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Systemic Review

Autophagy in Cancer Stem Cells: Friend, Foe, or Both?

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Abstract

Autophagy, a conserved cellular degradation process, exhibits dual roles in cancer—suppressing tumorigenesis early while promoting progression in established tumors. Cancer stem cells (CSCs), key drivers of therapy resistance and metastasis, leverage autophagy for survival, yet the therapeutic potential of autophagy inhibition remains contested. This meta-analysis evaluates autophagy's context-dependent role in CSCs and the efficacy of its inhibition across malignancies. Following PRISMA guidelines, 45 experiments from 26 preclinical and clinical studies were analyzed. Autophagy inhibition significantly reduced CSC populations (pooled SMD = -1.89; 95% CI: -2.75 to -1.03; $p < 0.001$), with heterogeneity ($I^2 = 72\%$) reflecting cancer-type variability. Subgroup analyses revealed pronounced effects in leukemia (SMD = -1.85) and breast cancer (SMD = -3.02), while glioblastoma showed moderate reductions (SMD = -1.01). Clinically, combining chloroquine with temozolomide improved glioblastoma survival (HR = 0.36; $p = 0.001$). Autophagy supports CSC resilience through metabolic adaptation, stemness maintenance, and therapy resistance, yet its tumor-suppressive roles in normal cells necessitate precision. Findings underscore autophagy inhibition as a promising strategy to target CSCs, particularly in advanced disease, but highlight the imperative for context-driven approaches, biomarker-guided patient stratification, and combinatorial regimens to optimize therapeutic outcomes. This duality positions autophagy as both friend and foe in CSCs.

Introduction

Autophagy, an evolutionarily conserved cellular mechanism, plays a paradoxical role in cancer biology, functioning as both a tumor suppressor and promoter depending on the disease stage and cellular context [1,2]. This lysosome-dependent process eliminates damaged organelles and protein aggregates, maintaining genomic stability and cellular homeostasis under physiological conditions [3,4].

In early carcinogenesis, autophagy acts as a protective mechanism by preventing the accumulation of dysfunctional mitochondria and reactive oxygen species (ROS), thereby reducing oncogenic stress [5]. For instance, Beclin-1-mediated autophagy suppresses HER2-driven tumorigenesis in breast cancer, while its reduced expression correlates with poor prognosis in cervical and pancreatic malignancies [6-8]. However, in established tumors, autophagy is co-opted by cancer cells to sustain survival under metabolic stress, fostering therapy resistance and recurrence [1,9]. This duality is particularly evident in cancer stem cells (CSCs), a subpopulation endowed with self-renewal, differentiation potential, and tumor-initiating capacity, which drive tumor heterogeneity, metastasis, and therapeutic failure [10,11].

CSCs, first identified in leukemia [12] and later in solid tumors such as breast [11] and glioblastoma [13], resist conventional therapies through mechanisms like quiescence, enhanced DNA repair, and drug efflux [14,15]. Their resilience is bolstered by autophagy, which supports CSC metabolic adaptation, stemness, and survival in hostile microenvironments [16,17]. For example, hypoxia-inducible factor 1α (HIF1α) activates BNIP3-mediated mitophagy in glioblastoma CSCs, preserving mitochondrial function under hypoxia [18]. Autophagy also intersects with pluripotency pathways, stabilizing NANOG while suppressing p53 in hepatocellular CSCs to maintain an undifferentiated state [16]. These adaptations enable CSCs to evade apoptosis and persist post-treatment, highlighting autophagy's role in therapeutic resistance [19].

The interplay between autophagy and CSC plasticity further complicates therapeutic targeting. Epithelial-mesenchymal transition (EMT), a process linked to metastasis, is regulated by autophagy through pathways like SOX2-β-catenin/Beclin1 in colorectal CSCs [20]. Similarly, H. pylori-induced gastric inflammation drives EMT via autophagy, enhancing migratory capacity [21]. These interactions highlight autophagy's dual function: while it may suppress early

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tumorigenesis by clearing damaged components, it promotes CSC survival and dissemination in advanced disease [1,22]. This context-dependent duality necessitates precision in therapeutic strategies, as indiscriminate autophagy modulation could inadvertently fuel tumor progression.

Clinically, autophagy inhibition has shown promise in sensitizing CSCs to therapy. Combining chloroquine with temozolomide improved survival in glioblastoma patients (HR = 0.36)[23], while targeting mitophagy via PINK1-PARKIN inhibition disrupted CSC mitochondrial homeostasis [24]. However, challenges persist due to autophagy's tumor-suppressive roles in normal cells and the risk of enriching therapy-resistant CSC subclones [25]. Emerging approaches, such as ATG4B inhibitors and intermittent autophagy blockade, aim to balance efficacy with safety [26,27].

Literature Review

Autophagy: A Brief Overview

Autophagy is a highly conserved cellular process responsible for the degradation and recycling of intracellular components, ensuring cellular homeostasis and adaptation to stress [28]. The two primary forms of autophagy; macroautophagy and mitophagy, play distinct yet complementary roles in maintaining cellular integrity.

Macroautophagy

Macroautophagy is the predominant form of autophagy, characterized by the formation of double-membrane vesicles called autophagosomes that sequester cytoplasmic material, including damaged organelles and protein aggregates [2]. The process begins with the elongation of a phagophore, derived from membranes of the endoplasmic reticulum, mitochondria, or plasma membrane, which engulfs cellular debris [29]. The autophagosome then fuses with lysosomes to form autolysosomes, where hydrolytic enzymes degrade the enclosed contents at acidic pH [30]. Macroautophagy is tightly regulated by nutrient availability, with amino acids such as leucine, tyrosine, and methionine acting as key suppressors, while glucagon and amino acid deprivation enhance its activity [29].

Mitophagy

Mitophagy, a selective form of macroautophagy, specifically targets damaged or superfluous mitochondria for degradation, ensuring mitochondrial quality control and metabolic efficiency [31]. The best-characterized mitophagy pathways include the PINK1/Parkin and BNIP3/NIX/FUNDC1 mechanisms. Under conditions of mitochondrial depolarization, PINK1 accumulates on the outer mitochondrial membrane (OMM), recruiting and activating Parkin, an E3 ubiquitin ligase that marks mitochondria for autophagic clearance via ubiquitination [24]. Alternatively, hypoxia-inducible proteins such as BNIP3, NIX, and FUNDC1 directly interact with LC3 on autophagosomal membranes, promoting mitochondrial engulfment [32].

Role in Cellular Homeostasis

Macroautophagy and mitophagy are essential for maintaining cellular homeostasis by eliminating dysfunctional components, recycling macromolecules, and mitigating oxidative stress [3]. Macroautophagy provides bulk degradation during nutrient deprivation, while mitophagy ensures mitochondrial fitness by removing damaged organelles that could otherwise generate excessive reactive oxygen species (ROS) [33]. Dysregulation of these processes is implicated in various pathologies, including neurodegeneration and cancer, underscoring their critical role in cellular health [34].

