From Worms to Tumors: Conserved Strategies of Cellular Arrest and Survival Governing Dormancy

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ABSTRACT

The recurrence of metastatic lesions months to years after the treatment of primary cancers remains a major contributor to cancer-related mortality, highlighting the need to better understand the mechanisms that govern dormancy and dormancy reawakening. A major hurdle is the lack of adequate *in vitro* and *in vivo* models to dissect the complex cascades that trigger tumor cell dissemination, adoption of the dormant state, or tumor cell outgrowth in the new metastatic microenvironmental niche. However, many organisms use dormancy to survive stressful environments or periods of nutrient deprivation. Of these, the dauer state of the free-living nematode *Caenorhabditis elegans* has unparalleled characterization. In this study, we discuss the remarkable physiologic, signaling, genomic, and metabolic similarities between dormant cancer cells and *C. elegans* dauers, arguing for the use of dauers as a facile model to help dissect dormancy and reawakening pathways in cancer cells.

Introduction

The cancer treatment field can take solace that treatment innovations for many primary cancers have increased survival rates over the first 5 years. However, the vast majority of cancer-related deaths are associated with disease recurrence, typically at distal sites, months to years after "successful" ablation of the primary disease. The increased aggressiveness and therapeutic resistance of metastatic disease often correlate with the acquisition of additional oncogenic driver mutations and epigenetic changes over those found in their primary lesions (1, 2). Inherent to this process of cancer recurrence is the ability of disseminated cancer cells to either adapt to or be selected for dormancy-related transcriptional and metabolic programs. The dormant state renders tumor cells resistant to treatments that target cell proliferation and glycolytic pathways, allowing them to evade the stress of novel microenvironments and protecting them from attack by multiple classes of immune cells (3). However, there remains a poor understanding of the genes and pathways that induce and maintain dormancy, as well as those that induce macrometastasis progression following dormancy reawakening (4). Indeed, long-term patient survival would benefit from identifying actionable pathways that might, for example, greatly delay reawakening. This gap in understanding is largely because of the difficulties inherent in identifying and characterizing dormant cancer cells in sufficient numbers *in vivo*, the paucity of biomarkers, and the primary use of static IHC markers, such as Ki67 or TUNEL staining, which limits insights into a dynamic process that likely underlies cellular dormancy. An additional challenge is that *in vitro* dormancy models that reflect *in vivo* microenvironmental niches involve multiple primary cell types with limited passage numbers and complex growth media conditions (5). Thus, novel approaches are required to identify and characterize dormancy and reawakening programs of disseminated tumor cells in a systematic and unbiased manner so that driver pathways can be elucidated and then therapeutically targeted.

Several organisms, plants, invertebrates, and even vertebrate species such as the killifish naturally undergo dormancy during their life cycles (6). Although the term "dormancy," when applied to a metazoan is challenging to define, it is typically used to describe cellular, metabolic, and physiologic quiescence to varying degrees that enhance survival in temporarily hostile environments. In some cases, dormancy programs can be a constitutive part of development, shaped by evolutionarily selected advantages of colonizing unique habitats. In other cases, dormancy can be a facultative survival mechanism triggered by stressful conditions such as food deprivation or exposure to extreme environmental conditions such as high temperatures or drought. In most cases, the extent of dormancy can vary between different individuals or sexes of a species and even amongst the different cells and tissues of the organism, ranging from simple metabolic flexibility to metabolic suppression, hypometabolism, diapause, or full dormancy. Thus, estivation, brumation, torpor, and hibernation are all dormancy-related programs that allow organisms to temporarily and systemically arrest or slow cell division, decrease metabolic requirements, and postpone growth and development to best fit a changing environment (7). These varying dormancy-related programs depend on intrinsic or extrinsic factors. For instance, in some species of root-knot (*Meloidogyne* spp.) and cyst (*Heterodera* spp. and *Globodera* spp.) nematodes, a portion of the eggs hatch quickly, whereas others hatch slowly over time, depending on the temperature, intrinsic levels of natural anti-desiccation factors such as trehalose, the host plant, or root leachate (8–10). In the context of cancer, as pointed out by Miller and colleagues (5), dormancy can also arise from either nonproliferating disseminated tumor cells or small metastatic foci with similar levels of proliferation and apoptosis, or through ultra-slow cycling cells, which, although refractory to antimitotic drugs, are not arrested in G_0 (11). Although all these "dormant" cell types are clinically undetectable, their metabolic states may differ drastically, as would their therapeutic vulnerabilities. As will be

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described, these states are regulated by tumor-intrinsic and environmental (tumor-extrinsic) mechanisms.

The inherent reversibility of cell-cycle arrest by individual cells or cell clusters in fast-dividing cell populations (12, 13) is an important hallmark of tumor cell dormancy, as this capability could result in disease recurrence (14). This distinguishes dormancy from senescence, which in most cases is considered irreversible (15). Examples of dormancy/diapause mechanisms that temporarily suspend cell-cycle progression include hematopoietic stem cell diapause, which minimizes the damage induced by cell division and metabolic activity, or embryonic diapause to optimize postimplantation development (16). This contrasts with the senescence of pancreatic β cells, a contributor to types of diabetes in humans: cells enter an irreversible cell-cycle arrest and lose the ability to produce insulin but retain continued metabolic activity. This influences niche environmental cells through the secretion of senescence-associated factors (17).

A compelling genetic model in which diapause and dormancy mechanisms have been extensively characterized is the dauer state in the free-living nematode *Caenorhabditis elegans* (bioRxiv 2024.08.15.608164; refs. 18–21). Nematodes are the most abundant metazoan species on the planet (22) and have colonized all trophic levels in the food web (22, 23). Amongst the mechanisms that facilitate their dispersal, survival, and adaptation to diverse, unpredictable, and often hostile niches are forms of dormancy or hypobiosis, marked by elongated or slow-cycling developmental stages, as in the case of the extraordinary nematode *Scottnema lindsayae*, in which individuals have survived for decades through anhydrobiosis in the McMurdo Dry Valleys of Antarctica (24).

A specialized form of dormancy is a developmental diapause called "dauer," an alternative to the third larval stage of "normal" developmental progression (25, 26). Although *C. elegans* are not slow-cycling and reproduce prolifically (more than 300 progeny per individual within 4 days of adulthood under optimal conditions), individual larvae readily enter dauer in response to harsh environmental conditions (26, 27). Dauer is an example of dramatic phenotypic, epigenetic, and transcriptional plasticity associated with the extensive tissue, gene expression, metabolic, and behavioral remodeling required for the extended survival and colonization of new niches. During dauer arrest, all cells of the larvae exit the cell cycle and remain in G_0/G_1 (and sometimes G_2) for periods lasting more than 6 months compared with the normal ~20-day lifecycle (~500–700 cells are present at the stage when the dauer decision is made, and these cells constitute all tissue types such as intestine, neuronal, and muscle). Larvae exit dauer and resume development into reproductive adults when favorable conditions return but retain an epigenetic imprint of passage through dauer that alters various aspects of their subsequent physiology, reproductive capacity, stress resistance, and behavior (described in greater detail below).

The molecular mechanisms that mediate dauer are strikingly similar to the regulatory pathways found in cancer cell dormancy and reawakening (**Table 1**). In this review, we will briefly describe these commonalities and also describe conditions in which dauers and dormant tumor cells differ. It is important to note that the *C. elegans* dauer arrest *per se* may only share mechanistic similarity to tumor cells adopting quiescence (full cell-cycle arrest) or possibly to ultra-slow cycling tumor cells but not to micrometastases with dynamic equilibria between proliferating and dying cells. However, other developmental stages of *C. elegans* can undergo dormancy, which may differ in duration or completeness. For example, larvae at stage 1 (L1) slow their metabolic activity and cell-cycle progression if food is scarce, delaying progressing into larval stage 2 (L2) for 2 weeks (instead of 12 hours); adult *C. elegans* deprived of nutrients adopt a reproductive diapause state involving decreased energy requirements, increased lifespan, and selective pauses in germline cell-cycle progression (27–29). These partial diapause-like states likely arise amongst proliferating populations but are less well characterized.

