Review

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Dae Joong Kim *

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Review

Mechanisms of Cancer Metastasis: Dormancy, Immune Evasion, Pre-Metastatic Niches, and Emerging Therapeutic Strategies

Dae Joong Kim

Department of Orthopaedics, West Virginia University1; daejoong.kim@hsc.wvu.edu

Abstract

Metastatic relapse often reflects the survival of a small population of disseminated tumor cells (DTCs) that take up residence in distant organs and then shift into a dormant state. Rather than dividing, these cells sit quietly for long periods and rely on local niche signals to stay inactive and avoid therapy. Dormant cells are difficult to eliminate because the immune system cannot detect them, and treatments aimed at actively growing cells are ineffective. DTCs stop oncogenic signaling and start stress-response and cell-cycle arrest pathways. These pathways are often characterized by higher levels of cyclin-dependent kinase (CDK) inhibitors and greater p38 signaling than ERK signaling. LIFR–STAT3 signaling in the bone marrow supports quiescence in breast cancer cells, while inflammatory cytokines and Wnt/BMP antagonists in the lung microenvironment can trigger reactivation of cancer DTCs. Because these dormant DTCs are not cycling, standard cytotoxic agents rarely remove them. Current strategies are now testing immune-directed therapies. Recent single-cell and long-read sequencing efforts have started to reveal the transcriptional programs that mark DTCs, including stress-response and quiescence signatures that differ from the primary tumor. These insights are shaping therapies for interrupting dormancy and lowering the risk of late metastatic relapse.

Keywords: metastasis; dormancy; osteosarcoma; melanoma; glioblastoma; breat tumor; dormant disseminated tumor cells; STAT3; BRAFV; ERK; EMT

Introduction

Metastasis, which is the spread and growth of cancer cells in other organs, is the most dangerous part of cancer and causes most cancer deaths[1]. Many primary tumors do not respond favorably to surgery or radiation; however, metastasis is a systemic process in which tumor cells disseminate via blood or lymphatic vessels and subsequently adapt, survive, and proliferate in remote organs[2]. The dynamic alteration of tumor cell behavior and their manipulation of adjacent tissues and immune cells is crucial for effective metastatic dissemination. The distinct responses of primary and metastatic tumors to treatment underscore the unique biology and resistance associated with metastatic disease[3]. Modern sequencing technologies have changed how we think about metastasis. Genetic profiling of primary tumors, circulating tumor DNA, and circulating tumor cells has unveiled significant variation and evolutionary distinctions between primary and metastatic lesions[4]. These technologies allow for real-time monitoring of diseases, accelerate the search for biomarkers and treatment targets, and reveal how cancer cells spread by using host tissues to live and grow[5].

Dormancy is a long-standing way for organisms to survive stress, and cancer cells seem to use this evolutionary program to wait out bad conditions[6]. When T cells enter a resting memory state, similar pathways are activated in immune cells. Tumor dormancy appears to hijack these conserved programs, allowing malignant cells to endure adverse conditions, such as immune pressure and toxic treatments, by entering a reversible growth arrest[7]. Dormancy may manifest locally before the proliferation of the primary tumor or systemically before the development of evident metastasis.

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Metastatic dormancy may occur before the detection of primary tumors. Recent data contradict the classical stepwise model, demonstrating that dissemination can occur very early, even from tumors smaller than 5 millimeters, followed by extended dormancy at remote locations[6]. Dormant cells can be single cells, small groups of cells, or tiny lesions that stay the same size because of balanced cell division and death[8]. The cancer cell's own survival pathways, like autophagy and stress response systems, as well as physical factors in the environment, like the composition of the tissue scaffolding, the stiffness of the tissue, and the availability of growth factors, control dormancy[8, 9]. Metastasis is now recognized as a complex systemic process necessitating collaboration between tumor cells and host tissue, encompassing tissue remodeling, immune evasion, angiogenesis, metabolic adaptability, and intercellular cooperation among various tumor cell types[2].

Finding hidden metastases early is a big problem when it comes to treating cancer. Evidence suggests that dissemination may transpire unexpectedly early in tumor development, potentially preceding clinical diagnosis. New blood tests, like the liquid biopsy platform, that look for circulating tumor cells, tumor DNA, or RNA-containing vesicles, show promise for catching minimal disease in real time[1011]. These tools are beginning to show how early metastatic colonies form and change when used with single-cell genetic analysis and spatial mapping techniques[5]. When scans show metastases, they often look different genetically from the original tumor. This is because of pressures on specific organs, differences in local tissue, and changes that happen during treatment[3]. This causes significant differences between metastases and even within the same metastases, making standard lab models less useful and treatment responses harder to predict. Modern metastasis treatment increasingly necessitates personalized strategies predicated on biomarkers that correspond to the evolving biology of disseminated cancer cells and their microenvironment[11]. There are two main goals for improving metastasis treatment: killing dormant cancer cells and stopping them from coming back[8]. Immune-based methods, such as reprogramming tumor-associated immune cells, activating natural killer cells, or making cancer cells more visible to the immune system, show promise for getting rid of dormant and early metastatic cells[2, 12]. Making markers that are specific to dormancy will be important for early intervention, customizing preventive therapy, and, in the end, lowering the risk of metastatic relapse[8].

1. Metastasis-Inducing Genes and Mechanisms

One of the hardest things about cancer is that it can spread to other parts of the body. It happens when cancer cells can leave where they started, travel through the bloodstream, and settle in new places. Cells must change their shape and behavior, survive harsh conditions, and adapt to very different environments throughout the body. This journey isn't easy. Scientists need to understand how all of this works so they can develop ways to stop cancer from spreading. Snail transcription factors are a group of proteins that help cancer cells make these changes. Snail1, Snail2 (also called Slug), and Snail3 are the three types. They all help initiate a process that converts epithelial cells (which usually adhere in organized tissues) into mesenchymal cells (which can move more freely). Each one does something a little different. This change is an important step that allows cancer cells to move and invade other cells.

A. SNAIL1: The Master Orchestrator of the Epithelial to Mesenchymal Transition (EMT) Snail1 is the leading player in starting EMT. It works by turning off genes that keep epithelial cells together, like E-cadherin, and changing the cell's structure so that it can move and invade more easily[13]. Snail1 does this by binding to specific DNA sequences in the E-cadherin gene, preventing its transcription. Studies in mice show that Snail1 is essential at many stages of metastasis[14]. When cancer cells express active Snail1, they are much better at entering blood vessels and forming new tumors in the lungs. But Snail1 doesn't just change the cancer cells. It also alters the surrounding tissue by turning normal support cells (fibroblasts) into cancer-supporting fibroblasts (cancer-associated fibroblasts, or CAFs). These cells have a very pro-invasive and inflammatory phenotype that helps the tumor grow and spread. These changed fibroblasts make prostaglandin E2 and enzymes that break down the scaffolding between cells. This makes it easier for cancer to move through tissues. This makes the

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environment stiffer, which activates some signaling pathways in the tumor cells and helps them stay hidden from the immune system[15]. Snail1 controls the spread of cancer by directly altering tumor cells and their environment.

B. SNAIL2 (SLUG): Stemness and Resistance to Treatment

Snail2 shares many features with Snail1 in terms of structure. It also stops epithelial adhesion molecules like E-cadherin, which start EMT programs that help cells move. Even though there is some overlap, Snail2 has functional traits that set it apart from other Snail family members[16]. One crucial difference is that it significantly affects the traits of cancer stem cells and their response to treatment. In breast cancer, elevated Snail2 levels are closely linked to recurrence and metastatic spread, highlighting its role in maintaining stem-like populations that can endure long-term and subsequently regenerate metastatic lesions[17]. Snail2 also helps tumors spread to other parts of the body by making tumor cells more likely to survive while they are circulating and making it easier for them to settle in new places[18]. This is true for melanoma, colorectal cancer, glioblastoma (GBM), and hepatocellular carcinoma (HCC). While Snail2 can alter stromal cell organization, its roles are less clear than those of Snail1. Snail3, on the other hand, is more involved in immune and developmental pathways and only plays a small role in the progression of metastasis[19].

C. The TWIST Family: Specialization in EMT and Invasion

The Twist family of basic helix-loop-helix (bHLH) transcription factors includes Twist1 and Twist2. Both of these proteins are often inappropriately activated in cancer, and they play essential roles in the spread of cancer cells through distinct yet complementary mechanisms[20].

D. TWIST1: Master EMT Inducer and Invasion Coordinator Twist1 is a key regulator of EMT. It stops E-cadherin and starts a wide range of transcriptional changes that make cells less sticky, change the structure of the cytoskeleton, and make cells move more easily[20]. Twist1 not only plays a key role in EMT but also activates PDGFRα-Src signaling, which drives invadopodia formation. These are actin-rich protrusions that bring together membrane-type 1 matrix metalloproteinase (MT1-MMP), MMP2, and MMP9 to create focused proteolysis at the leading edge. This way, Twist1 helps tumor cells break through basement membranes and move into the stroma around them[21]. The increased expression of Twist1 in breast cancer and osteosarcoma (OS) is linked to more aggressive metastasis and worse clinical outcomes. This shows that it is an important prognostic marker for metastasis in many types of tumors[22].

E. TWIST2: Improving survival and changing the immune system

Twist2, while less well known than Twist1, plays essential roles in strengthening EMT programs and helping tumor cells survive. It boosts the levels of anti-apoptotic regulators like Bcl-2 and survivin, which makes treatment less effective and leads to a disease that keeps coming back[23]. Twist2 also affects critical signaling pathways like NF-κB and STAT3, which help create conditions in the tumor microenvironment (TME) that suppress the immune system and make it harder for the immune system to find and kill the tumor[24].

F. Specificity Protein 1 (SP1): Master Transcriptional Coordinator Specificity Protein 1 (SP1) is a zinc-finger transcription factor with a wide range of pro-metastatic effects. It promotes EMT by activating major EMT regulators such as Snail, Twist, and ZEB1, and it increases the expression of matrix-modifying enzymes, including MMP-2, MMP-9, and MT1-MMP, that support extracellular matrix degradation and tissue invasion[25]. In addition to EMT regulation, Sp1 stimulates angiogenesis by directly inducing VEGF and PDGF, thereby supporting the vascular expansion required for tumor growth and metastatic spread[26]. Sp1 enhances metastatic fitness by increasing the levels of survival factors such as Bcl-2 and survivin, making cells more resistant to treatments that kill cancer cells[27]. Oncogenic signaling pathways, such as EGFR/ERK and PI3K/AKT, stabilize Sp1 and create feedback loops that enhance its activity[28]. This enhances its transcriptional output. Increased Sp1 expression is consistently associated with poor outcomes in multiple malignancies, such as breast, lung, colorectal, pancreatic, and liver cancers, highlighting its critical role in cancer progression[29].

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2. Epigenetic Regulators of Metastasis

A wide variety of epigenetic regulators directly promote metastasis. EZH2, the catalytic subunit of PRC2, is one of the most important of these. EZH2 represses tumor-suppressive genes, such as E-cadherin, by depositing H3K27me3. It also strengthens EMT by supporting transcription factors like Snail and Slug[30, 31]. EZH2 overexpression is significantly associated with an unfavorable prognosis in various carcinomas[32]. EZH2 diminishes epithelial integrity by silencing adhesion genes, facilitating invasion, and inducing fibroblast-to-myofibroblast conversion and wound-healing stromal remodeling that further enhances metastasis[33]. Various non-epigenetic oncogenic drivers also facilitate metastatic progression. PTTG1 (securin) encourages genomic instability and increases invasive behavior[34]. BIRC5 (survivin) helps circulating tumor cells stay alive by stopping apoptosis[35]. YBX1 controls EMT, stemness, and treatment resistance[36]. Transcription factors like E2F1 and MYB, which control the cell cycle, also turn on gene programs that are involved in invasion[37, 38]. These factors facilitate invasion, survival, and microenvironmental remodeling during metastasis. In the end, epigenetic reprogramming is crucial for metastatic competence because it gives cells the flexibility to invade, spread, remain dormant, and form new tumors.

DNA Methylation: Abnormal methylation alters genes that control tumor growth. DNMT1, DNMT3A, and DNMT3B inhibit adhesion molecules like CDH1 and enhance the expression of EMT transcription factors such as Snail, Twist, and ZEB[39]. Global hypomethylation at repetitive sequences and enhancers also activates oncogenic and inflammatory pathways that promote dissemination[40].

