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Understanding Tumor Dormancy: from Experimental Models to Mechanisms and Therapeutic Strategies

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Abstract

Tumor dormancy represents a clinically significant but poorly understood state in which disseminated cancer cells persist in a quiescent, non-proliferative state, evading conventional therapies and driving late relapse. This review summarizes recent advancements in experimental models—both *in vitro* and *in vivo*—that recapitulate the full spectrum of dormancy, including its induction, maintenance, and reactivation. Crucial intrinsic pathways such as ERK/p38 signaling shifts, epigenetic remodeling, and metabolic adaptations and microenvironmental and immune-mediated cues that regulate dormant cell fate are discussed. Therapeutic strategies aimed at maintaining dormancy, reactivating dormant cells for elimination, or directly targeting their survival pathways have been highlighted. By integrating insights from model systems, molecular regulation, and therapy, this review aims to provide a comprehensive framework that informs future efforts to target dormant cancer cells and ultimately reduce recurrence and improve patient outcomes.

Key Words: Tumor dormancy, Dormancy models, Dormancy reactivation, Tumor microenvironment

INTRODUCTION

One of the hallmarks of cancer cells is their ability to proliferate rapidly and continuously, in contrast to normal cells (Hanahan and Weinberg, 2011). However, certain subgroups of cancer cells exhibit a remarkably atypical phenomenon: cell cycle arrest during specific stages or under particular conditions. Such periods of slowed proliferation have been observed in disseminated tumor cells (DTCs) that migrate to secondary sites and remain dormant before reactivating to form metastatic lesions or in minimal residual disease (MRD), where cancer cells survive in undetectable quantities after cancer therapy (Sosa *et al*., 2014; Yeh and Ramaswamy, 2015). Intriguingly, recent studies suggest that these slow-cycling cancer cells may already exist as a subset within the primary tumor from its initial stages (Basu *et al*., 2022). The phenomenon of cancer cells temporarily halting proliferation is not unique to cancer. Similar cell cycle arrest is also observed during the early stages of human development, where cells deliberately enter a quiescent state as part of tightly regulated developmental programs (Wilson *et al*., 2008, 2009). This striking resemblance suggests that dormant cancer cells (DCCs) may hijack fundamental developmental processes to ensure survival and dissemination, adding a fascinating dimension to the study of tumor biology.

Tumor dormancy refers to a dynamic and reversible state in which cancer cells enter a period of cell cycle arrest and remain in a non-proliferative or slowly cycling state for extended periods without forming overt lesions. This state can occur either at the single-cell level, known as cellular dormancy, where individual tumor cells are quiescent (G0 phase), or as tumor mass dormancy, characterized by a balance between cell proliferation and death within an avascular or immune-restricted microenvironment (Aguirre-Ghiso, 2007; Sosa *et al*., 2014). Key biological features of tumor dormancy include resistance to chemotherapy due to lack of proliferation, dependence on stress-adaptive signaling pathways such as p38 MAPK, altered metabolic activity, epigenetic reprogramming, and interaction with dormancy-permissive niches in distant organs (Vera-Ramirez *et al*., 2018; Basu *et al*., 2022; Rosano *et al*., 2024). Whether arising from therapy-resistant cancer cells or disseminated cells that survived the metastatic cascade, DCCs pose a significant challenge in oncology, as they can evade detection and therapy for years and eventually trigger metastatic relapse, leading to poor clinical outcomes and reduced patient survival (Weaver *et al*., 2011). Despite the

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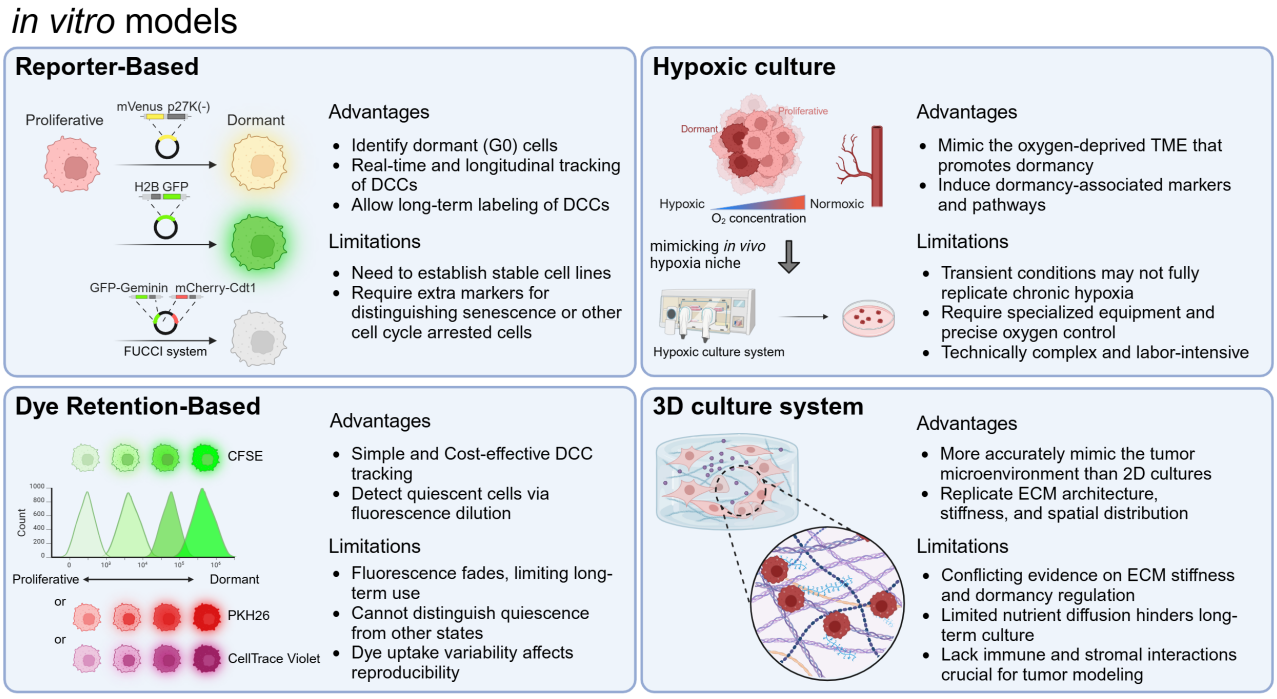

Fig. 1. *In vitro* models for studying tumor dormancy. Reporter-based and dye retention-based methods allow for visualization and tracking of quiescent cells based on cell cycle status or dye dilution. Hypoxic and 3D culture systems mimic dormancy-inducing microenvironmental cues, such as low oxygen tension and extracellular matrix architecture. Each model offers unique advantages in recapitulating dormancy-associated features but also presents limitations in terms of physiological relevance, technical complexity, or long-term tracking. H2B, Histone H2B; GFP, Green fluorescent protein; Cdt1, Chromatin licensing and DNA replication factor 1; DCC, Dormant cancer cells; FUCCI, Fluorescent ubiquitination-based cell cycle indicators; TME, Tumor microenvironment; CFSE, Carboxyfluorescein succinimidyl ester; ECM, Extracellular matrix.

growing recognition of their importance, there are currently no FDA-approved therapies specifically targeting DCCs. Therefore, a comprehensive understanding of the biology of DCCs is imperative for the development of effective therapeutic strategies aimed at preventing cancer recurrence and improving long-term survival in cancer patients (Ganesh and Massague, 2021; Liu *et al*., 2024).

EXPLORING EXPERIMENTAL MODELS FOR TUMOR DORMANCY

Despite its critical implications in metastasis, recurrence, and patient prognosis, the study of DCCs has been limited by several intrinsic challenges. These include the difficulty in isolating dormant cells from patients, their low abundance below diagnostic thresholds, and the lack of experimental models capable of replicating the complete life cycle of DCCs—from dormancy induction to reactivation (Agudo *et al*., 2023). However, recent advancements have led to the development of various *in vitro* and *in vivo* models that allow researchers to investigate the molecular mechanisms governing tumor dormancy and to test potential therapeutic strategies. This section discusses these experimental models, with an emphasis on their applications, advantages, and limitations.

