

Unraveling the crucial clues on the role of cellular dormancy and plasticity in cancer recurrence

Nguyen Van Hung^{1,*}, Tran Ngoc Minh^{2,3}, Nguyen Tuan Thanh⁴

ABSTRACT

Cancer recurrence remains a major clinical challenge. Cellular dormancy and phenotypic plasticity have emerged as key contributors to this phenomenon. Dormancy is not a universal trait; it is restricted to the subset of malignant cells that acquire stem-cell-like characteristics, termed cancer stem cells (CSCs), enabling entry into a quiescent state. CSCs display both dormancy and plasticity, conferring marked therapy resistance. The crosstalk between these processes is orchestrated by an intricate framework of signaling cascades, microRNA circuits, cell-cycle regulators, and transcription-factor networks. Through this framework, tumor cells acquire stem-like features, switch phenotypes, and adopt a dormant program that permits immune evasion. Paradoxically, immune surveillance can further reinforce CSC traits, thereby promoting survival under hostile conditions, treatment resistance, and self-renewal. Sustained dormancy of residual malignant cells could therefore allow disease to be contained as minimal residual disease (MRD) rather than progressing to overt relapse. This review consolidates current insights into tumor-cell plasticity and dormancy, delineates their molecular underpinnings, and critically appraises the contentious notion of therapeutically sustaining dormancy. Emerging strategies targeting these pathways are also discussed.

Key words: cellular dormancy, cellular plasticity, cancer recurrence, cancer stem cells, signaling pathways, microRNAs

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INTRODUCTION

Cancer recurrence denotes the return of malignant disease after a period of clinical remission following definitive therapy.¹ The interval to recurrence varies widely among patients, even among individuals with identical histologic subtype, clinical stage, and therapeutic regimen. The biological mechanisms driving recurrence are multifactorial and remain incompletely elucidated. Multiple hypotheses implicate intrinsic factors—including host anti-tumour immunity, alterations within the tumour microenvironment (TME) that either suppress or facilitate malignant proliferation, and the mutational evolution of cancer cells—in the recurrent process. Recently, the paradigms of cellular dormancy and cellular plasticity have been recognized as central to recurrence biology.

Recurrence may manifest at the primary site (local recurrence), in regional lymph nodes or contiguous tissues (regional recurrence), or at distant organs (distant recurrence).¹ To harmonize terminology, an international workshop convened in Toronto, Canada, in February 2018 defined early recurrence as disease returning within five years of diagnosis and late recurrence as recurrence developing more than five years after diagnosis.²

Cellular dormancy and plasticity have therefore attracted considerable investigative attention. Accumulating evidence supports their pivotal contribution to recurrence. Tumour-cell dormancy is a dynamic state in which malignant cells enter temporary growth arrest or quiescence³ (the terms dormancy and quiescence are used interchangeably in this review). Because these cells are non-proliferative, they can withstand hostile conditions, evade immune surveillance, and resist conventional cytotoxic therapies.⁴ Dormant cells may persist for prolonged periods and can subsequently be reactivated by diverse stimuli.^{5,6} Nevertheless, the precise role of dormancy in recurrence and metastasis remains contentious.^{7–9} Whether long-term maintenance of dormancy confers clinical benefit is addressed in the following section. Dormancy is induced by both intrinsic factors, such as oncogenic mutations, and extrinsic cues, such as signals derived from the TME.^{10,11}

Cellular plasticity denotes the capacity of cancer cells to alter their phenotype in response to environmental stimuli, thereby promoting therapeutic resistance, adaptation to heterogeneous niches, and metastatic dissemination.^{12–14} Plasticity is orchestrated by genetic and epigenetic reprogramming that enables transitions between epithelial

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and mesenchymal states—epithelial–mesenchymal transition (EMT) and its reverse, mesenchymal–epithelial transition (MET).¹⁵ Micro-RNAs (miRNAs) have emerged as critical regulators of both dormancy and plasticity; by modulating target mRNAs, these small non-coding RNAs can maintain quiescence or, conversely, trigger re-activation of dormant cells, ultimately facilitating recurrence and metastasis.¹⁶

This review consolidates current insights into tumour-cell plasticity and dormancy, delineates the molecular pathways governing these phenomena, evaluates the controversy surrounding therapeutic induction or maintenance of dormancy, and highlights novel treatment strategies under investigation.

DORMANCY AND PLASTICITY IN CANCER

Definitions of dormancy and plasticity

Cancer dormancy

Cancer cell dormancy is an evolutionarily conserved survival strategy that enables malignant cells to endure adverse conditions by entering a hypometabolic state. Key features of dormant cancer cells include cell-cycle arrest (typically in the G0/G1 phase), chromatin condensation, and dysregulated signalling pathways. Two inter-related dormant states have been described: cellular and tumour dormancy. Cellular dormancy (single-cell dormancy) usually occurs in disseminated tumour cells that have metastasised to distant organs; these cells can be reactivated by microenvironmental cues.¹⁷ Tumour dormancy denotes a dynamic equilibrium between cellular proliferation and death within the entire tumour mass, so that tumour volume remains stable for prolonged periods, generally owing to limited angiogenesis or immune-mediated growth suppression (Figure 1). The tumour can resume growth once environmental conditions become favourable.¹⁸ Programmed dormancy is governed by defined genetic programmes involving transcription factors such as SRY-box transcription factor 2 (SOX2) and SRY-box transcription factor 9 (SOX9), and is frequently associated with the acquisition of stem-cell-like traits by tumour cells.¹⁹

Metastatic and treatment-induced dormancy

Both metastatic and treatment-induced dormancy are emerging concepts that are receiving considerable research attention. Metastatic dormancy refers

to the quiescent state adopted by disseminated tumour cells during the early phases of colonisation of a distant, pre-metastatic niche. During this phase, the cells remain dormant to evade immune surveillance, and their survival as well as subsequent re-awakening critically depend on the local tumour microenvironment (TME).²⁰ Treatment-induced dormancy describes a reversible quiescent state entered by cancer cells upon exposure to cytotoxic therapies (Figure 1). During this period, cellular metabolism is minimised to support survival, and proliferation can resume once favourable conditions return.²¹ (Table 1).

Cellular plasticity

Cancer cell plasticity is the capacity of malignant cells to alter their phenotype in response to microenvironmental changes, thereby facilitating adaptation and evolution under selective pressures such as chemotherapy or radiotherapy. This adaptive process is driven by Darwinian selection, whereby cells with advantageous traits persist and expand, ultimately contributing to tumour recurrence and metastasis.³⁶ Specifically, plasticity encompasses (i) reversible transitions between epithelial and mesenchymal states (EMT and MET, respectively) and (ii) the acquisition or loss of stem-cell properties. EMT endows tumour cells with stemness, enabling them to remain dormant within pre-metastatic niches.¹⁵ The ability of tumour cells to modulate phenotype in response to environmental cues is therefore critical for tumour survival and progression.¹⁷ Stem-cell-like characteristics are confined to cancer stem cells (CSCs), a sub-population capable of self-renewal and multilineage differentiation.³⁷ Plasticity allows dynamic inter-conversion between CSC and non-CSC states and represents one of the principal drivers of intratumoural heterogeneity, migration, invasion, and therapy resistance.^{15,17,38} (Figure 2).

Basic mechanism

Dormancy mechanisms in cancer cells

To enter a dormant or quiescent state, cancer cells must be induced to arrest in the G0 phase of the cell cycle. Only a subset of cells at the primary tumor site can do so—namely those that have acquired stem-cell-like characteristics, referred to as cancer stem cells (CSCs). The underlying regulatory network is complex and is being progressively elucidated. Several classes of factors have been implicated. First, cell-cycle regulators such

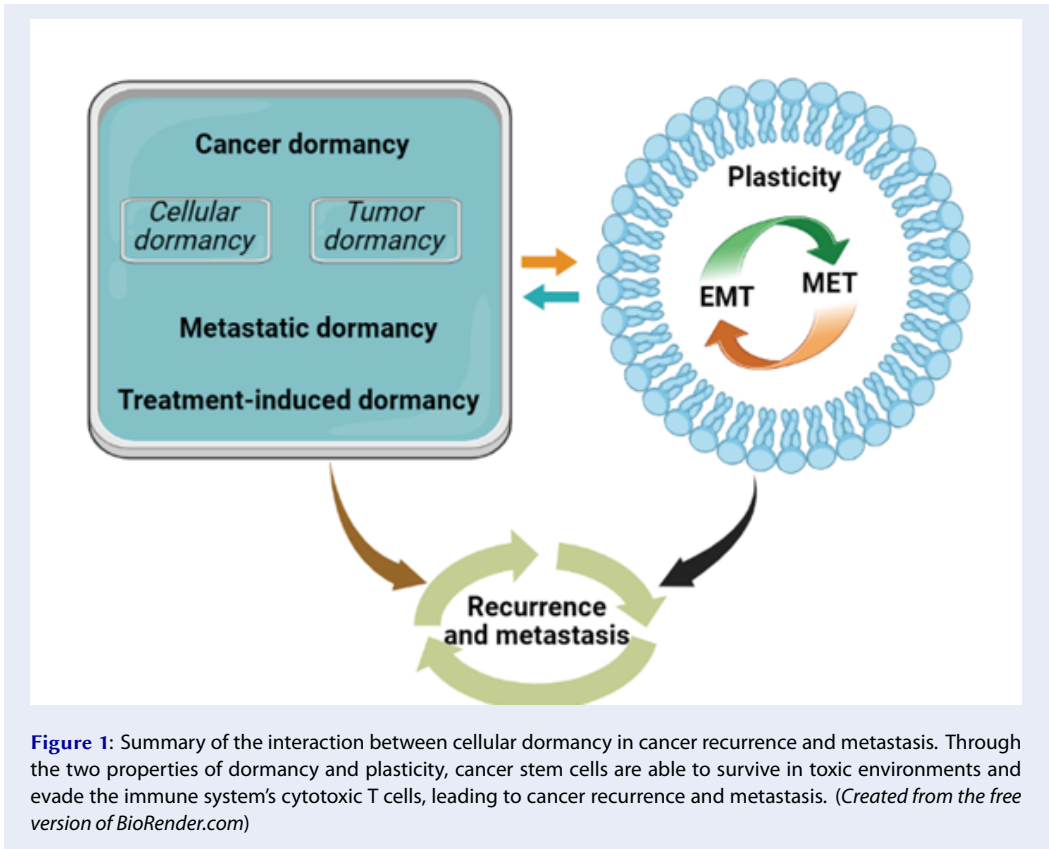
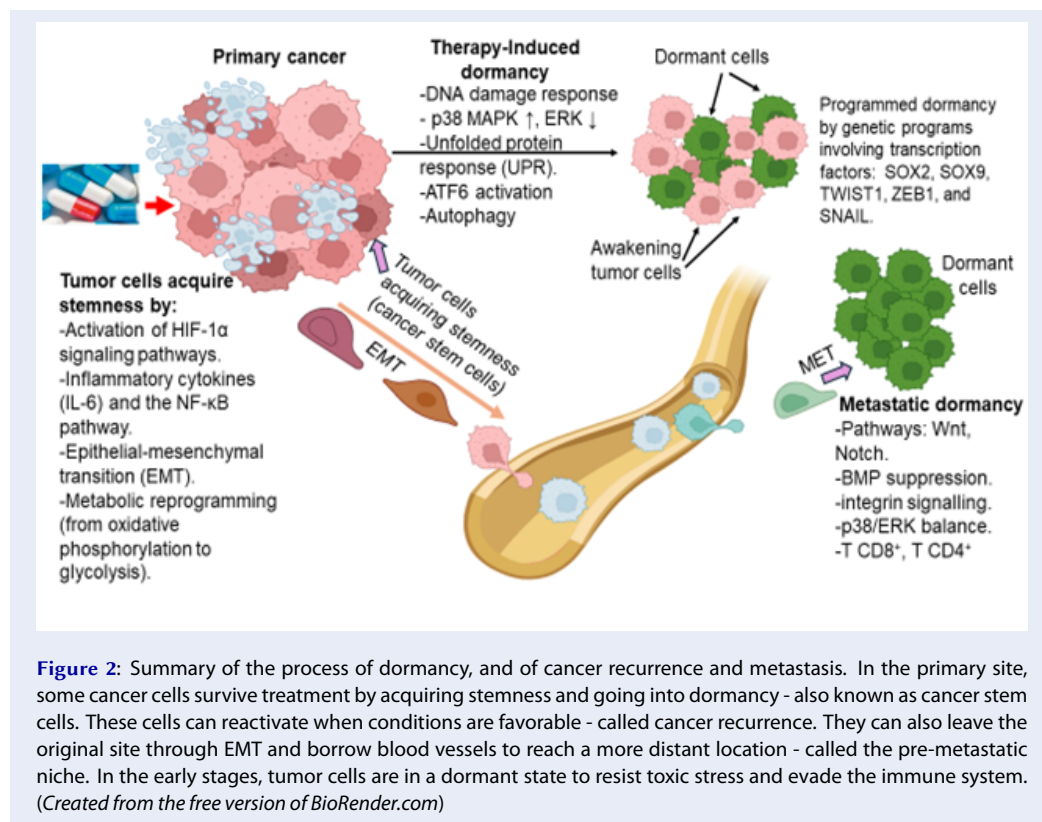