Histone Methylation: EZH2-driven H3K27me3 inhibits tumor suppressors, lineage regulators, and immune-related genes[30, 41]. Other methyltransferases, like G9a (EHMT2; H3K9) and SUV39H1, keep epithelial identity from being expressed and help keep mesenchymal states[42]. The absence of demethylases like KDM6A (UTX) or KDM6B (JMJD3) enhances the stability of epithelial-mesenchymal transition (EMT) programs and facilitates metastasis[43].

Histone acetylation and deacetylation: Histone acetyltransferases (p300/CBP) activate EMT drivers[44] and, when metastatic disease is present, they stop epithelial programs while boosting angiogenesis and immune evasion[45]. HDAC inhibitors can reverse EMT characteristics and enhance responses to immunotherapy[46].

Chromatin Remodeling: Changes in SWI/SNF (BAF) complexes affect metastasis, depending on the situation. The absence of ARID1A or SMARCA4 enhances dissemination in various cancers, whereas different BAF configurations encourage invasion and therapeutic resistance[47].

Noncoding RNAs and Interactions: Long noncoding RNAs and microRNAs regulate chromatin-modifying enzymes. HOTAIR, for instance, brings PRC2 to shut down epithelial genes and speeds up EMT and distant metastasis in breast cancer[48]. The reversibility of epigenetic modifications presents therapeutic prospects in clinical settings. Targeting epigenetic plasticity thus constitutes a promising strategy to halt or treat metastatic progression. Human cancer studies have linked each of the genes above to cancer spread, usually through the mechanisms described. For example, Snail1 and Twist1 have been shown to directly cause invasion through EMT programs. IL-6 and IL-8 are well-known cytokines that promote metastatic phenotypes in many cell types, and MMPs degrade the extracellular matrix, enabling cells to spread.

Noncoding RNAs and Crosstalk: Long noncoding RNAs and microRNAs coordinate chromatin-modifying enzymes. HOTAIR, for example, recruits PRC2 to silence epithelial genes and promotes EMT and distant metastasis in breast cancer. Clinically, the reversibility of epigenetic alterations offers therapeutic opportunities[49, 50]. Targeting epigenetic plasticity, therefore, represents a promising approach to interrupt or treat metastatic progression.

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Table 1. Key genes and their primary mechanisms driving tumor metastasis.

Gene name	Function	Description	REF
Snail	EMT, CAF activation, Prostaglandin E2 (PGE2)	Induces EMT and invasion in carcinoma cells (Represses E-cadherin). Required for CAF activation; CAFs secrete PGE_2 and cytokines to drive tumor invasion (Regulates mesenchymal differentiation, wound healing)	[51]
TWIST1	EMT, PDGFRα→Src, invadopodia	TWIST1 EMT TF: invadopodia formation (via PDGFRα/Src) Drives EMT, motility, invadopodia-mediated ECM degradation (Not directly studied). Upregulated in CAFs of many tumors: Twist1 promotes invasion and tumor growth.	[21]
SP1	Pan-cancer TF, survival/invasion, WNT/β-catenin	Pan-cancer TF; induces WNT signaling, survival, and invasion. Master regulator of metastasis genes; enhances WNT/β-catenin signaling in tumor cells. Drives expression of angiogenic factors (e.g., VEGF); WNT signals from stroma to endothelium.	[52, 53]
IL-6	STAT3/EMT; CAF source; angiogenesis	Pro-inflammatory cytokine; activates JAK/STAT3, EMT receptor-expressing carcinoma cells undergo STAT3-dependent EMT and proliferation. Promotes angiogenesis and leukocyte recruitment in tumor vessels. Secreted by CAFs (and tumor cells); drives EMT/migration of cancer cells. IL-6 can recruit and modulate MSCs (MSC chemotaxis, differentiation)	[54, 55]
CXCL8 (IL-8)	Angiogenesis, EMT/invasion, CXCR1/2	Promotes angiogenesis, EMT, and invasion. Tumor-derived IL-8 induces autocrine EMT/invasion and survival. Potent angiogenic factor; stimulates endothelial proliferation and vessel permeability. CAFs secrete IL-8 to boost tumor angiogenesis and invasion. MSCs respond to IL-8 (via CXCR1/2), promotes MSC migration and possibly MSC-to-CAF transition.	[56, 57]
CXCL1	Neutrophil recruitment, angiogenesis	CXCL1 Chemokine (ELR^+); recruits neutrophils, fosters angiogenesis. Tumor-secreted CXCL1 creates a pro-inflammatory niche for invasion (by analogy to IL-8). Angiogenic; contributes to neovascularization (via CXCR2). Expressed by CAFs and TAMs; enhances tumor cell motility	[58, 59]

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		and chemoresistance (paracrine). May attract MSCs to the tumor; role is less defined than IL-8	
CXCR4	CXCL12 homing, organotropism	CXCR4 Chemokine receptor; guides cells to CXCL12-rich organs. Binds CXCL12 to direct cancer cell homing/migration to metastatic sites (lung, liver, bone). Endothelial cells produce CXCL12; $CXCR4^{+}$ tumor cells adhere to the vasculature and extravasate. CXCR4 is expressed on fibroblasts/CAFs; CXCL12 from stroma promotes tumor-CAF interactions. Highly expressed on MSCs; mediates MSC homing and survival.	[60, 61]
MMP9	ECM degradation, growth-factor activation, angiogenesis	MMP9 Secreted matrix metalloprotease; cleaves ECM, activates growth factors. Tumor cells secrete MMP9 to breach the basement membrane (promoting intravasation). Degrades endothelial basement membranes to enable angiogenesis and metastasis. CAFs/myofibroblasts produce MMP9 to remodel the stroma and release pro-metastatic signals. MSCs secrete MMP9 to facilitate migration; MSC-derived MMPs shape the metastatic niche.	[62, 63]
MMP1	Interstitial collagenase, invasion/angiogenesis	MMP1 Interstitial collagenase; degrades type-I/III collagen. Tumor-derived MMP1 promotes invasion through dense stroma, enabling new vessel growth by remodeling perivascular ECM. CAFs produce MMP1 to stiffen or remodel the matrix, enabling tumor spreading. MSCs may also express MMP1 in differentiation contexts.	[64, 65]
EZH2	H3K27me3 silencing, EMT, stromal remodeling	EZH2 Histone methyltransferase; epigenetic silencer of adhesion genes. Silences E-cadherin/epithelial genes, activating EMT and invasion (May promote EndMT by methylating endothelial promoters). Drives fibroblast-to-myofibroblast transition; promotes fibrotic stroma. Regulates MSC proliferation/differentiation (Wound healing analogies).	[66, 67]
FOXM1	EMT, MMPs, angiogenesis	FOXM1 Forkhead TF; drives cell cycle, EMT (upregulates Snail/MMPs). In tumor cells, FOXM1 induces MMP2/9 and EMT factors,	[68, 69]

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		enhancing invasion. Promotes angiogenesis via VEGF expression; also implicated in EndMT in fibrosis. Shown to regulate CAF proliferation and extracellular proteases (in some tumors). May influence MSCs' proliferative and migratory potential FOSL1 (FRA1) AP-1 subunit; EMT and invasion activator. Upregulates genes involved in motility (e.g., MMPs); promotes a mesenchymal phenotype. Stimulates VEGF and inflammatory cytokines, aiding vessel formation. In stromal cells, it supports the production of pro-tumorigenic ECM factors. In MSCs, differentiation may tilt toward a CAF-like state.	
E2F1	Cell cycle invasion/angiogenesis programs	E2F1 Cell-cycle TF; pro-metastatic when overexpressed. Aside from proliferation, E2F1 can induce MMPs and EMT-associated genes. Drives expression of angiogenic factors (FGF, VEGF); can act in the endothelium. Linked to fibroblast proliferation; may contribute to desmoplasia. Activates proliferation of MSCs and endothelial precursors.	[70]
MYB	stemness/invasion; angiogenic transcription	MYB Transcription factor can promote stemness and invasion. Activates target genes (including MMPs, EMT factors) in carcinomas. Regulates angiogenic gene expression (e.g., VEGFR). Influences fibroblast proliferation; MYB is expressed in some CAF subsets. Helps maintain MSC self-renewal; influences differentiation pathways.	[71]
PTTG1 (Securin)	Genomic instability, EMT, invasion	PTTG1 (Securin) Promotes genetic instability and EMT. Overexpressed PTTG1 drives EMT and cell motility in cancer cells. May enhance secretion of angiogenic factors (through p53 inhibition). In fibroblasts, PTTG1 can promote proliferation and matrix production. In MSCs, PTTG1 supports proliferation, possibly aiding their tumorigenic roles.	[72, 73]
YBX1	EMT, stress survival, drug resistance	YBX1 RNA/DNA-binding protein; induces EMT and stress survival. Activates EMT-related mRNAs (Snail, Twist) and drug resistance pathways in tumors. Regulates VEGF	[74, 75]

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		expression under hypoxia, promoting angiogenesis. Contributes to fibroblast activation by stabilizing cytokine mRNAs. Modulates MSC plasticity and response to microenvironmental stress.	
BIRC5 (Survivin)	Anoikis resistance, survival of CTCs/ endothelium	BIRC5 (Survivin) Inhibitor of apoptosis; cell division regulator. Upregulated in metastatic tumors to allow anoikis resistance and survival in circulation. Supports the survival of proliferating endothelium in tumor vessels. Protects CAFs/myofibroblasts from apoptosis, sustaining pro-metastatic stroma. Ensures MSC survival in harsh metastatic niches.	[76, 77]
ZEB2	EMT TF; metastasis and stromal/EndMT links	ZEB2 EMT transcription factor; represses epithelial genes. Drives EMT and mesenchymal phenotype in carcinoma cells (analogous to Snail/Zeb1) (Possible role in EndMT/transdifferentiation of endothelium). Induces fibroblast-like program in epithelial and endothelial cells. In MSCs, ZEB2 may regulate multilineage differentiation toward mesenchyme.	[78, 79]

Each gene above is implicated by human cancer studies in promoting metastasis, often through the described mechanisms. For instance, Snail1 and Twist1 have been directly shown to stimulate invasion via EMT programs, IL-6 and IL-8 are well-known cytokines that activate metastatic phenotypes in multiple cell types, and MMPs remodel the extracellular matrix to permit dissemination.

3. Extracellular Proteases and Matrix Modifiers in Metastatic Progression

Recent accumulating evidence consistently identifies the extracellular matrix (ECM) as a pivotal factor influencing cancer risk and progression. For instance, women with breast tissue that is rich in collagen have a fourfold higher risk of getting breast cancer[80]. In established tumors, the ECM serves as both a structural framework and a source of biochemical signals. Metastatic cells release enzymes that degrade the ECM, such as extracellular proteases and matrix-modifying enzymes. These enzymes dismantle the matrix structure, liberate growth factors previously sequestered within the ECM, and produce biologically active fragments that facilitate invasion, angiogenesis, inflammation, and the establishment of pre-metastatic niches. Cross-species xenograft studies indicate that extracellular matrix (ECM) remodeling occurs through unique yet synergistic contributions from malignant and stromal compartments. Tumor cells primarily synthesize matrix-modifying and matrix-degrading enzymes, while stromal fibroblasts and other mesenchymal cells predominantly provide ECM glycoproteins; both cell types are involved in the production of fibrillar collagens[81]. Collagen I, specifically, is consistently elevated in primary tumors of the breast, liver, lung, and esophagus, and is similarly heightened in metastatic ovarian cancer[82-84]. Hyaluronic acid (HA) builds up in breast, prostate, bladder, and colon cancers and is linked to metastasis and a bad outcome[85, 86]. Elevated epithelial fibronectin in breast cancer indicates diminished survival. Laminin-111 is reduced

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in tumors compared to normal tissues[87], whereas laminin-332 is elevated in various cancers[88], including breast cancer, and is associated with a poorer prognosis. In advanced omental metastases of ovarian cancer, there are more glycoproteins (like fibrinogen and fibronectin), proteoglycans, secreted factors, and ECM-associated proteins than in smaller lesions[89]. Proteomic analyses have identified tenascin-C as a prognostic marker in lung cancer and SERPINB1 as a factor influencing brain tropism in breast cancer metastasis[90]. RGD-modified HA improves cooperative chemotherapy resistance in GBM[91], PEG hydrogels with MMP-degradable linkers enable GBM cells to develop actin-rich protrusions, while non-degradable matrices confine cells to a rounded morphology[91].

