EDITORIAL

New insights into tumor dormancy: Targeting DNA repair pathways

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Abstract

Over the past few decades, major strides have advanced the techniques for early detection and treatment of cancer. However, metastatic tumor growth still accounts for the majority of cancer-related deaths worldwide. In fact, breast cancers are notorious for relapsing years or decades after the initial clinical treatment, and this relapse can vary according to the type of breast cancer. In estrogen receptor-positive breast cancers, late tumor relapses frequently occur whereas relapses in estrogen receptor-negative cancers or triple negative tumors arise early resulting in a higher mortality risk. One of the main causes of metastasis is tumor dormancy in which cancer cells remain concealed, asymptomatic, and untraceable over a prolonged period of time. Under certain conditions, dormant cells can re-enter into the cell cycle and resume proliferation leading to recurrence. However, the molecular and cellular regulators underlying this transition remain poorly understood. To date, three mechanisms have been identified to trigger tumor dormancy including cellular, angiogenic, and immunologic dormancies. In addition, recent studies have suggested that DNA repair mechanisms may contribute to the survival of dormant cancer cells. In this article, we summarize the recent experimental and clinical evidence governing cancer dormancy. In addition, we will discuss the role of DNA repair mechanisms in promoting the survival of dormant cells. This information provides mechanistic insight to explain why recurrence occurs, and strategies that may enhance therapeutic approaches to prevent disease recurrence.

Key words: Quiescence; Homologous recombination; Non-homologous end joining; Tumor dormancy; DNA repair

Core tip: One of the main causes of metastasis is tumor dormancy in which cancer cells remain concealed, asymptomatic, and untraceable over a prolonged period of time. Recent studies have suggested that DNA repair mechanisms may contribute to the survival of dormant

cancer cells. Under certain conditions, dormant cells can re-enter into the cell cycle and resume proliferation leading to recurrence. Understanding the molecular and cellular regulators underlying the transition from tumor dormancy to metastatic disease may provide insight into how recurrence occurs and also discover strategies that may enhance therapeutic approaches to prevent metastatic cancer.

INTRODUCTION

Metastatic tumor growth can account for the majority of cancer-related deaths worldwide[1]. In fact, nearly 30% of breast cancers will relapse years or decades after the initial treatment[2-4]. Different subtypes of breast cancer display different recurrence behaviors. For examples, late tumor relapses frequently occur in estrogen receptor-positive (ER+) breast cancers whereas relapses in estrogen receptor-negative breast cancers or triple negative breast tumors arise early resulting in a higher mortality risk[2,5]. Tumor dormancy, one of the main causes of metastasis, occurs when disseminated tumor cells remain concealed, asymptomatic, and untraceable over a prolonged period of time. Cancer cells can become dormant at the onset of disease or after the initial therapeutic treatment, and can remain dormant for years or even decades after the first treatment[6]. Dormant cells can be characterized by exhibiting slow growth rates, having the ability to escape frontline treatment and the host's immune system, and demonstrating the capability to self-renew. Multiple studies have shown that many cancers such as breast and prostate cancers, melanoma, B-cell lymphoma, leukemia, and carcinoma contain dormant cancer cells[7-15]. Therefore, it is important to understand the molecular mechanisms that govern the transition of dormant cells into metastatic disease.

To date, three mechanisms have been identified to trigger tumor dormancy including cellular, angiogenic, and immunologic dormancies (Figure 1)[16]. Cellular dormancy is characterized as a state in which cells are quiescent and halted in the G0 phase of the cell cycle (Figure 1). The microenvironment of tumors can prompt cancer cells to enter into cellular dormancy like hypoxic environments, which is associated with malignancies, and causes cancer cell proliferation to decrease[17]. Under certain circumstances such as the addition of growth factor, cytokines, nutrients or chemical agents, dormant cells can re-enter into the cell cycle and resume proliferation. Many cancer therapeutic treatments target the cell cycle which permits the cells to enter into quiescence. This allows the cancer cells

to escape treatment subsequently leading to disease recurrence[16,18-20]. Once dormant cancer cells exit G0 arrest, a second mechanism termed angiogenic dormancy can limit the tumor size by preventing angiogenesis and therefore the tumor cannot obtain the nutrients required for continual growth. These cells can maintain a balance between proliferation and apoptosis resulting in the inability to detect the tumor[6,16] (Figure 1). The immune system can also contribute to cancer cell dormancy by maintaining a balance between clearance and proliferation[16] (Figure 1). During immunologic dormancy, DTCs can be eliminated or they can stay in an equilibrium state and, over time, environmental factors and genomic instability can cause the cells to exit the equilibrium state resulting in tumor growth and recurrence[21].

