Tumor cell dormancy: threat or opportunity in the fight against cancer

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Running title: Leveraging tumor cell dormancy to control cancer

Abstract

Tumor dormancy, a clinically undetectable state of cancer, makes a major contribution to the development of multidrug resistance (MDR), minimum residual disease (MRD), tumor outgrowth, cancer relapse, and metastasis. Despite its high incidence, the whole picture of dormancy-regulated molecular programs is far from clear. That is, it is unknown when and which dormant cells will resume proliferation causing late relapse, and which will remain asymptomatic and harmless to their hosts. Thus, identification of dormancy-related culprits and understanding their roles can help predict cancer prognosis and may increase the probability of a timely therapeutic intervention for the desired outcome. Here, we provide a comprehensive review of the dormancy-dictated molecular mechanisms, including an angiogenic switch, immune escape, cancer stem cells, extra cellular matrix (ECM) remodeling, metabolic reprogramming, miRNAs, epigenetic modifications, and stress-induced-p38 signaling pathways. Further, we analyze the possibility of leveraging these dormancy-related molecular cues to outmaneuver cancer, and discuss the implications of such approaches in cancer treatment.

Key words: tumor dormancy; tumor relapse; tumor escape; metastasis; cancer therapy

Introduction

Microorganisms adopt different mechanisms to survive under hostile conditions. They undergo drastic changes in cellular physiology to shape the surrounding microenvironment to best fit their requirements [1, 2]. In response to a stressor such as chemotherapy, radiation therapy, or O_2/nutrient scarcity, stressed-tumor cells that survive apoptosis become dormant [3, 4, 5, 6]. After cessation of the therapy, the dormant cells may repopulate, resulting in tumor recurrence and development of chemotherapy-resistant cancer cells [7, 8].

Dormant cells can be detected as circulating tumor cells (CTCs) in the bloodstream or disseminated cells (DTCs) in the bone marrow [9, 10]. Once metastatic cells find a new home to settle, they may have different fates: they either die, may remain silent (restrictive soil), or seek vengeance and come back with an even more aggressive and lethal behavior than before (permissive soil) [11, 12]. The implication of tumor cell dormancy is very well established in the development of multidrug resistance (MDR), minimum residual disease (MRD), tumor outgrowth, and metastatic relapse [13, 14, 15], leading to cancer treatment failure.

With regard to their nature, two type of dormant cancer cells can be recognized: dormant cells within the hypoxic middle layers of primary tumor which survive anti-proliferative treatments including chemotherapy, anti-angiogenesis, and tumor vascular disruption, in which a ring of viable tumor cells remain at the edge of tumor [16, 17] following therapy and derive tumor regrowth and drug resistance [18, 19, 20, 21, 22]. These dormant cells, namely rim cells are discussed in depth elsewhere [18]. The second type of dormant cells referred to as disseminated tumor cells (DTCs), is responsible for the emergence of lethal and metastatic outbreaks which are detected mostly within several years after therapy [23, 24, 25]. Given to their critical significance in patient survival, this article is focused on the roles of DTCs in cancer.

Since the complete cure of cancer is tied to the dormancy state of tumor cells, the question is whether we can leverage this threat into an opportunity to cure cancer for good. Is there any way around killing sleeping devil or putting it to sleep for a lifespan? Alternatively, can we avoid the emergence of dormant cells in the first place to put an end to the worries of tumor relapse? To answer these questions, we review the stealth mechanisms dictating tumor dormancy and then we analyze the possibility of leveraging dormancy related molecular cues to outmaneuver cancer. Finally, the implication of each approach to cancer treatment and prognosis is discussed.

Learn dormancy tactics, use it against cancer, and rewrite cancer cell fate

The equilibrium between tumor hibernation and tumor awaking is governed by several mechanisms including an angiogenic switch, immune escape, cancer stem cells, ECM remodeling, metabolic reprogramming, miRNAs, epigenetic modifications, and p38 signaling (Table. 1).

Angiogenic switch

One contributing factor to tumor dormancy is the incompetence of proliferating tumors to acquire the angiogenic potential to induce the formation of new blood vessels [26]. In the same way, the ability to drive tumor angiogenesis process will promote the escape from latency and initiate tumor outgrowth. This point of cancer progression is recognized as an angiogenic switch, the induction

of which is under the control of intricate biological processes comprising the cancer cells, bone marrow-derived endothelial precursors, and tumor associated-stromal microenvironment [27].

Angiogenesis switch, or in a better word, angiogenic failure is a key piece of the dormancy puzzle. The role of angiogenic dormancy has been highlighted by the observations that anti-angiogenic therapies or angiogenic therapies could induce tumor dormancy or rescue dormant cells, respectively (Table. 1). As such, angiogenic factors display a reduced expression in dormant cells, meanwhile, the high transcription level of angiogenesis inhibitors such as Angiostatin, Endostatin, and Thrombospondin-1 is associated with the tumor dormancy.

With regard to the role of the angiogenic switch in tumor dormancy, two therapeutic approaches follow: in the first approach, long-term dormancy can be induced using anti-angiogenic therapy [28]. For example, cancer patients may benefit from bioactive Angiostatin gene therapy; however, transgene delivery may necessitate repetitive drug administration to assure persistent latency state of primary tumors and control metastatic expansion, that is not clinically feasible because of off-target effects and also efficiency [29]. Also, eradication of primary tumors which result in inducing dormant tumor cells is evidenced by the high expression level of angiogenic inhibitor Thrombospondin-1 in human melanoma xenografts (D-12, R-18, and U-25). In contrast to wild-type tumors with no Thrombospondin-1 expression, a tumor suppressive index was demonstrated only in mice bearing D-12, U-25, or Thrombospondin-1 overexpressing R-18 tumors, as validated by melanoma angiogenesis, lung colonization, and spontaneous pulmonary metastasis [30]. These results suggest a combination of sustained anti-angiogenic therapy besides local treatment for melanoma therapy. Impaired tumor angiogenesis also drives prolonged dormancy of human liposarcoma. This type of tumor with no angiogenic activity produce moderately high amount of the anti-angiogenesis agents TIMP-1 and Thrombospondin-1, proposing that the nonangiogenic, microscopic, dormant stage of melanoma might be susceptible to anti-angiogenic treatment years prior to manifestation of malignant disease, or macroscopically detection of anatomical site of a given tumor, by current approaches [31]. Notably, metastatic dormancy can be realized once proliferation of tumor cell is well-balanced with an equal ratio of tumor cell apoptosis, indicating that anti-angiogenic treatment regulates metastatic outgrowth through increasing of cancer cell death [32].