Table 1: Differences between metastatic dormancy and therapy induced dormancy

Feature	Metastatic Dormancy	Therapy-Induced Dormancy
Trigger	Microenvironmental cues at distant metastatic sites. ²²	Cellular stress from chemotherapy, radiation, or targeted therapy. ²³
Cell Type	Disseminated tumor cells (DTCs) in secondary organs. ²⁴	Residual tumor cells surviving treatment. ²³
Location	Bone marrow, lungs, liver, brain niches. ²⁵	Primary tumor site or micrometastatic lesions
Mechanism	ECM signals (e.g. thrombospondin-1), immune surveillance, angiogenic suppression. ^{26,27}	DNA damage response, p38 MAPK activation, unfolded protein response (UPR). ^{28,29}
Pathway Involvement	Wnt, Notch, BMP suppression, integrin signaling, p38/ERK balance. ^{30,31}	p38 MAPK↑, ERK↓, ³² ATF6 activation, autophagy, senescence-like states. ^{33,34}
Phenotype	Quiescent (G0/G1 arrest), immune-evasive, slow-cycling. ²⁵	Drug-tolerant persister cells, senescent-like, metabolically active but non-dividing. ³⁵
Escape Triggers	ECM remodeling, angiogenesis, immune suppression. ²⁴	Loss of p53/p16, metabolic reprogramming, SASP signaling, therapy cessation. ³⁵
Clinical Implication	Late relapse (years/decades post-treatment), often undetectable until reactivation. ²⁴	Resistance to therapy, early relapse, minimal residual disease (MRD). ²³



as the cyclin-dependent kinase inhibitors CDKN1B (p27^{Kip1}) and CDKN1A (p21), together with the tumor suppressor TP53 (p53), can promote dormancy. While p53 arrests the cell cycle in response to cellular stress and DNA damage, p27 and p21 inhibit cyclin-dependent kinases, thereby blocking proliferation and enforcing cell-cycle arrest.^{31,39,40} Second, a high p38/ERK low activity ratio favors dormancy; experimental cancer models demonstrate that elevated p38 and suppressed ERK signaling support a dormant phenotype.^{31,41} Third, adverse elements within the tumor microenvironment (TME)—including hypoxia, nutrient deprivation, and the absence of matrix-binding integrins in the pre-metastatic niche—constitute prerequisites for tumor-cell dormancy.^{31,42} The pre-metastatic niche is a specialized microenvironment in a distant organ where circulating tumor cells (CTCs) can lodge, survive immune attack, and ultimately initiate secondary tumors.⁴³ Fourth, immune-mediated cues such as interferon- γ (IFN γ /IFN- γ) acting through the IDO1–kynurenine–aryl hydrocarbon receptor (AHR)–p27^{Kip1} axis, together with T cells, macrophages, and cytokines present in the TME, can promote dormancy.⁴⁴ Finally, sustained short-

ages of nutrients and oxygen further limit tumor-cell growth and enforce dormancy.⁴⁵

Mechanisms driving plasticity

Tumor-cell plasticity arises from the convergence of several molecular processes. First, epigenetic modifications, by regulating messenger RNA expression, alter gene output and protein function, thereby generating phenotypic diversity.⁴⁶ Second, dysregulation of signaling cascades—including MAPK, phosphatidylinositol-3-kinase (PI3K), Wnt, and epithelial-to-mesenchymal transition (EMT) pathways—enables tumor cells to shift phenotype in response to the TME, promoting metastasis and recurrence.^{14,47,48} Third, microRNAs and long non-coding RNAs (lncRNAs) modulate chromatin remodeling, mRNA stability, and transcription, thereby governing stemness and phenotypic heterogeneity.⁴⁶ Lastly, altered DNA methylation of genes such as PPARG coactivator-1 α (PPARGC1A/PGC1 α) and death-associated protein kinase-3 (DAPK3), which orchestrate metabolic pathways, equips tumor cells with enhanced resistance to stress.^{49–51} (Table 2).

Table 2: Summary of some differences in cellular dormancy and plasticity in cancer

Feature	Cellular Dormancy	Cellular plasticity
Cell State	Quiescent (non-dividing)	Dynamic (switching between phenotypes)
Proliferation	Suppressed	Variable (can increase or decrease)
Therapy Resistance	High (due to low proliferation)	High (due to adaptive phenotype switching)
Reversibility	Reversible (can re-enter cell cycle)	Reversible (can shift between states)
Key Pathways	p38 MAPK, PI3K-Akt suppression, Notch	Wnt, Notch, EMT, stemness-related pathways
Role in Metastasis	Enables long-term survival pre-relapse	Facilitates invasion, metastasis, resistance
Stemness Association	Often overlaps with cancer stem cells	Strongly linked to stem-like traits
Environmental Influence	Strongly influenced by microenvironment	Highly responsive to external cues

Molecular crosstalk of dormancy and plasticity

Cellular plasticity is a critical determinant of tumour dissemination and distant metastasis. It enables cancer cells within the pre-metastatic niche to evade immune surveillance by undergoing epithelial-to-mesenchymal transition (EMT)^{7,52,53}. Through this phenotypic switch, tumour cells detach more readily from the primary lesion, facilitating dissemination to secondary sites.^{54,55}

A subsequent mesenchymal-to-epithelial transition (MET) allows disseminated cells to exit dormancy, resume proliferation, and colonise distant organs.^{56,57} Thus, phenotypic plasticity endows cancer cells with the adaptability required for survival, growth, and dissemination. In an evolutionary context, cellular plasticity drives both phenotypic diversification and dormancy.⁵⁷ These processes recapitulate Darwinian natural selection, whereby only cells capable of phenotypic switching and dormancy survive unfavourable conditions and expand when the environment becomes permissive.⁵⁸

Alternative evolutionary models—including clonal, neutral, punctuated and barrier theories—have also been proposed. These models consider stochastic mutations, non-genetic influences, and tumour–microenvironment interactions in tumour progression.⁵⁹ A detailed discussion of these theories is beyond the scope of this review.

To withstand hostile cues such as immune attack or chemotherapy, tumour cells may enter dormancy. This state is orchestrated by the transcription factors TWIST1, ZEB1 and SNAI1/SNAIL, which induce EMT via p38-MAPK activation and ERK suppression, culminating in G0/G1 arrest and repression of the cell-cycle regulators NR2F1 and SOX9.^{39,60,61} Dormant cells simultaneously

acquire stem-like traits, characterised by expression of POU5F1/OCT4, NANOG and SOX2, thereby preserving phenotypic flexibility.^{40,62} (Table 3) Epigenetic modifiers—including EZH2, DNA methyltransferases (DNMTs) and histone deacetylases (HDACs)—cooperate or compete to re-model chromatin, silencing proliferation-associated genes while activating survival pathways through locus-specific histone and DNA modifications.^{63–65} (Table 3)

THE REGULATORY NETWORKS OF CELLULAR DORMANCY AND PLASTICITY IN CANCER RECURRENCE

The regulatory networks that govern cancer cell dormancy and plasticity comprise multiple, complex, and interacting molecular mechanisms that can act in opposition to each other, such as maintaining cancer cell dormancy while reactivating their proliferative capacity. These networks involve cell cycle regulators, transcription factors, signaling pathways, and miRNAs.

Cell cycle regulatory networks

Cell-cycle arrest in the G0 phase constitutes a hallmark of cellular dormancy. Multiple intricate signaling cascades modulate this state. For instance, the p38 MAPK pathway suppresses cell-cycle progression by down-regulating cyclins and up-regulating CDK inhibitors, thereby enforcing dormancy^{31,66}. The transforming-growth-factor-β (TGF-β) pathway, acting in concert with p53, induces the CDK inhibitors cyclin-dependent kinase inhibitor 2B (CDKN2B/p15), p21, and p27Kip1, similarly promoting dormancy^{67,68}. Activation of the Notch pathway induces target genes including

Table 3: Summary of some molecular interactions in dormancy and plasticity

Functional Group	Molecules/Pathways	Interaction Type	Effect on Dormancy/Plasticity
Environmental Triggers	Host immune system, Chemotherapy	Activate stress signaling	Initiates dormancy via p38 MAPK activation and ERK suppression
Stress Signaling Pathways	p38 MAPK↑, ERK↓	Antagonistic signaling balance	p38 promotes dormancy; ERK promotes proliferation
EMT Transcription Factors	<i>TWIST1</i> , <i>ZEB1</i> , <i>SNAIL</i>	Cooperative activation during EMT	Induce mesenchymal phenotype and stemness traits
Cell Cycle Regulators	<i>NR2F1</i> , <i>SOX9</i>	Downregulated by EMT TFs and stress signaling	Enforce G0/G1 arrest and suppress proliferation
Stemness Genes	<i>OCT4</i> , <i>NANOG</i> , <i>SOX2</i>	Upregulated by EMT and epigenetic changes	Maintain survival and plasticity during dormancy
Epigenetic Modifiers	<i>EZH2</i> , DNMTs, HDACs	Synergistic repression of proliferation genes	Stabilize dormancy by silencing growth-promoting genes
Phenotypic Plasticity	EMT ↔ MET	Reversible transitions driven by TFs and signaling shifts	EMT induces dormancy; MET enables escape and recurrence
Recurrence Pathways	MET, ERK↑	Reactivation of epithelial traits and proliferation signaling	Promote exit from dormancy and tumor expansion

HES1, HEY1, MYC, cyclin D1 (CCND1), p21, and p27Kip1, thereby maintaining cells in a quiescent state and retarding tumour growth^{69,70}.

Transcription factor networks

Master regulatory transcription factors

Cell-cycle regulatory transcription factors such as p53 and NR2F1 are upregulated by p38-activated CDK inhibitors, driving cancer cells into dormancy. Members of the forkhead box family, such as forkhead box O1 (FOXO1) and forkhead box O2 (FOXO2), participate in multiple cellular processes, including cell-cycle arrest, apoptosis and DNA damage repair.^{68,71,72}

EMT-related transcription factors

Zinc finger E-box-binding homeobox 2 (ZEB2) maintains cellular dormancy by modulating EMT.^{73,74} Downregulation of basigin (BSG/EMMPRIN/CD147) increases the expression of waveform proteins, EMT-induced transcription factors and dormancy markers, thereby suppressing proliferation and angiogenesis.⁷⁵ EMMPRIN is a transmembrane glycoprotein that is critical for cancer progression, cell-cycle regulation and diverse cellular processes.⁷⁶ EMMPRIN is regulated by transcription factors such as hypoxia-inducible factor 1 subunit alpha (HIF1A/HIF-1α) and nuclear

factor kappa B (NF-κB). NF-κB is a major transcriptional regulator of EMMPRIN, particularly during inflammation and tumorigenesis.⁷⁶ HIF-1α directly regulates EMMPRIN expression under hypoxic conditions. EMMPRIN downregulation induces G1 cell-cycle arrest through reduced CCND1 and cyclin levels.^{77,78}

Signaling pathway networks

In addition to a network of regulatory and EMT-related transcription factors, signaling pathways constitute crucial regulators of cancer-cell dormancy and plasticity. Through these pathways, tumor cells can rapidly adapt to an ever-changing extracellular milieu, thereby maintaining their viability.

Major dormancy-inducing pathways

The coordinated activity of multiple signaling cascades—including p38 MAPK/ERK (balance), PI3K–protein kinase B (AKT) (suppression), transforming growth factor-β2 (TGFB2/TGF-β2), ERK/MAPK (suppression), Wnt, Notch, RAS/MAPK, and the unfolded protein response—forms a network in several cancers that establishes and sustains stemness, enabling certain cancer cells to enter a dormant state (Table 4).

Table 4: Signaling pathways inducing dormancy of cancer cells

Pathway	Main Effectors	Molecular Cascade Summary	Clinical Impact on Cancer
p38 MAPK / ERK Balance. ^{79,80}	p38 MAPK, ERK	High p38/ERK low → dormancy/apoptosis. p38 inhibits ERK via feedback	Dormancy in head & neck cancer; ERK-driven proliferation in melanoma, breast cancer
PI3K-Akt Suppression. ⁸¹	PI3K, Akt, PTEN	PI3K → PIP3 → Akt → downstream targets. PTEN inhibits PI3K	Promotes apoptosis; inhibits growth; used in therapy resistance strategies
TGF-β2 Signaling. ^{82,83}	TGF-β2, TβRI/II, SMAD2/3/4	Canonical: SMAD2/3 → SMAD4 → gene regulation. Non-canonical: PI3K/Akt, MAPK, Rho/ROCK	Drives EMT, immune evasion, fibrosis; dual role in tumor suppression & progression
ERK/MAPK Suppression. ^{80,84}	Ras, Raf, MEK, ERK	MEK/ERK inhibitors ↓ERK activity. Activates compensatory survival pathways	Suppresses proliferation; resistance may involve PI3K, NF1 loss; dual inhibition in trials
Wnt and Notch Pathways. ⁸⁴	β-catenin, Frizzled, NICD, CSL complex	Wnt stabilizes β-catenin → transcription. Notch cleavage → NICD → transcription	Maintains stemness; increases EMT & therapy resistance; common in colon, breast, glioblastoma
RAS/MAPK pathway. ^{85,86}	RAS, RAF, MEK, ERK	RAS→RAF→MEK→suppress ERK→ G1/G0, silencing genes (p21, p27).	Cell dormancy and reactivation of dormant cells depending on environmental signals.
Unfolded Protein Response. ⁸⁷	PERK, IRE1, ATF6	ER stress → PERK/IRE1/ATF6 → CHOP, XBP1, eIF2α. Adaptive or apoptotic outcome	Enables survival in hypoxia; associated with dormancy, resistance, and metastatic potential

Major cellular plasticity-inducing signaling pathways

Via distinct mechanisms, the Wnt/β-catenin (CTNNB1), Notch, TGF-β, PI3K–AKT–mTOR^{88,89}, Hedgehog (Hh), Janus kinase (JAK)–signal transducer and activator of transcription 3 (STAT3), and NF-κB pathways often assemble into complex, interconnected networks that, in a context-dependent manner, modulate diverse aspects of cellular plasticity—such as EMT/MET transitions, acquisition of stem-like properties, evasion of immune surveillance, and adaptation to adverse microenvironments (Table 5).

Network of miRNAs

MicroRNAs (miRNAs) are small, single-stranded, non-coding RNAs of approximately 20–24 nucleotides that modulate gene expression at the post-transcriptional level.⁹⁸ In addition to transcriptional repression, miRNAs orchestrate diverse biological programmes, including cell growth, differentiation, proliferation and apoptosis, and help to maintain tissue homeostasis. They also participate in metabolism, immune surveillance and stress responses. Aberrant miRNA expression has

been linked to numerous diseases, notably cancer, where individual miRNAs may behave as oncogenes or tumour suppressors; consequently, they are considered promising therapeutic targets.⁹⁹ Several miRNAs serve as key regulators of cellular dormancy and plasticity: miR-34a, the miR-let-7 family and miR-125b control stem-cell characteristics;^{100,101} miR-200, miR-21 and miR-10b regulate the epithelial–mesenchymal transition (EMT);^{102–104} and miR-190, miR-223, miR-101, miR-126 and miR-26b govern cellular dormancy.^{105–109} (Tables 6 & 7).

