Al-Rafidain J Med Sci. 2026;11(1):1-10.
DOI: https://doi.org/10.54133/ajms.v11i1.2841

AJMS

Online ISSN (3219-2789)

Review Article

Insights Into the Molecular Mechanisms and Use of Cancer Dormancy and Reawakening

Ismail Ibrahim Al-Janabi*
Retired Academic and Science Writer, Epsom, Surrey, United Kingdom

Received: 25 March 2026; Revised: 7 May 2026; Accepted: 11 May 2026

Abstract

The ability of disseminated cancer cells from primary tumors to persist in a quiescent state for extended periods of years or even decades is a phenomenon known as cancer dormancy. This non-proliferative state represents a critical clinical challenge and constitutes a major barrier to therapy. Dormancy is often followed by stochastic relapses, or "reawakening," leading to metastasis of the primary cancer after its successful treatment. This narrative review synthesizes our current understanding of the complex and dynamic molecular mechanisms that govern dormancy and the eventual outgrowth of dormant cancer cells. We explore both cell-intrinsic factors and the microenvironmental determinants of establishing and maintaining dormant cancer cells. Crucially, this review translates these mechanistic insights into therapeutic strategies, highlighting the latest advances in targeting dormant cancer cells, preventing their reawakening, and the challenges of developing useful predictive biomarkers. By integrating our knowledge of the molecular underpinnings of dormancy, we aim to provide a roadmap for therapeutic interventions that can lead to a permanent state of cancer suppression.

Keywords: Dormancy; Cancer relapse; Biomarkers; Reawakening; Exiting dormancy.

رؤى حول الآليات الجزيئية واستخدامات خمول ونشاط السرطان

الخلاصة

تُعرف قدرة الخلايا السرطانية المنتشرة من الأورام الاولية على البقاء في حالة سكون، لفترات طويلة تمتد لسنوات او حتى عقود، بظاهرة خمول السرطان. تمثل هذه الحالة غير التكاثرية تحدياً سريرياً بالغ الأهمية، وعائقاً رئيسياً امام العلاج. غالباً ما يتبع الخمول انتكاس عشوائي يؤدي إلى انتشار السرطان الاولي بعد نجاح علاجه. يستعرض هذا المقال السردي فهمنا الحالي للآليات الجزيئية المعقدة والديناميكية التي تتحكم بالخمول ونمو الخلايا السرطانية الخاملة في نهاية المطاف. نستكشف هنا العوامل الخلوية الداخلية، بالإضافة إلى المحددات البيئية الدقيقة التي تُسهم في تكوين الخلايا السرطانية الخاملة والحفاظ عليها. والاهم من ذلك، يُترجم هذا المقال هذه الرؤى الآلية إلى استراتيجيات علاجية، مسلطاً الضوء على احدث التطورات في استهداف الخلايا السرطانية الخاملة، ومنع نشاطها، والتحديات التي تواجه تطوير مؤشرات حيوية تنبؤية فعالة. من خلال دمج معرفتنا بالأسس الجزيئية للخمول، نهدف إلى تسليط الضوء بشكل لى خارطة طريق للتدخلات العلاجية للوصول إلى حالة دائمة من قمع السرطان.

* ***Corresponding author***: Ismail I. Al-Janabi, Retired Academic and Science Writer, Epsom, Surrey, United Kingdom; Email: ismail.janabi@gmail.com

Article citation: Al-Janabi II. Insights Into the Molecular Mechanisms and Use of Cancer Dormancy and Reawakening. *Al-Rafidain J Med Sci.* 2026;11(1):1-10. doi: https://doi.org/10.54133/ajms.v11i1.2941

INTRODUCTION

Considerable progress has been made in the last few decades in therapy, surgical interventions, and detection of cancer. However, a significant number of patients still experience relapse and metastatic outbreaks following variable periods of remission, which can last for years or even decades [1–5]. The extended period between successful treatment of the initial cancer and relapse with distant metastases is generally referred to as "dormancy," in which the neoplastic cells remain viable but non-proliferative [6,7]. These dormant cancer cells (DCCs) are likely to exhibit mitotic arrest during a reversible G0-G1 phase of the cell cycle [8,9]. Additionally, they display key biological features that include resistance to chemotherapy due to lack of proliferation, altered metabolic activity, and dependence on signaling pathways such as p38 MAPK and have been shown to evade immune surveillance [10–12]. It appears that dormancy is employed by cancer cells as an adaptive mechanism in response to stress exerted by the environment or the use of therapies, and the surviving dormant cells will act as a reservoir for relapse [2]. DCCs survive therapy, especially chemotherapy, by arresting the cell cycle and becoming insensitive to treatments that target dividing cells [13]. The halting of cell division is not unique to cancer, and the phenomenon has a striking resemblance to the early stages of a regulated program in human development. The similarity between the two events suggests that dormant cancer cells may be hijacking fundamental biological processes to ensure the survival of the cancer [14]. Dormant cancer cells may experience conditions unfavorable for their continued cell division, such as chemotherapy stress, nutrient starvation, and lack of sufficient oxygen [15]. The existence of a dormancy state in cancer cells can be established by comparing the gene expression profiles between DCCs and their parental lines [16]. The DCCs express genes that are necessary for the initiation and/or maintenance of dormancy that are absent or downregulated in their ancestral cells. Moreover, patients who received organ transplants from donors who had no previous cancer diagnosis or had been cured of cancer and remained free of it for over 10 years went on to develop tumors, pointing to the presence of DCCs in the organs they had

received [5]. Dormancy can arise at any stage of cancer progression from the primary tumor cells, during the journey of disseminated cells before reaching a distant organ, or at the formation of the micrometastasis stage [17,18]. The micrometastases, composed largely of proliferative cells, can progress to "tumor mass dormancy," where the bulk of cancer is held below a clinically detectable size due to immune pressure and lack of blood supply. This scenario gives rise to two distinct forms of dormancy: A) tumor mass dormancy and B) cellular dormancy, as illustrated in Figure 1.

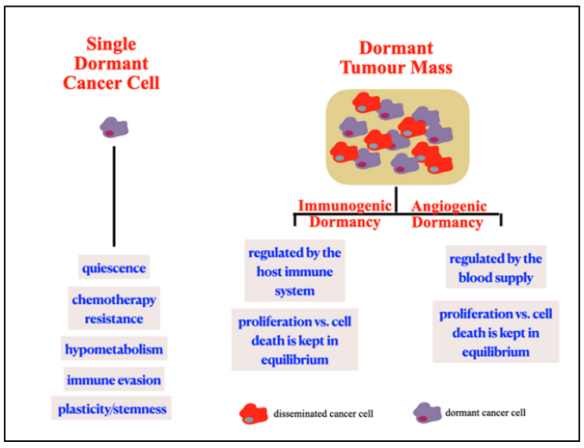

Figure 1: A schematic illustration of the differences between a single dormant cancer cell and a dormant tumour mass. A single dormant cancer cell shows quiescence, therapy resistance, lower metabolic rates, plasticity and immune evasion, while in a dormant tumour mass, an established balance exists between proliferation and apoptosis.

In tumor mass dormancy, the whole of the tumor's bulk is maintained at a constant size, balancing cell proliferation and cell death [19,20]. The restrictive pressures against outgrowth can be immune system suppression, leading to “immunogenic dormancy," or lack of adequate vasculature, reducing nutrient and oxygen supply and leading to “angiogenic dormancy." In cellular dormancy, individual cells are quiescent and stagnant in a state of cell cycle arrest within the tumor [21]. Cancer cells experiencing cellular dormancy are additionally characterized by lower metabolism, resistance to chemotherapy, stemness, and immune evasion. In mechanisms not too dissimilar to those that drive dormancy, the relapse (reawakening) of DCCs is driven by numerous biological processes and often results in a more aggressive malignancy [22,23]. A more profound understanding of the drivers behind dormancy and relapses is important in developing innovative and effective early detection and management of metastatic cancer. This narrative review aims to provide a comprehensive view of the mechanisms involved in cancer dormancy and relapse and how different drivers could be employed to control this stage of cancer progression.

