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Tumor Microemboli, Dormancy, and Premetastatic Niches as Three Mechanisms of Metastasis: Which to Target? And When?

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Abstract

Metastasis is a complex process driven by multiple, incompletely understood mechanisms that enable disseminated tumor cells (DTCs) to colonize distant organs. It remains the leading cause of cancer-related death, yet definitive preventive strategies are still lacking. In this narrative review, we focus on three major mechanisms of metastasis: tumor microemboli, tumor cell dormancy, and premetastatic niche (PMN) formation. These mechanisms represent critical hallmarks associated with a high probability of successful metastasis. Hypothetically, when targeting one of these mechanisms, ensuring the absence or therapeutic control of the other two appears necessary if the goal is to suppress metastasis rather than merely block a single pathway. We discuss current and emerging therapeutics targeting each mechanism and propose a timing- and context-dependent framework to optimize their efficacy.

We highlight that therapeutic targeting of tumor microemboli is most relevant for larger heterotypic clusters, whereas smaller clusters may rely on alternative mechanisms for successful metastasis. PMN formation follows a sequential cascade of tumor-derived and host tissue signals. This sequence makes the timing of intervention critical, such that the same agent may be effective at an early stage but lose efficacy later. For tumor dormancy, we distinguish between the timeframes before and after the establishment of dormant DTCs, and we review the therapeutics accordingly. We further propose that dormancy is a dynamic state characterized by cycles of awakening and rapid re-entry into quiescence, comparable to herpes simplex virus reactivation and dormancy. This timely re-entry into dormancy would be conditioned by the presence in situ of an interferon-gamma (IFN-γ)-secreting T-cell pool. Dormancy is also expected to serve as a last-resort mechanism of metastasis in a given tissue when efficient multicellular microemboli and a PMN are absent at that site. The rationale for this consideration is based on differences in metastatic efficiency. Multicellular microemboli and an established PMN possess a higher and more immediate capacity to generate metastases than DTCs that enter dormancy and only later reawaken under favorable conditions. Consequently, ensuring the absence or the suppression of these mechanisms appears necessary before targeting tumor dormancy. This timing-oriented perspective aims to shift the focus from treating established metastases toward the rational prevention of metastatic colonization.

Categories: Radiology, Oncology, Allergy/Immunology
Keywords: metastasis, premetastatic niche, tnf-α, tumor dormancy, tumor microemboli

Introduction And Background

Metastasis is driven by mechanisms that enable disseminated tumor cells (DTCs) to survive, persist, and ultimately colonize distant organs [1]. Among them, tumor microemboli, tumor cell dormancy, and premetastatic niche (PMN) formation represent three pillars of the metastatic process. Tumor microemboli are multicellular clusters of circulating tumor cells (CTCs) that travel together in the blood and show higher metastatic efficiency than single cells. PMNs are distant organ sites that are prepared by the primary tumor before the arrival of cancer cells, creating a favorable environment for colonization. Tumor cell dormancy refers to the ability of DTCs to survive for prolonged periods in a non-proliferative or balanced state before eventually reactivating. Primary tumors orchestrate the formation of PMNs through secreted factors, exosomes, and inflammatory signals that recruit immunosuppressive cells and remodel distant microenvironments, making them suitable for the homing of metastatic tumor cells [2]. Tumor microemboli benefit from collective interactions that confer resistance to shear stress, anoikis, and immune attack, dramatically increasing their metastatic efficiency compared with single cells [3]. Some metastatic tumor cells enter a dormant state, surviving in a quiescent or balanced equilibrium for extended periods before reactivation [4]. In this narrative review, we synthesize the current understanding of these three mechanisms with particular emphasis on therapeutics. We propose a timing- and context-dependent framework to guide therapeutic intervention for each of these three processes.

Review

Tumor microemboli

Tumor microemboli, also known as CTC clusters, consist of multicellular aggregates of tumor cells (homotypic clusters) that may be associated with platelets, neutrophils, cancer-associated fibroblasts (CAFs), and other stromal components (heterotypic clusters) [5,6]. Their superior metastatic efficiency arises from multiple cooperative advantages, including collective resistance to shear stress and anoikis [3,7], immune evasion through platelet-mediated "cloaking" [8,9], enhanced endothelial adhesion [10], and preservation of stem-like properties that facilitate collective invasion and niche colonization [11]. After reviewing detection methods and therapeutics in this section, we will propose the clinical contexts in which targeting tumor microemboli is likely to have the greatest impact.

