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Dormacy in Cancer and Tumor Cells

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The phenomenon of dormancy in cancer and tumor cells is defined by the halting of cell division and the preservation of a dormant or slow-growing condition. Cells can stay in this state long after the underlying tumor has been excised or after surveillance and therapeutic intervention, and it can endure for years or even decades. During the course of a cancer, cancer cells are likely to spread, and some may go into dormancy, remaining alive but not multiplying. With today's diagnostic tools, it is extremely rare to find these latent cancer cells (DCCs). Additionally, they are able to decipher homoeostatic signals from the microenvironment to avoid immune monitoring and treatment. DCCs may eventually reawaken in response to not recognized signals, which would cause recurrence and metastasis. Therefore, avoiding metastasis requires an understanding of the biology of DCC reawakening. Chronic inflammation can revive cancer proliferation in distant places, and immune cells' cytotoxic activities can put cancer cells into a latent condition. Circulating DCCs bind to extracellular molecules, activating a number of signaling cascades and resuming cell growth. Recent research has revealed that dormant cells can reactivate and develop metastatic illness, which is the main factor contributing to cancer-related mortality. Therefore, it is essential to comprehend the variables that control dormancy and reactivation in order to create efficient methods to stop the spread of metastatic illness. In summary, dormancy in cancer and tumor cells is a complicated and poorly understood phenomena that is crucial to the development and

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metastasis of cancer. To understand the mechanisms that control dormancy and to create efficient therapeutic approaches to stop cancer development and metastasis, more research is required.The objective of this review article is to provide a valuable and critical summary of the area of dormancy in cancer and tumor cells. Articles used in this review were sourced from websites like researchgate, Elsevier, etc using keywords like cancer, dormancy, tumor, etc.

Keywords: Cancer; tumor; dormancy; cells; cellular; metastasis.

1. INTRODUCTION

"Cancer dormancy is a term used to describe the duration between the removal of a primary tumor and the occurrence of metastatic relapse. This time can range from months to decades. This may be caused by lone, non-proliferating cancer cells that have spread from the primary tumor or by small, non-expanding cancer cell populations (tumor mass dormancy). Despite the possibility of clinically undetectable cancer in each of these categories, they each describe various molecular pathways" [1]. In addition to being characterized by growth stagnation, cancer dormancy also refers to a condition in which cells may exist that are neither hypometabolic nor non-proliferative [1]. "While cancer cells are in a dormant condition during cellular dormancy, there is a balance between the growth of cancer cells through proliferation and their loss through cell death during tumor mass dormancy. The processes of initial tumor growth and secondary metastasis make up the majority of the cancer progression. More specifically, it refers to the phenotypic alterations in already-formed neoplastic lesions, which incorporate a wide range of signals and mechanisms and alter tumor cells' morphology, molecular makeup, and functional properties. Importantly, the appearance of tumor relapse, tumor escape from dormancy, and metastasis, which can happen years or even decades after successful completion of therapy, are attributed as a major cause of cancer-related fatalities. The term "tumor dormancy" refers to a situation in which the number of cancer cells remains constant due to the equilibrium between cell division and apoptosis, as opposed to cellular dormancy, which is described as a transient mitotic G0-G1 arrest and a growth arrest of a dormant cancer mass. Several factors, including hypoxia, nutrient deficits, and chemotherapeutic stimulation, can prevent the development of dormant cancer cells. Then, based on the production of substances that control different signaling pathways and their interactions with the tumor microenvironment (TME), a state of cell proliferation or dormancy is established" [2].