METHODS

Literature searches were confined to the years of September 2000–December 2025. Relevant articles were retrieved using the keywords above and the search engines PubMed, Google Scholar, Web of Science, and ResearchGate. The initial collection of publications was screened by the author, who considered the citations of the manuscript and the impact factor of the publishing journal. Studies deemed to fall outside the concept of an anticipated basic review were excluded. Publications before September 2000 were only considered if their content represented a significant and/or historic contribution to the topic.

Drivers of Dormancy

When faced with hostile conditions such as the immune attack, hypoxia, lack of nutrients, and the presence of therapeutic chemicals, cancer cells will have to make a choice between surviving these stresses or death [24]. Choosing survival involves entering a quiescent state of dormancy and then eventual relapses upon the removal of the stress and the reversal of the cues. The drivers of cancer cell dormancy can be conveniently grouped into two mechanisms: 1) autonomous (intrinsic) mechanisms, including epigenetic modifications, autophagy-related mechanisms, and genetic alterations; and 2) microenvironment, extrinsically controlled mechanisms, which include immune surveillance and angiogenic-regulated dormancy [14,16]. It should be noted that these signaling mechanisms are quite often interconnected despite being discussed here under separate headings for simplicity and convenience (Figure 2).

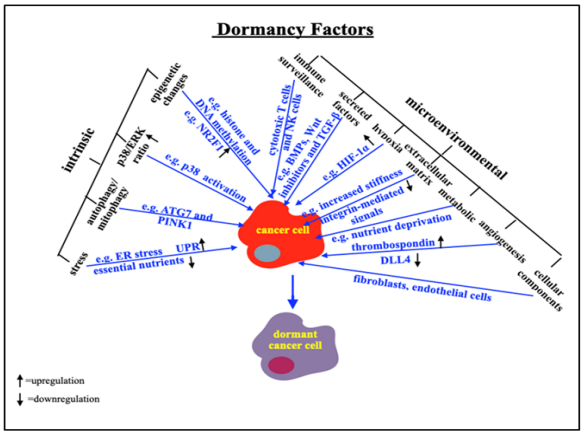

Figure 2: Drivers of cancer dormancy. Intrinsic factors, relating to the cancer cell themselves, can include epigenetic alterations, changes to the p38/ERK ratio, autophagy and stress. Microenvironmental factors may include immune surveillance, cellular and secreted soluble molecules, hypoxia, extracellular matrix, angiogenesis and metabolic changes. Refer to the list of abbreviations given at the end of this manuscript.

Intrinsic Mechanisms

These mechanisms arise from autocrine signaling originating from within the cancer cells, which might accumulate while they are in the dormant stage. These signals relate to genetic or epigenetic alterations that enable the cancer cells to adjust to the new metastases' microenvironment.

p38/ERK signaling ratio

The activation of p38 protein, a member of a larger family of kinases called MAPK, resembles the influence of endoplasmic reticulum (ER) stress. While ERK is another member of MAPK that drives cell

proliferation, growth, and differentiation in response to growth factors. As such, high ratios of p38/ERK drive dormancy, and conversely, low ratios promote tumor growth [16,25]. The transcriptional activation of p38 induces the unfolded protein response (UPR), which can be exploited by dormant cancer cells to adapt to stress [14]. UPR is a vital cellular stress response in managing the homeostasis of the ER by sensing the accumulation of folded proteins. In addition to its role in survival, the p38 protein is also involved in the control of the cell cycle, partly through the upregulation of CDK inhibitors such as p27 and p21 [26].

Epigenetic modifications

These types of alterations can include DNA methylation, histone modifications, and non-coding RNA influence [27]. A prime example of this is the epigenetic overexpression of the nuclear receptor NR2F1, which is an established dormancy biomarker that has been linked to dormancy in prostate cancer and head and neck squamous cell carcinomas (HNSCC) [28,29]. The overexpression of NR2F1 is driven by specific histone modifications, rather than DNA methylation. In recent years, an agonist of NR2F1 was discovered that can activate dormancy in cancer cells [28]. Endocrine treatment can also induce dormancy through epigenetic modifications involving alterations of specific histones to maintain dormancy until the cells are stochastically awakened. The genes involved in epigenetic repression could include CDC6 and CCND1 (cell cycle genes), in addition to MYC and mTORC1 [12]. Another nuclear kinase protein, MSK1, regulates gene expression by phosphorylating histone H3 and maintaining active chromatin states over specific genes required for keeping the cancer cell in a dormant state. MSK1 works as a key regulator of metastatic dormancy in estrogen-positive breast cancer by acting to stop tumor growth [30].

Autophagy

Autophagy is a cellular recycling process that has a dual role in cancer [31]. The pro-survival function of autophagy in cancer allows DTCs to adapt to the hostile microenvironment and promote their stay in a quiescent state. Autophagy can be activated in several ways, including nutrient starvation, hypoxia, ER stress, high temperature, and pharmacological agents. It can also be triggered by the knockout of critical genetic components, such as *ATG7,* which is essential for core autophagy. The expression of aplasia Ras homolog member I (ARHI) in xenograft ovarian tumors was associated with the induction of reversible dormancy through the activation of autophagy [32]. ARHI is an inhibitor of the PI3K/Akt/mTOR cascade through the upregulation of ATG4 cysteine protease. ARHI also drives the nuclear localization of important mediators such as FOXO3a and TEFB for the expression of critical autophagy effectors [16]. Numerous other studies using cancer cells derived from different sources confirmed the presence of active autophagy in dormant metastatic cells [33,34].

Cellular stress

Cellular stress in this context includes ER stress, lack of nutrients, and UPR. High levels and persistent ER stress are acknowledged to be one of the hallmarks of cancer [35,36]. ER stress promotes cancer dormancy by activating UPR, which enables dormant cancer cells to withstand harsh microenvironmental conditions such as hypoxia and nutrient deprivation. Dormant cancer cells exploit UPR signaling, specifically PERK and IRE1, to induce quiescence [35]. The UPR signaling pathways work by increasing the cell's protein folding capacity to promote survival but can trigger cell death if the stress is too severe. Nutrient deprivation was also found to induce phenotypic changes in cancer cells through translational programming. This enables cancer cells to survive metabolic stress by suppressing global protein synthesis and, hence, promoting dormancy [37,38].

Microenvironmental Drivers

These are exocrine signals that often originate from the tumor microenvironment and include hypoxia, angiogenesis, immune influence, metabolic nutrient deprivation, extracellular matrix, cytokines, and growth factors. The initiation and maintenance of cancer dormancy is dependent on the communications between cancer cells and these microenvironmental drivers [39].

Hypoxia

Low oxygen levels often drive cancer cells' dormancy as a survival mechanism and serve as a crucial guide for cells to enter the dormant state [40,41]. Cancer cells, like all cells, require sufficient oxygen to proliferate, and when the oxygen level drops below a critical threshold, it triggers a strong signal for the cell to stop dividing. The key player here is the HIF-1α factor. This factor is stabilized under low oxygen and activates genes like *p21* and *p27* to promote cell cycle arrest. Oxygen acts as a substrate for the enzymes that degrade HIF-1α; hence, in normoxic (well-oxygenated TME), HIF-1α is rapidly destroyed, whereas under hypoxic conditions, it is stabilized and allowed to perform its function [42]. Large parts of the tumor mass that are unable to survive chronic hypoxic conditions will die. However, those cancer cells that can adapt and survive will remain in a quiescent, reversible state for long periods. In glioblastoma models of cancer, the activation of protein phosphatase 2A (PP2A) has been implicated in G1/S arrest of the cell cycle following the induction of hypoxia [43]. In prostate cancer, HIF-1α promotes expression of the well-known chemokine, CXCR4, that is associated with dormancy [44]. Hypoxia can also stimulate autophagy, allowing dormant cancer cells to survive in a low-nutrient, low-oxygen microenvironment.

