

# Biological and Clinical Evidence for Metabolic Dormancy in Solid Tumors Post Therapy

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**Abstract** Despite many advances in the understanding of cancer biology, patient survival has only modestly improved over the past few decades. This is partly due to the dismissal of an important phase of cancer progression called therapy-induced dormancy which arises during the course of (neo)adjuvant therapy. This review describes recent efforts in understanding the mechanisms that ‘dormant’ cancer cells adopt to survive and develop resistance prior to their relapse into secondary tumors. The focus is particularly on metabolic reprogramming that ensues as a consequence of tumor adaptation to therapy.

**Keywords** Metabolic dormancy • Solid tumors • Tumor *dormancy* • Metabolism • Therapy induced tumor resistance • Therapy induced dormancy

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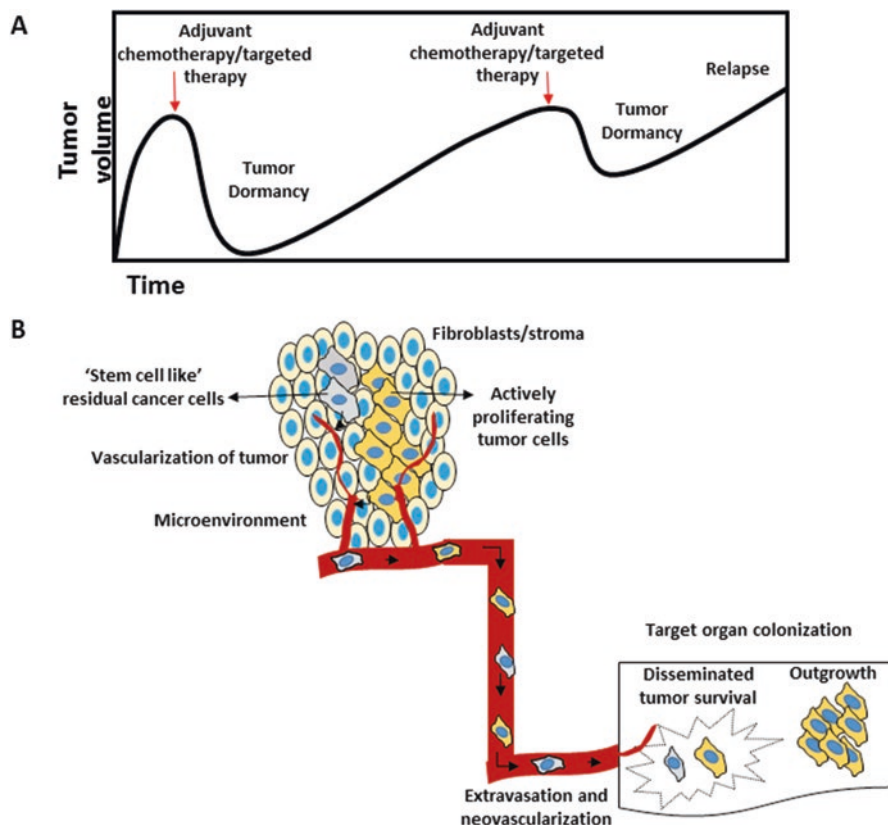
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**Fig. 1** (a) The clinical course of a majority of cancer types initiating with an increasing tumor burden until treatment with first (neo)adjuvant chemotherapy or targeted therapy. The dormancy phase ensues upon reduction of tumors to a minimum size before emergence as therapy resistant tumor. (b) Cancer cell's metastatic dissemination in distant organs through extravasation and neovascularization of new tissues

## Introduction

Tumor dormancy is signified by the period in cancer progression during which there is a minimal residual disease-state as a consequence of surgical resection or neo-adjuvant treatment of primary tumors and prior to relapse either locally or in distant organs (Fig. 1a). Tumor dormancy post-therapy ensues when proliferation is counter-balanced by apoptosis, and the transition has been ascribed to four main attributes: (i) angiogenic dormancy, (ii) immunologic dormancy, (iii) micrometastatic dormancy, and (iv) dormancy regulation through microenvironmental factors [1]. Cellular dormancy occurs when cancer cells transition to a stem-cell like reversible growth arrest phase following treatment, the mechanisms of which are poorly understood. These quiescent residual dormant cells must acquire profound genetic or epigenetic reprogramming that allow them to escape immunosurveillance, and

help them adapt to an unwelcoming microenvironment in order to relapse. Whether these are cancer stem cells is still an active topic of debate in many cancer fields.

