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Targeting Cancer Stem Cells in Obese Individuals: Role of Natural Product-Derived Epigenetic Modifiers

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ABSTRACT

Obesity is a well-established risk factor for cancer initiation, progression, and recurrence. One of the key drivers of tumorigenesis in obese individuals is the presence of cancer stem cells (CSCs), a subpopulation of tumor cells with self-renewal, differentiation, and tumor-initiating capabilities. Emerging evidence highlights that obesity-induced chronic inflammation, insulin resistance, and adipokine dysregulation contribute to the maintenance and expansion of CSCs, exacerbating cancer aggressiveness and therapy resistance. Epigenetic modifications, such as DNA methylation, histone acetylation, and non-coding RNA regulation, play a pivotal role in CSC plasticity and adaptation to the obesogenic tumor microenvironment. Natural product-derived compounds with epigenetic-modifying properties have gained significant attention as promising therapeutic agents for targeting CSCs in obesity-associated malignancies. Phytochemicals such as curcumin, resveratrol, epigallocatechin gallate (EGCG), sulforaphane, and genistein demonstrate potent anti-CSC activities by modulating key epigenetic regulators, reprogramming oncogenic gene expression, and sensitizing CSCs to conventional therapies. This review provides an in-depth analysis of the molecular mechanisms by which obesity promotes CSC maintenance, outlines the epigenetic landscape of CSCs, and explores the potential of natural product-derived epigenetic modifiers in eradicating CSCs in obese cancer patients. The integration of these agents into clinical regimens may offer a novel, non-toxic, and multifaceted strategy to improve cancer treatment outcomes in the context of obesity.

Keywords: Cancer stem cells, Obesity, Epigenetic modifiers, Natural products, Tumor microenvironment

INTRODUCTION

The worldwide surge in obesity prevalence over the last several decades has emerged as a critical public health crisis, fundamentally altering patterns of morbidity and mortality across the globe[1–3]. Once primarily viewed as a metabolic disorder characterized by excessive adiposity and associated complications such as diabetes and cardiovascular disease, obesity is now unequivocally recognized as a potent oncogenic condition[4–6]. This shift in perspective has been driven by an increasing body of epidemiological and experimental evidence linking obesity to elevated risks of numerous cancers, including but not limited to breast, colorectal, liver, pancreatic, endometrial, and esophageal malignancies[7–10].

Obesity contributes to cancer incidence and progression through a complex network of biological mechanisms that extend far beyond mere fat accumulation[11–13]. Central to this nexus are endocrine disruptions, chronic low-grade inflammation, and profound metabolic alterations, each acting synergistically to promote tumorigenesis. In obese individuals, excess adipose tissue is metabolically active, secreting a myriad of adipokines and inflammatory mediators such as leptin, adiponectin (which is usually reduced), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6)[14–16]. These factors establish a pro-tumorigenic systemic milieu that favors malignant transformation and tumor progression. From a metabolic standpoint, obesity induces insulin resistance, leading to hyperinsulinemia and elevated levels of insulin-like growth factor-1 (IGF-1), both of which have mitogenic and anti-apoptotic effects on pre-neoplastic and cancer cells. Moreover, excess circulating free fatty acids in obesity not only serve as fuel for rapidly dividing tumor cells but also generate lipotoxicity that exacerbates oxidative stress and DNA damage, further driving carcinogenesis.

A particularly important and emerging concept in cancer biology is the role of cancer stem cells (CSCs), a small subpopulation within tumors endowed with the capacity for self-renewal, differentiation, and resistance to conventional therapies[17–19]. CSCs are implicated in tumor initiation, progression, metastasis, and relapse, making them critical targets for effective cancer treatment. The obesogenic environment profoundly influences

