Neutrophils to Enhance Anti-Tumor Immune Responses. *Nat. Commun.* **2021**, *12*, 3622. [\[CrossRef\]](#) [\[PubMed\]](#)
126. Guo, R.; Fierro-Fine, A.; Goddard, L.; Russell, M.; Chen, J.; Liu, C.Z.; Fung, K.-M.; Hassell, L.A. Increased Expression of Melanoma Stem Cell Marker CD271 in Metastatic Melanoma to the Brain. *Int. J. Clin. Exp. Pathol.* **2014**, *7*, 8947–8951.
127. Redmer, T. Deciphering Mechanisms of Brain Metastasis in Melanoma—the Gist of the Matter. *Mol. Cancer* **2018**, *17*, 106. [\[CrossRef\]](#)
128. Marchetti, D.; Denkins, Y.; Reiland, J.; Greiter-Wilke, A.; Galjour, J.; Murry, B.; Blust, J.; Roy, M. Brain-Metastatic Melanoma: A Neurotrophic Perspective. *Pathol. Oncol. Res.* **2003**, *9*, 147–158. [\[CrossRef\]](#)
129. Redmer, T.; Welte, Y.; Behrens, D.; Fichtner, I.; Przybilla, D.; Wruck, W.; Yaspo, M.-L.; Lehrach, H.; Schäfer, R.; Regenbrecht, C.R.A. The Nerve Growth Factor Receptor CD271 Is Crucial to Maintain Tumorigenicity and Stem-Like Properties of Melanoma Cells. *PLoS ONE* **2014**, *9*, e92596. [\[CrossRef\]](#)
130. Bailey, C.M.; Morrison, J.A.; Kulesa, P.M. Melanoma Revives an Embryonic Migration Program to Promote Plasticity and Invasion. *Pigment. Cell Melanoma Res.* **2012**, *25*, 573–583. [\[CrossRef\]](#)
131. Tizpa, E.; Young, H.J.; Bonjoc, K.-J.C.; Chang, C.-W.; Liu, Y.; Foulks, J.M.; Chaudhry, A. Role of AXL in Metastatic Melanoma and Impact of TP-0903 as a Novel Therapeutic Option for Melanoma Brain Metastasis. *J. Clin. Oncol.* **2020**, *38*, e22021. [\[CrossRef\]](#)
132. Willemsen, M.; Bulgarelli, J.; Chauhan, S.K.; Lereim, R.R.; Angeli, D.; Grisendi, G.; Krebbers, G.; Davidson, I.; Kyte, J.A.; Guidoboni, M.; et al. Changes in AXL and/or MITF Melanoma Subpopulations in Patients Receiving Immunotherapy. *Immuno Oncol. Technol.* **2024**, *24*, 101009. [\[CrossRef\]](#)
133. Yaeger, R.; Cowell, E.; Chou, J.F.; Gewirtz, A.N.; Borsu, L.; Vakiani, E.; Solit, D.B.; Rosen, N.; Capanu, M.; Ladanyi, M.; et al. RAS Mutations Affect Pattern of Metastatic Spread and Increase Propensity for Brain Metastasis in Colorectal Cancer. *Cancer* **2015**, *121*, 1195–1203. [\[CrossRef\]](#) [\[PubMed\]](#)
134. Liu, J.; Zeng, W.; Huang, C.; Wang, J.; Yang, D.; Ma, D. Predictive and Prognostic Implications of Mutation Profiling and Microsatellite Instability Status in Patients with Metastatic Colorectal Carcinoma. *Gastroenterol. Res. Pract.* **2018**, *2018*, 14. [\[CrossRef\]](#)
135. Lee, Y.; Park, K. P14.12 Molecular Characteristics of Metastatic Brain Tumor. *Neuro Oncol.* **2017**, *19*, iii104–iii105. [\[CrossRef\]](#)
136. Michl, M.; Taverna, F.; Woischke, C.; Li, P.; Klauschen, F.; Kirchner, T.; Heinemann, V.; von Bergwelt-Baildon, M.; Stahler, A.; Herold, T.M.; et al. Identification of a Gene Expression Signature Associated with Brain Metastasis in Colorectal Cancer. *Clin. Transl. Oncol.* **2024**, *26*, 1886–1895. [\[CrossRef\]](#) [\[PubMed\]](#)
137. Stremitzer, S.; Berghoff, A.S.; Volz, N.B.; Zhang, W.; Yang, D.; Stintzing, S.; Ning, Y.; Sunakawa, Y.; Yamauchi, S.; Sebio, A.; et al. Genetic Variants Associated with Colorectal Brain Metastases Susceptibility and Survival. *Pharmacogenomics J.* **2017**, *17*, 29–35. [\[CrossRef\]](#)
138. Shindorf, M.L.; Jafferji, M.S.; Goff, S.L. Incidence of Asymptomatic Brain Metastases in Metastatic Colorectal Cancer. *Clin. Colorectal Cancer* **2020**, *19*, 263–269. [\[CrossRef\]](#)
139. Müller, S.; Köhler, F.; Hendricks, A.; Kastner, C.; Börner, K.; Diers, J.; Lock, J.F.; Petritsch, B.; Germer, C.-T.; Wiegering, A. Brain Metastases from Colorectal Cancer: A Systematic Review of the Literature and Meta-Analysis to Establish a Guideline for Daily Treatment. *Cancers* **2021**, *13*, 900. [\[CrossRef\]](#)
140. Ma, J.; del Balzo, L.; Khaleel, S.S.; Flynn, J.; Zhang, Z.; Voss, M.H.; Freeman, B.; Hakimi, A.A.; Lee, C.-H.; Eichholz, J.; et al. Molecular Profile and Clinical Outcomes of Renal Cell Carcinoma Brain Metastases Treated with Stereotactic Radiosurgery. *J. Clin. Oncol.* **2022**, *40*, 4526. [\[CrossRef\]](#)
141. Kinoshita, F.; Kohashi, K.; Sugimoto, M.; Takamatsu, D.; Kiyozawa, D.; Eto, M.; Oda, Y. The SWI/SNF Chromatin-Remodeling Complex Status in Renal Cell Carcinomas with Sarcomatoid or Rhabdoid Features. *Virchows Arch.* **2020**, *477*, 651–660. [\[CrossRef\]](#)
142. Ma, J.; del Balzo, L.; Walch, H.; Khaleel, S.; Knezevic, A.; Flynn, J.; Zhang, Z.; Eichholz, J.; Doshi, S.D.; Voss, M.H.; et al. Clinical Outcomes and Targeted Genomic Analysis of Renal Cell Carcinoma Brain Metastases Treated with Stereotactic Radiosurgery. *Eur. Urol. Oncol.* **2024**, *in press*. [\[CrossRef\]](#)
143. Wyler, L.; Napoli, C.U.; Ingold, B.; Sulser, T.; Heikenwälder, M.; Schraml, P.; Moch, H. Brain Metastasis in Renal Cancer Patients: Metastatic Pattern, Tumour-Associated Macrophages and Chemokine/Chemoreceptor Expression. *Br. J. Cancer* **2014**, *110*, 686–694. [\[CrossRef\]](#) [\[PubMed\]](#)
144. Harter, P.N.; Bernatz, S.; Scholz, A.; Zeiner, P.S.; Zinke, J.; Kiyose, M.; Blasel, S.; Beschorner, R.; Senft, C.; Bender, B.; et al. Distribution and Prognostic Relevance of Tumor-Infiltrating Lymphocytes (TILs) and PD-1/PD-L1 Immune Checkpoints in Human Brain Metastases. *Oncotarget* **2015**, *6*, 40836–40849. [\[CrossRef\]](#)

145. Paget, S. The Distribution of Secondary Growths in Cancer of the Breast. *Lancet* **1889**, *133*, 571–573. [[CrossRef](#)]
146. Fidler, I.J. Seed and Soil Revisited: Contribution of the Organ Microenvironment to Cancer Metastasis. *Surg. Oncol. Clin. N. Am.* **2001**, *10*, 257–269. [[CrossRef](#)]