Tumor Microemboli Detection

Traditional methods for isolating CTCs can be used with caution to detect clusters, as CTC clusters are fragile and prone to dissociation, which can lead to underestimation of their true abundance [12]. These techniques can be divided into antibody-based and physical property-based methods [12]. Antibody-based methods target antigens expressed on CTCs but not on blood cells; the epithelial cell adhesion molecule (EpCAM) is the most widely used marker for epithelial tumor cell detection [13]. The CellSearch system, the only FDA-approved platform for CTC enumeration, defines a CTC cluster as three or more EpCAM- and cytokeratin-positive cells that lack CD45 expression and contain DAPI-stained nuclei [14]. High-throughput microfluidic devices, such as the herringbone chip, have improved capture efficiency through enhanced cell-antibody interactions [15].

Physical property-based methods exploit differences in cell size, density, and deformability independent of tumor antigens. Size-based filtration platforms, such as Isolation by Size of Epithelial Tumor Cells (ISET), have shown higher sensitivity for CTC clusters compared with antibody-based techniques [12,16]. Microfluidic advancements have further improved these approaches; for example, the Cluster-Chip uses specialized bifurcating traps under low-shear conditions to capture intact clusters [17].

Therapeutics for Tumor Microemboli

Disrupting homotypic tumor cell-cell interactions: Disrupting homotypic tumor cell-cell interactions within CTC clusters may be achieved by targeting adhesion molecules involved in these interactions, such as E-cadherin, CD44, and plakoglobin [18-20]. Pharmacological inhibition of these molecules has been shown to dissociate clusters and suppress metastasis in preclinical models [3].

While most agents targeting these molecules remain in the preclinical phase, RG7356 has progressed to a phase I clinical trial [21]. This humanized anti-CD44 monoclonal antibody was generally well tolerated, but clinical efficacy was modest, with stable disease as the best response observed in some patients. Although disease stabilization does not directly prove anti-cluster activity, it is consistent with the hypothesis that interfering with CD44-mediated homotypic interactions may limit de novo metastasis formation. The marked inter-individual variability in response further supports the need, as proposed later, for identifying the optimal timing and tumor molecular context for such interventions.

Some drugs already approved for other indications have shown potential to disrupt homotypic tumor cell interactions in CTC clusters. Digoxin, a cardiac glycoside that inhibits Na^+/K^+-ATPase, has been shown to downregulate adhesion molecules and reduce CTC cluster size [11]. In a proof-of-concept clinical study in patients with metastatic breast cancer, digoxin treatment led to a significant reduction in CTC cluster formation [22].

Another example is paxalisib (GDC-0084), a brain-penetrant PI3K/mTOR inhibitor. Ex vivo studies reported by Kazia Therapeutics demonstrated complete disruption of large CTC clusters in samples from patients with Stage IV HER2-positive breast cancer [23]. One possible mechanism is the inhibition of E-cadherin downregulation mediated by the PI3K/mTOR pathway [24]. Preliminary data from an ongoing phase 1b trial combining paxalisib with pembrolizumab and chemotherapy in metastatic triple-negative breast cancer showed rapid suppression of CTCs and CTC clusters, with a >50% reduction in CTC clusters observed in one case [25]. While these early signals are encouraging, it is important to note that they derive from small proof-of-concept or very early-phase studies. Larger, well-controlled trials are needed for confirmation.

Disrupting heterotypic cell-cell interactions: Targeting the heterotypic interactions that stabilize tumor microemboli provides an additional approach to impair cluster survival and metastatic seeding.
CAFs interact with tumor cells primarily through N-cadherin-mediated junctions, promoting and directing collective invasion [26]. In vivo studies have shown that ADH-1 (Exherin), a cyclic peptide antagonist of N-cadherin, induces a significant reduction in tumor growth and metastasis [27]. In phase I/II trials, ADH-1 was generally well tolerated; however, clinical efficacy was modest, with stable disease as the best response in most cases [28].

Neutrophils form heterotypic clusters with tumor cells through adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and CD44v on CTCs, and β2 integrin and L-selectin on neutrophils [29-31]. Although targeting these molecules can disrupt CTC-

neutrophil interactions, greater specificity for CTCs is required before clinical translation, given the important role of these molecules in immune defense [32]. An interesting therapeutic strategy that exploits the interaction between neutrophils and CTCs was tested by Kang et al. They developed nanoparticles coated with neutrophil membranes containing proteasome inhibitors [33]. This nanoformulation selectively induced in vivo depletion of CTCs in the blood and prevented early metastasis.

Platelets play a central role in the formation and stabilization of tumor microemboli. Upon entering the bloodstream, CTCs rapidly recruit platelets, forming heterotypic tumor cell-platelet clusters [34]. Platelet receptors, including C-type lectin-like receptor 2 (CLEC-2), P-selectin, and integrins α6β1 and αIIbβ3, mediate interactions with tumor cells by binding to podoplanin, P-selectin glycoprotein ligand-1 (PSGL-1), a disintegrin and metalloproteinase domain-containing protein 9 (ADAM-9), and fibrinogen/αvβ3, respectively [35]. Platelets provide physical shielding against shear stress and natural killer (NK) cell-mediated cytotoxicity, while simultaneously delivering pro-survival signals through the release of growth factors (e.g., TGF-β, PDGF) and activation of the NF-κB and PI3K/AKT pathways in tumor cells [36,37]. These clusters exhibit enhanced anoikis resistance, immune evasion, and metastatic seeding efficiency compared with single CTCs.