CSC biology by providing the necessary biochemical and cellular signals to support CSC maintenance and expansion[20–23].
This supportive niche in obesity is characterized by elevated systemic and local concentrations of insulin, leptin, proinflammatory cytokines, and free fatty acids, all of which modulate CSC behavior through distinct but interconnected signaling pathways. The interplay of these factors facilitates CSC survival, self-renewal, and plasticity, which translates clinically into more aggressive tumors with poorer prognoses[24]. Underlying these biological changes are epigenetic mechanisms—heritable yet reversible modifications of DNA and chromatin structure that do not alter the genetic code but profoundly influence gene expression. These include DNA methylation, histone modifications, and the regulation by non-coding RNAs such as microRNAs and long non-coding RNAs. Epigenetic dysregulation is a hallmark of CSCs, underpinning their ability to adapt to environmental changes such as those induced by obesity[24]. Recent advances have highlighted natural products as promising epigenetic modulators that can target CSCs. Many bioactive compounds derived from dietary sources (e.g., polyphenols like resveratrol and curcumin, alkaloids like berberine, and flavonoids like quercetin) possess multi-targeted actions that can reverse aberrant epigenetic marks in CSCs, reduce tumorigenicity, and sensitize cancer cells to conventional therapies[1, 25–27]. These natural agents offer a potentially safer, more accessible approach to cancer therapy, especially in obesity-associated cancers where metabolic and inflammatory dysregulations complicate treatment. This review thus focuses on the complex interface between obesity, CSC biology, and epigenetic regulation, emphasizing the therapeutic potential of natural product-derived epigenetic modifiers. Understanding these interactions can pave the way for novel, more effective interventions to combat obesity-driven cancer aggressiveness and improve patient outcomes.

2. Obesity and Cancer Stem Cell Biology

Obesity significantly alters the systemic and local tumor microenvironment (TME), creating conditions highly favorable for the survival, proliferation, and expansion of cancer stem cells (CSCs)[28]. The traditional view of adipose tissue as a mere energy reservoir has evolved dramatically, recognizing it as a highly dynamic and active endocrine organ that secretes numerous bioactive molecules influencing tumor biology. In obese individuals, dysfunctional adipose tissue undergoes hypertrophy and hypoxia, leading to an inflammatory state characterized by increased secretion of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and adipokines like leptin and resistin, all of which play pivotal roles in promoting CSC traits[28].
Leptin, a hormone primarily produced by adipocytes, is elevated in obesity and exerts significant oncogenic effects on CSC populations[29–31]. It activates critical signaling pathways such as STAT3, Notch, and Wnt/β-catenin, which are fundamental for CSC self-renewal, maintenance of stemness, epithelial-mesenchymal transition (EMT), and resistance to chemotherapy. EMT is a process by which epithelial cells acquire mesenchymal features, enhancing motility and invasiveness, essential properties for metastasis and tumor dissemination. By promoting EMT, leptin contributes to the plasticity and aggressiveness of CSCs, thereby driving tumor progression[23, 32, 33].
Chronic inflammation in the obese state leads to elevated reactive oxygen species (ROS) generation, which, while damaging at high levels, at moderate levels can function as signaling molecules to activate NF-κB, a transcription factor intimately involved in inflammation and cancer. NF-κB activation further enriches the CSC population by inducing the expression of stemness-related genes and promoting cellular heterogeneity within tumors[14, 34–36]. This inflammatory milieu also influences the TME by recruiting immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs), which protect CSCs from immune surveillance and clearance.
Obesity also drives metabolic reprogramming, a hallmark of cancer and particularly prominent in CSCs. Unlike differentiated tumor cells, CSCs preferentially utilize glycolysis (the Warburg effect) and lipid biosynthesis pathways to meet their increased energetic and biosynthetic needs[37]. The elevated availability of free fatty acids in obesity provides essential substrates for membrane synthesis, energy production, and the generation of signaling molecules that sustain CSCs. Additionally, metabolic intermediates produced through altered pathways can influence epigenetic modifications, creating a feedback loop that stabilizes the CSC phenotype[37].
The obesity-induced TME is further characterized by hypoxia, a condition of reduced oxygen availability, which activates hypoxia-inducible factors (HIFs). HIF signaling supports CSC maintenance by promoting metabolic adaptation, angiogenesis, and immune evasion. Hypoxia also synergizes with oxidative stress to induce genetic and epigenetic changes, fostering tumor heterogeneity and CSC plasticity[24, 38]. Importantly, the immune landscape in obesity is skewed toward an immunosuppressive profile. The increase in regulatory T cells, MDSCs, and TAMs, combined with chronic inflammation, dampens anti-tumor immune responses. This immunosuppressive niche not only allows CSCs to evade immune destruction but also facilitates tumor growth and metastasis[38].
Taken together, these insights highlight the intricate crosstalk between obesity-induced systemic factors, local adipose-derived signals, metabolic reprogramming, and immune modulation that collectively support CSC survival and expansion[39]. This complex interplay underscores the necessity of developing targeted