The precise molecular mechanism in which cancer cells enter and exit dormancy remains to be elucidated. One mechanism that plays a major role in cancer growth is the DNA repair pathways, and recently, studies indicate that the DNA repair pathways can lead to tumor dormancy[15,22]. Therefore, it may be possible to target dormant cancer cells through these pathways. Below, we will discuss the current understanding of the three mechanism of tumor dormancy and the role of double-strand breaks (DSBs) DNA repair pathways in dormant cancer cells. This information may improve the development of relevant study models and enhance therapeutic approaches to prevent disease recurrence.

CELLULAR DORMANCY

Cellular dormancy or quiescence is a process that occurs naturally in normal adult stem cells such as hemopoietic and spermatogonial stem cells. These stem cells serve as a source for self-renewal and maintenance of tissues throughout a person's lifetime. However, in a heterogeneous cancer cell population, dormancy can be disadvantageous because cancer cells can evade treatments leading to metastatic recurrence[16,18-20] (Figure 1).

Several studies have demonstrated that the expression of the cellular proliferation, Ki-67, and apoptotic markers are significantly diminished in patients with clinical dormancy[23-27]. In addition, positive Ki-67 expression was correlated with breast cancer recurrence and poor prognosis[28]. The stepwise progression of the cell cycle is regulated by cyclins and cyclin-dependent kinases (CDKs). In particular, cellular quiescence is controlled either directly or indirectly by these regulators. Within the microenvironment, the interactions between the CDK inhibitors, p27 (Kip1) and p21 (Cip1, Waf1), maintain a balance between proliferative and dormant hematopoietic stem cells[29]. Recently, Fitzgerald *et al*[30] (2015) demonstrated that treatment of head and neck squamous cell carcinoma patients with radiation resulted in cellular quiescence *via* the upregulation of p21. In addition, the DREAM complex which consist of a Retinoblastoma (Rb)-like pocket protein, E2F, and
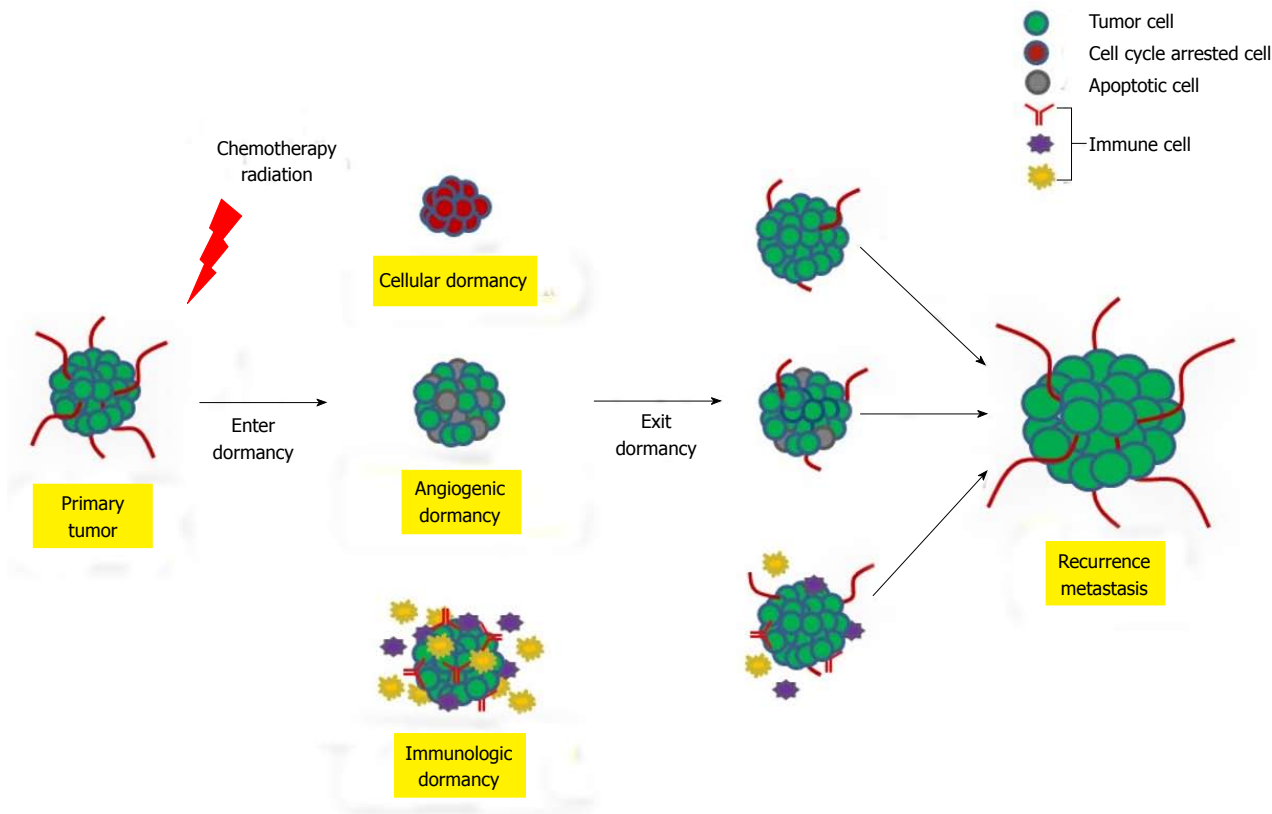
Figure 1 Mechanisms of human tumor dormancy. Schematic depicting three mechanisms that lead to tumor dormancy after the initial clinical treatment. Tumor dormancy can result from cell cycle arrest (cellular dormancy), tumor size limitation due to a lack of functional blood vessels (angiogenic dormancy), or immunosurveillance (immunologic dormancy). Figure adapted from Almog[16] (2010) and Wang and Lin[6] (2013).