Maintenance of cellular dormancy and re-activation of dormant cells

Factors regulating cellular dormancy, encompassing both the maintenance of dormancy and the reactivation of dormant cells (Table 8), play an important role in contemporary cancer treatment strategies. Keeping cancer cells dormant may help prevent disease progression, recurrence, and metastasis.^{119,120} The prevailing clinical perspective holds that preserving tumor dormancy is preferable to aggressive eradication because dormant cells proliferate slowly and frequently remain clinically silent. The central question remains: is it more beneficial to awaken

Table 5: Comparison of major signaling pathways influencing cell plasticity

Pathway	Main Function	Activation Mechanism	Key Transcription Factors	Impact on Plasticity	Relevance to Disease
Wnt/ β -Catenin. ⁹	Cell fate & stem cell renewal	Wnt inhibits β -catenin degradation	TCF/LEF	Promotes expansion & differentiation	Cancer, regeneration
Notch. ⁹²	Binary cell fate decisions	Ligand binding $\rightarrow$ NICD cleavage & nuclear translocation	CSL (RBP-J κ), MAML	Maintains quiescence & EMT regulation	Neurodegeneration, fibrosis, cancer
TGF- β . ⁹³	EMT, immune modulation, fibrosis	Ligand binds T β R $\rightarrow$ Smad activation	Smad2/3 + Smad4	Induces stemness & fibroblast activation	Tumor progression, fibrotic diseases
PI3K/AK	Cell survival, metabolism, growth	PIP3 activation $\rightarrow$ AKT $\rightarrow$ mTOR	FOXO, HIF-1 α	Enhances proliferation, survival, metabolic adaptation	Cancer, metabolic disorders
Hedgehog (Hh). ⁹⁵	Patterning, regeneration	Ligand binding $\rightarrow$ SMO activation via cilia	Gli1/2/3	Controls stem cell proliferation & niche maintenance	Medulloblastoma, basal cell carcinoma
JAK/STAT	Cytokine signaling, inflammation	Ligand activates JAKs $\rightarrow$ STAT3 phosphorylation	STAT3	Supports stemness, immune suppression	Cancer, chronic inflammation
NF- κ B. ⁹⁷	Inflammation, survival, stress response	IKK activation $\rightarrow$ I κ B degradation $\rightarrow$ NF- κ B nuclear entry	NF- κ B (p65/p50)	Facilitates reprogramming & inflammatory microenvironment	Autoimmunity, cancer, aging

Table 6: MiRNA networks in the regulation of cellular plasticity and dormancy in cancer recurrence

miRNA	Key target	Activity
miR-200 family. ¹⁰²	ZEB1, ZEB2	Inhibits EMT, maintains epithelial phenotype
miR-34a. ¹⁰⁰	Notch1, BCL2, CD44	Inhibits stemness, promotes cell death
let-7 family. ¹⁰¹	HMGA2, RAS, LIN28	Inhibition of cell self-renewal and stemness
miR-21. ¹⁰³	PTEN, PDCD4, TPM1	Promote EMT, increase survival and treatment resistance
miR-190. ¹⁰⁵	ATF4, HIF1A	Induces dormancy, responds to stress
miR-223. ¹⁰⁶	IGF1R, FOXO3a	Regulation of immune response and dormancy
miR-101. ¹⁰⁷	EZH2, COX-2	Inhibition of proliferation, associated with dormancy
miR-126. ¹⁰⁸	VEGF, PI3K	Inhibits angiogenesis, supports dormancy
miR-125b. ¹¹⁰	BAK1, LIN28B	Promotes quiescence and inhibits stemness
miR-29b. ¹⁰⁹	DNMT3A/B, MCL1	Epigenetic regulation; promotes dormancy and apoptosis
miR-155. ¹¹¹	SOC1, SHIP1	Increased inflammation and plasticity; associated with relapse
miR-10b. ¹⁰⁴	HOXD10, RHOC	Promotes EMT, invasion and metastasis

Table 7: Key miRNAs participate in networks such as signaling pathways, transcription factor networks, cell cycle regulatory networks involved in cellular plasticity and dormancy, and cancer recurrence.

miRNA	Main target	Related Networks	Biological function	Related Cancers
miR-190 ¹⁰⁵	ATF4, HIF1A	Transcription factor, stress	Induces dormancy through inhibition of proliferation and stress response	Breast, melanoma
miR-223 ¹¹²	IGF1R, FOXO3a	Cell cycle, immune signaling	Promote dormancy and immune regulation	Leukocytes, stomach
miR-101 ¹¹³	EZH2, COX-2	Transcription, epigenetic silencing	Reduced pro-oncogene expression; maintained dormancy via EZH2	prostate, lung
miR-126 ¹¹⁴	VEGF, PI3K	Vascular signaling and cell survival	Inhibits angiogenesis; supports non-mitotic state	Breast, lung
miR-125b ¹¹⁵	BAK1, LIN28B	Apoptosis signaling, stemness	Promotes static state; reduces stemness	Breast, leukocytes
miR-29b ¹¹⁶	DNMT3A/B, MCL1	Epigenetics, apoptosis	Modulates DNA methylation; promotes dormancy through survival gene regulation	Leukocytes, bone marrow
miR-155 ¹¹⁷	SOCS1, SHIP1	Immune signaling, plasticity	Increased inflammation, altered cell phenotype, and associated with relapse	Lymphoma, breast,leukocytes
miR-10b ¹¹⁸	HOXD10, RHOC	EMT, metastasis	Induce EMT and invasion; support awakening	Breast, glioma

dormant tumor cells to target and eliminate them, or to keep them in a dormant state? This issue has sparked significant debate within the medical community.

Some researchers have suggested that keeping tumor cells in a dormant state can be beneficial because these dormant cells are growth-inhibited and do not contribute to tumor growth or metastasis. This dormancy is believed to be maintained by the immune system and by specific signals from the microenvironment,^{121,122} which include a stable extracellular matrix, the suppression of angiogenesis,^{122,123} and surveillance by cytotoxic T cells.^{123,124} The focus of therapeutic efforts should be on supporting the microenvironment that allows disseminated tumor cells (DTCs) to remain dormant, rather than aggressively trying to eliminate them.^{71,125} Clinical observations have indicated that disruptions to this microenvironment—such as inflammation, tissue remodeling, surgery, or trauma—can reactivate dormant cells.^{126,127} Therefore, proponents of this approach have suggested that maintaining a stable state of dormancy may be a better strategy when cell removal is not feasible, as it may help prevent recurrence and metastasis.

Other researchers hold the opposing view that dormant tumor cells pose a long-term threat due to their unpredictable reactivation, which often leads to more aggressive disease recurrence and therapeutic resistance. These dormant cells can evade chemotherapy and radiotherapy because they

are non-proliferative, allowing them to survive initial therapy.^{124,128,129} Once reactivated, they often acquire adaptive drug resistance, evade immune surveillance, and display an increased propensity for metastasis.^{129,130} For example, systemic recurrences of breast cancer and melanoma that occur 5–20 years after primary therapy are thought to result from dormant cancer cells re-entering the cell cycle. This perspective underscores the necessity for therapeutic strategies that specifically target and eradicate dormant cells.¹³¹ Potential approaches include modulation of the ERK/p38 signaling balance,¹³² inhibition of β 1-integrin/FAK pathways,¹³³ and enhancement of immune-mediated clearance mechanisms.¹²⁴

These differing opinions highlight a significant dilemma between disease prevention and eradication. Controlled reactivation of dormant cells may have both beneficial and detrimental effects, but it also offers several therapeutic opportunities. First, reactivation can sensitize chemoresistant dormant cells to conventional treatments.^{21,120} Second, a planned activation–elimination strategy may help prevent late recurrence by avoiding the sudden awakening of dormant cells that leads to metastasis years later.¹¹⁹ Third, elucidating the pathways that regulate the re-entry of dormant cells into the cell cycle could improve our understanding of cancer progression and drug resistance.²¹ We contend that both therapeutic strategies—sustaining dormancy and eradicating dormant tu-

Table 8: Summary of some factors related to maintaining dormancy and reactivation of dormant cells

Factors Involved in Maintaining Cellular Dormancy	Factors Involved in Reactivating Dormant Cells
Cell Cycle Dormant cells typically arrest in G0/G1 phase. Suppression of cyclins and CDKs helps maintain this arrest.	Immune Awakening Immune surveillance changes (e.g., inflammation or loss of immune suppression) can trigger reactivation. Pro-inflammatory cytokines may signal dormant cells to awaken.
Gene Regulation Repressors of proliferation genes (like p21, p27) are upregulated. Epigenetic silencing of growth-promoting genes reinforces dormancy.	Gene Regulation Reactivation involves switching on genes that promote growth, cell cycle progression, and survival. Epigenetic reprogramming plays a key role.
Transcription Factors Certain TFs like FOXO3, p53, and NR2F1 maintain dormancy by repressing growth and survival pathways.	Transcription Factors TFs like MYC, AP-1, and NF-κB promote re-entry into the cell cycle and are often reactivated during awakening.
Signaling Pathways Downregulation of mitogenic signals (e.g., MAPK/ERK) and upregulation of stress/maintenance signals (e.g., TGF-β, p38 MAPK).	Signaling Pathways Reactivation often involves ERK reactivation, Wnt/β-catenin signaling, and PI3K/AKT pathway upregulation.
Metabolic Programming Dormant cells tend to favor low metabolic activity. Shift toward oxidative phosphorylation and minimal biosynthesis to conserve energy.	Single Cell Dynamics Heterogeneity in signaling thresholds and cell state predisposes certain cells to reawaken. Stochastic fluctuations can prime cells for escape from dormancy.
Microenvironmental Factors Niche-derived cues (hypoxia, ECM stiffness, cytokine levels) support dormancy. For example, a low-nutrient, immune-quiet environment can reinforce quiescence.	Metabolic Programming Cells shift to higher metabolic activity to support growth (e.g., increased glycolysis and anabolic metabolism).

Note: some factors, such as gene regulators and transcription factors, play a role in both dormancy and reactivation-just different genes or states are involved.

mor cells (DTCs)—offer distinct advantages and limitations contingent upon the underlying pathobiology and available surveillance modalities. Preservation of the niche to maintain dormancy may be appropriate when the tumor microenvironment is relatively stable and robust monitoring systems are in place. Conversely, when stimuli that promote reactivation—such as inflammation, surgical trauma, or remodeling of the extracellular matrix—are present, interventions designed to detect and eliminate DTCs should be prioritized. At present, evidence is insufficient to endorse either strategy as universally superior. A pragmatic strategy is to individualize therapy according to microenvironmental attributes, biomarkers predictive of dormancy or reawakening, and patient-specific risk–benefit profiles. The principal challenge lies in determining whether dormancy is sufficiently stable to be maintained or if dormant cells are poised to reactivate. Future therapeutic paradigms will likely integrate both tactics: reinforcing the microenvironment to preserve dormancy while deploying precision agents

to selectively ablate residual dormant clones. Priority research objectives include the development of biomarkers capable of quantifying dormancy stability, detecting incipient awakening, and guiding clinical trials that evaluate these combinatorial strategies.

EVOLUTIONARY PERSPECTIVES ON CELLULAR DORMANCY AND PLASTICITY

Examining the evolution of cells from unicellular to multicellular organisms is crucial to understanding the dormancy and plasticity of cancer cells. Consequently, many properties of cancer cells have been discovered that help them proliferate, metastasize, develop drug resistance, and reactivate.

Cellular dormancy: From evolutionary adaptation to cancer

Cellular dormancy represents an evolutionarily conserved survival strategy that enables cells to withstand adverse conditions by entering a state of

reduced metabolic activity. This phenomenon is observed in organisms ranging from unicellular species that generate spores or cysts to complex multicellular species in which tissue-resident stem cells employ dormancy to facilitate tissue repair and preserve homeostasis.^{134,135} Underlying molecular mechanisms rely on sophisticated sensing systems mediated by G-protein-coupled receptors (GPCRs) and downstream signaling cascades, including PI3K-AKT and p38 MAPK, which ultimately activate gene programs required for spore or cyst formation and entry into dormancy.¹³⁶ Cancer cells similarly deploy diverse surface receptors to detect environmental stressors: integrins sense alterations in the extracellular matrix,¹³⁷ Toll-like receptors (TLRs) recognize danger-associated signals,¹³⁸ receptor tyrosine kinases (RTKs) coordinate survival pathways under stress,¹³⁹ and Notch receptors modulate cell-fate decisions.⁹² Collectively, these receptor-mediated mechanisms enable cancer cells to evade immune surveillance, acquire therapeutic resistance, and remain poised for reactivation, thereby driving disease relapse.

Cellular plasticity in evolution and adaptation to the environment

Cellular plasticity—the capacity of a cell to alter its phenotype in response to environmental cues—is critical for development, tissue repair, and disease progression.^{57,140} In unicellular organisms, this plasticity relies on quorum sensing and epigenetic remodeling, enabling adaptation without genetic change.^{141,142} In multicellular organisms, plasticity is indispensable for embryogenesis and for adaptation to environmental challenges.¹⁴³ Cancer cells display pronounced plasticity, shuttling between epithelial and mesenchymal states to augment their migratory and invasive capabilities.¹⁴⁴ This adaptability allows them to acquire stem-cell-like properties, thereby fostering tumor heterogeneity and resistance to therapy.¹⁴⁴ Anticancer treatments impose strong selective pressures; consequently, cancer cells develop genetic or epigenetic alterations that enable them to survive through enhanced drug efflux, epigenetic reprogramming, and the activation of alternative signaling cascades, including PI3K-AKT, MAPK, and NF- κ B.¹⁴⁵ Cellular dormancy and plasticity may likewise have been pivotal for the origin and survival of early life on Earth. Only organisms capable of switching to a suitable phenotype and acquiring sufficient resistance to adverse environmental conditions could

avoid extinction.¹³⁴ By analogy, only tumor cells that attain stemness—cancer stem cells (CSCs)—during their lifespan can survive adverse environmental conditions and resist therapy owing to their ability to become dormant and their plasticity.^{7,143}

CLINICAL MANIFESTATIONS OF DORMANCY AND PLASTICITY IN CANCER RECURRENCE

The dormancy and plasticity of cancer cells are pivotal determinants of the clinical course of cancer. Only those cancer cells capable of genome reprogramming toward a stem-like state under adverse conditions survive therapy. Dormant cells typically display plasticity and resistance to chemotherapy, radiotherapy, and immune-mediated apoptosis, thereby forming a reservoir for recurrence once conditions become favorable.¹⁴⁶

Dormant tumour cells are continuously shaped by the tumour microenvironment (TME), which remains in intimate contact with them and modulates both dormancy and phenotypic plasticity. Consequently, the TME orchestrates cancer-cell proliferation, migration, invasion, and drug resistance. Integrin receptors within the stromal extracellular matrix (ECM) are critical in this regard,^{133,147} as they constitute the first point of contact for disseminating cancer cells, permitting adhesion to the pre-metastatic niche.¹⁴⁸ Cancer-associated fibroblasts (CAFs) define ECM composition and promote tumour progression by regulating integrins and signalling pathways such as TGF- β .¹⁴⁹ Nevertheless, the precise mechanisms by which the ECM governs cancer-cell dormancy remain to be elucidated.