Targeting platelet-tumor cell interactions represents a promising and clinically accessible strategy. Several antiplatelet agents already used in clinical practice have demonstrated anti-cluster activity. Low-molecular-weight heparin and unfractionated heparin interfere with P-selectin- and integrin-mediated binding, thereby disrupting heterotypic cluster formation and reducing metastasis in experimental models [38]. Aspirin, through irreversible inhibition of COX-1 and suppression of thromboxane A2-mediated platelet activation, has been shown to prevent platelet recruitment to CTCs and limit microemboli formation [39]. A meta-analysis demonstrated that aspirin reduced the incidence of metastasis in solid cancers, particularly colorectal cancer [40].

Optimal Therapeutic Timing and Context for Targeting Tumor Microemboli

We propose a therapeutic approach guided by the size and composition of tumor microemboli and by the clinical context. We suggest that smaller CTC clusters are more likely to rely on dormancy mechanisms or PMN priming for successful metastasis. Targeting these later events may therefore be more effective than early intervention against small clusters. In contrast, larger heterotypic clusters exhibit greater immediate metastatic potential and are more likely to benefit from tumor microemboli-specific therapeutics.

The optimal timing for intervention is defined either by direct detection of CTC clustering or by clinical prediction in high-risk settings. These high-risk contexts include the postoperative period following resection of highly invasive tumors and the use of therapies that may inadvertently promote cluster formation, such as certain anti-angiogenic agents. Histopathologic features, such as strong plakoglobin expression at the invasive front of the primary tumor, may further indicate an elevated risk of tumor microemboli dissemination [41].

Finally, these suggestions remain hypothetical at present. Incorporating them into clinical trials evaluating agents directed against tumor cell clusters, such as low-molecular-weight heparin, aspirin, and digoxin, will be essential to validate this timing- and context-dependent strategy.

Premetastatic niches

The formation of PMNs represents one of the earliest and most critical steps in the metastatic cascade. First conceptualized by Paget's "seed and soil" hypothesis over a century ago, the modern framework of the PMN was established by Kaplan et al. in 2005, who demonstrated that bone marrow-derived hematopoietic progenitor cells (HPCs) are recruited to distant sites prior to the arrival of tumor cells, thereby initiating a permissive microenvironment for subsequent metastatic colonization [42]. Primary tumors actively remodel future metastatic organs through the systemic release of tumor-derived secreted factors (TDSFs), including VEGF, TGF-β, tumor necrosis factor-alpha (TNF-α), as well as tumor-derived exosomes and extracellular vesicles, which induce profound cellular and molecular changes at selected permissive distant sites [43,44]. The permissivity of these sites may be explained by differences in the expression of certain factors among tissues, such as the COX-2/PGE_2 pathway that potentiates the effects of these TDSFs [45]. TDSFs induce the secretion of chemokines by host tissues that lead to the recruitment of immunosuppressive cells, notably myeloid-derived suppressor cells (MDSCs), and eventually tumor cells, thereby establishing a metastatic site [43].

In this paper, we review a simplified version of this cascade for illustration (Figure *1*). TNF-α induces the secretion of S100A8/A9, considered as the amplification node, CCL2 and CXCL12 in selective sites characterized by overexpression of COX-2. These chemokines attract MDSCs that create a permissive immunotolerant milieu, as well as CTCs. The available therapeutics and suggested optimal timing of intervention will be discussed.