mutilvulval class B (MuvB) proteins, is a critical regulator of cell cycle arrest[31]. The MuvB protein is known to recruit, bind, and direct transcription regulators to the promoter of key cell cycle genes during various stages within the cell cycle[32]. During dormancy, MuvB binds to all of the components of the DREAM complex and represses the transcription of all cell cycle-dependent genes[32-34]. Disruption of various components of the DREAM complex results in the inability to repress the cell-cycle dependent genes and subsequently the cells re-enter the cell cycle[35,36]. Quiescence is also established by the dual specificity tyrosine phosphorylation-regulated kinase (DYRK). This protein activates the DREAM complex by phosphorylating a MuvB subunit, LIN52, which promotes the interaction of MutB with the other core components of the DREAM complex[31]. An isoform of DYRK, DYRK1B, can stabilize p27 (Kip1) which increases the turnover of cyclin D consequently inhibiting cell from entering into the cell cycle[37,38]. CDK4 and CDK6 inactivate the tumor suppressor, Rb, subsequently allowing cells to enter into the cell cycle. By pharmaceutically blocking these kinases, Rb-cells can exit the cell cycle and enter into a dormant state[39]. These results clearly demonstrate the need for balance between the DREAM and proliferative complexes in order to maintain cells in a quiescent state.

Mis-regulation of cell cycle proteins can result in tumor formation, dormancy, and recurrence. Prostate cancer, breast cancer, and renal cell carcinoma are linked to the loss of p27 (Kip1)[40-42]. In addition, reduction in p27 (Kip1) is used as a strong prognostic marker for recurrence and poor outcomes in renal cell carcinoma patients[42]. Loss of p53, the upstream regulator of p21, was correlated with drug resistance and recurrence in colorectal cancer[43]. Overexpression of cyclin D is associated with recurrence of multiple neoplasms including breast, lymphomas, prostate, and non-small cell lung cancers[44-46]. Overexpression of cyclin D1 can occur *via* a multitude of different mechanisms including genetic rearrangements, amplification of the gene locus, oncogenic signaling, and mutation in the gene that result in the inability to degrade the protein[44]. Recently, Kim *et al*[47] (2014) reported that overexpression of the cell cycle regulators CDK4, CDK6, pRB, and cyclin D1 was correlated with the recurrence of atypical meningioma. Furthermore, some evidence suggested that overexpression of CDK4 may be connected to nasopharyngeal carcinoma tumor aggression and serve as a diagnostic biomarker[48]. Clearly, these results demonstrate the importance in controlling the cell cycle and how aberrant regulation may lead to tumor recurrence and poor prognosis.

