Review Article
Cancers

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Metabolic Adaptation and Cellular Stress Response As Targets for Cancer Therapy

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Cancer cells, which divide indefinitely and without control, are frequently exposed to various stress factors but manage to adapt and survive. The mechanisms by which cancer cells maintain cellular homeostasis and exploit stress conditions are not yet clear. Here, we elucidate the roles of diverse cellular metabolism and its regulatory mechanisms, highlighting the essential role of metabolism in cellular composition and signal transduction. Cells respond to various stresses, including DNA damage, energy stress, and oxidative stress, thereby causing metabolic alteration. We provide profound insight into the adaptive mechanisms employed by cancer cells to ensure their survival among internal and external stressors through a comprehensive analysis of the correlation between metabolic alterations and cellular stress. Furthermore, this research establishes a robust framework for the development of innovative therapeutic strategies that specifically target the cellular adaptations of cancer cells.

Keywords: Cellular reprogramming; DNA damage; Metabolic disease; Metabolism; Prostatic neoplasms; Stress, physiological

INTRODUCTION

Organisms acquire nutrients for energy and building essential structures, while cells utilize specific nutrients to synthesize genetic material, organelles, and cell membranes. Understanding intracellular metabolism is crucial because impaired metabolism contributes to diseases such as type-2 diabetes, metabolic-associated fatty liver disease, and promotes cancer initiation and progression through metabolic reprogramming. This reprogramming enables cancer cells to adapt and thrive in dynamic environments.

Cancer cells exhibit distinct metabolic pathways to meet their energy demands, support structural growth, and overcome stress. The Warburg effect, characterized by aerobic glycolysis and the supply of biosynthetic precursors, prominently emerges in specific cancer contexts. The inhibition of glucose metabolism has shown promise as an effective therapeutic approach [1]. Nonetheless, cancer metabolism displays variability contingent on the stage and tissue of origin. For instance, a disparity in glycolytic capacity exists between normal prostate epithelial cells and prostate cancer cells, where the latter exhibit tricarboxylic acid (TCA) cycle rewiring. This metabolic shift is coupled with heightened lipogenesis and oxidative phosphorylation. Significantly, increased extracellular citrate secretion has been correlated with an unfavorable prognosis for prostate cancer

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patients [2,3]. These dynamic metabolic alterations during cancer initiation and progression raise important questions regarding the impact of cellular adaptations on metabolic changes and their role in cancer advancement. In this review, we elucidate the intricate mechanisms connecting cellular stress response to metabolic alterations and explore their implications for cancer progression. Additionally, we emphasize the critical involvement of the cellular stress response across diverse cell types, offering a framework for the identification of novel therapeutic targets within metabolic pathways.

METABOLIC FLEXIBILITY IN RESPONSE TO CELLULAR STRESS

Metabolism plays a vital role in cellular functions, encompassing energy generation, cellular signaling, and its tight association with cancer proliferation and progression (Fig. 1). Glucose, amino acids, and lipid metabolism are key pathways supplying carbon within cells, critical for essential functions like adenosine triphosphate (ATP) production, biosynthesis, and stress responses. Among these sources, glutamine stands out due to its dual role—providing carbon and directly regulating non-essential amino acid (NEAA) synthesis. In contrast to glycine, methionine, and aspartate, which also contribute carbon, glutamine modulates NEAA biosynthesis, underscoring its pivotal role in cellular metabolism [4]. Although amino acid and lipid metabolic pathways are crucial in cancer progression, the mechanism of cancer cell adaptation to stress conditions remains unclear. This review focuses on highlighting the significance of glutamine and lipid metabolism, which encompass various aspects of cellular functions. Moreover, the discussion revolves around the utilization of increased iron by cancer cells for DNA synthesis and cellular signaling, considering its regulatory role in metabolism [5]. This review uncovers the involvement of metabolism in cancer progression by providing insights into these metabolic pathways and offering valuable targets for innovative cancer therapies.