Cancer Stem Cells: Characteristics and Significance

Cancer stem cells (CSCs), also referred to as tumor-initiating cells or tumor-propagating cells, constitute a rare subpopulation within tumors that exhibit stem-like properties, including self-renewal, differentiation potential, and tumorigenicity [35]. First identified in acute myeloid leukemia [12] and subsequently in various solid malignancies such as breast, pancreatic, colon, and brain cancers [13,36,37], CSCs are functionally defined by their ability to initiate and sustain tumor growth, recapitulate tumor heterogeneity upon transplantation, and resist conventional therapies [10][11]. These cells are typically identified through specific surface markers (e.g., CD44+/CD24− in breast cancer, CD133+ in glioblastoma and colon cancer) and demonstrate a hierarchical organization within tumors, where they give rise to differentiated progeny that comprise the bulk tumor mass [38,39].

Self-Renewal

Self-renewal is a defining feature of CSCs, enabling them to maintain their population while generating differentiated progeny [10]. This capacity is mediated through both symmetric and asymmetric cell divisions. Symmetric divisions produce two identical CSCs, expanding the stem cell pool, whereas asymmetric divisions yield one CSC and one differentiated cell, preserving the balance between stemness and differentiation [40]. The regulation of self-renewal is governed by conserved developmental signaling pathways, including Wnt/β-catenin, Hedgehog (Hh), and Notch, which are frequently dysregulated in cancer [41,42]. Additionally, epigenetic modifications and alterations in key regulatory molecules such as PTEN and polycomb group proteins further contribute to the aberrant self-renewal capacity of CSCs [43]. The sustained proliferative potential of CSCs underpins tumor initiation, progression, and recurrence, making them a critical therapeutic target [44].

Differentiation Potential

CSCs possess the ability to differentiate into multiple cell lineages, contributing to the cellular heterogeneity observed within tumors [10]. This plasticity is exemplified by their capacity to generate not only tumorigenic daughter cells but also non-tumorigenic differentiated progeny that form the bulk of the tumor [45]. In some cases, CSCs can transdifferentiate into specialized cell types, such as vascular endothelial cells, thereby promoting tumor angiogenesis [46,47]. This differentiation potential is tightly regulated by the tumor microenvironment, which provides cues that influence CSC fate decisions. For instance, the epithelial-mesenchymal transition (EMT) has been implicated in conferring stem-like properties to differentiated cancer cells, further amplifying the CSC pool [48]. The dynamic interplay between CSCs and their microenvironment underscores their adaptability and role in tumor evolution.

Tumorigenicity

The tumorigenic potential of CSCs is a hallmark of their functional significance in cancer biology [10]. Transplantation assays have demonstrated that as few as 100–1,000 CSCs can initiate tumor formation in immunocompromised mice, whereas bulk tumor cells fail to engraft [11],49]. This robust tumor-initiating capacity is attributed to their self-renewal

and differentiation properties, as well as their ability to evade immune surveillance and adapt to hostile microenvironments [45]. Furthermore, CSCs exhibit enhanced resistance to conventional therapies, including chemotherapy and radiation, due to mechanisms such as quiescence, upregulated drug efflux pumps (e.g., ABC transporters), and efficient DNA repair systems [14,50]. These attributes not only facilitate tumor recurrence but also contribute to metastatic dissemination, as CSCs are often implicated in the colonization of distant organs [51].

Role of Cancer Stem Cells in Tumor Heterogeneity, Metastasis, and Therapy Resistance

Cancer stem cells (CSCs) play a pivotal role in shaping tumor biology through their contributions to intratumoral heterogeneity, metastatic dissemination, and resistance to conventional therapies. These properties collectively render CSCs formidable adversaries in cancer treatment and key drivers of poor clinical outcomes.

Tumor Heterogeneity

CSCs serve as the primary architects of tumor heterogeneity through their unique capacity for both self-renewal and multilineage differentiation [10]. This dual functionality enables a single CSC to generate the diverse cellular populations that characterize malignant tumors [11]. The resulting heterogeneity manifests not only in cellular morphology and marker expression but also in functional behaviors, creating a tumor ecosystem where distinct subpopulations occupy specialized niches [52]. Such heterogeneity poses significant challenges for treatment, as different cellular subsets may exhibit varying sensitivities to therapeutic agents [15]. Furthermore, the dynamic plasticity of CSCs, particularly their ability to undergo epithelial-mesenchymal transition (EMT), amplifies this diversity by generating transitional cell states with hybrid phenotypes [48]. This plasticity is regulated by key developmental pathways including Wnt/β-catenin, Notch, and Hedgehog signaling, which are frequently dysregulated in cancer [53].

Metastatic Dissemination

Cancer stem cells (CSCs) are principal mediators of metastatic dissemination, leveraging unique adaptations to navigate the metastatic cascade [54]. Their association with epithelial–mesenchymal transition (EMT) confers enhanced migratory capacity and resistance to anoikis, enabling detachment from primary sites and survival during circulation [55]. Specific CSC subpopulations, such as CD133+/CXCR4+ pancreatic cancer cells and CD44+/α2βhi1/CD133+ prostate cancer cells, exhibit marked proficiency for metastatic homing [36,56]. Successful colonization of distant organs requires CSCs to overcome immune surveillance and adapt to foreign microenvironments, a process facilitated by niche-modifying factors like periostin (POSTN) [51,57]. Notably, circulating CSC clusters demonstrate 25–50-fold higher metastatic efficiency compared to single cells, underscoring their collective survival advantage [58].

Emerging evidence reveals intricate connections between EMT and CSC phenotypic plasticity, with autophagy serving as a critical regulatory node. In colorectal CSCs, EMT is governed by the SOX2-β-catenin/Beclin1/autophagy signaling axis, linking stemness maintenance to invasive potential [20]. Similarly, H. pylori-induced chronic inflammation drives EMT in gastric cancer, where autophagy inhibition reduces mesenchymal phenotypes and migratory capacity [21]. Two conceptual frameworks elucidate the autophagy-EMT-CSC relationship:

1. **Branching Model:** Paracrine signals in the tumor microenvironment (TME) direct EMT-transformed cells toward either circulating CSCs (metastasis-competent) or non-circulating autophagic CSCs (adapted to local hypoxia/stress) [59].
2. **Hierarchical Model:** EMT-derived cells transition into autophagic CSCs under microenvironmental stress (e.g., hypoxia), reverting to circulating CSCs upon exposure to pro-metastatic signals [60]. Both models emphasize bidirectional plasticity, where phenotypic shifts correlate with functional changes in metastatic competence.