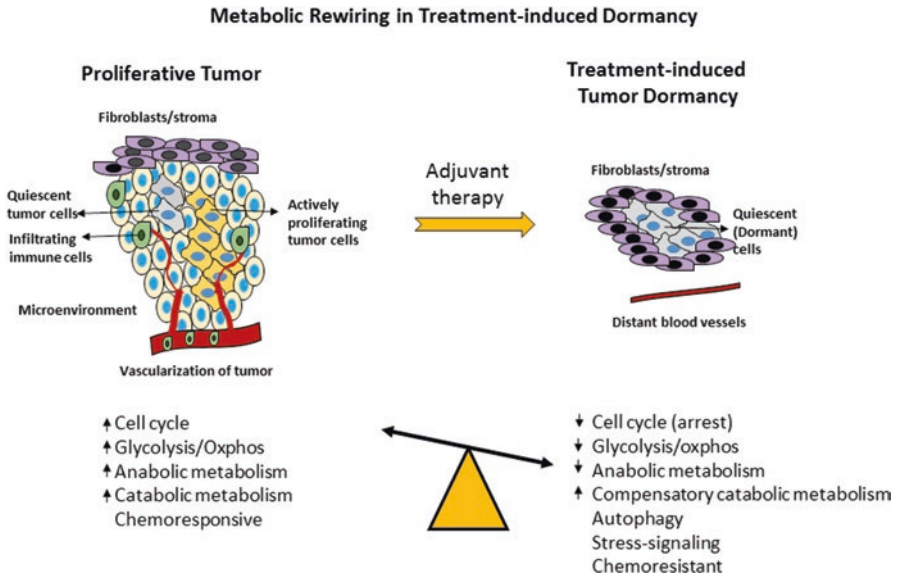
Hence, dormancy is an important phase to consider clinically because patient mortality is often due to the permanence of residual tumor cells (RTCs) or disseminated tumor cells (DTCs) that are highly resistant to therapy and capable of generating metastatic and incurable diseases. Circulating tumor cells (CTCs), on the other hand, are associated with active and metastatic malignancies [2] and distinct from the former two (Fig. 1b). The ‘seed and soil’ hypothesis of ‘tumor and stroma’ interactions account for relapse and metastasis of tumors that eventually cause a majority of patient deaths in many cancer types [3]. This is important because the expression of many of the tumor suppressors and oncogenes is context-dependent and require specific tissue microenvironments to exert their functions [4].

Considering the conflicting clinical results and logistical challenges in addressing tumor dormancy, animal models that closely recapitulate the clinical discourse of cancer are incredibly valuable [5–9]. Use of post-treatment patient-derived xenograft models allow one to rule out the confounding metabolic adaptations typically found *in vitro* models due to tissue culture conditions.

Some of the challenging questions that remain to be investigated include the causes of dormant cancer cell re-awakening, distinctions and similarities of various dormant cancer types, and the dormant cancer cell signature of long-term versus short-term patient survivors.

Here, we introduce ‘metabolic dormancy’ in the context of cancer. Previously, this term has been used to describe aquatic invertebrates (e.g. *Caenorhabditis elegans*) entering a state of developmental and metabolic dormancy for coping with their extreme environmental conditions [10]. In microbiology, metabolic dormancy has been used to describe *Mycobacterium avium*’s evolved response to starvation [11]. *E. coli* and *S. cerevisiae* also enter a stationary phase during which the metabolism of carbohydrates, amino acids, and phospholipids are considerably reduced [12] under the close regulation of reactive oxygen species (ROS) and superoxide dismutases, MTOR, and stress response transcription factors [13, 14]. Metabolic dormancy in the context of cancer is attributed to a reprogramming and switch in metabolism during dormancy in order to use a minimum supply of energy for survival either at the site of origin, as minimal residual disease post-treatment, or in a new microenvironmental niche occupied by disseminated dormant tumor cells. Since the bone marrow acts as the recipient organ of many cancer cell metastases (dissemination to the bone), understanding the hematopoietic stem cells niche of the bone marrow is also essential [15–17]. Therefore, it is not surprising that many different mechanisms need to converge in order to result in maintenance of quiescence (Fig. 2).

Thus, there exists an urgent need for identifying the effective survival strategies of dormant cancer cells and for determining prognostic and diagnostic markers of specific cancers. The ultimate aim of this chapter is to evaluate recent findings that intervene in progression, and metastatic relapse of cancer, targeting the energetics switch of cancer cells after therapy. Understanding the intricate biology of dormant tumors and metabolic mechanisms that lead to their switch from dormancy to relapse into secondary tumors are critical steps towards designing therapeutic strategies.