1. Glutamine metabolism

Glutamine is a vital metabolite that contributes to cellular homeostasis by serving as a nitrogen donor and playing a crucial role in synthesizing NEAA and nucleotides and generating ATP. It can be synthesized within cells by glutamine synthetase or taken up from the extracellular environment through cellular plasma glutamine transporters such as SLC1A5, SLC38A1, and SLC38A2 [6]. Glutamine assumes a central role in nucleotide synthesis, acting as a source for NEAAs like aspartate, serine, and glycine. Its availability as a nitrogen donor and precursor significantly influences various biosynthetic pathways, especially those critical for purine and pyrimidine synthesis. Moreover, glutamine plays essential roles in maintaining DNA replication, facilitating DNA damage repair, and regu-

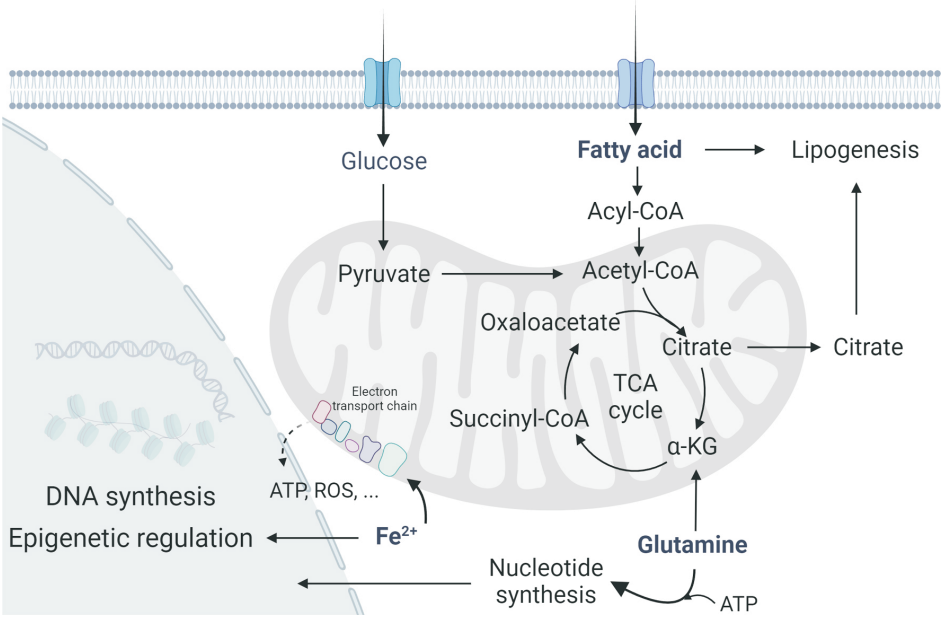

Fig. 1. Metabolism plays a crucial role in regulating cellular processes. This schematic shows the essential role of metabolism in regulating various cellular processes. It highlights key metabolic pathways such as the tricarboxylic acid (TCA) cycle, DNA synthesis, fatty acid metabolism, glutamine metabolism, and ion regulation. These pathways are critical for the proper functioning and maintenance of cells. Understanding the intricate connections and regulation of these metabolic processes is crucial for studying cellular physiology and developing innovative approaches for therapeutic interventions. ATP: adenosine triphosphate, ROS: reactive oxygen species.

lating transcription processes. Within the mitochondria, glutamine is transported and converted into glutamate, which enters the TCA cycle, promoting ATP synthesis. This process generates aspartate or citrate, contributing to nucleotide synthesis, NADPH formation, or fatty acid synthesis [7]. Alpha-ketoglutarate (α-KG), a byproduct, plays a role in cell proliferation and histone modification [8]. The metabolism of glutamine assumes a paramount role as a significant contributor, generating methyl groups and α-KG, a pivotal cofactor essential for activating enzymes like ten-eleven translocation proteins, which are engaged in the intricate process of DNA demethylation [9]. Furthermore, the profound impact of glutamine extends to the realm of epigenetic regulation. Its active participation in histone acetylation pathways is facilitated through its conversion into citrate, a crucial precursor for synthesizing acetyl coenzyme A (acetyl-CoA) [10]. Consequently, the orchestration of glutamine metabolism exerts a profound and pervasive influence on the multifaceted modulation of epigenetic pathways, underscoring its central role in the intricate tapestry of cellular regulatory mechanisms.