Angiogenesis

The influence of angiogenesis on cancer dormancy is both fundamental and paradoxical, as it acts as a primary switch that controls the transition into and out

of dormancy. The balance of the pro- and anti-angiogenic signals in the metastatic niche determines the fate of the disseminated cancer cells, and inhibiting angiogenesis can lead to dormancy [45]. Endothelial cells generate signals that regulate dormancy in cancer cells, with Notch signaling being vital in controlling the fate of decisions of proliferation or apoptosis. A prime example of these signals is the Notch ligand DLL4, which regulates the switch between tumor dormancy and tumor growth [46]. This protein, DLL4, is upregulated during the angiogenic switch and the transition from dormant to fast-growing cells. The expression of pro-angiogenic genes increases in the presence of relevant stimuli such as hypoxia, activated oncogenes, or deactivated tumor suppressor genes. Dormant cancer cells can release more of the angiogenic inhibitor, thrombospondin, thus maintaining the dormancy status of the cells. Thrombospondin has been shown to have a direct impact on the growth of breast cancer cells, particularly in inducing and maintaining its dormant state [47]. On the contrary, periostin (an important secreted protein that is involved in reawakening dormant cells) and TGF-β lead to increased angiogenesis and the production of highly vascularized tumors [48]. The presence of VEGF can also help cancer cells to escape tumor dormancy [49]. MicroRNAs like miR-34a, miR-93, and miR-200c may further induce dormancy through deactivating the mRNAs of genes critical to angiogenesis [50].

The extracellular matrix (ECM)

The mechanical properties of TME are not just a passive scaffold but also an active regulator of cell functions. Collagen and fibronectin, being key components of the ECM, can interact with mechano-transducers such as integrin to regulate dormancy/quiescence [14]. The softness or stiffness of the ECM exerts a significant influence on the fate of tumor cells and whether they become dormant or proliferate and metastasize. A soft ECM can induce and maintain this state through several mechanisms [51]. A soft cytoskeleton leads to the formation of small, immature anchoring of cells to ECM and low focal adhesion kinase (FAK) signaling, which is usually an indication of quiescence [52]. Moreover, on a soft cytoskeleton, the tension is low and YAP/TAZ, a crucial transcriptional coactivator responsible for sensing physical signals in the ECM and converting them into gene expression changes, remains unphosphorylated and eventually degraded [53]. Additionally, p38 activity relative to ERK is high on soft ECM, promoting cell cycle arrest through the G0/G1 phase and a dormancy phenotype, while stiffness flips this balance, favoring pro-growth ERK [54]. The primary site where cancer cells originate, in comparison with their metastatic niche, may also influence the stiffness of the cytoskeleton. For example, bone marrow, brain, and liver sinusoids are often characterized by having a soft ECM. Disseminated cancer cells that arrive there may undergo stiffness-induced signaling because the mechanical environment does not support the proliferative signaling, they were used to in the primary tumor. It is important to note that the relationship between softness/stiffness and dormancy is not always straightforward. The optimal stiffness for dormancy may vary by cancer type and metastatic site. For instance, breast cancer cells may become dormant in the soft brain tissue but proliferate in the stiffer osteolytic bone lesions [55]. Furthermore, as the ECM is remodelled over time, a dormant niche may eventually become fibrotic to provide the necessary mechanical reawakening signal.

Cellular components of the niche

Cellular components of TME, other than cancer cells, can also contribute to dormancy. These include fibroblasts, endothelial cells, and immune cells; the influence of the latter cells on dormancy is discussed under a separate subsection here. The “education” of fibroblasts, which involves differentiation, activation, and specialization, takes place within the tissue microenvironment and is driven by cues including molecular signaling such as TGF-β and PDGF. These educated fibroblasts are usually referred to as cancer-associated fibroblasts (CAFs) and may support dormancy through the secretion of ECM-modelling enzymes like matrix metalloproteinases and factors such as TGF-β and CXCL12 [56]. Endothelial cells, particularly those in bone marrow sinusoids, can release thrombospondin-1, a potent dormancy inducer [57].

Nutrient availability

Limited availability of glucose and certain amino acids, like glutamine, can force cancer cells into a reversible dormant state. The replenishment of such nutrients can facilitate exiting dormancy [58].

Secreted soluble factors

A variety of secreted soluble factors can influence the dormancy of cancer cells, including bone morphogenetic proteins (BMPs), Wnt inhibitors, and TGF-β. BMPs, particularly BMP-4 and BMP-7, can activate p38 signaling, leading to cell cycle arrest and dormancy [59]. Wnt inhibitors secreted by stromal cells can block the Wnt-related proliferative signaling and enforce a dormancy state [6]. The canonical TGF-β axis often induces dormancy via p38 signaling in the early stages following the dissemination of cancer cells [60].

Immune surveillance

The immune context of TME is shaped by the three Es of immunoediting: elimination, equilibrium, and escape. Cancer cell dormancy in this context represents the equilibrium phase. Immune pressure, arising primarily from cytotoxic T cells and NK cells, continuously suppresses outgrowth but not enough to fully eliminate the cancer cells. Escaping from this immune pressure, as in immunosuppression, can tip the balance towards exit from dormancy.

Exiting (Reawakening) Dormancy

While metastases themselves are the cause of about 90% of cancer-related deaths, the reawakening of dormant cancer cells, which is clinically manifested as metastatic recurrence or relapse, is increasingly recognized as a major driving factor [61]. The reawakening process is currently viewed as a dynamic interplay between the dormant cancer cells and their microenvironment, quite often involving reversal of dormancy cues. Figure 3 schematically illustrates the factors that aid cancer cells in exiting dormancy.

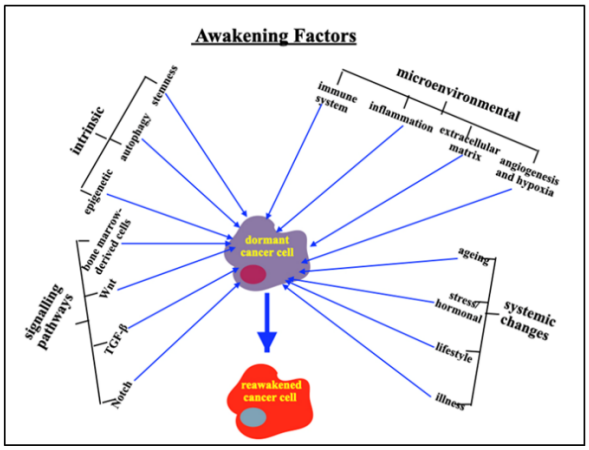

Figure 3: Drivers of cancer cell reawakening. Exiting dormancy is facilitated by a range of factors, including microenvironmental, intrinsic, signalling pathways and systemic changes. Refer to the list of abbreviations given at the end of this manuscript.