147. Kienast, Y.; von Baumgarten, L.; Fuhrmann, M.; Klinkert, W.E.F.; Goldbrunner, R.; Herms, J.; Winkler, F. Real-Time Imaging Reveals the Single Steps of Brain Metastasis Formation. *Nat. Med.* **2010**, *16*, 116–122. [[CrossRef](#)] [[PubMed](#)]
148. Zhan, Q.; Liu, B.; Situ, X.; Luo, Y.; Fu, T.; Wang, Y.; Xie, Z.; Ren, L.; Zhu, Y.; He, W.; et al. New Insights into the Correlations between Circulating Tumor Cells and Target Organ Metastasis. *Signal Transduct. Target. Ther.* **2023**, *8*, 465. [[CrossRef](#)]
149. Peinado, H.; Lavotshkin, S.; Lyden, D. The Secreted Factors Responsible for Pre-Metastatic Niche Formation: Old Sayings and New Thoughts. *Semin. Cancer Biol.* **2011**, *21*, 139–146. [[CrossRef](#)]
150. Liu, Y.; Cao, X. Characteristics and Significance of the Pre-Metastatic Niche. *Cancer Cell* **2016**, *30*, 668–681. [[CrossRef](#)]
151. Coussens, L.M.; Werb, Z. Inflammation and Cancer. *Nature* **2002**, *420*, 860–867. [[CrossRef](#)]
152. Kaplan, R.N.; Riba, R.D.; Zacharoulis, S.; Bramley, A.H.; Vincent, L.; Costa, C.; MacDonald, D.D.; Jin, D.K.; Shido, K.; Kerns, S.A.; et al. VEGFR1-Positive Haematopoietic Bone Marrow Progenitors Initiate the Pre-Metastatic Niche. *Nature* **2005**, *438*, 820–827. [[CrossRef](#)]
153. Liu, S.; Jiang, M.; Zhao, Q.; Li, S.; Peng, Y.; Zhang, P.; Han, M. Vascular Endothelial Growth Factor Plays a Critical Role in the Formation of the Pre-Metastatic Niche via Prostaglandin E2. *Oncol. Rep.* **2014**, *32*, 2477–2484. [[CrossRef](#)] [[PubMed](#)]
154. Dysthe, M.; Parihar, R. Myeloid-Derived Suppressor Cells in the Tumor Microenvironment. *Adv. Exp. Med. Biol.* **2020**, *1224*, 117–140. [[PubMed](#)]
155. Adler, O.; Zait, Y.; Cohen, N.; Blazquez, R.; Doron, H.; Monteran, L.; Scharff, Y.; Shami, T.; Mundhe, D.; Glehr, G.; et al. Reciprocal Interactions between Innate Immune Cells and Astrocytes Facilitate Neuroinflammation and Brain Metastasis via Lipocalin-2. *Nat. Cancer* **2023**, *4*, 401–418. [[CrossRef](#)] [[PubMed](#)]
156. Shi, F.; Duan, S.; Cui, J.; Yan, X.; Li, H.; Wang, Y.; Chen, F.; Zhang, L.; Liu, J.; Xie, X. Induction of Matrix Metalloproteinase-3 (MMP-3) Expression in the Microglia by Lipopolysaccharide (LPS) via Upregulation of Glycoprotein Nonmetastatic Melanoma B (GPNMB) Expression. *J. Mol. Neurosci.* **2014**, *54*, 234–242. [[CrossRef](#)]
157. Tomihari, M.; Chung, J.-S.; Akiyoshi, H.; Cruz, P.D.; Ariizumi, K. DC-HIL/Glycoprotein Nmb Promotes Growth of Melanoma in Mice by Inhibiting the Activation of Tumor-Reactive T Cells. *Cancer Res.* **2010**, *70*, 5778–5787. [[CrossRef](#)]
158. Neal, M.L.; Boyle, A.M.; Budge, K.M.; Safadi, F.F.; Richardson, J.R. The Glycoprotein GPNMB Attenuates Astrocyte Inflammatory Responses through the CD44 Receptor. *J. Neuroinflamm.* **2018**, *15*, 73. [[CrossRef](#)]
159. Hoshino, A.; Costa-Silva, B.; Shen, T.-L.; Rodrigues, G.; Hashimoto, A.; Tesic Mark, M.; Molina, H.; Kohsaka, S.; Di Giannatale, A.; Ceder, S.; et al. Tumour Exosome Integrins Determine Organotropic Metastasis. *Nature* **2015**, *527*, 329–335. [[CrossRef](#)]
160. Minciacchi, V.R.; Freeman, M.R.; Di Vizio, D. Extracellular Vesicles in Cancer: Exosomes, Microvesicles and the Emerging Role of Large Oncosomes. *Semin. Cell Dev. Biol.* **2015**, *40*, 41–51. [[CrossRef](#)]
161. Morad, G.; Carman, C.V.; Hagedorn, E.J.; Perlin, J.R.; Zon, L.I.; Mustafaoglu, N.; Park, T.-E.; Ingber, D.E.; Daisy, C.C.; Moses, M.A. Tumor-Derived Extracellular Vesicles Breach the Intact Blood–Brain Barrier via Transcytosis. *ACS Nano* **2019**, *13*, 13853–13865. [[CrossRef](#)]
162. Jung, T.; Castellana, D.; Klingbeil, P.; Hernández, I.C.; Vitacolonna, M.; Orlicky, D.J.; Roffler, S.R.; Brodt, P.; Zöller, M. CD44v6 Dependence of Premetastatic Niche Preparation by Exosomes. *Neoplasia* **2009**, *11*, 1093–1105. [[CrossRef](#)]
163. Pasquier, J.; Al Thawadi, H.; Ghiabi, P.; Abu-Kaoud, N.; Maleki, M.; Guerrouahen, B.S.; Vidal, F.; Courderc, B.; Ferron, G.; Martinez, A.; et al. Microparticles Mediated Cross-Talk between Tumoral and Endothelial Cells Promote the Constitution of a pro-Metastatic Vascular Niche through Arf6 up Regulation. *Cancer Microenviron.* **2014**, *7*, 41–59. [[CrossRef](#)] [[PubMed](#)]
164. Ruan, X.; Yan, W.; Cao, M.; Daza, R.A.M.; Fong, M.Y.; Yang, K.; Wu, J.; Liu, X.; Palomares, M.; Wu, X.; et al. Breast Cancer Cell-Secreted MiR-199b-5p Hijacks Neurometabolic Coupling to Promote Brain Metastasis. *Nat. Commun.* **2024**, *15*, 4549. [[CrossRef](#)] [[PubMed](#)]
165. Fong, M.Y.; Zhou, W.; Liu, L.; Alontaga, A.Y.; Chandra, M.; Ashby, J.; Chow, A.; O'Connor, S.T.F.; Li, S.; Chin, A.R.; et al. Breast-Cancer-Secreted MiR-122 Reprograms Glucose Metabolism in Premetastatic Niche to Promote Metastasis. *Nat. Cell Biol.* **2015**, *17*, 183–194. [[CrossRef](#)] [[PubMed](#)]
166. Rodrigues, G.; Hoshino, A.; Kenific, C.M.; Matei, I.R.; Steiner, L.; Freitas, D.; Kim, H.S.; Oxley, P.R.; Scandariato, I.; Casanova-Salas, I.; et al. Tumour Exosomal CEMIP Protein Promotes Cancer Cell Colonization in Brain Metastasis. *Nat. Cell Biol.* **2019**, *21*, 1403–1412. [[CrossRef](#)]
167. Yuzhalin, A.E.; Yu, D. Brain Metastasis Organotropism. *Cold Spring Harb. Perspect. Med.* **2020**, *10*, a037242. [[CrossRef](#)]
168. Widodo, S.S.; Dinevska, M.; Cuzcano, L.; Papanicolaou, M.; Cox, T.R.; Stylli, S.S.; Mantamadiotis, T. Spatial Analysis of the Metastatic Brain Tumor Immune and Extracellular Matrix Microenvironment. *Adv. Cancer Biol. Metastasis* **2023**, *7*, 100096. [[CrossRef](#)]
169. Deasy, S.K.; Erez, N. A Glitch in the Matrix: Organ-Specific Matrisomes in Metastatic Niches. *Trends Cell Biol.* **2022**, *32*, 110–123. [[CrossRef](#)]