Glutamine metabolism is implicated in cancer progression, particularly through the interaction between 2-hydroxyglutarate (2-HG) and α-KG in cancer cells with isocitrate dehydrogenase mutations [11]. Additionally, glutamate helps maintain redox balance by reducing reactive oxygen species (ROS) through glutathione formation. However, the regulation of redox homeostasis through glutamate is still under investigation, as its conversion to α-KG may increase ROS levels and promote cancer metastasis [12,13]. Glutamine metabolism, specifically the enzyme glutaminase 1 (GLS1), is upregulated in several types of cancer. Inhibiting GLS1 induces apoptosis and exhibits therapeutic efficacy, particularly in prostate cancer, where the androgen receptor (AR) upregulates GLS1 expression and activates glutamine metabolism [14,15]. Therefore, understanding glutamine metabolism in cancer is crucial for the development of effective cancer therapies.

2. Lipid metabolism

Lipids are vital for cellular processes like membrane structure, energy metabolism, and signal transduction [16,17], making lipid metabolism crucial for cell growth and proliferation. Research has shown a link between lipid metabolism, tumorigenesis, and chemoresistance in tumors [18,19]. Disruptions in lipid homeostasis and excessive accumulation can lead to lipotoxic stress and cell death. Understanding and targeting lipid metabolism hold promise for effective cancer treatment.

Lipid metabolism involves various cellular pathways, including energy generation and lipid synthesis. Fatty acids are taken up by cells through transporters like FATP and CD36 and can be stored or transported to the mitochondria as fatty acyl-CoA. Moreover, lipid metabolism orchestrates lipids synthesis, breakdown, and utilization, playing a pivotal role in influencing epigenetic modifications and gene expression. Bioactive lipid molecules including fatty acids, phospholipids, and sphingolipids indirectly impact histone-modifying enzymes like DNA methyltransferases, acting as potent signaling agents [20,21]. Acetyl-CoA directly engages in dynamic histone acetylation. Changes in lipid levels trigger responses from lipid-sensing nuclear receptors, exemplified by peroxisome proliferator-activated receptor (PPAR) and liver X receptor (LXR), which wield direct or indirect gene expression control through DNA binding or epigenetic modifier recruitment [22,23]. These intricate lipid metabolism nuances collectively converge, skillfully choreographing profound epigenetic modifications through a network of intricate interplays [24]. Within the mitochondria, lipids are converted to acetyl-CoA for energy production. Long-chain fatty acids undergo fatty acid oxidation (FAO) to generate shorter forms, while very long-chain or branched-chain fatty acids can be metabolized in the peroxisome [17,25]. Lipid production also occurs during glycolysis, and cytosolic acetyl-CoA can be used for fatty acid synthesis. Citrate, produced in the mitochondria, can be exported for cholesterol and steroid synthesis, and acetate can be utilized for de novo lipogenesis [26]. Regulatory proteins like sterol regulatory element binding protein (SREBP) and PPAR play important roles in lipid biosynthesis and proliferation [27,28].

Recent studies revealed increased *de novo* lipogenesis in prostate cancer, and inhibiting CD36 has shown therapeutic potential [29]. Furthermore, an excessive engagement in FAO contributes to an elevation in ROS, thereby triggering the peroxidation of polyunsaturated fatty acids (PUFA) and instigating the process of ferroptosis [17]. Significantly, specific cancer cells exhibit a remarkable ability to respond by deploying antioxidant defense mechanisms [30]. CD36 and FAO have also been linked to cancer metastasis [31]. Therefore, studying lip-

id utilization in cancer can improve our understanding of tumor development and lead to innovative strategies for advanced cancer treatment, including addressing chemotherapy resistance and metastasis.

3. Iron metabolism

Iron, a heavy metal, regulates various metabolic processes and plays a crucial role in cellular functions. It is necessary for DNA synthesis, repair, and the formation of Fe-S clusters, which maintain genomic integrity [32]. Proper iron homeostasis is essential for cell proliferation and survival and its involvement in cancer. Cancer cells with high iron levels often exhibit aggressive progression [33]. However, the mechanisms by which cancer cells utilize iron without succumbing to its toxicity are not fully understood. Studying iron metabolism regulation can provide insight into how cancer cells effectively utilize iron while preventing oxidative damage. Understanding these mechanisms is crucial for unraveling the complex relationship between iron and cancer and may contribute to the development of innovative therapeutic approaches.