The ECM also confers therapy resistance by functioning as a mechanical barrier and by engaging integrin-dependent signalling that sustains cancer stem-cell (CSC) pools.¹⁵⁰ Within the tumour stroma, immune cells contribute to immune-mediated dormancy: CD8⁺ and CD4⁺ T cells secrete interferon- γ (IFN- γ) and tumour necrosis factor- α (TNF- α), which arrest tumour cells in G0/G1, thereby suppressing proliferation and preserving dormancy.^{124,151} Immune-checkpoint pathways further modulate this balance; engagement of programmed cell death protein-1 (PD-1/PDCD1) and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) can maintain dormancy or prevent reactivation. Dormancy is additionally reinforced by CD4⁺ T-cell-derived chemokines CXCL9 and CXCL10, whose anti-angiogenic properties restrict tumour activity and promote quiescence.¹⁵²

Within minimal residual disease (MRD) niches, dormant cells may escape immune surveillance by up-regulating the checkpoint ligand PD-L1 (CD274/B7-H1), thereby suppressing cytotoxic T-lymphocyte (CTL) activity. Resistance to apoptosis is further mediated by epigenetic silencing of suppressor of cytokine signalling-1 (SOCS1) in concert with cytokine signalling.¹⁵³ Natural killer (NK) cells likewise exert direct cytotoxicity and shape T-cell responses, whereas CD8⁺ T cells help preserve equilibrium with dormant tumour cells.¹⁵³

Clinical investigations are increasingly clarifying the roles of dormancy, plasticity, immune effectors, and signalling pathways in recurrence and therapy resistance (Table 9). Emerging biotechnologies will be indispensable for devising interventions that eradicate dormant cancer cells and modulate their plasticity.

TREATMENT STRATEGIES BASED ON THE MECHANISM OF TUMOR CELL DORMANCY AND PLASTICITY

Targeting cancer-cell dormancy and its associated plasticity represents an increasingly important avenue in oncology. Owing to their stem-like properties, dormant tumour cells display marked plasticity, resist conventional therapy, and are capable of self-renewal after re-awakening, ultimately driving disease relapse. Current therapeutic concepts include:

- Inhibition of pro-survival signalling. Quiescent cells depend on pathways such as PI3K/AKT/mTOR and ERK/MAPK for survival under stress. Agents such as selumetinib, a MEK inhibitor, can suppress their reactivation.¹⁵⁴
- Prevention of re-entry into the cell cycle. Dormant-cell awakening can be curtailed by neutralising cytokines (e.g., interleukin-6 and colony-stimulating factor-3) and by disrupting extracellular-matrix–integrin interactions that trigger proliferative signalling.¹⁵⁴
- Exploitation of cellular plasticity. Because plasticity underlies drug resistance and metastatic competence, strategies that either lock cells in a non-proliferative state or force terminal differentiation may limit relapse. Combination regimens that simultaneously target proliferating and dormant populations are showing promise.¹⁵⁵

- Immunotherapeutic eradication. Dormant cells can evade immune surveillance; therefore, immune-checkpoint blockade and other immunomodulators are being investigated to facilitate their clearance.^{154,156}
- Biomarker development. Mechanistic insights into dormancy are enabling identification of biomarkers that forecast recurrence risk and therapeutic response.^{120,154} Elevated circulating levels of specific microRNAs—miR-21 (promotes proliferation and metastasis), miR-200c (regulates epithelial–mesenchymal transition) and miR-23b (linked to dormancy)—have been correlated with breast-cancer relapse.¹⁵⁷

KEY CHALLENGES AND FUTURE RESEARCH DIRECTIONS

Cancer cells behave as independent, autonomous entities that evade physiological control, surpassing even the most sophisticated mechanisms of the human immune system. They can inactivate the PD-1 immune checkpoint on cytotoxic T lymphocytes by endogenously expressing its ligand, PD-L1. Notably, the efficacy of virtually every novel therapeutic regimen declines soon after implementation as treatment-resistant cancer cell clones emerge. A further challenge is the capacity of malignant cells to acquire stem-like characteristics, entering a quiescent state that permits immune evasion and therapeutic resistance, yet preserves plasticity enabling proliferation and phenotypic switching upon reactivation. Consequently, identifying strategies to eradicate tumor cell dormancy and plasticity remains one of the most formidable objectives in oncology. Although substantial progress has been achieved, considerable obstacles persist.

Key challenges

- The lack of reliable biomarkers: Because dormant tumor cells cannot be visualized by conventional methodologies such as histopathology or standard imaging modalities, the identification and validation of robust, specific biomarkers are critical.^{120,154}
- Drug resistance: Dormant tumor cells are arrested in the G0/G1 phase of the cell cycle, and their basal metabolism is markedly reduced, allowing them to evade therapies that target proliferating cells. Their phenotypic plasticity enables rapid switching, contributing to drug tolerance and relapse.¹⁴⁴

- Limitations of current in vitro and in vivo models: Existing models fail to recapitulate the dormant state of tumor cells and do not accurately reproduce the tumor microenvironment (TME) or pre-metastatic niches.^{120,156} Consequently, therapeutic testing in these systems may yield misleading results.
- Gap in clinical translation (“the valley of death”): Although promising preclinical data have been generated for a limited number of dormancy-targeted therapies, comparable benefits have not yet been demonstrated in the clinic. Integrating such strategies into standard-of-care regimens therefore remains a substantive challenge.¹²⁰

Table 9: Crucial original research related to many aspects of tumor cell dormancy and plasticity in clinical and preclinical settings.

Dormancy & Plasticity	Preclinical/clinical model	Sample/ experimental	Key findings	Reference
Signalling-driven dormancy — ERK/p38 ratio controls proliferation vs dormancy	Human carcinoma cell lines + mouse xenografts (mechanistic in vivo model)	Multiple human lines and several mouse cohorts/ xenograft experiments (see paper for per-experiment n).	High p38 : ERK activity (low ERK) drives long-term growth arrest (dormancy) in vivo; manipulating uPAR/integrin/ERK–p38 converts dormancy ↔ outgrowth. Mechanistic foundation for microenvironmental control of dormancy.	Aguirre-Ghiso JA ⁷⁹
Transcriptional/ep dormancy node (plasticity to quiescence) — NR2F1-driven program	Preclinical mouse DTC models + analyses of human DTC samples (translational)	Multiple in vivo DTC experiments + human DTC cohorts/validation samples (see methods).	NR2F1 activates SOX9 / RARβ / CDK inhibitors and global chromatin repression to induce quiescence in disseminated tumour cells (DTCs); blocking NR2F1 reactivates DTC outgrowth.	Sosa MS et al. ¹⁵⁸
Pharmacologic induction of dormancy — NR2F1 agonist shows dormancy induction across models	Preclinical: 3D cultures, patient-derived organoids, PDXs, and mouse metastasis models	Multiple in vitro and in vivo experiments across cell lines, organoids, and PDXs (replicates described in paper).	An NR2F1-specific small-molecule agonist induced transcriptional dormancy programs, arrested growth of cancer cells, and reduced metastatic outgrowth in vivo — proof of concept that dormancy can be therapeutically induced.	Khalil BD et al. ¹⁵⁹
ECM-driven dormancy & reactivation (plasticity via matrix remodeling) — fibronectin matrix maintenance and MMP-mediated awakening	Long-term in vitro dormancy assays on defined ECM / 3D matrices (breast cancer lines)	Screened 23 human breast cancer cell lines; subsets sustained dormancy for weeks in culture (detailed line counts/timepoints in paper).	Cells that enter long dormancy build a fibrillar fibronectin matrix (α5β1/αvβ3, ROCK, TGFβ2); outgrowth after dormancy required MMP-2–mediated fibronectin degradation — ECM assembly/disassembly controls dormancy ↔ reactivation.	Barney LE et al. ¹⁶⁰

Organ-specific microphysiologic niche induces dormancy — liver MPS shows spontaneous quiescence	All-human liver microphysiologic system (primary hepatocytes + NPCs) seeded with breast cancer cells (ex vivo organoid-like MPS)	Experiments with MDA-MB-231 (and other lines) using donor primary hepatocytes; system maintains hepatic function over 2 weeks (multiple donors/replicates).	A subset of breast cancer cells became viable but non-proliferative (spontaneous dormancy) within the human liver microphysiologic system — demonstrates organ niche alone can impose dormancy.	Clark AM et al. ¹⁶¹
Engineered bone-marrow microenvironment (eBM) — bone niche remodeling and colonization	Tissue-engineered human bone-marrow construct colonized by breast cancer cell lines and patient organoids	Multi-condition experiments; validated with primary patient-derived breast cancer organoids and TNBC lines (replicates reported).	An engineered human bone-marrow model supports colonization and reveals how breast cancer cells remodel hematopoietic niche cues that influence proliferation vs quiescence — humanized platform to interrogate dormancy.	Baldassarri I et al. ¹⁶²
Bone-on-a-chip (microfluidic) — niche heterogeneity controlling dormancy	3D-printed bone-on-a-chip with GelMA hydrogels, MSCs, osteoclast precursors and tumour cells	Device experiments with cancer cell lines (A549 example), MSCs and osteoclast lineage cells; multiple technical/biological replicates.	The platform recapitulates discrete bone niches (dormancy vs perivascular vs “vicious cycle”) and allows study of niche-dependent reactivation, invadopodia formation and tumor–bone interactions under flow.	Ji X et al. ¹⁶³
Cell-cell 3D interactions drive dormancy (cannibalism & plasticity) — hanging-drop cocultures of MSCs + cancer cells	3D hanging-drop spheroid cocultures with MDA-MB-231 BCCs and bone marrow MSCs; multiple culture replicates; confirmatory in vivo experiments in paper	Authors show in vitro cannibalism phenomena across replicates; in vivo corroboration reported.	In hanging-drop 3D cocultures, breast cancer cells cannibalize MSCs under stress, which correlates with a dormancy-like, more resilient phenotype and suppressed immediate tumor formation — highlights how direct cell–cell interactions in 3D influence dormancy/plasticity.	Bartosh TJ et al. ¹⁶⁴
EMT/partial-EMT plasticity states — high-resolution single-cell evidence	Genetic mouse tumour models (SCC) and single-cell profiling; translational profiling across tumours	Extensive single-cell datasets from mouse models and patient samples (hundreds–thousands of cells across tumors).	Identified discrete intermediate (hybrid) EMT states in vivo with distinct invasiveness, stemness and plasticity properties — supports a model where plasticity (not binary EMT) enables survival, dissemination and therapy resistance relevant to recurrence.	Pastushenko I et al. ¹⁶⁵

Single-cell EMT/MET trajectories in human tumours — mapping plasticity in clinical samples	Patient tumour specimens + mass-cytometry and single-cell analyses (translational)	Single-cell / mass-cytometry datasets across patient samples and time-course experiments (detailed counts in paper).	Constructed an EMT–MET phenotypic map (PHENOSTAMP) showing multiple EMT/MET states in human lung tumours and trajectories between them — clinically relevant single-cell evidence of plasticity that can underpin dormancy/reactivation dynamics.	Karacosta LG et al. ¹⁶⁶
Adaptive immunity enforces an ‘equilibrium’ (immune-mediated dormancy) — immune system restrains occult tumours (immune equilibrium).	Chemical carcinogenesis mouse model comparing immunocompetent vs immunodeficient hosts (in vivo).	Wild-type mice were tumorigenic with the chemical carcinogen 39-methylcholanthrene treated with immunoglobulin, and monitored for tumor progression.	Demonstrated an immune-mediated equilibrium phase in which adaptive immunity (T cells/IFN γ) holds transformed cells in check (occult, poorly proliferative neoplastic cells) — distinct from elimination or escape. Foundational experimental proof that adaptive immunity can maintain long-term tumour dormancy.	Koebel et al. ¹⁶⁷
Cytostatic CD8⁺ T cells restrain disseminated cells (tissue-specific dormancy control) — CD8 T cells slow/hold DTCs.	Spontaneous murine melanoma model; depletion/functional studies of CD8 T cells (in vivo).	Mouse cohorts, depletion experiments; ATCC TIB-210 rat and depleted CD8 ⁺ T cells	Showed disseminated tumour cells appear early and that cytostatic CD8 ⁺ T cells contribute to tissue-specific dormancy (CD8 depletion accelerated metastatic outgrowth). Supports role of cytostatic T cells in maintaining dormancy.	Eyles et al. ¹⁵¹
NETs (neutrophil extracellular traps) awaken dormant cells — inflammation → proteolytic ECM remodelling → reactivation	Mouse lung inflammation / experimental metastasis models (tumour cell lines D2.0R, MCF7; LPS or smoke models to trigger NETs).	Multiple mouse experiments/ conditions; murine D2.0R cell line, human MCF-7 cell line, Isolated neutrophils were cultured	Sustained inflammation caused neutrophil-NET formation; NET-associated proteases (NE, MMP9) cleaved laminin → remodeled ECM that activated integrin $\alpha 3 \beta 1$ on DTCs and triggered exit from dormancy. NET blockade or DNase prevented awakening. Strong mechanistic link: inflammation/NETs awaken dormant DTCs.	Albregues et al. ¹⁶⁸
A defined CD8⁺ T-cell subset (CD39⁺PD-1⁺) enforces metastatic dormancy — T-cell-mediated dormancy with translational correlation.	Preclinical murine breast cancer dormancy models + high-dimensional single-cell mapping; translational correlation with human breast cancer samples (IHC / multiplex IF and survival analysis).	Preclinical single-cell and functional studies; human cohort n = 54 for disease-free survival correlation.	Identified CD39 ⁺ PD-1 ⁺ CD8 ⁺ T cells in tumors and dormant metastases; blocking TNF α /IFN γ disrupted dormancy in mice. In human samples, high intra-tumoral density of this subset correlated with longer disease-free survival — supports specific T-cell subsets as dormancy enforcers.	Tallón de Lara et al. ¹⁶⁹

Future research directions

Cellular dormancy and cellular plasticity are recognized as pivotal drivers of cancer recurrence, yet they remain incompletely understood. Therefore, future investigations should prioritize refined methodologies that accurately identify dormant cells and either prevent their re-activation or the initiation of dormancy.