In addition, the dormancy process can be reversed when dormant cells are fed with adequate angiogenic factors. The reversibility of dormancy affords the second approach based on awakening the ugly sleepy by switching silent cells into proliferative and yet susceptible cancer cells to further anti-angiogenic therapy. Studies on engineered organotypic microvascular niches established that while a Thrombospondin-1 secretion from endothelial cells induces maintained BCC dormancy, bioactive Periostin and TGF-β1 function as tumor-promoting factors in sprouting neovasculature which further sparks micrometastatic outgrowth [33]. Moreover, the shift of resting tumors was shown to be correlated with the downregulation of Thrombospondin and a reduced response to Angiostatin in angiogenic tumors. The transformation of quiescent tumors to highly proliferating tumors was also associated with the activation and regulation of molecular cues connected to tumor dormancy [34]. Also, engineered WM1341B cells constitutively overexpressing the vascular endothelial growth factor (VEGF)/vascular permeability factor (VPF) isoform are shown to terminate long-term melanoma dormancy and can induce overt and progressively growing tumors. These effects were largely counteracted by neutralizing VEGF activity in mice [35].

Immunoediting/ immune escape

The tumor-host interactions are progressively known as crucial constituents of cancer growth or inhibition. Particularly, infiltrating immune cells are critical features of tumor microenvironment [36]. Cancer cells are encircled by stromal cells, including macrophages, fibroblasts, mast cells, neutrophils, and lymphocytes, which communicate through an intricate system of intercellular signaling pathways, mediated by cytokines, adhesion molecules, and the receptor-ligand network [37]. The immune system can confine the metastatic spread of cancer cells, encouraging their long-lasting latency. Nonetheless, the perturbation of the equilibration in favor of immune escape tumor clones will result in tumor outgrowth rather than the destruction of cancer cells, otherwise, immune surveillance could maintain angiogenic control and impede cancer cell growth [38] (Fig. 1). To this end, CD8+ T cells play a key role in maintaining tumor dormancy, and the expression of MHC class I on the surface of tumor cells also play a role in this critical equilibrium. Natural killer (NK) cells act as activators that prompt a cytotoxic T lymphocyte (CTL) response [39], meanwhile, an association of human Tregs, neutrophils and inflammatory mediators such as interferon gamma (IFNγ) are rather context-dependent [40]. Immunotherapeutics that target disseminated cancer dormancy may aid to control or eliminate cancer state. In this view, treatment modalities that induce or amplify the CTL immune response or abrogate CTL immunosuppression mediated by cancer cells might be beneficial to confine or eradicate metastatic cells [41, 42].

Dormancy state induced by the elimination of primary tumor can be avoided by a 'recombinant T cell receptor ligand therapy', dosing days in advance to tumor resection and lasting throughout the whole treatment course, that is a highly speculative therapy [43]. Alternatively, immune-stimulated dormancy pathway can be tuned to reverse dormancy and favor dormant cell eradication. For instance, blocking IDO-kynurenine-AhR metabolic circuitry abolishes immunologic latency mediated by IFN-γ in tumor-repopulating cells (TRCs). Hypothetically, the IFN-γ-STAT1 signaling induces apoptosis in proliferating tumor cells; however, TRCs-induced overexpression of IDO1 and AhR, shifts IFN-γ action and give rise to IDO1/AhR-induced p27 activation and inhibition of STAT1 signaling. Further, these events translate into the inhibition of tumor cell apoptosis and thus switching to dormancy program. Blockade of IDO/AhR metabolic circuitry not only nullifies IFN-γ-mediated latency but also promotes amplified tumor cell growth arrest by IFN-γ-dependent killing of TRCs *in vitro* and *in vivo* [44, 45]. Dormant tumor cells may hinder CTL-mediated tumor lysis via overexpressing B7-H1 and B7.1 [37, 46]. They also counteract apoptosis by paracrine secretion of cytokines (e.g. IL-3) and simultaneous inactivation of SOCS1, the expression of which negatively controls JAK/STAT signaling [47]. In this context, demethylation or gene transfer was shown to restore the expression of SOCS1, which further rendered dormant cells sensitive to apoptosis and abrogated resistance to CTL-induced tumor cell destruction. Moreover, the cross-resistance to apoptosis emanating from dormant tumor cell-induced overproduction of Interleukin 3 (IL-3) was upturned using anti-IL-3 antibody [47].

Alternatively, 'recombinant T cell receptor ligand therapy' of overt cancer may retain all undetectable DTCs quiescent providing that the treatment is continued as a plan to control cancer [43]. Thus, preventing metastatic expansion would be more feasible than eliminating an established metastasis [43]. As such, tumor-cell immunization prompts tumor cell latency in mice bearing B-cell aggressive leukemia/lymphoma (BCL1). In this line, while an anti-idiotypic immunity was insufficient to eliminate BCL1 cells, it was capable of suppressing growth activating signals, which further promoted cell cycle arrest, apoptosis and persistent BCL1 dormancy in mice[48]. Also, immunity to BCL1, which was achieved by numerous inoculations of irradiated carcinoma cells,

precludes leukemia growth in primary and adoptive transfer recipients even with the lifelong perseverance of residual cancer cells [49].

Increasing inflammation promotes tumor recurrence, thus interventions that inhibit inflammatory signaling could inhibit tumor recurrence[50, 51]. To this end, it was reported that inflammation and wound healing process following surgery is enough to induce distant cancer outgrowth[52], especially when the tumor outgrowth was attenuated by the adaptive immune system [53]. Accordingly, anti-inflammatory medications can benefit cancer patients undergoing surgery by avoiding the awakening of latent micrometastatic cells. Furthermore, it was shown that the lipopolysaccharide treatment-induced localized inflammation in the lungs, sends a wake-up signal to metastatic latency in the lung parenchyma through Zeb1 expression, a key regulator of the epithelial-to-mesenchymal transition (EMT). Likewise, Zeb1-orchestrated stimulation of EMT program by itself is sufficient to provoke metastatic spread by triggering stable entry of tumor cells into a state of metastasis-initiating cells [54]. Accordingly, inhibition of Zeb1, LIFR: STAT3 signaling [55] as well as blocking the actions of inflammatory cytokines such as tumor necrosis factor α (TNFα) and IL-1β cytokines could confer dormancy and thus eliminate cancer outgrowth [56].

Metabolic reprogramming

Impaired vascular system observed in solid tumors encourage establishing oxygen and nutrients deprived microenvironments that harbor metabolically stressed slow growing cells [20, 21, 57]. Tumor cells under hypoxia and nutrient deprivation become dormant by reducing or shifting their metabolic needs. A second deprivation assault would shut down the possible energy compensatory options for tumor cells and succumb them to apoptotic death. As such, small molecule VLX600 displays superior cytotoxic action in nutrient-starved environments and is preferentially active against quiescent cells. The anti-tumor potential is correlated with dampened mitochondrial respiration, culminating in bioenergetic catastrophe and tumor cell apoptosis [58]. Another study has shown the superior performance of FF-10502, a pyrimidine nucleoside antimetabolite over gemcitabine on pancreatic dormant cells, by inducing dormant cell injury in chemotherapy-resistant cells through blocking with DNA polymerase β activity and DNA repair [59].