In vitro models

In vitro systems provide controlled environments to study tumor dormancy at the cellular and molecular levels, enabling high-resolution analysis of cancer cell-intrinsic mechanisms. These models offer flexibility in manipulating specific signaling pathways, microenvironmental factors, and cell states, which is challenging to achieve *in vivo*. Although they lack the full complexity of the tumor microenvironment (TME), *in vitro* models remain indispensable for identifying dormancy markers, screening drugs, and dissecting mechanisms of cell cycle arrest and reactivation. A variety of platforms have been developed to model dormancy, each with distinct advantages and limitations depending on the experimental objective (Fig. 1). The following sections highlight key *in vitro* approaches, including reporter-based systems, dye retention assays, hypoxic culture, and 3D culture models.

Reporter-based models: Reporter-based models have emerged as essential tools for studying DCCs *in vitro*. These models utilize fluorescent or luminescent reporters to mark quiescent/dormant cells based on their unique molecular and cellular characteristics, enabling dynamic and longitudinal observation of DCC behavior. For example, the mVenus-p27K(-) probe has been widely adopted as a reporter for quiescence due to its ability to highlight cells expressing p27, a key cell cycle inhibitor upregulated in G0-phase cells (Oki *et al*., 2014). Additionally, H2B-GFP-based reporters allow for the long-term labeling of cells by tagging histone proteins with fluorescent markers, providing insights into the persistence of quiescent states in heterogeneous cancer populations (Kanda *et al*.,

1998). FUCCI systems (Fluorescent Ubiquitination-based Cell Cycle Indicators) represent another advanced method, distinguishing between G1, S, and G2-M phases using color-coded fluorescence, while indirectly identifying G0 cells based on the absence of fluorescence (Sakaue-Sawano *et al*., 2008). Such reporter models facilitate real-time tracking of quiescence induction, maintenance, and reactivation within complex cellular environments. While these reporter models offer significant advantages, they also come with certain limitations. Many reporter constructs require the generation of stable cancer cell lines, which may not accurately reflect the heterogeneity of primary tumors. Furthermore, distinguishing between true quiescence and other non-proliferative states, such as senescence or drug-induced cell cycle arrest, often necessitates additional markers or experimental validation. Nevertheless, reporter-based systems remain invaluable for elucidating the dynamic processes underlying tumor dormancy and for identifying potential therapeutic targets.

Dye retention-based models: Dye retention methods represent a distinct approach for studying quiescent or DCCs *in vitro*. Unlike reporter-based systems, these methods utilize fluorescent dyes to label cells based on their division rates. CFSE (carboxyfluorescein succinimidyl ester) and CellTrace Violet are cell-permeable dyes that bind to intracellular proteins, whereas PKH26 is a lipophilic dye that intercalates into the cell membrane (Azari *et al*., 2018; Begum *et al*., 2013; Horan and Slezak, 1989). In both cases, as the fluorescent signal becomes progressively diluted with each cell division, researchers can distinguish between rapidly dividing cells and those that cycle more slowly or remain quiescent. For example, CFSE has been widely used to track quiescent populations *in vitro*, providing a straightforward and cost-effective method for isolating slow-cycling cells (Cho *et al*., 2023). Non-fluorescent CFDA-SE (Carboxyfluorescein Diacetate-Succinimidyl Ester) freely diffuses into cells and is converted by intracellular esterases into a fluorescent compound CFSE, which then covalently binds to an amine group on intracellular proteins. Each cell division dilutes the CFSE by roughly half, allowing quiescent or slowly cycling cells to retain higher fluorescence. Similarly, CellTrace Viol*et al*so relies on a succinimidyl ester-based mechanism that covalently labels intracellular proteins and is progressively reduced with each round of cell division. PKH26 stably integrates into the cell membrane and when the cell divides, the labeled membrane is split between the daughter cells, halving the fluorescence in each generation. These dyes have demonstrated utility in heterogeneous cancer cell populations, thereby facilitating the study of their proliferation dynamics, survival mechanisms, and responses to environmental or therapeutic cues (Perego *et al*., 2020; Regan *et al*., 2021). While these methods are simple and effective, the fluorescence intensity diminishes over time in culture, restraining long-term studies, and these techniques often cannot distinguish quiescence from other non-dividing states, such as senescence or terminal differentiation, without additional markers. Additionally, variability in dye uptake and retention across cell types can introduce inconsistencies, necessitating rigorous controls and careful validation for reproducibility.

Hypoxic culture system: Although reporter-based methods and dye-retention assays allow researchers to identify DCCs within a heterogeneous tumor population, the *in vitro* culture conditions employed in these approaches differ substantially from the actual TME. To overcome this limitation, investigators have developed culture systems that more closely mimic the conditions under which DCCs naturally occur.

Hypoxia, a hallmark of the TME, is a critical factor in inducing and maintaining tumor dormancy (Butturini *et al*., 2019). DCCs—whether surviving post-therapy or disseminated to distant sites—often persist in poorly vascularized, oxygen-deprived niches, a phenomenon sometimes referred to as 'angiogenic dormancy'. By reducing oxygen concentrations (typically <1%), hypoxic chambers or incubators recapitulate these conditions *in vitro*, thereby promoting or sustaining dormancy for experimental study. Studies by Fluegen *et al*. revealed that tumors in hypoxic conditions upregulate dormancy markers such as TGFβ, NR2F1, and p27, driving quiescence in disseminated tumor cells (Fluegen *et al*., 2017). Hypoxic culture systems provide a controlled environment to study hypoxia-specific signaling pathways and facilitate the identification of hypoxia-responsive genes and proteins related to tumor dormancy. Nevertheless, hypoxic conditions are often transient and may not fully replicate the chronic hypoxia experienced *in vivo*. To address this limitation, cobalt chloride has been employed as an alternative to stabilize hypoxia-induced cellular responses, allowing researchers to investigate the cellular changes through sustained HIF1α expression (Lee *et al*., 2018). However, despite this alternative effort, *in vitro* hypoxia conditions often require specialized equipment for continuous monitoring of O_2 partial pressures, and meticulous calibration to prevent small fluctuations that could alter cellular phenotypes. Consequently, experimental setups can become technically complex and labor-intensive, limiting their accessibility and replicability.

Three-dimensional (3D) culture systems: Two-dimensional (2D) culture systems have been widely used as a fundamental method in cancer cell research. However, they represent an artificial environment that poorly reflects the complexity of *in vivo* conditions, posing significant challenges in translating *in vitro* findings into clinically relevant outcomes. To address these limitations, three-dimensional (3D) culture systems have been developed to better recapitulate the physiological and mechanical properties of the *in vivo* microenvironment. By utilizing 3D culture systems, researchers emulate the extracellular matrix (ECM) architecture and mechanical properties of the TME, providing a physiologically relevant context for studying tumor dormancy. Collagen-based hydrogels, Matrigel, and synthetic polymers have been widely used to recreate the dense ECM conditions that induce quiescence in cancer cells (Liu and Vunjak-Novakovic, 2016).

These 3D culture systems mimic native ECM stiffness and composition while allowing for the spatial distribution and heterogeneity of cancer cells. However, maintaining long-term cultures is challenging due to nutrient diffusion constraints, and the models often fail to replicate immune-tumor and stromal-tumor interactions, which are critical components of the TME.