- **State-of-the-art single-cell and spatial transcriptomics:** Single-cell transcriptomics enables interrogation of gene-expression profiles in individual cells, facilitating the detection of cells with dormancy-associated signatures that may be missed by conventional bulk analyses. Spatial transcriptomics simultaneously maps these signatures in situ, permitting evaluation of micro-environmental cues that sustain dormancy or trigger re-awakening, and allows longitudinal tracking of phenotypic evolution that underlies drug resistance and recurrence.¹⁷⁰
- **Artificial-intelligence-driven predictive modelling:** Advances in AI are ushering in a new era of understanding and managing cancer recurrence, particularly through the identification of dormant cells and characterization of cellular plasticity. With multidimensional data-integration capacity, the Clinical Histopathology Imaging Evaluation Foundation (CHIEF) model can infer tumour molecular attributes from histological images, aiding in the recognition of dormant cells that pose a risk of relapse.¹⁷¹ AI-based platforms can also synthesise genomic, transcriptomic, proteomic and epigenomic data, enabling comprehensive appraisal of tumour biology, refined recurrence prediction and subsequent personalisation of therapeutic regimens and follow-up.¹⁷²
- **Targeting epigenetic and metabolic vulnerabilities:** Epigenetic analyses can reveal chromatin states that permit tumour cells to persist in dormancy, and pharmacological modulation of these states can suppress EMT by regulating pertinent genes.¹⁷³ Metabolic profiling can distinguish dormant cells by their low-flux signatures—such as reliance on oxidative phosphorylation and fatty-acid oxidation—thereby differentiating them from proliferative counterparts. Because metabolic and epigenetic programmes interact to dictate cancer-cell state, co-targeting both processes may enhance therapeutic efficacy and diminish recurrence risk.¹⁷⁴

- **Modulating the tumour micro-environment (TME):** Dormancy is maintained by TME factors including hypoxia, cytokine milieu and extracellular-matrix stiffness, which also foster immune evasion and drug resistance.¹⁷⁵ Strategies that re-engineer the TME—e.g., adjusting pH, oxygenation or extracellular-matrix composition—to improve drug penetration, invigorate antitumour immunity and curtail dormant-cell survival are therefore under active investigation.¹⁷⁶

CONCLUSIONS

Cancer recurrence remains a major clinical challenge, largely driven by two interrelated phenomena: cellular dormancy and cellular plasticity. These mechanisms enable subsets of cancer stem cells (CSCs) to withstand therapy and subsequently re-enter the cell cycle. Through phenotypic plasticity, malignant cells can disseminate from the primary tumour to distant organs, including pre-metastatic niches. During the initial phase of niche colonisation, disseminated tumour cells frequently enter a dormant state that permits survival under cytotoxic stress and evasion of immune surveillance. A complex signalling network—including miRNAs, cell-cycle regulators, and transcription factors—orchestrates the crosstalk between dormancy and plasticity. Paradoxically, prolonging dormancy, rather than triggering reactivation, may be clinically beneficial, as the disease then persists only as minimal residual disease (MRD). Consequently, it is imperative to predict and prevent recurrence by identifying dormant tumour cells and developing interventions that either eradicate them or maintain their quiescence. Future research should prioritise the use of advanced biological technologies to devise strategies that actively modulate dormancy and plasticity in cancer cells.

ABBREVIATIONS

Akt: Ak strain transforming; **AP1:** activator protein 1; **ATF4:** Activating Transcription Factor 4; **ATF6:** Activating Transcription Factor 6; **BAK1:** BRI1-Associated Receptor Kinase 1; **BAG:** Basigin (another name of EMMPRIN); **BMP:** Bone Morphogenetic Protein; **CAFs:** Cancer-associated fibroblasts; **CD147:** cluster of differentiation 147 (another name of EMMPRIN); **CDK:** Cyclin-Dependent Kinase; **CHOP:** C/EBP homologous protein; **CKIs:** Cyclin-dependent kinase inhibitors; **COX-2:** Cyclooxygenase-2; **CSCs:** cancer stem cells; **CSL:** CBF1, Suppressor of Hairless (Su(H)), and

Lag-1 protein: CBF1; **CTCs**: Circulating tumor cells; **CTL**: Cytotoxic T-lymphocyte; **CTLA-4**: Cytotoxic T-lymphocyte associated protein 4; **CXCL9**: Chemokine (C-X-C motif) ligand 9; **DAPK3**: Death-Associated protein kinase 3; **DNMTs**: DNA Methyltransferases; **DTCs**: Disseminated tumor cells; **ECM**: Extracellular matrix; **eIF2 α** : eukaryotic translation initiation factor 2 α ; **EMMPRIN**: Extracellular Matrix Metalloproteinase Inducer; **EMT**: Epithelial-mesenchymal transition; **ERK**: Extracellular signal-regulated kinase; **EZH2**: Enhancer of zeste 2 polycomb repressive complex 2 subunit; **FOXO1**: Forkhead box O1; **G-CSF**: Granulocyte-Colony Stimulating Factor; **Gli1**: Glioma-associated oncogene homolog 1; **GPCRs**: G protein-coupled receptors; **HDACs**: histone deacetylases; **HES1**: Hairy and Enhancer of Split-1; **HEY1**: Hairy/enhancer of split related with YRPW motif 1; **HIF-1 α** : Hypoxia-Inducible Factor 1 Alpha; **HMGA2**: High Mobility Group AT-hook 2; **hNanog**: Homeobox protein NANOG; **HOXD10**: Homeobox D10; **IFN- γ** : Interferon-gamma; **IGF1R**: Insulin-Like growth factor 1 receptor; **IKK/IKB**: Ikbpp kinase; **IL-6**: Interleukin-6; **IRE1**: Inositol-requiring enzyme type 1; **JAKs**: Janus Kinase; **LIN28**: conserved RNA-binding protein called lin-28 homolog; **lncRNAs**: long non-coding RNAs; **MANL**: Mammalian Mastermind-like proteins; **MCL1**: Myeloid cell leukemia-1; **MEK**: mitogen-activated extracellular signal-regulated kinase; **MET**: Mesenchymal-epithelial transition; **MiRNAs**: MicroRNAs; **MRD**: Minimal residual disease; **mRNA**: Messenger RNA; **MYC**: Myeloid Cytomatosis; **NF1**: Neurofibromatosis 1 gene; **NF- κ B**: Nuclear Factor Kappa B; **NICD**: Notch intracellular domain; **NR2F1**: Nuclear Receptor Subfamily 2 Group F Member 1; **OCT4**: Octamer-binding transcription factor 4; **PD1**: Programmed cell death protein-1; **PDCD4**: Programmed Cell Death 4; **PD-L1**: Programmed Death-Ligand 1; **PERK**: protein kinase RNA-like endoplasmic reticulum kinase; **PGC1 α** : Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; **PI3K**: phosphatidylinositol-3 kinase; **PIP3**: Phosphatidylinositol (3,4,5)-trisphosphate; **PTEN**: Phosphatase and TENsin homolog deleted on chromosome 10; **RAF**: Rapidly accelerated fibrosarcoma; **RAT**: RAT Sarcoma; **RBP-Jk**: Recombination signal sequence-binding protein Jk; **RhoC**: Ras homolog gene family, member C; **ROCK**: Rho-associated protein kinase; **RTKs**: Receptor tyrosine kinases; **SASP**: Senescence-Associated secretory phenotype; **SHIP1**: inositol polyphosphate 5-phosphatase

1; **SMAD4**: Mothers against decapentaplegic homolog 4; **SMO**: smoothened, frizzled class receptor; **SNAIL**: zinc-finger transcription factor family; **SOCS1**: Suppressor of cytokine signaling 1; **SOX2**: SRY-box transcription factors 2; **SOX9**: SRY-related HMG box gene 9; **STAT3**: Signal Transducer and activator of transcription 3; **TCF/LEF**: T cell factor/lymphoid enhancer factor family; **TGF- β 2**: transforming growth factor β 2; **TFs**: transcription factors; **TLRs**: Toll-like receptors; **TPM1**: Tropomyosin 1; **TWIST1**: transcription factor Twist-related protein 1; **T β RI**: T β RI receptor; **UPR**: unfolded protein response; **VEGF**: Vascular endothelial growth factor; **XBP1**: IRE1 α -X-box-binding protein 1; **ZEB1**: Zinc finger E-box binding homeobox 1.

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The authors declare that they did not use AI in writing the manuscript before submission.

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The authors declare that they have no competing interests.

REFERENCES

- Zarghami A, Mirmalek SA. Differentiating Primary and Recurrent Lesions in Patients with a History of Breast Cancer: A Comprehensive Review: Differentiating Primary and Recurrent Lesions in Patients with BC. *Galen Med J*. 2024;13:e3340. Available from: <https://doi.org/10.31661/gmj.v13i.3340>.
- Dowling RJO, Kalinsky K, Hayes DF, et al. Toronto Workshop on Late Recurrence in Estrogen Receptor-Positive Breast Cancer: Part 1: Late Recurrence: Current Understanding, Clinical Considerations. *JNCI Cancer Spectr*. 2019;3(4):pkz050. Available from: <https://doi.org/10.1093/jncics/pkz050>.
- Morales-Valencia J, David G. The origins of cancer cell dormancy. *Curr Opin Genet Dev*. 2022;74:101914. Available from: <https://doi.org/10.1016/j.gde.2022.101914>.
- Aguirre-Ghiso JA. Models, mechanisms and clinical evidence for cancer dormancy. *Nat Rev Cancer*. 2007;7(11):834–846. Available from: <https://doi.org/10.1038/nrc2256>.
- Heidrich I, Deitert B, Werner S, Pantel K. Liquid biopsy for monitoring of tumor dormancy and early detection of disease recurrence in solid tumors. *Cancer Metastasis Rev*. 2023;42(1):161–182. Available from: <https://doi.org/10.1007/s10555-022-10075-x>.
- Agudo J, Aguirre-Ghiso JA, Bhatia M, Chodosh LA, Correia AL, Klein CA. Targeting cancer cell dormancy. *Nat Rev Cancer*. 2024;24(2):97–104. Available from: <https://doi.org/10.1038/s41568-023-00642-x>.
- Malladi S, Macalinao DG, Jin X, et al. Metastatic Latency and Immune Evasion through Autocrine Inhibition of WNT. *Cell*. 2016;165(1):45–60. Available from: <https://doi.org/10.1016/j.cell.2016.02.025>.
- lei Gao X, Zheng M, fan Wang H, et al. NR2F1 contributes to cancer cell dormancy, invasion and metastasis of salivary adenoid cystic carcinoma by activating CXCL12/CXCR4 pathway. *BMC Cancer*. 2019;19(1):743. Available from: <https://doi.org/10.1186/s12885-019-5925-5>.
- Ghiso JAA, Kovalski K, Ossowski L. Tumor Dormancy Induced by Downregulation of Urokinase Receptor in Human Carcinoma Involves Integrin and MAPK Signaling. *J Cell Biol*. 1999;147(1):89–104. Available from: <https://doi.org/10.1083/jcb.147.1.89>.
- Chia SB, Johnson BJ, Hu J, et al. Respiratory viral infections awaken metastatic breast cancer cells in lungs. *Nature*. 2025;645(8080):496–506. Available from: <https://doi.org/10.1038/s41586-025-09332-0>.
- Laguillaumie MO, Titah S, Guillemette A, et al. Deciphering genetic and nongenetic factors underlying tumour dormancy: insights from multiomics analysis of two syngeneic MRD models of melanoma and leukemia. *Biol Res*. 2024;57(1):59. Available from: <https://doi.org/10.1186/s40659-024-00540-y>.
- Li B, Zheng L, Yang J, Qu L. Targeting oncogene-induced cellular plasticity for tumor therapy. *Adv Biotechnol*. 2024;2(3):24. Available from: <https://doi.org/10.1007/s44307-024-00030-y>.
- Zhao F, Zhang T, Wei J, et al. Integrated single-cell transcriptomic analyses identify a novel lineage plasticity-related cancer cell type involved in prostate cancer progression. *eBioMedicine*. 2024;109:105398. Available from: <https://doi.org/10.1016/j.ebiom.2024.105398>.
- Moorman A, Benitez EK, Cambulli F, et al. Progressive plasticity during colorectal cancer metastasis. *Nature*. 2025;637(8047):947–954. Available from: <https://doi.org/10.1038/s41586-024-08150-0>.
- Yang X, Liang X, Zheng M, Tang Y. Cellular Phenotype Plasticity in Cancer Dormancy and Metastasis. *Front Oncol*. 2018;8:505. Available from: <https://doi.org/10.3389/fonc.2018.00505>.
- D'Antonio C, Liguori GL. Dormancy and awakening of cancer cells: the extracellular vesicle-mediated cross-talk between Dr. Jekyll and Mr. Hyde. *Front Immunol*. 2024;15:1441914. Available from: <https://doi.org/10.3389/fimmu.2024.1441914>.
- Min HY, Lee HY. Cellular Dormancy in Cancer: Mechanisms and Potential Targeting Strategies. *Cancer Res Treat*. 2023;55(3):720–736. Available from: <https://doi.org/10.4143/crt.2023.468>.
- Endo H, Inoue M. Dormancy in cancer. *Cancer Sci*. 2019;110(2):474–480. Available from: <https://doi.org/10.1111/cas.13917>.
- Truskowski K, Amend SR, Pienta KJ. Dormant cancer cells: programmed quiescence, senescence, or both? *Cancer Metastasis Rev*. 2023;42(1):37–47. Available from: <https://doi.org/10.1007/s10555-022-10073-z>.
- Neophytou CM, Kyriakou TC, Papageorgis P. Mechanisms of Metastatic Tumor Dormancy and Implications for Cancer Therapy. *Int J Mol Sci*. 2019;20(24):6158. Available from: <https://doi.org/10.3390/ijms20246158>.
- Yeh AC, Ramaswamy S. Mechanisms of Cancer Cell Dormancy—Another Hallmark of Cancer? *Cancer Res*. 2015;75(23):5014–5022. Available from: <https://doi.org/10.1158/0008-5472.CAN-15-1370>.
- Bakhshandeh S, Werner C, Fratzl P, Cipitria A. Microenvironment-mediated cancer dormancy: Insights from metastability theory. *Proc Natl Acad Sci*. 2022;119(1):e2111046118. Available from: <https://doi.org/10.1073/pnas.2111046118>.
- Francescangeli F, De Angelis ML, Rossi R, et al. Dormancy, stemness, and therapy resistance: interconnected players in cancer evolution. *Cancer Metastasis Rev*. 2023 February; Available from: <https://doi.org/10.1007/s10555-023-10092-4>.
- Spano D, Zollo M. Tumor microenvironment: a main actor in the metastasis process. *Clin Exp Metastasis*. 2012;29(4):381–395. Available from: <https://doi.org/10.1007/s10585-012-9457-5>.
- Ring A, Spataro M, Wicki A, Aceto N. Clinical and Biological Aspects of Disseminated Tumor Cells and Dormancy in Breast Cancer. *Front Cell Dev Biol*. 2022;10:929893. Available from: <https://doi.org/10.3389/fcell.2022.929893>.
- Pradhan L, Moore D, Ovadia EM, et al. Dynamic bioinspired coculture model for probing ER+ breast cancer dormancy in the bone marrow niche. *Sci Adv*. 2023;9(10):eade3186. Available from: <https://doi.org/10.1126/sciadv.ade3186>.
- Mu Y, Wallenius A, Zang G, et al. The TβRI promotes migration and metastasis through thrombospondin 1 and ITGAV in prostate cancer cells. *Oncogene*. 2024;43(45):3321–3334. Available from: <https://doi.org/10.1038/s41388-024-03165-3>.
- Deng Y, Li Y, Yang M, et al. Carfilzomib activates ER stress and JNK/p38 MAPK signaling to promote apoptosis in hepatocellular carcinoma cells. *Acta Biochim Biophys Sin*. 2024 March; Available from: <https://doi.org/10.3724/abbs.2024040>.
- Della Volpe L, Midea F, Vacca R, et al. A p38 MAPK-ROS axis fuels proliferation stress and DNA damage during CRISPR-Cas9 gene editing in hematopoietic stem and progenitor cells. *Cell Rep Med*. 2024;5(11):101823. Available from: <https://doi.org/10.1016/j.xcrm.2024.101823>.
- Trotter TN, Dagotto CE, Serra D, et al. Dormant tumors circumvent tumor-specific adaptive immunity by establishing a Treg-dominated niche via DKK3. *JCI Insight*. 2023;8(22):e174458. Available from: <https://doi.org/10.1172/jci.insight.174458>.
- Bakhshandeh S, Heras U, Taieb HM, et al. Dormancy-inducing 3D engineered matrix uncovers mechanosensitive and drug-protective FHL2-p21 signaling axis. *Sci Adv*. 2024;.
- Aguirre-Ghiso JA, Estrada Y, Liu D, Ossowski L. ERK(MAPK) activity as a determinant of tumor growth and dormancy: regulation by p38(SAPK). *Urol Oncol Semin Orig Invest*. 2004;22(1):82. Available from: <https://doi.org/10.1016/j.urolonc.2003.12.012>.
- Kim JW, Bae SH, Moon Y, et al. Transcriptomic analysis of cellular senescence induced by ectopic expression of ATF6α in human breast cancer cells. *PLOS ONE*. 2024;19(10):e0309749.