The influence of the local microenvironment is crucial in shifting the balance between dormancy and reawakening. Inflammation, acute and chronic, and its signals like TNF-α and IL-6 are major drivers to activate pro-growth pathways such as NF-κB in the dormant cell [62]. Recent research on mice suggested that persistent inflammation involves the generation of neutrophil extracellular traps (NETs), web-like structures released by neutrophils to trap pathogens, which are essential for cancer cells to exit the dormant state [63]. Signals that stimulate blood vessel growth, e.g., VEGF, can participate in the formation of adequate vasculature to provide nutrients and oxygen for regrowth and remove waste products from cells [64]. Reversing the hypoxic conditions through the formation of new blood vessels can restore oxygen supply to dormant cells and contribute to their reawakening. The ECM is another crucial part of the influence of TME on exiting dormancy [65]. ECM undergoes dynamic remodeling of its different components driven by ECM-associated enzymes and cancer-associated fibroblasts [66]. Changes in the scaffolding around the cells can release growth factors or physically trigger growth through integrin proteins. The immune cells that normally send signals to respond to infections or trauma can be subverted by cancer cells to exit dormancy. A weakened surveillance by the immune system, or if the immune cells themselves secrete pro-growth factors, can be a crucial stimulus for dormant cancer cells to escape dormancy. Intrinsic changes in the dormant cells themselves can also drive cells to adapt. One of these adaptations is the acquisition of stemness properties, allowing cells to self-renew and initiate tumors when conditions are more suitable [65]. Cancer stem cells (CSCs) are generally accepted to be the seeds for this disease's initiation, progression, and relapse [67,68] Cancer stem cells can alternate between quiescent and proliferating states, characterized by temporal and spatial heterogeneity and plasticity [68]. One such important property of cancer stem cells is their ability to enter and exit dormancy. The activation of mTOR was able to increase the CSC pool in bone marrow metastatic niches in prostate cancer models [69]. Dormant cells often use autophagy, which is activated and fine-tuned in response to conditions such as hypoxia, DNA damage, growth factors, and nutrient deficiency, to enable survival under stress [34]. The complex role of autophagy in carcinogenesis is often described as a double-edged sword. It suppresses tumors in the early stages of cancer development, while in established cancers, autophagy can promote cancer growth and elicit resistance to therapies [31,33]. Epigenetic switches can silence, or downregulate, pro-dormancy genes and activate pro-growth pathways in response to external cues. These mechanisms can include DNA methylation, histone modifications, and non-coding RNA regulations [70–72]. It has been demonstrated by Sosa et al. that the gene *NR2F1* is downregulated through promoter hypermethylation during active cancer growth but significantly upregulated during cellular dormancy, clearly illustrating the epigenetic roles of the dormancy/relapse drivers [29]. The key signaling pathways involved in orchestrating the reawakening of cancer cells are Wnt signaling, TGF-β signaling, Notch signaling, and signaling arising from bone marrow cells [3]. The Wnt signaling, which is often reactivated during reawakening, is critical for stem cell maintenance, which is responsible for cancer recurrence, metastasis, and resistance to therapies. The relationship between Wnt-driven stem cells and tumorigenesis is seen in the evidence linking Wnt-signaling intensity to stem cell characteristics in colon cancer [73–75]. Signaling involving the TGF-β axis has a dual role; it can induce dormancy or promote growth depending on the context. TGF-β signaling acts as a tumor suppressor in the early stages of cancer development but as a potent promoter of cancer progression and relapse in advanced stages [76]. Communications between cells and fate decisions are often facilitated by Notch signaling. Notch signaling, like Wnt signaling, also promotes cancer relapse by maintaining cancer stem cell phenotypes, facilitating tumor dormancy, and resisting therapies [77]. Bone marrow-derived cells (BMDCs), due to their varied and complex nature, can play a dual role in cancer, acting as cancer-promoting agents and anti-tumor cells [78]. The recruitment of immune cells, or their progenitors, from the bone marrow to a dormant site delivering pro-growth factors can often be the initiating event in the emergence from dormancy. Systemic changes that influence the overall function of the body, such as aging, stress, lifestyle, and disease, can also disturb the dormant niches [65]. With aging, the tissues can become more pro-inflammatory, undergo remodeling,

and create favorable conditions for reawakening. Furthermore, stress releases hormones like cortisol and norepinephrine, which can promote inflammation that directly influences carcinogenesis. For hormone-sensitive cancers, such as breast and prostate cancer, fluctuations in estrogen and testosterone, respectively, can stimulate dormant cancer cells [79]. Animal studies suggest that factors like a high-fat diet and obesity can create a chronic pro-inflammatory stressful state, promoting reawakening. Additionally, systemic infections can cause widespread inflammation, potentially reawakening dormant cancer cells. Viral respiratory infections are usually associated with inflammation with a concomitant rise in pro-inflammatory cytokines such as IL-6 and TNFs and an expansion of immune cells like neutrophils, macrophages, and T cells. Such an immune defensive action has been identified as a regulator of metastatic processes in cancer [80].

Biomarkers for Dormancy/Reawakening

Biomarkers that indicate the presence of resting cancer cells or predict their reactivation are usually molecules or cellular components that fall into two categories. They could either be intrinsic to the cancer cells themselves or indicative of the microenvironment they exist in, as illustrated in Figure 4. Despite their usefulness in several preclinical settings, none have been adopted for widespread clinical applications. A few of the more commonly employed biomarkers to predict cancer dormancy/reawakening are given in Figure 4.

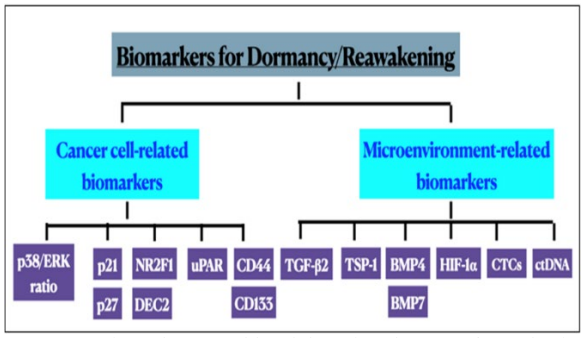

Figure 4: Biomarkers capable of detecting dormancy/reawakening are grouped as cancer cell-related and microenvironment-related. These markers have not yet gained regulatory approval for clinical use but are widely employed in pre-clinical investigations. Refer to the list of abbreviations at the end of the manuscript.

Of the intrinsic cancer cell-related biomarkers, the ratio p38/ERK stands out as a well-established indicator of dormancy. When the p38/ERK ratio is high, it signals growth arrest and the entrance into the G0 phase from the G1 phase of the cell cycle [54]. The cyclin-dependent kinase inhibitors p21 and p27 maintain cells in their non-proliferative, quiescent state and are also considered useful biomarkers of dormancy [81]. The high expression of NR2F1 and DEC2 induces a state of dormancy by promoting a repressive chromatin state. Low expression of uPAR, a cell surface receptor that drives ECM degradation and tissue remodeling, is associated with dormancy, while high expression of uPAR signals a switch to a proliferative, aggressive phenotype [82]. The stemness biomarkers CD44 and CD133, while not exclusively linked to dormancy, are associated with slow growth and resistance to therapy [81]. The microenvironment-related biomarkers often hide in the niche, reflecting the interactions between cancer cells and the surrounding tissues and structures. High levels of TGF-β2, particularly in bone marrow, are indicative of dormancy in squamous cell carcinoma and breast cancer. Tu and colleagues discovered a close relationship between the overexpression of TGF-β2 and the prognosis of colorectal cancer, as well as the infiltration of immune cells [83]. High levels of thrombospondin-1 (TSP-1), an angiogenesis inhibitor, can prevent cancer from developing and can act as a potential biomarker for angiogenesis [84]. BMP4 and BMP7, particularly the latter, can promote stemness and stem cell-like phenotypes in the bone marrow [85]. The hypoxia-inducing factor, HIF-1α, can sustain dormancy through the induction of hypoxia but can also induce dormancy-associated genes like *NR2F1*. Circulating tumor cells (CTCs), particularly Ki67-negative (non-proliferative) and M30-negative (non-apoptotic), can point to these cells as being dormant [3]. A rise in the levels of circulating tumor DNA (ctDNA) usually precedes any clinical manifestation of relapse, indicating reactivation of dormant cells. These ctDNAs constitute highly specific and minimally invasive biomarkers that allow real-time monitoring of tumor burden. The short half-lives of these ctDNAs, usually less than 2 hours, make them attractive biomarkers for detecting disease recurrence months before it is visible on conventional imaging [86].

Exploiting Cancer Dormancy/Reawakening for Therapy

Therapeutic strategies exploiting the dormancy/reawakening programs fall into three main areas: a) maintaining the dormant cells in a quiescent non-proliferative state, b) eliminating the dormant cells, and c) modifying the microenvironment of cancer cells to achieve objectives (a) or (b) of maintenance or elimination (Figure 5). Due to the non-proliferative, albeit therapy-resistant, characteristics of dormant cancer cells, they could be maintained as such for therapeutic purposes. Cell-intrinsic mechanisms can be leveraged to induce dormancy, as in the case of using Debio-0719, an inhibitor of the lysophosphatidic acid receptor 1 (LPA1). This inhibitor was shown to promote the dormancy of triple-negative breast cancer (TNBC) cells at metastatic sites by inducing the p38high/ERKlow signaling axis [87]. Employing such inhibitors in TNBC to maintain residual dormant disease at bay could be considered an optional therapeutic strategy. A further strategy that could be considered in maintaining dormancy is combining a DNA-demethylating agent (5-Aza-C) with trans-retinoic acid (ATRA) to re-establish NR2F1-induced dormancy in head and neck squamous cell carcinoma [29]. CDK4/6 inhibitors (like palbociclib, ribociclib, and abemaciclib) are targeted therapies that have been widely used, in combination with endocrine therapy, to treat hormone receptor-positive (HR+), HER2-

negative breast cancer by forcing cancer cells into a dormant or senescent state [88].