1.1 Identification of Dormant Cancer Cells

"Using clinical samples, it is required to create experimental models of dormant cancer cells in order to find dormancy-associated biomarkers that are clinically meaningful. For locating dormant cancer cells in preclinical and clinical settings, various methods have been suggested. The existence of dormant cancer cells has been determined by evaluating the level of proliferation and apoptosis-related marker expression [for example, Ki67 and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) expression (Ki67 and TUNEL-double-negative population is considered as the dormant population) [3]; Ki67 and M30 expression (Ki67 and M30-double negative population is considered as the dormant population), and the mitotic activity index (the total number of mitoses in 10 fields of vision according to the Multicenter Mammary Carcinoma Project protocol) or mitotic index (determination of the level of phosphorylated histone H3 expression)". "Several experimental approaches, such as the pulse and chase experiment using nucleotides that can be incorporated into DNA during DNA replication [for example BrdU (5-bromo-2'-deoxyuridine), EdU (5-ethynyl-2'-deoxyuridine), or tritiated thymidine (3H-T)], label-retention methods using carboxyfluorescein succinimidyl ester (CSFE), PKH26, or DiD dyes, the labeling and chase method using a doxycycline-inducible green fluorescence protein (GFP)-tagging histone H2B (H2B-GFP) reporter, use of the Fluorescent Ubiquitination-based Cell-Cycle Indicator (FUCCI) reporter, gene promoter reporters using *CDKN2A* (that encodes p16) or *KDM5B* promoters, and a cell cycle indicator (the mVenus-p27K- probe) have been used for identification of slow-cycling/dormant cancer cells" [3,4]. "Bioencapsulation in a stiff and porous 3D matrix using synthetic materials has been recently developed for isolating dormant cancer cells" [3,5]. "In addition, a number of in

vitro models for tumor dormancy and genetically modified mice models for the construction of therapeutically relevant in vivo dormancy models models have been produced, as detailed in recently published literature" [3,6].

1.2 Main Characteristics of Dormant Cancer Cells

"The reversible suppression or arrest of cell proliferation that is accompanied by cell cycle arrest at the G0/G1 phase of the cell cycle, induction of cyclin-dependent kinase inhibitors like p21 and p27, and downregulation of markers of cell proliferation like Ki67 and proliferating cell nuclear antigen (PCNA) are typical cellular changes associated with dormancy" [7]. The p38 mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK) activity have been proposed as prototypical markers of cancer cells that are dormant. But in more recent research, ERK activation was also observed in cells that underwent dormancy-like states, such as cells forced to develop dormancy-like phenotypes by incubation onto biomaterials under serum deprivation conditions or those with SCC-like phenotypes [drug-tolerant persister (DTP)] by treatment with irinotecan (CPT-11) [3]. Additionally, latent cancer cells demonstrate negligible cell death and carry anticancer drug resistance despite growth stoppage and/or retardation, as well as environmental damages [8]. Additionally, these cells exhibit a decreased cellular metabolism, which includes a decline in glycolysis, protein translation, and energy synthesis. Due to K20 methylation of histone H4 in dormant cancer cells, the chromatin structure is also compact [3,9].

2. TUMOR MASS DORMANCY

A "tumor mass dormancy" concept that presupposed the equilibrium between the growth of cancer cells through proliferation and the decrease of cancer cells through cell death was put forth to explain late recurrence. Angiogenic dormancy and immunomediated dormancy are two distinct processes that can result in tumor mass hibernation [10].

2.1 Angiogenic Dormancy

A tumor's cancer cells coexist alongside fibroblasts, endothelial and inflammatory cells, growth factors, cytokines, vasculature, and lymphatic arteries in a highly dynamic and interactive microenvironment. These constitute the tumor ecology as a whole. Lack of nutrients or available space, negative interactions with normal cells, or fluctuations or stoppage in blood flow across or within parts of a tumor can all cause cancer cells to halt their rapid proliferative cycle, as well as the tumor population as a whole [1,11]. Cancer cells use a significant quantity of energy resources to support active proliferation. A new blood vessel network, known as angiogenesis, must be produced alongside tumor growth in order to fulfill this requirement. Pro- and anti-angiogenic factors work together to tightly control angiogenesis. A tumor begins the progression phase after the angiogenic switch, when the balance shifts to the pro-angiogenic side. Prior to the angiogenic switch, a greater proportion of cancer cells cause cell death due to a lack of oxygen and nutrients in an area far from pre-existing blood vessels. Angiogenic dormancy describes the balance between the growth and death of cancer cells. [10,12].