170. Virga, J.; Szemcsák, C.D.; Reményi-Puskár, J.; Tóth, J.; Hortobágyi, T.; Csósz, É.; Zahuczky, G.; Szivos, L.; Bognár, L.; Klekner, A. Differences in Extracellular Matrix Composition and Its Role in Invasion in Primary and Secondary Intracerebral Malignancies. *Anticancer Res.* **2017**, *37*, 4119–4126. [\[CrossRef\]](#)
171. Huang, J.-Y.; Cheng, Y.-J.; Lin, Y.-P.; Lin, H.-C.; Su, C.-C.; Juliano, R.; Yang, B.-C. Extracellular Matrix of Glioblastoma Inhibits Polarization and Transmigration of T Cells: The Role of Tenascin-C in Immune Suppression. *J. Immunol.* **2010**, *185*, 1450–1459. [\[CrossRef\]](#)
172. Wang, S.; Liang, K.; Hu, Q.; Li, P.; Song, J.; Yang, Y.; Yao, J.; Mangala, L.S.; Li, C.; Yang, W.; et al. JAK2-Binding Long Noncoding RNA Promotes Breast Cancer Brain Metastasis. *J. Clin. Investig.* **2017**, *127*, 4498–4515. [\[CrossRef\]](#)
173. Foo, S.L.; Sachaphibulkij, K.; Lee, C.L.Y.; Yap, G.L.R.; Cui, J.; Arumugam, T.; Lim, L.H.K. Breast Cancer Metastasis to Brain Results in Recruitment and Activation of Microglia through Annexin-A1/Formyl Peptide Receptor Signaling. *Breast Cancer Res.* **2022**, *24*, 25. [\[CrossRef\]](#) [\[PubMed\]](#)
174. Blazquez, R.; Wlochowitz, D.; Wolff, A.; Seitz, S.; Wachter, A.; Perera-Bel, J.; Bleckmann, A.; Beißbarth, T.; Salinas, G.; Riemen-schneider, M.J.; et al. PI3K: A Master Regulator of Brain Metastasis-promoting Macrophages/Microglia. *Glia* **2018**, *66*, 2438–2455. [\[CrossRef\]](#) [\[PubMed\]](#)
175. Izraely, S.; Ben-Menachem, S.; Malka, S.; Sagi-Assif, O.; Bustos, M.A.; Adir, O.; Meshel, T.; Chelladurai, M.; Ryu, S.; Ramos, R.I.; et al. The Vicious Cycle of Melanoma-Microglia Crosstalk: Inter-Melanoma Variations in the Brain-Metastasis-Promoting IL-6/JAK/STAT3 Signaling Pathway. *Cells* **2023**, *12*, 1513. [\[CrossRef\]](#) [\[PubMed\]](#)
176. Qiao, S.; Qian, Y.; Xu, G.; Luo, Q.; Zhang, Z. Long-Term Characterization of Activated Microglia/Macrophages Facilitating the Development of Experimental Brain Metastasis through Intravital Microscopic Imaging. *J. Neuroinflamm.* **2019**, *16*, 4. [\[CrossRef\]](#)
177. Bowman, R.L.; Klemm, F.; Akkari, L.; Pyonteck, S.M.; Sevenich, L.; Quail, D.F.; Dhara, S.; Simpson, K.; Gardner, E.E.; Iacobuzio-Donahue, C.A.; et al. Macrophage Ontogeny Underlies Differences in Tumor-Specific Education in Brain Malignancies. *Cell Rep.* **2016**, *17*, 2445–2459. [\[CrossRef\]](#)
178. Schreurs, L.D.; vom Stein, A.F.; Jünger, S.T.; Timmer, M.; Noh, K.-W.; Buettner, R.; Kashkar, H.; Neuschmelting, V.; Goldbrunner, R.; Nguyen, P.-H. The Immune Landscape in Brain Metastasis. *Neuro Oncol.* **2024**, *27*, 50–62. [\[CrossRef\]](#)
179. Karimi, E.; Yu, M.W.; Maritan, S.M.; Perus, L.J.M.; Rezanejad, M.; Sorin, M.; Dankner, M.; Fallah, P.; Doré, S.; Zuo, D.; et al. Single-Cell Spatial Immune Landscapes of Primary and Metastatic Brain Tumours. *Nature* **2023**, *614*, 555–563. [\[CrossRef\]](#)
180. Thapa, B.; Lee, K. Metabolic Influence on Macrophage Polarization and Pathogenesis. *BMB Rep.* **2019**, *52*, 360–372. [\[CrossRef\]](#)
181. Klemm, F.; Maas, R.R.; Bowman, R.L.; Kornete, M.; Soukup, K.; Nassiri, S.; Brouland, J.-P.; Iacobuzio-Donahue, C.A.; Brennan, C.; Tabar, V.; et al. Interrogation of the Microenvironmental Landscape in Brain Tumors Reveals Disease-Specific Alterations of Immune Cells. *Cell* **2020**, *181*, 1643–1660.e17. [\[CrossRef\]](#)
182. Schulz, M.; Michels, B.; Niesel, K.; Stein, S.; Farin, H.; Rödel, F.; Sevenich, L. Cellular and Molecular Changes of Brain Metastases-Associated Myeloid Cells during Disease Progression and Therapeutic Response. *iScience* **2020**, *23*, 101178. [\[CrossRef\]](#)
183. Guldner, I.H.; Wang, Q.; Yang, L.; Golomb, S.M.; Zhao, Z.; Lopez, J.A.; Brunory, A.; Howe, E.N.; Zhang, Y.; Palakurthi, B.; et al. CNS-Native Myeloid Cells Drive Immune Suppression in the Brain Metastatic Niche through Cxcl10. *Cell* **2020**, *183*, 1234–1248.e25. [\[CrossRef\]](#) [\[PubMed\]](#)
184. Friebe, E.; Kapolou, K.; Unger, S.; Núñez, N.G.; Utz, S.; Rushing, E.J.; Regli, L.; Weller, M.; Greter, M.; Tugues, S.; et al. Single-Cell Mapping of Human Brain Cancer Reveals Tumor-Specific Instruction of Tissue-Invasive Leukocytes. *Cell* **2020**, *181*, 1626–1642.e20. [\[CrossRef\]](#) [\[PubMed\]](#)
185. Christensson, G.; Bocci, M.; Kazi, J.U.; Durand, G.; Lanzing, G.; Pietras, K.; Gonzalez Velozo, H.; Hagerling, C. Spatial Multiomics Reveals Intratumoral Immune Heterogeneity with Distinct Cytokine Networks in Lung Cancer Brain Metastases. *Cancer Res. Commun.* **2024**, *4*, 2888–2902. [\[CrossRef\]](#)
186. Rubio-Perez, C.; Planas-Rigol, E.; Trincado, J.L.; Bonfill-Teixidor, E.; Arias, A.; Marchese, D.; Moutinho, C.; Serna, G.; Pedrosa, L.; Iurlaro, R.; et al. Immune Cell Profiling of the Cerebrospinal Fluid Enables the Characterization of the Brain Metastasis Microenvironment. *Nat. Commun.* **2021**, *12*, 1503. [\[CrossRef\]](#) [\[PubMed\]](#)
187. Lei, P.-J.; Fraser, C.; Jones, D.; Ubellacker, J.M.; Padera, T.P. Lymphatic System Regulation of Anti-Cancer Immunity and Metastasis. *Front. Immunol.* **2024**, *15*, 1449291. [\[CrossRef\]](#)
188. Mohammed, S.I.; Torres-Luquis, O.; Walls, E.; Lloyd, F. Lymph-circulating Tumor Cells Show Distinct Properties to Blood-circulating Tumor Cells and Are Efficient Metastatic Precursors. *Mol. Oncol.* **2019**, *13*, 1400–1418. [\[CrossRef\]](#)
189. Fujimoto, N.; Dieterich, L.C. Mechanisms and Clinical Significance of Tumor Lymphatic Invasion. *Cells* **2021**, *10*, 2585. [\[CrossRef\]](#)