Likewise, in residual breast cancer, metabolic shifts promote tumor relapse. Blockade of either transportation of fatty acid into mitochondria or synthesis of cellular fatty acid lessens DNA damages and cellular reactive oxygen species (ROS) levels, connecting these hallmarks to lipid metabolism. Tumor relapse can be prevented by direct disruption of these features, either by mitigating expansion of the residual breast cell population or scavenging ROS [60].

Also, reinforcing a quiescence-like metabolic state can block tumor evasion. In this regard, a novel metabolic tumor suppressor, LACTB reduce PISD protein abundance and PE/LPE production, resulting in a mitochondrial state compatible consisted of reduced proliferation, increased epithelial phenotype, and a decrease in mesenchymal and cancer stem cell markers, which associate to tumor regression and inhibition of tumor formation. Conversely, LACTB silencing in non-tumorigenic breast cell lines cooperated with oncogenic drivers (HRASG12V and MYCT58A) supporting tumor formation in xenotransplants [61, 62]. Notably, results from a recent study showed the role of autophagy as an important regulator of tumor cell dormancy. That, the

lack of autophagy, which exploits as an important compensatory mechanism by tumor cells for providing energy, associated with an early breast cancer recurrence and escape from dormancy[63]

Extracellular matrix (ECM) remodeling

The likely involvement of communications between ECM and tumor cells in metastatic niches determine tumor latency against the metastatic outbreak. Generally, the inability of cancer cells to appropriately adhere the ECM may potentiate their entry into a dormancy state [64]. As shown in Fig. 2, inhibition of one of the components of Fibronectin/uPAR/Integrin/ERK/MLCK signaling axis as well as suppressing PI3K/Akt pathway is enough to prevent/treat metastatic tumor growth, meanwhile promoting dormancy state through favoring the p38 MAPK signaling [65, 66]. In one study, the switch from dormancy to the proliferating state of D2A1 cells was reliant on the production of Fibronectin and β1 Integrin signaling, the formation of filamentous actin (F-actin) stress fiber and cytoskeletal reorganization. Integrin β1-dependant phosphorylation of myosin light chain (MLC) by MLC kinase (MLCK) was a prerequisite for F-actin stress fiber formation and exponentially growing of cancer cells. Blockade of β1 integrin or MLCK favored dormancy state and MLCK inhibition significantly reduced metastatic expansion *in vivo* [67]. Similarly, deposition of type I collagen (Col-I) is shown to induce transition of dormant D2.0R cells to proliferating cells by β1 Integrin-mediated Src and focal adhesion kinase (FAK) activation, causing extracellular signal-regulated kinase (ERK)-dependent phosphorylation of MLC by MLCK and formation of actin stress fiber. Blockade of β1-integrin, MLCK, ERK, Src counteracted Col-I-mediated induction of this signaling cascade, cytoskeletal rearrangement, and proliferating state [68]. Likewise, Src knockdown or pharmacological blocking of SFK signaling promote p27 localization to the nucleus and thwarts transition of quiescent breast cancer cells (BCCs) into the proliferative and metastatic outbreak; still, SFK inhibition is not enough to eradicate residual cells. ERK1/2 activation was also needed for proliferation and awaking dormant cell. Combined therapy of cells undergoing the transition from dormancy to proliferating state with the MEK1/2 inhibitor (AZD6244) and Src inhibitor (AZD0530) potentiated apoptotic death in a large population of the latent cells and postponed development of disseminated disease, none of these was achieved with single-agent therapy [69]. Meanwhile, EGFR signaling via activation of PI3K/AKT/mTOR and Ras/Raf/ERK axis is another contribution to tumor proliferation [70]. Conversely, TGFβ signaling represents a therapeutic opportunity to activate a spell of dormancy (Table. 1) [71, 72].

An alternative therapeutic approach can be envisioned by preventing cancer cell dormancy. Such that, results of a valuable study unveiled that proliferating and dormant BCCs home in distinct areas within BM niche, with dormant BCCs, mainly occupy perisinusoidal vascular regions that are rich in stromal cell-derived factor 1 (SDF-1) and E-selectin. SDF-1 and E-selectin coordinate opposing functions in BCC, where the SDF-1/CXCR4 axis facilitates adherence of BCCs to the vascular niche, and E-selectin permits BCC entrance into the BM where they remain dormant. Thus, a combined therapy involving CXCR4/E-selectin inhibition will push cells out of their protective niches and aid trapping of the cells in the vasculature, where they could be destroyed with chemotherapy, thus provide an opportunity to control recurrent disease [73].

Cancer stem cells (CSCs)

DTCs or surviving cells within the tumor during therapy could be stem cells. And, stemness is inherent to dormancy phenotype (Table. 1) [74]. Cumulative evidence suggests that CSCs are indeed metastasis-initiating cells, or metastatic cells acquire CSC-like phenotype upon infiltration into target organs[75]. Tumor cell entrance into and out of dormancy are regulated by contextual cues and intrinsic programs, like those that control the self-renewal ability of mature stem cells [74, 75, 76]. Furthermore, a specialized ECM niche nurse reactivation-undergoing metastatic cells, by supporting positive cues, such as Notch and Wnt, and attenuating negative cues, such as BMP [77, 78]. Adopting a dormant state, CSCs not only can evade therapeutic killing, the likely reversibility of this situation poses the real threat, which can potentiate deadly relapse or recurrence decades later [79]. Notably, CSCs can adjust the expression of different surface markers which help them to colonize their desired target organs, in particular, the bone[76]. Such that, expression of chemokine receptor CXCR4 (SDF-1 receptor) by BCCs facilitate bone metastasis where osteoblasts express high levels of SDF-1[80]. Moreover, the CXCR4/SDF-1 axis not only derive EMT for bone metastasis, it also promotes cancer cell stemness, plasticity and maintenance of CSC-like properties [80, 81, 82].

Epigenetic modification

As another key regulator of tumor dormancy, epigenetic modifications are involved in the epithelial to mesenchyme transition (EMT) which are associated with CSC phenotype and emergence of drug resistance, tumor dissemination, and high risks of disease relapse. Identifying genes that encode these reversible alterations is an appealing therapeutic plan to combat metastatic disease by inducing differentiation of the mesenchymal cell into an epithelial phenotype [83].

In this respect, epigenetic upregulation of orphan nuclear receptor NR2F1 is detected in DTCs from prostate cancer patients harboring the lifelong dormant disease and in experimental latency models of head and neck squamous cell carcinoma (HNSCC). NR2F1-induced dormancy depends on RARβ, SOX9 and CDK inhibitors. Also, NR2F1 induces pluripotency gene NANOG, and global chromatin repression, favoring dormancy of DTCs in the bone marrow [84].

Likewise, polycomb-like proteins 1-3 (PCL1-3) are substoichiometric modules of the Polycomb-repressive complex 2 (PRC2) that are indispensable for complex association with chromatin. Their functional redundancy is due to their opposing roles in the positive and negative regulation of cellular proliferation. Such that, in quiescent cells, expression of PCL1, a p53 target gene is predominant, while proliferating cells express E2F-regulated genes PCL2 and PCL3. Ectopic expression of any PCL protein employs PRC2 to suppress the INK4A gene; nevertheless, only PCL2 and PCL3 render an INK4A-evolved proliferative benefit. Of note, PCL1 confer a PRC2 function which acts independent of chromatin, possessing anti-proliferating effect and induce cellular dormancy through binding to and stabilizing p53 [85].