2.2 Immunomediated Dormancy

Long known to play a key role in the inhibition of tumor growth and progression, immune surveillance also gives tumor cells in advanced tumors the capacity to evade the immune system. In addition to preventing early tumor development, the immune system is essential for tumor mass dormancy. Eyles et al. [13] demonstrated that CD8+ T lymphocytes are crucial in the maintenance of tumor dormancy at the metastatic site using a spontaneous melanoma model in metallothionein (MT)-ret/AAD mice. In this animal, CD8+ antibody-mediated immune system repression markedly accelerated the development of metastatic disease. Genome-wide single-nucleotide polymorphism analysis revealed that there is a high degree of genetic similarity between the primary and metastatic sites, suggesting that metastases may have originated from tumor cells that disseminated from the primary tumor at an early stage. These findings suggested that disseminated tumor cells would go dormant, avoid immune surveillance, and expand metastatically if they managed to evade the immune system. According to Liang et al. [14], immune cells and their cytokines play a crucial role in inhibiting tumor cell proliferation following radiotherapy, and disruption of the immune system can cause the post-radiation balance to be upset [10]. In a mouse B cell lymphoma model (BCL1), the presence of cytostatic CD8 T-cells was necessary for the maintenance of

dormancy; their removal altered cancer cell dormancy. Further proof that the immune system controls metastatic growth was obtained in a mouse melanoma model, where it was discovered that CD8 T cells regulate cancer cell dormancy in the lung and that their depletion causes visceral metastases and quicker outgrowth. Through the production of interferon (IFN), which has been proven to be able to arrest tumor cells to the G0/G1 phase, T lymphocytes can also maintain the dormant state of metastatic cells [15].

2.3 Cellular Dormancy

“Cellular dormancy is another model of tumor dormancy. Cellular dormancy is characterized by three features: (i) minimum proliferation; (ii) minimum death; and (iii) reversibility. At the cellular level, the dormant status is observed in tissue stem cells and cancer. Cellular dormancy of cancer has mainly been studied in the context of late recurrence, especially metastasis, in which the microenvironment of the metastasis site plays a critical role.Cellular dormancy, however, can also be present in tumors developing at the main site, for instance, in the hypoxic areas. Tumors contain latent cells, which are probably immune to treatments like radiation and anticancer medications that focus on rapidly reproducing cells. Numerous cellular dormancy mechanisms have been described” [10].

3. HYPOXIC MICROENVIRONMENT AND DORMANCY

The cancer microenvironment is hypoxic due to the disordered growth of cancer cells and the disorderly angiogenesis. Tumor cells' oxygen consumption is crucial in creating a hypoxic microenvironment. According to Endo et al. [10], hypoxia causes a malignant phenotype and therapeutic resistance in cancer. In addition to DTCs being latent in hypoxic areas of an organ, cancer cells in tumors that are actively growing also suffer hypoxia due to temporal fluctuations in intratumoral blood flow and instability of the vasculature [16]. Though many tumor cells die in hypoxic conditions, some do so by going into a dormant state. Understanding the characteristics of these inactive cells is difficult because there aren't many in vitro models of tumor cell dormancy known. Evidence already in existence points to either a cell-cycle arrest in the G0/G1 phases or significantly reduced proliferation in these cells. In hypoxia-resistant cells, glucose intake is reduced by 80%, and pyruvate and lactate production are also decreased. Chronic hypoxia causes glucose consumption to decrease, yet hypoxia-resistant cells still upregulate autophagy to get nutrients. After a period of delay, the growth rate of hypoxia resistant cells returns to normal after reoxygenation.The decrease in their reversibility Therefore, metabolic activation and cell remodeling are necessary for proliferation. Because they proliferate less slowly or because the chemotherapy cannot penetrate the hypoxic areas of the tumor, hypoxia resistant cells are more resistant to chemotherapy. Cancer cells may use anaerobic glycolysis during acute hypoxia, increasing glucose intake and lactate production, but some enter dormancy or multiply more slowly under chronic hypoxia. Therefore, in hypoxic conditions, the length of hypoxia affects the metabolic activity of cancer cells [1]. Transcriptional regulator HIF plays an important role for cancer cells' acute hypoxia response. Intensive research on acute hypoxic reactions has been conducted using well-established cell lines that were given all the nutrients they needed—apart from oxygen—for a brief period of time, ranging from a few hours to 48 hours. Due to active glycolysis, glucose intake dramatically increases in such severe hypoxic situations. It seems unlikely that cancer cells will continue to consume high amounts of glucose in a microenvironment where the glucose supply is constrained. Therefore, new pathways for the dormant cancer cells under hypoxia should exist in addition to the conventional acute hypoxic response. Near the necrotic area of solid tumors, hypoxia-inducible gene domain family member 1A (HIGD1A) is expressed.The HIGD1A promoter is methylated, hence hypoxia alone does not trigger the gene. When glucose is scarce, the HIGD1A promoter is demethylated, DNA methyltransferase activity is reduced, and HIGD1A is activated. In addition to activating AMPK and inhibiting the formation of reactive oxygen species (ROS), HIGD1A also inhibits oxidative phosphorylation. As a result, HIGD1A promotes cancer cell survival in extremely hypoxic environments.47 Through the use of SOX9, PAR, and CDK inhibitors, the orphan nuclear receptor NR2F1 contributes to the maintenance of dormancy in HEp3 cells [10].