Autophagy also influences metastasis through EMT-independent mechanisms. In medulloblastoma, AMBRA1 knockdown disrupts oncogenic signaling, impairing CSC migration and growth [61]. Glioblastoma stem cells rely on autophagy-related factors DRAM1 and p62 to regulate invasion, independent of EMT [62]. Furthermore, microenvironmental stressors dynamically modulate autophagic activity in CSCs: hypoxia and hypoglycemia suppress CD133+ laryngeal CSC proliferation and migration when autophagy is inhibited [63], while oxidative stress in ovarian CSCs triggers ferroptosis, counteracting their tumorigenic and invasive properties [64].

The Dual Role of Autophagy in Cancer Stem Cells

Autophagy demonstrates fundamentally contradictory roles in cancer stem cell (CSC) biology, functioning as both a tumor suppressor and tumor promoter depending on the disease stage and cellular context [1]. This dichotomy presents a significant challenge for therapeutic targeting, as autophagy modulation may produce opposing effects in early versus advanced malignancies. The complex interplay between autophagy and CSC maintenance involves multiple molecular pathways that regulate cellular homeostasis, stress responses, and genomic stability [4]. Understanding these context-dependent mechanisms is crucial for developing effective CSC-targeted therapies that account for autophagy's dual nature.

Tumor-Suppressive Mechanisms in Early Carcinogenesis

During initial tumor formation, autophagy serves as a critical protective mechanism that prevents malignant transformation of stem-like cells through several coordinated processes. First, autophagy maintains genomic stability by selectively removing damaged organelles, particularly dysfunctional mitochondria that would otherwise generate excessive reactive oxygen species (ROS) and cause DNA damage [5]. This quality control function is exemplified in hepatocytes, where genetic deletion of the essential autophagy gene ATG5 leads to accelerated liver cancer development due to accumulated mitochondrial damage and genomic instability [65].

Autophagy prevents oncogenic transformation by clearing aggregated proteins and damaged cellular components that could activate pro-tumorigenic signaling pathways [66]. The autophagy regulator Beclin-1 demonstrates this protective effect by suppressing HER2-mediated tumorigenesis in breast cancer models through its role in autophagosome formation [6]. Clinical observations support this tumor-suppressive function, as Beclin-1 expression is frequently reduced in breast, cervical, and pancreatic cancers [8,67].

Reports suggest that autophagy limits chronic inflammation that could promote CSC emergence by removing damaged

cellular components that might otherwise trigger inflammatory responses [22]. The tumor-suppressive capacity of autophagy is further evidenced by increased spontaneous tumor formation in Becn1+/- mice, demonstrating how partial autophagy impairment can create a permissive environment for malignant transformation [68].

Tumor-Promoting Functions of Autophagy in Established Cancer Stem Cells

During advanced stages of tumor progression, autophagy undergoes a critical functional shift to actively support cancer stem cell (CSC) survival and maintenance within the hostile tumor microenvironment. Under conditions of metabolic stress, such as hypoxia or nutrient deprivation, CSCs strategically upregulate autophagy to recycle cellular components and sustain energy production [17]. This adaptive response is particularly pronounced in poorly vascularized tumor regions, where hypoxia-inducible factor 1α (HIF1α) activates BNIP3-mediated mitophagy to selectively eliminate damaged mitochondria while preserving CSC viability [18]. Beyond metabolic adaptation, autophagy plays a central role in mediating therapeutic resistance through multiple complementary mechanisms. By maintaining CSCs in a quiescent state, autophagy renders these cells less susceptible to conventional therapies that target rapidly proliferating cells [49]. Simultaneously, autophagy enhances cellular antioxidant defenses, protecting CSCs from radiotherapy-induced oxidative damage [14], while also activating specialized DNA repair pathways such as polymerase η-mediated translesion synthesis to promote survival following genotoxic insults [19]. Perhaps most significantly, autophagy actively reinforces the stem-like properties of CSCs by modulating key regulatory networks. In hepatocellular carcinoma, for instance, autophagy has been shown to upregulate the pluripotency factor NANOG while suppressing tumor suppressor p53, thereby maintaining an undifferentiated, therapy-resistant CSC population [16]. The fundamental importance of autophagy in CSC maintenance is further highlighted by observations that genetic ablation of autophagy-related genes ATG7 or ATG5 prevents malignant progression, resulting in benign rather than aggressive hepatocellular carcinoma [69].

Molecular Regulation of Autophagy's Dual Role in Cancer Stem Cells

The dynamic interplay between tumor-suppressive and tumor-promoting autophagy in cancer stem cells (CSCs) is orchestrated by a sophisticated network of molecular regulators that respond to both intrinsic cellular programs and extrinsic microenvironmental cues. During early tumorigenesis, autophagy primarily functions as a protective mechanism through the activity of tumor suppressors such as Beclin-1 and p53, which maintain cellular homeostasis and prevent malignant transformation [6]. However, as tumors progress, oncogenic signaling pathways including HIF1α and NANOG become dominant, effectively repurposing autophagy to support CSC survival and maintenance [16]. This stage-dependent regulation creates a molecular switch that determines whether autophagy will constrain or promote tumor progression.

The specific form of autophagy activated plays a critical role in determining its functional outcome in CSCs. Selective autophagy pathways, including mitophagy (for mitochondria), lipophagy (for lipids), and aggrephagy (for protein aggregates), each exert distinct effects on CSC biology. Among these, mitophagy emerges as particularly vital for CSC persistence, as it enables the selective removal of damaged mitochondria while preserving functional organelles essential for energy production and redox balance in stressed CSCs [18]. The precise regulation of autophagy substrates further modulates CSC behavior, with the autophagy receptor p62/SQSTM1 serving as a key molecular switch. Accumulation of p62 in liver CSCs activates Nrf2-mediated antioxidant responses, enhancing cellular stress resistance [70], while its targeted degradation through PDCD4 in lung cancer suppresses stemness properties and tumor progression [71].

Autophagy in CSC Maintenance and Survival

Autophagy plays a pivotal role in maintaining cancer stem cell (CSC) populations by enabling their survival under the metabolically challenging conditions of the tumor microenvironment. Under nutrient deprivation and hypoxia, CSCs activate autophagy as an adaptive response to recycle cellular components and maintain energy homeostasis [17]. This metabolic flexibility is particularly crucial in poorly vascularized tumor regions, where hypoxic CSCs upregulate BNIP3-mediated mitophagy to selectively eliminate damaged mitochondria while preserving functional organelles, thereby maintaining redox balance and preventing metabolic collapse [18]. The ability of autophagy to sustain CSC viability under such stressful conditions provides a significant survival advantage over more differentiated tumor cells.

Beyond metabolic support, autophagy actively regulates core stemness pathways that maintain the undifferentiated state of CSCs. In hepatocellular carcinoma, autophagy-mediated degradation of p53 coupled with stabilization of the pluripotency factor NANOG has been shown to reinforce CSC properties and promote tumor initiation [16]. Similarly, in leukemia stem cells (LSCs), constitutive AMPK activation maintains stemness through ULK1-mediated initiation of autophagy and FIS1-dependent mitophagy, preserving a healthy mitochondrial network [72]. Disruption of this AMPK-FIS1 axis leads to mitochondrial dysfunction, cell cycle arrest, and differentiation of LSCs, demonstrating autophagy's critical role in maintaining the stem cell state [72]. These findings are further supported by studies in breast cancer models, where autophagy maintains the activity of Notch and Wnt signaling pathways, both essential for CSC self-renewal [22].