Also, in vivo genome-wide short hairpin RNA screening has revealed a novel epigenetic-related mechanism involved in bone metastatic latency of estrogen receptor-positive (ER+) breast cancer. Clinical studies were reported that low levels of mitogen-and stress-activated kinase 1 (MSK1) expression links with an early relapse in ER+ breast cancer patients. In this study, reduced MSK1 impaired the differentiation of breast cancer cells, and increased their bone homing and growth capacities. From a molecular perspective, MSK1 downregulation induces chromatin remodeling and decreases differentiation traits by modulating promoter chromatin status of genes encoding

GATA3 and FOXA1 transcription factors and accelerates bone colonization by cells in distant micrometastatic sites[86].

Noncoding RNAs (miRNA)

While the critical role of microRNAs in tumorigenesis is well documented[87], the implication of dormancy miRNAs (Dmirs) are recently illuminated [88]. For example, mesenchymal stem cell-derived exosomes comprising different miRNA contents, such as miR-222/223, are shown to induce cycling dormancy and early BC quiescent in BM and give rise to drug resistance. Further, administration of MSC-loaded antagomiR-222/223 sensitized BC cells to carboplatin-based therapy and increased host survival [89]. Also, a recent study showed that metastatic outgrowth of the claudin-low mammary tumor cell line, RJ423 can be avoided by re-expression of the miR-200b/200a/429 cluster which promotes epithelial phenotype and induces tumor dormancy [90].

Moreover, a study on experimental models of fast-growing and dormant human osteosarcoma identified three dormancy-associated DmiRs regulating osteosarcoma latency: miR-200c, miR-34a, and miR-93. Accordingly, the expression of these microRNAs is lost upon the shift from avascular dormant into angiogenic fast-growing tumor state. Introduction of these miRNAs by dPG-NH2 polyplexes into MG-63 and Saos-2 cells dampened expression levels of their target genes, including hypoxia-inducible factor 1α (HIF1α), MET proto-oncogene, and moesin, vital to tumor migration and angiogenesis process. Furthermore, therapy with dPG-NH2 containing each of these microRNAs considerably extended the latency state of fast-growing osteosarcomas in mice [91].

Loss of DmiRs expression is also verified in human dormant liposarcoma, breast carcinoma, osteosarcoma and glioblastoma tumors. Transcriptional reprogramming of tumors via over-expression of DmiR-190, 588, or 580 caused reduced expression of pro-angiogenic factors bFGF, TIMP-3, and TGFα while upregulated anti-angiogenic and dormancy stimulating factors Angiomotin and EphA5 [92]. In all dormant tumors analyzed, overexpression of miR-190 was predominant where upregulation of this Dmir encouraged long-term dormancy of otherwise proliferative osteosarcomas and glioblastomas [93].

Stress-induced p38 signaling

Stress-induced activation of p38 signaling is one of the critical pathways related to tumor dormancy, which regulates a transcriptional network of 46 core genes that includes 16 transcription factors (TFs) [94]. p38 MAPK signaling coordinates the induction of growth arrest and drug-resistance in different models of carcinoma dormancy [95]. Imbalances in the activity ratio of ERK to p38 signaling is fundamental to decide the outcome of dormancy vs. tumorigenicity of different experimentally established cancer models (Fig. 2) [96].

Stress-dependent p38 activation induces dormancy by adopting a prosurvival mechanism via enhanced activation of the PERK and up-regulating the endoplasmic reticulum (ER) chaperone BiP, conferring dormant cells resistant to drug toxicity. Moreover, up-regulation of BiP suppresses activation of Bax. Thus, p38 activation via PERK activation and BiP up-regulation secures dormant cancer cells from stress insults, such as chemotherapy [97]. Besides, p38

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activation induces the transcription of the TFs BHLHB3 and p53, while blocking FoxM1 and c-Jun expression. Also, p38-mediated activation of p53 requires down-regulation of c-Jun [94].

ATF6α as another p38-controlled transcription factor is crucial to the survival of dormancy state. Such that, ATF6α is crucial for dormant cells adaptation to nutritional stress, chemotherapy, and, most importantly, the *in vivo* microenvironment. In dormant cancer cells, MKK6 and p38α/β control nuclear translocation and transcriptional activation of ATF6α. Downstream, ATF6α promotes survival via Akt-independent activation of mTOR signaling and up-regulation of Rheb. Thus, targeting the survival signaling axis ATF6α-Rheb-mTOR in dormant carcinoma cells may help to remove residual disease during dormancy periods [98].

As discussed before, dormant cells and active cells occupy different soils to settle in. That is, non-proliferative DTCs reside in the BM while metastatic growth occurs in other organs such as the lung. Accordingly, BM niche in patients serves as a metastasis 'restrictive soil' by coding dormancy activating clues in DTCs. In this view, in an HNSCC carcinoma model, specific and strong TGF-β2 signaling in the BM triggers the MAPK p38α/β, and result in low ERK/p38 signaling ratio. This favor dormancy of malignant DTCs via induction of DEC2/SHARP1 and p27, and CDK4 downregulation. Also, TGF-β2-induced latency calls for activation of SMAD1/5, TGF-β receptor-I (TGF-β-RI) and TGF-β-RIII to induce p27. In lungs, a metastasis 'permissive soil' with low TGF-β2 levels, DTC latency state was transitory and continued by metastatic expansion. Importantly, systemic inhibiting of p38α/β or TGF-β-RI activities awaked dormant DTCs, and fuelled multi-organ metastasis. This work reveals a 'seed and soil' mechanism whereby p38α/β regulate TGF-β2 and TGF-β-RIII signaling to determine the fate of DTC dormancy and delineates permissive (lung) and restrictive (BM) microenvironments for HNSCC metastasis [99].

Conclusion and clinical implication

However, tumor dormancy is commonly regarded as the most threatening face of cancer, leading to the emergence of resistance in a short time and advent of lethal metastatic outbreaks after a long latency period of months to years. Now that we begin to realize dormancy tactics, several therapeutic approaches can be envisioned to outsmart cancer. As illustrated in Fig. 3, these schemes are (i) prolonging dormant state; (ii) eradication of dormant cells; (iii) awakening dormant cells and (iv) avoiding dormancy state. Prolonging dormant state is upon the observation that immunotherapeutic targeting of advanced stage cancers has prolonged the survival of cancer patients, yet its curative efficacy is limited due to tumor immunoediting and escape. On the other hand, human vaccines have been able to eradicate and control many infectious diseases. The success has resulted from the administration of vaccines in prophylactic settings or during latency periods in order to protect an individual during future exposure to the disease rather than curing an established disease. Therefore, administration of immunotherapy at the right time is the key to success. Immunotherapeutic targeting of tumor dormancy could be more promising than targeting of advanced stage disease to achieve a cure for cancer [36]. Besides immunotherapy, identification of Dmirs advocates novel tools to inverse the malignant aggressive phenotype into a microscopic dormant state and may deliver encouraging targets for timely detection or prevention of cancer. Eradication of dormant cells without awakening them is the second tactic in which tricks of dormancy are leveraged against dormant cells. For example, their restrict dependence on survival pathway or altered energy metabolism could be their Achilles heel to interfere with cancer evolution and relapse. Additionally, dormant and resistant cells could be awakened by external stimuli such as growth factors and angiogenic cues, turning them into proliferative yet therapy-

sensitive tumors. Finally, avoiding dormancy in the first place, by inhibiting pathways leading to the acquisition of dormancy phenotype as discussed in this paper can put an end to all worries about unleashing metastatic cancer.