3.1 Role of Microenvironment in Dormancy

Three general categories can be used to describe how dormant cancer cells interact with the TME. Notably, none of the dormancy-

inducing signals are isolated from or exclusive of the others. Instead, to sustain the latent state, dormancy-inducing signals from the TME coexist and collaborate with one another, frequently converging on the same intracellular pathways.

3.2 Paracrine signals Involved in Cancer Dormancy (Secreted Factors and Exosomes)

Soluble factors released by TME cells play a critical role in the dormancy of cancer cells. For example, it has been demonstrated that the proteins bone morphogenetic protein 7 (BMP7) and growth arrest-specific protein 6 (GAS6) cause dormancy in a variety of cancer cell types that have invaded the bone marrow [17]. “In perivascular niches found in the lung, bone marrow, and brain, it has been demonstrated that the glycoprotein thrombospondin-1, released by endothelial cells, causes breast cancer cells to enter a dormant state. Growth differentiation factor 10 (GDF10) and TGF-2, which are released by osteoclasts, are also thought to contribute to the induction of tumor cell dormancy. Several extracellular mediators of dormancyconverge on inducing a $p38^{high}$/ ERK^{low} state, resulting in cell cycle arrest or slowdown. Recently, soluble factors released by macrophages have been reported to induce NR2F1 and dormancy in disseminated breast cancer cells” [18]. “Exosomes are intraluminal vesicles with an averagediameter of 100 nm that contain intracellular componentsincluding proteins, microRNAs (miRNAs), and messengerRNAs. Exosomes play a critical role in cancer cell communicationand unsurprisingly are emerging as important mediators of chemoresistance, EMT, and dormancy” [19,20]. “The effects of miRNAs shuttled within exosomeshave been studied particularly in breast cancer, where miR-23b and miR-222/223 have been shown to induce a dormantphenotype in tumor cells” [21].

3.2.1 Juxtacrine signals involved in cancer dormancy (extracellular matrix and cell–cell interactions)

“A critical component of the TME is the extracellular matrix (ECM), which plays a crucial role in the development and spread of cancer. Particularly in breast and lung cancer, several ECM proteins have been demonstrated to be associated with cellular dormancy and reawakening. COL17A1, a hemidesmosome protein that mediates cell adhesion to the basement membrane, has recently been revealed to enhance contacts between cells and the extracellular matrix (ECM) in colorectal cancer cells that are quiescent and LGR5+ p27+” [22]. The regulation of lysyl oxidase (LOX) activity and subsequent collagen deposition constitute a key dormancy-inducing mechanism at the ECM level. The amount of collagen produced controls the stiffness of the matrix and balances tumor development and dormancy. Dormancy induction is also thought to be mediated via interactions between cells at intercellular junctions, adhesion molecules, and receptor-ligand binding. According to reports, CSCs develop gap junctions (GJs) with TME cells, which transport cytokines, exosomes, and even mitochondria from one cell to the next. By transporting miRNAs and exosomes, GJs and their composition have been explicitly linked to cancer dormancy [21,23].