The tremendous overlap in mechanisms between dauers and dormant tumor cells, the amenability of *C. elegans* to genetic analyses, its defined cell numbers and fates, and well-described developmental stages suggest that analyzing mechanisms in the dauer larvae could substantially accelerate our ability to identify mechanisms that control cancer cell dormancy (**Fig. 1**). *C. elegans* are hermaphrodites, i.e., essentially females that make a limited amount of sperm, which is stored and used to self-fertilize oocytes. Barring low-frequency spontaneous mutations (estimated to be approximately 2.8×10^{-8}/generation in a genome of roughly 2×10^9 bases; ref. 30), they are a clonal population. Dauer onset within populations of *C. elegans* can be efficiently and synchronously triggered when starting with developmentally staged embryos or signaling pathway mutants, producing large numbers of larvae synchronized in their arrest. These features provide a foundation for dissecting the molecular underpinnings of cancer dormancy using dauers.

Molecular Mechanisms and Pathways Triggering Dormancy

Specific hallmarks have been used to define dormant cancer cells as described in recent reviews (4, 14, 31–33). *C. elegans* dauers also exhibit shared "hallmarks," i.e., stereotypic phenotypes, behavior, physiologies, metabolism, and transcriptional signatures irrespective of the trigger that induces dauer entry (bioRxiv 2024.08.15.608164; refs. 18, 19, 21, 27). The hallmarks of cancer dormancy that share parallel mechanisms to *C. elegans* dauer larvae formation include some or all of the following.

Triggers for dormancy

Cancer

The induction of dormancy (and reawakening) is typically dependent on cell-intrinsic mechanisms as well as extrinsic signals from the microenvironmental niche. The intrinsic mechanisms typically involve the suspension of conserved pathways required for cell-cycle progression and proliferation during normal development and growth of organisms, whereas extrinsic mechanisms include cytokine signaling from the microenvironment, hypoxia, or the availability of nutrients required for survival and proliferation. An example of a tumor-intrinsic dormancy-inducing factor is the urokinase receptor, uPAR, which can induce dissemination and dormancy at peripheral sites (34). Because it is difficult to recapitulate the complex cross-talk between tumor and microenvironmental cells in *in vitro* dormancy systems, many tumor-intrinsic pathways typically linked to proliferation and metastatic progression may also foster dormancy given the appropriate environmental context. For example, the ubiquitous PI3K/AKT pathway activated by external growth factors through receptor tyrosine kinase and G-protein–coupled receptors is indispensable for normal cell proliferation. Hyperactivation of this pathway can drive tumor growth. Yet there is a paradoxical relationship between AKT activation levels and dormancy: whereas some studies show that cancer cell

Table 1. Shared/overlapping genomic and metabolic pathways controlling the entry, maintenance, and exit from tumor dormancy vs. the *C. elegans* dauer state.

Dormant cancer cells	*C. elegans* dauers
Formed by individual cells or cell clusters within fast-dividing cell populations (12, 13)	Formed by individual larvae in fast-reproducing populations of individuals (21, 27, 66)
Formed in response to stressors in the tumor microenvironment (123)	Formed in response to ecological factors, e.g., nutrient scarcity, high temperatures, or high population densities (21, 27, 66)
Triggered by antitumor immune response (3)	Triggered by host immune response in parasitic nematodes (23, 25, 191)
Reversibly arrested in the G_0/G_1 phase (183)	Cells in animals reversibly arrested in the G_0/G_1 phase (72, 75, 81, 94, 96, 98, 104)
Upregulate cell-cycle inhibitors, e.g., p21, p27, and GAS1 (240)	Upregulate cell-cycle inhibitors, e.g., p21/p27 ortholog *CKI-1*, growth arrest–specific (GAS1) ortholog *PHG-1* (21, 72, 78, 82, 93–102)
Exhibit a lowered metabolic state (111, 112)	Exhibit a lowered metabolic state (21, 26, 69, 72, 126–129)
Adapted for dispersal and stress survival (123)	Adapted for dispersal and stress survival (21, 27, 66)
Long-lived (57)	Long-lived (26, 75, 127)
Use of anaplerotic pathways for metabolism (111)	Use of glyoxylate pathway (anaplerotic TCA pathway for gluconeogenesis; refs. 69, 129, 136)
Compacted chromatin (141)	Decrease in active chromatin marks (150, 151)
Activate unfolded protein response (114)	Activate unfolded protein response (18, 21, 73)
Triggered by downregulated AKT signaling (40)	Triggered by decreased insulin receptor/AKT signaling (21, 27, 66)
Triggered by dysregulated TGFβ signaling (45, 46)	Triggered by decreased TGFβ signaling (21, 27, 66)
Increased autophagy (116–120)	Increased autophagy gene expression (126, 128, 129)
Activate p38MAPK and increase expression of 38MAPK-downstream targets (54)	Activate p38MAPK and increase expression of p38MAPK-downstream targets (73, 102)
Low ERK activity (31, 54)	Decreased ERK target expression (97)
Reawakening depends on downregulation of FOXO1/3A/4, SMAD4, PTEN, activation of steroid hormone, and mTOR signaling (37, 38, 47, 49, 84, 146, 149)	Dauer exit and proliferation depend on loss of p53/CEP1, FOXO/DAF-16, SMAD4/DAF-3, Ski oncoprotein/DAF-5, PTEN/DAF-18, activation of cholesterol metabolism, steroid hormone, and mTOR signaling (95, 98, 102, 106, 107)
Disseminated cancer cells that resume growth typically form aggressive metastasis and phenotypic plasticity (214, 232)	Dauers that exit and resume reproductive growth display phenotypic plasticity and enhanced reproductive capabilities (150, 151)
Reawakening depends on the microenvironment (58)	Dauer exit depends on favorable environmental conditions but occurs stochastically even under continued stress (21, 27, 66)

dormancy is favored by low levels of AKT or mTOR (35–37), or by interactions between the PI3K–AKT suppressor, PTEN, and the G_2/M checkpoint kinase, ATM (38), others show that sustained AKT–mTOR signaling maintains dormancy (39–41). Wnt5a can promote parameters of oncogenic progression under certain circumstances while also inducing metastatic dormancy in cancer cells (42–44). TGFβ signaling can induce or suppress tumor cell dormancy in a context-dependent manner, depending on the cancer cell type, its niche, the use of TGFβ1 versus TGFβ2, and the activation of TGFβ co-signaling pathways (45–47). Bone morphogenic protein 7, another TGFβ family member, induces cell-cycle arrest in prostate cancer stem-like cells when they disseminate to the bone (48). SMAD4, a downstream mediator of TGFβ signaling, prevents macrometastasis formation in prostatic intraepithelial neoplastic cells induced by the loss of PTEN (49). Lastly, early models indicated that p38αMAPK was required for the metastatic potential of breast cancer cell lines (50–53), although these models lacked inherent dormancy phenotypes. In contrast, there are multiple studies showing that high p38αMAPK activity, concomitant with low ERK1/2 MAPK activity, is a requisite for dormancy in many tumor systems (reviewed in ref. 54). Albeit poorly understood, cancer types that exhibit early dissemination activity, even at early stages of primary tumor development, are associated with the early establishment of dormancy niches (55–57). The fact that some pathways can function as core regulators of proliferation and survival, as well as inducers and sustainers of dormancy, suggests that their role in dormancy is dependent on context (e.g., microenvironmental niche) and temporal effects (e.g., stage in the metastatic cascade or aging; ref. 58). For example, expression of the integrated stress response kinase, PERK, is required for the reawakening of ultra-slow proliferating micrometastases, yet it is involved in many other endoplasmic reticulum (ER) processes (59).