A. Functions of the Matrix Metalloproteinase Family

Matrix metalloproteinases (MMPs) are the most well-known extracellular proteases in cancer. MMP-9, a highly active gelatinase, is abundant in aggressive tumors. It releases growth factors like VEGF and TGF-β that are bound to the matrix, thereby strengthening signals that drive invasion and angiogenesis. MMP-1, an interstitial collagenase, cleaves fibrillar collagens, making it easier for stromal cells to enter tissues and penetrate them[92] . MMP-9 facilitates various stages of metastatic progression, encompassing EMT induction, enhanced cell migration, angiogenic activation, and the sustenance of tumor-associated inflammatory responses[93]. MMP-9 remodels collagen structure and promotes endothelial sprouting at invasive fronts. This makes neovascularization easier, which is necessary for tumor growth and spread[94]. MMP-9 from tumors facilitates intravasation, while MMPs from CAFs alter the stroma, making it stiffer to help the tumor keep invading[95].

B. Additional Protease Systems

High uPA pathway activity is consistently associated with poorer prognosis in breast and colorectal cancers, underscoring its clinical significance[96]. This system performs necessary supplementary functions to MMP systems by degrading fibrillar collagens and components of the basement membrane. Cathepsins, particularly cathepsins B, L, and S, enhance matrix-degrading capabilities and are instrumental in compromising vascular barriers, thereby facilitating intravasation and aiding metastatic dissemination[97].

C. Enzymes that change the matrix and control biomechanics

Tumor cells release specialized matrix-modifying enzymes that alter the biomechanical properties of the ECM, thereby accelerating cancer spread. The lysyl oxidase (LOX) family of enzymes links collagen fibers together, which makes the matrix stiffer. This rigidity triggers mechanosensitive signaling pathways that include integrins, FAK, and RhoA, which help cells move. In breast cancer research, hypoxic conditions stimulate LOX, which remodels collagen and creates a pre-metastatic niche in the lung[98]. LOXL2, a related enzyme, stabilizes EMT transcription factors like Snail by chemically changing them after they are made. This strengthens mesenchymal traits and makes cells more likely to spread to other parts of the body[99]. Heparanase alters the extracellular matrix (ECM) by cleaving heparan sulfate proteoglycans, which releases angiogenic and pro-invasive factors like FGF and VEGF and makes it easier for tumor cells to move around[100].

4. Mechanisms of Immune Evasion in Metastatic Cancer

Immune evasion during metastasis occurs via multiple overlapping mechanisms, including suppressive immune cells, checkpoint signals, and physical barriers within the tissue. Monocytic myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) inhibit the immune system by secreting molecules such as TGF-β, reactive oxygen species, and arginase, which diminish the cytotoxic capacity of T cells and natural killer (NK) cells. TAMs frequently transition to an alternatively activated M2-like phenotype that promotes angiogenesis and facilitates tumor evasion of immune surveillance[101]. Platelets help hide tumor cells from the immune system by coating them as they move through the blood. Platelets release thromboxane A2, which can stop T-cells from becoming active through the ARHGEF1 signaling pathway. Targeting platelets with antiplatelet drugs significantly impairs the efficiency of metastatic cells in establishing new tumors, indicating the potential efficacy of this strategy in patients[102]. Within established metastases, T-cell dysfunction is exacerbated by various immune checkpoint pathways. In metastases, especially in protected areas

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like the brain, tumor-infiltrating T cells often have a lot of inhibitory receptors like PD-1, LAG-3, and TIGIT[103]. Stromal barriers that are very thick in the tumor microenvironment also prevent immune cells from reaching cancer cells. A thick extracellular matrix and the presence of cancer-associated fibroblasts (CAFs) can physically prevent effector immune cells from reaching tumor sites. For instance, in pancreatic cancer, a dense stroma rich in hyaluronan impedes blood flow and prevents T cells from entering the tumor core. Research in the lab has shown that using enzymes to break down these matrix components can make it easier for drugs to enter cells and for T cells to enter the stroma. This is evidence that strategies to normalize the stroma could be helpful[104].

5. Cytokine and Chemokine Networks in Metastatic Dissemination

Cytokines and chemokines are the main things that control the spread of cancer cells to other parts of the body. They create networks of communication that guide cancer cells, establish pre-metastatic niches, and coordinate complex interactions between cancer cells and host tissues.

A. Chemokine-Mediated Organ Tropism

The CXCL12-CXCR4 axis is the best-known chemokine pathway that controls how cancer cells migrate to other organs. It directs breast and prostate cancer cells to CXCL12-rich tissues, including the lung, liver, and bone marrow, where elevated chemokine concentrations establish conducive environments for incoming tumor cells[105]. The CCR7-CCL21 chemokine axis facilitates lymphatic dissemination, as CCL21 is continuously expressed by lymphatic endothelial cells and lymph node stromal cells, directing CCR7-expressing tumor cells towards lymphatic vessels and draining lymph nodes[106]. The CCR9-CCL25 axis also causes metastasis in the gut by directing tumor cells to intestinal sites that are rich in CCL25[107].

B. Pro-Metastatic Cytokine Signaling

Cytokine networks facilitate metastasis via multiple coordinated pathways. Interleukin-6 (IL-6) activates JAK/STAT3 signaling, which promotes epithelial-mesenchymal transition (EMT) and cancer stem cell properties, as demonstrated in gastric cancer research examining the interaction between cancer-associated fibroblasts and tumor cells[108]. TGF-β has different effects depending on the situation. In early cancer, it stops tumors from growing, but in advanced cancer, it helps EMT, immune evasion, and metastasis[109, 110]. TNF-α enhances invasion by activating NF-κB, which elevates the expression of adhesion molecules and matrix metalloproteinases that facilitate cellular penetration and tissue remodeling. The collaboration of IL-1β and CXCL8/IL-8 activity attracts neutrophils, stimulates tumor angiogenesis, and sustains epithelial-mesenchymal transition (EMT) at the peripheries of invading tumors, thereby fostering inflammatory environments that facilitate tumor progression[111].

C. Cytokine Networks in the Pre-Metastatic Niche

Certain cytokine combinations, such as VEGF-A, TNF-α, and TGF-β, act together to increase levels of S100A8/A9 and fibronectin in the lung's supporting tissue during the formation of pre-metastatic niches. This methodically brings in myeloid cells to set up conditions that make it easier for tumor cells to settle later[112]. In patients, elevated levels of chemokines and cytokines are significantly associated with adverse outcomes, preferences for particular metastatic sites, and treatment resistance. Because of these results, clinical trials are now testing targeted therapies like CXCR4 inhibitors (plerixafor), CCR5 inhibitors (maraviroc, NCT01736813), IL-6 receptor antagonists (tocilizumab, NCT03999749), and TGF-β antagonists for the treatment of metastatic disease[113].

6. Pre-Metastatic Niche Formation and Organ-Specific Colonization

A. Niche Preparation Orchestrated by the Primary Tumor

Primary tumors send signals that prepare other organs for cancer cells to move in long before they actually do. Significant research has shown that bone marrow cells expressing VEGFR1 travel to these distant sites in response to molecules released by the original tumor. This creates a support structure that makes it easier for metastases to grow later[114]. LOX is essential for this preparation

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because it crosslinks collagen molecules and attracts myeloid cells that remodel tissue structure in target organs like the lungs. It is made when tumors have low oxygen levels. VEGF and other chemokine signals, on the other hand, attract immune-suppressing cells that produce the environment better for metastatic cells[115] to come in.

B. Communication Between Cells Through Exosomes

Exosomes released by primary tumors serve as communication vehicles that instruct resident fibroblasts and endothelial cells in remote organs on their behavior. These small vesicles also alter the function of circulating neutrophils and monocytes, turning them into cells that either help build new blood vessels or suppress immune responses. This makes it easier for metastatic cells to settle in later[116].

C. Organ-Specific Niche Architecture and Upkeep

Pre-metastatic niches (PMNs) form in a way that is specific to the biology of each target organ. In the lung, early PMNs exhibit significant neutrophil clusters and infiltration by inflammatory macrophages. In bone, homing mediated by CXCR4-CXCL12 and signals that activate osteoclasts are very important. In the brain, PMN formation relies on specific adhesion interactions with endothelial cells and on alterations in the structure of the blood-brain barrier. Once these sites are ready, resident stromal cells help sustain metastatic growth through organ-specific mechanisms. In the lung, for example, perivascular fibroblasts produce tenascin-C, which attracts and activates macrophages. This strengthens a microenvironment that helps cancer cells spread[117].

7. Tumor dormancy

Tumor dormancy is a complex mechanism by which cancer cells can survive. They stay quiet, keep their metabolic activity low, and respond to signals from their surroundings. These changes allow tumor cells to survive for a long time, avoid the effects of treatment, and retain the ability to resume growth. Dormancy is not a passive state; it is sustained by coordinated gene expression, metabolism, epigenetic regulation, and signals from the local tissue environment that determine whether a cell remains quiescent or resumes division. Controlling dormancy depends a lot on the conditions in the area. Cells go into dormancy when there isn't enough oxygen, nutrients, or blood vessels. Cells that try to divide in these harsh conditions usually die. Hypoxic stress, on the other hand, leads to aggressive traits and resistance to treatment[118, 119]. In the RIP1-Tag2 pancreatic islet tumor model, the removal of VEGF leads to highly hypoxic, slowly expanding tumors reliant on HIF1α for survival, while the inhibition of angiogenesis can enhance invasive characteristics[12 120, 121]. Cells that don't get enough oxygen also resist treatment and can start tumors again, as shown by lineage tracing studies after radiation[122]. Low oxygen levels trigger HIF-driven glycolysis, but when cells lack both oxygen and glucose for a long time, they enter a dormant state in which their metabolism slows down[123]. In conditions of extreme oxygen deprivation, the removal of methyl marks from the HIGD1A gene promoter induces this protein, which facilitates survival by reducing mitochondrial respiration, activating AMPK, decreasing reactive oxygen species, and maintaining cellular viability[124]. Extracellular matrix (ECM) and integrin signaling also play a role in dormancy. The balance between ERK and p38 MAPK activity is a critical control point. When p38 signaling is stronger than ERK signaling following uPAR–α5β1 interactions, HEp3 carcinoma cells enter a dormant state[125]. In breast cancer, blocking β1-integrin causes dormancy[126], and the amount of fibronectin deposited and the amount of tension in the cytoskeleton decide whether D2.0R cells stay dormant or D2A1 cells keep dividing in 3D culture[127]. Thrombospondin-1 released by endothelial cells[128] is another signal from the surrounding tissue that keeps cells dormant. The lack of CXCR4 expression, observed in dormant lung metastases, is another signal. Changes in genes and epigenetics within the cell also help keep it dormant[129]. NR2F1 induces dormancy by activating SOX9, p27, and CDK inhibitor pathways[130]. In models derived from patient tumors, NR2F1 collaborates with HIF1α to maintain dormant cancer cells[131]. Dormant cells usually have fewer MHC molecules and antigen-processing parts, which makes it harder for T cells and NK cells to find them. At the same time, they

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turn on stress-response systems that help them live longer. In melanoma models, $CD8^+$ T cells inhibit metastatic expansion, and the removal of immune cells leads to rapid tumor growth[132]. Dormancy is a major obstacle for doctors seeking cures. Spread cancer cells can stay dormant for decades in a quiet, treatment-resistant state. This is why breast, prostate, and other cancers sometimes come back years later[133]. Many molecular pathways control the switch between dormancy and reactivation. Proteins that change chromatin, like KDM5B, EZH2, KDM6A/KDM6B, and TET2, decide if chromatin is open or closed. Transcription factors such as c-JUN, FOXM1, NR2F1, NANOG, and SOX2, on the other hand, control transitions between the resting and dividing states[134]. The p38-NR2F1-p53 signaling pathway keeps cells dormant, while the ERK activation, uPAR-FAK/PI3K, and other pathways that promote growth push cells out of dormancy. Other ways to control things include protein degradation systems (FBXW7, SKP2), noncoding RNAs (NR2F1-AS1, ELEANOR, miRNAs), and signals from nearby tissues, such as WNT modulators, IL-6/LIFR–STAT3, and STING signaling[135]. There are three main types of treatment strategies. Reactivation strategies aim to induce dormant cells to re-enter the cell cycle, rendering them vulnerable to cytotoxic agents targeting proliferating cells. However, incomplete eradication of all cells may expedite tumor progression, as observed following the TGFβ/p38 in head and neck cancer. Dormancy-maintenance strategies aim to prolong cellular dormancy through the utilization of retinoids that activate NR2F1 and TGFβ2 signaling, STING activators, glutaminase inhibitors, anti-SFRP1 therapies, and signals derived from the extracellular matrix, such as type III collagen or factors from senescent tissue[136-139]. Eradication strategies focus on vulnerabilities specific to dormant cells, including YAP/TEAD activity, ROCK signaling, fibronectin-integrin interactions, and particular metabolic deficiencies[140]. Improvements in computational oncology are making it easier for us to find dormant disease. Combined models that use tissue microscopy, patient information, and blood tests such as ctDNA methylation, mutation profiles, and DNA fragment patterns can detect very small amounts of residual disease and predict relapse early[141,142]. Long-read sequencing and analysis of extrachromosomal DNA are expected to reveal superior markers at the isoform and structural levels that signify persistence and recurrence.