190. Pereira, E.R.; Kedrin, D.; Seano, G.; Gautier, O.; Meijer, E.F.J.; Jones, D.; Chin, S.-M.; Kitahara, S.; Bouta, E.M.; Chang, J.; et al. Lymph Node Metastases Can Invade Local Blood Vessels, Exit the Node, and Colonize Distant Organs in Mice. *Science* **2018**, *359*, 1403–1407. [\[CrossRef\]](#)
191. Brown, M.; Assen, F.P.; Leithner, A.; Abe, J.; Schachner, H.; Asfour, G.; Bago-Horvath, Z.; Stein, J.V.; Uhrin, P.; Sixt, M.; et al. Lymph Node Blood Vessels Provide Exit Routes for Metastatic Tumor Cell Dissemination in Mice. *Science* **2018**, *359*, 1408–1411. [\[CrossRef\]](#)

192. García-Silva, S.; Benito-Martín, A.; Nogués, L.; Hernández-Barranco, A.; Mazariegos, M.S.; Santos, V.; Hergueta-Redondo, M.; Ximénez-Embún, P.; Kataru, R.P.; Lopez, A.A.; et al. Melanoma-Derived Small Extracellular Vesicles Induce Lymphangiogenesis and Metastasis through an NGFR-Dependent Mechanism. *Nat. Cancer* **2021**, *2*, 1387–1405. [[CrossRef](#)]
193. Riedel, A.; Helal, M.; Pedro, L.; Swietlik, J.J.; Shorthouse, D.; Schmitz, W.; Haas, L.; Young, T.; da Costa, A.S.H.; Davidson, S.; et al. Tumor-Derived Lactic Acid Modulates Activation and Metabolic Status of Draining Lymph Node Stroma. *Cancer Immunol. Res.* **2022**, *10*, 482–497. [[CrossRef](#)] [[PubMed](#)]
194. Hoshida, T.; Isaka, N.; Hagendoorn, J.; di Tomaso, E.; Chen, Y.-L.; Pytowski, B.; Fukumura, D.; Padera, T.P.; Jain, R.K. Imaging Steps of Lymphatic Metastasis Reveals That Vascular Endothelial Growth Factor-C Increases Metastasis by Increasing Delivery of Cancer Cells to Lymph Nodes: Therapeutic Implications. *Cancer Res.* **2006**, *66*, 8065–8075. [[CrossRef](#)]
195. Kim, M.; Koh, Y.J.; Kim, K.E.; Koh, B.I.; Nam, D.-H.; Alitalo, K.; Kim, I.; Koh, G.Y. CXCR4 Signaling Regulates Metastasis of Chemoresistant Melanoma Cells by a Lymphatic Metastatic Niche. *Cancer Res.* **2010**, *70*, 10411–10421. [[CrossRef](#)] [[PubMed](#)]
196. Das, S.; Sarrou, E.; Podgrabinska, S.; Cassella, M.; Mungamuri, S.K.; Feirt, N.; Gordon, R.; Nagi, C.S.; Wang, Y.; Entenberg, D.; et al. Tumor Cell Entry into the Lymph Node Is Controlled by CCL1 Chemokine Expressed by Lymph Node Lymphatic Sinuses. *J. Exp. Med.* **2013**, *210*, 1509–1528. [[CrossRef](#)] [[PubMed](#)]
197. Issa, A.; Le, T.X.; Shoushtari, A.N.; Shields, J.D.; Swartz, M.A. Vascular Endothelial Growth Factor-C and C-C Chemokine Receptor 7 in Tumor Cell–Lymphatic Cross-Talk Promote Invasive Phenotype. *Cancer Res.* **2009**, *69*, 349–357. [[CrossRef](#)]
198. Lund, A.W.; Duraes, F.V.; Hirosue, S.; Raghavan, V.R.; Nembrini, C.; Thomas, S.N.; Issa, A.; Hugues, S.; Swartz, M.A. VEGF-C Promotes Immune Tolerance in B16 Melanomas and Cross-Presentation of Tumor Antigen by Lymph Node Lymphatics. *Cell Rep.* **2012**, *1*, 191–199. [[CrossRef](#)]
199. Reticker-Flynn, N.E.; Zhang, W.; Belk, J.A.; Basto, P.A.; Escalante, N.K.; Pilarowski, G.O.W.; Bejnood, A.; Martins, M.M.; Kenkel, J.A.; Linde, I.L.; et al. Lymph Node Colonization Induces Tumor-Immune Tolerance to Promote Distant Metastasis. *Cell* **2022**, *185*, 1924–1942.e23. [[CrossRef](#)]
200. Tokumoto, M.; Tanaka, H.; Tauchi, Y.; Tamura, T.; Toyokawa, T.; Kimura, K.; Muguruma, K.; Yashiro, M.; Maeda, K.; Hirakawa, K.; et al. Immunoregulatory Function of Lymphatic Endothelial Cells in Tumor-Draining Lymph Nodes of Human Gastric Cancer. *Anticancer. Res.* **2017**, *37*, 2875–2883. [[CrossRef](#)]
201. Lei, P.-J.; Pereira, E.R.; Andersson, P.; Amoozgar, Z.; Van Wijnbergen, J.W.; O'Melia, M.J.; Zhou, H.; Chatterjee, S.; Ho, W.W.; Posada, J.M.; et al. Cancer Cell Plasticity and MHC-II–Mediated Immune Tolerance Promote Breast Cancer Metastasis to Lymph Nodes. *J. Exp. Med.* **2023**, *220*, e20221847. [[CrossRef](#)]
202. Jiang, M.; Wu, N.; Xu, B.; Chu, Y.; Li, X.; Su, S.; Chen, D.; Li, W.; Shi, Y.; Gao, X.; et al. Fatty Acid-Induced CD36 Expression via O-GlcNAcylation Drives Gastric Cancer Metastasis. *Theranostics* **2019**, *9*, 5359–5373. [[CrossRef](#)]
203. Pascual, G.; Avgustinova, A.; Mejetta, S.; Martín, M.; Castellanos, A.; Attolini, C.S.-O.; Berenguer, A.; Prats, N.; Toll, A.; Hueto, J.A.; et al. Targeting Metastasis-Initiating Cells through the Fatty Acid Receptor CD36. *Nature* **2017**, *541*, 41–45. [[CrossRef](#)] [[PubMed](#)]
204. Lee, C.; Jeong, S.; Jang, C.; Bae, H.; Kim, Y.H.; Park, I.; Kim, S.K.; Koh, G.Y. Tumor Metastasis to Lymph Nodes Requires YAP-Dependent Metabolic Adaptation. *Science* **2019**, *363*, 644–649. [[CrossRef](#)] [[PubMed](#)]
205. Li, X.; Tian, M.; Yu, L.; Qian, J.; Yang, J.; Wang, X.; Lu, C.; Xiao, C.; Liu, Y. The Role of Ferroptosis Resistance in Lymph-Associated Tumour Metastasis. *Biochim. Biophys. Acta Rev. Cancer* **2024**, *1879*, 189200. [[CrossRef](#)] [[PubMed](#)]
206. Ubellacker, J.M.; Tasdogan, A.; Ramesh, V.; Shen, B.; Mitchell, E.C.; Martin-Sandoval, M.S.; Gu, Z.; McCormick, M.L.; Durham, A.B.; Spitz, D.R.; et al. Lymph Protects Metastasizing Melanoma Cells from Ferroptosis. *Nature* **2020**, *585*, 113–118. [[CrossRef](#)]
207. Reiter, J.G.; Hung, W.-T.; Lee, I.-H.; Nagpal, S.; Giunta, P.; Degner, S.; Liu, G.; Wassenaar, E.C.E.; Jeck, W.R.; Taylor, M.S.; et al. Lymph Node Metastases Develop through a Wider Evolutionary Bottleneck than Distant Metastases. *Nat. Genet.* **2020**, *52*, 692–700. [[CrossRef](#)]
208. Hong, M.K.H.; Macintyre, G.; Wedge, D.C.; Van Loo, P.; Patel, K.; Lunke, S.; Alexandrov, L.B.; Sloggett, C.; Cmero, M.; Marass, F.; et al. Tracking the Origins and Drivers of Subclonal Metastatic Expansion in Prostate Cancer. *Nat. Commun.* **2015**, *6*, 6605. [[CrossRef](#)]