Iron is taken up by cells through various pathways, including transferrin-mediated transport via the transferrin receptor (TFRC) and CD44/hyaluronate-mediated uptake of multiple iron molecules. Recent studies linked intracellular iron regulation to the mesenchymal state of cancer, particularly through the positive regulation of CD44 by intracellular iron [34]. Intracellular iron plays a crucial role in ATP synthesis, DNA synthesis, and epigenetic regulation [35]. However, excessive intracellular iron can lead to increased ROS, necessitating mechanisms to maintain iron homeostasis. One such mechanism involves ferritin, an iron-binding protein that stores and regulates iron within cells. Excess Fe^{2+} is delivered to ferritin by poly(rC) binding protein (PCBP), and iron can be excreted via prominin-2 in the form of exosomes or targeted for degradation through ferritinophagy mediated by nuclear receptor coactivator 4 (NCOA4) in the cytosol. Ferritinophagy reduces cellular ferritin levels and can induce cell death through ferroptosis, a process driven by excessive intracellular iron [36]. Iron metabolism is implicated in cancer growth and aggressiveness, with elevated iron levels often associated with more aggressive cancers [34,37]. Targeting iron-related mechanisms has emerged as a promising therapeutic approach for cancer treatment [38,39]. These findings highlight the ability of cancer cells to adapt to stress induced by labile iron pools from internal or external sources. Understanding cancer cells' stress response and the restoration of cellular homeostasis can contribute to improving cancer treatment outcomes. Insight into how cancer cells respond to stress and strategies that disrupt cellular adaptation to excessive iron accumulation, leading to cell death, can enhance the effectiveness of cancer therapies.

CELLULAR STRESS AND ITS IMPACT ON CELLULAR FUNCTION AND DISEASE

Maintaining cellular homeostasis is essential for cell survival and proper functioning [40]. Stress-induced adaptation and metabolic alterations play key roles in cancer's response to various stressors, such as DNA damage, energy stress, and oxidative stress (Fig. 2). Metabolic rewiring, distinct from normal cells, plays a significant role in cancer malignancy, with different metabolites contributing to signaling, structure, and proliferation [2]. Understanding cellular stress responses

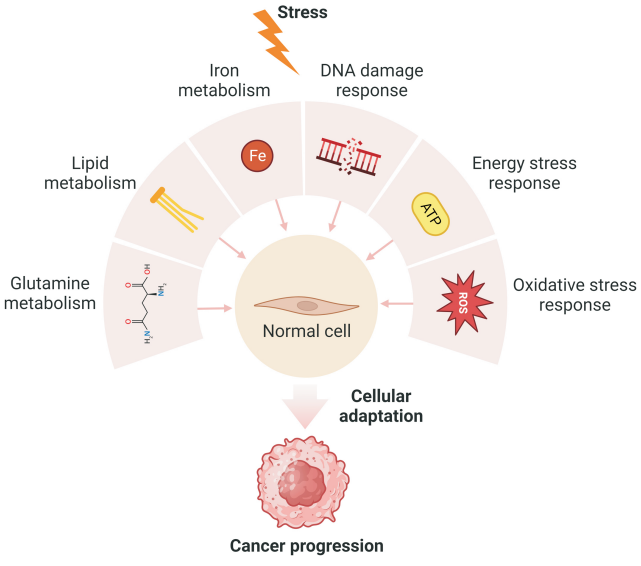

Fig. 2. Cancer cells evade cellular stress-induced cell death through activation of metabolic alteration and damage response pathway. Cancer cells manage to respond to and adapt to cellular stress by activating specific cellular pathways related to metabolic alterations and damage response. These pathways include DNA damage response, energy response, and oxidative stress response. Cancer cells adapt and survive stress-induced cell death by altering their metabolism in response to cellular stress that triggers regulated cell death. Understanding these mechanisms is crucial for developing effective strategies to target cancer cells and improve treatment outcomes.

and metabolic rewiring in cancer can offer valuable insight into cancer adaptation and resistance, suggesting innovative therapeutic strategies in cancer treatment.

1. DNA damage

The preservation of DNA integrity and effective response to damage is critical for cellular function as genetic information is stored within the nucleus. The DNA damage response (DDR) mechanism enables cells to adapt and maintain their functionality in the presence of DNA damage from internal and external sources. A comprehensive understanding of cellular responses and adaptations to DNA damage offers valuable insight into the persistence and proliferation of cancer cells despite these challenges [41].