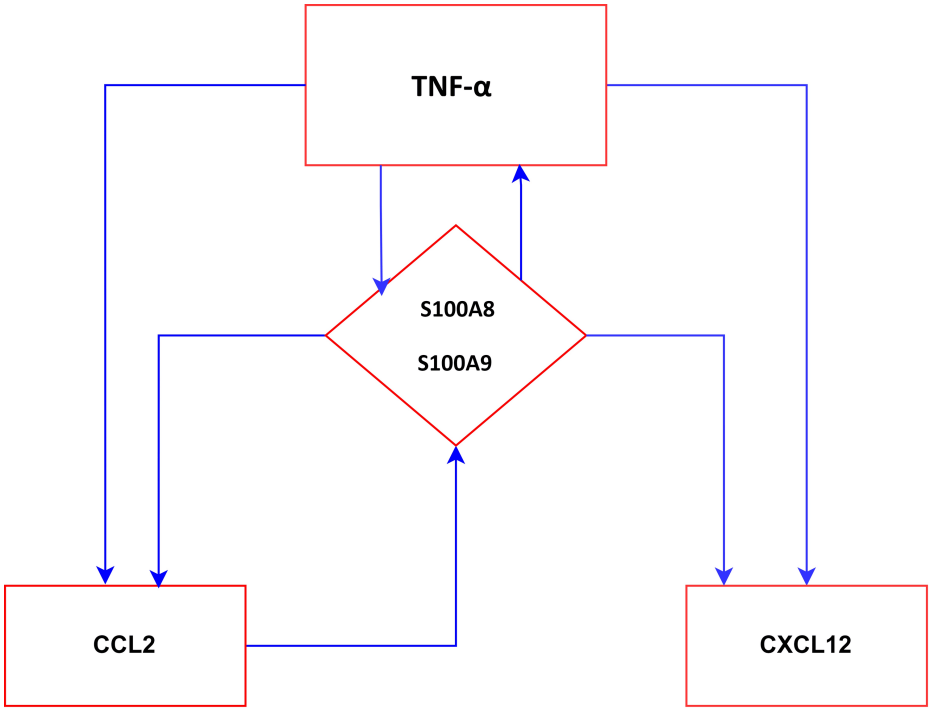


FIGURE 1: Diagram illustrating the stimulatory effects between soluble factors responsible for premetastatic niche formation

TNF-α: Tumor necrosis factor-alpha

TNF-α

Although TNF-α is a key proinflammatory cytokine involved in the homeostasis of the immune system and host defense, it also contributes to the induction of PMNs at distant organ sites [46,47]. Secreted by tumor cells, tumor-associated macrophages, and other stromal components, TNF-α cooperates with VEGF-A and TGF-β to induce the expression of chemoattractants, such as S100A8/S100A9, CCL2, and CXCL12, both directly and via inflammation induction [43,46].

Preclinical studies have shown a paradoxical antimetastatic effect of TNF-α inhibitors [48]. The TICIMEL trial is a phase Ib clinical trial combining anti-TNF-α agents (infliximab or certolizumab) with the immune checkpoint inhibitors (nivolumab or ipilimumab) in patients with advanced melanoma [49]. This combination has shown biological activity consisting of activation and maturation of systemic T-cell responses. Although it is a small cohort in a phase Ib safety trial, the clinical response is encouraging. in the certolizumab arm, seven out of seven evaluable patients achieving an objective response, including four complete responses (CRs) and three partial responses (PRs).

Anti-TNF-α agents are associated with a decreased risk of certain malignancies such as prostate carcinoma, non-Hodgkin lymphoma, and leukemia, but they are linked to an increased risk of cutaneous melanoma and basal cell carcinoma in patients with systemic immune disorders [50]. In the TICIMEL study, with a median follow-up of 20 months, no such cases were reported. However, screening with total-body skin examinations for patients receiving TNF-α inhibitors is still suggested by some authors [50]. This safety concern also highlights the relevance of defining the optimal timing for introducing anti-TNF-α therapy, as will be discussed later, to prevent the risks of long-term exposure.

COX-2/PGE_2 Pathway

The contribution of the COX-2/PGE_2 pathway to site-specific PMN formation is supported by three converging lines of evidence. First, COX-2 is induced in distant organs by primary tumor-derived factors such as TNF-α and IL-1β ,through NF-κB-dependent transcriptional activation in resident stromal cells [45,51]. Second, differential expression of COX-2 exists across tissues and depends on localization and inflammation status [45,52,53]. Third, PGE_2 actively primes the PMN by recruiting MDSCs and impairing dendritic cell (DC) maturation and function, thereby generating an immunosuppressive milieu conducive to tumor cell seeding [45]. Genetic ablation of Ptgs2 and EP2/EP4 antagonism reverses these immunosuppressive phenotypes and significantly reduces metastatic burden in preclinical models [45]. Collectively, these findings provide solid arguments for the role of COX-2/PGE_2 in the preferential

development of PMNs and highlight this axis as a promising targetable vulnerability in the early establishment of PMNs.

Clinical trials using COX-2 inhibitors, such as the European Celecoxib Trial in Primary Breast Cancer (REACT), have not shown significant benefit for breast cancer patients, in contrast to experimental data [54]. A plausible explanation is the incomplete blockade of the axis by COX-2 inhibitors due to compensatory effects of the COX-1 isoform. The combination of EP2 and EP4 inhibitors is encouraged to ensure more complete suppression [45]. In the context of targeting the PMN, we also emphasize the necessity of correctly identifying the timing, as will be discussed later, to gain greater benefits.