34. Liu R, Su S, Xing J, et al. Tumor removal limits prostate cancer cell dissemination in bone and osteoblasts induce cancer cell dormancy through focal adhesion kinase. *J Exp Clin Cancer Res.* 2023;42(1):264. Available from: <https://doi.org/10.1186/s13046-023-02849-0>.
35. Ain QU. Cellular senescence and tumor dormancy at the crossroads of therapy resistance, metastasis and cancer stemness. *Asia-Pac J Oncol.* 2024 October; Available from: <https://doi.org/10.32948/ajo.2024.12.25>.
36. Pérez-González A, Bévant K, Blanpain C. Cancer cell plasticity during tumor progression, metastasis and response to therapy. *Nat Cancer.* 2023;4(8):1063–1082. Available from: <https://doi.org/10.1038/s43018-023-00595-y>.
37. Stem Cells and Cancer. 2009; Available from: <https://doi.org/10.1007/978-1-60327-933-8>.
38. Khan BD, Nhi NTY, Nhan TNT, Khuong PD. Cancer cell dormancy: An update to 2025. *Biomed Res Ther.* 2025;12(7):7559–7575. Available from: <https://doi.org/10.15419/ttm97s19>.
39. Singh DK, Carcamo S, Farias EF, et al. 5-Azacytidine and retinoic-acid-induced reprogramming of DCCs into dormancy suppresses metastasis via restored TGF- β -SMAD4 signaling. *Cell Rep.* 2023;42(6):112560. Available from: <https://doi.org/10.1016/j.celrep.2023.112560>.
40. Zhang M. Nanog mediated by FAO/ACLY signaling induces cellular dormancy in colorectal cancer cells. *Cell Death Dis.* 2022;.
41. Kim H, Wirasaputra A, Mohammadi F, et al. Live Cell Lineage Tracing of Dormant Cancer Cells. *Adv Healthc Mater.* 2023;12(14):2202275. Available from: <https://doi.org/10.1002/adhm.202202275>.
42. Dai L, Xian H, Wang H, et al. Hypoxia induced cell dormancy of salivary adenoid cystic carcinoma through miR-922/DEC2 axis. *Transl Oncol.* 2024;40:101868. Available from: <https://doi.org/10.1016/j.tranon.2023.101868>.
43. Celià-Terrassa T, Kang Y. Metastatic niche functions and therapeutic opportunities. *Nat Cell Biol.* 2018;20(8):868–877. Available from: <https://doi.org/10.1038/s41556-018-0145-9>.
44. Liu Y, Liang X, Yin X, et al. Blockade of IDO-kynurenine-AhR metabolic circuitry abrogates IFN- γ -induced immunologic dormancy of tumor-repopulating cells. *Nat Commun.* 2017;8(1):15207. Available from: <https://doi.org/10.1038/ncomms15207>.
45. Singh KK, Ghosh S, Bhola A, et al. Sleep and Immune System Crosstalk: Implications for Inflammatory Homeostasis and Disease Pathogenesis. *Ann Neurosci.* 2025;32(3):196–206. Available from: <https://doi.org/10.1177/09727531241275347>.
46. Zhang C, Liang S, Zhang H, Wang R, Qiao H. Epigenetic regulation of mRNA mediates the phenotypic plasticity of cancer cells during metastasis and therapeutic resistance (Review). *Oncol Rep.* 2023;51(2):28. Available from: <https://doi.org/10.3892/or.2023.8687>.
47. Yu F, Huang D, Kuang Y, et al. IRS1 promotes thyroid cancer metastasis through EMT and PI3K/AKT pathways. *Clin Endocrinol (Oxf).* 2024;100(3):284–293. Available from: <https://doi.org/10.1111/cen.15005>.
48. Leppänen N, Kaljunen H, Takala E, et al. SIX2 promotes cell plasticity via Wnt/ β -catenin signalling in androgen receptor independent prostate cancer. *Nucleic Acids Res.* 2024;52(10):5610–5623. Available from: <https://doi.org/10.1093/nar/gkae206>.
49. Wang G, Han JJ. Connections between metabolism and epigenetic modifications in cancer. *Med Rev.* 2021;1(2):199–221. Available from: <https://doi.org/10.1515/mr-2021-0015>.
50. Song J, Zhao A, Li R, et al. Association of PPARGC1A gene polymorphism and mtDNA methylation with coal-burning fluorosis: a case-control study. *BMC Genomics.* 2024;25(1):908. Available from: <https://doi.org/10.1186/s12864-024-10819-9>.
51. Xie S, Hagen D, Becker GM, et al. Analyzing the relationship of RNA and DNA methylation with gene expression. *Genome Biol.* 2025;26(1):140. Available from: <https://doi.org/10.1186/s13059-025-03617-3>.
52. Kudo-Saito C, Shirako H, Takeuchi T, Kawakami Y. Cancer Metastasis Is Accelerated through Immunosuppression during Snail-Induced EMT of Cancer Cells. *Cancer Cell.* 2009;15(3):195–206. Available from: <https://doi.org/10.1016/j.ccr.2009.01.023>.
53. Dongre A, Rashidian M, Reinhardt F, et al. Epithelial-to-Mesenchymal Transition Contributes to Immunosuppression in Breast Carcinomas. *Cancer Res.* 2017;77(15):3982–3989. Available from: <https://doi.org/10.1158/0008-5472.CAN-16-3292>.
54. Pastushenko I, Brisebarre A, Sifrim A, et al. Identification of the tumour transition states occurring during EMT. *Nature.* 2018;556(7702):463–468. Available from: <https://doi.org/10.1038/s41586-018-0040-3>.
55. Sahoo S, Nayak SP, Hari K, et al. Immunosuppressive Traits of the Hybrid Epithelial/Mesenchymal Phenotype. *Front Immunol.* 2021;12:797261. Available from: <https://doi.org/10.3389/fimmu.2021.797261>.
56. Kallinag A, Olszewski M, Maciejewska N, Brankiewicz W, Baginski M. Cancer immune escape: the role of antigen presentation machinery. *J Cancer Res Clin Oncol.* 2023;149(10):8131–8141. Available from: <https://doi.org/10.1007/s00432-023-04737-8>.
57. Mani SA, Guo W, Liao MJ, et al. The Epithelial-Mesenchymal Transition Generates Cells with Properties of Stem Cells. *Cell.* 2008;133(4):704–715. Available from: <https://doi.org/10.1016/j.cell.2008.03.027>.
58. Rosenbaum SR, Fields KM, Ford HL, Kang Y. Masters of adaptation: How cancer and immune cell plasticity mediates tumor progression. *PLOS Biol.* 2025;23(7):e3003301. Available from: <https://doi.org/10.1371/journal.pbio.3003301>.
59. Niida A, Iwasaki WM, Innan H, Kumar S. Neutral Theory in Cancer Cell Population Genetics. *Mol Biol Evol.* 2018;35(6):1316–1321. Available from: <https://doi.org/10.1093/molbev/msy091>.
60. Lindner P, Paul S, Eckstein M, et al. EMT transcription factor ZEB1 alters the epigenetic landscape of colorectal cancer cells. *Cell Death Dis.* 2020;11(2):147. Available from: <https://doi.org/10.1038/s41419-020-2340-4>.
61. Foubert E, De Craene B, Bex G. Key signalling nodes in mammary gland development and cancer. The Snail1-Twist1 conspiracy in malignant breast cancer progression. *Breast Cancer Res.* 2010;12(3):206. Available from: <https://doi.org/10.1186/bcr2585>.
62. Deng M. SOX2 control activation of dormant prostate cancer cells in bone metastases by promoting CCNE2 gene expression. *Am J Clin Exp Urol.* 2024;12(6):375–388. Available from: <https://doi.org/10.62347/ASCY2532>.
63. Lou L, Deng T, Yuan Q, Wang L, Wang Z, Li X. Targeted silencing of SOCS1 by DNMT1 promotes stemness of human liver cancer stem-like cells. *Cancer Cell Int.* 2024;24(1):206. Available from: <https://doi.org/10.1186/s12935-024-03322-4>.
64. Nokin MJ, Darbo E, Richard E, et al. In vivo vulnerabilities to GPX4 and HDAC inhibitors in drug-persistent versus drug-resistant BRAFV600E lung adenocarcinoma. *Cell Rep Med.* 2024;5(8):101663. Available from: <https://doi.org/10.1016/j.xcrm.2024.101663>.
65. Zhang Z, Qin S, Chen Y, et al. Inhibition of NPC1L1 disrupts adaptive responses of drug-tolerant persister cells to chemotherapy. *EMBO Mol Med.* 2022;14(2):e14903. Available from: <https://doi.org/10.15252/emmm.202114903>.
66. Pai JT, Hsu MW, Leu YL, Chang KT, Weng MS. Induction of G2/M Cell Cycle Arrest via p38/p21Waf1/Cip1-Dependent Signaling Pathway Activation by Bavachinin in Non-Small-Cell Lung Cancer Cells. *Molecules.* 2021;26(17):5161. Available from: <https://doi.org/10.3390/molecules26175161>.
67. Kawarada Y, Inoue Y, Kawasaki F, et al. TGF- β induces p53/Smads complex formation in the PAI-1 promoter to activate transcription. *Sci Rep.* 2016;6(1):35483. Available from: <https://doi.org/10.1038/srep35483>.