In conclusion, detection of minimal residual disease in the patients is difficult. Targeting the dormant cells by induction of dormant-to-proliferative switch involves the risk of inducing metastatic progression, while drugs that target DTCs or CSCs might affect normal stem cells. At the end of the day, it is the depth of our knowledge regarding tumor dormancy schemes that will determine the fate of our fight against cancer.

Conflict of interest

Authors declare none.

Acknowledgments

Table 1. Molecular cues involved in tumor cell dormancy.

Dormancy factor	Mode	Major findings	Ref
Angiostatin	Angiogenic dormancy	Upregulation of Angiostatin drive long-term dormancy of primary tumors, inhibit tumor growth, and reduce cancer metastases.	[29]
Thrombospondin-1	Angiogenic dormancy	Overexpression of Thrombospondin-1 inhibits melanoma angiogenesis, lung colonization, and spontaneous pulmonary metastasis.	[30]
VEGF/VPF121	Angiogenic dormancy	Overexpression of VEGF/VPF121 result in tumor growth and escape from dormancy.	[35]
(VEGF(121) VEGF(165) overexpression	Angiogenic dormancy	The level and VEGF isoforms determine a fate of aggressive tumor growth vs. nontumorigenic and dormant tumor.	[100]
VEGF(189) overexpression	Angiogenic dormancy		
Thrombospondin-1	Angiogenic dormancy	Endothelial-derived Thrombospondin-1 induces long-lasting BCC dormancy. This repressive nod is lost in sprouting neovasculature where active TGFβ1 and periostin act as tumor-promoting factors derived from endothelial tip cells.	[33]
TGFβ1, Periostin	Angiogenic dormancy		
Thrombospondin, Angiomotin, Tropomyosin, TGF-β2, P4HA1, EphA5, H2BK, IGFBP-5	Angiogenic dormancy	Dormant tumors undergo a stable genetic reprogramming during their switch to the fast-growing phenotype by downregulation of angiogenesis inhibitors such as Thrombospondin and decreased the sensitivity	[34]

EGFR-1, IGF-IR, CD73 ESM-1, PIK3CB, TIMP-3	Aangiogenic dormancy	of angiogenic tumors to Angiostatin along with upregulation of angiogenesis-related genes.	
MME1(NM23)	Angiogenic dormancy	NM23 inhibits the EGF-induced cell migration. Increase the expression of metastasis-related genes TIMP-1, E-Cadherin and β-Catenin, reduce the expression of VEGR, CD44V6, and MMP-2 and reduce metastasis.	[101, 102, 103]
Kai-1 (CD82)	Angiogenic dormancy	Binding of tumor cell surface expressed Kai1 with endothelial DARC inhibit tumor cell proliferation, induce senescence by modulating the expression of TBX2 and p21 and suppress metastasis.	[104]
BRMS1	Angiogenic dormancy	BRMS1 inhibits angiogenesis through blocking NF/KB activity. It can also reduce metastatic potential but not tumorigenicity.	[105]
HSP27	Angiogenic dormancy	Downregulation of HSP27 associate with reduced endothelial cell proliferation and decreased secretion of VEGF-A, VEGF-C, and induction of long-term dormancy.	[106]
CTL response, MHC class I, NK cells	Immunologic dormancy	An activate CTL response can maintain immune equilibrium with metastatic dormant cells. Immune dormancy arrest cancer cell growth and promotes angiogenic control.	[41]
B7-H1 and B7.1	Immunologic dormancy	Dormant tumor cells up-regulate B7 -H1 and B7.1 and resist CTL- mediated lysis.	[37]
Neutrophils	Immunologic dormancy	14,15-EET trigger neutrophil infiltration in metastatic lesions by activating STAT3/JNK-hIL-8/mCXCL15 and mir-155 which converts tumor-suppressing function of neutrophils to tumor-promoting in vivo. In presence of G-CSF/IL-6, 14,15-EET enhance STAT3 activation in neutrophils to decrease TRAIL expression and increase MMP-9 expression to induce angiogenesis during dormant micrometastases growth. Neutrophil depletion or blocking hIL-8/mCXCL15 abrogate micrometastases induced by 14,15-EET.	[107]
Zeb1	Immunologic dormancy	Inflammation triggers Zeb1 to promote EMT and give rise to metastatic outgrowth.	[54]
TNFα, IL-β	Immunologic dormancy	Addition of bone remodeling cytokines, TNFα and IL-β to dormant cancer cells induce proliferation and occurrence of latent bone metastasis.	[56]
SOCS1, IL-3	Immunologic dormancy	T-cell inactivation and resistance to apoptosis are mediated by methylation of SOCS1, deregulation of JAK/STAT and overproduction of IL-3 by dormant cells.	[47]
IFN-γ	Immunologic dormancy	IFN-γ signaling triggers differentiated tumor cell apoptosis via STAT1; however, when IDO1 and AhR are overexpressed as in DTCs, IFN-gamma induce p27	[44]