C. elegans

Similar to dormant tumor cells, dauer induction in *C. elegans* can also be triggered by extrinsic stimuli or intrinsic growth signaling pathways (27). The extrinsic signals are stress conditions that limit growth and proliferation. Dauer entry is a regulated process, and although dauers are developmentally equivalent to larval stage 3 (L3), the decision to enter dauer is made early, during L1. Larvae prepare for diapause by slowing development and accumulating fat in their intestines and epidermis (hypodermal cells; refs. 60–62). Early studies identified three types of extrinsic stimuli that promote dauer entry: high temperatures, limited food availability, and crowding (either by conspecifics or other related nematode species), which are likely to occur concordantly or in some combination in natural populations. Subsequent work has uncovered several other dauer-inducing stimuli such as hypoxia (and activation of HIF1 alongside heightened temperatures), cold temperatures, severe desiccation (anhydrobiosis), pathogen exposure, and changes in osmolarity (63, 64). In addition, interspecies competition has

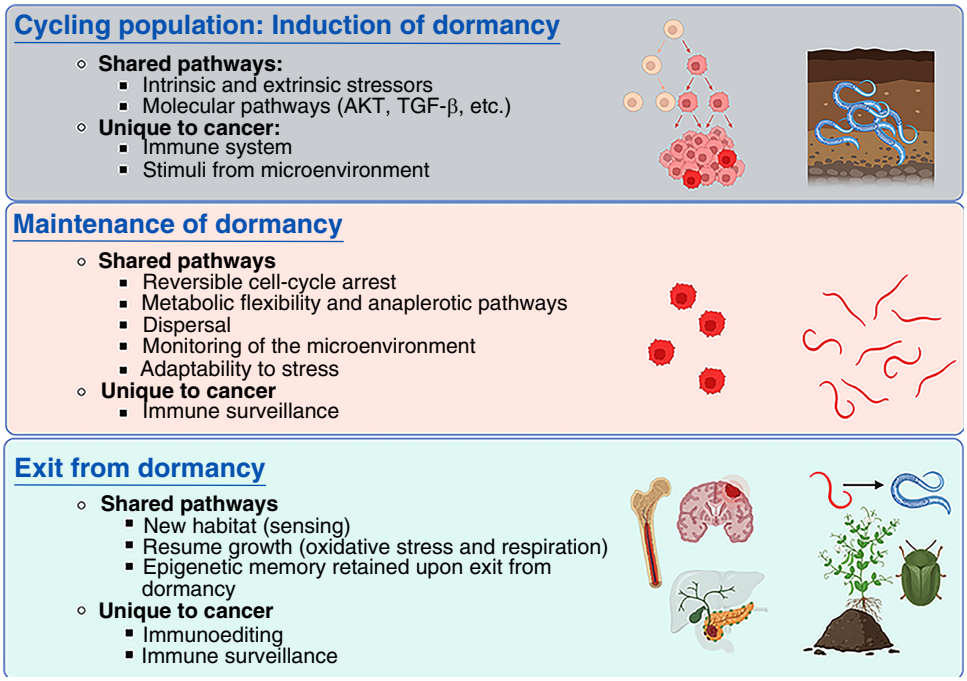

Figure 1.
Similarities and differences between dormant tumor cells and *C. elegans* dauers.

recently been shown to induce dauer arrest through complex chemical cross-talk (65).

The intrinsic mechanisms that induce dauer are also related to interrupting cell-cycle progression. To complete development, larval cells require an almost continuous assurance of optimal conditions. This is provided by growth-promoting signals released by sensory neurons and associated cells during early larval stages; disruption of the neuronal activity that triggers secretion or the direct disruption of neurosecretion, or dysregulation of downstream signaling pathways that transduce these growth signals, all trigger dauer arrest (18, 21, 62, 66–69). The best studied of these signaling mediators are the insulins [mediating insulin-like signaling (ILS)], cytokines such as the TGFβ ligand (DAF-7), cholesterol-derived steroid hormones, and more recently, IL17 (ILC-17.1). ILS is a critical regulator of growth, such that downregulated insulin signaling (decreased expression of the insulin receptor ortholog gene, *daf*-2, or decreased DAF-2 activation resulting in decreased AKT signaling) induces dauer arrest. Likewise, decreased TGFβ ligand or type I and type 4 receptor activity, or activation of the SMAD family of TGFβ signaling effectors, trigger dauer arrest. TGFβ signaling also promotes dauer entry by signaling through LIN-40 and BLMP-1, whose human orthologs, metastasis-associated protein 1 and BLIMP-1, function as prometastasis transcription factors (27, 70, 71). Other triggers include (i) decreased expression and secretion of the IL17 cytokine ortholog, ILC-17.1, leading to the activation of the *C. elegans* p53 ortholog, CEP1 (72), (ii) activation of stress-activated MAPK signaling pathways (73), (iii) activation of ER stress or the unfolded protein response (74), and (iv) disruption of tissue remodeling induced by the activation of vitamin D steroid nuclear hormone receptor (DAF-12/vitamin D receptor; refs. 21, 75) by cholesterol-derived dafachronic acids (60, 68, 76). In low dafachronic acid conditions, DAF-12 forms a complex with DIN-1S/SPEN (77, 78), an ortholog of SHARP1/DEC2/BHLHE41, a known cancer dormancy-inducing factor (bioRxiv 2020.04.13.037374; refs. 45, 79, 80), resulting in decreased reproductive programming and increased dauer entry. Under these conditions, DAF-12 also induces the upregulation of the *let-7* microRNA pathway that controls a heterochronic circuit of stage-wise temporal changes during development (81).

Induction of cell cycle arrest

Cancer

Cancer cell dormancy involves the G_0/G_1 phase arrest, with cells adopting quiescence or low proliferative indices while retaining proliferative capacity. Cell-cycle progression is inhibited by the upregulation of cyclin-dependent kinase (CDK) inhibitors (CKI) such as p21 and p27, marked by the downregulation of proliferation markers such as Ki67 and proliferating cell nuclear antigen. The upregulation of CKIs is facilitated by a simultaneous decrease in the activity of ERK and the upregulation of p38MAPK (54). This contrasts with the role for ERKs in inducing cellular proliferation through stabilization of MYC, induction of cyclin D1, and suppression of CKI expression (82). Similarly, activation of the PI3K–AKT signaling axis facilitates proliferation by inhibiting glycogen synthase kinase 3-β, preventing the nuclear localization of FOXO transcription factors, and promoting CDK activity. In contrast, the loss of this signaling axis leads to the nuclear localization of FOXO transcription factors, destabilization of cyclin D, induction of CKI expression, and mitotic arrest (83). Interestingly, amongst the FOXO factors, FOXO4 uniquely encodes metastasis-suppressing activity that functions through the inhibition of the PI3K/Akt axis (84).

Another control axis for cell-cycle arrest in cancer cells is through the ability of the tumor suppressor, LKB1/STK11, to phosphorylate and activate the cAMP-activated protein kinase, AMPK (85). Loss-of-function mutations in *STK11* are found in up to 30% of non–small cell lung cancers driven by oncogenic *KRAS* (86), whereas the

upregulation of LKB1-AMPK signaling in metastatic epithelial ovarian cancer cells increases dormancy-like cellular quiescence and autophagy in spheroids (87).