Two important mechanisms in the field of DNA damage are cell cycle arrest and DNA damage repair. When cells experience DNA damage, the cell cycle halts in order to prevent mutations. This process is regulated by the ataxia telangiectasia mutated (ATM) and the ATM- and Rad3-related signaling pathways. During cell cycle arrest, cells repair or bypass the damage, allowing replication to continue. Different pathways, such as single-strand break repair, base excision repair, homologous recombination, and non-homologous end joining for double-strand break repair, exist for repairing different types of DNA damage. Cells have developed avoidance mechanisms to counteract DNA damage and replication stress. These mechanisms include replication fork reversal and translesion synthesis. DDR assumes a pivotal role in orchestrating cell death, thereby maintaining the organism's overarching homeostasis during instances of profound DNA damage [40]. Consequently, the inability to trigger cell death might potentially fuel the initiation of cancer and the onset of senescence. Furthermore, cancer cells possess the capability to dampen their susceptibility to anti-cancer medications by deploying strategies that obstruct cell death pathways triggered by cellular stress [42]. Cancer cells exploit the dysregulated DDR to sustain proliferation [43]. Targeting DDR with anticancer agents like platinum derivatives, topoisomerase inhibitors, alkaloids, and taxanes has displayed therapeutic efficacy [44]. However, conventional therapies have limitations, and cancer metabolism plays a role in therapy resistance [45]. Metabolites and DDR alterations influence each other [46,47]. Understanding their interplay could enhance cancer treatment strategies.

2. Energy stress

Energy stress is a critical factor in tumorigenesis and cancer progression, as cellular survival heavily relies on the availability of energy. It can arise from a decrease in energy production or an increase in energy consumption [48]. However, the mechanisms through which cancer cells adapt to energy stress conditions and their impact on cancer progression remain poorly understood. Mitochondria play a significant role in responding to energy stress, primarily through oxidative phosphorylation (OXPHOS) [49]. Since solid tumors often face microenvironmental stressors like nutrient and oxygen deficiencies, understanding energy stress in cancer is crucial for targeting various pathways.

Proteins, including AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR), have a significant impact on cellular responses to energy stress, influencing cell survival. AMPK senses energy stress by detecting ATP depletion through its binding domain [50]. It restores ATP balance by inhibiting ATP-consuming processes and promoting ATP-generating processes, regulating metabolic pathways that enable cells to survive energy stress [48,51]. Under severe energy stress, AMPK suppresses mTORC1 signaling, resulting in cell cycle arrest and the activation of apoptosis-inducing factors [52]. mTOR, in turn, responds to cellular energy and nutrient levels, modulating gene expression for cell proliferation. Energy availability determines mTORC1 pathway activity, which affects cancer cell proliferation and resistance to anti-cancer therapies [53,54]. Although more research is needed to fully understand how cancer cells exploit energy stress for tumor progression, it is clear that energy stress-responsive mechanisms can impact cellular metabolism, promoting cancer cell growth or inhibiting cell death. Targeting energy stress through diverse pathways holds great promise as a more effective strategy for cancer treatment, considering the heightened energy and nutrient demands of cancer cells compared to normal cells.

3. Oxidative stress

ROS, which are metabolic byproducts, have dual roles in cellular processes. They regulate transcription and metabolism. However, excessive ROS can cause oxidative damage, impacting cellular organelles and DNA. Cells employ mechanisms to maintain redox homeostasis [55,56]. The effective management of oxida-

tive stress is crucial in cancer, where ROS levels are elevated due to hyperproliferation. Remarkably, cancer cells use ROS as signaling molecules for cancer progression. However, excessive ROS accumulation can be cytotoxic. Understanding the regulatory mechanisms of ROS in cancer is important for developing effective cancer therapies.