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		via IDO1/AhR and inhibits STAT1 signaling, and favors dormancy state.	
LPS/EGF	Immunologic dormancy	Activated immune/stromal cells stimulate the resident hepatic cells to derive tumor growth.	[108]
Mitochondrial dysfunction	Metabolic dormancy	VLX600 impairs OXPHOS and drives a HIF-1α-dependent switch to glycolysis, which this metabolic pathway can't meet energy demands of tumor cells, thus induction of autophagy is unavoidable. Yet, due to lack of HIF-1α-stabilization and glucose inaccessibility in metabolically stressed environments, shifting to glycolysis mode will be restricted, consequently, tumor cells undergo apoptosis.	[58]
LACTB	Metabolic dormancy	Mitochondrial tumor suppressor, LACTB potently inhibits the proliferation of BC cells via altering mitochondrial lipid metabolism and differentiation of BC cells by reduction of the levels of mitochondrial phosphatidylserine decarboxylase, which is involved in the synthesis of mitochondrial phosphatidylethanolamine.	[62]
FA metabolism, ROS, oxidative DNA damage	Metabolic dormancy	Residual cells display altered lipid metabolism, elevated ROS, and increased oxidative DNA damage. Thus, lipid metabolism and ROS as therapeutic targets for reducing tumor recurrence in BC patients.	[60]
NR2F1	Hypoxic dormancy	Hypoxic HNSCC and breast primary tumor microenvironments display upregulation of key dormancy (NR2F1, DEC2, p27) and hypoxia (GLUT1, HIF1α) genes. Post-hypoxic DTCs were frequently NR2F1^{hi}/DEC2^{hi}/p27^{hi}/TGFβ2^{hi}, dormant and chemotherapy resistant.	[3]
LIFR	Hypoxic dormancy	In BC patients with bone metastases, low LIFR levels negatively correlate with HIF-1α activity and disease outcome. Hypoxia reduces the LIFR:STAT3:SOCS3 signaling in BC cells. Loss of the LIFR or STAT3 reactivates dormant BC cells to proliferate and to downregulate stem cell-related genes and specifically benefit their bone colonization.	[55]
E6/E7 antigen	Hypoxic dormancy	Human papillomavirus-infected cancer cells can enter into reversible dormancy state, with reducing the synthesis of viral antigen and enhanced therapeutic resistance, and uphold tumor recurrence upon reoxygenation.	[109, 110]
Kiss-1, CRSP3	ECM dormancy	Kiss-1 expression suppresses malignant melanoma metastasis, inhibits motility, chemotaxis, and invasion, perhaps by suppressing the expression of MMP-9. CRSP3 regulate the transcriptional expression of Kiss-1.	[111, 112]

Type I collagen (Col-I)	ECM dormancy	Atypical tetraspanin TM4SF1 as a potent inducer of metastatic recurrence of BC couples DDR1 to PKCα. This kinase activates JAK2. Then, JAK2/STAT3 activates the expression of SOX2 and NANOG, maintain the manifestation of CSC traits, and fuel metastatic recurrence in the bone, lung, and brain.	[113]
Fibronectin	ECM dormancy	Fibronectin/β1 Integrin/MLCK axis induces a transition from a quiescent to proliferative, metastatic outgrowth.	[67]
Col-I	ECM dormancy	Col-I/β1 Integrin/SRC/FAK/ERK/MLCK signaling induce dormant cells to switch to proliferative metastatic lesions.	[68]
u-PAR	ECM dormancy	u-PAR, is an essential molecule in BM disseminated tumor cells for long-standing survival during dormancy by regulation of u-PAR of α5β1 integrins, and signal propagation from Fibronectin through the p38, ERK, and EGF-receptor signaling.	[66, 114, 115, 116]
FAK, Src, MEK1/2 (ERK1/2)	ECM dormancy	Targeting Src prevents the proliferative response of dormant cells to external stimuli. MEK1/2 inhibition suppresses their survival and eliminates tumor relapse.	[69]
KRAS/C-Myc, IGF1/AKT	ECM dormancy	KRAS/C-Myc negative dormant cells represent an increase in autocrine IGF1/AKT. Inhibition of IGF-1R reduces residual disease burden and cancer recurrence.	[117]
TGFB2	ECM dormancy	Cellular adhesion promotes PC cells escape from dorm ancy and lethal metastasis. The mechanism involves downregulation of TGFB2, E2F4, and upregulation of MLCK, CDK6.	[72]
TGFβ2/ GDF10	ECM dormancy	Osteoblast-secreted proteins induce TGFβRIII-p38MAPK-pS249/T252RB pathway to mediate dormancy of metastatic PC in the bone.	[118]
Axl, Gas6	ECM dormancy	Axl is a tyrosine kinase receptor for growth arrest-specific 6 (Gas6). Axl and Gas6 are required for TGF-β2-induced dormancy of PC cells in the bone marrow.	[71]
E-selectin, SDF-1	ECM dormancy	Proliferating and dormant BCCs inhabit different regions, whereas E-selectin interactions allow BCC residency in the BM, the SDF-1/CXCR4 binding anchors BCCs to the metastatic niche. Blocking CXCR4 (SDF receptor) and E-selectin eliminates latent micrometastases residing in supportive bone, excising occurrence of relapsed disease.	[73]
MED12	ECM dormancy	The lack of MED12 induces tumor cell dormancy. Re-expression of MED12 abrogates tumor cell dormancy by positively controlling EGFR expression.	[119]
N-cadherin	CSC dormancy	N-cadherin upregulation leads to downregulation of E-cadherin, upregulation of Connexin, EMT, and dormancy.	[120]

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Notch	CSC dormancy	Notch remain activated in dormant residual cells and accelerates tumor recurrence.	[121]
CD13	CSC dormancy	CD13 is a cancer stem cell dormancy marker in HCC.	[122]
Coco	CSC dormancy	Coco enhances cancer stem cell traits and antagonizes TGF-β activity. Coco reactivates dormant BC cells in the lung whereas BMP signaling revives metastasis dormancy in the lung.	[123]
BMP7	CSC dormancy	Bone stromal cells-derived BMP7 stimulates senescence in prostate CSCs by activating BMP7-BMPR2/p38/p21/NDRG1 axis.	[124]
SPARC	CSC dormancy	SPARC demethylation (activation) significantly stimulate the expression of BMP7 in bone marrow stromal cells and is required for BMP7 mediated stemness and senescence of PC cells.	[125]
HMGA1	CSC dormancy	HMGA1 reprogram triple negative BC cells to a stem-like state, driving their metastatic outgrowth. HMGA1 silencing excise cancer stem/initiator cells and prevents oncogenesis.	[126]
TBK1	CSC dormancy	PC cells target the HSC niche in mouse bone marrow during metastasis. Interaction with niche osteoblasts activate TBK1 expression and inhibit mTOR in PCa cells. Silencing TBK1 dampen drug resistance and formation of PCa stem-like cells.	[127]
p53, Necdin	CSC Dormancy	Necdin-knock out adult HSCs is more proliferative and less quiescent than wild-type HSCs, indicating that Necdin resembles p53 function in supporting HSC dormancy during stable conditions.	[128, 129]
Zeb1, G9a, SMAD5, SMARCD3, KAT5, DOT1L	Epigenetic dormancy	These genes control EMT and control dormancy by reversible activation of stem cell-like properties.	[83]
PCL1,2,3	Epigenetic dormancy	PCL2 and PCL3 are expressed in proliferative tumor state, whereas PCL1 mainly expressed in dormant cells.	[85]
NR2F1	Epigenetic dormancy	NR2F1 is epigenetically upregulated in tumors and induce dormancy by global chromatin repression.	[84]
MSK1	Epigenetic dormancy	MSK1 epigenetically controls the differentiation of cancer cells and its expression promotes metastatic dormancy.	[86]
miR-222/223	Dmir dormancy	Promotes quiescence and drug resistance.	[89]
miR-34a, miR-93, miR-200c	Dmir dormancy	Loss of DmiRNAs happens during the transition from avascular dormant into angiogenic fast-growing phenotype.	[91]