therapeutic approaches that disrupt these interactions. Interventions that modulate key signaling pathways like STAT3, Wnt/β-catenin, and NF-κB, or that reprogram the metabolic and immune landscape, hold promise in mitigating the enhanced tumorigenic potential conferred by obesity on CSCs[39].
In sum, obesity transforms the TME into a fertile ground for CSC maintenance and propagation, thereby contributing to more aggressive cancers with poor clinical outcomes. Understanding these mechanisms is critical for designing effective therapies that can overcome obesity-driven cancer progression.

3. Epigenetic Regulation of Cancer Stem Cells

Epigenetic modifications constitute a fundamental layer of regulation that controls cancer stem cell (CSC) biology by modulating gene expression patterns without altering the underlying DNA sequence[40]. This dynamic and reversible mechanism enables CSCs to rapidly adapt to environmental stimuli, maintain their stemness, and drive tumor heterogeneity and progression. Unlike genetic mutations, epigenetic changes are reversible, making them attractive therapeutic targets in oncology, particularly for eradicating CSCs, which are often resistant to conventional therapies[40].
One of the most extensively studied epigenetic mechanisms in CSC regulation is DNA methylation, primarily mediated by DNA methyltransferases (DNMTs). DNMTs catalyze the addition of methyl groups to the cytosine residues of CpG dinucleotides, typically leading to transcriptional repression. In CSCs, aberrant hypermethylation often silences critical tumor suppressor genes such as p16^INK4a^ and PTEN, thereby promoting uncontrolled self-renewal and survival[41]. Conversely, hypomethylation of oncogenes or repetitive elements can also occur, contributing to genomic instability and tumor aggressiveness. Dysregulated DNA methylation patterns in CSCs thus create an epigenetic landscape favorable for tumor initiation, progression, and metastasis[41].
In addition to DNA methylation, histone modifications serve as another pivotal epigenetic mechanism influencing CSC fate. Histones, the protein components around which DNA is wrapped, undergo various post-translational modifications including acetylation, methylation, phosphorylation, and ubiquitination[42]. These modifications are catalyzed by specific enzymes such as histone acetyltransferases (HATs), histone deacetylases (HDACs), histone methyltransferases, and demethylases[42]. For example, histone acetylation typically relaxes chromatin structure, enhancing gene transcription, while deacetylation condenses chromatin, silencing gene expression. CSCs exploit these histone modifications to regulate genes involved in self-renewal, differentiation, and epithelial-mesenchymal transition (EMT)—a process closely linked to invasion and metastasis. Altered activity of HDACs in CSCs, for instance, has been associated with maintenance of stemness and resistance to chemotherapy[42].
Beyond these classical epigenetic marks, **non-coding RNAs**, especially microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), have emerged as central regulators of CSC functions. MiRNAs are short RNA molecules that bind to messenger RNAs to suppress their translation or promote degradation, thereby fine-tuning the expression of genes controlling proliferation, apoptosis, and differentiation[43]. Dysregulation of miRNAs such as miR-34a and let-7 has been implicated in enhanced CSC self-renewal and chemoresistance. Similarly, lncRNAs long transcripts without protein-coding potential, modulate gene expression through diverse mechanisms, including chromatin remodeling and interaction with transcription factors. Certain lncRNAs have been shown to promote CSC phenotypes by regulating key signaling pathways like Wnt, Notch, and Hedgehog[43].
In the context of obesity, systemic metabolic and inflammatory changes create an epigenetic environment that further supports CSC maintenance and expansion. Chronic inflammation, hyperinsulinemia, and increased oxidative stress, common in obese individuals, induce aberrant epigenetic modifications that reinforce oncogenic gene expression profiles[44]. For example, inflammatory cytokines such as TNF-α and IL-6 can modulate DNMT and HDAC activities, resulting in the epigenetic reprogramming of CSCs. This interplay partially explains why obesity is linked with higher incidence and poorer prognosis in several cancers.
Targeting the epigenetic machinery offers a promising strategy for CSC eradication. However, many synthetic epigenetic drugs, such as DNMT inhibitors (e.g., 5-azacytidine) and HDAC inhibitors (e.g., vorinostat), often lack specificity and may induce off-target toxicities. To overcome these limitations, attention has shifted toward natural epigenetic modifiers derived from dietary and medicinal plants[44]. Compounds such as curcumin, resveratrol, and epigallocatechin gallate (EGCG) have demonstrated the ability to modulate DNMT and HDAC activity, restore normal epigenetic patterns, and reduce CSC viability with minimal side effects[45, 46]. These natural agents hold potential not only as monotherapies but also as adjuvants to sensitize CSCs to conventional treatments.
In sum, epigenetic regulation is a cornerstone of CSC biology, orchestrating their self-renewal, plasticity, and therapy resistance. A deeper understanding of the epigenetic networks in CSCs, especially within obesity-driven tumor contexts, will facilitate the development of more effective, targeted, and safer therapeutic approaches aimed at eliminating these critical tumor-initiating cells.