C. elegans

Several parallels exist between the mechanisms that induce cell-cycle arrest in dauers and those during cancer dormancy. The adult *C. elegans* hermaphrodite and male possess 959 and 1,031 somatic cells, respectively (germ cell numbers are more variable, and they divide throughout the animal's lifespan). When the developmental decision for dauer arrest is made during L1, many of these cells (~500–700 at this stage) have differentiated and exited G_1 or are either in the process of completing division or differentiating (88–91). However, a subset of larval somatic cells (ventral somatic progenitor blast cells or P cells and stem cells of the epidermis, called seam cells) and all germline cells have stem-cell or stem-like properties, namely the ability, with continued development, to generate neurons, epidermis, vulva, germline, oocytes, or sperm (88, 89, 92). Upon dauer entry, all these cells exit their ongoing cell-cycle programs, arrest in G_1, and maintain the ability to continue dividing and differentiating when conditions become favorable (18, 21, 93). Cell-cycle inhibition in these cells is activated by different pathways in the different cell types involving (i) the upregulation of members of the CIP/KIP family of CKI, (ii) the upregulation of the mammalian GAS1 ortholog PHG-1, and/or (iii) the downregulation of *CYD1* (cyclin D ortholog) or *CDK4* (CDK4 ortholog). The increased expression of the cell-cycle inhibitors or decreased cyclin D expression occurs downstream of (i) the PI3K–(PTEN)–AKT pathway, through its increased phosphorylation of the sole FOXO ortholog, DAF-16; (ii) alterations in the TGFβ pathway and increased activity of DAF-5 (an ortholog of the mammalian SKI oncoproteins) that cooperates with SMADs to alter gene expression; (iii) downregulation of EGFR–RAS–ERK activity in specific P blast cells (P6.p), which in turn, also decreases cyclin D1/CDK activity; (iv) decreased cytokine ILC-17.1 signaling that leads to the activation of the *C. elegans* p53 ortholog, CEP1 or (v) reprogramming by the conserved RNA-binding protein LIN-28 that regulates microRNAs that control developmental timing (27, 72, 78, 81, 94–97).

Germline stem cells undergo a G2 cell-cycle arrest also mediated by ILS, but unlike arrest in somatic cells, larvae fated to enter dauer use TGFβ-dependent AMPK signaling for germline arrest. Activated AMPK cooperates with the activator PAR-4, the LKB1 ortholog, to modulate DAF-18, the PTEN ortholog, and to coordinate ILS to arrest germline proliferation (78, 98–101). Similarly, TGFβ/bone morphogenic protein blocks neuroblast divisions by inhibiting the PP2A–MAPK axis in a DAF-18/AMPK–dependent manner, and decreases Q neuroblast cell division (another P blast cell that differentiates during L1 but arrests in dauer; ref. 102).

As with tumor cells, the G_0/G_1 phase arrest of dauers is reversible as demonstrated using the cell-cycle reporter, FUCCI (103, 104). Indeed, the dauer state induced by the loss of TGFβ signaling in *daf-7* mutants (105) can be overcome by the subsequent loss of *daf-18*/*PTEN* (106, 107). Likewise, dauer induction in *daf-2* (*IRS1*) and *age-1* (*PI3K*) mutants can be suppressed by a GTPase-activating mutation in *let-60/RAS* (n1046gf; refs. 27, 107). Dauer larvae upregulate the expression of thymidylate synthase, an enzyme crucial for DNA synthesis (108), right after nutrient supplementation, presumably to prepare for S phase induction leading to dauer exit. It is noteworthy that high thymidylate synthase levels correlate with worse clinical outcomes in cancer (109).

Decrease in anabolic pathways such as protein synthesis and respiration, and alterations in energy metabolism

Cancer

Decreased or altered cellular metabolism, such as decreased energy production, protein translation, activation of ER stress or the unfolded protein response, activation of autophagy pathways, utilization of anaplerotic pathways, or glycolysis, have been identified as hallmarks of tumor dormancy (110–114). The catabolic process of autophagy likely allows dormant tumor cells to adapt to and survive in microenvironments marked by nutrient deprivation (115–120). Thus, tumor cells are more likely to adopt dormancy states in microenvironments that favor reduced metabolic rates and increased resistance to oxidative stress (121–123), or, as in the case of the bone microenvironment, increased hypoxia-driven signaling (124). In addition, dormant cancer cells favor *de novo* lipogenesis for their energy needs, likely as a means to protect themselves from increased sensitivity to oxidative stress (125).

C. elegans

Dauers display alterations in metabolic pathways that parallel effects in dormant tumor cells: gene expression in anabolic pathways involved with energy production and protein translation is downregulated, whereas expression of genes required for catabolic processes such as autophagy is upregulated (72, 126, 127). Moreover, the forced downregulation of autophagy genes prevents dauer entry (128). Pre-dauer (L2d) larvae exhibit declining levels of high-energy phosphate carriers (ATP, ADP, AMP, and pentose phosphates) while maintaining high glyoxylate cycle activity (129), a modified tricarboxylic acid (TCA) pathway cycle that allows microorganisms, plants, and invertebrates to utilize ethanol and acetate as their C_2 source for energy, bypassing CO_2 production (69). Whereas the main enzymes that drive the glyoxylate cycle are absent in most mammalian cells, enzymes that convert fatty acids to acetate and allow the utilization of acetate, as in the glyoxylate cycle, are present in mammalian cells and have been implicated in cancer stemness and dormancy (130, 131). Dauer larvae display a shift from aerobic to anaerobic pathways for carbohydrate metabolism, utilizing anaerobic fermentation to metabolize carbohydrates (26, 27, 69, 132). This also decreases the generation of life-shortening radical oxygen species (ROS) while sustaining sufficient energy requirements during dormancy (132, 133). Glyoxalases, upregulated during dormancy in leukemia (134), detoxify aldehyde by-products of metabolism and are essential for dauer arrest, perhaps by stabilizing mitochondria during cellular stress and starvation (135). Additionally, as with mammalian cells under metabolic and respiratory quiescence, dauers accumulate glycogen as a readily available short-term energy source (69, 136, 137).

As with dormant cancer cells, dauer larvae also upregulate lipid biogenesis pathways (138, 139). Prior to dauer formation, young larvae accumulate triglycerides as intestinal and hypodermal lipid droplets as an energy reserve in response to DAF-16/FOXO and/or AMPK activity (99, 101, 138). NHR-79, an HNF4α nuclear receptor family member, its co-receptor, NHR-49, and AMPK activity prolong the dauer state by modulating how fats are stored and metabolized (99, 139).

Epigenetic changes

Cancer

Several epigenetic changes have been implicated in cancer dormancy. These changes are often variable between different cancer

types and include differential microRNA expression. Hallmarks that contribute to increased levels of compact chromatin during dormancy include (i) increased K20 methylation of histone H4, (ii) alterations in histone isoform expression, (iii) increased H3K9 acetylation at promoters of specific genes such as tissue inhibitor of metalloproteinase-3, and (iv) decreased H3K27 methylation (140, 141). Using models of ovarian cancer cell lines that were induced to become dormant *in vivo* after the forced overexpression of ARHI/DIRAS3, Lyu and colleagues (142) showed that the increased levels of the angiogenesis genes, *TIMP1* and *CDH1*, could be controlled by increased H3K9 acetylation and decreased H3K27 trimethylation, respectively. Variants of the histone MacroH2A (either encoded by *MACROH2A1* and *MACROH2A2* genes or as alternatively spliced transcripts of *MACROH2A1*) induce both dormancy and senescence in head and neck squamous cell carcinoma (HNSCC) models by downregulating E2F and MYC signaling, likely via direct interactions with H3K27me3 and H3K9me3 repressive marks (143). CD49f also regulates HNSCC cell dormancy by suppressing H2K4/K27me3 expression (144). High NR2F1 expression, a hallmark of dormant HNSCC cells, is controlled by decreased promoter hypermethylation (145). NR2F1 also induces dormancy in uveal melanoma models by silencing YAP1/TEAD1 transcription through the alteration of histone H3 marks (bioRxiv 2024.03.05.583565). The ability to suppress metastasis formation using a novel NRF21 agonist strongly suggests that it is a direct dormancy driver (146).