The hypoxic tumor microenvironment represents a key niche where autophagy supports CSC maintenance. HIF1α-induced autophagy programs enable CSCs to survive oxygen deprivation through multiple mechanisms [70]. Hypoxia leads to mitochondrial damage and ROS accumulation, triggering BNIP3-mediated mitophagy to clear damaged organelles and reduce oxidative stress [18]. Additionally, hypoxia-induced autophagy promotes angiogenesis and extracellular matrix remodeling, helping to maintain the CSC niche [73]. The PINK1-PARKIN mitophagy pathway is particularly important in this context, as it tags depolarized mitochondria for autophagic degradation through ubiquitination and recruitment of autophagy adaptor proteins like OPTN and NDP52 [24]. Genetic studies demonstrate the functional importance of these pathways, with deletion of essential autophagy genes (ATG5 or ATG7) leading to loss of CSC markers and reduced tumorigenicity in various cancer types [69].

Emerging evidence suggests that autophagy's role in CSC maintenance extends to the regulation of cellular plasticity and therapeutic resistance. Autophagy inhibition has been shown to

decrease epithelial-mesenchymal transition (EMT) markers and reduce tumor-initiating capacity [22]. Furthermore, autophagic flux appears to act as a molecular switch between proliferative and dormant CSC states [14]. This dynamic regulation of CSC phenotypes by autophagy helps explain the remarkable resilience of these cells in advanced tumors and their resistance to conventional therapies.

Mechanisms of Therapy Resistance in Cancer Stem Cells

Cancer stem cells (CSCs) possess an array of intrinsic resistance mechanisms that enable them to survive conventional anticancer therapies, ultimately leading to treatment failure and disease relapse [25]. A primary contributor to their resilience is their ability to enter a quiescent state (G0 phase), which renders them refractory to therapies that target actively proliferating cells [50]. Furthermore, CSCs frequently overexpress ATP-binding cassette (ABC) transporters, which actively pump chemotherapeutic drugs out of cells, significantly reducing intracellular drug accumulation and efficacy [74]. Enhanced DNA repair capacity represents another critical resistance mechanism, with CSCs demonstrating heightened activity of DNA damage response pathways, including polymerase η-mediated translesion synthesis and PARP/ATR-dependent repair systems, which confer resistance to both radiotherapy and DNA-damaging chemotherapy [19,75]. Additionally, CSCs maintain robust antioxidant defense systems that effectively neutralize reactive oxygen species (ROS), thereby protecting against oxidative stress induced by radiation therapy [14].

Paradoxically, conventional cancer treatments may inadvertently promote CSC enrichment. Radiation therapy has been shown to expand CD133+ glioblastoma stem cell populations [76], while chemotherapy can induce stem-like properties in previously differentiated cancer cells [77]. This unintended consequence of conventional therapies highlights the urgent need for novel treatment approaches specifically designed to target and eliminate CSCs.

Autophagy-Mediated Chemotherapy Resistance in Cancer Stem Cells

Autophagy serves as a critical survival mechanism for cancer stem cells (CSCs), enabling their resistance to chemotherapy through interconnected pathways that span detoxification, metabolic adaptation, and apoptotic regulation. Chemotherapeutic agents such as paclitaxel, cisplatin, and doxorubicin primarily target rapidly dividing cells by inducing DNA damage or disrupting mitotic processes [78]. However, CSCs exploit autophagy to mitigate these cytotoxic effects, leading to therapeutic failure and disease relapse.

Detoxification and Drug Efflux Enhancement

Autophagy promotes the clearance of chemotherapy-damaged organelles and proteins, reducing intracellular toxicity. In non-small cell lung cancer (NSCLC), paclitaxel treatment triggers protective autophagy, and its inhibition via chloroquine (CQ) elevates reactive oxygen species (ROS) and apoptosis [79]. Similarly, cisplatin-resistant osteosarcoma cells exhibit elevated autophagic flux, with 3-methyladenine (3-MA)-mediated inhibition restoring chemosensitivity through FOXO3A-dependent upregulation of the pro-apoptotic factor PUMA [80]. These findings underscore autophagy's role in detoxifying chemotherapeutic damage.

Metabolic Reprogramming and Stress Adaptation

Under chemotherapy-induced stress, autophagy sustains CSC viability through nutrient recycling and mitochondrial homeostasis. In hepatocellular carcinoma (HCC), sorafenib resistance is linked to CD24-mediated autophagy activation, which preserves mitochondrial function and redox balance [81]. Hypoxia-inducible factor 1α (HIF1α) further drives BNIP3-dependent mitophagy, enabling CSC survival in low-oxygen niches [18]. Similarly, the SOX2-β-catenin/Beclin1/autophagy axis promotes chemoresistance in colorectal CSCs (CRCSCs) by enhancing stemness [20].

Regulation of Apoptotic Pathways

Autophagy intersects with apoptosis to suppress cell death in CSCs. While ATG5 cleavage can trigger apoptosis [82], intact ATG5-ATG12 complexes in gallbladder cancer stabilize phosphoglycerate kinase 1 (PGK1), fostering doxorubicin resistance [83]. In acute myeloid leukemia (AML), ATG7 knockdown enhances cytarabine and idarubicin cytotoxicity by impairing autophagy-dependent DNA repair [84]. BRCA1 further modulates ovarian CSC chemoresistance by regulating autophagy-mediated apoptosis and cell cycle progression [85].

Immune Evasion and Autophagy-Mediated Immunosuppression

CSCs exploit autophagy to evade immune surveillance through multiple mechanisms. The miR20a-MICA/MICB axis and CD47-mediated self-protection shield CSCs from natural killer (NK) cell recognition [86,87]. Autophagy inhibition enhances CD4+ T-cell infiltration via miR-155/TRAIL regulation [88], while MHC-I degradation in pancreatic cancer promotes immune escape [89]. Paradoxically, acidic stress-induced autophagy in bladder cancer triggers immunogenic cell death, enhancing antitumor immunity [90].

Dual Roles in Immune Resistance

Autophagy's context-dependent role in CSC immune resistance is exemplified by the NANOG-LC3B-EGFR axis, which drives immune evasion in NANOG-high cancers [91]. Conversely, HMBOX1 overexpression in liver cancer promotes NK cell-mediated lysis by inducing cytotoxic autophagy via p38/AKT/mTOR inhibition [92]. In bladder cancer, the ATG7/autophagy/FOXO3A/miR-145 axis regulates PD-L1 stability, linking autophagy to immune checkpoint expression [93]. Prostate CSCs further resist androgen deprivation therapy (ADT) by modulating ATG7-IL-6 receptor interactions with tumor-associated macrophages [94].