4. Natural Product-Derived Epigenetic Modifiers: Mechanisms and Efficacy

Natural products such as polyphenols, alkaloids, and isothiocyanates exhibit potent epigenetic-modulating properties with anti-CSC effects. These compounds influence multiple pathways simultaneously, making them ideal candidates for CSC-targeted therapies in obesity-associated cancers.

4.1 Curcumin: Curcumin is a bioactive polyphenol extracted from the rhizome of *Curcuma longa*, widely known for its anti-inflammatory and anticancer properties[47–49]. At the epigenetic level, curcumin modulates key enzymes such as DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), which are often dysregulated in cancer stem cells (CSCs)[47, 50]. By inhibiting DNMTs and HDACs, curcumin can reactivate silenced tumor suppressor genes that play a critical role in halting tumor growth and progression. Moreover, curcumin disrupts important oncogenic signaling pathways, including STAT3 and NF-κB, both of which are activated by leptin, a hormone elevated in obesity and implicated in CSC expansion. By attenuating leptin-induced STAT3 and NF-κB signaling, curcumin reduces the self-renewal and survival capabilities of CSCs. In obesity-related cancers, this dual epigenetic and signaling inhibition makes curcumin especially promising. Additionally, curcumin's antioxidant effects help mitigate the oxidative stress common in obese tumor microenvironments, further contributing to its anticancer efficacy[51, 52]. Its safety profile and natural origin position curcumin as a potential adjunct to conventional therapies targeting CSCs, especially in obese patients, where leptin signaling drives aggressive cancer phenotypes.

4.2 Resveratrol: Resveratrol is a naturally occurring polyphenol predominantly found in grape skins, berries, and peanuts, renowned for its cardioprotective and anticancer activities[53–55]. At the epigenetic level, resveratrol inhibits both class I and class II histone deacetylases (HDACs), leading to a more relaxed chromatin state that favors the expression of tumor-suppressive genes. This includes the upregulation of microRNAs such as miR-34a, which has tumor suppressor functions and plays a role in inhibiting epithelial-to-mesenchymal transition (EMT), a process linked to cancer metastasis and CSC plasticity[54, 56]. In obesity models, resveratrol improves insulin sensitivity, reduces systemic inflammation, and lowers oxidative stress, which are critical factors contributing to CSC maintenance and expansion. Importantly, resveratrol treatment has been shown to reduce the expression of CSC markers, thereby impairing their ability to drive tumor growth and resistance to therapy[56, 57]. By targeting both epigenetic regulators and metabolic dysfunctions typical of obesity, resveratrol offers a multi-faceted approach to limit CSC-driven tumor progression, making it a promising natural compound for combined therapeutic strategies.

4.3 Epigallocatechin Gallate (EGCG): Epigallocatechin gallate (EGCG) is the predominant catechin found in green tea and is recognized for its powerful antioxidant, anti-inflammatory, and anticancer effects. EGCG acts as a potent epigenetic modulator by inhibiting DNA methyltransferase 1 (DNMT1), Enhancer of Zeste Homolog 2 (EZH2), and histone deacetylases (HDACs), enzymes often overexpressed in cancer and involved in silencing tumor suppressor genes[45, 46]. Through these actions, EGCG restores the expression of key tumor suppressors such as p16 and E-cadherin, which regulate cell cycle and cell adhesion, respectively. Moreover, EGCG interferes with the Wnt/β-catenin signaling pathway, a critical pathway for the maintenance and self-renewal of CSCs[58]. By disrupting Wnt signaling, EGCG impairs the proliferative and survival capacity of CSCs. Additionally, in the context of obesity, EGCG has been shown to improve metabolic parameters and reduce chronic inflammation, both of which contribute to a tumor-promoting environment[46]. Due to its multifaceted epigenetic and metabolic actions, EGCG represents a valuable natural agent for targeting CSC populations and enhancing the effectiveness of conventional cancer therapies.