In vivo models

Compared to *in vitro* models, *in vivo* models—primarily mouse models—offer several advantages, including the native interactions between cancer cells, stromal cells, and im-

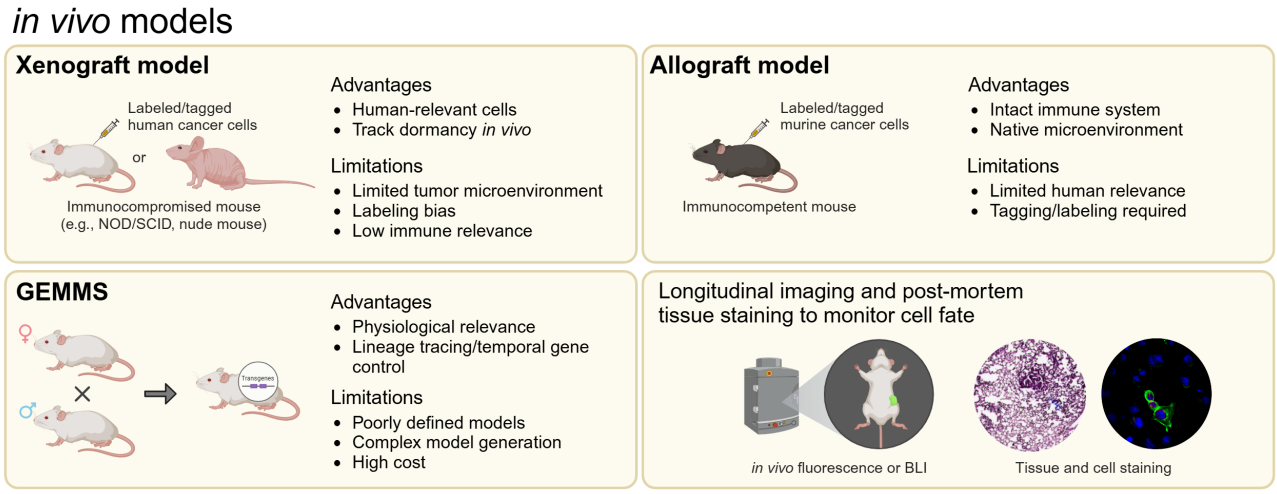

Fig. 2. *In vivo* models used to study tumor dormancy. Xenograft, allograft, and genetically engineered mouse models (GEMMs) represent key *in vivo* platforms for investigating the behavior of DCCs within a living organism. Each model offers unique advantages in terms of physiological relevance, immune system involvement, and clinical translatability. While xenograft models utilize human cancer cells in immunocompromised hosts, allografts and GEMMs allow dormancy studies in immunocompetent environments. Despite technical and biological limitations, these models enable longitudinal monitoring and endpoint analyses using *in vivo* imaging (e.g., fluorescence or bioluminescence) and post-mortem tissue staining to track cell fate and dormancy dynamics. NOD/SCID, Non-obese diabetic/severe combined immunodeficient mouse; GEMM, Genetically engineered mouse model; BLI, Bioluminescence imaging.

mune cells, all of which play a crucial role in tumor dormancy. Depending on the approach used to introduce dormant tumor cells *in vivo*, various model options are available. However, current *in vivo* models for dormancy research remain underdeveloped, and recent efforts have focused on establishing novel systems that faithfully recapitulate the critical processes of tumor dormancy and reactivation (Fig. 2) (Bushnell *et al*., 2021; Gu *et al*., 2022).

Xenograft and allograft models: Xenograft and allograft mouse models are widely used in cancer research and have also proven useful for studying tumor dormancy. These models allow researchers to introduce DCCs—isolated via *in vitro* procedures—into *in vivo* environments to assess their behavior and long-term fate. This enables the interrogation of how dormant tumor cells interact with stromal and microenvironmental components, particularly in metastatic niches.

In xenograft models, human cancer cells are typically introduced into immunodeficient mice, allowing for the evaluation of dormancy-associated traits in the absence of host immune rejection. For example, the U-87 glioblastoma cell line, enriched for dormancy-associated gene expression—characterized by elevated levels of thrombospondin-1 and insulin-like growth factor-binding protein 5 (IGFBP5)—was implanted into SCID mice to investigate dormancy-associated phenotypes, such as impaired angiogenesis and reduced invasive capacity (Satchi-Fainaro *et al*., 2012). Similarly, tumorigenic HEp3 and dormant HEp3 were injected into immunocompromised mice to investigate how DCCs persist in secondary sites in a quiescent state without forming overt metastases, partly through sustained p38 signaling and reduced ERK activity (Bragado *et al*., 2013).

DCCs can also be selected by applying *in vivo* selection pressures, such as chemotherapeutic treatments administered after tumor cell implantation. For instance, after subcutaneous injection of non-small cell lung cancer (NSCLC) cells, mice were treated with clinically relevant chemotherapy regimens, enabling the enrichment and longitudinal tracking of DCCs under physiologically relevant conditions. This strategy provides a valuable opportunity to examine how DCCs maintain quiescence and respond to environmental changes that drive relapse. Additionally, it allows researchers to capture dynamic features of tumor mass dormancy and characterize key interactions between DCCs and the surrounding stroma (Cho *et al*., 2020b, 2021).

Despite these advantages, xenograft models present limitations. The requirement for *in vitro* labeling (e.g., with fluorescent reporters or antibiotic resistance) may lead to selection bias and reduced cellular heterogeneity. Furthermore, the lack of a functional immune system in immunodeficient hosts constrains the exploration of immune-mediated regulation of dormancy, limiting the translational relevance of findings.

To address this limitation, allograft models, in which murine cancer cells are transplanted into immunocompetent syngeneic hosts, offer an additional layer of biological relevance. When used with label-retaining cells or reporter systems, these systems enable the study of DCCs–immune microenvironment interactions, including the role of immune surveillance in controlling metastatic latency. For example, the use murine mammary tumor cells expressing firefly luciferase and/or enhanced green fluorescent protein in immunocompetent BALB/c mice demonstrated that $CD8^+$ T cells suppress metastatic outgrowth by maintaining disseminated tumor cells in a dormant state (Goddard *et al*., 2024).

However, allograft models rely on syngeneic murine cancer cell lines, which may not fully capture the molecular complexity or heterogeneity of human tumors. As such, careful interpretation and complementary use of humanized or patient-derived xenograft models are required to bridge translational gaps.

Genetically engineered mouse models (GEMMs): GEMMs are powerful tools for studying tumor dormancy in a physiologically relevant context. These models incorporate specific genetic alterations found in human DCCs, enabling the study of DCCs within the native immune and stromal microenvironment. Unlike xenograft or allograft models, GEMMs preserve immune-tumor interactions and allow for lineage tracing and temporal control of gene expression, thereby providing a robust and dynamic platform for dormancy research (Richmond and Su, 2008).

Although no single GEMM has been universally accepted as the gold standard for dormancy research, a few transgenic models have demonstrated dormancy-like phenotypes based on insights from *in vitro* and clinical DCC analyses. For example, mammary tumor virus (MMTV)-driven transgenic models, such as MMTV–PyV mT or MMTV–ERBB2, when crossed with β1-integrin knockout mice, exhibited impaired tumorigenesis and persistence of residual, non-proliferative tumor cells in a dormant-like state (White *et al*., 2004; Bui *et al*., 2022). These DCCs showed increased p53 activation, leading to cell cycle arrest, senescence, and apoptosis, and displayed hallmark dormancy features such as low proliferation indices and elevated quiescence-associated markers (Bui *et al*., 2022).

In another approach, MMTV–rTA; TetO–NEU-NT mice were used to investigate HER2/neu (ERBB2)-driven breast tumors and its dormancy. This doxycycline-inducible system allows for the suppression of NEU expression in pre-established mammary tumors, simulating the withdrawal of oncogenic signaling. Upon withdrawal of NEU, tumor cells entered a prolonged dormant state, offering a tractable platform to examine both dormancy maintenance and eventual re-emergence upon NEU re-expression (Moody *et al*., 2002).