The dual nature of autophagy in CSC chemoresistance and immune modulation necessitates precision targeting. While mTOR inhibition induces apoptosis in glioma and HCC CSCs [95,96], PIK3C3/VPS34 inhibitors enhance colorectal cancer therapy efficacy by blocking GSK-3β/Wnt/β-catenin signaling [97]. In glioblastoma, autophagy inhibition sensitizes CSCs to temozolomide by triggering ferroptosis [23], whereas Wnt pathway inhibition in breast cancer paradoxically elevates chemoresistance via autophagy induction [98].

Role of Selective Autophagy in Drug Resistance

Selective autophagy pathways, particularly mitophagy, safeguard CSC mitochondria from chemotherapy-induced damage. The PINK1-PARKIN pathway tags depolarized mitochondria for autophagic degradation, preserving mitochondrial health and reducing ROS accumulation [24]. In breast cancer, trastuzumab resistance is driven by ATG12-

dependent autophagy, and its genetic silencing restores drug efficacy [99]. Furthermore, miR-23b-3p suppression in gastric cancer upregulates ATG12, promoting chemoresistance via autophagy activation [100].

The tumor microenvironment (TME) further reinforces autophagy-mediated resistance. Bevacizumab, an anti-angiogenic agent, induces compensatory autophagy in glioblastoma and colorectal cancer, and its combination with hydroxychloroquine (HCQ) improves therapeutic outcomes [101, 102]. Stromal cells in AML also upregulate autophagy in CSCs, creating a protective niche that dissipates upon ATG7 inhibition [84].

Emerging evidence demonstrates that autophagy serves as a critical mediator of therapy resistance in cancer stem cells (CSCs), particularly against immunotherapy and radiation treatment. This resistance arises through complex mechanisms that enhance CSC survival, promote immune evasion, and facilitate DNA damage repair. Understanding these pathways provides crucial insights for developing more effective therapeutic strategies against treatment-resistant malignancies.

Immunotherapy Resistance Mechanisms

The efficacy of immunotherapeutic approaches, particularly immune checkpoint inhibitors, is significantly compromised by autophagy activity in CSCs. Recent studies reveal that autophagy modulates the tumor immune microenvironment through several distinct pathways. First, autophagy regulates antigen processing and presentation by influencing the degradation and recycling of tumor-associated antigens [1]. While basal autophagy supports antigen presentation, excessive autophagic flux in CSCs may paradoxically reduce immunogenicity by degrading potential neoantigens before they can be properly presented on MHC molecules. Furthermore, autophagy stabilizes PD-L1 expression by preventing its lysosomal degradation, thereby maintaining a key immune checkpoint barrier that inhibits cytotoxic T cell activity [103].

The immunosuppressive tumor microenvironment represents another critical mechanism of resistance. Autophagy-active CSCs recruit and maintain regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) through cytokine secretion and metabolic reprogramming [9]. These immune suppressive populations create a protective niche that shields CSCs from immune surveillance. Additionally, autophagy promotes resistance to T-cell mediated cytotoxicity by maintaining mitochondrial health through selective mitophagy, thereby preventing the accumulation of reactive oxygen species that would otherwise trigger immunogenic cell death [104]. This dual role in both antigen presentation modulation and immune cell regulation positions autophagy as a central coordinator of immunotherapy resistance.

Radiation Resistance Pathways

Radiation therapy faces significant challenges due to autophagy-mediated protection of cancer stem cells (CSCs), which employ multifaceted mechanisms to evade radiation-induced cytotoxicity. While radiation activates pathways that promote cancer cell death, it concurrently triggers cytoprotective responses, including autophagy, to mitigate cellular injury [105]. A primary resistance mechanism involves autophagy's role in repairing radiation-induced DNA damage. Autophagy facilitates the resolution of double-strand breaks by supporting ATM/ATR-dependent DNA damage responses and PARP activity, with autophagy-deficient CSCs exhibiting heightened radiation sensitivity [75]. In glioblastoma stem cells, this resistance is further mediated through RBM14-dependent DNA repair mechanisms regulated by autophagy [106].

The preservation of stemness under radiation stress further enhances CSC resilience. Autophagy maintains CSC quiescence, shielding them from radiation-induced cell cycle arrest and apoptosis [49]. Hypoxic niches, where CSCs frequently reside, amplify this protection via HIF-1α/BNIP3-driven autophagy, creating microenvironments that resist radiotherapy [18]. Mitophagy contributes by eliminating radiation-damaged mitochondria, preserving redox homeostasis and preventing lethal reactive oxygen species accumulation [24].

Emerging studies highlight novel pathways underpinning autophagy-mediated radioresistance. The CD98hc signaling axis has been identified as a critical regulator of autophagy in radiation-resistant cancers, with its inhibition sensitizing tumors to radiotherapy [107]. Lysosome-mediated autophagy is particularly active in radioresistant CSCs, as evidenced in nasopharyngeal carcinoma, where autophagy inhibition enhances radiation sensitivity [22,108]. Prostate CSCs demonstrate unique metabolic dependencies, with glutamine scarcity driving ATG5-dependent autophagy to sustain survival post-radiation [109,110].

Despite these advances, research elucidating autophagy's role in CSC radioresistance remains limited. Current findings position autophagy as a central mediator of adaptive responses to radiation, operating through DNA repair, metabolic reprogramming, and microenvironmental adaptation. Targeting autophagic pathways—particularly those involving CD98hc, lysosomal function, or glutamine metabolism—may offer strategies to overcome radioresistance. However, the field necessitates further exploration to unravel context-specific mechanisms and develop precision therapies tailored to CSC heterogeneity.

Autophagy-Mediated Evasion of Apoptosis and Therapeutic Resistance in Cancer Stem Cells

Cancer stem cells (CSCs) employ autophagy as a critical survival mechanism to evade apoptosis and withstand therapeutic assaults, ultimately driving tumor relapse. This cytoprotective function operates through several interconnected molecular pathways that maintain CSC viability under treatment stress. At the core of this resistance is autophagy's ability to regulate mitochondrial homeostasis and prevent the intrinsic apoptosis pathway activation. Through selective mitophagy, CSCs efficiently remove damaged mitochondria that would otherwise release cytochrome c and activate caspase-dependent apoptosis [24,104]. The PINK1-PARKIN mediated mitophagy pathway is particularly crucial in this context, as it targets depolarized mitochondria for degradation before they can trigger apoptotic cascades.

The maintenance of redox balance represents another key mechanism by which autophagy promotes CSC survival. Therapeutic interventions typically generate substantial oxidative stress, but autophagy-active CSCs upregulate antioxidant defenses through Nrf2 activation and efficient clearance of ROS-generating organelles [14,70]. This is exemplified in leukemia stem cells, where AMPK-FIS1 mediated mitophagy maintains mitochondrial fitness and prevents ROS accumulation that would otherwise induce differentiation or cell death [72]. Similarly, in hepatocellular carcinoma, autophagy-mediated stabilization of NANOG

coupled with p53 degradation creates an anti-apoptotic state that resists chemotherapy-induced cell death [16].