S100A8/A9

The S100A8/A9 heterodimer appears to function as a central amplification node in the PMN cytokine cascade. It is secreted by activated myeloid cells and tissue-resident cells in response to primary tumor-derived factors such as TNF-α, while it also potentiates TNF-α secretion [55,56]. S100A8/A9 signals through TLR4 and RAGE to activate NF-κB, which in turn drives the expression of downstream chemokines including CCL2 and CXCL12 [45,57]. Reciprocally, CCL2 can further stimulate S100A8/A9 release from newly recruited myeloid cells, establishing a positive feedback loop [58]. Beyond its chemotactic role, S100A8/A9 promotes niche formation by increasing vascular permeability and remodeling the extracellular matrix, thereby facilitating subsequent tumor cell adhesion [59,60].

Genetic deletion or pharmacological inhibition of S100A8/A9 significantly reduces MDSC accumulation and dampens inflammatory signaling [61,62]. Experimental studies of tasquinimod, an oral agent that binds to S100A9 and blocks the interaction of this ligand with its receptors, have confirmed its inhibitory effect on immunosuppression and MDSC function [63]. A phase II randomized trial of tasquinimod in men with minimally symptomatic metastatic castration-resistant prostate cancer showed that it significantly slowed progression and improved progression-free survival [64]. A phase III study of tasquinimod in men with metastatic castration-resistant prostate cancer showed that it significantly improved radiographic progression-free survival compared with placebo, but no overall survival benefit was observed [65]. In contrast, a phase II multicenter study of tasquinimod in hepatocellular, ovarian, renal cell, and gastric cancers failed to demonstrate clinical activity in those heavily pre-treated patients [66]. It should be noted that the latter study enrolled patients with advanced overt metastases, while, as will be discussed later, the proposed optimal timing based on mechanistic rationale would be at the PMN stage, before the establishment of overt metastasis.

CCL2

CCL2, in response to inflammatory signals such as TNF-α and TGF-β, plays a central role in recruiting CCR2-expressing inflammatory monocytes and MDSCs to distant sites [45]. These cells induce local immunosuppression and promote vascular permeability, thereby creating a permissive niche for subsequent tumor cell seeding [67]. Blockade of CCL2 or CCR2 using neutralizing antibodies, small-molecule inhibitors (e.g., propagermanium or PF-04136309), or genetic approaches significantly reduces MDSC recruitment, S100A8/A9 expression, and metastatic burden in multiple preclinical models of breast, colorectal, and pancreatic cancer [68,69]. These findings support the therapeutic potential of CCL2/CCR2 inhibition as an upstream preventive intervention against PMN formation. The outcome of ongoing early-phase clinical trials may elucidate the clinical impact of targeting CCL2/CCR2 [70].

CXCL12

Targeting the CXCL12/CXCR4 axis is a promising strategy to interfere with PMN formation and disrupt organ-specific metastatic homing. CXCL12 (also known as SDF-1), produced by stromal cells, fibroblasts, and endothelial cells in distant organs, creates chemotactic gradients that recruit CXCR4-expressing immunosuppressive cells and tumor cells to future metastatic sites [71,72]. Pharmacological blockade using CXCR4 antagonists such as plerixafor (AMD3100), NOX-A12 (an RNA aptamer), or small-molecule inhibitors has been shown to significantly decrease metastatic burden in preclinical tumor models, notably NSCLC [73,74]. Given the clinical tolerability and proven CXCR4 inhibition of plerixafor in humans, this drug represents an attractive opportunity to test its preventive effect on PMN formation and metastasis development, notably if optimal timing and context, as will be suggested, are applied [75].

Before discussing the timing of PMN targeting, we first review promising imaging techniques for PMN detection that, when incorporated into clinical settings, may help in therapeutic decision-making.

Premetastatic Niche Imaging

S100A8/A9 imaging: Eisenblaetter et al. (2017) developed an antibody-based single-photon emission computed tomography (SPECT) probe targeting S100A9 [58]. The probe consisted of a specific anti-S100A9 antibody radiolabeled with ^{111}In. In syngeneic murine models of breast cancer (highly metastatic 4T1.2 vs. non-metastatic 67NR), SPECT/CT imaging demonstrated significantly higher probe uptake in premetastatic

lungs of metastatic tumor-bearing mice compared with controls, detectable prior to tumor cell arrival. Signal intensity quantitatively correlated with subsequent metastatic burden ($r^2 = 0.788$; $p < 0.0001$). Ex vivo validation confirmed co-localization of the probe with S100A8/A9-positive MDSCs and fibronectin-rich stromal regions, supporting specificity for the molecularly primed niche. Importantly, the imaging signal was markedly reduced upon pharmacological inhibition of niche formation (e.g., CCL2 blockade), demonstrating utility not only for early detection but also for monitoring therapeutic response. This work establishes S100A8/A9-directed molecular imaging as a powerful approach to identify the PMN at its earliest functional stages, offering a valuable tool for studying metastasis prevention strategies and potential clinical translation.