3.2.2 Cancer-immune system interactions involved in dormancy

All stages of cancer evolution are influenced by the host immune system, which either inhibits or promotes tumor growth. Both occult primary tumors and metastatic tumors' long-term latency is maintained by interactions between immune cells and tumor cells. States of immune suppression thus eliminate the restriction that the adaptive immune system places on latent tumor cells, facilitating the formation of metastatic lesions. On the other hand, the emergence of dormant tumor cells is thought to be mediated by the innate immune system and its soluble mediators. Downregulating the expression of major histocompatibility molecules and tumor-specific antigens allows dormant cancer cells to evade the host's anticancer defenses.In addition, immune-privileged niches are places where dormant cancer cells can infiltrate and remain hidden for extended periods of time. Finally, certain cancers develop the ability to render immune cells dead or lethal, shielding them from immune clearance. Baldominos et al.'s latest study, which demonstrates that QCCs can interfere with immune cell activity and create niches where they are protected from T cell-mediated killing, represents a significant advance in our understanding of the processes of immune evasion by QCCs [24]. Particularly, damaged dendritic cells, suppressive fibroblasts, and a higher percentage of terminally exhausted T cells than progenitor T cells were seen in QCC niches. The capacity of QCCs to create an immunosuppressive TME was crucially

dependent from a hypoxia-relatedgene expression signature and possibly from the creation of aglucose-poor and lactate-rich environment as a consequenceof tumor metabolism [21].

3.3 Endoplasmic Reticulum Stress and Dormancy

Cancer cells that are actively dividing are more likely to stimulate protein synthesis, which uses up a lot of energy resources. Cancer cells cultivated in hypoxic environments show downregulation of protein synthesis and the critical enzyme mTORC1. Insulin-like growth factor (IGF) boosted the COLO320 colorectal cancer cell line in a hypoxic environment, causing a strong apoptosis through an enhanced ER stress response. The cause of ER stress is impaired protein folding under hypoxic conditions, and IGF may cause ER stress by promoting aberrant protein synthesis and subsequent cell death. Consequently, excessive ER stress needs to be avoided [10].

4. ROLE OF AUTOPHAGY IN DORMANCY ESTABLISHMENT, DORMANT CELL SURVIVAL, AND REACTIVATION

In many ways, autophagy regulates the survival and behavior of dormant cells. When SKOv3 ovarian cancer cells were cultured in mice as xenografts, ARHI re-expression allowed them to maintain their latent state in the DIRAS3-induced ovarian cancer dormancy model. Inhibition of ARHI-induced autophagy with chloroquine significantly inhibited tumor regrowth. Reduction of ARHI levels in dormant cells allowed xenografts to develop more quickly. Autophagy was essential for the maintenance of the dormant phenotype in cancer cells as well as their survival in the D2.0R dormant and D2.A1 metastatic breast cancer cell lines.Dormant D2.0R cells in 3D cultures experienced viability loss after being exposed to the autophagy inhibitors hydroxychloroquine, bafilomycin, or 3-methyladenine, although their non-dormant counterparts were unaffected. In 3D cell cultures, the knockdown of the autophagy genes Atg3, Atg7, p62, or FIP200 caused the expansion of dormant cells. Additionally, La Belle Flynn et al. [25] found that Atg3-deficient D2.0R cells had a higher propensity to develop lung tumors in mice. Similar to this, animals that were intravenously injected with ADR-treated Atg5 knockdown cancer cells instead of wild-type dormant cells dramatically developed lung metastases in the ADR-induced dormancy model of Neu-driven breast cancer.Atg5 knockdown mammary tumors showed a higher frequency of Ki67 positive, polyploid-like cells as was predicted. According to these findings, autophagy was downregulated in proliferating metastatic cells, although it was discovered that this downregulation occurred prior to the development of overt metastatic lesions. Because proliferative lesions (i.e., lesions that went beyond the dormant-to-proliferative flip) had already developed, treatment with autophagy inhibitors had less of an effect on the metastatic burden. These findings suggest that autophagy is involved actively in the beginning, maintenance, and transition from a dormant to a proliferative state [26].

4.1 Mechanisms of Mammalian Autophagy in Cancer Dormancy

Another important mechanism for the reactivation, survival, and adaptability of dormant DTCs is autophagy. Autophagy is a physiological mechanism of fitness and cell survival that has been retained throughout evolutionary time. Its activation is largely dependent on the presence of unfavorable metabolic stress conditions, such as nutrition restriction. In order to maintain homeostasis and lessen cell damage, its method of action involves the breakdown and subsequent recycling of damaged cytosol components, misfolded proteins, organelles, and other macromolecules. As a result, there is growing evidence that tumor cells use autophagy to support their ability to survive under oxidative stress, enhance their bioenergetics, and accelerate the growth of the tumor. Autophagy levels are often lower in proliferating cells than in dormant cells. The expression of the tumor suppressor gene Aplasia Ras homolog member 1 (ARHI1) has also been linked to the establishment of a reversible dormancy state through activating autophagy in xenograft ovarian cancers. Following ARHI1 suppression, tumor development accelerated, indicating a function in preserving tumor dormancy. According to Vera-Ramirez et al. [27], the mammalian target of rapamycin and phosphatidylinositol 3-kinase-protein signaling pathway (PI K/AKT/mTOR) are inhibited by ARHI1 while ATG4 cysteine protease is upregulated. By promoting the nuclear localization of transcription factors EB (TFEB) and Forkhead box O3 (FOXO3a), two essential

