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Tumor Cell Dormancy: How It Performs in Drug Resistance and Relapse*

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Abstract Despite progresses achieved in the therapy of tumors, the prognosis of patients is still limited by reccurence of residual tumor cells. Cancer cell dormancy plays a pivotal role in cancer relapse and drug resistance. In recent years, tumor cells undergoing EMT (epithelial-mesenchymal transition), CSCs (cancer stem cells) and CTCs (circulating tumor cells) are proved to share some common characteristics and show a cell cycle arrest phenotype. Thus, understanding the dormant stage of tumor cells could facilitate us in discovering ways to accelerate the development of tumor therapy and prevent its reccurence. In this review, we summarize the specific process of tumor cell dormancy induced by pharmacotherapy, and consider that dormancy is an initiative response rather than a passive defense to cytotoxicity. Besides, we probe into the mechanisms of tumor cell dormancy-mediated drug resistance, anticipating paving a way to target dormant tumor cells and result in better clinical outcomes.

Key words tumor cell dormancy, drug resistance, tumor relapse, targeted therapy
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Cell dormancy is a state in which cells are in quiescent phase, whereas, cells can escape from growth arrest and re-enter into cell cycle under certain conditions[1]. Hitherto, it is widely demonstrated that cell dormancy performs a pivotal role in a range of cancer activity, including drug resistance, metastasis, CSCs maintenance, and tumor relapse. While, the knowledge about dormant tumor cell is still very limited due to the poorness of established models that faithfully recapitulated tumor dormancy[2].

Tumor cell dormancy was identified for long years. Both clinical and experimental evidences show the widespread existence of dormant/growth-arrest cancer cells[3-4]. Tumor cells could stay in a dormant state as single cells or as micrometastases for many years before growing out into a macrometastatic lesion[5]. Furthermore, it is believed that we are all cancer survivors rather than cancer-free individuals because of harboring dormant malignant cells in our organs[6]. Due to the asymptomatic feature, dormant tumor cells are hard to be detected by present techniques, meanwhile, dormant tumor cells are refractory to traditional therapy due to their lack of proliferation[7], thus escaping from anti-proliferating drugs.

Pharmaceutical drugs are widely used in clinical tumor therapy, in conjunction with other remedial

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methods or not. While, despite of initial response, tumor cells become more and more recalcitrant to drug treatment along with follow-up treatment and disease progress [8]. Hence, drug resistance is still one of the major problems in cancer treatment [9], which eventually leads to clinical treatment failure[10]. Recent years, a thriving number of studies have suggested that there is an intimate connection between drug resistance and tumor cell dormancy [3]. While, the specific process of tumor cell dormancy induced by drug therapy and the mechanisms underlying it remain unclear. How tumor cells function during dormant phase, and how they escape from dormancy and recur are rather foreign to us. Thus, deciphering these questions could facilitate us to understand it and develop new strategies to interfere with it.

1 Dormancy, an initiative stress response to protect tumor cells against cytotoxicity

Tumor microenvironment is the cellular environment in which the tumor exists, which is usually featured with serum/nutrient starvation [11], low pH, oxidative stress [12], and hypoxia [13-14]. Cells could exhibit a corresponding adaptive variation in response to these environmental stimuluses [15]. Cancer cell dormancy is a dynamic cell state conferring a fitness advantage to an evolving malignancy under external and internal stress, including cytotoxicity caused by medicinal reagents[3, 15].

After exposure to pharmaceuticals, residual cancer cells escaping from drug killing will enter into a quiescent state, and exert adjustment in signaling pathway, protein expression and modulation to survive from cytotoxic stress. Fra-1 could functionally promote tumor cell proliferation, while Lu *et al.* [16] found that after treating breast tumor cells with doxorubicin and cyclophosphamide, drug resistant cells have a downregulation of Fra-1 and a corresponding growth cessation，which facilitates these cells survive from chemotherapy. Nathanson *et al.* [17] showed that in the treatment of erlotinib, the extrachromosomal EGFR Ⅷ DNA of glioblastoma carcinoma cell was almost completely lost, thus, causing the growth arrest of these cells. While, cessation of erlotinib treatment could notably increase extrachromosomal EGFR Ⅷ DNA and resensitized tumor cells to erlotinib-induced cell death. Obviously, the dynamic regulation of $EGFR^+$ extrachromosomal DNA mediates molecular target therapy resistance *via* a transition between growth and dormancy state. Under chemotherapeutic stress, IGF2 was reported to preserve osteosarma cell survival by creating an autophagic state of dormancy. This dormant state is correlated with IGF2 activation and downregulation of its downstream signaling pathway[18].