^{18}F-labeled VEGFR-1 imaging: Another molecular imaging strategy for the PMN targets vascular endothelial growth factor receptor-1 (VEGFR-1), which is highly expressed on bone marrow-derived HPCs and myeloid cells that are among the earliest cellular constituents of the niche. In a key study, Mason et al. developed an ^{18}F-labeled single-chain VEGF mutant (scVR1) re-engineered for selective binding to VEGFR-1 [76]. This protein-based tracer ([^{18}F]AlF-NODA-scVR1), prepared via site-specific click chemistry, was evaluated in murine models of metastatic breast cancer (orthotopic 4T1). PET/CT imaging demonstrated uptake in the lungs and metastatic sites, enabling visualization of VEGFR-1$^+$ cell clusters prior to or during early metastatic colonization. Signal intensity correlated with metastatic burden, and ex vivo autoradiography and immunofluorescence confirmed co-localization with VEGFR-1$^+$ CD11b$^+$ myeloid cells in fibronectin-rich regions of the primed microenvironment. These findings position ^{18}F-labeled VEGFR-1 PET imaging as a promising non-invasive tool for identifying active niche priming and guiding metastasis-preventive interventions.

Positron emission tomography-computed tomography: Mabuchi and colleagues demonstrated that pretreatment tumor-related leukocytosis, a paraneoplastic phenomenon frequently observed in gynecological malignancies, significantly reduces the specificity of ^{18}F-FDG PET/CT during lymph node staging by generating false-positive findings in benign, inflammatory lymph nodes [77]. The underlying mechanism involves tumor-derived G-CSF-driven systemic mobilization of metabolically active MDSCs and neutrophils, which accumulate in draining lymph nodes and exhibit high glucose uptake, mimicking the metabolic signature of metastatic disease. This observation has direct implications for PMN detection. The false-positive lymph nodes identified in their study represent sites of MDSC-mediated immunological priming by tumor-derived factors. These are closely resembling the cellular and molecular features of the PMN, including recruitment of immunosuppressive myeloid populations and abundant expression of proinflammatory alarmins such as S100A8/A9, prior to the arrival of DTCs. Consequently, these metabolic similarities between inflammatory lymph nodes and PMNs make it plausible that ^{18}F-FDG PET/CT may detect metabolically active niche formation. This remains a hypothesis that warrants further investigation.

The Timing of Targeting Premetastatic Niches

The optimal window for targeting the PMN may be defined by the elevation of early TDSFs (e.g., circulating TNF-α or tumor-derived exosomes with organotropic integrin signatures) in patients with tumors having a high risk of metastasis, in the absence of clinically detectable metastases.

In this window, the choice of molecular target can be guided by premetastatic imaging (e.g., S100A8/A9-SPECT/PET) and by the pattern of chemokine upregulation. When only early mediators such as TNF-α are elevated and downstream chemokines (CCL2, CXCL12) remain low, interventions directed against early factors such as TNF-α, the COX-2/PGE_2 pathway, and S100A8/A9 are mechanistically plausible. Conversely, if late chemokines are already upregulated, particularly when accompanied by imaging evidence of an established PMN, the therapeutic emphasis should shift toward blocking the chemokine axes such as CCL2 and CXCL12 that directly drive MDSC recruitment and tumor cell homing.

Tumor dormancy

Tumor dormancy represents the persistent stage of the metastatic cascade, during which DTCs survive in a non-proliferative or balanced state at distant sites for months to decades before reactivating to form clinically detectable metastases [78,79]. In this phase, DTCs typically reside in specialized niches such as the bone marrow, lung, or liver, maintained in quiescence through intrinsic mechanisms (e.g., p38/ERK signaling imbalance, autophagy, and epigenetic reprogramming via NR2F1) and extrinsic pressures including immune surveillance and angiogenic suppression [4,78]. This dormant reservoir is widely recognized as the primary source of late cancer relapse and treatment failure.

The activation of the indoleamine 2,3-dioxygenase (IDO)/kynurenine/aryl hydrocarbon receptor (AhR) axis is among the immune-mediated pathways leading to dormancy [80]. It is triggered by inflammatory signals, particularly interferon-gamma (IFN-γ) released by immune cells. This stimulus upregulates IDO1, a rate-limiting enzyme that degrades the essential amino acid tryptophan (Trp) into kynurenine (Kyn). Kyn acts as a ligand, binding to and activating the AhR in the cytoplasm. The AhR then translocates to the nucleus. In the nucleus, the activated AhR complex directly induces the expression of p27, a cyclin-dependent kinase inhibitor. This is the critical molecular switch that enforces cell-cycle arrest, driving cells into a quiescent, dormant G0 state.