Despite their advantages, GEMMs for studying tumor dormancy remain relatively underdeveloped. This limitation is largely due to the incomplete understanding of the molecular mechanisms governing dormancy and the lack of well-defined genetic targets for manipulating this process. Given the critical role of the TME and immune system in dormancy regulation, further identification of key dormancy-associated genes and their functional validation through novel GEMMs will be essential.

REGULATORY MECHANISMS OF CANCER CELL DORMANCY: INDUCTION AND MAINTENANCE

When cancer cells encounter hostile conditions such as hypoxia, chemotherapy, nutrient deprivation, or immune attack, their fate bifurcates into two outcomes: survival or death. To evade elimination, cancer cells undergo profound reprogramming of intrinsic signaling pathways, enabling adaptation to these stressors (Ma and Hendershot, 2004; Payne, 2022). Survival under such adversity often involves entering a dormant state—a transient, reversible quiescence—that permits

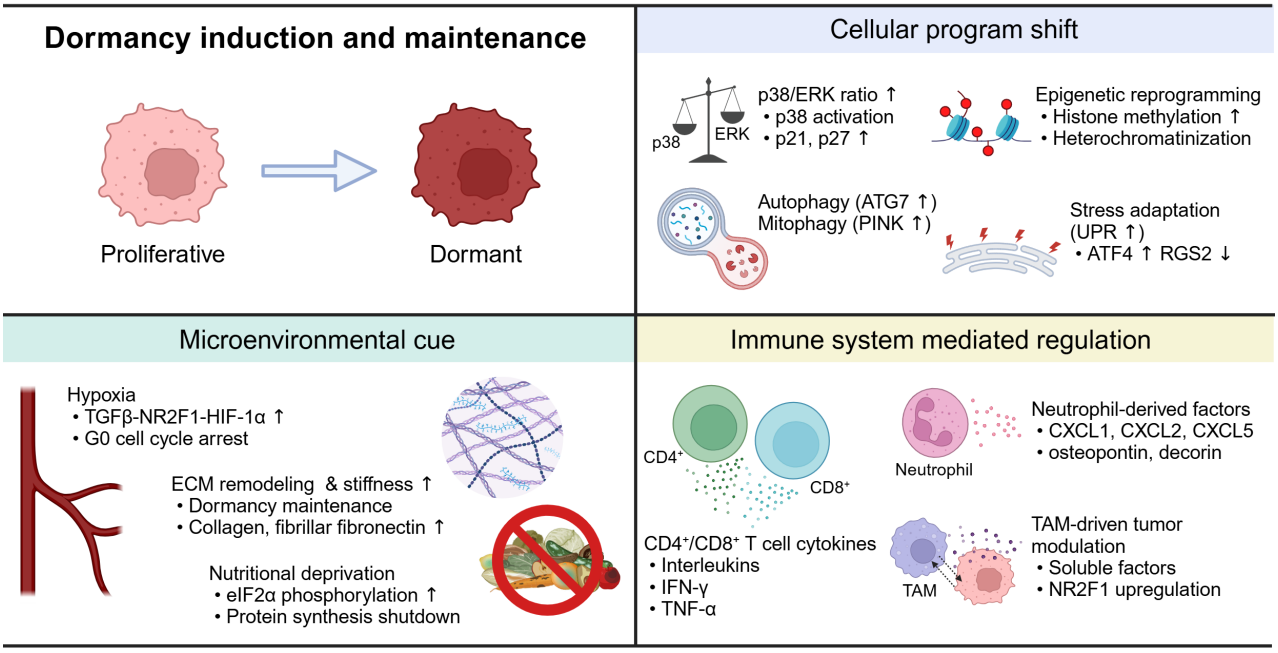

Fig. 3. Key regulatory mechanisms involved in the induction and maintenance of tumor dormancy. The transition from a proliferative to a dormant state is governed by a combination of intrinsic and extrinsic cues. Cellular dormancy is maintained through coordinated shifts in intracellular signaling, transcriptional reprogramming, and metabolic adaptation. Microenvironmental factors such as hypoxia, nutrient deprivation, and extracellular matrix remodeling further contribute to dormancy induction. Additionally, immune-mediated signals, particularly from T cells, neutrophils, and tumor-associated macrophages, play a crucial role in regulating dormant cell survival and reactivation potential. Together, these mechanisms establish and sustain the dormant state of disseminated tumor cells. ERK, Extracellular signal-regulated kinase; ATG7, Autophagy related 7; PINK, PTEN-induced putative kinase 1; UPR, Unfolded protein response; ATF4, Activating transcription factor 4; RGS2, Regulator of G-protein signaling 2; TGFβ, Transforming Growth Factor β; NR2F1, Nuclear receptor subfamily 2 group F member 1; HIF1α, Hypoxia-Inducible Factor 1 α; eIF2α, Eukaryotic Initiation Factor 2 α; CD4/8+, Cluster of differentiation 4/8+; CXCL1/2/5, C-X-C motif chemokine ligand 1/2/5; IFN-γ, Interferon γ; TNF-α, Tumor necrosis factor α; TAM, Tumor-associated macrophage.

long-term persistence and eventual relapse. Understanding the mechanisms that regulate this transition is critical for addressing therapeutic resistance and tumor relapse. Below, key factors influencing the shift from proliferative to dormant state and maintenance of DCCs were discussed (Fig. 3).

Intrinsic cellular program shift

A notable feature of DCCs is the alteration in the ERK/p38 activation ratio, where p38 MAPK signaling is upregulated, and ERK activation is reduced. This shift halts cell proliferation and promotes a stress-resistant state, allowing cells to endure adverse conditions (Aguirre-Ghiso *et al*., 2003; Sosa *et al*., 2011). The increased activation of p38 has been linked to enhanced survival under stress, as it facilitates cellular adaptations such as autophagy and metabolic reprogramming, while also promoting resistance to apoptosis (Gutierrez-Uzquiza *et al*., 2012; Kudaravalli *et al*., 2022). In addition to these survival mechanisms, p38 signaling is also involved in the regulation of cell cycle arrest, partly through the upregulation of cyclin-dependent kinase inhibitors (CDKIs) such as p27 and p21, which reinforce dormancy by inhibiting cell cycle progression (Whitaker and Cook, 2021).

Epigenetic changes, including histone modifications and DNA methylation, also contribute to dormancy by regulating the expression of genes critical for cell cycle progression and survival. Recent studies have demonstrated that endocrine therapy (ET) can induce dormancy in estrogen receptor-positive (ER+) breast cancer cells through epigenetic reprogramming, rather than recurrent genetic mutations. This adaptation involves alterations in histone modifications (H3K9me2, H3K27me3, and H4K20me), leading to a stable heterochromatin state that maintains dormancy until cells stochastically awaken and acquire resistance. Specifically, cell cycle-involved genes (e.g., CDC6, CCND1), MYC signaling, and mTORC1 signaling were significantly repressed, while genes related to quiescence and stress response (e.g., BCL11B, RASAL1) were upregulated (Rosano *et al*., 2024).

Additionally, dormant cells exploit the unfolded protein response (UPR) to adapt to stress. Among the three UPR main branches, persistent phosphorylation of eIF2α via the PERK pathway reduced protein synthesis and prevented ER stress-induced apoptosis. RGS2, a regulator of G protein signaling 2, was overexpressed in chemotherapy-resistant DCCs and promoted proteasomal degradation of ATF4. By decreasing ATF4-mediated protein translation and suppressing the generation of oxidative stress during the protein synthesis process, cancer cells entered cellular dormancy and survived under stress conditions (Cho *et al*., 2021).