Epigenetic modulation refers to covalent modification of DNA, protein, or RNA, resulting in changes of the function and/or regulation of these molecules, but without altering their primary sequences. Just as genetic mechanism, epigenetic modulation could regulate nearly all cellular processes, meanwhile, it is also proved to function vital roles in cell dormancy[19]. Doxycycline could induce autophagic cell death and cell dormancy in ovarian cancer cells, in which reversible DNA methylation and histone acetylation patterns govern dormancy and recurrence *via* regulating TIMP3 and CDH1 [20]. Ameri *et al.* [21] found that demethylating agents or glucose starvation-mediated downregulation of DNMT expression triggered HIGD1A expression in tumor cells, which could promote survival and dormancy by repressing oxygen consumption and act as a cancer-promoting gene in such circumstances. As a post-transcriptional mechanism, miRNA expression level has changed during the treatment of chemotherapy [22], and performed a crucial role in cell dormancy[23]. Galluzzi *et al.* [24] showed that Pre-miR-630 could diminish sensitivity of A549 cells to cisplatin *via* arresting cells in the G0-G1 phase and reducing their proliferation rates, which is accompanied by increased levels of the cell cycle inhibitor p27 (Kip1). Moreover, it was showed that miR-192/miR-215 impeded progression into the S phase and were involved in cell cycle control at multiple levels and subsequently avoided 5-FU cytotoxicity[25]. MiR-139-5p induces S-phase cell cycle arrest in breast cancer cells, and downexpression of miR-139-5p increases the chemosensitivity to docetaxel to induce apoptosis *via* Notch1 targeting in breast cancer cells [26]. Besides, CXCL12-specific miRNAs could be transmitted from stromal cells to breast cancer cells *via* gap junction and exosomes, which reduces CXCL12 levels and decreases cancer cell proliferation[27]. Therefore, the phenotype of tumor cell dormancy is regulated by epigenetic factors to a huge extent, and could be also regarded as an epigenetic disease.

Besides genetic and epigenetic facets, tumor microenvironment is a complex system that can influence the function of tumor cells. A series of cytokines secreted in tumor microenvironment, like growth GAS6, BMP4, BMP7 and TGFβ2, could induce residual cell dormancy in different types of cancer [28]. Immune system, the default constituent of the tumour microenvironment [29], also exhibits a significant influence on tumor cell dormancy. $CD8^+$ T cell-mediated cytotoxicity could hold tumor cells in a dormant state, however, these cells could resume growth after $CD8^+$ and $CD4^+$ T cell depletion [30]. Marlow *et al*.[31] reported that breast cancer cells in the inhibitory niche were in reversible cell cycle arrest. After removed from the inhibitory niche, these dormant cells were capable to re-proliferate and fuel tumour growth. It is suggested that the acidic microenvironment is associated with a poor prognosis of tumor-bearing patients and provides a possible niche of dormant tumor cells [32]. In addition, the sprouting neovasculature niche is believed to perform a crucial role in tumor cell dormancy and sustain solitary breast tumour cell dormancy *via* suppressing angiogenesis[33].

Respecting the above-mentioned facts, it is no hard to ratiocinate that dormancy is an initiative response rather than a passive defense to cytotoxicity. In front of pharmacotherapy, tumor cells could flexibly have a modulation in genetic and epigenetic level to keep a dormant state, thus sheltering from lesion and diminishing energy expenditure and substrate consumption. In this way, these dormant tumor cells avoid apoptosis and conserve strength for further relapse.