Three groups screened for epigenetic regulators that control the balance between actively proliferating versus dormant tumor cells. Rosano and colleagues (147) used a CRISPR-interference screen that extended to promoters, enhancers, and topologically associating domain boundaries to identify likely areas of chromatin landscape changes and subsequent gene expression changes that correlated with the ability of hormone receptor–positive breast cancer to enter dormancy upon antiestrogen therapy. Chung and colleagues (148) performed a loss-of-function screen for 60 epigenetic regulators, identifying CBX8 as capable of inducing breast cancer progression by upregulating NOTCH signaling through increased H3K4me3 marks in NOTCH-regulated gene promoters. Gao and colleagues (149) identified gain-of-function cDNAs from metastatic mouse 4T1 mammary carcinoma cells that would induce macrometastasis formation by 4T07 cells, which normally only disseminate to lungs from orthotopic sites.

C. elegans

Dauer arrest *per se* is accompanied by a general reduction in active chromatin marks globally or at specific genomic loci (150). However, dauer-specific epigenetic modifications remain to be investigated more thoroughly. As with cancer dormancy, dauer arrest alters H3K4 methylation and H4 acetylation. These changes are not always associated with gene expression changes and are thought to poise genes for future regulation upon dauer exit; post-dauer gene expression changes occur in these poised genes through the activity of other chromatin factors such as the histone deacetylase, HDA-2, and the HP1 orthologs, HPL-1 and HPL-2 (150). Dauer induction can be triggered by several epigenetic pathways: (i) DAF-2/insulin/IGF1 signaling (IIS) and TGFβ signaling pathways that are regulated by HPL-2, and (ii) decreased AKT activation after DAF-2/IIS downregulation, leading to DAF-16/FOXO activation and the regulation of gene expression through engagement with the SWI/SNF complex (151). Other studies have shown that dauer arrest requires H3K20 methylation by the methyltransferase, SET-4, such that the absence of SET-4 prevents dauer formation by activating INS-9–dependent insulin signaling (152).

Molecular Mechanisms and Pathways That Maintain Dormancy

Mechanisms that define the duration of dormancy in cancer cells or dauer larvae have been characterized only with regard to the exit from dormancy; no inherent timing mechanism or "clock" determining the time-in-dormancy has been discovered, although it should be noted that expression of BHLHE41/DEC2/SHARP1, a known regulator of circadian rhythms (153), is required for dormancy maintenance (bioRxiv 2020.04.13.037374; refs. 45, 79, 154). Nevertheless, for cancer cells and dauers to remain in dormancy, they must be able to either respond to prodormancy microenvironment cues or fail to respond to cues that promote proliferation. Additionally, dormant tumor cells and dauers maintain a basal level of metabolism to support their continued pause in nutrient uptake and possess stress resistance mechanisms to survive in novel environments. For cancer, the role of the metastatic microenvironment in maintaining (and inducing) dormancy relates to three major factors: secreted factors induced by the unique interaction between tumor and local cells, cell–cell or cell–extracellular matrix (ECM) interactions, and distal communications regulated by tumor-produced exosomes and extracellular vesicles (EV). The secretome in metastatic microenvironments is akin to the altered nutrient environment or increased stress conditions that induce and maintain diapause in *C. elegans* dauers, as these conditions favor survival through quiescence pathways.

Monitoring of the microenvironment

Cancer

The ability of tumor cells to remodel the local ECM in their disseminated microenvironments contributes to their establishment and maintenance of the dormant state. For example, HNSCC or mammary carcinoma cell variants that produce dormant nodules on chicken chorioallantoic membranes assemble type III collagen matrices (155). Collagen cross-linking is mediated by lysyl oxidase and lysyl oxidase–like enzymes, with high levels associated with dormancy (156). Cross-linked collagen, which induces increased microenvironmental stiffness, a factor that also limits antitumor immune infiltration, signals through DDR1 on tumor cells as well as the expression of DDR2 and integrin α11β1 on cancer-associated fibroblasts (157). Disseminated prostate cancer cells bind annexin II in bone microenvironments, which in turn upregulates the expression of the AXL family and TGFβRII receptors that can induce tumor cell dormancy by responding to GAS6 and thrombospondin-1 secreted by microenvironmental cells (reviewed in ref. 158).

The role played by exosomes and EVs to distally influence microenvironments in order to produce so-called premetastatic niches was described in a landmark study from the Lyden Lab (159). Subsequent research has shown that vesicles contain specific DNA, microRNA, long noncoding RNA, mRNA, and protein cargo that "educates" distal niche cells to secrete chemotactic factors for bone marrow–derived stem cells as well as tumor cell populations (160). How these vesicles influence actively progressing macrometastases versus dormant colonizations remains understudied (158).

C. elegans

Long-term imaging of dauer larvae shows that their nervous systems actively integrate environmental changes that maintain the dauer state until conditions are favorable for exit (161), whereupon they switch to a highly mobile state. In the absence of nutrient signals, the behavioral switch is reversed, and dauers reenter their

immobile state. The behavioral adaptation of *C. elegans* dauers, called nictation, further allows dauers to explore their environments and "hitchhike," i.e., adhere, onto other organisms for dispersal (162). This latter activity requires KPC-1, the *C. elegans* ortholog of Furin, which plays a role in cancer cell invasiveness (163). As with dormant cancer cells, dauers are also known to secrete EVs that can alter the physiology and metabolism of recipient nematodes (164). However, whether the EVs play a role in altering the microenvironment is still to be investigated.

Metabolic flexibility and anaplerotic pathways

Cancer

The shift from active proliferation by primary tumor or reawakened dormant cells to dormancy is associated with a massive shift from anabolism to catabolism (110). Under anaplerosis, energy-consuming pathways such as glycolysis, TCA, serine synthesis, and the pentose phosphate pathway are facilitated by normoxic microenvironments enriched with nutrients and oxidized lipids. In contrast, hypoxic microenvironments deficient in nutrients or damaged by cytotoxic chemotherapies facilitate increased catabolic pathways in tumor cells that favor dormancy, such as those governing fatty acid oxidation, oxidative phosphorylation, and autophagy (111, 112). Some targeted treatments, such as the use of CDK4/6 inhibitors for BRAF/MEK inhibitor–resistant $BRAF^{V600E}$ melanomas or recurrent hormone receptor–positive breast cancers, may select for dormant cells by inducing long-term G_0 arrest marked by increased glutamine metabolism and fatty acid oxidation that fuels oxidative phosphorylation–mediated energy production (165, 166). Alhasan and colleagues (37) argue that the increased expression of FOXO genes induced by environmental cues in pro-dormancy niches facilitates tumor cell dormancy by increasing autophagy gene expression and suppressing mTOR activity, a similar scenario that occurs with diapausing embryonic stem cells.

C. elegans

Dauer larva shift toward catabolic pathways over anabolism, and they also downregulate mTOR and activate autophagy. In addition, they utilize alternative carbon sources to maintain their dauer state. These alternative sources enter the intermediary metabolic network, well-conserved among eukaryotes. For instance, larvae can convert external ethanol to acetone to enter the TCA cycle and other metabolic pathways (167). The toxic byproducts of ethanol metabolism are thought to be neutralized by the overactive anti-ROS defense and detoxification systems of dauers (21, 168). Dauers also use both DAF-16/FOXO and AAK-2/AMPKα to facilitate the use of glutamine and lipids as carbon sources (137). The upregulation of alcohol dehydrogenase, aldehyde dehydrogenase, and inorganic pyrophosphatase enables dauers to utilize alternative high-energy sources (132, 169); dormant tumor cells also express increased levels of aldehyde dehydrogenase (170). In addition, by entering a gluconeogenic mode of metabolism, dauers and dormant tumor cells prioritize the production of sugars from noncarbohydrate sources (121, 136, 137, 171).