In parallel, DCCs undergo metabolic reprogramming to adapt to limited nutrients and stress. Notably, activation of AMPK, a key energy sensor, shifts cancer cells from anabolic growth toward catabolic metabolism to support survival under stress. In ovarian cancer spheroid models, AMPK activity was required for dormant cell viability—LKB1 knockdown (which impairs AMPK) reduces survival and increases chemotherapy sensitivity. This metabolic shift includes the upregulation of fatty acid oxidation enzymes like CPT1C, which help buffer against nutrient scarcity and oxidative stress (Peart *et al*., 2015; Hampsch *et al*., 2020). Moreover, DCCs in the lung rely more heavily on mitochondrial oxidative phosphorylation (OXPHOS) and fatty acid oxidation activity. Pharmacological inhibition of OXPHOS significantly impaired the survival of these dormant cells and reduced tumor recurrence, highlighting the metabolic dependency of dormant cells on mitochondrial function (Havas *et al*., 2017).

Microenvironmental cues

The TME plays a vital role in driving dormancy. DCCs often localize to poorly vascularized or avascular niches where oxygen availability is severely limited. Under such conditions, cells activate adaptive stress programs primarily governed by hypoxia-inducible factor 1-alpha (HIF-1α), which drives transcriptional changes that promote survival and entry into a quiescent state. In glioblastoma models, for example, hypoxia-induced activation of protein phosphatase 2A (PP2A) has been implicated in G1/S cell cycle arrest and dormancy induction (Hofstetter *et al*., 2012). Similarly, in prostate cancer, HIF-1α promotes the expression of CXCR4, a chemokine receptor associated with dormancy maintenance in bone marrow niches (Wang *et al*., 2015). These findings collectively highlight hypoxia as a critical microenvironmental cue that enforces cellular dormancy. Alterations in ECM stiffness influence mechanosensitive pathways that regulate dormancy. Key ECM components such as collagen and fibronectin interact with mechanotransducers—including integrins, DDRs, and YAP/TAZ—to regulate quiescence. In oral squamous cell carcinoma (OSCC) models, increased ECM stiffness was found to induce a dormant, slow-cycling subpopulation characterized by enhanced drug resistance and EMT through cGAS-STING signaling axis (Jingyuan *et al*., 2023). Similarly, in breast cancer, low-level matrix stiffness (~45 Pa) activated integrin β1/3–cytoskeleton–AIRE signaling, promoting stemness and quiescence—highlighting how mechanical cues can directly enforce dormancy; conversely, excessive stiffness (~450 Pa) drove dormant stem-like cells into cell cycle arrest via DDR2–STAT1–p27 signaling, with relaxation of tension triggering reactivation (Li *et al*., 2023).

Nutritional deprivation is another key factor that facilitates the induction of tumor dormancy. To mimic the nutrient-deprived TME, serum starvation is commonly employed in experimental models (Zhang *et al*., 2022). Emerging evidence suggests that starvation and pseudo-starvation states can drive phenotypic transitions in cancer cells through translation reprogramming, primarily via eIF2α phosphorylation. This adaptive response enables cancer cells to survive under metabolic stress by suppressing global protein synthesis while selectively upregulating stress response pathways, ultimately promoting dormancy and therapy resistance (García-Jiménez and Goding, 2019; Cho *et al*., 2021).

Immune-mediated mechanisms on dormancy induction and maintenance

One proposed mechanism underlying tumor mass dormancy is the dynamic equilibrium between cancer cell proliferation and immune cell-mediated elimination. Various immune cells—including $CD4^+$, $CD8^+$ T cells, macrophages, and neutrophils in metastatic niches—play crucial roles in this process by secreting cytokines or through direct interactions with cancer cells.

Cytokines such as Interleukins (ILs), IFN-γ, and TNF-α, have been shown to induce dormancy in cancer cells (Müller-Hermelink *et al*., 2008; Wang *et al*., 2019). In an early study, Koebel *et al*. demonstrated a crucial role of adaptive immunity in maintaining tumor dormancy. Using a mouse model of pri-

mary chemical carcinogenesis, the authors showed that $CD4^+$ and $CD8^+$ T cells, along with IFN-γ, restrain tumor growth, preventing DCCs from escaping immune control. When adaptive immunity was disrupted, previous DCCs resumed proliferation (Koebel *et al*., 2007). A recent study showed that some immune cell subsets, such as $CD39^+PD\text{-}1^+CD8^+$ T cells, actively contribute to breast tumor dormancy by secreting TNFα and IFN-γ, which induced cell cycle arrest and suppressed cancer cell proliferation (Tallón de Lara *et al*., 2021). Moreover, primary tumor-associated macrophages (TAMs) influence tumor dormancy by promoting dissemination and priming DCCs enhancing their survival in secondary sites (Borriello *et al*., 2022). By employing biomaterial scaffolds that mimic metastatic environments, Wang *et al*. revealed that certain neutrophil subpopulations can induce and maintain breast cancer dormancy in lung-like niches by orchestrating potent antitumor immune responses. Antitumor neutrophils secreted pro-inflammatory cytokines and chemokines (e.g., CXCL1, CXCL2, CXCL5) as well as extracellular matrix components such as osteopontin and decorin shaping an immune-activated environment that restrains tumor cell proliferation (Wang *et al*., 2023).

CONTEXT-DEPENDENT ROLES OF DORMANCY-ASSOCIATED MECHANISMS

While dormancy-associated pathways are often described as consistent and linear mechanisms supporting cancer cell quiescence and survival, growing evidence reveals that their roles can be highly context-dependent and even paradoxical. Key regulators such as autophagy, TGF-β signaling, and ERK/p38 MAPK dynamics exhibit opposing effects depending on the tumor type, microenvironmental context, and stage of disease progression.

For instance, autophagy is widely regarded as a survival mechanism that sustains DCCs under nutrient-deprived or hypoxic conditions (Jahangiri and Ishola, 2022). In breast and pancreatic cancers, autophagy enables dormant cells to evade apoptosis and persist long-term in a quiescent state (Loizzo *et al*., 2022; Dwyer *et al*., 2024). However, in other contexts—or when excessively activated—autophagy can promote cell death or sensitize cells to therapy, thereby reducing dormancy persistence (Feng *et al*., 2023). This dual role makes autophagy a particularly nuanced target for therapeutic intervention.

Similarly, the TGF-β signaling pathway plays conflicting roles. TGF-β2, acting through p38 MAPK, has been shown to induce and maintain dormancy in disseminated tumor cells, particularly in bone marrow niches (Oskarsson *et al*., 2014; Yumoto *et al*., 2016). In contrast, TGF-β1 signaling is often associated with tumor progression and EMT, facilitating the escape from dormancy and metastatic outgrowth (Katsuno *et al*., 2013). These divergent effects may be driven by differences in receptor subtype engagement, ligand concentration, or crosstalk with other pathways in distinct tissue environments.

Even canonical dormancy regulators like the ERK/p38 activity ratio are not universally predictive. While a low ERK/p38 ratio is generally associated with dormancy induction, certain cancers display exceptions where ERK signaling remains active in dormant-like cells or p38 activity contributes to reactivation, underscoring the plasticity of these signaling networks (Aguirre-Ghiso *et al*., 2003; Barney *et al*., 2020).

Taken together, these conflicting observations suggest that dormancy is not a static or uniformly regulated state, but rather a dynamic equilibrium influenced by intrinsic cellular programs and extrinsic niche signals. In some contexts, the same pathway that maintains quiescence may become a trigger for awakening under altered environmental cues or selective pressures.

The transition from dormancy to proliferation is not merely a passive escape but often involves active sensing of microenvironmental changes, loss of suppressive signals, or acquisition of growth-promoting stimuli. Understanding these context-dependent reversals in dormancy control mechanisms is critical for deciphering how minimal residual disease evolves into clinical relapse. In the following section, we examine the key molecular and environmental factors that drive DCCs toward reactivation and overt metastasis.