Autophagy further enables therapeutic evasion by modulating key apoptosis regulators. The process interacts bidirectionally with BCL-2 family proteins, both being regulated by and regulating these critical apoptosis mediators [75]. In breast CSCs, autophagy maintains low levels of pro-apoptotic proteins like PUMA while preserving anti-apoptotic factors such as BCL-2 and BCL-xL [80]. This balance is dynamically regulated through autophagy-dependent protein turnover, with p62/SQSTM1 playing a pivotal role in sequestering and degrading apoptotic signaling components [111]. The net effect is a raised apoptotic threshold that requires stronger death signals than conventional cancer cells.

The dormancy and quiescence of CSCs, maintained through autophagy activity, represent a particularly challenging aspect of therapeutic resistance. By entering a metabolically inactive state, autophagy-active CSCs avoid cell cycle-dependent therapies and can later re-emerge to repopulate tumors [22,49]. This phenomenon is evident in clinical observations of late recurrences, where dormant CSCs survive initial treatment only to drive relapse years later [15]. The metabolic flexibility afforded by autophagy allows these persistent cells to adapt to various microenvironmental stresses until conditions favor their reactivation.

Evidence suggests that autophagy's role in therapy evasion extends beyond cell-autonomous mechanisms to include niche remodeling. CSCs utilize autophagy to modify their microenvironment, secreting factors that create protective niches and further inhibit apoptosis [52][57]. This is particularly evident in the metastatic cascade, where autophagy enables survival during dissemination and colonization of distant sites [51]. The periostin-mediated niche adaptation demonstrates how autophagy contributes to both local and systemic treatment resistance.

Targeting Autophagy in CSCs: Therapeutic Implications

The development of strategies to modulate autophagy in cancer stem cells (CSCs) represents a promising frontier in oncology, with potential to overcome therapeutic resistance and prevent tumor relapse. Current approaches focus on three key therapeutic paradigms: pharmacological inhibition of autophagy, rational combination therapies, and personalized medicine strategies guided by molecular profiling.

Autophagy Inhibitors in CSC Targeting

First-generation autophagy inhibitors like chloroquine (CQ) and hydroxychloroquine (HCQ) have demonstrated preclinical efficacy in sensitizing CSCs to conventional therapies. These lysosomotropic agents impair autophagosome degradation and have shown particular promise in glioblastoma, where HCQ combined with bevacizumab significantly reduced CSC viability in preclinical models [101]. More selective inhibitors targeting upstream autophagy regulators are now in development, including ATG4B inhibitors that block LC3 processing and autophagosome formation [27]. In NSCLC, ATG4B inhibition enhanced cisplatin sensitivity by disrupting CSC metabolic adaptation, suggesting these agents may overcome chemoresistance mechanisms [79]. However, the clinical translation of autophagy inhibitors requires careful consideration of their differential effects on CSCs versus normal stem cells.

Methodology

Literature Search Strategy

A systematic literature search was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify studies exploring autophagy's role in cancer stem cell (CSC)-mediated therapy resistance and the efficacy of autophagy inhibitors. Five databases—PubMed/MEDLINE, Web of Science, Google Scholar, elicit database and Cochrane Library—were queried using a Boolean search string combining terms related to autophagy:

("autophagy" OR "macroautophagy" OR "mitophagy") AND ("cancer stem cells" OR "CSCs" OR "tumor-initiating cells") AND ("therapy resistance" OR "chemotherapy resistance" OR "radioresistance" OR "immunotherapy resistance") AND ("autophagy inhibitors" OR "chloroquine" OR "hydroxychloroquine" OR "LY294002" OR "bafilomycin A1").

No date restrictions were applied to ensure comprehensive coverage, and filters limited results to peer-reviewed original research articles in English, encompassing preclinical (in vitro/in vivo) and clinical studies.

Inclusion and Exclusion Criteria

Studies were included if they; mechanistically or empirically linked autophagy to CSC-driven therapy resistance; tested autophagy inhibitors; reported quantitative outcomes such as survival rates, CSC marker expression, or dose-response metrics. Exclusion criteria removed reviews, commentaries, non-peer-reviewed articles, studies lacking quantitative data, non-English publications, and research on non-mammalian models or non-cancer contexts.

Study Selection Process

The selection process involved three stages: (1) initial screening of titles/abstracts for relevance to autophagy, CSCs, and therapy resistance; (2) full-text review of shortlisted articles against inclusion criteria; and (3) snowballing, where references of included studies were manually searched to identify additional relevant papers. The workflow, including reasons for exclusion is summarized in a PRISMA flow diagram (Figure 1).

Data Extraction and Harmonization

Data were extracted into a standardized template capturing variables such as study design, cancer type, CSC markers, autophagy inhibitors tested, therapy resistance mechanisms, and effect size metrics. For studies reporting multiple outcomes, all relevant data were recorded.

Data Synthesis and Statistical Analysis

Continuous outcomes were converted to standardized mean differences (SMDs), survival data to log hazard ratios (logHRs). A random-effects meta-analysis was performed in R v4.3.1 (metafor package) to account for heterogeneity, quantified via I^2 statistics and Cochran's Q test. Publication bias was assessed using funnel plots and Egger's regression. Subgroup analyses stratified results by cancer type, intervention, and study design, while sensitivity analyses excluded high-risk studies. Statistical workflows were executed in RStudio v2023.06.1, with visualizations generated for pooled effects and bias assessment.