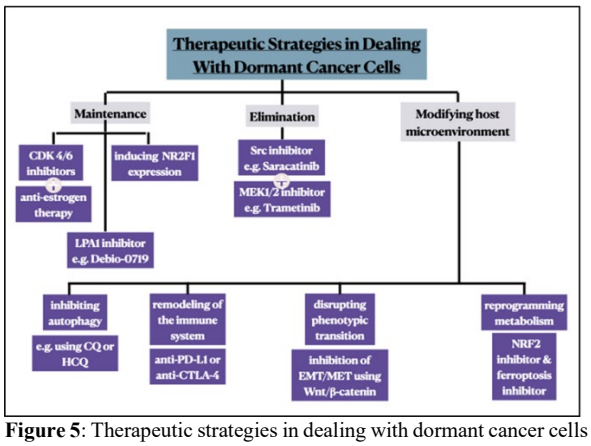

Figure 5: Therapeutic strategies in dealing with dormant cancer cells are basically those of maintenance or elimination. In maintenance, cell intrinsic properties are leveraged to keep the cancer cells in a quiescent non-proliferative state. On the other hand, a combination of Src and ERK1/2 inhibitors could be employed to eliminate dormant cancer cells. Additionally, manipulating the microenvironment to achieve maintenance or elimination is also a choice that is gaining more investigative curiosity. Refer to the abbreviations listed at the end of this manuscript.

As stated above, dormant non-proliferative cancer cells resist traditional and newer targeted therapies due to their quiescence and/or induced senescence-like state [48]. Consequently, the removal of residual dormant cells might constitute an attractive therapy option before they are awakened. The activation of Src and ERK1/2 was previously established to be necessary for the survival and outgrowth of dormant cancer cells [89]. The protein Src acts as the target of matrine, a bioactive naturally occurring alkaloid, to inhibit the proliferation of cancer cells by regulating phosphorylation signaling pathways [3]. The combined inhibition of Src and ERK1/2 in dormant breast cancer cells was shown to contribute to their elimination [89]. This led to the suggestion that combining a Src inhibitor like saracatinib with an approved MEK1/2 inhibitor such as Trametinib may eradicate dormant breast cancer cells before relapse. The field of the therapeutic modulation of dormancy/reawakening that is gaining the most research interest is modifying the tumor microenvironment. The use of hydroxychloroquine to inhibit autophagy in breast cancer cells promoted the apoptosis of those cells that had colonized the lungs [10]. The influence of the immune system on TME in relation to dormancy/reawakening is clearly demonstrated in several studies, suggesting that reinstating MHC-I and NK cell ligands, as well as inhibiting immune checkpoint proteins on dormant cancer cells, may re-sensitize them for immune clearance [90,91]. The expression of microRNA, miR-125b, an inducer of dormancy, reduces Wnt-associated stem cell signaling and mesenchymal-associated genes, leading to a reduction of the metastasis of breast cancer cells to the bone [92]. Dormant cancer cells often utilize hyperactivated NRF2 to maintain redox homeostasis and survive the high oxidative stress of dormancy. Therefore, a combination of NRF2 inhibitors and ferroptosis (an iron-dependent cell death characterized by the accumulation of lipid peroxides) inducers acts together as a potent therapeutic strategy to eliminate cancer cells by breaking down their defense mechanisms against lipid peroxidation and iron accumulation [93]. Several other strategies have been investigated in relation to the influence of the microenvironment in overcoming dormancy/relapse, the details of which are beyond the scope of this limited narrative review.

Conclusions

The journey of cancer from a localized, treatable disease to a lethal systemic one is complex and often has periods of deceptive silence. In this simple narrative review, we have dissected two predominant, often interconnected, types of dormancies: tumor mass dormancy and cellular dormancy. The tumor mass dormancy represents an equilibrium where cell proliferation is counterbalanced by apoptosis and constrained by the inability to recruit new blood vessels or by heightened immune surveillance. In cellular dormancy, a single cancer cell enters a reversible growth arrest controlled by intrinsic signaling and cues from the surrounding microenvironment. Reawakening from this dormancy state represents an often-fatal step in the metastatic process. Knowledge and mechanistic insights into dormancy/relapse could be a valuable opportunity in designing cancer therapies that appear to converge on three approaches of maintenance, elimination, and microenvironmental manipulation. In maintenance therapy, kinase inhibitors or the induction of NR2F1 expression are used to lock dormant cancer cells in a permanent quiescence. In the elimination therapy, Src and MEK1/2 inhibitors are used to target certain unique vulnerabilities of cancer cells. Microenvironmental manipulation can be wide-ranging and include interventions such as targeting autophagy, disrupting phenotypic transition, and remodeling the immune system.

Abbreviations

AKT: protein kinase B; ARH1: Aplasia Ras homolog; ATG4: autophagy-related protein 4; ATRA: trans-retinoic acid; BMDCs: bone marrow-derived cells; BMPs: bone morphogenetic proteins; C-X-CL: chemokine (C-X-C motif) ligand; CAFs: cancer-associated fibroblasts; CCND1: cyclin D1; CDC6: cyclin-dependent kinase 6; CD: cluster of differentiation; CDK: cyclin-dependent kinase; CTCs: circulating tumor cells; CTLA-4: cytotoxic T lymphocyte-associated protein 4; CQ: chloroquine; CSCs: cancer stem cells; CXCR4: C-X-C motif chemokine receptor 4; DCCs: dormant cancer cells; DEC: differentiated embryonic chondrocyte expressed gene; DLL4: delta-like notch ligand 4; ECM: extracellular matrix; EMT: epithelial-mesenchymal transition; ER: endoplasmic reticulum; ERK: another member of mitogen-activated protein kinases responding to growth factors to promote cell proliferation; FAK: focal adhesion kinase; FOXO: forkhead box subclass; O; HCQ: hydroxychloroquine; HER2: human epidermal growth factor receptor 2; HIF-α: hypoxia-inducing factor alpha; HR+: hormone

receptor positive; IRE1: inositol-requiring enzyme 1; IL: interleukin; LPA 1: lysophosphatidic acid receptor; MEK: mitogen-activated protein kinase; MET: mesenchymal-epithelial transition; MHC1: major histocompatibility complex 1; MMPs: matrix metalloproteinases; MSK1: mitogen and stress-activated protein kinase 1; mTORC1: mechanistic target of rapamycin complex 1; Myc: avian myelocytomatosis viral oncogene homolog; NF-κB: nuclear factor-kappa B; NETs: neutrophil extracellular traps; NK: natural killer; Notch: a highly conserved receptor essential for differentiation and tissue development; NR2F1: nuclear receptor subfamily 2 group F members 1. NRF2: nuclear factor erythroid 2-related factor 2; PD-L1: programmed death ligand 1; PDGF: platelet-derived growth factor; PERK: protein kinase-like endoplasmic reticulum kinase; PI3K: phosphoinositide-3-kinase; PINK1: PTEN-induced protein kinase 1; PP2A: protein phosphatase 2A; p38-MAPK: a member of mitogen-activated protein kinases activated by environmental stress; Src: a non-receptor tyrosine kinase protein crucial in regulating cell growth and division; TAD: transcriptional co-activator with PDZ-binding motif; TEFB: transcription elongation factor B: TGF-β: transforming growth factor beta; TME: tumor microenvironment; TNBC: triple-negative breast cancer; TNF-α: tumor necrosis factor alpha; TSP: thrombospondin; uPAR: urokinase plasminogen activator receptor; UPR: unfolded protein response; VEGF: vascular endothelial growth factor; Wnt: wingless-related integration site; Wnt/β-catenin: fundamental signaling regulator for growth, differentiation, and stemness; YAP: yes-associated protein.

ACKNOWLEDGMENTS

The author is grateful for the help and support received from Mrs. Joanna S. Al-Janabi in the preparation of this manuscript.

Conflict of interests

The author declares no conflict of interest.

Funding source

The author did not receive any source of funds.