MECHANISMS OF REACTIVATION OF DCCS

While dormancy enables cancer cells to evade therapeutic pressure and immune surveillance, long-term persistence in this state is not guaranteed. Changes in the surrounding microenvironment or alterations in intrinsic signaling can trigger DCCs to re-enter the cell cycle. This reawakening process is often associated with aggressive tumor outgrowth, metastatic relapse, and poor clinical outcomes. Understanding the mechanisms that drive DCCs toward reactivation is essential for preventing recurrence and improving long-term patient survival. Below, we outline key pathways and microenvironmental cues implicated in the escape from dormancy (Fig. 4).

Intrinsic cellular programs for reawakening

DCCs possess an inherent ability to re-enter the cell cycle through the activation of intrinsic cellular programs. A key mechanism involves the reactivation of ERK signaling, which occurs in tandem with the downregulation of p38 MAPK activity. An increase in the ERK/p38 activation ratio facilitates the transition of dormant tumor cells from a stress-tolerant dormant state to a proliferative phenotype, promoting tumor reactivation. ERK reactivation promotes cell cycle progression by upregulating cyclins and downregulating cyclin-dependent kinase inhibitors (CDKIs) such as p21 and p27, a process that is the reverse of the mechanisms involved in tumor dormancy induction (Sosa *et al*., 2011). In addition, the mTOR signaling pathway plays a crucial role in regulating DCCs. Restoration of nutrient availability or alleviation of metabolic stress activates mTORC1, driving anabolic processes and cellular growth. DCCs exploit these changes to rebuild their biosynthetic capacity and re-enter the proliferative cycle (Aleksandrova *et al*., 2024). Epigenetic reprogramming further facilitates this transition by reversing suppressive modifications such as histone acetylation and DNA demethylation. For instance, demethylation of NR2F1 regulates the expression of dormancy-associated genes, facilitating re-entry into the cell cycle (Sosa *et al*., 2015). Furthermore, inhibition of histone acetylation at the promoters of leukemia inhibitory factor receptor (LIFR), which induces pro-dormancy phenotype in breast cancer cells, influences tumor cell reawakening through reversible chromatin accessibility (Clements *et al*., 2021). These intrinsic cellular programs reflect the dynamic adaptability of DCCs in response to favorable microenvironmental or systemic changes.

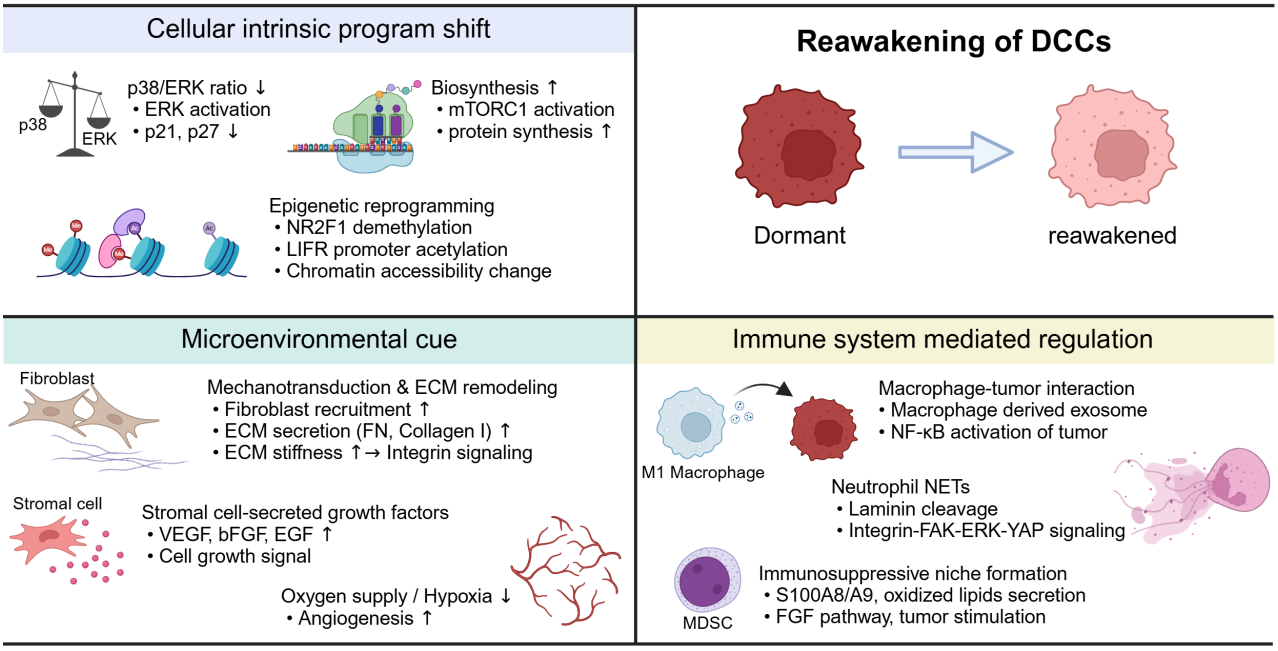

Fig. 4. Mechanisms driving the reawakening of DCCs. Dormant disseminated cancer cells (DCCs) can re-enter the cell cycle in response to a variety of intrinsic and extrinsic signals. Intracellular program shifts—including changes in ERK/p38 signaling balance, epigenetic states, and biosynthetic activity—support the transition toward a proliferative phenotype. Microenvironmental cues such as extracellular matrix remodeling, stromal-derived growth factors, and increased oxygen or angiogenic support promote reactivation. In parallel, immune components, including macrophages, neutrophils, and immunosuppressive myeloid cells, modulate the tumor niche and facilitate escape from dormancy. These interconnected mechanisms collectively enable dormant cells to resume growth and contribute to disease relapse. ERK, Extracellular signal-regulated kinase; mTORC1, Mechanistic target of rapamycin complex 1; NR2F1, Nuclear receptor subfamily 2 group F member 1; LIFR, Leukemia inhibitory factor receptor; DCCs, Dormant cancer cells; ECM, Extracellular matrix; FN, Fibronectin; VEGF, Vascular endothelial growth factor; bFGF, Basic fibroblast growth factor; EGF, Epidermal growth factor; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated b cells; NET, Neutrophil extracellular trap; FAK, Focal adhesion kinase; YAP, Yes-associated protein; MDSC, Myeloid-derived suppressor cell.

Microenvironmental triggers: Mechanical, nutritional factors

In the transition from tumor dormancy to reactivation, extrinsic cues from the TME—particularly modifications in the ECM—constitute one of the most critical driving forces (Barkan *et al*., 2010b; Linde *et al*., 2016). Fibroblast recruitment to the TME is a key factor in remodeling ECM. Fibroblasts secrete various ECM components, including fibronectin and collagen type I, which increase ECM stiffness and provide integrin-mediated signals to DCCs (Barkan *et al*., 2010a; Cho *et al*., 2020a; Spada *et al*., 2021). These signals facilitate cellular reactivation by modulating mechanotransduction pathways and activating proliferation-associated signaling cascades, such as focal adhesion kinase (FAK) signaling and downstream cascades (Mukherjee and Bravo-Cordero, 2023). Additionally, growth factors such as VEGF, basic FGF (bFGF), and EGF, secreted by stromal cells, further enhance the activation of dormant cells, facilitating their re-entry into the cell cycle (Indraccolo *et al*., 2006; Cho *et al*., 2020b). Oxygen supply restoration, often driven by angiogenesis, is another potent reactivation stimulus. Increased oxygen levels resolve hypoxic stress, leading to the reactivation of DCCs through the downregulation of hypoxia-responsive genes and the reactivation of oxidative metabolism (Qiu *et al*., 2017).