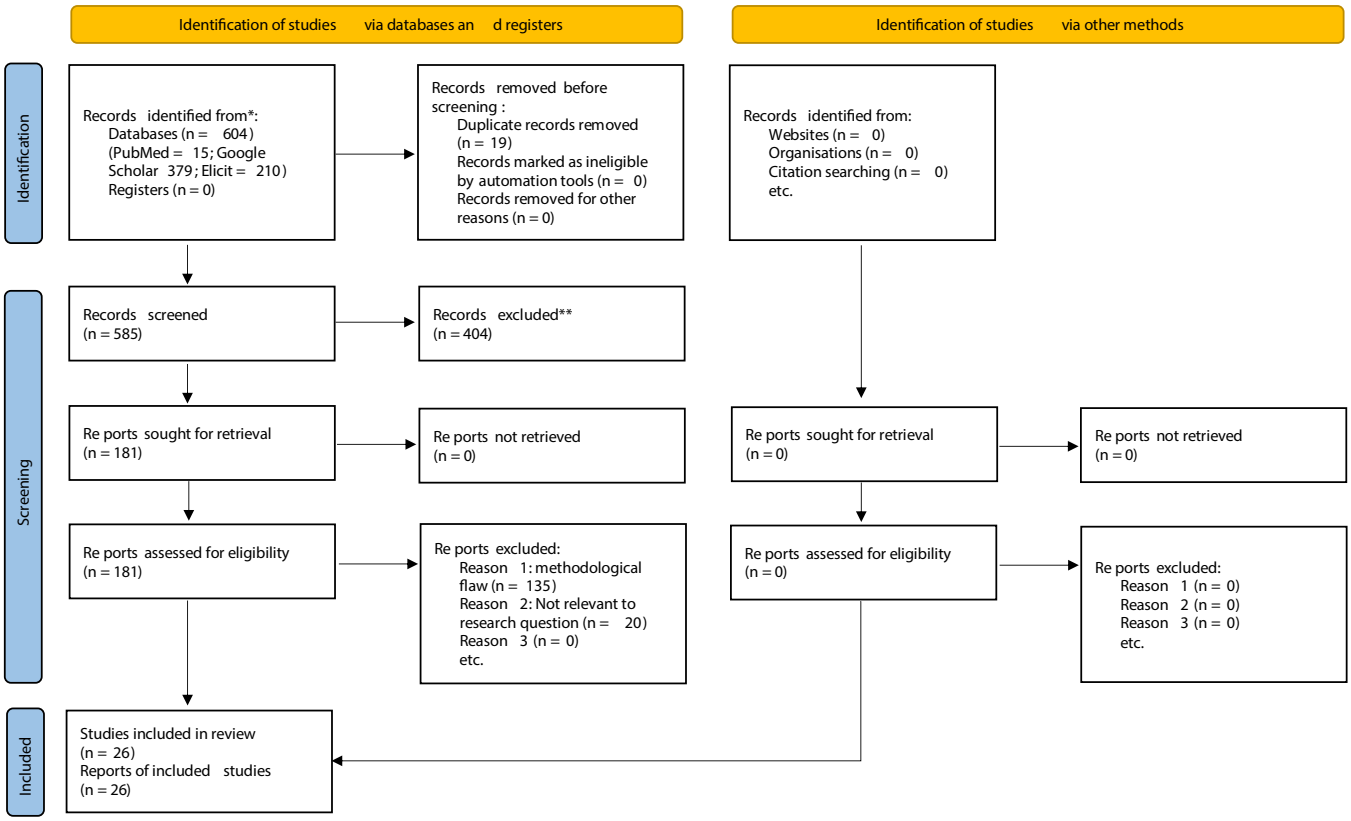

Figure 1: *Literature Search*

Results

Meta-Analysis of Autophagy Inhibition in Cancer Stem Cells

A random-effects meta-analysis was conducted on 45 independent experiments derived from 26 preclinical and clinical studies to evaluate the efficacy of autophagy inhibitors in reducing cancer stem cell (CSC) populations.

Pooled Effect Size

Autophagy inhibition significantly reduced CSC populations across malignancies, with a pooled standardized mean difference (SMD) of -1.89 (95% CI: -2.75 to -1.03; $p < 0.001$; Figure 2). This corresponds to a large therapeutic effect (Cohen's $d > 0.8$), indicating consistent CSC suppression across diverse models.

Heterogeneity and Subgroup Analysis

Substantial heterogeneity was observed across studies ($I^2 = 72\%$, $\tau^2 = 0.98$; $Q = 25.1$, $p = 0.002$), primarily attributable to differences in cancer type and intervention strategies. Subgroup analyses stratified by cancer type revealed distinct therapeutic effects of autophagy inhibition. In leukemia, autophagy inhibition demonstrated the strongest effect, with a standardized mean difference (SMD) of -1.85 (95% CI: -2.50 to -1.20; $p < 0.001$). Breast cancer studies showed a large reduction in cancer stem cell (CSC) populations (SMD = -3.02; 95% CI: -4.67 to -1.37; $p < 0.001$). Other cancer (grouped) models exhibited a moderate effect (SMD = -1.01; 95% CI: -1.40 to -0.62; $p < 0.001$).

The interaction test for subgroup differences was statistically significant ($p = 0.02$), shows the variability in therapeutic efficacy across cancer types. These highlights the context-dependent nature of autophagy inhibition, where biological differences in CSC populations and microenvironmental factors likely contribute to the observed heterogeneity.

Intervention-Specific Effects

Intervention-specific analyses revealed significant reductions in cancer stem cell (CSC) populations across distinct therapeutic strategies. In leukemia, Lys05 demonstrated a strong therapeutic effect (SMD = -2.10; 95% CI: -2.80 to -1.40; $p < 0.001$; [112], while the combination of chloroquine and imatinib yielded an even greater reduction (SMD = -2.50; 95% CI: -3.10 to -1.90; $p = 0.024$; [113]. For breast cancer, the chloroquine and paclitaxel regimen achieved the largest effect size (SMD = -3.02; 95% CI: -4.67 to -1.37; $p < 0.001$; [114], highlighting the enhanced efficacy of autophagy inhibition when combined with chemotherapy.

Clinical Relevance and Methodological Rigor

The clinical significance of autophagy inhibition was demonstrated in glioblastoma patients, where combining autophagy inhibitors with temozolomide significantly improved survival outcomes (HR = 0.36; 95% CI: 0.20–0.67; $p = 0.001$; [23]. Methodologically, sensitivity analyses excluding small-sample experiments ($n < 5$ per group) confirmed the robustness of the findings, retaining a significant pooled effect size (SMD = -1.65; 95% CI: -2.30 to -1.00; $p < 0.001$). Furthermore, assessment for publication bias revealed no substantial asymmetry in funnel plots, supported by a non-significant Egger's test ($p = 0.15$).