**Fig. 2** Comparison between properties of proliferative active tumors and quiescent treatment induced dormant tumors. A heterogeneous mass of proliferative tumors exhibit increased cell cycle, anabolic and catabolic metabolism to supply energy for growth. Other attributes include chemoresponsiveness and vascularization. Dormant tumors, on the other hand, exhibit lowered cycling and metabolic activities to support their survival. Other attributes include development of chemoresistance and profound genetic/epigenetic reprogramming

## The Derangement of Metabolic Wiring in Cancer

In the presence of oxygen, most normal tissues derive their energy by metabolizing glucose to pyruvate through glycolysis, and then oxidize the majority of the generated pyruvate to carbon dioxide in the mitochondria through the tricarboxylic acid (TCA) cycle coupled to oxidative phosphorylation (OXPHOS) [18]. Under anaerobic conditions, normal cells redirect the pyruvate generated from glycolysis away from oxphos towards lactate production [19]. The fundamental paradigm shift that Otto Warburg proposed was that in contrast to normal cells, rapidly proliferating cancer cells rewire their metabolic programming and switch to accelerated aerobic glycolysis and lactate production [20]. Recent studies now show that in addition to high rates of glucose metabolism, some cancer cells can maintain high rates of oxphos as well [21]. The process of aerobic glycolysis is more rapid than oxphos and while it provides the increased rate of ATP production required for increased cell division it also diverts glucose into anabolic biosynthetic pathways upstream of pyruvate production [22] required for the vital replication of cellular biomass. These anabolic pathways include the pentose phosphate pathway which generates pentose phosphates for ribonucleotides and NADPH; and the serine biosynthesis pathway which generates amino acids and initiates the one-carbon metabolism cycle [23]. Besides NADPH generation, one-carbon metabolism is also involved in the anabolic synthesis of amino acids, proteins,

nucleotides and phospholipids, and has a role in the methylation reactions involved in post-translational modifications [24]. Additionally, during aerobic glycolysis, some glucose is diverted to glycerol-3 phosphate for fatty acid synthesis [21] and in the mitochondria, to the precursor, acetyl CoA for eventual cytosolic synthesis of lipids [22].

Apart from glucose metabolism, several other highly interconnected and multistep metabolic pathways and intermediates are involved in energy production and *de novo* synthesis of biomolecules. Other carbon fuels including glutamine, proline, serine, and fatty acids can ultimately feed into the TCA cycle to provide electron donors for the electron transport chain (ETC) and the generation of ATP [25]. Emerging evidence suggests a role for non-essential amino acids in tumor cell proliferation. For instance, arginine can promote tumor cell proliferation through nitric oxide synthesis. Additionally, the conversion of arginine to ornithine in the urea cycle, interconnects with the proline cycle leading to the generation of glutamate for the TCA cycle and glutamine synthesis [26]. Additionally, proline metabolism promotes cancer cell survival and energy production and regulates redox balance and biomass production [27]. The chemical energy of these fuels is harnessed by reducing electron carriers NAD<sup>+</sup> and FAD to NADH and FADH<sub>2</sub>. These pathways eventually satisfy the three metabolic demands of cancer cells: (i) bioenergetics, (ii) macromolecular biosynthesis, and (iii) redox maintenance through NADPH/NADP<sup>+</sup> ratios. Additional pathways that regulate metabolic flux include MTOR, PI3K, AMPK, and autophagy [14].