68. Nobre AR, Risson E, Singh DK, et al. Bone marrow NG2+/Nestin+ mesenchymal stem cells drive DTC dormancy via TGF- β 2. *Nat Cancer*. 2021;2(3):327–339. Available from: <https://doi.org/10.1038/s43018-021-00179-8>.
69. Wu Y, Chen X, Dong W, et al. ST3Gal IV Mediates the Growth and Proliferation of Cervical Cancer Cells In Vitro and In Vivo Via the Notch/p21/CDKs Pathway. *Front Oncol*. 2021;10:540332. Available from: <https://doi.org/10.3389/fonc.2020.540332>.
70. Maeda Y, Isomura A, Masaki T, Kageyama R. Differential cell-cycle control by oscillatory versus sustained Hes1 expression via p21. *Cell Rep*. 2023;42(5):112520. Available from: <https://doi.org/10.1016/j.celrep.2023.112520>.
71. Khalil BD, Sanchez R, Rahman T, et al. An NR2F1-specific agonist suppresses metastasis by inducing cancer cell dormancy. *J Exp Med*. 2022;219(1):e20210836. Available from: <https://doi.org/10.1084/jem.20210836>.
72. Tomiyasu H, Habara M, Hanaki S, Sato Y, Miki Y, Shimada M. FOXO1 promotes cancer cell growth through MDM2-mediated p53 degradation. *J Biol Chem*. 2024;300(4):107209. Available from: <https://doi.org/10.1016/j.jbc.2024.107209>.
73. Cuccu A, Francescangeli F, De Angelis ML, Bruselles A, Giuliani A, Zeuner A. Analysis of Dormancy-Associated Transcriptional Networks Reveals a Shared Quiescence Signature in Lung and Colorectal Cancer. *Int J Mol Sci*. 2022;23(17):9869. Available from: <https://doi.org/10.3390/ijms23179869>.
74. Francescangeli F, Contavalli P, De Angelis ML, et al. A pre-existing population of ZEB2+ quiescent cells with stemness and mesenchymal features dictate chemoresistance in colorectal cancer. *J Exp Clin Cancer Res*. 2020;39(1):2. Available from: <https://doi.org/10.1186/s13046-019-1505-4>.
75. Zhang N, Liu Z, Lai X, Liu S, Wang Y. Silencing of CD147 inhibits cell proliferation, migration, invasion, lipid metabolism dysregulation and promotes apoptosis in lung adenocarcinoma via blocking the Rap1 signaling pathway. *Respir Res*. 2023;24(1):253. Available from: <https://doi.org/10.1186/s12931-023-02532-0>.
76. De La Cruz Concepción B, Bartolo-García LD, Tizapa-Méndez MD, et al. EMMPRIN is an emerging protein capable of regulating cancer hallmarks. *Eur Rev Med Pharmacol Sci*. 2022;26(18):6700–5724. Available from: https://doi.org/10.26355/eurrev_202209_29771.
77. Feigelman G, Simanovich E, Brockmeyer P, Rahat MA. Knocking-Down CD147/EMMPRIN Expression in CT26 Colon Carcinoma Forces the Cells into Cellular and Angiogenic Dormancy That Can Be Reversed by Interactions with Macrophages. *Biomedicines*. 2023;11(3):768. Available from: <https://doi.org/10.3390/biomedicines11030768>.
78. Ke X, Fei F, Chen Y, et al. Hypoxia upregulates CD147 through a combined effect of HIF-1 α and Sp1 to promote glycolysis and tumor progression in epithelial solid tumors. *Carcinogenesis*. 2012;33(8):1598–1607. Available from: <https://doi.org/10.1093/carcin/bgs196>.
79. Aguirre-Ghiso JA, Estrada Y, Liu D, Ossowski L. ERK(MAPK) activity as a determinant of tumor growth and dormancy; regulation by p38(SAPK). *Urol Oncol Semin Orig Invest*. 2004;22(1):82. Available from: <https://doi.org/10.1016/j.urolonc.2003.12.012>.
80. Xiao YQ, Malcolm K, Worthen GS, et al. Cross-talk between ERK and p38 MAPK Mediates Selective Suppression of Pro-inflammatory Cytokines by Transforming Growth Factor- β . *J Biol Chem*. 2002;277(17):14884–14893. Available from: <https://doi.org/10.1074/jbc.M111718200>.
81. Fadhil E. A Comprehensive Analysis of the PI3K/AKT Pathway: Unveiling Key Proteins and Therapeutic Targets for Cancer Treatment. *Cancer Inform*. 2023;22:11769351231194273. Available from: <https://doi.org/10.1177/11769351231194273>.
82. Recalde-Percas L, De La Guía-Lopez I, Linzoain-Agos P, et al. Neuropilin-2 upregulation by stromal TGF β 1 induces lung disseminated tumor cells dormancy escape and promotes metastasis outgrowth. *Neoplasia*. 2025;68:101220. Available from: <https://doi.org/10.1016/j.neo.2025.101220>.
83. Prunier C, Baker D, Ten Dijke P, Ritsma L. TGF- β Family Signaling Pathways in Cellular Dormancy. *Trends Cancer*. 2019;5(1):66–78. Available from: <https://doi.org/10.1016/j.trecan.2018.10.010>.
84. Kumar V, Vashishta M, Kong L, et al. The Role of Notch, Hedgehog, and Wnt Signaling Pathways in the Resistance of Tumors to Anticancer Therapies. *Front Cell Dev Biol*. 2021;9:650772. Available from: <https://doi.org/10.3389/fcell.2021.650772>.
85. Ren D, Dai Y, Yang Q, et al. Wnt5a induces and maintains prostate cancer cells dormancy in bone. *J Exp Med*. 2019;216(2):428–449. Available from: <https://doi.org/10.1084/jem.20180661>.
86. Bragado P, Estrada Y, Parikh F, et al. TGF- β 2 dictates disseminated tumour cell fate in target organs through TGF- β -RIII and p38 α / β signalling. *Nat Cell Biol*. 2013;15(11):1351–1361. Available from: <https://doi.org/10.1038/ncb2861>.
87. Hsu SK, Chiu CC, Dahms HU, et al. Unfolded Protein Response (UPR) in Survival, Dormancy, Immunosuppression, Metastasis, and Treatments of Cancer Cells. *Int J Mol Sci*. 2019;20(10):2518. Available from: <https://doi.org/10.3390/ijms20102518>.
88. Pelullo M, Zema S, Nardoza F, Checquolo S, Screpanti I, Bellavia D. Wnt, Notch, and TGF- β Pathways Impinge on Hedgehog Signaling Complexity: An Open Window on Cancer. *Front Genet*. 2019;10:711. Available from: <https://doi.org/10.3389/fgene.2019.00711>.
89. Glaviano A, Foo ASC, Lam HY, et al. PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. *Mol Cancer*. 2023;22(1):138. Available from: <https://doi.org/10.1186/s12943-023-01827-6>.
90. Wu X, Que H, Li Q, Wei X. Wnt/ β -catenin mediated signaling pathways in cancer: recent advances, and applications in cancer therapy. *Mol Cancer*. 2025;24(1):171. Available from: <https://doi.org/10.1186/s12943-025-02363-1>.
91. Nazli D, Bora U, Ozhan G, Turksen K. Wnt/ β -catenin Signaling in Central Nervous System Regeneration. *Cell Biology and Translational Medicine, Volume 23*. 2024;1474:13–33. Available from: https://doi.org/10.1007/s584_2024_830.
92. Gozlan O, Sprinzak D. Notch signaling in development and homeostasis. *Development*. 2023;150(4):dev201138. Available from: <https://doi.org/10.1242/dev.201138>.
93. Van Meeteren LA, Ten Dijke P. Regulation of endothelial cell plasticity by TGF- β . *Cell Tissue Res*. 2012;347(1):177–186. Available from: <https://doi.org/10.1007/s00441-011-1222-6>.
94. Glaviano A. PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. 2023;.
95. Petrova R, Joyner AL. Roles for Hedgehog signaling in adult organ homeostasis and repair. *Development*. 2014;141(18):3445–3457. Available from: <https://doi.org/10.1242/dev.083691>.
96. Hu Q, Bian Q, Rong D, et al. JAK/STAT pathway: Extracellular signals, diseases, immunity, and therapeutic regimens. *Front Bioeng Biotechnol*. 2023;11:1110765. Available from: <https://doi.org/10.3389/fbioe.2023.1110765>.
97. Spiros AV. Aberrant control of NF- κ B in cancer permits transcriptional and phenotypic plasticity, to curtail dependence on host tissue: molecular mode. *Cancer Biol Med*. 2017;14(3):254. Available from: <https://doi.org/10.20892/j.issn.2095-3941.2017.0029>.
98. Leitão AL, Enguita FJ. A Structural View of miRNA Biogenesis and Function. *Non-Coding RNA*. 2022;8(1):10. Available from: <https://doi.org/10.3390/ncrna8010010>.
99. Arif KMT, Elliott EK, Haupt LM, Griffiths LR. Regulatory Mechanisms of Epigenetic miRNA Relationships in Human Cancer and Potential as Therapeutic Targets. *Cancers*. 2020;12(10):2922. Available from: <https://doi.org/10.3390/cancers12102922>.

100. Li WJ, Liu X, Dougherty EM, Tang DG. MicroRNA-34a, Prostate Cancer Stem Cells, and Therapeutic Development. *Cancers*. 2022;14(18):4538. Available from: <https://doi.org/10.3390/cancers14184538>.
101. Ma Y, Shen N, Wicha MS, Luo M. The Roles of the Let-7 Family of MicroRNAs in the Regulation of Cancer Stemness. *Cells*. 2021;10(9):2415. Available from: <https://doi.org/10.3390/cells10092415>.
102. Klicka K, Grzywa TM, Mielniczuk A, Klinke A, Włodarski PK. The role of miR-200 family in the regulation of hallmarks of cancer. *Front Oncol*. 2022;12:965231. Available from: <https://doi.org/10.3389/fonc.2022.965231>.
103. Mortoglou M, Miralles F, Arisan ED, et al. microRNA-21 Regulates Stemness in Pancreatic Ductal Adenocarcinoma Cells. *Int J Mol Sci*. 2022;23(3):1275. Available from: <https://doi.org/10.3390/ijms23031275>.
104. Gabrieli G, Wurdinger T, Kesari S, et al. MicroRNA 21 Promotes Glioma Invasion by Targeting Matrix Metalloproteinase Regulators. *Mol Cell Biol*. 2008;28(17):5369–5380. Available from: <https://doi.org/10.1128/MCB.00479-08>.
105. Yu Y, Yin W, Yu ZH, et al. miR-190 enhances endocrine therapy sensitivity by regulating SOX9 expression in breast cancer. *J Exp Clin Cancer Res*. 2019;38(1):22. Available from: <https://doi.org/10.1186/s13046-019-1039-9>.
106. Shi M, Lu Q, Zhao Y, et al. miR-223: a key regulator of pulmonary inflammation. *Front Med*. 2023;10:1187557. Available from: <https://doi.org/10.3389/fmed.2023.1187557>.
107. Wu RS, QIU EH, Zhu JJ. MiR-101 restrains NPC proliferation. *European Review for Medical and Pharmacological Sciences*. 2018;22:150–157.
108. Fish JE, Santoro MM, Morton SU, et al. miR-126 Regulates Angiogenic Signaling and Vascular Integrity. *Dev Cell*. 2008;15(2):272–284. Available from: <https://doi.org/10.1016/j.devcel.2008.07.008>.
109. Setijono SR, Kwon HY, Song SJ. MicroRNA, an Antisense RNA, in Sensing Myeloid Malignancies. *Front Oncol*. 2018;7:331. Available from: <https://doi.org/10.3389/fonc.2017.00331>.
110. Le MTN, Teh C, Shyh-Chang N, et al. MicroRNA-125b is a novel negative regulator of p53. *Genes Dev*. 2009;23(7):862–876. Available from: <https://doi.org/10.1101/gad.1767609>.
111. Kong W, He L, Richards EJ, et al. Upregulation of miRNA-155 promotes tumour angiogenesis by targeting VHL and is associated with poor prognosis and triple-negative breast cancer. *Oncogene*. 2014;33(6):679–689. Available from: <https://doi.org/10.1038/onc.2012.636>.
112. Zeng Z, Xia L, Fan X, et al. Platelet-derived miR-223 promotes a phenotypic switch in arterial injury repair. *J Clin Invest*. 2019;129(3):1372–1386. Available from: <https://doi.org/10.1172/JCI124508>.
113. Joo HS, Suh JH, Lee HJ, Bang ES, Lee JM. Current Knowledge and Future Perspectives on Mesenchymal Stem Cell-Derived Exosomes as a New Therapeutic Agent. *Int J Mol Sci*. 2020;21(3):727. Available from: <https://doi.org/10.3390/ijms21030727>.
114. Wang S, Aurora AB, Johnson BA, et al. The Endothelial-Specific MicroRNA miR-126 Governs Vascular Integrity and Angiogenesis. *Dev Cell*. 2008;15(2):261–271. Available from: <https://doi.org/10.1016/j.devcel.2008.07.002>.
115. Zhou S, Cheng W, Liu Y, Gao H, Yu L, Zeng Y. MiR-125b-5p alleviates pulmonary fibrosis by inhibiting TGFβ1-mediated epithelial-mesenchymal transition via targeting BAK1. *Respir Res*. 2024;25(1):382. Available from: <https://doi.org/10.1186/s12931-024-03011-w>.
116. Amodio N, Stamato MA, Gullà AM, et al. Therapeutic Targeting of miR-29b/HDAC4 Epigenetic Loop in Multiple Myeloma. *Mol Cancer Ther*. 2016;15(6):1364–1375. Available from: <https://doi.org/10.1158/1535-7163.MCT-15-0985>.
117. Tili E, Michaille JJ, Wernicke D, et al. Mutator activity induced by microRNA-155 (*miR-155*) links inflammation and cancer. *Proc Natl Acad Sci*. 2011;108(12):4908–4913. Available from: <https://doi.org/10.1073/pnas.1101795108>.
118. Ma L, Reinhardt F, Pan E, et al. Therapeutic silencing of miR-10b inhibits metastasis in a mouse mammary tumor model. *Nat Biotechnol*. 2010;28(4):341–347. Available from: <https://doi.org/10.1038/nbt.1618>.
119. Wang Y, Wang L, Wei Y, et al. Advances in the molecular regulation mechanism of tumor dormancy and its therapeutic strategy. *Discov Oncol*. 2024;15(1):184. Available from: <https://doi.org/10.1007/s12672-024-01049-2>.
120. Boydell E, Borgeaud M, Tsantoulis P. Dormant Tumor Cells: Current Opportunities and Challenges in Clinical Practice. *Onco*. 2025;5(1):3. Available from: <https://doi.org/10.3390/onco5010003>.
121. Goddard ET, Linde MH, Srivastava S, et al. Immune evasion of dormant disseminated tumor cells is due to their scarcity and can be overcome by T cell immunotherapies. *Cancer Cell*. 2024;42(1):119–134.e12. Available from: <https://doi.org/10.1016/j.ccell.2023.12.011>.
122. Di Martino JS, Nobre AR, Mondal C, et al. A tumor-derived type III collagen-rich ECM niche regulates tumor cell dormancy. *Nat Cancer*. 2021;3(1):90–107. Available from: <https://doi.org/10.1038/s43018-021-00291-9>.
123. Wei JR, Zhang B, Zhang Y, et al. QSOX1 facilitates dormant esophageal cancer stem cells to evade immune elimination via PD-L1 upregulation and CD8 T cell exclusion. *Proc Natl Acad Sci*. 2024;121(44):e2407506121. Available from: <https://doi.org/10.1073/pnas.2407506121>.
124. Goddard ET, Linde MH, Srivastava S, et al. Immune evasion of dormant disseminated tumor cells is due to their scarcity and can be overcome by T cell immunotherapies. *Cancer Cell*. 2024;42(1):119–134.e12. Available from: <https://doi.org/10.1016/j.ccell.2023.12.011>.
125. Dai J, Cimino PJ, Gouin KH, et al. Astrocytic laminin-211 drives disseminated breast tumor cell dormancy in brain. *Nat Cancer*. 2021;3(1):25–42. Available from: <https://doi.org/10.1038/s43018-021-00297-3>.
126. Krall JA, Reinhardt F, Mercury OA, et al. The systemic response to surgery triggers the outgrowth of distant immune-controlled tumors in mouse models of dormancy. *Sci Transl Med*. 2018;10(436):eaan3464. Available from: <https://doi.org/10.1126/scitranslmed.aan3464>.
127. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. *Nat Med*. 2013;19(11):1423–1437. Available from: <https://doi.org/10.1038/nm.3394>.
128. Cuesta-Borrás E, Salvans C, Arqués O, et al. DPPA3-HIF1α axis controls colorectal cancer chemoresistance by imposing a slow cell-cycle phenotype. *Cell Rep*. 2023;42(8):112927. Available from: <https://doi.org/10.1016/j.celrep.2023.112927>.
129. Duy C, Li M, Teater M, et al. Chemotherapy Induces Senescence-Like Resilient Cells Capable of Initiating AML Recurrence. *Cancer Discov*. 2021;11(6):1542–1561. Available from: <https://doi.org/10.1158/2159-8290.CD-20-1375>.
130. Hu J, Sánchez-Rivera FJ, Wang Z, et al. STING inhibits the reactivation of dormant metastasis in lung adenocarcinoma. *Nature*. 2023;616(7958):806–813. Available from: <https://doi.org/10.1038/s41586-023-05880-5>.
131. Braun S, Janni W, Schlimok G, et al. A Pooled Analysis of Bone Marrow Micrometastasis in Breast Cancer. *N Engl J Med*. 2005;.
132. Sarker P, Shevde LA, Rao SS. An in vitro hydrogel-based model to study dormancy associated drug resistance in metastatic breast cancer spheroids. *Npj Biomed Innov*. 2025;2(1):39. Available from: <https://doi.org/10.1038/s44385-025-00043-9>.
133. Bui T, Gu Y, Ancot F, Sanguin-Gendreau V, Zuo D, Muller WJ. Emergence of β1 integrin-deficient breast tumours from dormancy involves both inactivation of p53 and generation of a permissive tumour microenvironment. *Oncogene*. 2022;41(4):527–537. Available from: <https://doi.org/10.1038/s41388-021-02107-7>.