8. Tumor Metastasis Mechanisms by Tumor Type

Metastasis is when cancer cells, the surrounding tissue, and the immune system all work together in complicated ways. This is what kills most people with cancer. This review integrates organ- and tissue-specific metastatic patterns with their underlying biological mechanisms. These include how cancer cells change their behavior, how they alter nearby tissues and the extracellular matrix, how tumors evade immune responses, and how they prepare to spread to other parts of the body. This review talks about the most common tumors. The conclusion emphasizes clinical applications, including biomarkers that indicate the potential for cancer metastasis to other organs and treatment strategies that target the vicinity of cancer cells.

8-1. Osteosarcoma (OS)

Early metastasis, particularly to the lungs, is the principal factor influencing prognosis (Managing the immune microenvironment of OS and treatment). About 15-20% of patients have metastases at the time of diagnosis. Of those who are first diagnosed with localized disease, 30-40% will eventually have a relapse, most often with pulmonary disease. About 80-90% of distant metastases affect the lungs, with secondary bone involvement at approximately 8-11%, and, infrequently, visceral or CNS locations[143-145 146]. The lung is still the most common place for OS to come back and the most common cause of death from OS (The metastatic patterns of OS). At the genomic level, OS exhibits significant chromosomal instability and persistent disruption of established tumor-suppressor pathways[147]. The most common type of loss-of-function in TP53 and RB1 is when CDKN2A is deleted, and MYC/MDM2 is amplified[148]. These changes happen as part of complicated structural changes that help cancer cells adapt and spread. The Rab22a–NeoF1 fusion facilitates lung colonization by activating RhoA, remodeling the cytoskeleton, and forming invadopodia. Importantly, exosomes containing Rab22a-NeoF1 prepare pre-metastatic lung niches[149]. The histone

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demethylase KDM6B increases glycolytic flux by upregulating LDHA, which supports metastatic growth[150]. In the same way, the m^{6}A RNA demethylases FTO and ALKBH5 control post-transcriptional programs that strengthen metastatic traits, such as making cells more invasive and better able to withstand stress[151]. Metastatic OS cells frequently demonstrate significant aerobic glycolysis (the Warburg effect), which promotes anabolic metabolism, supports survival in hypoxic environments, and leads to the acidification of the surrounding microenvironment[152]. The TME is therefore a central determinant of OS progression and metastatic competence[153]. TAMs, especially M2-polarized subsets, are associated with a poor prognosis and increased lung colonization because they release pro-angiogenic and immunosuppressive factors. Matrix metalloproteinases, especially MMP-9, help the ECM change shape and release growth factors[154]. Platelets shield circulating tumor cells from shear stress and immune surveillance, promoting vascular adhesion and metastatic seeding[155]. The pulmonary niche signals that help cells survive, and lung-derived mediators activate MAPK signaling and increase the levels of anti-apoptotic molecules like MCL1, which supports micrometastatic growth[156]. Metastatic competence reflects the integration of various oncogenic pathways. PI3K/AKT improves survival and metabolic adaptation; MAPK/ERK promotes proliferation and invasion; WNT/β-catenin controls stemness and motility; and Rho/Rac GTPases manage cytoskeletal remodeling[157]. Chemokine networks, especially the CXCL12/CXCR4/CCR7 axis, help tumor cells find their way to the right place. Integrins such as αVβ3 and αVβ5 help cells adhere firmly to the endothelium and the extracellular matrix. Blocking these integrins with drugs reduces the spread of cancer to the lungs in preclinical models[158 159]. Experimental orthotopic and intravenous models utilizing highly metastatic cell lines (e.g., K7M2, 143B) and genetically engineered murine models exhibiting conditional p53/Rb loss in osteoblasts have facilitated an in-depth analysis of the mechanisms underlying lung metastasis[160 161]. Clinical genomic datasets validate these findings, underscoring the significance of TP53/RB1 disruption and pulmonary relapse as primary contributors to treatment failure[148]. The immune microenvironment (IME) of OS, which includes T lymphocytes, natural killer (NK) cells, tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs), plays two roles: it helps the body fight cancer and helps it evade immune attack. Standard immunotherapies, including vaccines, cytokine therapy, and immune checkpoint blockade (ICB), have demonstrated limited effectiveness in OS. Emerging nano-immunotherapy strategies, on the other hand, aim to reverse the immunosuppressive IME, induce immunogenic cell death (ICD), and enable targeted delivery to improve treatment outcomes. Genomic changes, such as losing TP53 or RB1 and amplifying MYC or MDM2, work with changes in metabolism and epigenetics, such as KDM6B-mediated chromatin remodeling and a shift toward glycolytic metabolism, to make OS more likely to spread. These changes within the tumor interact with signals from the tumor's microenvironment, which are generated by tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and activated platelets. Together, they help osteosarcoma cells spread and stay alive in other parts of the body. Pro-migratory signaling pathways (PI3K/AKT, MAPK, WNT/β-catenin, Rho/Rac) and chemokine–integrin networks (CXCL12/CXCR4/CCR7) work together to drive these processes. Rational combination strategies, including ICB with TAM/MDSC modulation, inhibition of chemokine or integrin axes, and nano-immunotherapy, represent promising therapeutic pathways. Future initiatives should emphasize biomarker-driven clinical translation, sophisticated delivery mechanisms, and single-cell/spatial analyses to address IME heterogeneity and surmount therapeutic resistance in OS. AXL is a key regulator of OS progression and is strongly associated with a bad prognosis[162]. It is a receptor tyrosine kinase (RTK). In murine models, AXL inhibition markedly diminished the pulmonary metastases from MG63.2 cells[163]. Clinical trials of multi-target tyrosine kinase inhibitors (TKIs) have demonstrated that AXL inhibition can elicit partial remission in some patients[164]. While these results are encouraging, no clinical trial has yet examined the impact of selective AXL inhibition alone on outcomes in OS patients. Preclinical studies further demonstrate that AXL knockdown inhibits OS cell proliferation and induces apoptosis[165]. AXL overexpression is observed in rapidly spreading, ubiquitously distributed OS cell lines, and blocking it slows tumor cell growth, invasion, and cell spread[162]. Fibroblast growth factor

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receptor (FGFR) is another RTK that is often overexpressed in OS. FGFRs control many bodily functions, such as the development of the nervous system, the formation of organs, and tissue healing[166]. FGFR1 is expressed in about 74% of OS samples, making it a very promising target for treatment[167].

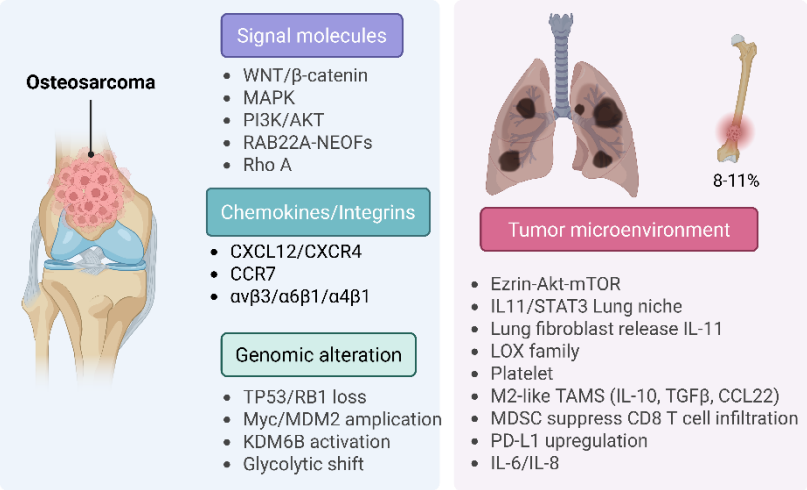

Figure 1. Key molecular drivers and microenvironmental determinants of OS metastasis in the lung. Molecular pathways in OS and lung microenvironmental elements that facilitate metastatic colonization. A combination of tumor-intrinsic signaling pathways, chemokine-integrin axes, and genomic changes drives OS metastasis. These changes make it easier for cancer cells to invade, intravasate, and colonize distant organs, mostly in the lungs. (Left) Signaling molecules that come from tumors, like WNT/β-catenin, MAPK, PI3K/AKT, RAB22A-NEOF fusions, and RhoA, make cells more mobile, help them survive, and make them better at spreading to other parts of the body. Chemokine networks, such as CXCL12/CXCR4 and CCR7, along with adhesion receptors $\alpha v\beta 3$, $\alpha 6\beta 1$, and $\alpha 4\beta 1$, help cells move in the right direction and out of blood vessels. Genomic changes that are typical of aggressive OS, like losing TP53/RB1, amplifying MYC/MDM2, activating KDM6B, and shifting to a glycolytic metabolism, make it easier for the disease to spread. (Right) The lung microenvironment offers a conducive "soil" that is actively influenced by signals from both the host and the tumor. Ezrin–Akt–mTOR signaling, IL11/STAT3 activation, fibroblast-derived IL-11, the LOX family driving ECM remodeling, and platelet-mediated tumor protection are all important immune and stromal mediators. Immunosuppressive elements within the metastatic niche, including M2-like tumor-associated macrophages (TAMs) such as IL-10, TGF-β, and CCL22, myeloid-derived suppressor cells (MDSCs) that inhibit $CD8^+$ T-cell function, and the upregulation of PD-L1, promote tumor immune evasion. Increased levels of IL-6 and IL-8 further promote inflammation, angiogenesis, and the spread of cancer. These tumor-intrinsic and microenvironmental mechanisms work together to make OS lung metastasis more effective.