Mir16/19, miR-580, 588 or 190	Dmir dormancy	Dmirs govern tumor dormancy, especially miR-190 induce long-lasting dormancy in glioblastomas and osteosarcomas.	[92, 93]
miR-100-5p	Dmir dormancy	miR-100-5p inhibition induces apoptosis in dormant PC cells and prevents the emergence of castration-resistant PC.	[130]
miR-200b/200a/429	Dmir dormancy	Expression of these Dmirs induce tumor cell dormancy and inhibit lung metastasis of BCCs.	[90]
miR-125b	Dmir dormancy	Its expression favors epithelial phenotype, reduces WNT-associated stem cell signaling and mesenchymal-associated genes and thus reduce metastasis of BCCs to the bone.	[131]
p38 Signaling	Stress-induced dormancy	p38 ^{Up}, ERK ^{down} leads to tumor dormancy. p38^{down}/ERK^{up} leads to mitogenesis.	[95, 96]
		p38/BiP/PERK axis promote drug resistance and survival of quiescent cells. BiP up-regulation averts Bax activation.	[97]
		p38 induce dormancy by expression of p53 and BHLHB3 while inhibiting c-Jun and FoxM1.	[94]
		MKK6 and p38α/β induce survival by regulating nuclear translocation and transcriptional activation of ATF6α in dormant cancer cells.	[98]
		TGF-β2-MAPK p38α/β-(ERK/p38)(low)-DEC2/SHARP1, p27, ↓CDK4, and dormancy of malignant DTCs.	[99]
		ꓒMERTK, the ↓ratio of P-Erk1/2 to P-p38, ↑ p27, NR2F1, SOX2, and NANOG, ↑histone H3K9me3 and H3K27me3, G1/G0 arrest and dormancy.	[132]
		MKK4 activates MAPK, p38 and JNK, up-regulate p21 and induce cancer cell growth arrest.	[133, 134]
		MKK6 activates MAPK and p38.	[133, 134]
		MKK7 activates MAPK and JNK.	[135]

Abbreviations: N-myc downstream-regulated gene 1 (NDRG1); BMP receptor 2 (BMPR2); indolamine 2,3-dioxygenase 1 (IDO1)-kynurenine (Kyn)-aryl hydrocarbon receptor (AhR) (IDO1/AhR); bone morphogenetic protein 7 (BMP7); N-myc downstream-regulated gene 1 (NDRG1); secreted protein acidic and rich in cysteine (SPARC); high mobility group A1 (HMGA1); polycomb-like proteins 1-3 (PCL1-3); protein kinase-like ER kinase (PERK); urokinase plasminogen activator receptor (uPAR); breast-cancer metastasis suppressor 1 (BRMS1); mammalian target of rapamycin (mTOR); Janus-activated kinase/signal transducers and activators of transcription (JAK/STAT); suppressor of cytokine signaling (SOCS); IL-6 cytokine leukaemia inhibitory factor (LIFR); transforming growth factor β2 (TGF-β2); proline hydroxylase I (P4HA1); Eph receptor A5 (EphA5); histone H2BK; insulin-like growth factor binding protein 5 (IGFBP-5); epithelial growth factor receptor (EGFR)-1; insulin-like growth factor type I receptor (IGF-IR); 5′-Ecto-nucleotidase (CD73); endothelial cell–specific molecule 1 (ESM-1); phosphatidylinositol 3-kinase PI3K

(PIK3); tissue inhibitor of metalloproteinase-3 (TIMP-3). RNA polymerase II transcriptional mediator subunit 12 (MED12). ꓕ denotes suppression, ↑ denotes upregulation, ↓ denotes downregulation.

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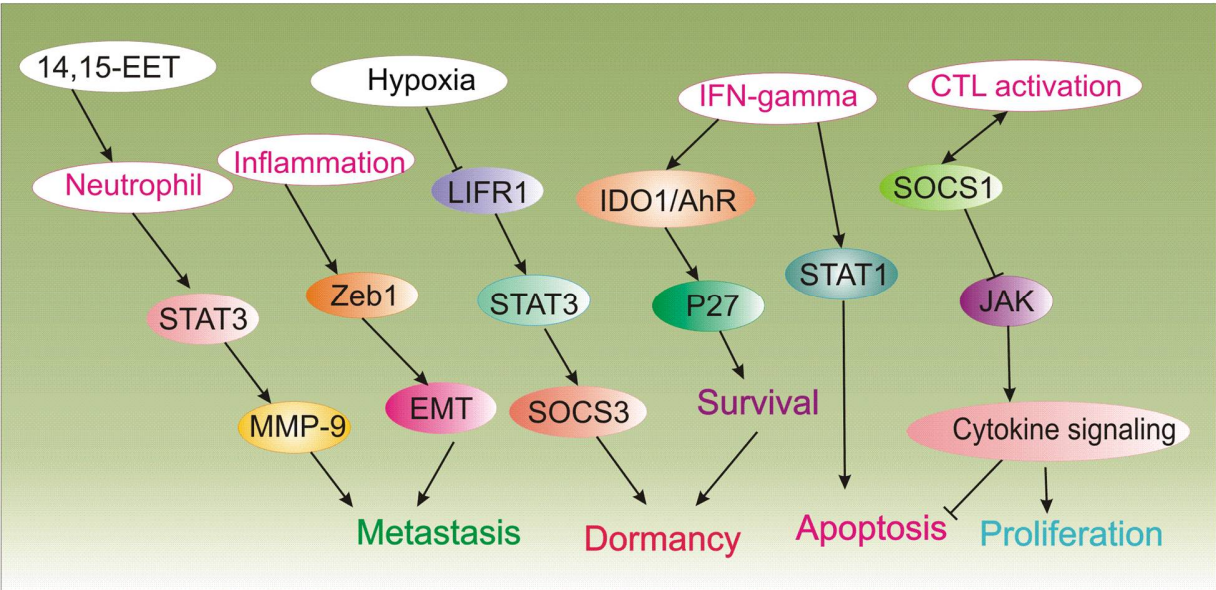
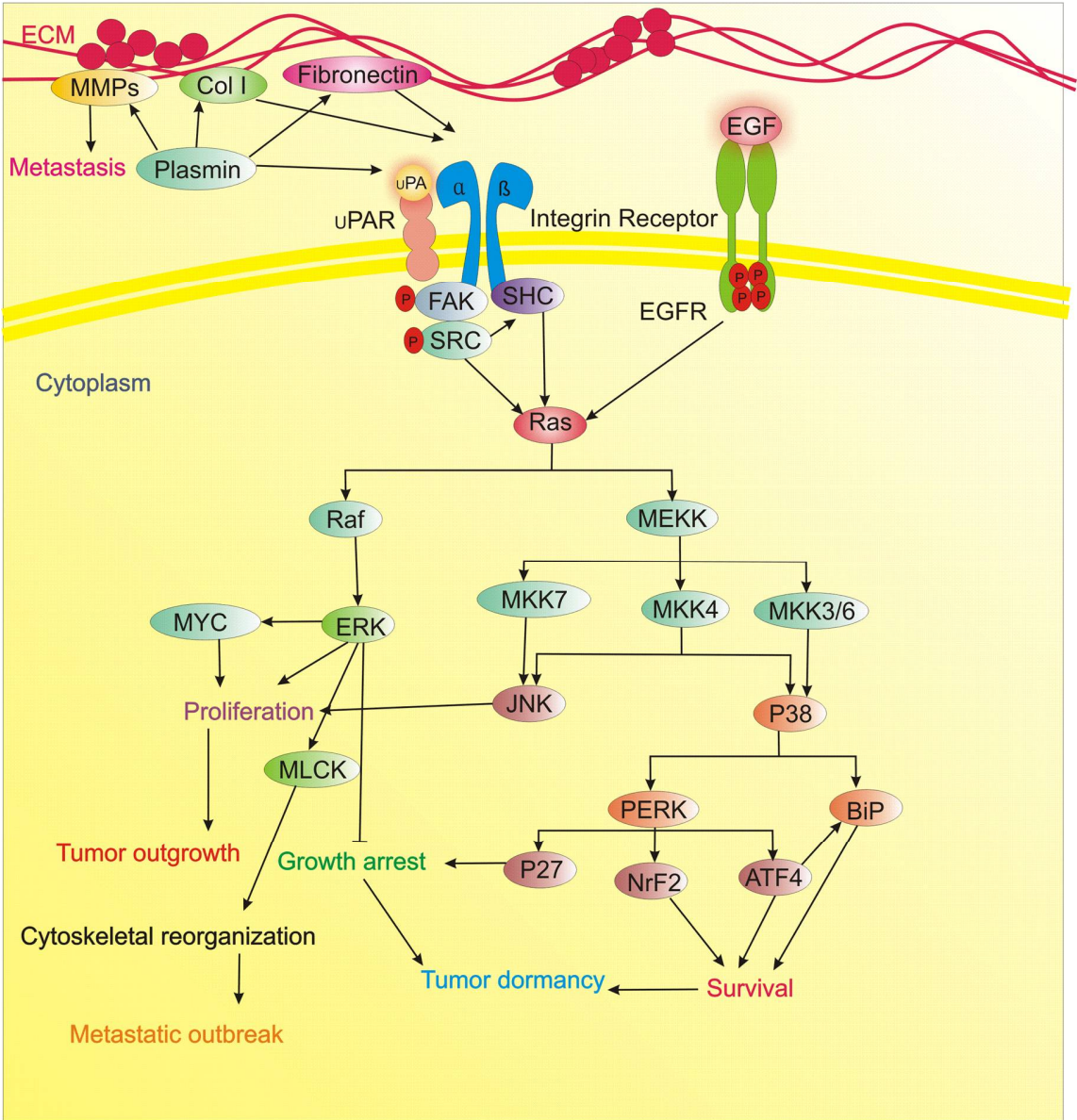Fig. 1. The implication of immune system in tumor cell dormancy.