Adaptability to stress and immune surveillance

Cancer

There is growing evidence that tumor cells adopt dormancy programs in order to escape the metabolic stresses induced by microenvironments (123). For example, the increased stiffness of ECMs, typified by fibrotic lungs (172) or aging (173, 174), enhances the formation of macrometastases (175, 176). Another example is epithelial–mesenchymal transition (EMT), in which the acquisition of mesenchymal programs facilitates tumor cell dissemination and invasion (177–179), yet which needs to reverse (mesenchymal–epithelial transition) in order for macrometastases to form at distal sites (180). High levels of some EMT factors, such as SNAIL or SLUG, can promote dormancy by increasing cell cycle arrest proteins such as CDK1 (181) or ID2 (182).

The ability of dormant tumor cells to adopt many characteristics of stem cells, including suspension of proliferation in G_0/G_1, allows them to evade drugs that target cell-cycle progression mechanisms (183). Stem cells and dormant tumor cells are believed to possess signaling plasticity that enables them to reawaken their proliferative state. However, only dormant tumor cells express markers of senescence, such as enlarged morphologies and senescence-associated β-galactosidase (57). Although the growth arrest in senescent cells is historically thought to be irreversible, examples exist in which chemotherapy- (184) or radiation-induced (185) tumor senescence can give rise to recurrent proliferative subpopulations.

Immune surveillance, especially by $CD8^+$ T cells, has been understood to suppress primary site and metastatic tumor growth by recognizing tumor-specific antigens, such as those encoded by mutated proteins or reexpressed fetal proteins (3, 186). Examples in which dormant cells evade immune surveillance by downregulating MHC-1–mediated antigen presentation (3) or alterations in the activities of immune cell subsets, including myeloid cells and T cells (187–190), are well established. Indeed, *C. elegans* as well as parasitic nematodes can alter the expression of surface proteins to evade attack by immune cells (191) or pathogenic bacteria (192).

There is also evidence that immune cells can sponsor tumor cell dormancy depending on microenvironment-specific factors. For example, Correia and colleagues (193) noted that livers containing foci of spontaneously disseminated dormant MDA-MB-231 breast cancer cells from orthotopic sites were enriched with NK cells, a phenomenon that could be boosted by adjuvant IL15 treatment. The ability of NK cells to promote dormancy could be mitigated by the ability of hepatic stellate cells to suppress NK proliferation through the secretion of CXCL12. Bushnell and colleagues (194) showed similar results with mouse mammary carcinoma cell lines, noting that dormant cells expressing stem-like properties had depressed STING and STING targets that normally induce NK cell–mediated anticancer cytotoxicity.

C. elegans

The dauer state in nematodes is a specialized stage of stress resistance that facilitates environmental dispersal of organisms. Being free-living, the dispersal mechanisms utilized by *C. elegans* include water and wind dissemination but also phoresy, whereby they transiently associate with other organisms (195). Their increased autophagy and decreased anabolic pathways and respiration during dauer render them naturally resistant to abiotic environmental changes that would otherwise challenge the ability to maintain biogenesis programs in cells (27). In addition, they activate several p38MAPK-mediated transcriptional programs (27, 196, 197) using transcription factors such as HIF1 (198) and DAF-16 (138, 199) to upregulate various aspects of innate immunity and stress resistance. Upregulated genes include those encoding several members of the α-crystallin family of small heat shock proteins, superoxide dismutases, and enzymes that serve as anti-ROS defense systems, as well as increased activity of cellular detoxification proteins (69, 200). Mutations that predispose larvae to arrest as dauers also confer life extension and resistance to UV (199, 201). Genes involved in EMT,

although conserved in *C. elegans*, have not been evaluated for their roles in dauer-regulating pathways, yet they are known to coordinate cell proliferation and cell fate determination (e.g., *CES1*/SNAIL ortholog; ref. 202).

Dauer entry by progeny of mothers exposed to pathogens has been documented (63) and interpreted to represent an alternative route to mounting an active response to infections. Similarly, parasitic nematode species seem to use constitutive or facultative dauer to evade host immune responses by secreting small molecules, peptides, proteases, extracellular antioxidants, or proteins (203).

Molecular Mechanisms and Pathways That Control the Exit from Dormancy

Mechanisms that control the exit from dormancy are the least understood for both cancer cells and dauers. The analysis of genes regulating tumor dormancy reawakening has been confounded by a dearth of *in vitro* culture systems recapitulating dormancy microenvironments and by the difficulty in isolating individual dormant cells from *in vivo* niches, including not knowing how these experimental interventions affect gene expression. Factors influencing the exit of *C. elegans* dauers from dormancy are more amenable to experimental analyses but have not been explored thoroughly in this context.

Sensing the appropriate environmental conditions to exit

Cancer

Some microenvironments are more conducive to sponsoring metastatic cell proliferation. For example, prostate or breast cancer cells found in the bone hematopoietic niche (HN)—marked by enrichment with mesenchymal and hematopoietic stem cells, normoxia, and low calcium levels—have higher levels of the proliferation marker, Ki67 (204–207). This contrasts with the osteoblast- and calcium-rich, hypoxic endosteal niche (EN), which promotes dormancy (208, 209). What remains unknown is whether reawakening signals cause dormant cells in the EN to gain proliferative activity as they move into the HN or whether tumor cells that disseminated to the HN have shorter dormancy programs. A hint comes from the study by Ghajar and colleagues (210) that showed that dormancy is induced by the association of disseminated tumor cells with a nonsprouting microvasculature in the bone marrow, and more specifically, by endothelial cell–derived thrombospondin-1. Nonetheless, reawakened cells exit from G_0/G_1 arrest and proliferate more than other cells of the same lineage. It is unclear whether reawakening is a stochastic event or whether it is influenced by host genetics and/or immune fitness (187), by the tropism of the dormant cancer cell for specific tissues or microenvironments (158, 207, 211, 212), by situational events such as transient immunosuppression or local inflammation associated with injury (213), or by aging mechanisms that affect all these parameters (214). Of note is that dormancy in disseminated tumor cells can be controlled by tumor-infiltrating macrophages (215) and that alveolar macrophages residing in the lung can promote dormancy through TGFβ2 receptor signaling (216). Additionally, dormancy reawakening can be promoted by the upregulation of several factors in the dormant microenvironment, such as EGF, periostin, or TGFβ1, by adipocyte-secreted factors such as FABP4, visfatin, or chemerin, or by stress pathways such as those controlled by β2-adrenergic receptors or systemic catecholamines and glucocorticoids (214).

C. elegans

While in the dauer state, larvae continuously assess their environment and exit dauer when conditions become favorable (27, 161, 217, 218). The decision to exit from dauer occurs predominantly downstream of neuronal sensing of favorable environments and signaling by a specific neuron (ASJ neuron) through the release of an insulin-related peptide, INS-6, as well as neurotransmitters and chemical messengers, such as serotonin (161, 217, 218). The extracellular molecules that trigger dauer exit from G_0/G_1 arrest include metabolites from bacteria such as fatty acids, NAD+, NADH, NADP+, and NADPH (219, 220). However, even if conditions remain unfavorable, larvae do not arrest indefinitely as dauers can spontaneously exit dauer in a seemingly stochastic manner. This suggests that to prevent permanent arrest in hypobiosis, the dauer state has evolved mechanisms to allow the escape of some larvae to potential reproductive adulthood, even at the cost of organismal health (27, 221, 222).