8-2. Chondrosarcoma (CS)

Chondrosarcoma (CS) is a diverse group of malignant bone tumors characterized by the synthesis of cartilaginous matrix[168]. It primarily impacts adults and exhibits a preference for the axial skeleton, particularly the pelvis and proximal long bones, including the femur and humerus[169]. Tumors arise from chondrocytes or their precursors, with most instances classified as conventional central CS[170]. Less common subtypes, like dedifferentiated and mesenchymal CS, have their own biological traits and are more aggressive in the clinic, which leads to worse outcomes[171]. The risk of metastasis varies significantly based on histologic subtype and grade, as established by classic studies that highlighted the prognostic significance of morphological characteristics[172]. In studies involving large populations, traditional CS demonstrates a relatively low metastatic rate, with approximately 6% of patients exhibiting metastases at diagnosis[173]. On the other hand, dedifferentiated variants and higher-grade lesions are more likely to spread early[174175]. When metastasis occurs, the lungs are the most common site, followed by the pleura and skeletal sites (ribs, spine). Nodal spread is not very

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common. The frequent and early dissemination in dedifferentiated and mesenchymal carcinoma signifies the necessity for accurate histological subtyping. Molecular pathogenesis signifies persistent genetic and epigenetic modifications. Mutations in IDH1 and IDH2 happen in about half of CS151 cases. These mutations make the oncometabolite D-2-hydroxyglutarate, which inhibits α-ketoglutarate–dependent dioxygenases and alters DNA and histone methylation[176177]. Several cohorts have reported that IDH mutation status is associated with enhanced metastasis-free survival, suggesting that alternative molecular pathways facilitate metastasis in IDH-mutant CS[178]. In addition to IDH, dysregulated Hedgehog signaling and PI3K/AKT activation are present; however, Smoothened inhibition has not produced significant clinical benefit[179]. Genomic studies have also found changes in COL2A1 (type II collagen) and TP53 in some patients, but we still don't know exactly what these changes do to help cancer spread[180]. The CS TME is characterized by a dense cartilaginous extracellular matrix (ECM) abundant in collagen and proteoglycans, which impedes drug delivery and transmits pro-invasive signals[181]. MMP-1/-2/-13 must change the ECM for invasion to happen, and their levels are linked to how aggressive the cells are[182]. Simultaneous overexpression of lysyl oxidase (LOX) enhances collagen cross-linking and matrix stiffening, a change that seems contradictory but can actually help migration by increasing integrin-mediated traction[183184]. CS is generally hypovascular and hypoxic, which stabilizes HIF-1α and starts programs for angiogenesis and migration[185]. Hypoxia also causes extracellular vesicles and exosomes to be released, which can change the way the immune system works in the area (for example, by changing macrophages to an M2 phenotype) and make an immunosuppressive niche through IL-10 and TGF-β[186]. Non-malignant stromal components, including mesenchymal stromal cells and fibroblasts, supply growth factors and matrix-modifying enzymes; elevated microvessel density is associated with tumor grade and metastatic potential[187]. There are many signaling pathways that work together to control growth, survival, invasion, and resistance to treatment. These include PI3K/AKT/mTOR, SRC, and TGF-β[188]. Dedifferentiated CS frequently accumulates additional genomic abnormalities akin to OS, thereby exacerbating the metastatic phenotype[189]. Interactions that favor bones, like RANKL signaling, may cause seeding to happen in the skeleton[190]. Due to the infrequency of the condition, a significant portion of the evidence base is derived from correlative human tissue analyses and in vitro studies. However, the data consistently associate elevated MMP expression, HIF-1α activity, and unique exosomal RNA signatures with metastatic risk[186]. Proof-of-concept studies indicate that targeting angiogenesis/HIF-1α or macrophage polarization may retard progression[191]. Anti-angiogenic tyrosine kinase inhibitors (TKIs), such as pazopanib and regorafenib, have demonstrated limited effectiveness in stabilizing disease progression in advanced CS[192]. Epidemiologically, CS constitutes approximately 20-30% of all malignant bone tumors, ranking as the second most prevalent primary malignant bone neoplasm after OS. CS primarily occurs in adults over 40 years old[193, 194], whereas OS is more common in children and adolescents. It is a term that includes groups of things that have different biology, genetics, and epigenetics. The occurrence of CS, especially atypical cartilaginous tumor (ACT), the low-grade variant, has risen, likely due to an aging population and enhanced diagnostic imaging[195]. Most patients have good outcomes after a wide resection because conventional CS grows slowly and doesn't spread very often. Nonetheless, advanced, metastatic, or unresectable disease presents a dismal prognosis due to its resistance to chemotherapy and radiotherapy, coupled with a scarcity of effective systemic treatments. Recent studies have underscored a range of genetic and molecular modifications associated with disease advancement and the transition to high-grade or dedifferentiated phenotypes. Some of the most important ones are changes to isocitrate dehydrogenase 1 and 2 (IDH1/2), an increase in EPAS1, which encodes the hypoxia-inducible factor 2-alpha (HIF-2α), and an increase in the SIRT1/HIF-2α signaling axis. These changes make tumors more aggressive, change their metabolism, and help them adapt to low oxygen levels, which leads to malignant transformation and resistance to treatment. It also delineates the progress and constraints of near-patient preclinical models and the potential of novel therapies that target cancer stem cell dependencies or utilize immunological strategies. Integrative profiling has improved risk stratification. A CS multi-omic signature derived from mRNA, microRNA, and DNA methylation

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identified high-risk patients in one of the largest genetically characterized cohorts to date, highlighting the combined effects of upregulated cell-cycle programs, silencing of the 14q32 imprinted locus (with downregulation of miR-154, miR-382, and miR-384, previously shown to suppress bone sarcoma growth), and genome-wide hypermethylation induced by IDH mutations in driving higher grade and worse prognosis[196]. This stratification framework delineated three favorable-prognosis subgroups-IDH^{wt}/14q32^{high}, IDH^{mut}/14q32^{high}, and IDH^{wt}/14q32^{low}, alongside two intermediate-risk groups (IDH^{mut}/14q32^{low} and Polif^{high}) and a dedifferentiated cohort (14q32^{low}/Prolif^{high}) correlated with the most adverse clinical outcomes[189]. These results highlight the importance of comprehensive molecular profiling beyond IDH mutation status alone and assist in resolving previously noted discrepancies in prognostic classification. Single-cell RNA sequencing identified four signatures based on proliferation, stromal, or leukocyte-related genes. High-grade and dedifferentiated tumors exhibited elevated proliferation indices, with an immunosuppression index distinguishing the dedifferentiated group, while a "active immune response" index characterized low-growing tumors[180]. The ER-stress regulators DDIT3/CHOP and HSPA5 were recognized as survival indicators in standard central CS, with increased expression linked to adverse outcomes. In CS PDX models, inducing ER stress accelerated growth, while its inhibition hindered progression, establishing ER stress as a therapeutic target. Epigenetic therapies are mechanistically justified due to IDH1/2-induced elevations in DNA and histone methylation; however, IDH-mutated dedifferentiated chronic lymphocytic leukemia (CS) displays reduced hypermethylation and distinct loci in comparison to IDH-mutated conventional CS[194]. The FDA has approved DNA hypomethylating agents (like 5-aza-2′-deoxycytidine and decitabine) and HDAC inhibitors (like vorinostat, romidepsin, belinostat, and Panobinostat) for use in hematologic malignancies. In preclinical studies, 5-aza plus vorinostat was more effective than either agent alone in vitro and in JJ012 xenografts. It also caused more DNA-damage responses, activated interferon-stimulated genes (including PD-L1), and activated the innate immune system[39, 197]. A phase II trial of guadecitabine (DNMTi) and belinostat (HDACi) in unresectable or metastatic conventional CS (NCT04340843) failed to achieve the primary overall response rate (ORR) endpoint[198]. The next steps involve assessing the efficacy of epigenetic therapy in conjunction with immune checkpoint inhibitors and chemotherapy. In general, CS metastasis happens when intrinsic factors (like IDH mutations, COL2A1/TP53 changes, and pathway dysregulation) and extrinsic factors (like ECM remodeling, hypoxia, and immune reprogramming) come together. The fact that IDH-mutant tumors may have better metastasis-free survival highlights molecular heterogeneity and suggests that there are different metastatic circuits in different subgroups[180]. Current research priorities concentrate on elucidating the metastatic mechanisms associated with IDH–wild-type CS, creating physiologically relevant preclinical models[199].

8-3. Liposarcoma (LPS)

Liposarcoma (LPS) is a biologically diverse group of malignant adipocytic tumors that includes many histologic subtypes that differ greatly in their genetic drivers, clinical behavior, and treatment weaknesses[200]. The primary variants include well-differentiated LPS (WDLS), dedifferentiated LPS (DDLS), myxoid/round-cell LPS (MLPS), and pleomorphic PLPS, each characterized by unique morphology, genetic alterations, and clinical features[201]. In older adults, WDLS and DDLS are most likely to occur in the deep soft tissues of the extremities or retroperitoneum. These entities illustrate a biological continuum wherein DDLS emerges from pre-existing WDLS via dedifferentiation. MLPS usually shows up in the arms and legs of younger adults and is marked by a lot of myxoid stroma and a branching vascular pattern. Its molecular signature is the FUS-DDIT3 (TLS-CHOP) fusion oncogene produced by the t(12;16)(q13;p11) chromosomal translocation[202]. PLPS is the rarest but most aggressive subtype, usually found in the limbs, with a high-grade pleomorphic shape and different types of fat cells[203]. The risk of metastasis varies significantly across subtypes[204]. WDLS seldom metastasizes, and mortality is generally associated with local recurrence, especially in retroperitoneal tumors where complete resection is difficult. DDLS, on the other hand, is very aggressive and can

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spread to other parts of the body in up to 30% of cases, usually to the lungs[205]. MLPS, on the other hand, is more likely to spread outside of the lungs, usually to the bone, spine, and retroperitoneal soft tissues; skeletal metastases happen in about 17% of cases[206]. PLPS exhibits characteristics akin to undifferentiated pleomorphic sarcoma, including rapid dissemination, pulmonary metastases, and unfavorable survival rates[207]. Molecular pathogenesis is specific to subtypes. WDLS and DDLS are marked by a steady increase in chromosome 12q13-15, which includes MDM2 (almost always) and CDK4 (often). These two genes work together to cause cancer by turning off p53-mediated checkpoints and speeding up the cell cycle[208]. The FUS-DDIT3 fusion is what makes MLPS. It stops adipocytic differentiation and causes tumors to grow. Some isoforms are linked to a higher risk of skeletal metastasis[209]. More mutations, like TP53 and RB1, may build up over time and are linked to resistance to treatment and the ability to spread to other parts of the body[210]. The TME also changes how metastasis works. DDLS frequently arises within a dense, fibrotic stroma populated by cancer-associated fibroblasts, which remodel the extracellular matrix and facilitate tumor growth[211]. Exosomes from tumors that carry oncogenic RNAs and microRNAs help form pre-metastatic niches, especially in the lungs[212]. Immune profiling of DDLS shows that there are inflamed and non-inflamed subtypes. The different types of T-cell infiltration and macrophage polarization affect the prognosis and response to treatment[213]. The CXCR4-CXCL12 chemokine axis is very important for guiding myxoid LPS cells to secondary organs that are rich in CXCL12. There, ligand–receptor gradients increase the cells' ability to move, chemotaxis, and survive during dissemination. When tumor-derived angiogenic mediators like VEGF, ANGPT2, and HIF-regulated cytokines are spread around, they cause new blood vessels to form and change the structure of the local stroma to make it easier for metastases to grow[214]. More generally, receptor tyrosine kinase pathways, such as PDGFR and IGF, along with the activation of PI3K/AKT/mTOR signaling, support proliferation, invasion, and survival across various LPS subtypes[215]. In clinical practice, these biological differences lead to different ways of keeping an eye on and treating patients. For instance, MLPS patients are now advised to have regular spinal imaging because they are at a high risk of bone metastases[216]. In DDLS, immune checkpoint blockade has demonstrated restricted effectiveness, highlighting the necessity for predictive biomarkers and combinatorial strategies that focus on TGF-β, angiogenesis, or immune evasion pathways[217]. The spread of LPS is controlled by a combination of genetic factors that are specific to each subtype, the environment around the cells, and signaling pathways. The different ways that MLPS and DDLS spread show that we need to be very careful when watching and treating them. Future priorities include turning genomic insights into targeted treatments, improving biomarker-driven stratification, and making preclinical models that accurately mimic metastatic niches to help new treatments get developed[218]. About 1% of all cancerous tumors are sarcomas. LPS, a type of soft tissue sarcoma, is the most common histological type, accounting for 15–20% of cases. LPS arises from adipocytic differentiation and primarily presents in the lower extremities or retroperitoneum[219]. It is classified according to immunohistochemical profiles, cellular morphology, and related genetic alterations220. Each subtype displays unique biological characteristics, molecular signatures, and pharmacological sensitivities[220]. Surgery is still the most important part of treating LPS. But the location of the anatomy has a big effect on resectability and prognosis. Retroperitoneal LPS frequently develop asymptomatically within a large cavity, complicating complete resection and leading to a high rate of recurrence. Because having surgery over and over again is hard on the body and mind, how well the first surgery was done is very important for the long-term outcome. Systemic therapy for LPS predominantly utilizes anthracycline-based chemotherapy, sometimes in conjunction with other cytotoxic agents to enhance efficacy, albeit at the cost of heightened toxicity[221]. Nonetheless, advancements in molecularly targeted and immunotherapeutic strategies are broadening the spectrum of treatment alternatives, most LPS subtypes do not respond well to standard chemotherapies. This review outlines the clinicopathologic characteristics, molecular pathogenesis, and contemporary management strategies of LPS subtypes, with a focus on novel approaches, including targeted therapies and immunotherapies. As our understanding of genetics and molecular biology grows, we can expect that better-designed treatments will lead to better

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clinical results. MLPS seems to be more sensitive to drugs than other subtypes, which is a good sign for drug development. New drugs, such as anthracycline derivatives, TKIs, marine-derived compounds, and immune modulators, are showing different levels of benefit, which supports the use of combination strategies in the future. Because LPS is rare and can change, it is very important to make an accurate diagnosis, use advanced imaging techniques, and work together with people from different fields. Ultimately, improvements in LPS management will depend on precision medicine techniques and large, multicenter clinical trials to find better treatment options and find a balance between effectiveness and side effects.