Immune-mediated mechanisms for dormancy escape

Beyond stromal components, immune cells represent critical regulators of dormancy escape. DCCs actively reshape the TME, leading to immune cell dysregulation and ultimately promoting tumor recurrence. Macrophages have been extensively studied for their role in creating a TME conducive to tumor reactivation. For example, M1-type macrophages in the bone marrow could reactivate dormant breast cancer cells through exosome-mediated NF-κB pathway activation, leading to increased proliferation and the exit of DCCs from quiescence (Walker *et al*., 2019). Neutrophils release neutrophil extracellular traps (NETs) that remodel the ECM creating a microenvironment favorable for tumor reactivation (Albrengues *et al*., 2018). Especially, NET-associated proteases sequentially cleaved laminin of ECM, exposing a cryptic epitope that triggers integrin activation and downstream FAK/ERK/MLCK/YAP signaling, leading to cancer cell proliferation. Moreover, myeloid-derived suppressor cells (MDSCs) establish an immunosuppressive niche that not only protects dormant cells from immune clearance but also secretes factors that promote their transition to an active state. Stress hormones caused the release of S100A8/A9 and oxidized lipids from the MDSC and these lipids promoted the fibroblast growth factor (FGF) pathway of tumor cells promoting tumor relapse (Perego *et al*., 2020).

THERAPEUTIC STRATEGIES TARGETING DCCS

Despite recent advances in understanding the biology of DCCs, translating these insights into clinical practice remains highly challenging. The lack of reliable and specific biomarkers for dormancy, the technical limitations in detecting minimal residual disease (MRD), and the absence of validated models for clinical trial design targeting dormant cells hinder therapeutic development (Linde *et al*., 2016; Basu *et al*., 2022). Furthermore, dormant cells often evade conventional detection methods and reside in inaccessible niches, complicating both patient stratification and treatment response assessment (Risson *et al*., 2020; Agudo *et al*., 2023). Given these constraints, the development of dormancy-targeted therapies is still in its early stages. Nevertheless, recent preclinical efforts have proposed three broad strategies to address DCCs; these include 1) maintaining their quiescent state to minimize proliferation and metastasis, 2) reactivating dormant cells to make them susceptible to conventional therapies, and 3) directly eliminating them by disrupting their unique survival mechanisms (Ganesh and Massague, 2021; Sauer *et al*., 2021). Although all three strategies demonstrate considerable therapeutic potential, each also presents distinct advantages and drawbacks, necessitating a careful and context-specific application (Table 1).

Potential therapeutic targets

Tumor dormancy maintenance: Reinforcing signals that preserve dormancy offers a long-term approach to managing residual disease by keeping cancer cells in a non-proliferative state. Epigenetic reprogramming has been identified as a critical mechanism underlying both the survival and maintenance of DCCs (Wang *et al*., 2021). By targeting epigenetic modulators such as EZH2, G9a (EHMT2), and KMT5B/C, researchers could disrupt dormancy-associated heterochromatin reprogramming in endocrine therapy-resistant ER+ breast cancer, thereby preventing both the establishment and the reactivation of tumor dormancy (Rosano *et al*., 2024). DNA methylation inhibitors, including 5-Aza-C and all-trans retinoic acid (ATRA), further strengthen this effect by promoting the expression of dormancy-regulating genes such as NR2F1, thus preventing cells from escaping tumor dormancy (Sosa *et al*., 2015). Targeting the ERK and Wnt signaling pathways with inhibitors like U0126 and itraconazole, respectively, has also been shown to suppress dormant cell reactivation (Barkan *et al*., 2010a; Buczacki *et al*., 2018). A recent study revealed that suppressing integrin signaling, particularly through targeting interaction between uPAR and β1-integrin, further reinforces dormancy preventing tumor cells from relapse (Bui *et al*., 2022; Shmakova *et al*., 2022).

Leveraging the mechanisms of immune-mediated tumor dormancy offers critical insights for the elimination of dormant tumor cells (Wang *et al*., 2019). For example, IFN-γ derived from tumor-specific CD4+ Th1 cells induced tumor dormancy by promoting antiangiogenic chemokines CXCL9 and CXCL10, which inhibit tumor angiogenesis and proliferation (Aqbi *et al*., 2018; Müller-Hermelink *et al*., 2008). However, prolonged therapy may inadvertently select for more aggressive clones or lead to drug resistance, underscoring the importance of balancing durability with potential adverse outcomes.

Resensitizing to Anticancer Drugs: Activating dormant cells can render them metabolically active and vulnerable to cytotoxic agents, allowing for effective eradication. DYRK1A inhibitors, such as harmine, target the DREAM complex to modulate the cell cycle and disrupt dormancy-associated pathways (Litovchick *et al*., 2011; Wang *et al*., 2022). DYRK1A inhibition released cells from quiescence and promoted their accumulation in the G1/S phase, thereby enhancing their sensitivity to G1/S-targeting chemotherapy drugs (Laham *et al*., 2024). PDE5 inhibitors, such as sildenafil, originally developed for vascular conditions, have shown potential in cancer therapy (Zhang *et al*., 2025). These inhibitors increase protein synthesis in dormant cells, exposing them to heightened oxidative stress. When combined with conventional chemotherapy, this approach enhances the efficacy of treatment by making dormant cells more vulnerable to oxidative damage (Cho *et al*., 2021). Yet, this strategy also carries the risk of promoting rapid tumor progression if eradication is not achieved efficiently and in tandem with reactivation.

Dormant cell elimination: DCCs exploit specific signaling pathways to maintain quiescence. Direct DCCs targeting strategies focus on targeting the metabolic pathways or autophagic processes that dormant cells rely upon for survival under stress (Recasens and Munoz, 2019; Damen *et al*., 2020). Src family kinase (SFK) activation is essential for the reactivation of DCCs. Therefore, co-targeting MEK to suppress ERK1/2 signaling, in combination with SFK inhibition, resulted in more effective elimination of dormant tumor cells (El Touny *et al*., 2014). Conversely, targeting immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) could reduce the protective niche for DCCs and facilitate their elimination (Marvel and Gabrilovich, 2015; Krall *et al*., 2018). Combining conventional therapies with drugs targeting DCCs-specific pathways has shown significant promise. For instance, COX-2 inhibitors, which inhibit Type I collagen production by fibroblasts in the TME, and Src inhibitors effectively prevent dormant cell reactivation and tumor recurrence when combined with chemotherapy (Cho *et al*., 2020a). Nevertheless, the low proliferative activity of dormant cells can hinder accurate detection, and the lack of truly dormancy-specific markers remains a key obstacle to complete elimination.

TUMOR DORMANCY BIOMARKERS AND EMERGING DETECTION TECHNOLOGIES

Identifying DCCs in patients remains one of the most significant translational challenges due to their non-proliferative nature and niche-specific localization. Several dormancy-associated biomarkers have been proposed based on preclinical studies, including Erk/p38 ratio, NR2F1 activity, $p27^{Kip1}$ and RGS2 expression, and secreted factors such as TGFβ2 (Sosa *et al*., 2015; Fluegen *et al*., 2017; Cho *et al*., 2021). These markers have provided valuable insights into the molecular programs sustaining dormancy, particularly in controlled experimental settings.