ROS can accumulate in cells, primarily from mitochondria during ATP production, generating O_2^- radicals [57]. Mitochondrial dysfunction or low oxygen levels can increase ROS production. Cells manage ROS by converting O_2^- radicals to H_2O_2 through superoxide dismutase, and hydroxyl radicals can form via iron-dependent Fenton reactions. Peroxiredoxin and glutathione peroxidase contribute to maintaining cellular ROS balance. These reactions rely on reduced thioredoxin, reduced glutathione, and NADPH as an electron donor. Cysteine and NADPH metabolism are crucial for responding to oxidative damage [58]. Thus, cellular processes regulate ROS levels, preserving redox balance. Elevated oxidative stress in skeletal muscle has been found to hinder metastatic cancer survival, suggesting the potential of targeting oxidative damage in cancer treatment [59]. However, cancer cells may activate antioxidant defense pathways, and traditional chemotherapy-induced oxidative damage can paradoxically promote cancer progression [60]. Understanding how cells adapt to stress is vital for maintaining redox balance and enhancing the efficacy of anti-cancer therapies.

STRATEGIES THAT TARGET DYSREGULATED CELLULAR HOMEOSTASIS IN CANCER

The heterogeneity of cancer presents challenges for conventional therapies, resulting in suboptimal treatment outcomes, the persistence of cancer cells, and the development of resistance, ultimately leading to cancer recurrence. Novel strategies are urgently needed for comprehensive cancer eradication. Cancer commonly undergoes metabolic rewiring, altering its metabolic pathways to create a favorable environment for cell survival even during anti-cancer treatments [61]. This adaptive response highlights the potential of combined therapies that induce stress while targeting specific metabolic alterations to enhance the efficacy of cancer treatment.

Cancer cells adapt to stress by inducing metabolic alterations, such as increased DNA synthesis and glutamine metabolism in radiotherapy-resistant cases [45,62]. The role of mTORC1 is crucial in promoting cancer growth and regulating diverse metabolic pathways, including glutamine metabolism [53,63]. Cancer exhibits heterogeneity through metabolic adaptations across various types, such as the metabolic plasticity of breast cancer via hypoxia-inducible factor-α [64]. Dysregulated DDR contributes to resistance in prostate cancer. However, targeting FAO or the intracellular phosphatidylinositol pool can overcome it [41,65]. The disruption of metabolic homeostasis triggers regulated cell death and ferroptosis in response to cellular stress [51]. Targeting specific metabolic pathways under stress conditions offers a promising strategy to reduce cancer's adaptability, enhancing treatment efficacy.

CONCLUSIONS

Cancer cells undergo metabolic alterations to adapt to increased stress levels, unlike normal cells. Recent studies have investigated the impact of cellular stress on metabolic changes (Table 1). Targeting specific metabolic pathways by inhibiting them has shown promise

Table 1. Promising metabolic pathways for novel therapeutic approaches targeting cellular stress responses in various cancer types

Therapy induced stress	Metabolic alteration	Promising strategy to overcome therapy resistance	Cancer	Reference
DNA damage	Purine metabolism	GTP synthesis inhibitor	Glioblastoma	Zhou et al [45]
Energy stress	Leucine metabolism	SLC7A5 inhibitor	ER+breast cancer	Saito et al [68]
Mitochondrial damage	Glutamine metabolism	Glutathione synthesis inhibitor	Breast cancer	McGuirk et al [69]
Oxidative stress	Pentose phosphate pathway	Glutaminase inhibitor	Melanoma	Aurora et al [70]
Oxidative stress	Fatty acids uptake	β-oxidation inhibitor	Ovarian cancer	Tan et al [71]
Oxidative stress	Iron metabolism	Nuclear factor erythroid 2-related factor 2 (NRF2) inhibitor	Ovarian cancer	Anandhan et al [72]

GTP: guanosine triphosphate, ER: estrogen receptor.

in overcoming cancer resistance and effectively treating the disease. For example, enzalutamide and apalutamide, which are Food and Drug Administration-approved drugs, target the lipid uptake pathway and are used for prostate cancer treatment [66,67]. Cancer can develop resistance to conventional anti-cancer drugs through metabolic adaptations [68-72]. The current strategies primarily focus on inducing stress in cancer cells, but the heterogeneity of cancer still allows for the possibility of recurrence. Therefore, by simultaneously regulating specific metabolite pools to adapt to stress while inducing stress, we can consistently steer cancer characteristics in a specific direction and ultimately drive various heterogeneous cancers to their demise. Such research efforts will contribute to reducing the risk of cancer recurrence and improving the overall survival rates of cancer patients.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Writing – original draft: CJL. Writing – review & editing: CJL, HY.

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