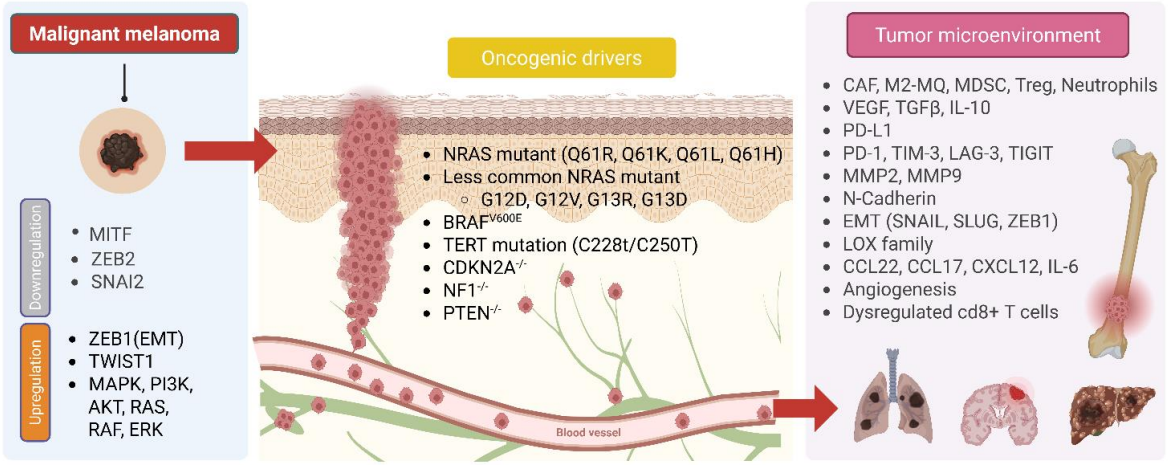

Figure 2. Oncogenic drivers and tumor microenvironmental mechanisms underlying malignant melanoma metastasis. Integrated oncogenic programs and tumor microenvironmental cues driving malignant melanoma progression and metastasis. Malignant melanoma progression initiates with deregulation of lineage and EMT-associated transcriptional programs. (Left) Loss of melanocytic differentiation factors such as MITF, along with downregulation of ZEB2 and SNAI2, shifts melanoma cells toward a dedifferentiated, invasive phenotype. Concurrent upregulation of ZEB1, TWIST1, and activation of MAPK, PI3K/AKT, RAS, RAF, and ERK signaling pathways promotes EMT, survival, motility, and therapy resistance. (Center) Key oncogenic drivers include NRAS mutations (Q61R, Q61K, Q61L, Q61H), less common NRAS variants (G12D, G12V, G13R, G13D), BRAFV600E, TERT promoter mutations (C228T/C250T), CDKN2A loss, NF1 loss, and PTEN loss, which collectively amplify proliferation, invasion, metabolic rewiring, and immune evasion. These drivers also facilitate intravasation, survival in circulation, and endothelial transmigration. (Right) The melanoma TME is enriched with CAFs, M2-like macrophages, MDSCs, Tregs, neutrophils, and vascular/lymphatic growth signals (VEGF, TGFβ, IL-10). Immune checkpoint ligands PD-L1, PD-1, TIM-3, LAG-3, and TIGIT induce profound T-cell exhaustion. Proteolytic remodeling via MMP2/MMP9, adhesion changes via N-cadherin, and EMT transcription factors (SNAIL, SLUG, ZEB1) collectively enhance invasion and dissemination. ECM-modifying enzymes including the LOX family, and chemokine axes such as CCL22, CCL17, CXCL12, and IL-6, foster metastatic niche formation. Dysregulated $CD8^+$ T cells and chronic inflammation create a permissive environment for metastatic outgrowth in lung, brain, bone, and visceral organs.

8-4. Melanoma

Melanoma is a highly aggressive malignancy originating from neural crest-derived melanocytes found in cutaneous, mucosal, and ocular regions; cutaneous melanoma is the predominant subtype[222]. Histologically, lesions range from radial growth-phase tumors limited to the epidermis to vertically invasive tumors that penetrate the basement membrane; cells may be pigmented or amelanotic, but the hallmark is invasive growth beyond the site of origin[223]. Melanoma is clinically significant because it spreads to other parts of the body early and often through both lymphatic and hematogenous pathways, which explains why it has such a big effect on skin cancer deaths[224]. The initial phase of dissemination typically entails migration via dermal lymphatics to regional lymph

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nodes; consequently, nodal status serves as a crucial prognostic indicator, informing staging and management[225]. After that, the disease spreads through the blood to the lungs, liver, brain, bones, and skin/subcutaneous tissue. Brain metastases happen in a lot of advanced cases and have a big effect on survival and quality of life[226]. In-transit metastasis, in which tumor deposits form between the primary site and the regional basin, is a unique sign of lymphatic dissemination. This is because melanoma has lymphotropism and is hard to treat because it spreads to multiple places[227]. At the molecular level, metastatic competence is based on well-defined oncogenic changes that occur repeatedly[228]. BRAF V600 mutations (most often V600E) turn on MAPK/ERK signaling all the time and are found in about half of cutaneous melanomas. NRAS mutations (about 15–20%) activate both the MAPK and PI3K/AKT pathways[229]. Events that cause tumor suppressors such as NF1, PTEN, and CDKN2A to stop functioning make growth and survival signaling even less stable[230]. Highly prevalent TERT promoter mutations that increase telomerase activity and cellular immortality are other factors that accelerate progression[231]. Melanoma cells use the MAPK, PI3K/AKT, WNT/β-catenin, and NF-κB signaling pathways to control growth, survival, immune evasion, and metastasis[232]. Invasion and dissemination rely on dynamic changes in adhesion and motility. Melanoma cells frequently downregulate E-cadherin and upregulate N-cadherin, facilitating detachment from keratinocyte constraints and enhancing interactions with stromal and endothelial components[233]. MMP-2 and MMP-9 promote the degradation of the basement membrane and extracellular matrix (ECM), whereas integrins, especially $\alpha v\beta 3$ and $\alpha 4\beta 1$, facilitate migration through various tissue matrices[234]. Cells can change their shape from mesenchymal to amoeboid in response to changes in their microenvironment[235]. Chemokine axes, like CCR4/CCR10 for skin homing and CCR7 for nodal migration, help direct organotropism. This is similar to how ligands are expressed in target tissues[236]. The TME determines how well a cancer spreads and how well it responds to treatment. Fibroblasts associated with cancer alter the ECM (fibronectin, collagens) and give cells signals to stay alive and move[237]. Tumor-associated macrophages often exhibit an M2-like phenotype, secreting VEGF, TGF-β, and IL-10 that facilitate angiogenesis, immune suppression, and invasion[238]. The immune landscape is critical for prognosis: a high number of $CD8^+$ T cells in the right places is a good sign, while a high number of regulatory T cells and M2 macrophages is a bad sign[239]. Melanoma promotes lymphangiogenesis in lymph nodes, enlarging lymphatic pathways for dissemination[240]. Immune evasion is crucial for successful metastasis. Upregulation of PD-L1 on melanoma cells activates PD-1 on T cells, impairing effector function and facilitating tumor progression, a pathway now effectively targeted in clinical settings[241]. The "immunotherapy revolution" underscores the TME's importance: checkpoint inhibitors have changed the lives of many patients, but primary and acquired resistance remain common and require biomarker-guided combinations[242]. Preclinical models closely resemble human disease and have elucidated the biology of metastasis and therapeutic resistance. Genetically engineered mouse models, like BRAFV600E with PTEM-/-, mimic spontaneous metastasis. B16 syngeneic and human xenograft models build on these results, especially for lung/brain spread and treatment evaluation[243]. Immune infiltration patterns and driver genotypes correlate with prognosis and therapeutic response, elucidating prevalent resistance mechanisms via secondary mutations or pathway reconfiguration[244].Overall, melanoma metastasis results from the interaction of well-known oncogenic drivers (such as mutations in BRAF, NRAS, and the TERT promoter), changes in adhesion and motility that help the cancer spread, chemokine-directed organotropism, and an immune-modulatory TME[245]. More investigation is needed to verify the factors influencing immune-infiltration heterogeneity, developing predictive biomarkers for targeted and immunotherapies, and devising logical combinations that concurrently tackle tumor-intrinsic pathways and TME-mediated resistance[246]. Single-cell/spatial multi-omics, liquid biopsy monitoring, and next-generation, immune-competent preclinical models that better mimic human metastatic disease[247] will speed up progress.

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8-5. Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC), the predominant form of primary liver cancer, originates from hepatocytes, usually in association with chronic liver disease and cirrhosis[248]. Most cases arise from chronic hepatic inflammation caused by hepatitis B or C infection, alcohol-related liver disease, or non-alcoholic steatohepatitis[249]. Histologically, HCC exhibits trabecular and pseudoglandular proliferation of atypical hepatocytes accompanied by architectural distortion. Fibrolamellar HCC is a unique type that happens in younger patients who don't have cirrhosis. It has its own molecular characteristics and clinical behavior[250]. Clinically, HCC is widespread worldwide and is marked by aggressive biology and early metastatic potential, leading to unfavorable survival outcomes[251]. HCC metastasis indicates its intrahepatic origin and significant vascular invasiveness into the portal and hepatic veins, which promote hematogenous dissemination and are associated with a poor prognosis[252]. The lung is the most common place outside the liver, followed by the lymph nodes in the abdomen, and the spread of cancer through the peritoneum. Bone metastases, which usually involve the axial skeleton, often cause severe pain and fractures[253]. Other targets include the diaphragm, brain, adrenal glands, and pleural surfaces[253]. Extensive clinical studies consistently indicate a decreasing prevalence of involvement in the lung, peritoneum, bone, spleen, adrenal glands, brain, pleura, and kidneys[254]. Brain metastases are infrequent but generally occur late and indicate a poor prognosis for survival[255]. At the molecular level, chronic inflammatory injury creates a mutagenic environment that promotes cancer growth and the spread of cancer cells to other parts of the body[256]. Recurrent alterations include TERT promoter mutations that reactivate telomerase[257], TP53 mutations that hinder genomic surveillance, and CTNNB1 (β-catenin) mutations that promote Wnt pathway activation [258259]. Other factors that sustain angiogenesis and promote metastatic colonization260 include MET activation and widespread upregulation of the VEGF pathway. Metastatic dissemination entails epithelial–mesenchymal transition, facilitated by Snail/Zeb factors and often triggered by TGF-β-rich inflammation, while matrix metalloproteinases, including MMP-9, degrade the extracellular matrix to permit invasion[261]. HCC develops in a microenvironment characterized by cirrhosis, fibrosis, and inflammation, which is intrinsically immunosuppressive[262]. Activated hepatic stellate cells and portal fibroblasts generate a collagen-rich matrix and induce tissue stiffening, which influences tumor behavior and hinders drug penetration[263]. CAFs alter ECM, release VEGF, PDGF, and chemokines, and keep the immune system out by signaling through IL-6 and TGF-β and building physical barriers[264]. Macrophages, particularly M2-like subsets, play roles in immune suppression, angiogenesis, and matrix remodeling[265]. VEGF-induced endothelial hyperproliferation results in disordered vasculature that promotes intravasation and is associated with vascular invasion[266]. These interactions between stromal and immune cells cooperate with oncogenic pathways such as PI3K/AKT activation, PTEN loss, FGF/IGF signaling, and PD-L1 upregulation to sustain tumor growth, invasion, and evasion of the immune system[260267268]. Molecular profiling has elucidated metastasis-associated signatures, including exosome-derived miRNAs that influence distant microenvironments and promote the formation of metastastatic niches[269]. In clinical practice, multiple-organ metastases frequently occur after surgical resection, with the lung, bone, and peritoneum being the most commonly affected sites[270]. In general, HCC metastasis is driven by chronic inflammation-induced mutagenesis, including mutations in TERT, TP53, and CTNNB1.