2 Dormancy, a common feature of EMT, CSCs and CTCs

It has long been convinced that EMT-transformed cancer cells, CTCs and CSCs are stubbornly refractory to pharmaceutical treatment, therefore, all of them are widely regarded as relapse-initiating sources and could be responsible for tumor recurrence[34]. Meanwhile, the subpopulation of dormant cancer cells bears the preferential ability to survive tumor therapy and persist long term, ultimately giving rise to tumor relapse [35]. Hence, it is of much interest to delve into the common phenotypic features and mechanistic links among them.

Up to now, huge number of evidences have shown that chemotherapy and target therapy could induce cancer cells to undergo a mesenchymal-like transition [36–40] and show a growth arrest phenotype because of cytotoxic stress, which facilitates cancer cells to be less sensitive to therapy. More extremely, it is concordantly reported that EMT could be dispensable for metastasis but contributes to chemoresistance in pancreatic[41] and lung cancer[42].

The biological relationship between EMT and CSCs has long been debated. It is supported that EMT programming is associated with a gain of stem cell-like behavior and lead to enrichment of CSCs [43–45]. At the same time, CSCs were also demonstrated to express EMT markers[46]. As we know, EMT transformed cells exhibit an elevated ability in migration and metastasis, consequently, these cells are inclined to infiltrate into circulation system and disseminate through the bloodstream [47], which contributes to the inhibition of anoikis [48] and the formation of CTCs [49–50]. EMT and CSCs markers are frequently overexpressed in CTCs of cancer patients, which manifests some phenotypic features of EMT and CSCs [51–53]. Likewise, CTCs could also transform into CSCs and then initiate tumor recurrence [54–55]. In addition, it is reported that acquisition of the EMT phenotype in CTCs can indicate the risk of relapse and survival, for example, in hepatocellular carcinoma patients, EMT-positive CTCs are associated with worse prognosis than epithelial CTCs[56].

To sum up, there are numerous phenotypic overlaps and biological links among EMT, CSCs and CTCs. Moreover, these cells share one fundamental property that they are relatively in a quiescent/dormant state [8, 57]. EMT-transformed cells are linked with decreased proliferation or quiescence [43, 58], showing a cell cycle arrest phenotype[59]. Beneath it, EMT related signaling pathway could regulate cell cycle arrest. TGF-β/smad cascade, the bestknown pathway mediating EMT, is confirmed to perform vital roles in CSCs maintenance, drug resistance and growth inhibition [60]. TGF-β could transcriptionally activate the cell-cycle inhibitor p21 and diminish effectiveness of anti-cancer therapeutics [61]. APC/C complex could also be activated by TGF-β/smad cascade, thus, mediating Skp2 degradation and cell cycle arrest[62]. In

addition, EMT transcription factor snail could block cell cycle[63] and confer resistance to cell death[64].

Because of the phenotypic plasticity and instability of CSCs[65], there are still some controversial issues about this model, *e.g.* whether CSCs represent a group of cell population or a kind of cell property[66]. Despite of these controversies, just as normal stem cells, CSCs also show the feature of entrance into a prolonged dormant state [19, 67]. Treatment induced dormancy is reported to be linked to CSCs[35, 47, 68]. The ECM and integrin composition of the tumor environment might regulate both CSC behavior and the tumor dormant state [69-70]. Reduced expression of Fra-1 not only inhibits growth cycle， but also correlates with an increase in tumor CSCs [16]. It was demonstrated that expression of p21 is indispensable for maintaining self-renewal of leukaemia stem cells (LSCs) [71]. Meanwhile, activated p21 is critical in preventing excess DNA-damage accumulation and functional exhaustion of LSCs [71]. p21 activation was also confirmed to induce reversible quiescence and prevention of apoptosis in dormant tumor populations[72]. Moreover, lung cancer cells could spontaneously fuse with mesenchymal stem cells, and exhibit a p21-regulated growth suppression and a stem-like state[73].

Extensive clinical tests show CTCs is a strong prognostic factor for overall survival in patients with metastatic cancer. CTCs profiles are regarded as a powerful clinical indicator for the transition from chemotherapeutic susceptibility to chemoresistance [74]. The disseminated CTCs don't resume proliferation, but persist in carcinoma patients who have received mastectomy several years ago and show asymptomatic state [74-75], however, these dormant tumor cells may or may not become clinically apparent within their lifetime [76]. Some biomarkers, like uPAR and integrin β1, known to be implicated in cell dormancy, were characterized in CTCs subsets of breast cancer with dormant phenotype [77]. Even in face of chemotherapy, CTCs could also be able to exist, which implys that CTCs might have developed adaptive mechanisms to survive under such chemotherapeutic stresses[78].