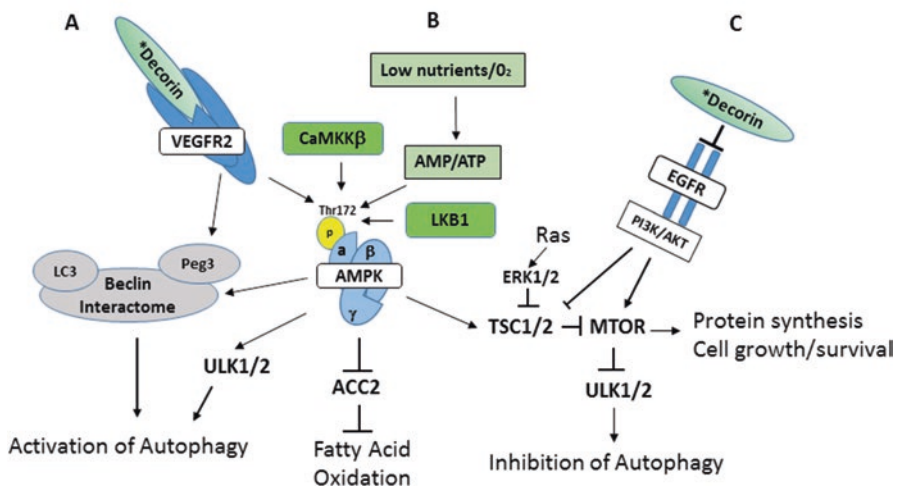
However, there are multiple layers of complexity that should be accounted for when considering cancer metabolism. The heterogeneity of metabolism is multiple folds and can be attributed to (i) lineage-specific or selective expression alterations of metabolic transcripts that affect uptake, secretion, or other functions, (ii) genomic aberrations in metabolic genes such as mutations, deletions, amplification, and splicing events, (iii) epigenomic or non-genetic landscape changes, (iv) ATP generation affected by both cell type and the conditional context, (v) secondary metabolites of metabolism acting as tumor suppressors or oncogenes and (vi) stromal influences/tumor microenvironment.

## **‘Metabolic’ Dormancy and Related Biological Mechanisms**

Altered tumor metabolism during dormancy need not consist entirely of adaptations that are driven to satisfy the bioenergetics demands of cell survival. Instead, such metabolic rewiring may also result in the development of specific dependencies that must be met to maintain cell survival [32–36]. For example, several tumor types are auxotrophic for one or more amino acids owing to deficiencies in a corresponding endogenous biosynthetic pathway. Particularly, some quiescent cells have a reliance on the import of amino acid(s), such as proline, from the extracellular matrix or serum [37] without which tumorigenesis ensues [38]. For instance, lymphoblastic leukemia and ovarian carcinomas depend on non-essential amino acid L-asparagine for survival [39]. Similarly, a large fraction of hepatocellular carcinomas, metastatic melanomas, and renal cell carcinomas are auxotrophic for L-arginine [40, 41]. The systemic depletion of such amino acids as a therapeutic strategy is of particular interest given the poor prognosis of these cancers and the difficulty in treating them with conventional chemotherapeutics.

Whereas tumor cells must maintain catabolic metabolism for the production of energy and anabolic metabolism for the synthesis of biomolecules required for rapid cell division, as mentioned above, dormant cells are relieved of this anabolic pressure and so presumably adopt a basal catabolic metabolism. Dormant tumor cells, thought to undergo a reversible cell cycle arrest in response to unfavorable conditions such as anti-neoplastic treatment, retain their ability to re-enter the proliferative cell cycle when conditions improve. This dormant phase is characterized by cell cycle arrest with 2N DNA, condensed chromosomes, reduced rRNA synthesis, decreased translation and decreased cell size [14]. Interestingly, non-neoplastic tissues including stem cells, eggs, spores and seeds respond similarly during conditions unfavorable to proliferation [28], accumulating DNA damage that is then repaired upon entry into cell cycle in the case of quiescent hematopoietic stem cells. In other accounts, such entry of hematopoietic stem cells into quiescence protects them from cytotoxic effects of chronic exposure to cytokines [29]. Survival of other types of tumors during stress-induced growth arrest, following therapy or growth factor withdrawal, depends on activation of stress and autophagy signaling pathways as well as survival signals (e.g. decorin) from the micro-environment (Fig. 3a) [30, 31]. Indeed, during dormancy, tumor cells are characterized by decreased rates of protein synthesis (via decreased MTOR activity) (Fig. 3c) and

#### Autophagy as a regulator of dormant tumour cell metabolism and survival



**Fig. 3** Autophagy as a regulator of dormant tumour cell metabolism and survival. Treatment-induced dormant tumour cells lack adequate growth factors and nutrients and in a context-dependent manner, rely on compensatory signals from the extracellular matrix (ECM) and catabolic processes, such as autophagy, for energy and survival. (a) Decorin (DCN), a partial agonist of VEGFR2 induces autophagy through activation of AMPK and the association of the autophagy-initiation complex (Beclin interactome). (b) AMPK is activated by nutrient deprivation and low AMP/ATP ratios, as well as by LKB1 and CaMKKB which also induce autophagy. AMPK also inhibits ACC2 thus stimulating Fatty Acid Oxidation as a fuel source. (c) Decorin, binds EGFR and inhibits EGFR activation of MTOR, an inhibitor of ULK1 and autophagy



macromolecule synthesis [14]. To compensate for these deficiencies, dormant tumor cells may activate energy-sensing pathways including LKB1/AMPK-induced autophagy for the breakdown of macromolecules that allow them to reclaim energy and metabolites (Fig. 3b). The supply of these macromolecules can either be intracellular or come from a repertoire of matrix constituents (e.g. collagen network, decorin, laminin) [31]. Additionally, stress-response transcription factors (ATFs) and forkhead box subclass O3 (FoxO3) may enhance survival of dormant cells by activating PI3K/Rheb/MTORC1 pathway in a context-dependent manner, thereby enabling these cells to adapt to their new environment [30].