8-6. Glioblastoma (GBM)

GBM is the most aggressive primary cancer of the central nervous system. The 2021 update of the World Health Organization classification[274] states that it is a WHO grade IV astrocytic tumor. GBM, which mainly arises from glial cells, primarily astrocytes, is characterized by pseudopalisading necrosis and microvascular proliferation under a microscope. These traits indicate a malignant biology and set it apart from lower-grade gliomas[275]. In clinical settings, GBM exhibits diffuse infiltration, rapid recurrence, and unfavorable outcomes despite aggressive multimodal treatment, including maximal resection, radiotherapy, and temozolomide chemotherapy, with median survival rarely exceeding 15 months[276]. Unlike most systemic malignancies, GBM infrequently metastasizes

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beyond the central nervous system. This unique confinement is due to the protective blood-brain barrier, the absence of a traditional lymphatic system, the specialized neural microenvironment, and the short clinical course that limits the time for systemic dissemination[277]. As a result, GBM "metastasis" is characterized not by distant organ colonization but by significant local invasion within the brain parenchyma. Tumor cells invade through white matter tracts, perivascular spaces, and cerebrospinal fluid pathways, sometimes resulting in leptomeningeal or spinal "drop" metastases[278]. Rare instances of extracranial dissemination are generally associated with surgical procedures, such as craniotomy or ventricular shunting, which may facilitate cellular egress[277]. This pattern of diffuse invasion within the brain, rather than hematogenous dissemination, characterizes the lethal persistence of GBM. The molecular composition of GBM is highly heterogeneous. Verhaak et al. (2010)[279] showed that transcriptomic profiling has identified three main molecular subtypes. Each of these subtypes is associated with specific driver changes. The classical subtype is distinguished by the amplification and mutation of the epidermal growth factor receptor (EGFR), often involving the constitutively active EGFRvIII variant. This change keeps the Ras/MAPK and PI3K/AKT pathways active all the time, which makes cells grow and spread more easily[280]. The mesenchymal subtype is often characterized by NF1 loss and activation of TGF-β signaling, leading to an EMT-like, highly invasive phenotype rich in inflammatory and angiogenic programs[281]. The proneural subtype is usually characterized by either PDGFRA amplification or IDH1 mutations. The latter is a sign of secondary GBMs that develop from lower-grade gliomas and have a CpG island methylator phenotype (G-CIMP) with a relatively good prognosis[276]. This classification highlights that GBM is not a singular disease but rather a spectrum of molecularly distinct entities characterized by convergent features of unregulated proliferation, invasion, and therapeutic resistance. Integrin-mediated adhesion and remodeling of the extracellular matrix control invasion. For instance, α6β1-laminin interactions help cells move around blood vessels, and matrix metalloproteinases like MMP-2 and MMP-9 break down type IV collagen and change the brain's extracellular matrix[282]. Glioma cells demonstrate motility plasticity, transitioning between elongated, protease-dependent mesenchymal migration and rounded, deformable amoeboid movement[283]. This flexibility allows it to spread through both dense and flexible parts of the brain. Hypoxia further increases invasiveness by stabilizing HIF-1α, which in turn increases VEGF and EMT transcription factors like ZEB1. This leads to angiogenesis and mesenchymal transition[284]. Tumor-associated macrophages and microglia reportedly comprise up to fifty percent of the tumor mass and frequently exhibit an M2-like phenotype, secreting IL-10 and TGF-β to inhibit T-cell activity[238]. Single-cell analyses have elucidated a range of tumor-associated macrophage (TAM) states and their reciprocal interactions with glioma cells that facilitate invasion and angiogenesis[285]. On the other hand, tumor-infiltrating lymphocytes are few and mostly worn out, which makes immune checkpoint blockade less effective[286]. Reactive astrocytes and endothelial cells also help by releasing growth factors and cytokines that make a tumor-supportive niche[287]. The outcome is a microenvironment that protects the tumor from immune destruction and promotes ongoing growth. Genetically, GBM is caused by the wrong activation of the receptor tyrosine kinase and the signaling pathways that follow it. EGFR amplification, PTEN loss, and TP53 mutation are among the most common changes[288]. EGFR activation continuously activates the MAPK and PI3K/AKT signaling pathways, which help cells grow, prevent cell death, and adapt to changes in metabolism[289]. The PI3K/AKT/mTOR pathway is modified in up to 86% of GBMs and serves as a crucial nexus for survival and metabolic control. Simultaneously, mTORC2-mediated AKT phosphorylation enhances invasive and therapy-resistant phenotypes[290]. The interactions among the MAPK, PI3K/mTOR, and PKC pathways form a robust signaling network that sustains tumor growth. The MNK-dependent phosphorylation of eIF4E for translational control is another place where things come together. Tomivosertib, an MNK inhibitor, prevents eIF4E activation, slowing angiogenesis and making tumors more sensitive to temozolomide. This shows that translational regulation is a therapeutic weakness that can be exploited[291]. Epigenetic dysregulation plays a major role in the diversity and adaptability of GBM. Phenotypic plasticity, recognized as a nascent characteristic of cancer in GBM, is profoundly associated with epigenetic

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reprogramming[292]. Patterns of DNA methylation affect both the biology of tumors and how well treatments work. For example, methylation of the MGMT promoter predicts a good response to temozolomide, and the G-CIMP phenotype linked to IDH1 mutations defines a unique epigenetic and prognostic subgroup[293]. At the chromatin level, EZH2-mediated H3K27 methylation inhibits tumor suppressors like PTEN and collaborates with PI3K signaling to promote oncogenic transcription[294]. By deacetylating α-tubulin and stabilizing EGFR[295], HDAC6 helps glioma cells grow and move. Pharmacological inhibition of HDAC6 or EZH2 diminishes invasiveness in preclinical models. Nonetheless, clinical trials involving broad HDAC inhibitors or DNA demethylating agents have thus far demonstrated limited efficacy, highlighting the necessity for more selective, brain-penetrant epigenetic modulators. Resistance to therapy in GBM is due to a combination of genetic variation, stem-like plasticity, and protection from the microenvironment[296]. Recurrence usually happens because of resistant subclones that were already there and survived chemoradiation. Recurrent tumors often show mesenchymal enrichment and changes induced by therapy[297]. Glioma stem-like cells remain dormant, facilitate DNA repair by activating ATM/ATR, and replenish tumors post-therapy[298]. These cells also increase the activity of efflux transporters and anti-apoptotic genes, which makes multidrug resistance even stronger. These mechanisms elucidate the reasons for the recurrent failures of targeted therapies targeting single pathways. EGFR inhibitors and anti-angiogenic agents like bevacizumab produce temporary responses but lack a sustained survival advantage[299]. Recent progress is changing the way we treat diseases. Researchers are looking into new ways to get drugs into the body, such as convection-enhanced drug infusion, nanoparticles, and peptide-mediated blood–brain barrier penetration[300]. Non-pharmacologic modalities, especially tumor-treating fields, have improved median survival when combined with temozolomide, underscoring the importance of integrating novel technologies[301]. PD-1 blockade, multi-antigen vaccines, and regionally administered CAR T cells that target IL13Rα2 or HER2, can trigger an anti-tumor immune response even in the immunosuppressive environment of GBM[302]. Oncolytic virotherapy has demonstrated potential; the HSV-1-derived Delytact (G47Δ) attained sustained disease control in a cohort of patients with recurrent GBM[303], representing the inaugural approved virotherapy for malignant glioma. Even with these small improvements, GBM is still a model of an adaptive cancer. Its confinement in the brain conceals a remarkable capacity to exploit the microenvironment, evade treatment, and recur. For future success, we will need to use combinations of treatments that target oncogenic signaling, epigenetic plasticity, and immune suppression simultaneously, while also making it easier for drugs to cross the blood-brain barrier. Combining genomic, epigenomic, and spatial single-cell analyses is helping us learn more about how different types of cells in a tumor work together and how to develop combination therapies[304]. With ongoing progress in multi-omic profiling, immunoengineering, and precision drug delivery, the enduring therapeutic stalemate of GBM may finally commence to dissolve.

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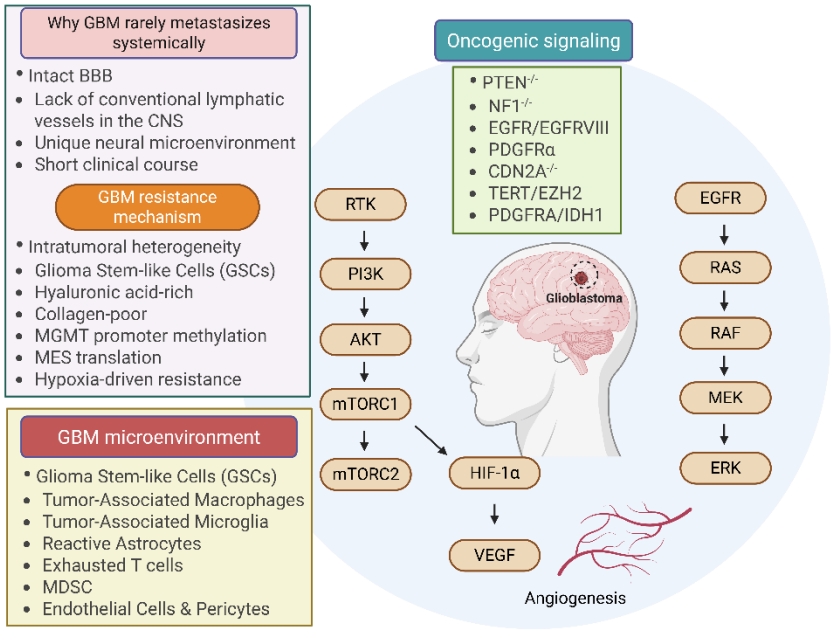

Figure 3. Integrated oncogenic signaling, microenvironmental factors, and resistance mechanisms in GBM. Characteristics of GBM biology encompass its restricted systemic metastasis, oncogenic drivers, microenvironmental composition, and the mechanisms that contribute to therapeutic resistance. (Top left) GBM rarely metastasizes beyond the central nervous system owing to the prohibitive blood-brain barrier, the absence of standard lymphatic drainage, and a neural microenvironment that constrains tumor cell spread. The brief clinical progression of GBM and physiological limitations that hinder systemic spread are additional factors. (Middle left—GBM resistance mechanisms) Therapeutic resistance is caused by a lot of different types of cells in the tumor, the presence of therapy-resistant glioma stem-like cells (GSCs), and an extracellular matrix that is rich in hyaluronic acid and poor in collagen, which protects tumor cells from drugs. Resistance is bolstered by the methylation status of the MGMT promoter, transitions in the mesenchymal state (MES), metabolic reprogramming, and adaptive pathways driven by hypoxia. (Bottom left: GBM microenvironment) The GBM TME is made up of many different types of cells that help tumors grow and suppress the immune system. These include GSCs, tumor-associated macrophages (TAMs), tumor-associated microglia, reactive astrocytes, exhausted T cells, myeloid-derived suppressor cells (MDSCs), and endothelial cells/pericytes. These parts work together to cause invasion, immune evasion, and local recurrence. (Right—Oncogenic signaling) PTEN loss, NF1 loss, EGFR/EGFRvIII activation, PDGFRα amplification, CDKN2A deletion, TERT promoter mutations, EZH2 upregulation, and PDGFRA/IDH1-mutant pathways are the main causes of GBM. These molecular events trigger standard receptor tyrosine kinase (RTK) signaling pathways, such as the PI3K–AKT–mTORC1/2 axis and the EGFR–RAS–RAF–MEK–ERK cascade. This signaling pathway increases the levels of HIF-1α, which in turn increases VEGF-mediated angiogenesis, leading to faster tumor growth and resistance to treatment.