In parallel, stemness-associated markers have also been explored as potential predictors of dormancy or relapse risk, as cancer stem cells (CSCs) frequently exhibit tumor-initiating capacity and chemoresistance. However, CSC markers are not synonymous with dormancy. For instance, $CD133^{+}$ and $CD44^{+}$ cells, two widely used CSC markers, can be ei-

Table 1. Therapeutic strategies targeting DCCs: mechanisms of action, key targets, and representative agents

Strategy	Mechanism of Action (MoA) / Key Targets / Drugs	Advantages and Limitations	Reference
Maintain dormancy	MoA: Reinforce signals that sustain quiescence and suppress reactivation - Epigenetic modulators: EZH2, G9a (EHMT2), KMT5B/C - DNA methylation inhibitors: 5-Aza-C, ATRA - Signaling inhibitors: ERK (U0126), Wnt (itraconazole), uPAR–β1-integrin - Immune-mediated dormancy: IFN-γ, CXCL9/10 from CD4+ Th1 cells	Advantages: - Prevents proliferation and metastasis - Long-term disease control Limitations: - Risk of selecting resistant clones - Potential drug resistance	Rosano *et al*., 2024 Sosa *et al*., 2015 Barkan *et al*., 2010a Buczacki *et al*., 2018 Bui *et al*., 2022 Shmakova *et al*., 2022 Müller-Hermelink *et al*., 2008
Eliminate dormant cells	MoA: Disrupt survival pathways specific to a dormant state - SFK inhibitors ± MEK inhibitors - Target MDSCs (myeloid-derived suppressor cells) - COX-2 inhibitors, Src inhibitors (with chemotherapy)	Advantages: - Direct removal of dormant reservoir - Reduces relapse potential Limitations: - Dormant cells are hard to detect - Lack of dormancy-specific markers	El Touny *et al*., 2014 Krall *et al*., 2018 Cho *et al*., 2020a
Reactivate and kill	MoA: Induce re-entry into cell cycle to sensitize to therapy - DYRK1A inhibitors (harmine) - PDE5 inhibitors (sildenafil) - Combined with G1/S phase-specific chemotherapy	Advantages: - Increased drug sensitivity - Enhanced oxidative stress vulnerability Limitations: - Risk of rapid tumor progression if not efficiently cleared	Litovchick *et al*., 2011 Wang *et al*., 2022 Laham *et al*., 2024 Cho *et al*., 2021

This table summarizes major therapeutic approaches to target DCCs, categorized by their mechanisms—maintenance of dormancy, selective elimination of dormant cells, and reactivation followed by cytotoxic therapy. Each strategy lists representative molecular targets or drugs, key mechanistic pathways, and notes potential advantages and limitations supported by relevant references. DCCs, Dormant cancer cells; EZH2, Enhancer of zeste homolog 2; EHMT2, Euchromatic histone-lysine N-methyltransferase 2; KMT5B/C, Lysine methyltransferase 5B/5C; ATRA, All-trans retinoic acid; ERK, Extracellular signal-regulated kinase; Wnt, Wingless/integrated; uPAR, Urokinase-type plasminogen activator receptor; IFN-γ, Interferon-γ; CXCL9/10, C-X-C motif chemokine ligand 9/10; CD4+, Cluster of differentiation 4+; Th1, T helper type 1; SFK, Src family kinase; MEK, Mitogen-activated protein kinase kinase; MDSC, Myeloid-derived suppressor cell; COX-2, Cyclooxygenase-2; Src, Sarcoma proto-oncogene tyrosine-protein kinase; DYRK1A, Dual-specificity tyrosine-regulated kinase 1A; PDE5, Phosphodiesterase type 5.

ther proliferative or dormant depending on the tumor context. $CD133^+$ populations show active cycling in some cancers but dormancy in others. Similarly, $CD44^+$ gastric cancer stem cells exhibit slow-cycling characteristics, but are highly proliferative in non-small cell lung cancer or head and neck cancer (Ishimoto *et al*., 2010; Perez *et al*., 2013; Hu *et al*., 2018). Consequently, relying on a single CSC marker fails to consistently predict dormancy. To address this limitation, recent efforts have combined functional assays—such as label-retention techniques—with multi-marker profiling or single-cell transcriptomics paired with surface-marker analysis to distinguish dormant CSC subpopulations (Alowaidi *et al*., 2018; Kester and van Oudenaarden, 2018; Davis *et al*., 2019).

While these molecular and stemness-related biomarkers hold promise for identifying dormancy-associated phenotypes, their application in clinical settings remains constrained. Detecting these markers typically requires invasive tissue sampling or in situ analysis, which is not feasible unless dormancy is already suspected or localized lesions are accessible. As such, their utility for routine surveillance or early detection of dormant disease in asymptomatic patients is currently limited.

Given the invasive nature and contextual limitations of current cellular and molecular profiling methods, liquid biopsy-based approaches are emerging as a promising alternative for dormancy detection. In light of these limitations, non-invasive strategies such as liquid biopsy-based detection methods are gaining increasing attention for their potential to monitor dormancy in real time. Extracellular vesicles (EVs) secreted by DCCs or surrounding normal cells have gained attention as potential biomarkers. In particular, bone marrow-derived mesenchymal stromal cells (BM-MSCs) have been shown to secrete EVs containing miR-127, miR-197, miR-222, and miR-223, which induce cell cycle arrest in breast cancer cells, while miR-9-3p and miR-300 have been implicated in chemotherapy resistance and dormancy maintenance in bladder cancer and leukemia models (Bliss *et al*., 2016; Cai *et al*., 2019; Silvestri *et al*., 2020). Although the presence of the circulating EVs has been correlated with dormancy status and metastatic risk in both *in vitro* and *in vivo* models, their low abundance in circulation remains a major limitation for reliable detection through blood-based assays. Therefore, the development of more sensitive EV detection technologies or entirely new diagnostic platforms is urgently needed to overcome this limitation and enable reliable monitoring of dormancy through liquid biopsy approaches (Pantel and Alix-Panabières, 2019).

FUTURE PERSPECTIVES

Developing effective therapies against DCCs is critical for preventing late relapse and metastasis. However, several key translational challenges must be addressed to facilitate clinical progress. First, the absence of standardized clinical criteria for defining dormancy limits our ability to identify and stratify at-risk patients. In addition, dormant cells often reside in anatomically protected niches—such as bone marrow or the central nervous system—making serial sampling for monitoring or biomarker development technically and ethically challenging. Furthermore, the long latency periods between initial dissemination and metastatic relapse complicate the design of clinical trials, especially in establishing appropriate endpoints. Currently, widely used clinical metrics such as progression-free survival or tumor size reduction are insufficient to capture the cytostatic nature of dormancy, emphasizing the need for surrogate markers that reflect dormant cell burden or reactivation risk.

To overcome these obstacles, new technologies for *in vivo* tracking of dormant disseminated tumor cells are essential, as conventional imaging and biomarkers remain inadequate. In parallel, *in vitro* platforms that recapitulate the microenvironmental conditions of metastatic niches—such as 3D cultures or tissue-engineered systems—are needed to elucidate the mechanisms governing dormancy entry, maintenance, and escape. Enhancing our capacity to visualize, isolate, and manipulate DCCs will enable more effective testing of interventions aimed at either sustaining dormancy or eliminating residual disease.

The systemic interplay between DCCs and the host environment also presents a critical frontier. Emerging evidence suggests that stress hormones, immune surveillance, skeletal muscles, and the gut microbiota can shift the balance between dormancy and reactivation, highlighting the need for interdisciplinary approaches (Zhu *et al*., 2020; Crist *et al*., 2022; He *et al*., 2024). Furthermore, physiological factors, such as neural signals and adipose-derived mediators, appear to shape the fate of DCCs in different tissues, potentially triggering or restraining outgrowth (Li *et al*., 2013; Roy *et al*., 2022). By elucidating these interactions at the organismal level, future research may reveal novel therapeutic strategies, including stress modulation, immunotherapy, or metabolic interventions, to maintain tumor cells in a dormant state or eradicate them. By integrating advances in bioengineering, immunology, and systems biology, future research should aim to prevent relapse and enhance long-term survival outcomes for cancer patients.

CONFLICT OF INTEREST

The author has declared that no competing interest exists.

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