Summing up the above, EMT, CSCs and CTCs are intensively correlated with each other both in phenotypic features and molecular mechanisms, especially, they all share the common features of dormancy (Figure 1), which mediates drug resistance and contributes to recurrence of these cells.

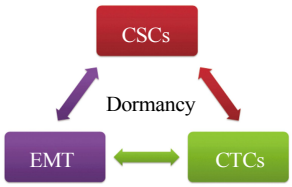

Fig. 1 Dormancy, the inner links and common features among EMT, CSCs and CTCs

It has been proved that EMT-transformed cells, CTCs and CSCs are all refractory to pharmaceutical therapy and responsible for tumor recurrence. There are some parallel features shared by the three kinds of tumor cells. Dormancy is one of the fundamental characteristics, which could probably mediate drug resistance and relapse of the three kinds of cells.

3 Dormancy, a preparation stage for metastasis and relapse

After exposure to therapeutic agents, the residual cancer cells survived from therapy will step into a slow-cycling/dormant state due to cytotoxic stress and lesion. Hitherto, evidences from scientific reports show that dormancy is not merely a passive stress response to harmful insults, nor these cells sustain a stationary state to the end. The dormant phase following pharmacotherapy is an initiative recurrence-preparation stage, during this period, residual carcinoma cells proactively adopt various strategies to survive from lesions and eventually outgrow into macroscopic colonization.

Autophagy is an evolutionarily conserved， intracellular self-defense process， which has multiple roles in various cellular functions [79]. Autophagy is confirmed as a switchable mechanism in cancer progression [80]. In parallel, autophagy is also regarded as a survival mechanism during tumor cell dormancy[81]. Recent studies have demonstrated that tumor cells' resistance to anticancer therapies including radiation therapy, chemotherapy and targeted therapies can be enhanced through upregulation of autophagy [82]. In dormant phase, autophagy-mediated stress tolerance can facilitate residual tumor cells' survival by sustaining energy production which can result in tumor growth and therapeutic resistance[18, 83]. Alessandra *et al.* manifested that chronic hypoxia induces autophagy that may be the survival mechanism of hypoxia-resistant human breast cancer cells. The

hypoxia-induced autophagy mediates breast cancer cells reversibly entering an inactive status, dormancy, under prolonged hypoxic condition[2]. Autophagy has also been shown to be a major factor for CSCs survival and drug resistance[83].

DNA damage repair refers to the correction of DNA lesions that threaten genome integrity. A various of chemotherapeutic drugs, like cisplatin, 5-FU, could lead to DNA damage of tumor cells. In response to DNA damage, cell cycle checkpoint is activated, further resulting in growth arrest and allowing more time for tumor cells to repair damaged DNA[84]. DNA damage repair pathways and molecules are essential to restore the DNA and maintain the genomic integrity[85]. For example, p53 is one of the most noted factors mediating cell cycle arrest and DNA repair. It is widely demonstrated that p53 plays a dual role after exposure to cytotoxic treatment, either activating apoptosis or launching processes directing to DNA repair and survival of the cell[86-87]. In the alternative pathway, p53 would provide both time and tools to reverse drug-induced DNA damage, namely, mediating G1 arrest and activating a series of DNA repair related molecules and signal pathways[86]. After finishing DNA damage repair, residual tumor cells could exit from dormant state and re-enter into cell cycle, eventually contribute to therapy failure and tumor relapse[88-89]. Besides, recurrent tumor cells evolving after chemotherapy withdrawal are more refractory to subsequent treatment than parental tumor cells[90]. It is generally believed that CSCs are characterized by significant enhancement of DNA repair mechanisms[91-92]. After chemotherapy treatment, cancer cells in dormant phase have an enrichment of CSCs and a higher expression of DNA repair-related genes[93-94]. Meanwhile, incomplete DNA repair, such as the NHEJ pathway could cause a high frequency of spontaneous mutagenesis subsequently resulting in genomic instability and tumor progression[95]. Genomic instability caused by DNA damage was also reported to induce enrichment of stem-like cancer cells, thus, contributing to these cells' drug resistance[96].