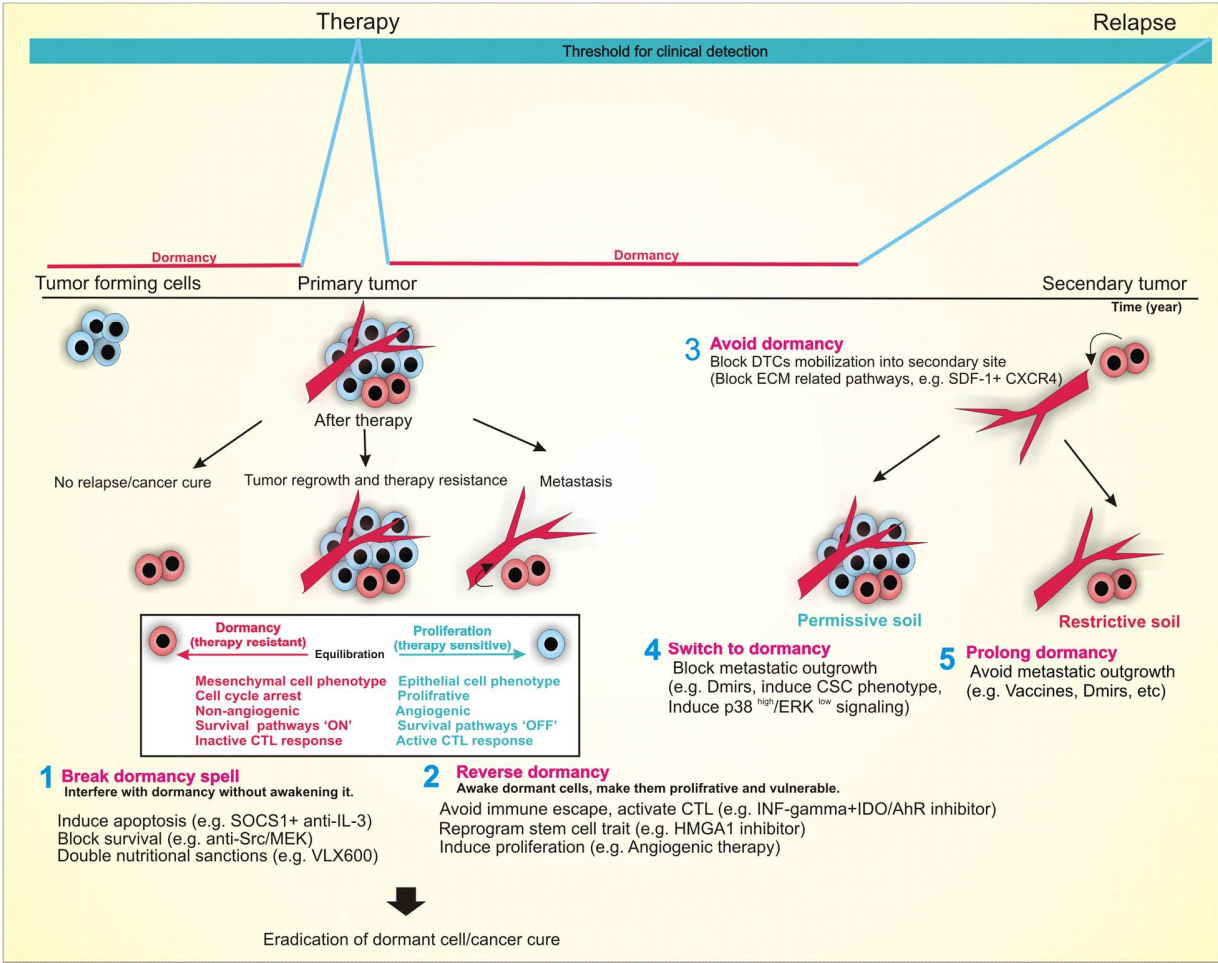Fig. 2. The implication of ECM and p38 signaling in tumor dormancy.

Fig. 3. Tumor dormancy as a therapeutic opportunity to fight cancer back.