209. Werner-Klein, M.; Scheitler, S.; Hoffmann, M.; Hodak, I.; Dietz, K.; Lehnert, P.; Naimer, V.; Polzer, B.; Treitschke, S.; Werno, C.; et al. Genetic Alterations Driving Metastatic Colony Formation Are Acquired Outside of the Primary Tumour in Melanoma. *Nat. Commun.* **2018**, *9*, 595. [[CrossRef](#)]
210. Leslie, P.L.; Chao, Y.L.; Tsai, Y.-H.; Ghosh, S.K.; Porrello, A.; Van Swearingen, A.E.D.; Harrison, E.B.; Cooley, B.C.; Parker, J.S.; Carey, L.A.; et al. Histone Deacetylase 11 Inhibition Promotes Breast Cancer Metastasis from Lymph Nodes. *Nat. Commun.* **2019**, *10*, 4192. [[CrossRef](#)]
211. Wagenblast, E.; Soto, M.; Gutiérrez-Ángel, S.; Hartl, C.A.; Gable, A.L.; Maceli, A.R.; Erard, N.; Williams, A.M.; Kim, S.Y.; Dickopf, S.; et al. A Model of Breast Cancer Heterogeneity Reveals Vascular Mimicry as a Driver of Metastasis. *Nature* **2015**, *520*, 358–362. [[CrossRef](#)]
212. Psaila, B.; Lyden, D. The Metastatic Niche: Adapting the Foreign Soil. *Nat. Rev. Cancer* **2009**, *9*, 285–293. [[CrossRef](#)]

213. Liu, X.; Taftaf, R.; Kawaguchi, M.; Chang, Y.-F.; Chen, W.; Entenberg, D.; Zhang, Y.; Gerratana, L.; Huang, S.; Patel, D.B.; et al. Homophilic CD44 Interactions Mediate Tumor Cell Aggregation and Polyclonal Metastasis in Patient-Derived Breast Cancer Models. *Cancer Discov.* **2019**, *9*, 96–113. [[CrossRef](#)] [[PubMed](#)]
214. Beerling, E.; Seinstra, D.; de Wit, E.; Kester, L.; van der Velden, D.; Maynard, C.; Schäfer, R.; van Diest, P.; Voest, E.; van Oudenaarden, A.; et al. Plasticity between Epithelial and Mesenchymal States Unlinks EMT from Metastasis-Enhancing Stem Cell Capacity. *Cell Rep.* **2016**, *14*, 2281–2288. [[CrossRef](#)] [[PubMed](#)]
215. Choi, H.Y.; Yang, G.-M.; Dayem, A.A.; Saha, S.K.; Kim, K.; Yoo, Y.; Hong, K.; Kim, J.-H.; Yee, C.; Lee, K.-M.; et al. Hydrodynamic Shear Stress Promotes Epithelial-Mesenchymal Transition by Downregulating ERK and GSK3 β Activities. *Breast Cancer Res.* **2019**, *21*, 6. [[CrossRef](#)] [[PubMed](#)]
216. Amintas, S.; Bedel, A.; Moreau-Gaudry, F.; Boutin, J.; Buscail, L.; Merlio, J.-P.; Vendrely, V.; Dabernat, S.; Buscail, E. Circulating Tumor Cell Clusters: United We Stand Divided We Fall. *Int. J. Mol. Sci.* **2020**, *21*, 2653. [[CrossRef](#)]
217. Wirtz, D.; Konstantopoulos, K.; Searson, P.C. The Physics of Cancer: The Role of Physical Interactions and Mechanical Forces in Metastasis. *Nat. Rev. Cancer* **2011**, *11*, 512–522. [[CrossRef](#)]
218. Au, S.H.; Storey, B.D.; Moore, J.C.; Tang, Q.; Chen, Y.-L.; Javaid, S.; Sarioglu, A.F.; Sullivan, R.; Madden, M.W.; O’Keefe, R.; et al. Clusters of Circulating Tumor Cells Traverse Capillary-Sized Vessels. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 4947–4952. [[CrossRef](#)]
219. Rajput, S.; Kumar Sharma, P.; Malviya, R. Fluid Mechanics in Circulating Tumour Cells: Role in Metastasis and Treatment Strategies. *Med. Drug Discov.* **2023**, *18*, 100158. [[CrossRef](#)]
220. Szczerba, B.M.; Castro-Giner, F.; Vetter, M.; Krol, I.; Gkoutela, S.; Landin, J.; Scheidmann, M.C.; Donato, C.; Scherrer, R.; Singer, J.; et al. Neutrophils Escort Circulating Tumour Cells to Enable Cell Cycle Progression. *Nature* **2019**, *566*, 553–557. [[CrossRef](#)]
221. Patel, S.; Fu, S.; Mastio, J.; Dominguez, G.A.; Purohit, A.; Kossenkova, A.; Lin, C.; Alicea-Torres, K.; Sehgal, M.; Nefedova, Y.; et al. Unique Pattern of Neutrophil Migration and Function during Tumor Progression. *Nat. Immunol.* **2018**, *19*, 1236–1247. [[CrossRef](#)]
222. Chen, M.B.; Hajal, C.; Benjamin, D.C.; Yu, C.; Azizgolshani, H.; Hynes, R.O.; Kamm, R.D. Inflamed Neutrophils Sequestered at Entrapped Tumor Cells via Chemotactic Confinement Promote Tumor Cell Extravasation. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 7022–7027. [[CrossRef](#)]
223. Cools-Lartigue, J.; Spicer, J.; McDonald, B.; Gowing, S.; Chow, S.; Giannias, B.; Bourdeau, F.; Kubes, P.; Ferri, L. Neutrophil Extracellular Traps Sequester Circulating Tumor Cells and Promote Metastasis. *J. Clin. Investig.* **2013**, *123*, 3446–3458. [[CrossRef](#)] [[PubMed](#)]
224. Najmeh, S.; Cools-Lartigue, J.; Rayes, R.F.; Gowing, S.; Vourtzoumis, P.; Bourdeau, F.; Giannias, B.; Berube, J.; Rousseau, S.; Ferri, L.E.; et al. Neutrophil Extracellular Traps Sequester Circulating Tumor Cells via B1-Integrin Mediated Interactions. *Int. J. Cancer* **2017**, *140*, 2321–2330. [[CrossRef](#)] [[PubMed](#)]
225. Huh, S.J.; Liang, S.; Sharma, A.; Dong, C.; Robertson, G.P. Transiently Entrapped Circulating Tumor Cells Interact with Neutrophils to Facilitate Lung Metastasis Development. *Cancer Res.* **2010**, *70*, 6071–6082. [[CrossRef](#)] [[PubMed](#)]
226. Li, D.; Hemati, H.; Park, Y.; Taftaf, R.; Zhang, Y.; Liu, J.; Cristofanilli, M.; Liu, X. ICAM-1-SuPAR-CD11b Axis Is a Novel Therapeutic Target for Metastatic Triple-Negative Breast Cancer. *Cancers* **2023**, *15*, 2734. [[CrossRef](#)]
227. Zhou, W.; Zhu, C.; Shen, P.; Wang, J.F.; Zhu, G.; Jia, Y.; Wu, Y.; Wang, S.; Sun, J.; Yang, F.; et al. Hypoxia Stimulates CTC-Platelet Cluster Formation to Promote Breast Cancer Metastasis. *iScience* **2024**, *27*, 109547. [[CrossRef](#)]
228. Best, M.G.; Sol, N.; Kooi, I.; Tannous, J.; Westerman, B.A.; Rustenburg, F.; Schellen, P.; Verschueren, H.; Post, E.; Koster, J.; et al. RNA-Seq of Tumor-Educated Platelets Enables Blood-Based Pan-Cancer, Multiclass, and Molecular Pathway Cancer Diagnostics. *Cancer Cell* **2015**, *28*, 666–676. [[CrossRef](#)]
229. Rodriguez-Martinez, A.; Simon-Saez, I.; Perales, S.; Garrido-Navas, C.; Russo, A.; de Miguel-Perez, D.; Puche-Sanz, I.; Alaminos, C.; Ceron, J.; Lorente, J.A.; et al. Exchange of Cellular Components between Platelets and Tumor Cells: Impact on Tumor Cells Behavior. *Theranostics* **2022**, *12*, 2150–2161. [[CrossRef](#)]