Intercellular communications play important roles in cancer progression. Anchoring junction serves to anchor cells to one another and attach cells to extracellular matrix. The anchoring proteins in adherens junction are composed of cadherins which anchor to other cells and integrins that anchor to extracellular matrix. Overexpression of N-cadherin is associated with cell cycle arrest, which correlates with a similar property of CSCs. Connexin expression, which is important in CSCs dormancy, is regulated by N-cadherin. Conversely, connexin reduced cancer cell invasion by suppressing the expression of N-cadherin and preventing tumor cell adhesion to endothelial cells[97]. Gap junction intercellular communication (GJIC) was reduced between epithelial cancer cells, loss of which is associated with enhanced migration capacity of cancer cells. Heterospecific GJIC between cancer cells and other cells within the tumor microenvironment may also affect the metastatic potential of cancer cells[98]. Heterologous communication with the adjacent non-transformed cells inhibits the cellular growth of cancer cells. Gap junctional intercellular communication between cancer cells and bone marrow stroma directs cancer cells from circulation and makes them quiescent in bone marrow[1]. Bone marrow is a major organ of cancer dormancy and a common source of cancer recurrence[99]. Formation of gap junctions between cancer cells and endothelial cells mediates cancer cells extravasation to distant site[100]. Cancer cells that overexpress Cx43 or Cx26 have enhanced capacity to adhere to endothelial, resulting in more metastatic potential. Ectopic expression Cx43 contributes to cancer cell adhesion and migration, through reducing OB-cadherin which expresses on osteoblast and in turn regulating the metastatic potential of cancer cells to bone[101]. As the circulating tumor cells always show dormancy, we speculated that heterologous communication between dormant epithelial cancer cells and endothelial is the main reason for CTCs dormancy. In addition, activation of cellular adhesion molecule, like MLCK, could also promote cancer cells escaping from dormancy, thus, confirming intercellular communication/adhesion has dual effect on tumor cell dormancy[102].

Due to its accurate treatment and diminished side-effect, target therapy is a promising strategy for cancer. While, despite of the initial response, residual carcinoma cells usually enter into re-proliferation cycle and become recalcitrant to target drugs. By now, a myriad of researches have demonstrated that, during drug holiday, cancer cells implement positive adoptions and alterations to counteract the cytotoxicity and growth arrest effect. HGF/MET signaling has shown extensive capability to make cancer cells resistant to many target drugs[103]. In lung cancer, it was shown that the resistant cells exhibit MET

amplification in contrast with parent cell lines, which further leads to gefitinib resistance by activating ERBB3 signaling[104]. Such results are also obtained in other literatures[105-106]. Likewise, upregulation of AXL occurs in human EGFR-mutant NSCLCs with EGFR TKI acquired resistance[107]. Dynamic regulation of EGFR Ⅷ extrachromosomal DNA was also observed in EGFR TKI-resistant glioblastoma, after drug withdrawal, reemergence of clonal EGFR Ⅷ on extrachromosomal DNA follows and leads to recurrence[17].

More and more evidences have shown tumor is not simply a "bag" of homogeneous malignant cells, cells in tumor tissue are heterogeneously organized. There is increasing awareness that intratumoral heterogeneity contributes to therapy failure and disease progression[108]. Even within single genetic subclones, not all cells function equally. Cells with the same genotype can exist in different states which could influence their behaviors[109]. Thus, intratumor heterogeneity presents a major hurdle in cancer therapy[110]. Emerging evidences have shown that tumor heterogeneity contributes to relapse following therapy-induced dormancy. Tumor cells escaping from dormancy is widely believed to be accompanied by a large increase in variance, namely heterogeneity[111]. In the recurrence of epithelial ovarian cancer, the tumor heterogeneity in genetic and epigenetic features was evaluated with heterogeneous expression of PcG proteins, which demonstrates there is an increasing tumor heterogeneity during dormant phase[112]. Lambrechts *et al*.[113] found that after platinum therapy, chromosomal instability was increased in recurrent ovarian cancer patients, which then contributed to acquired resistance of ovarian carcinoma cells. In addition, after chemo- and targeted therapies, CSC heterogeneity was also shown to act as a vital role in tumor recurrence[114].