ANGIOGENIC DORMANCY

The majority of tumors require the recruitment of blood vessels to support continual growth. When tumors fail to establish a sufficient vasculature, then they enter into

a state of avascular or angiogenic dormancy (Figure 1). Tumor dormancy *via* angiogenesis requires the interaction between the microenvironment and cell cycle regulators including p21, p27, Myc, urokinase receptor (u-PAR), extracellular regulated kinase (ERK), and p38[49]. Blockage of the metastasis-associated u-PAR, intergrins, focal adhesion kinase or epithelial growth factor receptor can result in tumor suppression and induction of tumor dormancy[49]. U-PAR can also regulate tumor dormancy by favoring p38 activation over ERK activation[50]. In addition, the activation of the PI3K/c-Myc pathway controls the level of thrombospondin (TSP), a vital factor of tumor dormancy[16]. Troyanovsky *et al*[51] (2001) also discovered that the expression of angiostatin can control tumor dormancy by suppressing tumor growth, and one mediator of angiostatin, angiomotin, was highly elevated in dormant cells.

The transition from avascular tumor to a highly vascularized tumor is termed the "angiogenic switch"[16,21]. Balancing the pro-angiogenic and anti-angiogenic factors is vital in regulating the angiogenic switch. Satchi-Fainaro *et al*[52] (2012) discovered that dormant glioblastoma cells express high levels of anti-angiogenic factors including TSP, angiomotin, and insulin-like growth factor binding protein 5, and low levels of pro-angiogenic proteins (endothelial cell-specific marker 1 and epithelial growth factor receptor). Furthermore, TSP-1 and endothelial-derived perlecan were found to maintain breast cancer cells in a dormant state therefore suppressing tumor growth[53,54]. Another key protein that plays a role in controlling the switch from dormancy to tumor growth is heat shock protein 27 (HSP27)[55]. Decreased expression of HSP27 in breast cancer cells resulted in reduced cell proliferation and migration caused by lower levels of secreted vascular endothelial growth factor (VEGF) and basic fibroblast growth factor, known pro-angiogenic factors[55]. Recently, the hypoxia inducible factor, HIF-2α, was shown to promote angiogenesis in hepatocellular carcinoma[56]. HIF-2α increased plasminogen activator inhibitor 1 which lowered active plasmin concentrations resulting in increased angiogenesis[56].

The formation of dormant cell niches can be controlled by the microenvironment. Several proteins such as latent transforming growth factor β (TGF-β) binding protein (LTBP), bone morphogenetic protein 7 (BMP7), and osteopontin (OPN) all influence the establishment of quiescent cell niches[57-59]. Overexpression of LTBP in nasopharyngeal carcinoma induced cancer cell dormancy and reduced VEGF expression thus inhibiting the migration and angiogenesis of tumor cells[57]. BMP7, a member of the TGF-β superfamily, signaling facilitates the balance between dormant prostate cancer cells and metastasis[58]. Administration of BMP7 in mice significantly reduced tumor growth whereas inhibition of BMP7, *via* the secreted antagonist COCO, resulted in metastasis[58,59]. Leukemic dormancy occurs within bone marrow niches and is influenced by the expression of OPN[14]. Acute lymphobaslic leukemia blasts express

high levels of the OPN receptor, VLA-4, which permits the cells to adhere to stroma-derived OPN secreted by osteoblasts within the bone marrow niche[14]. This interaction drives leukemia blast into dormancy and this causes the cells to escape chemotherapy and/or radiation treatment[14]. In addition, antibody neutralization of OPN resulted in leukemia blast to exit dormancy and re-enter the cell cycle[14]. Taken together, these data support the notion that communication between cancer cells and cells associated with the tumor microenvironment is important for controlling the transition between dormancy and angiogenesis.