Restarting anabolic pathways and respiration (oxidative stress)

Cancer

Physiologic and metabolic reawakening involves the restart of anabolic processes and respiration, with the potential to accrue ROS-induced oxidative damage. The techniques used to identify reawakening-regulating genes have varied: bioinformatics analyses to find genes or proteins both upregulated in quiescent breast cancer cell lines and downregulated in reactivated metastases (223, 224); gain-of-function cDNA expression libraries to identify genes that induce macrometastasis formation (149); genomic short hairpin RNA libraries to identify genes that suppress the induction of breast cancer cell proliferation in 3D bone EN cultures (154); single-cell RNA sequencing of disseminated tumor cells isolated from early metastatic niches (225, 226). Several dormancy-regulating genes common to these studies have been validated, i.e., that their upregulation or downregulation results in dormancy reawakening, including DEC2/BHLHE41/SHARP1, HBP1, DDR1, and IGFBP5. Yet because of the dearth of facile dormancy models, scores of other genes remain unanalyzed. Another model shows that doxorubicin-resistant human triple-negative breast cancer cell lines exhibit increased behaviors and markers of dormancy, correlating with decreased cholesterol and lipid biosynthesis and metabolism (227), such that the forced increase in lipid metabolism genes induced reawakening and increased sensitization to antiproliferative inhibitors (228), likely by protecting dormant cells from ferroptosis (125).

C. elegans

Whereas maintenance in dauer requires the continuous downregulation of growth signals such as EGFR-RAS-ERK activity in the vulvar P6.p precursor cell, exit from dauer requires the opposite, namely the restoration of this pathway (27, 97). RNA sequencing analysis of larvae exiting dauer also identified several transcriptomic changes found in proliferating nematodes, such as the upregulation of genes encoding insulin peptides, downregulation of β-oxidation, and increases in neuropeptide signaling (229). As with dormant tumor cells, mobilization of cholesterol usage is also required for exit from dauer. During entry into dauer, cholesterol bound to the small secreted proteins SCL-12 or SCL-13 is sequestered in the gut lumen during the dauer state (230, 231). Upon recovery from dauer, bound cholesterol undergoes endocytosis into lysosomes of intestinal cells, in

which SCL-12 and SCL-13 are degraded and cholesterol is released. The released cholesterol activates mTOR, initiating translational programs crucial to dauer exit (231).

Epigenetic memory retained upon exit from dormancy

Cancer

There is some evidence that macrometastases that recur after several years retain a heightened ability to reenter dormancy programs, especially in response to antiproliferative drug treatments (232). This is likely because of the aforementioned stem-like epigenetic plasticity found in dormant cells (141). Although this attribute suggests that efficacious treatments of recurrent disease will not be durable because of resulting cycles of new dormant and reawakened tumor cells, Rosano and colleagues (147) have argued that drugs targeting epigenetic modulators could help suppress these cycles.

C. elegans

Dauer entry is accompanied by changes in chromatin marks that, in many cases, are retained in larvae that exit dauer and alter post-dauer adult physiology, reproductive capability, and stress resistance (150). Many of these chromatin marks poise genes for altered expression in post-dauer adults. In some cases, the epigenetic memory can be transmitted transgenerationally through alterations to chromatin, with F3 progeny of post-dauer animals showing an increased capacity to tolerate starvation and continue to grow when compared with progeny of animals that have not passed through dauer (150, 233). These studies also showed, however, that this increased starvation tolerance occurred at the cost of lowering the ability of larvae to alter their transcriptional profiles in response to stimuli. In addition, post-dauer adults have increased reproductive capacities, leading to the rapid proliferation of post-dauer individuals that aid colonization of the new habitat (150).

Pathways in Which *C. elegans* Dauers and Dormant Tumor Cells Differ

There are multiple tumor dormancy–associated genes without orthologous functions in *C. elegans*, and thus, may represent pathways not involved with dauer formation (**Fig. 2**). For example, the plasminogen proteolytic cascade promotes inflammatory cell infiltration and tumor cell invasiveness in vertebrates, with high levels of the urokinase-type plasminogen activator receptor, uPAR, promoting tumor dormancy (34). Yet, *C. elegans* is devoid of this pathway.

As mentioned above, dauer arrest has many parallels to cell cycle–arrested dormant tumor cells, and possibly to ultra-slow cycling tumor cells, but not to proliferating tumor cells involved in stable tumor mass dormancy. Although ultra-slow cycling tumor cells enter a type of G_0 phase, Basu and colleagues (11) argue that these cells differ from those in quiescence because they can exit G_0 more quickly and start proliferative cycles with shortened G_1 phases. These cells also upregulate distinct survival pathways such as the integrated stress response kinase, PERK (59), or signatures of noncoding RNAs (234). Although dauers do not seem to be slow cycling, there are other diapause states in *C. elegans* with decreased metabolism that share dauer pathways, suggesting that they may mimic ultra-slow cycling tumor cells. Further characterization of these poorly understood alternative diapause states, therefore, may offer new opportunities to understand the molecular mechanisms underlying ultra-slow cycling tumor cells.

In nature, *C. elegans* nematodes adopt a boom versus bust lifestyle: they are primarily in dauer and skirt the effects of extreme environmental stressors, predators, and competition with other species (22, 66). In contrast, tumor dormancy is orchestrated through specific niche interactions with multiple environmental cells (endothelial cells, osteoblasts, immune cells, neuronal cells, and stromal cells) and secreted factors, under unfamiliar conditions such as hypoxia or increased ECM stiffness (235, 236), and selective pressures such as systemic chemotherapy or targeted therapies. The stressors experienced by nematodes and tumor cells, though biologically different, may be perceived by each as "extreme." This underlines the need to define shared versus unique genomic, pathway, and metabolic drivers of dauer versus tumor dormancy. Although driver pathways likely exist that are unique to dauer, the identification of drivers shared with dormant tumor cells would be a powerful argument that parts of tumor dormancy are facilitated by ancient evolutionary responses to stress.

Probably the largest divergence between tumor dormancy and *C. elegans* dauers is the role played by the immune system in the former. Disseminated tumor cells are likely subjected to constant immunoediting (237) that produces stable tumor mass dormancy by balancing tumor cell proliferation with equal levels of cell death induced by immune cells (e.g., T cells and NK cells; ref. 238) and secreted factors (e.g., IFNγ, IL12, and IL23). This produces at least two types of dormant tumor niches, neither of which has an overt parallel in the nematode biome: the first, in which nonproliferating tumor cells elude immune attack by downregulating immune-engaging proteins, and the second, in which net macrometastatic growth is attenuated by constant, yet exhaustible, local inflammatory responses (tumor mass dormancy). Wiecek and colleagues (239) note that tumor mass dormancy microenvironments in a pan-cancer study were enriched in cytotoxic and regulatory T cells with high levels of exhaustion markers, as well as decreased inflammatory Th17 signals.

How specific are dormancy pathways?

Several of the dormancy-associated pathways described here are not specific to dauer or cancer dormancy, strongly suggesting that their use in promoting dormancy is highly context-dependent, affected by temporal and/or environmental conditions. Even the ready use of anaplerotic pathways for energy metabolism or exaggerated stress resistance are features in normal cell biology. More research is needed to identify the companion pathways that *C. elegans* and tumor cells use to cause the more generic pathways to drive dormancy. Although such an endeavor is difficult for dormant cancer cells, *C. elegans* represents a facile model to parse how these pathways are used in normal versus dormant (dauer) cells.