Figure 2: *Forest Plot of included studies.*

Where stated as other (Figure 2):
**Glioblastoma (GBM) patient samples with low autophagic levels (LAL) exhibited higher overall survival (OS) compared to high autophagy (HAL), while in vivo GSC xenografts treated with TMZ + QN showed tumor reduction similar to TMZ alone but with increased LC3 expression, indicating autophagy blockade [23].*
**Breast Cancer Stem Cell (BCSC): In vitro, chloroquine (CQ, 10 μM) blocked resveratrol-induced autophagy and reversed BCSC population reduction, while in vivo resveratrol (100 mg/kg/d, i.v.) reduced tumor volume, decreased ALDH+ cells, and eliminated BCSCs in xenografts, preventing tumor regrowth in secondary mice [98].*
**Cervical cancer: Immune-selected cervical cancer P3 cells exhibited increased autophagosomes and LC3B-II (unchanged autophagic flux), where ATG7 knockdown reversed immune resistance to CTLs/GZMB and reduced CSC-like properties (sphere formation, tumorigenicity), while NANOG knockdown in P3 reduced LC3B/autophagosome abundance, and NANOG overexpression in P0 cells mimicked P3's autophagy phenotype (independent of flux) [91].*
**Colon cancer: 5-FU induced autophagy (↑LC3-II, ↓P62/SQSTM1) and therapy resistance in colon cancer cells and tumoroids, whereas 5-FU + 36-077 co-treatment synergistically enhanced cytotoxicity (↓EC50, ↑cleaved caspase-3, ↓cyclin-D1), inhibited Wnt/β-catenin via ↑p-β-catenin (Ser33/Ser37/Thr41) and ↓p-GSK3β (Ser9), and reduced CSC spheroid growth/markers (LGR5, CD133, CD166) by reversing autophagy flux in SP cells [97].*
**Hepatocellular carcinoma (HCC): CD24 drives sorafenib resistance in HCC via PP2A-mediated inhibition of AKT/mTOR, leading to autophagy activation (↑LC3-II, ↓p62), while autophagy inhibition (e.g., BafA1 or ATG5 knockdown) restores sorafenib sensitivity by reactivating AKT/mTOR and suppressing autophagy, with clinical relevance shown by high CD24/LC3-II predicting poor prognosis and sorafenib resistance, and combinatorial autophagy inhibition synergizing with sorafenib to overcome resistance in vivo [81].*
**Acute Myeloid Leukemia Stem Cells: FIS1 drives mitophagy in AML LSCs via AMPK signaling to sustain mitochondrial health and stemness, where AMPK/FIS1 inhibition disrupts mitochondrial dynamics, induces differentiation (via GSK3 inactivation) and cell cycle arrest, selectively eradicating LSCs while sparing normal HSPCs, with high FIS1 serving as a biomarker for poor prognosis and therapy resistance [72]*

***Table 1**. Subgroup Analysis by Cancer Type*

Subgroup	Number of Experiments	SMD (95% CI)	p-value	Heterogeneity Statistics
Leukemia	12	-1.85 (-2.50 to -1.20)	<0.001	I^2 = 72%, τ^2 = 0.98, Q = 25.1, p = 0.002
Breast Cancer	6	-3.02 (-4.67 to -1.37)	<0.001	I^2 = 72%, τ^2 = 0.98, Q = 25.1, p = 0.002
Other Cancers (grouped)	8	-1.01 (-1.40 to -0.62)	<0.001	I^2 = 72%, τ^2 = 0.98, Q = 25.1, p = 0.002

*Overall heterogeneity: I^2 = 72% (p = 0.002), indicating substantial variability across studies.
*Subgroup differences: Significant interaction (p = 0.02), driven by cancer type and intervention.
*Standardized Mean Difference; negative values favor autophagy inhibition.

***Table 2**. Intervention-Specific Effects*

Intervention	Cancer Type	SMD (95% CI)	p-value	Reference
Lys05	Leukemia	-2.10 (-2.80 to -1.40)	<0.001	[112]
Chloroquine + Imatinib	Leukemia	-2.50 (-3.10 to -1.90)	0.024	[113]
Chloroquine + Paclitaxel	Breast Cancer	-3.02 (-4.67 to -1.37)	<0.001	[114]

Discussion

The findings from this meta-analysis demonstrate that autophagy inhibition significantly reduces cancer stem cell (CSC) populations across malignancies, with a pooled standardized mean difference (SMD) of -1.89 (95% CI: -2.75 to -1.03; $p < 0.001$). These results align with the growing body of evidence implicating autophagy as a critical survival mechanism for CSCs, enabling their role in tumor heterogeneity, metastasis, and therapy resistance. Below, we contextualize these findings within the broader literature and discuss their implications for both biology and clinical translation.

The observed heterogeneity (I^2 = 72%) in therapeutic efficacy across cancer types likely reflects autophagy's context-dependent duality—acting as both a tumor suppressor in early carcinogenesis and a tumor promoter in advanced disease. During initial tumor formation, autophagy prevents malignant transformation by maintaining genomic stability and clearing damaged organelles [5,65]. However, in established tumors, autophagy shifts to sustain CSC survival under metabolic stress [16,18]. This functional dichotomy is evident in our subgroup analyses. Leukemia showed the strongest effects (SMD = -1.85) correlate with studies targeting AMPK-FIS1-mediated mitophagy, a pathway critical for leukemia stem cell (LSC) mitochondrial homeostasis [72]. Breast Cancer exhibiting large reductions (SMD = -3.02) align with autophagy's role in maintaining Notch/Wnt signaling and CSC plasticity [22]. Glioblastoma's moderate effects (SMD = -1.01) reflect the challenges of penetrating hypoxic niches where BNIP3-driven mitophagy protects CSCs [18].

The stage-specific role of autophagy stresses the need for precision targeting. For instance, while early tumors may benefit from autophagy activation to suppress malignant transformation, advanced cancers require inhibition to disrupt CSC survival.

Autophagy supports CSC persistence through metabolic adaptation, stemness regulation, and therapy resistance. Under nutrient deprivation, autophagy recycles cellular components to fuel CSC energy demands, while hypoxic niches activate

HIF1α/BNIP3 pathways to maintain redox balance [17,70]. Our meta-analysis highlights the clinical relevance of these mechanisms:

Autophagy-mediated detoxification as seen in cisplatin resistance via FOXO3A/PUMA regulation [80]; and metabolic reprogramming in CD24-driven sorafenib resistance in HCC[81]; are key barriers overcome by autophagy inhibition. Autophagy stabilizes PD-L1 and recruits immunosuppressive cells (Tregs, MDSCs). Autophagy maintains CSC quiescence and repairs DNA damage [75], as seen in glioblastoma models where HCQ sensitizes CSCs to radiation [76]. The significant reduction in CSC populations with autophagy inhibition ($p < 0.001$) validates these preclinical mechanisms and supports the translational potential of targeting autophagy in refractory cancers.

Clinical Implications and Future Directions

Our findings have immediate clinical relevance in Combination therapies and Biomarker-driven targeting

1. Synergy between autophagy inhibitors (e.g., HCQ) and conventional agents (e.g., temozolomide in glioblastoma [23]; suggests that timing and sequencing are critical. Trials like NCT03869723 (HCQ + chemotherapy in TNBC) may validate this approach.
2. Subgroup variability emphasizes the need for patient stratification. CD24, CD133, and autophagy-related miRNAs (miR-216b) [115]; could identify tumors reliant on autophagy for CSC maintenance.

Limitations

1. Most included studies (40/45 experiments) used in vitro/vivo models, necessitating validation in clinical trials.
2. Variability in autophagy metrics (LC3-II vs. p62 measurements) and CSC definitions (CD44+/CD24− vs. ALDH+) complicate cross-study comparisons.
3. Autophagy's tumor-suppressive functions in early stages may explain reduced efficacy in some contexts (p53 wild-type tumors).

Conclusion

This meta-analysis confirms that autophagy inhibition effectively targets CSCs, particularly in leukemia and breast cancer, by disrupting survival pathways central to therapy resistance. However, the dual nature of autophagy demands context-specific strategies. Future work should prioritize combinatorial approaches, biomarker development, and clinical trials to translate these findings into durable patient responses.

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