Data sharing statement

N/A.

REFERENCES

1. Yeh AC, Ramaswamy S. Mechanisms of cancer cell dormancy—Another hallmark of cancer? *Cancer Res*. 2015;75(23):5014–5022. doi: 10.1158/0008-5472.can-15-1370.
2. Truskowski K, Amend SR, Pienta KJ. Dormant cancer cells: programmed quiescence, senescence, or both? *Cancer Metastasis Rev*. 2023;42(1):37–47. doi: 10.1007/s10555-022-10073-z.
3. Tufail M, Jiang CH, Li N. Tumor dormancy and relapse: understanding the molecular mechanisms of cancer recurrence. *Mil Med Res*. 2025;12(1). doi: 10.1186/s40779-025-00595-2.
4. Fidler IJ. The biology of cancer metastasis. *Semin Cancer Biol*. 2011;21(2):71–71. doi: 10.1016/j.semcancer.2010.12.004.
5. Friberg S, Nystrom A. Cancer metastases: Early dissemination and late recurrences. *Cancer Growth Metastasis*. 2015;8:CGM.S31244. doi: 10.4137/cgm.s31244.
6. Liu R, Zhao Y, Su S, Kwabil A, Njoku PC, Yu H, et al. Unveiling cancer dormancy: Intrinsic mechanisms and extrinsic forces. *Cancer Lett*. 2024;591:216899. doi: 10.1016/j.canlet.2024.216899
7. Aouad P, Quinn HM, Berger A, Brisken C. Tumor dormancy: EMT beyond invasion and metastasis. *Genesis*. 2023;62(1). doi: 10.1002/dvg.23552.
8. Brown JA, Yonekubo Y, Hanson N, Sastre-Perona A, Basin A, Rytlewski JA, et al. TGF-β-Induced quiescence mediates chemoresistance of tumor-propagating cells in squamous cell carcinoma. *Cell Stem Cell*. 2017;21(5):650-664.e8. doi: 10.1016/j.stem.2017.10.001.
9. Gonzalez H, Robles I, Werb Z. Innate and acquired immune surveillance in the post dissemination phase of metastasis. *FEBS J*. 2017;285(4):654–664. doi: 10.1111/febs.14325.
10. Vera-Ramirez L, Vodnala SK, Nini R, Hunter KW, Green JE. Autophagy promotes the survival of dormant breast cancer cells and metastatic tumour recurrence. *Nat Commun*. 2018;9(1). doi: 10.1038/s41467-018-04070-6.
11. Basu S, Dong Y, Kumar R, Jeter C, Tang DG. Slow-cycling (dormant) cancer cells in therapy resistance, cancer relapse and metastasis. *Semin Cancer Biol*. 2022;78:90–103. doi: 10.1016/j.semcancer.2021.04.021.
12. Rosano D, Sofyali E, Dhiman H, Ghirardi C, Ivanoiu D, Heide T, et al. Long-term multimodal recording reveals epigenetic adaptation routes in dormant breast cancer cells. *Cancer Discov*. 2024;14(5):866–889. doi: 10.1158/2159-8290.cd-23-1161.
13. Damen MPF, van Rheenen J, Scheele CLGJ. Targeting dormant tumor cells to prevent cancer recurrence. *FEBS J*. 2020;288(21):6286–6303. doi: 10.1111/febs.15626.
14. Cho J. Understanding tumor dormancy: From experimental models to mechanisms and therapeutic strategies. *Biomol Ther (Seoul)*. 2025;33(5):770-784. doi: 10.4062/biomolther.2025.056.
15. Osisami M, Keller E. Mechanisms of Metastatic Tumor Dormancy. J Clin Med. 2013;2(3):136–50. doi:10.3390/jcm2030136
16. Tamamouna V, Pavlou E, Neophytou CM, Papageorgis P, Costeas P. Regulation of metastatic tumor dormancy and emerging opportunities for therapeutic intervention. *Int J Mol Sci*. 2022;23(22):13931. doi: 10.3390/ijms232213931.
17. Prager BC, Bhargava S, Mahadev V, Hubert CG, Rich JN. Glioblastoma stem cells: Driving resilience through chaos. *Trends Cancer*. 2020;6(3):223–235. doi: 10.1016/j.trecan.2020.01.009.
18. Shepherd TG, Dick FA. Principles of dormancy evident in high-grade serous ovarian cancer. *Cell Div*. 2022;17(1). doi: 10.1186/s13008-022-00079-y.
19. Gimbrone MA, Leapman SB, Cotran RS, Folkman J. Tumor dormancy in vivo by prevention of neovascularization. *J Exp Med*. 1972;136(2):261–276. doi: 10.1084/jem.136.2.261.
20. Endo H, Inoue M. Dormancy in cancer. *Cancer Sci*. 2019;110(2):474–480. doi: 10.1111/cas.13917.
21. Sosa MS, Bragado P, Aguirre-Ghiso JA. Mechanisms of disseminated cancer cell dormancy: an awakening field. *Nat Rev Cancer*. 2014;14(9):611–622. doi: 10.1038/nrc3793.
22. Fu H. Editorial: Novel molecular mechanisms and clinical strategies in solid tumor recurrence and metastasis: from bench to bedside. *Front Med (Lausanne)*. 2024;11. doi: 10.3389/fmed.2024.1364666.
23. Chakraborty G, Gupta K, Kyprianou N. Epigenetic mechanisms underlying subtype heterogeneity and tumor recurrence in prostate cancer. *Nat Commun*. 2023;14(1). doi: 10.1038/s41467-023-36253-1.
24. Payne KK. Cellular stress responses and metabolic reprogramming in cancer progression and dormancy. *Semin Cancer Biol*. 2022;78:45–48. doi: 10.1016/j.semcancer.2021.06.004.
25. Kudaravalli S, den Hollander P, Mani SA. Role of p38 MAP kinase in cancer stem cells and metastasis. *Oncogene*. 2022;41(23):3177–3185. doi: 10.1038/s41388-022-02329-3.