Coda

The considerable number of similarities in genomics, signaling, and metabolic pathways between the *C. elegans* dauer state and cancer dormancy underlines the likelihood that they share vestigial programs for survival under environmental stress conditions. This theme of co-opting vestigial programs is also manifest in metastatic progression: Metastatic cells reexpress embryonic factors such as SOX2, SNAIL1, TWIST, and GOOSECOID, and pathways such as WNT/β-catenin, Hedgehog, and Notch, to promote invasiveness and stemness (240), with many of these genes having orthologs in *C. elegans*. However,

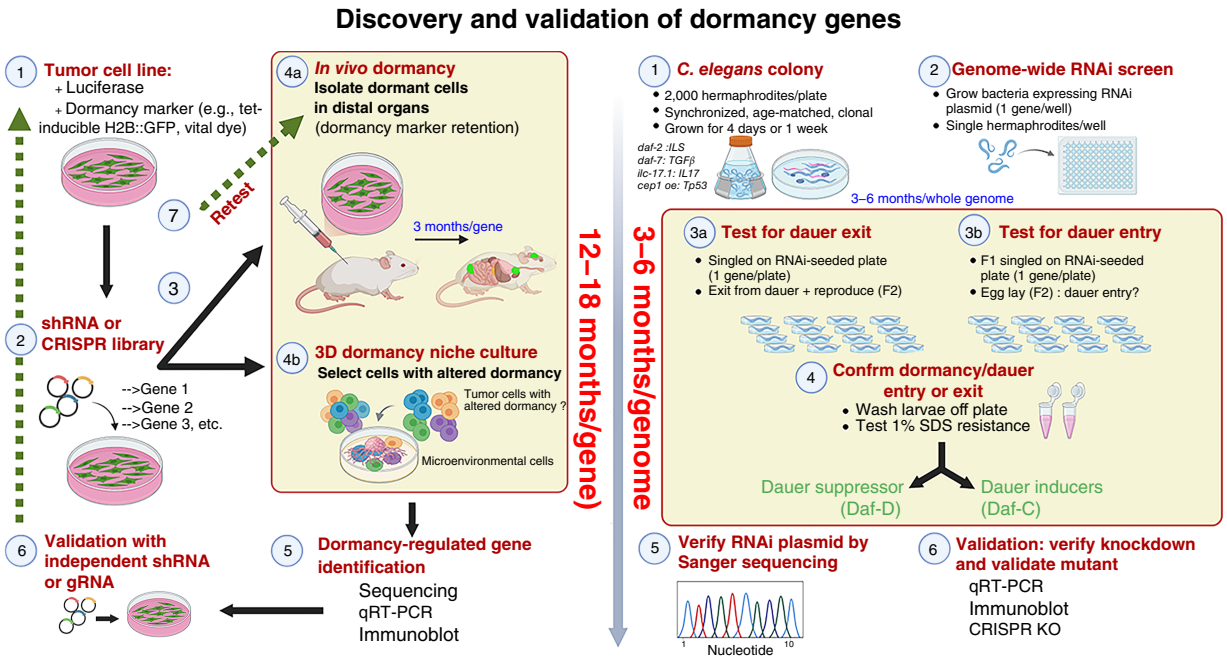

Figure 2.

Discovery and validation of dormancy- or dauer-regulating genes. In order to identify tumor dormancy–regulating genes (left), tumor cells need to be transduced with a constitutive marker such as luciferase as well as a marker that will be sustained in nonproliferating cells only. Examples of the latter include tetracycline-inducible H2B-GFP, whose expression is induced in culture before tumor cell injection, or vital fluorescent dyes that are retained in cells through nontoxic cross-linking to proteins via chloromethyl, bromomethyl or succinimidyl groups. These cells are then transduced with lentiviruses encoding genome-wide or focused shRNAs, CRISPR-Cas9/gRNAs, or cDNAs and then selected *in vitro* (e.g., 3D culture containing microenvironmental cells) or *in vivo* for increased or decreased dormancy. Large-scale screening of these genes in 3D cultures is confounded by the need to use primary cells with limited passage number, whereas *in vivo* systems often require difficult protocols such as intracardiac, intrailiac artery, or orthotopic injections and are confounded by yielding small numbers of cells retaining the dormancy marker (e.g., H2B-GFP or vital dye). Next-generation sequencing is then used to identify genes whose modulated expression (confirmed by qRT-PCR or Western blotting) correlates with gain or loss of dormancy. For shRNA and gRNA library screens, these genes need to be validated using different knockdown or knockout clones, followed by an additional round of retesting for dormancy using 3D cultures or *in vivo* injection models. In addition to the expense, only a small number of genes can be tested in this manner, requiring 12 to 18 months. In contrast, the genes regulating dauer entry, maintenance, and exit (right) can be screened in several months, using various dauer-inducing genetic backgrounds and making use of the fact that nematodes can take up RNAi by ingesting *E. coli* clones plated as large-format genomic arrays. Sequence verification of RNAi plasmids and functional RNAi validation experiments, including independent RNAi reagents, qRT-PCR, immunoblot, or CRISPR knockout, require several weeks more. The ability to rapidly screen multiple RNAis quickly and inexpensively for dauer control offers a possible advantage to screen *C. elegans* orthologs of human dormancy-regulating genes. gRNA, guide RNA; KO, knockout; shRNA, short-hairpin RNA.

given the complexities of how tumor cells interact with their varied microenvironmental niche cells, and how dormancy may be selected for by immune cell and therapeutic pressures, it is likely that vertebrates encode some distinct dormancy-regulated genes and pathways not reflected in *C. elegans* biomes.

The evidence that *C. elegans* that exit dauer undergo an epigenetic imprinting that affects their ability to survive future stressors (above) may have parallels to what Reimann and colleagues (241) argue are "chromatin scars" suffered by senescent cells that regain proliferative activity at the expense of long-term survival. Given the difficulties in isolating and studying dormant tumor cells from *in vivo* environments (below), let alone from secondary dormancy sites derived from reawakened cells, it may be more fruitful in the short term to compare dauer-exiters to reversible senescence models (17).

Our ability to identify and validate genes and pathways that control dormancy and reawakening is confounded by difficulties in isolating sufficient numbers of disseminated tumor cells in mouse xenograft models or from human biopsies, even with the presumption that these represent dormant populations. Moreover, there is no gold standard for either 2D or 3D culture systems that reflects tumor cell dormancy in the context of 3D microenvironments, though some groups, such as Marlow and colleagues (242), have developed 3D cultures incorporating bone niche microenvironments in collagen matrices in which human breast cancer cells enter dormancy in endosteal but not hematopoietic environments. Nevertheless, hurdles remain. The facile and powerful dauer model, on the other hand, has been studied extensively to identify dormancy-regulating mediators and pathways. Thus, the study of dauer biology offers a possible avenue to dissect many of the dormancy-reawakening pathways, and indeed, it will be interesting to determine which orthologs of the many candidate dormancy-regulating genes identified in tumor models might control dauer entry or exit. For example, a survey of OrthoList2, which matches more than 7,600 *C. elegans* protein-coding genes with their human orthologs (243), indicates that of the major cancer-related dormancy maintenance genes- DEC2/BHLHE41/SHARP1, HBP1, DDR1, and

IGFBP5, *C. elegans* only encodes a DDR1 ortholog (*DDR1*). Even more significantly, of the 412 dormancy reawakening suppressor genes identified as required to maintain dormancy of human breast cancer cells in 3D EN cultures (154), 225 have orthologs in *C. elegans*, and 151 (67.1%) were upregulated >2-fold in dauers induced by various genetic triggers (bioRxiv 2024.08.15.608164). The identification of shared dauer/dormancy genes and pathways would be consistent with the notion that metastatic tumor cells revert to deeply conserved, vestigial, evolutionary pathways in order to survive hostile microenvironments and antiproliferative therapeutics.

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