## Regulation of Metabolic Dormancy

The non-genetic component of metabolic dormancy attributed to stromal influences or metabolic intermediates cannot be underestimated as it can affect the final outcome of tumor fate. The hiding dormant niche can be exposed to differential vascularization that expose the tumors to varying spatial and temporal gradients of nutrients (energetics), oxygen (HIF1-induction in low concentrations), and pH (lactate secretion causing local acidification) [42, 43]. The alteration in metabolic pathways in dormancy is likely stimulated to adapt to such dynamic and energetically stressful conditions.

Both metabolic and proteostatic stress sensors are essential to adaptation to environmental stimuli such as therapy. These include transcription factors that regulate ER stress (i.e. IRE1 $\alpha$ , PERK, ATF6, and XBP-1) or chaperones regulating the unfolded protein response (BiP, Grp78, HSP70 and -90) [44, 45]. Apart from these, metastasis-related transcription factors such as p53 loss [46], Sharp-1 [47], and NR2F1, regulated by the p38/ERK pathway, are also responsible for quiescence or cell cycle arrest of squamous carcinoma cells *in vivo* [48, 49]. P38 mitogen-activated protein kinase (MAPK) is one of the signaling pathways responsive to the stress stimuli and have been shown to be activated in quiescent tumor cells [49]. In hematopoietic stem cells, P38MAPK pathway restricts their cycling and promotes their entry into dormancy in the bone marrow niche [50].

Additionally, ROS and MTOR signaling pathways have also been associated with switching to a quiescence state in hematopoietic stem cells [51–53].

The Myc family of oncogenes are other transcriptional regulators of tumorigenesis, including genes involved cell growth and metabolism. However, depletion of Myc has varying effects in a context-dependent manner. For example, in mouse embryonic stem cells, inhibition of Myc decreases transcription of several genes leading to reversible cell cycle arrest and biosynthetic quiescence/dormancy [54]. Furthermore, highly quiescent dormant hematopoietic stem cells survive in a Myc-depleted environment whereas all other hematopoietic cells undergo apoptosis [55].

Apart from metabolic enzymes that act as tumor suppressors and oncogenes (e.g. succinate dehydrogenase, fumarate hydrogenase, isocitrate dehydrogenase among others), secondary metabolites and metabolic pathways in the context of tumor dormancy, one should also consider the two main regulatory axes of energy sensing: (i) PI3K/Akt/

mTORC and (ii) LKB1/AMPK/Autophagy. The well-characterized PI3K/Akt/MTOR pathway lies directly downstream of receptor tyrosine kinase (RTK) activation regulating glucose transporters, fatty acid synthesis, and growth. The AMP-activated protein kinase (AMPK), on the other hand, senses changes in the cellular ratio of AMP to ATP, allowing for adaptation to a metabolic stress. Under energetic stress, liver kinase B1 (LKB1), a tumor suppressor, regulated by AMPK, further regulates the signaling axis of metabolic control. As outlined in Fig. 3, these opposing pathways appear to be actively involved in regulating cellular dormancy or quiescence [56, 57].

The dormancy phase of cancer brings a renewed interest for the role of cellular metabolism and reappraises the notion that metabolic dormancy is a key feature of cancers that survive in their niche post therapy. It further proposes a renaissance for the potentials of metabolic targeting that have escaped scrutiny over the years.

Although we can expect that the metabolic rewiring during dormancy can revert back to that of normal proliferating cells, the dormant cells are presumably aberrantly driven by a combination of genetic lesions and non-genetic factors such as the tumor microenvironment [32]. For this reason and the inherent context-dependent heterogeneity of tumors, a single model of altered tumor metabolism does not describe the sum of metabolic changes that can support cellular quiescence. Thus, better understanding of metabolic dormancy can enable the development and optimization of therapeutic strategies that target tumor metabolism.