IMMUNOLOGIC DORMANCY

Tumor dormancy can be established by preserving equilibrium between immune response and tumor cells (Figure 1). The mechanism of how tumor cells enter and exit immunologic dormancy is not well understood. The immune system can control dormancy *via* three different methods including elimination, equilibrium, and escape. The innate and adaptive immune systems work together to detect and eliminate transformed cancer cell prior to the host becoming clinically symptomatic. If the tumor cells are not completely eliminated, then the host's immunity can restrict tumor growth resulting in the continuance of cells within a dormant state. Over time, the tumor cells can adapt to the immune environment causing cells to exit dormancy leading to recurrence[60-62] and tumor metastasis (Figure 1). For example, DTC can reduce T-cell activation which weakens the cytotoxic T-lymphocyte response thus cells escape apoptosis[63]. Direct tumor immunosuppression can mediate the escape from dormancy by driving the overexpression of B7 homolog 1 (B7-H1) which inhibits T-cell activation and the cytotoxic T lymphocyte (CTL) response[63]. In addition, cancer cells can escape tumor dormancy by inhibiting antigen presentation and by methylating cytokine signaling 1 thus leading to resistance to CTL-induced apoptosis[63]. Furthermore, loss of CD4+ or CD8+ T-cells can result in tumor cell dormancy escape[64]. Several cell types within the immune system can indirectly regulate the escape from dormancy by secreting proteins that promote angiogenesis. Interleukin 23, produced by macrophages, suppresses anti-tumor effectors responses, whereas interleukin 12 represses tumor growth[65,66]. The glycoprotein, macrophage stimulating 1 (MS1) can bind to its receptor, MS1 receptor (MST1R), thus suppressing antitumor immune response and promoting cell proliferation, survival, and chemotaxis. The loss of MST1R increases antitumor CD8+ T-cell responses resulting in higher levels of secreted tumor necrosis factor α subsequently leading to the inability of micrometastatic cancer cells to generate macrometastases[67,68]. In addition, myeloid-derived suppressor cells, regulatory T-cells, and tumor-associated macrophages can also indirectly promote tumor cells to escape dormancy[63]. These cells can secrete mitogens and proangiogenic molecules which

promote cell proliferation, angiogenesis and immunosupression causing the cells to exit dormancy[63]. These results demonstrate the importance in controlling the immune system to prevent tumor recurrence and metastasis.

Genomic instability may facilitate the escape of dormant cancer cells from immunological dormancy. Over time, if cancers cells do not have the capability to repair their DNA, they can accumulate mutations allowing the cells to evade anti-tumor immunity leading to recurrence. Therefore, understanding how DNA repair mechanism function in dormant cells may lead to new developments to detect and treat dormant cancer cells.

DNA REPAIR MECHANISMS

Many cancer drugs induce high levels of DNA lesions both single-stranded (SSB) and double-stranded, which results in the death of proliferating cells. Mechanism involved in SSB and DSBs break repair significantly affect the cancer cells ability to evade radiation and chemotherapy treatments. SSBs are repair through the base excision repair pathway. The damaged base is recognized and excised by DNA glycosylases which generates abasic sites. PARP1 and PARP2 proteins sense the SSB and recruit other factors such as XRCC1 to the damaged region[69]. Loss of heterozygosity of OGG1, a DNA glycosylase, is associated with papillary thyroid cancer[70].

DSBs are considered to be the most toxic form of DNA lesions[71-73]. When DNA lesions occur, cells can utilize DNA damage repair pathways to restore the DNA and maintain the genomic integrity of the cell. Two of the major DSBs repair pathways are homologous recombination (HR) and non-homologous end jointing (NHEJ). HR utilizes the DNA sequence from the homologous sister chromatid to repair the DSBs, and occurs predominately in the S and G2 phases of the cell cycle. HR is a major mechanism to ensure the high fidelity of genetic information and because this process uses the homologous sequence as a template, it is considered to be a more error-free repair pathway. Once the HR process is initiated, the DSB is resected to create a 3' overhang that becomes coated with ssDNA-binding protein RPA. Once this filament is formed, RPA is replaced by RAD51 in an ATM/CHK2/BRCA1/BRCA2/PALB2-dependent manner[69]. RAD51 is a key HR repair protein with recombinase activity. One of the main functions of RAD51 is to invade the sister chromatid and identify the template sequence, and reduced RAD51 expression is associated with decreased HR activities[74].

In contrast to HR pathway, NHEJ takes place throughout the cell cycle and involves the direct ligation of broken ends without the need of homologous templates which results in more errors being incorporated within the DNA sequence[75]. Upon initiation of NHEJ, Ku70 and Ku80 form heterodimers that detect and bind the DNA ends. The Ku proteins will then recruit the catalytic subunit, DNA-Protein Kinase (DNA-PK). This step is required for XRCC4 and Lig4-mediated rejoining of the damaged DNA ends during NHEJ[69]. DNA-PK complex acts as a molecular sensor for NHEJ repair[76,77], and cells lacking DNA-PK function fail to show proper NHEJ[78-84]. Additionally, PARP1 may compete with Ku protein to bind the DSB ends resulting in an alternative NHEJ pathway.