230. Labelle, M.; Begum, S.; Hynes, R.O. Direct Signaling between Platelets and Cancer Cells Induces an Epithelial-Mesenchymal-Like Transition and Promotes Metastasis. *Cancer Cell* **2011**, *20*, 576–590. [[CrossRef](#)]
231. Liu, X.; Song, J.; Zhang, H.; Liu, X.; Zuo, F.; Zhao, Y.; Zhao, Y.; Yin, X.; Guo, X.; Wu, X.; et al. Immune Checkpoint HLA-E:CD94-NKG2A Mediates Evasion of Circulating Tumor Cells from NK Cell Surveillance. *Cancer Cell* **2023**, *41*, 272–287.e9. [[CrossRef](#)]
232. Sun, Y.; Li, T.; Ding, L.; Wang, J.; Chen, C.; Liu, T.; Liu, Y.; Li, Q.; Wang, C.; Huo, R.; et al. Platelet-Mediated Circulating Tumor Cell Evasion from Natural Killer Cell Killing through Immune Checkpoint CD155-TIGIT. *Hepatology* **2024**, *81*, 791–807. [[CrossRef](#)]
233. Eslami-S, Z.; Cortés-Hernández, L.E.; Glogovitis, I.; Antunes-Ferreira, M.; D’Ambrosi, S.; Kurma, K.; Garima, F.; Cayrefourcq, L.; Best, M.G.; Koppers-Lalic, D.; et al. In Vitro Cross-Talk between Metastasis-Competent Circulating Tumor Cells and Platelets in Colon Cancer: A Malicious Association during the Harsh Journey in the Blood. *Front. Cell Dev. Biol.* **2023**, *11*, 1209846. [[CrossRef](#)] [[PubMed](#)]

234. Haemmerle, M.; Taylor, M.L.; Gutschner, T.; Pradeep, S.; Cho, M.S.; Sheng, J.; Lyons, Y.M.; Nagaraja, A.S.; Dood, R.L.; Wen, Y.; et al. Platelets Reduce Anoikis and Promote Metastasis by Activating YAP1 Signaling. *Nat. Commun.* **2017**, *8*, 310. [[CrossRef](#)] [[PubMed](#)]
235. Liu, Q.; Liao, Q.; Zhao, Y. Myeloid-Derived Suppressor Cells (MDSC) Facilitate Distant Metastasis of Malignancies by Shielding Circulating Tumor Cells (CTC) from Immune Surveillance. *Med. Hypotheses* **2016**, *87*, 34–39. [[CrossRef](#)] [[PubMed](#)]
236. Sprouse, M.L.; Welte, T.; Boral, D.; Liu, H.N.; Yin, W.; Vishnoi, M.; Goswami-Sewell, D.; Li, L.; Pei, G.; Jia, P.; et al. PMN-MDSCs Enhance CTC Metastatic Properties through Reciprocal Interactions via ROS/Notch/Nodal Signaling. *Int. J. Mol. Sci.* **2019**, *20*, 1916. [[CrossRef](#)]
237. Li, K.; Shi, H.; Zhang, B.; Ou, X.; Ma, Q.; Chen, Y.; Shu, P.; Li, D.; Wang, Y. Myeloid-Derived Suppressor Cells as Immunosuppressive Regulators and Therapeutic Targets in Cancer. *Signal Transduct. Target. Ther.* **2021**, *6*, 362. [[CrossRef](#)]
238. Altevogt, P.; Sammar, M.; Hüser, L.; Kristiansen, G. Novel Insights into the Function of CD24: A Driving Force in Cancer. *Int. J. Cancer* **2021**, *148*, 546–559. [[CrossRef](#)]
239. Zhang, Y.; Zhou, N.; Yu, X.; Zhang, X.; Li, S.; Lei, Z.; Hu, R.; Li, H.; Mao, Y.; Wang, X.; et al. Tumacrophage: Macrophages Transformed into Tumor Stem-like Cells by Virulent Genetic Material from Tumor Cells. *Oncotarget* **2017**, *8*, 82326–82343. [[CrossRef](#)]
240. Fu, A.; Yao, B.; Dong, T.; Chen, Y.; Yao, J.; Liu, Y.; Li, H.; Bai, H.; Liu, X.; Zhang, Y.; et al. Tumor-Resident Intracellular Microbiota Promotes Metastatic Colonization in Breast Cancer. *Cell* **2022**, *185*, 1356–1372.e26. [[CrossRef](#)]
241. Ward, P.S.; Thompson, C.B. Metabolic Reprogramming: A Cancer Hallmark Even Warburg Did Not Anticipate. *Cancer Cell* **2012**, *21*, 297–308. [[CrossRef](#)]
242. Denes, V.; Lakk, M.; Makarovskiy, A.; Jakso, P.; Szappanos, S.; Graf, L.; Mandel, L.; Karadi, I.; Geck, P. Metastasis Blood Test by Flow Cytometry: In Vivo Cancer Spheroids and the Role of Hypoxia. *Int. J. Cancer* **2015**, *136*, 1528–1536. [[CrossRef](#)]
243. Quartieri, M.; Puspitasari, A.; Vitacchio, T.; Durante, M.; Tinganelli, W. The Role of Hypoxia and Radiation in Developing a CTCs-like Phenotype in Murine Osteosarcoma Cells. *Front. Cell Dev. Biol.* **2023**, *11*, 1222809. [[CrossRef](#)] [[PubMed](#)]
244. Godet, I.; Shin, Y.J.; Ju, J.A.; Ye, I.C.; Wang, G.; Gilkes, D.M. Fate-Mapping Post-Hypoxic Tumor Cells Reveals a ROS-Resistant Phenotype That Promotes Metastasis. *Nat. Commun.* **2019**, *10*, 4862. [[CrossRef](#)] [[PubMed](#)]
245. Paoli, P.; Giannoni, E.; Chiarugi, P. Anoikis Molecular Pathways and Its Role in Cancer Progression. *Biochim. Biophys. Acta Mol. Cell Res.* **2013**, *1833*, 3481–3498. [[CrossRef](#)] [[PubMed](#)]
246. Duda, D.G.; Duyverman, A.M.M.J.; Kohno, M.; Snuderl, M.; Steller, E.J.A.; Fukumura, D.; Jain, R.K. Malignant Cells Facilitate Lung Metastasis by Bringing Their Own Soil. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 21677–21682. [[CrossRef](#)]
247. Giannoni, E.; Bianchini, F.; Masieri, L.; Serni, S.; Torre, E.; Calorini, L.; Chiarugi, P. Reciprocal Activation of Prostate Cancer Cells and Cancer-Associated Fibroblasts Stimulates Epithelial-Mesenchymal Transition and Cancer Stemness. *Cancer Res.* **2010**, *70*, 6945–6956. [[CrossRef](#)]
248. Carbonell, W.S.; Ansorge, O.; Sibson, N.; Muschel, R. The Vascular Basement Membrane as “Soil” in Brain Metastasis. *PLoS ONE* **2009**, *4*, e5857. [[CrossRef](#)]
249. Correa, D.; Somoza, R.A.; Lin, P.; Schiemann, W.P.; Caplan, A.I. Mesenchymal Stem Cells Regulate Melanoma Cancer Cells Extravasation to Bone and Liver at Their Perivascular Niche. *Int. J. Cancer* **2016**, *138*, 417–427. [[CrossRef](#)]
250. Bentolila, L.A.; Prakash, R.; Mihic-Probst, D.; Wadehra, M.; Kleinman, H.K.; Carmichael, T.S.; Péault, B.; Barnhill, R.L.; Lugassy, C. Imaging of Angiotropism/Vascular Co-Option in a Murine Model of Brain Melanoma: Implications for Melanoma Progression along Extravascular Pathways. *Sci. Rep.* **2016**, *6*, 23834. [[CrossRef](#)]
251. Er, E.E.; Valiente, M.; Ganesh, K.; Zou, Y.; Agrawal, S.; Hu, J.; Griscom, B.; Rosenblum, M.; Boire, A.; Brogi, E.; et al. Pericyte-like Spreading by Disseminated Cancer Cells Activates YAP and MRTF for Metastatic Colonization. *Nat. Cell Biol.* **2018**, *20*, 966–978. [[CrossRef](#)]