26. Whitaker RH, Cook JG. Stress relief techniques: p38 MAPK determines the balance of cell cycle and apoptosis pathways. *Biomolecules*. 2021;11(10):1444. doi: 10.3390/biom11101444.
27. Robinson NJ, Parker KA, Schiemann WP. Epigenetic plasticity in metastatic dormancy: mechanisms and therapeutic implications. *Ann Transl Med*. 2020;8(14):903–903. doi: 10.21037/atm.2020.02.177.
28. Khalil BD, Sanchez R, Rahman T, Rodriguez-Tirado C, Moritsch S, Martinez AR, et al. An NR2F1-specific agonist suppresses metastasis by inducing cancer cell dormancy. *J Exp Med*. 2021;219(1). doi: 10.1084/jem.20210836.
29. Sosa MS, Parikh F, Maia AG, Estrada Y, Bosch A, Bragado P, et al. NR2F1 controls tumour cell dormancy via SOX9- and RARβ-driven quiescence programmes. *Nat Commun*. 2015;6(1). doi: 10.1038/ncomms7170.
30. Gawrzak S, Rinaldi L, Gregorio S, Arenas EJ, Salvador F, Urosevic J, et al. MSK1 regulates luminal cell differentiation and metastatic dormancy in ER+ breast cancer. *Nat Cell Biol*. 2018;20(2):211–221. doi: 10.1038/s41556-017-0021-z.
31. Al-Janabi I. The role of autophagy in the progression and treatment of tumors. *Al-Rafidain J Med Sci*. 2021;1:62–71. doi: 10.54133/ajms.v1i.37.
32. Lu Z, Luo RZ, Lu Y, Zhang X, Yu Q, Khare S, et al. The tumor suppressor gene ARHI regulates autophagy and tumor dormancy in human ovarian cancer cells. *J Clin Investig*. 2008. doi: 10.1172/jci35512.
33. Gunes D, Ustal A, Ertem YE, Akkoc Y, Gozuacik D. Autophagy in the regulation of cancer dormancy. *FEBS Lett*. 2025;599(16):2272–3200. doi: 10.1002/1873-3468.70139.
34. Akkoc Y, Peker N, Akcay A, Gozuacik D. Autophagy and cancer dormancy. *Front Oncol*. 2021;11. doi: 10.3389/fonc.2021.627023.
35. Payne KK. Cellular stress responses and metabolic reprogramming in cancer progression and dormancy. *Semin Cancer Biol*. 2022;78:45–48. doi: 10.1016/j.semcancer.2021.06.004.
36. Zhou R, Wang W, Li B, Li Z, Huang J, Li X. Endoplasmic reticulum stress in cancer. *MedComm (Beijing)*. 2025;6(7). doi: 10.1002/mco2.70263.
37. García-Jiménez C, Goding CR. Starvation and pseudo-starvation as drivers of cancer metastasis through translation reprogramming. *Cell Metab*. 2019;29(2):254–267. doi: 10.1016/j.cmet.2018.11.018.
38. Cho J, Min HY, Lee HJ, Hyun SY, Sim JY, Noh M, et al. RGS2-mediated translational control mediates cancer cell dormancy and tumor relapse. *J Clin Investig*. 2021;131(1). doi: 10.1172/jci136779.
39. Linde N, Fluegen G, Aguirre-Ghiso JA. The relationship between dormant cancer cells and their microenvironment. *Adv Cancer Res*. 2016;132:45–71. doi: 10.1016/bs.acr.2016.07.002.
40. Korotchkina LG, Leontieva OV, Bukreeva EI, Demidenko ZN, Gudkov AV, Blagosklonny MV. The choice between p53-induced senescence and quiescence is determined in part by the mTOR pathway. *Aging*. 2010;2(6):344–352. doi: 10.18632/aging.100160.
41. Bliss SA, Sinha G, Sandiford OA, Williams LM, Engelberth DJ, Guiro K, et al. Mesenchymal stem cell–derived exosomes stimulate cycling quiescence and early breast cancer dormancy in bone marrow. *Cancer Res*. 2016;76(19):5832–5844. doi: 10.1158/0008-5472.can-16-1092.
42. Basheeruddin M, Qausain S. Hypoxia-inducible factor 1-Alpha (HIF-1α): An essential regulator in cellular metabolic control. *Cureus*. 2024. doi: 10.7759/cureus.63852.
43. Hofstetter CP, Burkhardt JK, Shin BJ, Gürsel DB, Mubita L, Gorrepati R, et al. Protein phosphatase 2A mediates dormancy of glioblastoma multiforme-derived tumor stem-like cells during hypoxia. *PLoS One*. 2012;7(1):e30059. doi: 10.1371/journal.pone.0030059.
44. Wang N, Docherty F, Brown HK, Reeves K, Fowles A, Lawson M, et al. Mitotic quiescence, but not unique "stemness," marks the phenotype of bone metastasis-initiating cells in prostate cancer. *FASEB J*. 2015;29(8):3141–3150. doi: 10.1096/fj.14-266379.
45. Chang Y, Chen J. Dormant mechanisms reveal the clinical significance of tumor dormancy: a narrative review. *Ann Blood*. 2021;6:15–15. doi: 10.21037/aob-20-46.
46. Indraccolo S, Minuzzo S, Masiero M, Pusceddu I, Persano L, Moserle L, et al. Cross-talk between tumor and endothelial cells involving the Notch3-Dll4 interaction marks escape from tumor dormancy. *Cancer Res*. 2009;69(4):1314–1323. doi: 10.1158/0008-5472.can-08-2791.
47. Ghajar CM, Peinado H, Mori H, Matei IR, Evason KJ, Brazier H, et al. The perivascular niche regulates breast tumour dormancy. *Nat Cell Biol*. 2013;15(7):807–817. doi: 10.1038/ncb2767.
48. Saleh T, Tyutyunyk-Massey L, Gewirtz DA. Tumor cell escape from therapy-induced senescence as a model of disease recurrence after dormancy. *Cancer Res*. 2019;79(6):1044–1046. doi: 10.1158/0008-5472.can-18-3437.
49. Panigrahy D, Edin ML, Lee CR, Huang S, Bielenberg DR, Butterfield CE, et al. Epoxyeicosanoids stimulate multiorgan metastasis and tumor dormancy escape in mice. *J Clin Investig*. 2012;122(1):178–191. doi: 10.1172/jci58128.
50. Tiram G, Segal E, Krivitsky A, Shreberk-Hassidim R, Ferber S, Ofek P, et al. Identification of dormancy-associated microRNAs for the design of osteosarcoma-targeted dendritic polyglycerol nanopolyplexes. *ACS Nano*. 2016;10(2):2028–2045. doi: 10.1021/acsnano.5b06189.
51. Schrader J, Gordon-Walker TT, Aucott RL, van Deemter M, Quaas A, Walsh S, et al. Matrix stiffness modulates proliferation, chemotherapeutic response, and dormancy in hepatocellular carcinoma cells. *Hepatology*. 2011;53(4):1192–1205. doi: 10.1002/hep.24108.
52. Hu HH, Wang SQ, Shang HL, Lv HF, Chen BB, Gao SG, et al. Roles and inhibitors of FAK in cancer: current advances and future directions. *Front Pharmacol*. 2024;15. doi: 10.3389/fphar.2024.1274209.
53. Kurppa KJ, Liu Y, To C, Zhang T, Fan M, Vajdi A, et al. Treatment-induced tumor dormancy through YAP-mediated transcriptional reprogramming of the apoptotic pathway. *Cancer Cell*. 2020;37(1):104-122.e12. doi: 10.1016/j.ccell.2019.12.006.
54. Aguirre-Ghiso JA, Estrada Y, Liu D, Ossowski L. ERK(MAPK) activity as a determinant of tumor growth and dormancy; regulation by p38(SAPK). *Cancer Res*. 2003;63(7):1684–1695. PMID: 12670923.
55. Watson AW, Grant AD, Parker SS, Hill S, Whalen MB, Chakrabarti J, et al. Breast tumor stiffness instructs bone metastasis via maintenance of mechanical conditioning. *Cell Rep*. 2021;35(13):109293. doi: 10.1016/j.celrep.2021.109293.
56. Dai L, Li M, Zhang WL, Tang YJ, Tang YL, Liang XH. Fibroblasts in cancer dormancy: foe or friend? *Cancer Cell Int*. 2021;21(1):184. doi: 10.1186/s12935-021-01883-2.
57. Leone P, Malerba E, Susca N, Favoino E, Perosa F, Brunori G, et al. Endothelial cells in tumor microenvironment: insights and perspectives. *Front Immunol*. 2024;15. doi: 10.3389/fimmu.2024.1367875.
58. Wang Y, Liu L, Zhang X, Liang T, Bai X. Cancer dormancy and metabolism: From molecular insights to translational opportunities. *Cancer Lett*. 2025;635:218097. doi: 10.1016/j.canlet.2025.218097.
59. Kobayashi A, Okuda H, Xing F, Pandey PR, Watabe M, Hirota S, et al. Bone morphogenetic protein 7 in dormancy and metastasis of prostate cancer stem-like cells in bone. *J Exp Med*. 2011;208(13):2641–2655. doi: 10.1084/jem.20110840.