8-7. Breast Tumor

Breast cancer metastasis is a very slow and complicated process that only a small number of tumor cells can complete[305]. These metastasis-initiating cells (MICs) display stem-like characteristics and exceptional phenotypic plasticity, allowing them to endure systemic stresses, circumvent immune responses, and acclimatize to foreign tissue environments[306]. The induction of epithelial-mesenchymal transition (EMT) is a key factor in MIC plasticity. In breast tumors, transcription factors such as SNAIL, ZEB1, and PRRX1 control this process. These EMT-TFs inhibit epithelial markers (e.g., E-cadherin) and stimulate mesenchymal genes, imparting motility and stemness to cells[306]. The absence of the EMT inducer Prrx1 has been shown to facilitate MET and metastatic colonization in breast models, underscoring the dynamic and reversible nature of the EMT program[307]. The tumor microenvironment (TME) has a big effect on EMT activation in breast cancer. For example, cancer-

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associated fibroblasts (CAFs) secrete TGF-β1 and other substances that induce EMT[308]. On the other hand, TAMs release cytokines like CCL18 and IL-6 that help cells invade and spread[309]. For example, CCL18 from TAM starts a signaling cascade through PITPNM3/ANXA2 that turns on PI3K/Akt/GSK3β signaling and raises the level of Snail[310]. In the same way, IL-6 secreted by TAMs activates the JAK2/STAT3 pathway in breast cancer cells, increasing EMT-TF expression and conferring stem-like, therapy-resistant characteristics[55]. These microenvironmental signals work with cancer-intrinsic EMT programs to produce cells that are highly mobile and resistant to treatment. To leave the primary site, breast cancer cells need to break through the surrounding stroma and basement membranes. They do this mostly by increasing the levels of matrix metalloproteinases (MMPs), especially MMP-2, MMP-9, and the membrane-anchored MT1-MMP (MMP-14), which break down type IV collagen and other ECM components[311]. High levels of MMP-2/9 activity are strongly linked to invasive behavior and the spread of cancer to other parts of the body. MT1-MMP, on the other hand, is a key effector that activates pro-MMP-2 to boost proteolytic cascades at the invasive front[312]. Once in circulation, breast cancer cells endure shear stress and immune surveillance by moving as circulating tumor cell (CTC) clusters. These clusters are about 23-50 times more likely to spread than single CTCs[313]313. Platelet "cloaking" of circulating tumor cells (CTCs) increases the ability of the immune system to avoid detection while also promoting microvascular arrest and vascular loading[314]. Hypoxic conditions enhance this process by increasing CTC-platelet aggregation, thereby creating a temporary protective niche during hematologenous transit[315]. After extravasation, disseminated tumor cells (DTCs) that spread to distant organs, such as the lungs and additional bone marrow, can enter a dormancy bottleneck, where they can remain dormant for years. Microenvironmental remodeling often triggers reactivation from dormancy. For example, the neutrophil extracellular trap (NET)-mediated cleavage of laminin produces bioactive fragments that activate b1-integrin-YAP signaling, ultimately promoting metastatic outgrowth[316]. Organ-specific "seed and soil" interactions control metastatic growth. Breast cancer exhibits specific levels of COX2 (PTGS2) and MMP1, which facilitate vascular remodeling and extravasation[317]. In brain metastasis, breast cancer cells aberrantly express ST6GALNAC5, facilitating their penetration of the blood-brain barrier[318]. Blocking COX2 or MMP1 stops lung metastasis, and knocking down ST6GALNAC5 stops brain colonization. Invasive lobular carcinoma (ILC), characterized by the loss of E-cadherin, demonstrates distinct metastatic pathways and increased susceptibility to IGF1R pathway inhibition[319]. Metastatic colonies change how they use energy in different organs. Breast cancer cells that prefer bone tissue depend on glycolysis and lactate-driven osteolytic remodeling[320]. Brain metastases adapt to a glutamine-rich environment by enhancing glutamine anaplerosis and metabolic plasticity[321]. EMT-high cells exhibit a distinct susceptibility: ZEB1-mediated ferroptosis sensitivity via the repression of SCD1 and the accumulation of poly- unsaturated lipids[322]. New ways to treat people use these ideas. Blocking both TGF-β and CD73 reverses EMT and improves the efficacy of immunotherapy[323]. Inducing ferroptosis is another way to target cells that initiate metastasis by driving epithelial-mesenchymal transition (EMT)[324]. ENPP1, an enzyme that breaks down cGAMP, promotes metastasis to the brain and bones and stops STING signaling. It is a promising target for treatment[325]. Hedgehog-GLI signaling facilitates bone colonization and resistance to endocrine therapy, while SMO/GLI inhibitors have demonstrated preclinical efficacy[326]. A more in-depth understanding of how these processes work is now being combined with new treatments targeting EMT circuits, metabolic weaknesses such as ferroptosis, pro-metastatic enzymes such as ENPP1, and developmental pathways such as Hedgehog[327]. This gives hope for breast cancer-specific treatments that can get rid of dormant seeds and stop the deadly spread of metastases[327]. The ongoing challenge is to turn these discoveries into safe and effective treatments that stop the spread of cancer and improve survival in advanced breast cancer.

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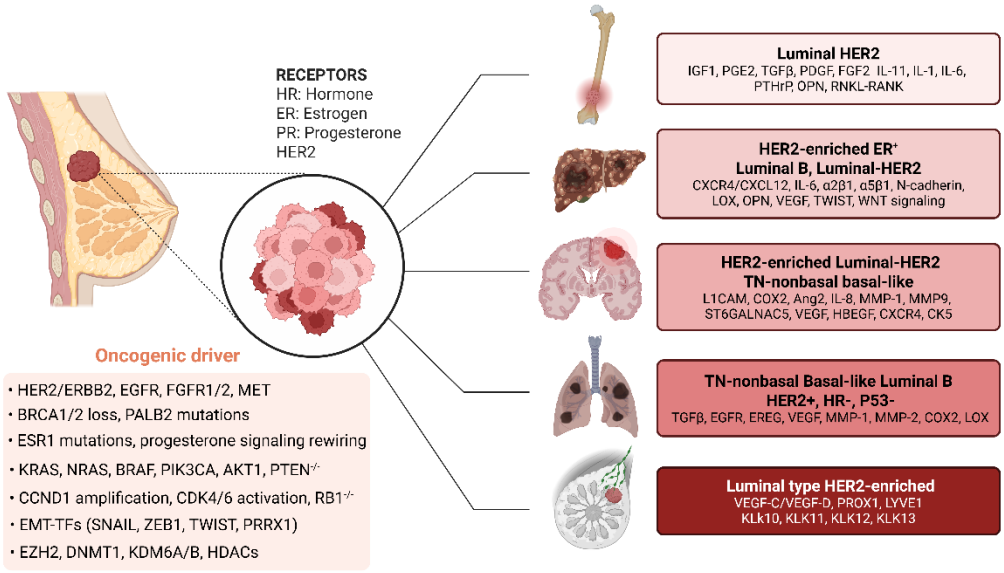

Figure 4. Oncogenic drivers, receptor profiles, and organ-specific metastatic pathways in various breast cancer subtypes. Combined oncogenic mechanisms and organotropism for metastasis in major subtypes of breast cancer. Breast tumors are characterized by their receptor status, specifically the expression patterns of ER, PR, HER2, and HR, which influence lineage identity, oncogenic dependencies, and metastatic pathways. (Left) Key oncogenic drivers consist of the amplification or activation of HER2/ERBB2, EGFR, FGFR1/2, and MET; mutations in BRCA1/2, PALB2, and ESR1; activating alterations in KRAS, NRAS, BRAF, PIK3CA, and AKT1; and the loss of PTEN. Other factors that play a role are cell-cycle deregulation (CCND1 amplification, CDK4/6 activation, RB1 loss), EMT regulators (SNAIL, ZEB1, TWIST, PRRX1), and epigenetic modifiers (EZH2, DNMT1, KDM6A/B, HDACs). These changes work together to help tumors survive, change shape, invade, and spread to other parts of the body. (Right) Different types of breast cancer have different ligand, cytokine, and adhesion profiles that control organotropic metastasis: The luminal HER2 subtype has more IGF1, PGE2, TGFβ, PDGF, FGF2, IL-11, IL-1, IL-6, PTHrP, OPN, and RANKL-RANK, which helps bone-trophic signaling. HER2-enriched ER$^+$ / Luminal B/ Luminal-HER2 tumors express CXCR4/CXCL12, IL-6, α2β1, α5β1, N-cadherin, LOX, OPN, VEGF, TWIST, and WNT, which makes it easier for them to spread to the liver and bones. L1CAM, COX2, Ang2, IL-8, MMP-1/2/8/9, ST6GALNAC5, VEGF, HBEGF, CXCR4, and CK5 are all present in HER2-enriched Luminal-HER2 and TN-nonbasal basal-like tumors. These markers help the tumors spread to the lungs and brain quickly. TN-nonbasal basal-like Luminal B and HER2$^+$/HR$^-$/p53-mutant tumors exhibit pronounced inflammatory and proteolytic profiles (TGFβ, EREG, VEGF, MMP-1/2, COX2, LOX), facilitating visceral and pulmonary metastasis. Luminal-type HER2-enriched tumors increase the levels of VEGF-C/VEGF-D, PROX1, LYVE1, and the kallikrein family (KLK10, KLK11, KLK12, KLK13). This shows that they have lymphangiogenic and HER2-driven metastatic traits.

9. Emerging Therapeutic Strategies for Metastatic Disease

Therapeutic advancements in metastatic cancer increasingly embody a mechanistic understanding of tumor evolution, immune evasion, and microenvironmental reconfiguration. Targeted inhibitors that block oncogenic drivers like EGFR and ALK have changed how metastatic lung cancer is treated by selectively breaking up signaling networks that keep cells growing[328]. This precision paradigm acknowledges that metastasis is regulated by distinct biological programs, such as epithelial-mesenchymal transition (EMT), niche formation, and immune suppression, which can be targeted with specific interventions[329]. Immune checkpoint inhibitors (ICIs) are still very important for melanoma and lung cancer because they help T-cells work again[330]. However, many metastatic lesions remain "cold," meaning they lack dendritic-cell priming and T-cell infiltration. Combination immunotherapies aim to overcome resistance: therapeutic cancer vaccines enhance neoantigen recognition and work in combination with PD-1 blockade[331], while CD40 and OX40 agonists boost

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dendritic-cell activation and T-cell costimulation[332]. Adoptive cell therapies improve immune system benefits. TIL therapy causes long-lasting responses in melanoma that doesn't respond to other treatments, and "armored" CAR-T cells that secrete IL-12 or IL-15 fight against solid tumor microenvironments that suppress the immune system[333]. Furthermore, CAR-macrophages represent an innovative frontier, reprogramming M2 macrophages into inflammatory M1 states and diminishing metastatic lesions in preclinical models[334]. It is just as important to target the "soil" where the cancer spreads. Stromal-directed agents like PEGPH20 break down hyaluronan, making tumors less dense and allowing drugs to reach them better[336]. FAP-targeted therapies, on the other hand, break up fibroblast-rich metastatic niches[337]. In bone metastasis, the inhibition of RANKL by denosumab diminishes skeletal events and decelerates progression[338]. Inhibition of CXCR4[339] or blockade of LOX/LOXL2 to stop ECM stiffening[340] are both promising ways to stop pre-metastatic niche formation. Simultaneous advancements in monitoring and delivery are transforming clinical management. Liquid biopsies allow for real-time tracking of how metastatic cancer is changing. The dynamics of ctDNA can predict when the cancer will come back sooner than imaging[341], and help doctors choose adaptive therapy methods that change treatment based on how the tumor is changing. Nanomedicine improves the delivery of drugs to metastatic lesions[342], and biomaterial-based depot systems like injectable immunostimulatory hydrogels provide long-lasting immune activation in an area to stop the disease from coming back[343]. New cellular technologies, such as CRISPR-edited T cells[344], tumor-homing MSC-based therapies[345], and universal iPSC-derived NK/T cells[346], hold the potential to provide new modular, off-the-shelf treatments for metastatic disease. These changes show a shift from broad cytotoxic strategies to more precise ones that combine targeted oncogenic blockade. This changing framework sees metastatic cancer as a disease that can be managed over the long term through coordinated therapeutic pressure, rather than as a disease that always leads to death.

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