252. Roesler, J.; Spitzer, D.; Jia, X.; Aasen, S.N.; Sommer, K.; Roller, B.; Olshausen, N.; Hebach, N.R.; Albinger, N.; Ullrich, E.; et al. Disturbance in Cerebral Blood Microcirculation and Hypoxic-Ischemic Microenvironment Are Associated with the Development of Brain Metastasis. *Neuro Oncol.* **2024**, *26*, 2084–2099. [[CrossRef](#)]
253. Wilhelm, I.; Molnár, J.; Fazakas, C.; Haskó, J.; Krizbai, I. Role of the Blood-Brain Barrier in the Formation of Brain Metastases. *Int. J. Mol. Sci.* **2013**, *14*, 1383–1411. [[CrossRef](#)] [[PubMed](#)]
254. Denkins, Y.; Reiland, J.; Roy, M.; Sinnappah-Kang, N.D.; Galjour, J.; Murry, B.P.; Blust, J.; Aucoin, R.; Marchetti, D. Brain Metastases in Melanoma: Roles of Neurotrophins. *Neuro Oncol.* **2004**, *6*, 154–165. [[CrossRef](#)] [[PubMed](#)]
255. Tiwary, S.; Morales, J.E.; Kwiatkowski, S.C.; Lang, F.F.; Rao, G.; McCarty, J.H. Metastatic Brain Tumors Disrupt the Blood-Brain Barrier and Alter Lipid Metabolism by Inhibiting Expression of the Endothelial Cell Fatty Acid Transporter Mfsd2a. *Sci. Rep.* **2018**, *8*, 8267. [[CrossRef](#)] [[PubMed](#)]
256. Wu, D.; Deng, S.; Li, L.; Liu, T.; Zhang, T.; Li, J.; Yu, Y.; Xu, Y. TGF- β 1-Mediated Exosomal Lnc-MMP2-2 Increases Blood–Brain Barrier Permeability via the MiRNA-1207-5p/EPB41L5 Axis to Promote Non-Small Cell Lung Cancer Brain Metastasis. *Cell Death Dis.* **2021**, *12*, 721. [[CrossRef](#)]

257. Wu, D.; Deng, S.; Liu, T.; Han, R.; Zhang, T.; Xu, Y. TGF- β -mediated Exosomal Lnc-MMP2-2 Regulates Migration and Invasion of Lung Cancer Cells to the Vasculature by Promoting MMP2 Expression. *Cancer Med.* **2018**, *7*, 5118–5129. [\[CrossRef\]](#)
258. Tominaga, N.; Kosaka, N.; Ono, M.; Katsuda, T.; Yoshioka, Y.; Tamura, K.; Lötvall, J.; Nakagama, H.; Ochiya, T. Brain Metastatic Cancer Cells Release MicroRNA-181c-Containing Extracellular Vesicles Capable of Destructing Blood–Brain Barrier. *Nat. Commun.* **2015**, *6*, 6716. [\[CrossRef\]](#)
259. Zhou, W.; Fong, M.Y.; Min, Y.; Somlo, G.; Liu, L.; Palomares, M.R.; Yu, Y.; Chow, A.; O'Connor, S.T.F.; Chin, A.R.; et al. Cancer-Secreted MiR-105 Destroys Vascular Endothelial Barriers to Promote Metastasis. *Cancer Cell* **2014**, *25*, 501–515. [\[CrossRef\]](#)
260. Wu, K.; Fukuda, K.; Xing, F.; Zhang, Y.; Sharma, S.; Liu, Y.; Chan, M.D.; Zhou, X.; Qasem, S.A.; Pochampally, R.; et al. Roles of the Cyclooxygenase 2 Matrix Metalloproteinase 1 Pathway in Brain Metastasis of Breast Cancer. *J. Biol. Chem.* **2015**, *290*, 9842–9854. [\[CrossRef\]](#)
261. Basile, J.R.; Barac, A.; Zhu, T.; Guan, K.-L.; Gutkind, J.S. Class IV Semaphorins Promote Angiogenesis by Stimulating Rho-Initiated Pathways through Plexin-B. *Cancer Res.* **2004**, *64*, 5212–5224. [\[CrossRef\]](#)
262. Sierra, J.R.; Corso, S.; Caione, L.; Cepero, V.; Conrotto, P.; Cignetti, A.; Piacibello, W.; Kumanogoh, A.; Kikutani, H.; Comoglio, P.M.; et al. Tumor Angiogenesis and Progression Are Enhanced by Sema4D Produced by Tumor-Associated Macrophages. *J. Exp. Med.* **2008**, *205*, 1673–1685. [\[CrossRef\]](#)
263. Franzolin, G.; Brundu, S.; Cojocaru, C.F.; Curatolo, A.; Ponzo, M.; Mastrantonio, R.; Mihara, E.; Kumanogoh, A.; Suga, H.; Takagi, J.; et al. PlexinB1 Inactivation Reprograms Immune Cells in the Tumor Microenvironment, Inhibiting Breast Cancer Growth and Metastatic Dissemination. *Cancer Immunol. Res.* **2024**, *12*, 1286–1301. [\[CrossRef\]](#) [\[PubMed\]](#)
264. Herrera, R.A.; Deshpande, K.; Martirosian, V.; Saatian, B.; Julian, A.; Eisenbarth, R.; Das, D.; Iyer, M.; Neman, J. Cortisol Promotes Breast-to-brain Metastasis through the Blood-cerebrospinal Fluid Barrier. *Cancer Rep.* **2022**, *5*, e1351. [\[CrossRef\]](#) [\[PubMed\]](#)
265. Johanson, C.E.; Stopa, E.G.; McMillan, P.N. The Blood–Cerebrospinal Fluid Barrier: Structure and Functional Significance. In *The Blood–Brain and Other Neural Barriers*; Springer: Berlin/Heidelberg, Germany, 2011; pp. 101–131.
266. Saatian, B.; Deshpande, K.; Herrera, R.; Sedighi, S.; Eisenbarth, R.; Iyer, M.; Das, D.; Julian, A.; Martirosian, V.; Lowman, A.; et al. Breast-to-brain Metastasis Is Exacerbated with Chemotherapy through Blood–Cerebrospinal Fluid Barrier and Induces Alzheimer's-like Pathology. *J. Neurosci. Res.* **2023**, *101*, 1900–1913. [\[CrossRef\]](#) [\[PubMed\]](#)
267. Khaled, M.L.; Tarhini, A.A.; Forsyth, P.A.; Smalley, I.; Piña, Y. Leptomeningeal Disease (LMD) in Patients with Melanoma Metastases. *Cancers* **2023**, *15*, 1884. [\[CrossRef\]](#)
268. Freret, M.E.; Boire, A. The Anatomic Basis of Leptomeningeal Metastasis. *J. Exp. Med.* **2024**, *221*, e20212121. [\[CrossRef\]](#)
269. Magbanua, M.J.M.; Melisko, M.; Roy, R.; Sosa, E.V.; Hauranieh, L.; Kablanian, A.; Eisenbud, L.E.; Ryazantsev, A.; Au, A.; Scott, J.H.; et al. Molecular Profiling of Tumor Cells in Cerebrospinal Fluid and Matched Primary Tumors from Metastatic Breast Cancer Patients with Leptomeningeal Carcinomatosis. *Cancer Res.* **2013**, *73*, 7134–7143. [\[CrossRef\]](#)
270. Chi, Y.; Remsik, J.; Kiseliavas, V.; Derderian, C.; Sener, U.; Alghader, M.; Saadeh, F.; Nikishina, K.; Bale, T.; Iacobuzio-Donahue, C.; et al. Cancer Cells Deploy Lipocalin-2 to Collect Limiting Iron in Leptomeningeal Metastasis. *Science* **2020**, *369*, 276–282. [\[CrossRef\]](#)
271. Duan, X.; He, K.; Li, J.; Cheng, M.; Song, H.; Liu, J.; Liu, P. Tumor Associated Macrophages Deliver Iron to Tumor Cells via Lcn2. *Int. J. Physiol. Pathophysiol. Pharmacol.* **2018**, *10*, 105–114.