Many cancers have abnormalities in the DNA repair pathways, therefore several therapeutics have been developed to exploit these defects. The NHEJ catalytic subunit, DNA-PK, is considered to be up-regulated in radiation-resistant glioblastoma and prostate cancers[85,86]. Recently, clinical trials have shown that inhibitors of DNA-PK have increased the sensitivity of cancer cells to DNA damaging agents however these drugs have been avoided due to the toxicity to normal cells[87]. Small molecular inhibitors of DNA ligase Ⅳ, which is involved in NHEJ, have also been used to decrease cell proliferation and increase the tumor inhibitory effect of chemotherapeutics that cause DSBs[88]. The mis-regulation of genes associated with HR, RAD51, BRCA1, ERCC1, APE1, and PARP1, are also observed in various cancers and are associated with resistance to chemotherapies[87]. Specifically, mutations in BRCA1, BRCA2, ATM, CHEK2, and RAD50 have been identified in several cancers including lung, ovarian, pancreatic, and leukemia[69]. Besides drugs that target RAD51, currently there are very little therapeutics that target other proteins involved in HR[87]. Alternatively, targeting the alternative NHEK pathway *via* PARP1 inhibitors have been used to treat BRCA1 or BRCA2-defected cancers[69].

DNA repair pathways have been shown to play a vital role in the survival of dormant cancer cells after the initial therapeutic treatments. In hepatocellular carcinoma, the stem cell population switches from actively dividing to dormant after the first round of chemotherapy, which allows for the survival of malignant cells[89,90]. The dormant cells contain less DSBs after chemotherapy treatment, and Nishikawa *et al*[15,22] (2012) demonstrated that these cells activated the NHEJ pathway to repair the DNA damage[15,22]. Furthermore, our unpublished data indicates that the NHEJ pathway is important in facilitating DSBs repair in ER+ dormant breast cancer cells after exposure to chemotherapy or radiation. In addition, we discovered that when these cells were treated with chemotherapeutics and exited dormancy, genomic instability increased leading to more aggressive phenotypes and chemotherapy resistance (Lin, unpublished data).

HR may also be involved in DNA repair of dormant cancer cells. The human Fanconi anemia monoubiquitination pathway has been implicated in promoting DNA repair *via* HR[91]. Recently, defects in this pathway resulted in the accumulation of DNA damage causing hematopoietic stem cells to exit their dormant state. The repeated activation of the hematopoietic stem cells out of their quiescent state can lead to the complete

collapse of the hematopoietic system triggering diseases such as Fanconi anemia and leukemia[92].

CONCLUSION

One of the most difficult clinical challenges that we face today is the effective treatment of malignant diseases due to the inability to detect dormant cancer cells[93]. Recently, Kim *et al*[94] (2012) established a dormancy gene signature in ER+ breast cancer cells. When two of these genes, BHLHE41 and NR2F1, are knocked-down in the breast cancer cells, *in vivo* cell growth increased[94]. While these data are promising in identifying dormant cells, it has yet to be used diagnostically. Therefore, it is important to continue investigating the mechanism that control cancer dormancy. Targeting pathways involved in cellular, angiogeneic or immunologic dormancy may provide a way to detect dormant cells as well as treating metastatic cancer.

A possible mechanism to target dormant cancer cells is through the DNA repair pathways, and recent studies have suggested that DNA repair mechanisms may contribute to the survival of dormant cancer cells. In particular, the NHEJ pathway may cause a high frequency of spontaneous mutagenesis subsequently resulting in genomic instability and tumor progression[75]. However, more studies need to be performed to determine if other DNA repair mechanism facilitate the maintenance and survival of dormant cells. In addition, these pathways are not intrinsic to dormant cancer cells. Therefore, understanding the mechanisms of how dormancy is involved in recurrence is urgent for the prevention of secondary tumors. Several advancements have been made to characterized dormant cancer cells, however, to date, there is a lack of suitable model systems to detect and maintain cells in a dormant state. Development of *in vivo* and *in vitro* model systems are imperative to identify key molecular determinants of dormancy, which may lead to strategies for detecting and eliminating dormant cancer cells thus preventing recurrence and reducing cancer mortality.

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