mediators for the expression of various autophagy effectors like the microtubule-associated proteins 1A/1B light chain 3B (MAPLC3B), it further promotes autophagy [28]. Tumor growth quickened after ARHI1 inhibition, suggesting a role in maintaining tumor dormancy. Vera-Ramirez et al. [27] found that ARHI1 inhibits the mammalian target of rapamycin and the phosphatidylinositol 3-kinase-protein signaling pathway (PI K/AKT/mTOR), while upregulating the ATG4 cysteine protease. It further promotes autophagy by encouraging the nuclear localization of transcription factors EB (TFEB) and Forkhead box O3 (FOXO3a), two crucial mediators for the expression of different autophagy effectors like the microtubule-associated proteins 1A/1B light chain 3B (MAPLC3B) [28].

5. DRUG RESISTANCE OF DORMANT CANCER

Dormant cells are thought to be chemotherapy resistant since they are not actively proliferating. The active survival mechanisms that have been identified in animal models may also shield disseminated tumor cells, but it is yet unclear if this mechanism explains cancer cell treatment resistance in humans. In vitro G1 arrest and doxorubicin resistance are brought on by the induction of p21 or p27 in colon cancer cells. Disseminated breast cancer cells that were green fluorescent protein (GFP)-tagged were shown to be growth-arrested and doxorubicin-resistant in in vivo tests. Additionally, dormant cells might be shielded from chemotherapy by active processes. Chemotherapy resistance increases in breast cancer cells that undergo re-differentiation following suppression of 1 integrin function. Unexpectedly, this depends on differentiation and polarity levels (appropriate polarity triggers an anti-apoptotic 4-integrin-nuclear factor-B (NF-B) pathway), but not on proliferation. Activation and induction of the chaperone protein HSPA5 and the eIF2 kinase RNA-dependent protein kinase-like endoplasmic reticulum kinase (EIF2AK3, also known as PERK) respectively protected dormant cells from chemotherapy independently of proliferation in squamous carcinoma cells where a low ERK:p38 activity ratio induces dormancy. HSPA5 achieved this by preventing the activation of BAX (BCL2-associated protein X).Accordingly, it has been demonstrated that HSPA5 inhibits the proapoptotic proteins BIK (BCL2-interacting killer) and BAX95, protecting breast cancer cells from oestrogen starvation. It's interesting to note that the presence of HSPA5 is predictive of a shorter time to recurrence and a poor response to either Adriamycin in the case of breast cancer patients or hormonal ablation in the case of prostate cancer patients. As a result, HSPA5-expressing disseminated tumor cells may be more resistant to therapy. Finally, ABC transporters like ABCG2 (ATP binding cassette G2) are expressed by both healthy and malignant stem cells. Cancer stem cells in neuroblastoma that express ABCA3 are resistant to mitoxantrone. However, it is still unclear how relapse and a poor prognosis are related to the expression of the ABC transporter in disseminated tumor cells. When patients are positively identified as having little residual disease, a more thorough examination of these mechanisms and the detection of these markers in disseminated cancer cells will be crucial for the selection of therapy [29].

6. CONCLUSION

Cancer cells may acquire a state of dormancy in unfriendly microenvironments to safeguard themselves from apoptotic and antiproliferative therapies so that the strongest can survive. Most significantly, the cells may continue growing, increasing the danger of lethal metastatic outbreaks even after a lengthy latency period of months to years, which is brought on by the existence of DCCs. Therapy resistance has emerged as a result of the existence of DCCs. Therefore, a greater understanding of the several mechanisms that cancer cells employ to go into dormancy would aid in preventing metastasis, which is a terrible killer.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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