272. Boire, A.; Zou, Y.; Shieh, J.; Macalinao, D.G.; Pentsova, E.; Massagué, J. Complement Component 3 Adapts the Cerebrospinal Fluid for Leptomeningeal Metastasis. *Cell* **2017**, *168*, 1101–1113.e13. [\[CrossRef\]](#)
273. Seike, T.; Fujita, K.; Yamakawa, Y.; Kido, M.A.; Takiguchi, S.; Teramoto, N.; Iguchi, H.; Noda, M. Interaction between Lung Cancer Cells and Astrocytes via Specific Inflammatory Cytokines in the Microenvironment of Brain Metastasis. *Clin. Exp. Metastasis* **2011**, *28*, 13–25. [\[CrossRef\]](#)
274. Schwartz, H.; Blacher, E.; Amer, M.; Livneh, N.; Abramovitz, L.; Klein, A.; Ben-Shushan, D.; Soffer, S.; Blazquez, R.; Barrantes-Freer, A.; et al. Incipient Melanoma Brain Metastases Instigate Astrogliosis and Neuroinflammation. *Cancer Res.* **2016**, *76*, 4359–4371. [\[CrossRef\]](#) [\[PubMed\]](#)
275. Doron, H.; Amer, M.; Ershaid, N.; Blazquez, R.; Shani, O.; Lahav, T.G.; Cohen, N.; Adler, O.; Hakim, Z.; Pozzi, S.; et al. Inflammatory Activation of Astrocytes Facilitates Melanoma Brain Tropism via the CXCL10-CXCR3 Signaling Axis. *Cell Rep.* **2019**, *28*, 1785–1798.e6. [\[CrossRef\]](#) [\[PubMed\]](#)
276. Hajal, C.; Shin, Y.; Li, L.; Serrano, J.C.; Jacks, T.; Kamm, R.D. The CCL2-CCR2 Astrocyte-Cancer Cell Axis in Tumor Extravasation at the Brain. *Sci. Adv.* **2021**, *7*, eabg8139. [\[CrossRef\]](#) [\[PubMed\]](#)
277. Mészáros, Á.; Molnár, K.; Fazakas, C.; Nógrádi, B.; Lüvi, A.; Dudás, T.; Tiszlavicz, L.; Farkas, A.E.; Krizbai, I.A.; Wilhelm, I. Inflammasome Activation in Peritumoral Astrocytes Is a Key Player in Breast Cancer Brain Metastasis Development. *Acta Neuropathol. Commun.* **2023**, *11*, 155. [\[CrossRef\]](#)
278. Motalebnejad, P.; Rajesh, V.V.; Azarin, S.M. Evaluating the Role of IL-1 β in Transmigration of Triple Negative Breast Cancer Cells Across the Brain Endothelium. *Cell Mol. Bioeng.* **2022**, *15*, 99–114. [\[CrossRef\]](#)

279. Yuzhalin, A.E.; Lowery, F.J.; Saito, Y.; Yuan, X.; Yao, J.; Duan, Y.; Ding, J.; Acharya, S.; Zhang, C.; Fajardo, A.; et al. Astrocyte-Induced Cdk5 Expedites Breast Cancer Brain Metastasis by Suppressing MHC-I Expression to Evade Immune Recognition. *Nat. Cell Biol.* **2024**, *26*, 1773–1789. [[CrossRef](#)]
280. Priego, N.; Zhu, L.; Monteiro, C.; Mulders, M.; Wasilewski, D.; Bindeman, W.; Doglio, L.; Martínez, L.; Martínez-Saez, E.; Ramón y Cajal, S.; et al. STAT3 Labels a Subpopulation of Reactive Astrocytes Required for Brain Metastasis. *Nat. Med.* **2018**, *24*, 1024–1035. [[CrossRef](#)]
281. Lörger, M.; Felding-Habermann, B. Capturing Changes in the Brain Microenvironment during Initial Steps of Breast Cancer Brain Metastasis. *Am. J. Pathol.* **2010**, *176*, 2958–2971. [[CrossRef](#)]
282. Jandial, R.; Choy, C.; Levy, D.M.; Chen, M.Y.; Ansari, K.I. Astrocyte-Induced Reelin Expression Drives Proliferation of Her2+ Breast Cancer Metastases. *Clin. Exp. Metastasis* **2017**, *34*, 185–196. [[CrossRef](#)]
283. Zou, Y.; Watters, A.; Cheng, N.; Perry, C.E.; Xu, K.; Alicea, G.M.; Parris, J.L.D.; Baraban, E.; Ray, P.; Nayak, A.; et al. Polyunsaturated Fatty Acids from Astrocytes Activate PPAR γ Signaling in Cancer Cells to Promote Brain Metastasis. *Cancer Discov.* **2019**, *9*, 1720–1735. [[CrossRef](#)]
284. Wang, S.; Riedstra, C.P.; Zhang, Y.; Anandh, S.; Dudley, A.C. PTEN-Restoration Abrogates Brain Colonisation and Perivascular Niche Invasion by Melanoma Cells. *Br. J. Cancer* **2024**, *130*, 555–567. [[CrossRef](#)] [[PubMed](#)]
285. Le Rhun, E.; Guckenberger, M.; Smits, M.; Dummer, R.; Bachelot, T.; Sahm, F.; Galldiks, N.; de Azambuja, E.; Berghoff, A.S.; Metellus, P.; et al. EANO–ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up of Patients with Brain Metastasis from Solid Tumours. *Ann. Oncol.* **2021**, *32*, 1332–1347. [[CrossRef](#)] [[PubMed](#)]
286. Chen, Q.; Xiong, J.; Ma, Y.; Wei, J.; Liu, C.; Zhao, Y. Systemic Treatments for Breast Cancer Brain Metastasis. *Front. Oncol.* **2023**, *12*, 1086821. [[CrossRef](#)]
287. Page, S.; Milner-Watts, C.; Perna, M.; Janzic, U.; Vidal, N.; Kaudeer, N.; Ahmed, M.; McDonald, F.; Locke, I.; Minchom, A.; et al. Systemic Treatment of Brain Metastases in Non-Small Cell Lung Cancer. *Eur. J. Cancer* **2020**, *132*, 187–198. [[CrossRef](#)] [[PubMed](#)]
288. Onofrio, L.; Gaeta, A.; D’Ecclesiis, O.; Cugliari, G.; Gandini, S.; Queirolo, P. Melanoma Brain Metastases: Immunotherapy or Targeted Therapy? A Systematic Review and Meta-Analyses. *Appl. Sci.* **2024**, *14*, 2222. [[CrossRef](#)]
289. Turner, N.C.; Reis-Filho, J.S. Genetic Heterogeneity and Cancer Drug Resistance. *Lancet Oncol.* **2012**, *13*, e178–e185. [[CrossRef](#)]
290. Ali, S.; Górska, Z.; Duchnowska, R.; Jassem, J. Molecular Profiles of Brain Metastases: A Focus on Heterogeneity. *Cancers* **2021**, *13*, 2645. [[CrossRef](#)]
291. Trigg, R.M.; Martinson, L.J.; Parpart-Li, S.; Shaw, J.A. Factors That Influence Quality and Yield of Circulating-Free DNA: A Systematic Review of the Methodology Literature. *Heliyon* **2018**, *4*, e00699. [[CrossRef](#)]
292. Boire, A.; Brandsma, D.; Brastianos, P.K.; Le Rhun, E.; Ahluwalia, M.; Junck, L.; Glantz, M.; Groves, M.D.; Lee, E.Q.; Lin, N.; et al. Liquid Biopsy in Central Nervous System Metastases: A RANO Review and Proposals for Clinical Applications. *Neuro Oncol.* **2019**, *21*, 571–584. [[CrossRef](#)]
293. Robinson, S.D.; de Boisanger, J.; Pearl, F.M.G.; Critchley, G.; Rosenfelder, N.; Giamas, G. A Brain Metastasis Liquid Biopsy: Where Are We Now? *Neuro-Oncol. Adv.* **2024**, *6*, vdae066. [[CrossRef](#)]
294. Morganti, S.; Parsons, H.A.; Lin, N.U.; Grinshpun, A. Liquid Biopsy for Brain Metastases and Leptomeningeal Disease in Patients with Breast Cancer. *NPJ Breast Cancer* **2023**, *9*, 43. [[CrossRef](#)] [[PubMed](#)]
295. McGregor, J.M.; Bell, S.D.; Doolittle, N.D.; Murillo, T.P.; Neuwelt, E.A. Blood-Brain Barrier Disruption Chemotherapy. In *Handbook of Brain Tumor Chemotherapy, Molecular Therapeutics, and Immunotherapy*; Elsevier: Amsterdam, The Netherlands, 2018; pp. 145–153.
296. Beccaria, K.; Canney, M.; Bouchoux, G.; Desseaux, C.; Grill, J.; Heimberger, A.B.; Carpentier, A. Ultrasound-Induced Blood-Brain Barrier Disruption for the Treatment of Gliomas and Other Primary CNS Tumors. *Cancer Lett.* **2020**, *479*, 13–22. [[CrossRef](#)]
297. Mitusova, K.; Peltek, O.O.; Karpov, T.E.; Muslimov, A.R.; Zyuzin, M.V.; Timin, A.S. Overcoming the Blood–Brain Barrier for the Therapy of Malignant Brain Tumor: Current Status and Prospects of Drug Delivery Approaches. *J. Nanobiotechnol.* **2022**, *20*, 412. [[CrossRef](#)] [[PubMed](#)]
298. Zhang, P.; Kuil, L.E.; Buil, L.C.M.; Freriks, S.; Beijnen, J.H.; van Tellingen, O.; de Gooijer, M.C. Acquired and Intrinsic Resistance to Vemurafenib in BRAFV600E-driven Melanoma Brain Metastases. *FEBS Open Bio* **2024**, *14*, 96–111. [[CrossRef](#)] [[PubMed](#)]
299. Twomey, J.D.; Zhang, B. Cancer Immunotherapy Update: FDA-Approved Checkpoint Inhibitors and Companion Diagnostics. *AAPS J.* **2021**, *23*, 39. [[CrossRef](#)]
300. Vesely, M.D.; Zhang, T.; Chen, L. Resistance Mechanisms to Anti-PD Cancer Immunotherapy. *Annu. Rev. Immunol.* **2022**, *40*, 45–74. [[CrossRef](#)]

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