Dormant tumor cells can be detected by lymph node biopsies and bone marrow aspirates. Markers such as cytokeratins and EpCAM for epithelial cancers and gp100 for melanoma are used to identify these tumor cells [81,82]. These techniques are used in clinical trials targeting dormant tumor cells, such as the phase II CLEVER trial [83]. However, some concerns have been raised by experts regarding the underestimation of DTCs by available techniques and the tendency to equate dormant DTCs with DTCs during the detection procedure [82].

Therapeutic and Timing of Intervention

From a conceptual standpoint, tumor dormancy may represent a residual mechanism of metastasis that becomes particularly relevant when PMN formation is limited, and tumor cells have not disseminated as multicellular microemboli. This corresponds generally to the remission state after a timely eradication of the primary tumor, in the absence of detected large tumor cell clusters and PMN establishment. The timing of therapeutic intervention is divided according to the presence or the absence of detectable dormant cells (Figure *2*).

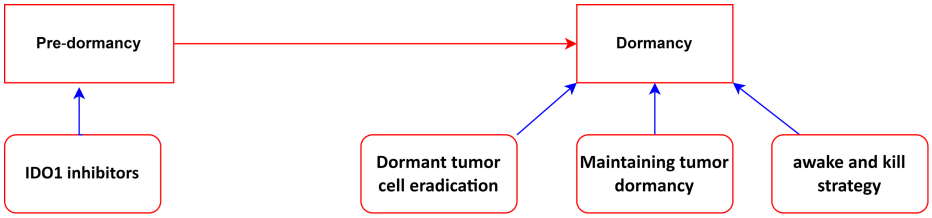


FIGURE 2: Therapeutic strategies for tumor dormancy

Targeting tumor dormancy mechanisms before the establishment of dormant tumor cells: Targeting the molecular pathways that drive DTCs into dormancy before they fully settle into a quiescent state represents a proactive strategy to limit the formation of de novo metastasis. A proposed "pre-dormancy therapeutic window" can be defined by the presence of CTCs in the absence of detectable quiescent DTCs in bone marrow or distant tissues.

One candidate pathway for intervention in this window is the IDO1/kynurenine/AhR axis, as discussed above. IDO1 inhibitors such as epacadostat demonstrated pharmacodynamic activity and acceptable tolerability in early-phase trials [84]. Also, their combination with PD-1 blockade showed encouraging signals in Phase I/II studies [85]. The large phase III ECHO-301/KEYNOTE-252 trial in subjects with unresectable or metastatic melanoma failed to improve response rates, progression-free survival, or overall survival [86]. However, these trials were designed to reverse immunosuppression in established disease rather than to prevent dormancy induction.

For a dormancy-prevention strategy to be rationally tested, several conditions would need to be met. First, the tumor type should be expected to rely on dormancy-driven late relapse, by verifying the absence of detectable PMNs and tumor microemboli. Second, patients should be selected in a pre-dormancy state, attested by the absence of detectable tumor dormant cells. Finally, the primary endpoint should focus on long-term relapse prevention after definitive therapy rather than short-term tumor shrinkage. Meeting these hypothetical criteria is technically and clinically demanding, rendering this approach highly selective.

Targeting tumor dormancy mechanisms after the establishment of dormant tumor cells: Once DTCs have entered a dormant state, therapeutic strategies often shift toward either direct eradication, maintaining dormancy, or employing an "awake and kill" approach.

Eradication of dormant tumor cells: Dormant cells are uniquely dependent on catabolic and stress-adaptive metabolic programs, notably autophagy and fatty acid oxidation [87,88]. Pharmacological disruption of these pathways, such as blocking autophagy with hydroxychloroquine (HCQ), leads to apoptosis of dormant tumor cells [87]. A phase II clinical trial of HCQ and everolimus (an mTOR inhibitor) in breast cancer survivors within five years of diagnosis who had detectable DTCs on bone marrow aspirate showed that the treatment is tolerable and led to reduced or undetectable DTCs compared with observation alone [83]. This trial provides proof of concept that direct targeting of dormant tumor cell metabolic pathways can be effective in depleting minimal residual disease. However, larger phase III trials are needed to confirm these encouraging results.

Maintaining tumor dormancy: Because dormant cell reactivation is thought to be triggered by changes in the niche, most notably inflammation, maintaining long-term dormancy may be achieved by suppressing the inflammatory effects on dormant cells. However, targeting all inflammatory stimuli on DTCs is challenging, given the multiplicity of mechanisms involved. Nevertheless, in a well-defined temporal window where a dominant mediator operates, such as the postoperative IL-6 surge that awakens DTCs, targeted intervention

is conceivable [89,90]. Immunotherapeutic targeting of the IL-6 receptor (IL-6R) has been shown to prevent relapse and metastasis of triple-negative breast cancer in orthotopic syngeneic mice [91].