4 Dormant tumor cells, the potential therapeutic target

Due to recurrent cancer cells show enhanced chemoresistance and more malignant phenotypes, thus, how to deal with cancer cells during drug-induced dormant stage is of fundamental significance for suppressing disease recurrence. A mounting number of evidences demonstrated that maintaining cancers in dormant stage or detecting these lesions prior to their transition to rapid expansion could well prevent dormant tumor cells from surviving and multiplying, and further lead to a reduction in cancer mortality.

Blocking survival signals during drug-induced dormancy is an attractive method to inhibit tumor relapse and metastasis[115]. Inhibition of eIF2α dephosphorylation could maximize bortezomib efficiency and eliminate quiescent multiple myeloma cells surviving from proteasome inhibitor therapy[116]. GSI is a γ-secretase inhibitor targeting Notch pathway, and it was proved that GSI-mediated inhibition effect could block recurrence of dormant residual breast tumor cells[117]. Lara *et al*.[118] found that targeting Src prevents the proliferative response of dormant cells to external stimuli, but it also requires MEK1/2 inhibition to suppress their survival. Thus, it indicates that targeting Src in combination with MEK1/2 may prevent breast cancer recurrence from dormant state[118].

Tumor angiogenesis is a process for creation of new blood vessels that supports the growth of tumor, and angiogenic switch functions a pivotal role in regulating tumor cell's release from dormancy[119]. Recent years, studies have implicated that failure of angiogenesis is a factor that contributes to the maintenance of cancer cell dormancy, and activation of angiogenesis could trigger the initiation of growth by dormant cells[20, 120]. While, the current limitations of anti-angiogenic cancer therapy may well be related to the use of these agents too late in the disease course[121]. Consequently, prior to tumor relapse, employing anti-angiogenic agents in dormant stage is a hopeful remedy to enhance therapy efficiency and diminish recurrence risk.

Tumor dormancy was also thought as a result of endogenous immune surveillance[122]. Immune cells and effector cytokines secreted by these cells could negatively modulate tumor cell growth, which is known as immune-mediated dormancy[123]. How tumor cells grow under immunosurveillance of body is magnetic to researchers all the time. Recently, it is demonstrated that the cancer immunoediting hypothesis describes a process, in which immune system shapes tumor immunogenicity and proceeds through three phases termed "elimication" "equilibrium" and "escape". A small fraction cancer cells that lack strong antigens survives the elimination phase and enter the equilibrium phase between the tumor and anti-tumor immune response by T-cell-dependent immunoselection[124]. Proliferating cancer cells are kept at a low number in the bone

marrow where memory T cells coordinate with $CD4^+$ and $CD8^+$ T cell-mediated responses [125]. Hence, in combination with conventional therapies, activation of endogenous immunity to achieve better clinical antitumor efficacy is advisable, which could result in suppression of dormant cancer cells' relapse under immunosurveillance[122].

DNA damage repair plays pivotal roles in residual cancer cells surviving from genotoxic chemical drugs. After chemotherapy, these residual cells enter into dormant state and undergo a process of DNA repair. Eventually, residual cancer cells escape from apoptosis induced by DNA damage and regain the ability of malignant proliferation. Up to now, quite a number of literatures suggest inhibition of DNA repair pathways could effectively enhance therapeutic efficacy of DNA damaging drugs in the clinic[126-127]. Thus, inhibitors of DNA repair pathway during dormant phase could induce residual cancer cells' apoptosis and result in better patient outcomes.

Oriental herbal medicines have evolved over thousands of years in ancient China, which exhibit specific functions in a variety of diseases. Some herbal medicines have been shown to inhibit cell cycle and promote apoptosis of cancer cells [128-130]. Thus, utilizing traditional oriental herbal medicines integrated with tumor dormancy therapy is of potential benefits after conventional therapy [131]. Due to relieving the side effects, traditional herbal medicines could also improve the survival quality of tumor patients.