## Technological, Biological, and Clinical Challenges to Study Metabolic Tumor Dormancy

The glycolytic activity of tumors is commonly exploited clinically by 18F-deoxyglucose positron emission tomography (FDG-PET). Radiolabeling of 18F-deoxyglucose helps in detecting tumors precisely by virtue of their enhanced ability to take up and metabolize glucose compared to normal tissue. However, the challenge with dormant tumors be it disseminated or residual, is that they are few in number, have minimal metabolic activities, and are often hidden from non-invasive detection (e.g. scanning technologies or blood stream circulation in the case of CTCs). Thus, the lack of drugs to target tumor dormancy and more specifically metabolic dormancy arises because of a lack of a mechanistic understanding of the dormancy phase and a lack of models for screening for new drugs that target this phase of cancer progression. Unfortunately, there are few cell lines that can exhibit a dormant phenotype in experimental mice partly because commonly used cell lines are selected for rapid metastatic ability. Hurst et al. has recently compiled recently compiled existing *in vitro* and *in vivo* models for dormancy for bone, lung, breast, ovarian, and pancreatic cancer [58]. We also wish to point to the existing models of patient-derived cell and tumor xenografts in prostate cancer [8, 9]. These *in vitro* and *in vivo* models can be therapeutically treated to enter a therapy-induced dormancy phase and so offer an improved alternative for the study of metabolic dormancy [1, 9] and understanding the inherent heterogeneous diversity of different cancer types. These models can be used for biochemical, transcriptomic, and metabolomics studies, not entirely dissimilar to approaches used for cancer stem cell



investigations [59–63]. These studies are expected to refine cancer-specific dormant cell markers that allow sorting of cells to a high purity for functional *in vitro* assays or *in vivo* re-transplantations. Beyond these studies, suitable models for tumor metabolism *in vivo* such that it mimics the physiological conditions of the microenvironment are extremely rare [64]. The metabolic dependencies and liabilities within a given tumor cell should then ideally guide the utilization of specific radiolabeling and technology requirements. This is further exacerbated by the challenges involved in designing clinical trials that address tumor and cellular dormancy. Although these reasons hamper the development of new approaches to *in vivo* metabolic analyses, there are several breast cancer clinical trials designed for studying breast cancer progression following adjuvant treatments, i.e. TEACH [64, 65], HERA trial [66], or metastatic prostate cancer progression in NCT00309985 trial [67]. Thus, recognition of tumor dormancy complexity aided by the progress of various “omics”-based strategies ideally leads to the continued exploitation and integration of imaging technologies.

## Premise of Therapeutic Targeting of Metabolic Dormancy

Given that metabolic reprogramming in cancers is widely recognized, therapeutic targeting of this rewiring has garnered significant attention and investigation. However, there remains a vast disconnect between identification of dormant tumors and the design of appropriate clinical trials. Targeting of tumor dormancy, therefore, remains an elusive field of research. This is expected for the difficulty of detecting and targeting this phase of cancer. Some of the first-line chemotherapeutic agents, such as nucleoside analogues and antimetabolites that target the direct inhibition of enzymes used in DNA synthesis, are no longer feasible for dormancy. Other therapeutic opportunities explored for cancers, small-molecule inhibition of key enzymes involved in metabolic pathways such as glycolysis and fatty acid synthesis, offer limited potential. These strategies are equally unspecific and irrelevant in the context of dormancy. Therefore, we need to rethink the development of strategies that target this ‘therapeutic window’ of cancer. One crucial consideration that remains common in the development of anticancer therapeutics irrespective of dormancy is to the extent to which a given drug can achieve its intended mechanism of action without additionally exerting unacceptable toxicities for normal cells. This is especially relevant as any targeting strategy for the dormancy phase will be aimed either for long-term maintenance of dormancy without stimulating a malignant evolution (let the sleeping dogs lie) or killing the cells as they sleep [64].

## Conclusions

The collection of advances made in our understanding of tumor metabolism in recent years is not sufficient for targeting metabolically dormant cancer cells. Therefore, a better understanding of the diversity of mechanistic adaptations and context-dependent

determinants that can drive metabolic rewiring of dormant cancer cells is direly required. As our understanding of dormant tumor metabolism continues to evolve by advances in analytical technologies and animal models, we can progress in capitalizing upon the exploitation of their atypical metabolic features. Finally, distinguishing the interplay between genetic and microenvironmental elements of tumor dormancy can serve as critical factors in determining therapeutic targets that enable maximal drug efficacy and minimal deleterious effects on normal cells.

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**Conflicts of Interest** The authors confirm that there are no conflicts of interest.

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