4.4 Sulforaphane: Sulforaphane is a naturally occurring isothiocyanate found in cruciferous vegetables such as broccoli, Brussels sprouts, and cabbage[59]. It is a well-characterized histone deacetylase (HDAC) inhibitor that exerts profound effects on the epigenetic regulation of cancer stem cells (CSCs)[60]. By inhibiting HDACs, sulforaphane promotes the re-expression of genes involved in differentiation and apoptosis, thereby disrupting CSC self-renewal and tumor-initiating capacity. It also downregulates aldehyde dehydrogenase 1 (ALDH1), a recognized CSC marker associated with chemoresistance and metastasis. Furthermore, sulforaphane suppresses β-catenin signaling, a key driver of CSC maintenance and proliferation. Beyond its direct effects on CSCs, sulforaphane reduces systemic and local inflammation—common hallmarks in obesity-driven cancers—by modulating inflammatory cytokines and signaling pathways[60]. It also improves metabolic health by enhancing insulin sensitivity and lipid metabolism, which helps normalize the tumor microenvironment. These combined actions make sulforaphane a potent natural compound with dual benefits in targeting CSCs and ameliorating obesity-associated cancer risks.

4.5 Genistein: Genistein is a naturally occurring isoflavone predominantly found in soy products and is noted for its anti-cancer and anti-inflammatory properties[61]. It exerts epigenetic effects primarily through modulation of microRNA (miRNA) expression, impacting pathways critical for cancer stem cell (CSC) survival and expansion. Genistein inhibits oncogenic signaling cascades such as Akt and NF-κB, both implicated in CSC maintenance, proliferation, and resistance to therapy[62]. By downregulating these pathways, genistein sensitizes CSCs to conventional chemotherapeutic agents, potentially overcoming drug resistance. Additionally, genistein exhibits beneficial effects on metabolic health by exerting anti-obesity properties, such as improving

insulin sensitivity and reducing adipose tissue inflammation[62]. These actions indirectly disrupt the pro-tumorigenic microenvironment that supports CSC expansion in obese individuals. The compound's capacity to simultaneously target epigenetic regulation, signaling pathways, and metabolic dysfunctions underscores its therapeutic potential as an adjunct agent to standard cancer treatments, particularly in obesity-associated malignancies.

5. Therapeutic Challenges and Future Perspectives

Despite promising preclinical evidence, clinical translation of natural epigenetic modifiers faces challenges. These include poor bioavailability, lack of standardized dosing, variability in natural product composition, and limited clinical trials focused on obese cancer patients. Advances in nanotechnology, such as nanoparticle encapsulation and prodrug design, can enhance the pharmacokinetics and tissue targeting of these compounds. Moreover, identifying biomarkers to stratify patients based on obesity status, CSC burden, and epigenetic signatures will be critical for precision therapy. Integrative approaches combining dietary intervention, natural epigenetic compounds, and standard anticancer regimens may offer durable responses in obese patients.

Future research should focus on well-designed clinical trials, mechanistic studies in obese-specific models, and combinatorial strategies that exploit the metabolic and epigenetic vulnerabilities of CSCs.

6. CONCLUSION

The interplay between obesity, cancer stem cells, and epigenetic dysregulation presents a complex but targetable axis in cancer pathogenesis. Natural product-derived epigenetic modifiers offer a promising avenue to disrupt this axis, reprogram CSCs, and improve cancer outcomes in obese individuals. Their multi-targeted mechanisms, low toxicity, and compatibility with conventional therapies make them attractive candidates for inclusion in future oncologic treatment protocols. Bridging the gap between bench and bedside will require concerted efforts in clinical research, formulation science, and systems biology.

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