In addition, it is theoretically feasible to awaken dormant tumor cells, then employ anti-proliferating drugs to eradicate these cells. While, awakened dormant tumor cells seem to rapidly fuel tumour recurrence in experimental systems [31, 118] and could worsen patient outcome [28]. Thus, the authors argue against awakening dormant tumor cells and instead support keeping them dormant or eradicating them while dormant as an alternative strategy.

To sum up, there are plenty of available strategies to deal with tumor cells in dormant phase. Successfully suppressing or eradicating tumor cells in dormant state would be a good strategy for treating cancer in the near further.

5 Conclusions and perspectives

To date our knowledge on how tumor cell dormancy performs in drug resistance and relapse is relatively limited. Traditionally, tumor cell dormancy is believed as a passive shirking of proliferation after pharmacotherapy. However, growing number of evidences have shown that tumor cells could take an initiative process into dormancy through regulation of dormancy-related genes, and modulation of epigenetic and microenvironment factors. After entering into dormant phase, instead of resting, these cells undergo a series of processes, like autophagy, DNA repair, cell adhesion and other ways to avoid apoptosis and anoikis. In addition, intratumor heterogeneity is accumulated in dormant phase, which leads to a more malignant phenotype of dormant tumor cells and filial generations. Dormancy is also demonstrated to be a common feature shared by EMT, CSCs and CTCs. Thus, targeting tumor cells in dormant phase is a promising strategy to prevent tumor relapse (Figure 2). In combination with conventional agents, using

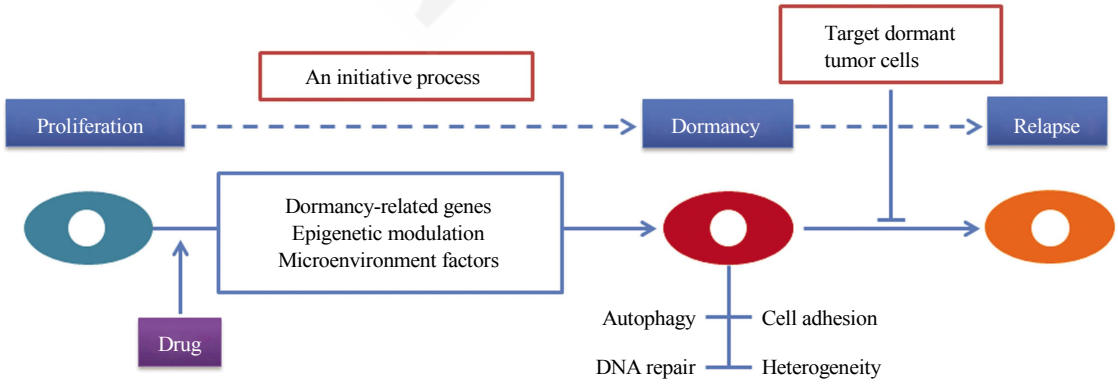

Fig. 2 The mechanism of therapy-induced dormancy and the potential target of dormant tumor cells

Upon exposure to anti-tumor drugs, the residual tumor cells take an initiative process into dormancy through regulation of dormancy-related genes, and modulation of epigenetic and microenvironment factors. Tumor cells in dormant phase could undergo autophagy, DNA repair, cell adhesion and heterogeneity, thus avoiding apoptosis and making preparations for further relapse. Hence, these dormant cells are promising therapy targets to prevent tumor relapse, blocking survival signals, inhibiting tumor angiogenesis, enhancing immune surveillance and other effective ways could probably achieve better clinical results.

anti-angiogenic drugs, DNA repair inhibitors, oriental herbal medicines or enhancing immune surveillance in dormant state could availably eradicate tumor cells and restrain their further proliferation.

Overall, due to the complexities of tumor cell dormancy, there are still some challenges existing at the present studies, such as identification of reliable molecular markers, establishing *in vivo* model and tracing minimal residual of dormant tumor cells. But, deciphering the mechanism of therapy-induced dormancy and solving the problems induced by tumor cell dormancy would be of great benefits for cancer patients.

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