An alternative proposed strategy is ensuring the timely reinduction of dormancy after awakening. This is derived from the speculation that metastasis is not just an inflammation-induced awakening of dormant tumor cells, but a failure of the immune system to rapidly reinduce dormancy. In support of this hypothesis, inflammatory events with the potential to induce tumor awakening seem more frequent than the development of metastasis, notably in organs such as the lungs. This resembles the recurrent episodes of reactivation of herpes simplex virus, that are attenuated by the immune system. For tumor cells, one strategy to ensure the timely reinduction of dormancy would be by maintaining the presence of an IFN-γ-secreting T-cell pool (notably memory T cells), given their role in dormancy induction.

A limiting step in applying this strategy is quantifying the presence of memory T cells in potential dormancy sites and, if absent, to consider replenishing the stock. Assessing the presence and functional state of memory T cells, particularly tissue-resident memory T (TRM) cells, within dormant tumor niches is technically demanding, limiting routine clinical use. In tissue biopsies, multiplex immunohistochemistry or flow cytometry enables the simultaneous detection of memory T cell-defining markers (CD103, CD69, CD49a, and CD8) alongside dormant tumor cells. The main practical challenges remain the low frequency of antigen-specific T cells, which pushes detection limits, and the absence of a single lineage-defining marker for memory T cells, necessitating combinatorial panels [92].

If the host's endogenous pool of tumor-specific memory T cells proves lacking, it may be replenished by emerging therapeutic strategies such as immune vaccines and adoptive cell immunotherapy. Vaccines have shown encouraging results in preclinical and clinical studies. A prime-and-boost strategy consisting of tumor DNA priming immunization followed by a mucosal intranasal boost induces lung-resident memory $CD8^+$ T cells derived from central memory T cells that prevent tumor lung metastasis [93]. In clinical settings, an approach that uses multi-epitope, personalized neoantigen vaccination generated circulating polyfunctional neoantigen-specific $CD4^+$ and $CD8^+$ T-cell responses that were enriched in a memory phenotype and showed an increase in the number of tumor-infiltrating T cells, translating to antitumoral effects [94].

As for DC-based vaccination, recent preclinical work has demonstrated that vaccines composed of conventional type-1 dendritic cells (cDC1s) pulsed with tumor lysates induce a robust effector and memory $CD4^+$ and $CD8^+$ T-cell response, notably increasing tissue-resident memory $CD4^+$ T-cell infiltrates with a preventive effect on tumor relapse in postsurgical models [95]. In a phase I trial of a personalized neoantigen-targeted DC vaccine in resected non-small cell lung cancer, the vaccine induced durable T-cell responses detectable up to 19 months post-vaccination. Single-cell analyses revealed that responding T cells spanned the full spectrum of differentiation states, including naïve-like and stem-cell memory populations associated with long-lived immunity [96].

Chimeric antigen receptor (CAR) T cell therapy is a form of adoptive cell therapy that seeks to engineer or select for TRM-like phenotypes. Jung et al. have reported success in generating tissue-resident memory CAR T cells with stem-like characteristics by exposing patient T cells to TGF-β during the engineering process. These cells display enhanced efficacy against solid and liquid tumors with resistance to exhaustion [97]. Although conducted in hematological rather than solid tumors, a recent clinical trial (Gattinoni et al., 2026) showed that CAR-modified stem-cell memory T cells exhibited greater expansion and persistence than standard CAR T cells, enabling complete responses with mild cytokine-release syndrome dominated by IFN-γ [98].

Awake and kill strategy: The "awake and kill" paradigm seeks to eliminate dormant tumor cells by first forcing their exit from quiescence, thereby rendering them susceptible to antiproliferative agents that spare non-cycling cells. Although this strategy carries the risk that the awakened cells may acquire invasive properties and disseminate, studies of this combination are encouraging. The addition of a phosphatase 2A inhibitor, a reawakening agent, to chemotherapy and radiation in head and neck squamous cell carcinoma led to enhanced anticancer activity [99]. A constructed conjugate of docetaxel (DTX) and a heptapeptide (P7) preferentially suppressed tumor growth compared with DTX in vivo [100]. According to the authors, this conjugate demonstrates a "proliferate to kill" mechanism by promoting cell-cycle reentry of slow-proliferating dormant cancer stem-like cells and subsequently killing them.

Conclusions

In this review, we have examined three fundamental mechanisms that enable DTCs to colonize distant organs: tumor microemboli, PMN formation, and tumor dormancy. We discussed current and emerging therapeutics targeting each of these processes and argued for a shift toward a timing-oriented and personalized therapeutic strategy. Rather than applying uniform interventions, treatment should be guided by the more likely responsible mechanism operating in each patient and by the time window for each therapy. Carefully designed clinical trials that incorporate both timing and mechanism selection will be essential to validate this approach and to move metastasis prevention closer to clinical reality.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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