60. Bragado P, Estrada Y, Parikh F, Krause S, Capobianco C, Farina HG, et al. TGF-β2 dictates disseminated tumour cell fate in target organs through TGF-β-RIII and p38α/β signalling. *Nat Cell Biol*. 2013;15(11):1351–1361. doi: 10.1038/ncb2861.
61. Min HY, Lee HY. Cellular dormancy in cancer: Mechanisms and potential targeting strategies. *Cancer Res Treat*. 2023;55(3):720–736. doi: 10.4143/crt.2023.468.
62. Zhang J, Zhang J, Han L, Wu S, Li J, Eaton EN, et al. Inflammation awakens dormant cancer cells by modulating the epithelial–mesenchymal phenotypic state. *Proc Natl Acad Sci*. 2025;122(36). doi: 10.1073/pnas.2515009122.
63. Albrengues J, Shields MA, Ng D, Park CG, Ambrico A, Poindexter ME, et al. Neutrophil extracellular traps produced during inflammation awaken dormant cancer cells in mice. *Science (1979)*. 2018;361(6409). doi: 10.1126/science.aao4227.
64. Zuazo-Gaztelu I, Casanovas O. Unraveling the role of angiogenesis in cancer ecosystems. *Front Oncol*. 2018;8. doi: 10.3389/fonc.2018.00248.
65. 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. doi: 10.3389/fimmu.2020.02166.
66. Prakash J, Shaked Y. The Interplay between extracellular matrix remodeling and cancer therapeutics. *Cancer Discov*. 2024;14(8):1375–1388. doi: 10.1158/2159-8290.cd-24-0002.
67. Dean M, Fojo T, Bates S. Tumour stem cells and drug resistance. *Nat Rev Cancer*. 2005;5(4):275–284. doi: 10.1038/nrc1590.
68. Batlle E, Clevers H. Cancer stem cells revisited. *Nat Med*. 2017;23(10):1124–1134. doi: 10.1038/nm.4409.
69. Shiozawa Y, Berry JE, Eber MR, Jung Y, Yumoto K, Cackowski FC, et al. The marrow niche controls the cancer stem cell phenotype of disseminated prostate cancer. *Oncotarget*. 2016;7(27):41217–41232. doi: 10.18632/oncotarget.9251.
70. Seligson DB, Horvath S, Shi T, Yu H, Tze S, Grunstein M, et al. Global histone modification patterns predict risk of prostate cancer recurrence. *Nature*. 2005;435(7046):1262–1266. doi: 10.1038/nature03672.
71. Zhou M, Xu W, Yue X, Zhao H, Wang Z, Shi H, et al. Relapse-related long non-coding RNA signature to improve prognosis prediction of lung adenocarcinoma. *Oncotarget*. 2016;7(20):29720–29738. doi: 10.18632/oncotarget.8825.
72. Li M, Zhu C, Xue Y, Miao C, He R, Li W, et al. A DNA methylation signature for the prediction of tumour recurrence in stage II colorectal cancer. *Br J Cancer*. 2023;128(9):1681–1689. doi: 10.1038/s41416-023-02155-8.
73. Vermeulen L, De Sousa E Melo F, van der Heijden M, Cameron K, de Jong JH, Borovski T, et al. Wnt activity defines colon cancer stem cells and is regulated by the microenvironment. *Nat Cell Biol*. 2010;12(5):468-476. doi: 10.1038/ncb2048.
74. Merlos-Suárez A, Barriga FM, Jung P, Iglesias M, Céspedes MV, Rossell D, et al. The intestinal stem cell signature identifies colorectal cancer stem cells and predicts disease relapse. *Cell Stem Cell*. 2011;8(5):511–524. doi: 10.1016/j.stem.2011.02.020.
75. Xue C, Chu Q, Shi Q, Zeng Y, Lu J, Li L. Wnt signaling pathways in biology and disease: mechanisms and therapeutic advances. *Signal Transduct Target Ther*. 2025;10(1). doi: 10.1038/s41392-025-02142-w.
76. Prunier C, Baker D, ten Dijke P, Ritsma L. TGF-β family signaling pathways in cellular dormancy. *Trends Cancer*. 2019;5(1):66–78. doi: 10.1016/j.trecan.2018.10.010.
77. Abravanel DL, Belka GK, Pan T chi, Pant DK, Collins MA, Sterner CJ, et al. Notch promotes recurrence of dormant tumor cells following HER2/neu-targeted therapy. *J Clin Investig*. 2015;125(6):2484–96. doi: 10.1172/jci74883.
78. Vorontsova A, Kan T, Raviv Z, Shaked Y. The dichotomous role of bone marrow derived cells in the chemotherapy-treated tumor microenvironment. *J Clin Med*. 2020;9(12):3912. doi: 10.3390/jcm9123912.
79. Perego M, Tyurin VA, Tyurina YY, Yellets J, Nacarelli T, Lin C, et al. Reactivation of dormant tumor cells by modified lipids derived from stress-activated neutrophils. *Sci Transl Med*. 2020;12(572). doi: 10.1126/scitranslmed.abb5817.
80. Chia SB, Johnson BJ, Hu J, Valença-Pereira F, Chadeau-Hyam M, Guntoro F, et al. Respiratory viral infections awaken metastatic breast cancer cells in lungs. *Nature*. 2025;645(8080):496–506. doi: 10.1038/s41586-025-09332-0.
81. Fernández-Hernández S, Hidalgo-León MÁ, Lacalle-González C, Olivera-Salazar R, Ochieng' Otieno M, García-Foncillas J, et al. Dormancy in colorectal carcinoma: Detection and therapeutic potential. *Biomolecules*. 2025;15(8):1119. doi: 10.3390/biom15081119.
82. Shmakova AA, Klimovich PS, Rysenkova KD, Popov VS, Gorbunova AS, Karpukhina AA, et al. Urokinase receptor uPAR downregulation in neuroblastoma leads to dormancy, chemoresistance and metastasis. *Cancers (Basel)*. 2022;14(4):994. doi: 10.3390/cancers14040994.
83. Tu Y, Han J, Dong Q, Chai R, Li N, Lu Q, et al. TGF-β2 is a prognostic biomarker correlated with immune cell infiltration in colorectal cancer. *Medicine*. 2020;99(46):e23024. doi: 10.1097/md.0000000000023024.
84. Zaslavsky A, Baek KH, Lynch RC, Short S, Grillo J, Folkman J, et al. Platelet-derived thrombospondin-1 is a critical negative regulator and potential biomarker of angiogenesis. *Blood*. 2010;115(22):4605–4613. doi: 10.1182/blood-2009-09-242065.
85. Zhou W, Yan K, Xi Q. BMP signaling in cancer stemness and differentiation. *Cell Regen*. 2023;12(1). doi: 10.1186/s13619-023-00181-8.
86. de Abreu AR, Wyninckx A, Vandamme T, Op de Beeck K, Van Camp G, Peeters M, et al. Circulating tumor DNA detection in cancer: a comprehensive overview of current detection methods and prospects. *Oncologist*. 2025;30(9). doi: 10.1093/oncolo/oyaf204.
87. Marshall JCA, Collins JW, Nakayama J, Horak CE, Liewehr DJ, Steinberg SM, et al. Effect of inhibition of the lysophosphatidic acid receptor 1 on metastasis and metastatic dormancy in breast cancer. *JNCI*. 2012;104(17):1306–1319. doi: 10.1093/jnci/djs319.
88. Liu Y, Park S, Li Y. Breaking cancer's momentum: CDK4/6 inhibitors and the promise of combination therapy. *Cancers (Basel)*. 2025;17(12):1941. doi: 10.3390/cancers17121941.
89. El Touny LH, Vieira A, Mendoza A, Khanna C, Hoenerhoff MJ, Green JE. Combined SFK/MEK inhibition prevents metastatic outgrowth of dormant tumor cells. *J Clin Investig*. 2013;124(1):156–168. doi: 10.1172/jci70259.
90. Saudemont A, Jouy N, Hetuin D, Quesnel B. NK cells that are activated by CXCL10 can kill dormant tumor cells that resist CTL-mediated lysis and can express B7-H1 that stimulates T cells. *Blood*. 2005;105(6):2428–2435. doi:10.1182/blood-2004-09-3458.
91. Saudemont A, Quesnel B. In a model of tumor dormancy, long-term persistent leukemic cells have increased B7-H1 and B7.1 expression and resist CTL-mediated lysis. *Blood*. 2004;104(7):2124–2133. doi: 10.1182/blood-2004-01-0064.
92. Maroni P, Bendinelli P, Matteucci E, Desiderio MA. The therapeutic effect of miR-125b is enhanced by the prostaglandin endoperoxide synthase 2/cyclooxygenase 2 blockade and hampers ETS1 in the context of the microenvironment of bone metastasis. *Cell Death Dis*. 2018;9(5):472. doi: 10.1038/s41419-018-0499-8.
93. Jiang X, Yu M, Wang WK, Zhu LY, Wang X, Jin HC, et al. The regulation and function of Nrf2 signaling in ferroptosis-activated cancer therapy. *Acta Pharmacol Sin*. 2024;45(11):2229–2240. doi: 10.1038/s41401-024-01336-2.