134. Webster KD, Lennon JT. Dormancy in the origin, evolution and persistence of life on Earth. *Proc R Soc B Biol Sci.* 2025;292(2038):20242035. Available from: <https://doi.org/10.1098/rspb.2024.2035>.
135. Miller AK, Brown JS, Enderling H, Basanta D, Whelan CJ. The Evolutionary Ecology of Dormancy in Nature and in Cancer. *Front Ecol Evol.* 2021;9:676802. Available from: <https://doi.org/10.3389/fevo.2021.676802>.
136. Situ J, Xi P, Lin L, et al. Signal and regulatory mechanisms involved in spore development of *Phytophthora* and *Peronosphythora*. *Front Microbiol.* 2022;13:984672. Available from: <https://doi.org/10.3389/fmicb.2022.984672>.
137. Nayak A, Warriar NM, Kumar P. Cancer Stem Cells and the Tumor Microenvironment: Targeting the Critical Crosstalk through Nanocarrier Systems. *Stem Cell Rev Rep.* 2022;18(7):2209–2233. Available from: <https://doi.org/10.1007/s12015-022-10426-9>.
138. Kavari SL, Shah K. Engineered stem cells targeting multiple cell surface receptors in tumors. *Stem Cells.* 2020;38(1):34–44. Available from: <https://doi.org/10.1002/stem.3069>.
139. Zeng Z, Fu M, Hu Y, Wei Y, Wei X, Luo M. Regulation and signaling pathways in cancer stem cells: implications for targeted therapy for cancer. *Mol Cancer.* 2023;22(1):172. Available from: <https://doi.org/10.1186/s12943-023-01877-w>.
140. Ito M, Liu Y, Yang Z, et al. Stem cells in the hair follicle bulge contribute to wound repair but not to homeostasis of the epidermis. *Nat Med.* 2005;11(12):1351–1354. Available from: <https://doi.org/10.1038/nm1328>.
141. González JE, Keshavan ND. Messing with Bacterial Quorum Sensing. *Microbiol Mol Biol Rev.* 2006;70(4):859–875. Available from: <https://doi.org/10.1128/MMBR.00002-06>.
142. Hastings JW, Greenberg EP. Quorum Sensing: the Explanation of a Curious Phenomenon Reveals a Common Characteristic of Bacteria. *J Bacteriol.* 1999;181(9):2667–2668. Available from: <https://doi.org/10.1128/JB.181.9.2667-2668.1999>.
143. Takahashi K, Yamanaka S. Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. *Cell.* 2006;126(4):663–676. Available from: <https://doi.org/10.1016/j.cell.2006.07.024>.
144. Bhat GR, Sethi I, Sadida HQ, et al. Cancer cell plasticity: from cellular, molecular, and genetic mechanisms to tumor heterogeneity and drug resistance. *Cancer Metastasis Rev.* 2024;43(1):197–228. Available from: <https://doi.org/10.1007/s10555-024-10172-z>.
145. Cordani M, Dando I, Ambrosini G, González-Menéndez P. Signaling, cancer cell plasticity, and intratumor heterogeneity. *Cell Commun Signal.* 2024;22(1):255, s12964–024–01643–01645. Available from: <https://doi.org/10.1186/s12964-024-01643-5>.
146. Radic Shechter K, Kafkia E, Zirngibl K, et al. Metabolic memory underlying minimal residual disease in breast cancer. *Mol Syst Biol.* 2021;17(10):e10141. Available from: <https://doi.org/10.15252/msb.202010141>.
147. Chaudhary P, Yadav K, Lee HJ, Kang KW, Mo J, Kim JA. siRNA treatment targeting integrin $\alpha 11$ overexpressed via EZH2-driven axis inhibits drug-resistant breast cancer progression. *Breast Cancer Res.* 2024;26(1):72. Available from: <https://doi.org/10.1186/s13058-024-01827-4>.
148. Cáceres-Calle D, Torre-Cea I, Marcos-Zazo L, et al. Integrins as Key Mediators of Metastasis. *Int J Mol Sci.* 2025;26(3):904. Available from: <https://doi.org/10.3390/ijms26030904>.
149. Najafi M, Farhood B, Mortezaee K. Extracellular matrix (ECM) stiffness and degradation as cancer drivers. *J Cell Biochem.* 2019;120(3):2782–2790. Available from: <https://doi.org/10.1002/jcb.27681>.
150. Kesh K, Gupta VK, Durden B, et al. Therapy Resistance, Cancer Stem Cells and ECM in Cancer: The Matrix Reloaded. *Cancers.* 2020;12(10):3067. Available from: <https://doi.org/10.3390/cancers12103067>.
151. Eyles J, Puaux AL, Wang X, et al. Tumor cells disseminate early, but immunosurveillance limits metastatic outgrowth, in a mouse model of melanoma. *J Clin Invest.* 2010;120(6):2030–2039. Available from: <https://doi.org/10.1172/JCI42002>.
152. fan Wang H, sha Wang S, Chang HM, Hua LX, Tang YJ, Ling TY. Targeting Immune-Mediated Dormancy: A Promising Treatment of Cancer. *Front Oncol.* 2019;9:498. Available from: <https://doi.org/10.3389/fonc.2019.00498>.
153. Romero I, Garrido F, García-Lora AM. Metastases in Immune-Mediated Dormancy: A New Opportunity for Targeting Cancer. *Cancer Res.* 2014;74(23):6750–6757. Available from: <https://doi.org/10.1158/0008-5472.CAN-14-2406>.
154. Tufail M, Jiang CH, Li N. Tumor dormancy and relapse: understanding the molecular mechanisms of cancer recurrence. *Mil Med Res.* 2025;12(1):7. Available from: <https://doi.org/10.1186/s40779-025-00595-2>.
155. Li B, Zheng L, Yang J, Qu L. Targeting oncogene-induced cellular plasticity for tumor therapy. *Adv Biotechnol.* 2024;2(3):24. Available from: <https://doi.org/10.1007/s44307-024-00030-y>.
156. Yang S, Seo J, Choi J, et al. Towards understanding cancer dormancy over strategic hitching up mechanisms to technologies. *Mol Cancer.* 2025;24(1):47. Available from: <https://doi.org/10.1186/s12943-025-02250-9>.
157. Papadaki C, Stratigos M, Markakis G, et al. Circulating microRNAs in the early prediction of disease recurrence in primary breast cancer. *Breast Cancer Res.* 2018;20(1):72. Available from: <https://doi.org/10.1186/s13058-018-1001-3>.
158. Sosa MS, Parikh F, Maia AG, et al. NR2F1 controls tumour cell dormancy via SOX9- and RAR β -driven quiescence programmes. *Nat Commun.* 2015;6(1):6170. Available from: <https://doi.org/10.1038/ncomms7170>.
159. Khalil BD, Sanchez R, Rahman T, et al. An NR2F1-specific agonist suppresses metastasis by inducing cancer cell dormancy. *J Exp Med.* 2022;219(1):e20210836. Available from: <https://doi.org/10.1084/jem.20210836>.
160. Barney LE, Hall CL, Schwartz AD, et al. Tumor cell-organized fibronectin maintenance of a dormant breast cancer population. *Sci Adv.* 2020;6(11):eaaz4157. Available from: <https://doi.org/10.1126/sciadv.aaz4157>.
161. Clark AM, Wheeler SE, Young CL, et al. A liver microphysiological system of tumor cell dormancy and inflammatory responsiveness is affected by scaffold properties. *Lab Chip.* 2017;17(1):156–168. Available from: <https://doi.org/10.1039/C6LC01171C>.
162. Baldassarri I, Tavakol DN, Graney PL, Chramiec AG, Hibshoosh H, Vunjak-Novakovic G. An engineered model of metastatic colonization of human bone marrow reveals breast cancer cell remodeling of the hematopoietic niche. *Proc Natl Acad Sci.* 2024;121(42):e2405257121. Available from: <https://doi.org/10.1073/pnas.2405257121>.
163. Ji X, Bei H, Zhong G, et al. Premetastatic Niche Mimicking Bone-On-A-Chip: A Microfluidic Platform to Study Bone Metastasis in Cancer Patients. *Small.* 2023;19(49):2207606. Available from: <https://doi.org/10.1002/smll.202207606>.
164. Bartosh TJ, Ullah M, Zeitouni S, Beaver J, Prockop DJ. Cancer cells enter dormancy after cannibalizing mesenchymal stem/stromal cells (MSCs). *Proc Natl Acad Sci.* 2016;113(42). Available from: <https://doi.org/10.1073/pnas.1612290113>.
165. Pastushenko I, Brisebarre A, Sifrim A, et al. Identification of the tumour transition states occurring during EMT. *Nature.* 2018;556(7702):463–468. Available from: <https://doi.org/10.1038/s41586-018-0040-3>.
166. Karacosta LG, Anchang B, Ignatiadis N, et al. Mapping lung cancer epithelial-mesenchymal transition states and trajectories with single-cell resolution. *Nat Commun.* 2019;10(1):5587. Available from: <https://doi.org/10.1038/s41467-019-13441-6>.
167. Koebel CM, Vermi W, Swann JB, et al. Adaptive immunity maintains occult cancer in an equilibrium state. *Nature.* 2007;450(7171):903–907. Available from: <https://doi.org/10.1038/nature06309>.

168. Albrengues J, Shields MA, Ng D, et al. Neutrophil extracellular traps produced during inflammation awaken dormant cancer cells in mice. *Science*. 2018;361(6409):eaao4227. Available from: <https://doi.org/10.1126/science.aao4227>.
169. Tallón De Lara P, Castañón H, Vermeer M, et al. CD39+PD-1+CD8+ T cells mediate metastatic dormancy in breast cancer. *Nat Commun*. 2021;12(1):769. Available from: <https://doi.org/10.1038/s41467-021-21045-2>.
170. Jin Y, Zuo Y, Li G, et al. Advances in spatial transcriptomics and its applications in cancer research. *Mol Cancer*. 2024;23(1):129. Available from: <https://doi.org/10.1186/s12943-024-02040-9>.
171. Wang X, Zhao J, Marostica E, et al. A pathology foundation model for cancer diagnosis and prognosis prediction. *Nature*. 2024;634(8035):970–978. Available from: <https://doi.org/10.1038/s41586-024-07894-z>.
172. Alum EU. AI-driven biomarker discovery: enhancing precision in cancer diagnosis and prognosis. *Discov Oncol*. 2025;16(1):313. Available from: <https://doi.org/10.1007/s12672-025-02064-7>.
173. Ferrer AI, Trinidad JR, Sandiford O, Etchegaray JP, Rameshwar P. Epigenetic dynamics in cancer stem cell dormancy. *Cancer Metastasis Rev*. 2020;39(3):721–738. Available from: <https://doi.org/10.1007/s10555-020-09882-x>.
174. Choi JE, Baek I. Interplay between epigenetics and metabolism controls cancer stem cell plasticity. *Front Epigenetics Epigenomics*. 2024;2:1424163. Available from: <https://doi.org/10.3389/freae.2024.1424163>.
175. Sistigu A, Musella M, Galassi C, Vitale I, De Maria R. Tuning Cancer Fate: Tumor Microenvironment's Role in Cancer Stem Cell Quiescence and Reawakening. *Front Immunol*. 2020;11:2166. Available from: <https://doi.org/10.3389/fimmu.2020.02166>.
176. Glaviano A, Lau HSH, Carter LM, et al. Harnessing the tumor microenvironment: targeted cancer therapies through modulation of epithelial-mesenchymal transition. *J Hematol Oncol J Hematol Oncol*. 2025;18(1):6. Available from: <https://doi.org/10.1186/s13045-024-01634-6>.