PIBB 生物化学与生物物理进展
Progress in Biochemistry and Biophysics
XXXX, XX(XX): 1~17
www.pibb.ac.cn

Lysosomes as Regulators of Cancer Stemness and Drug Resistance*

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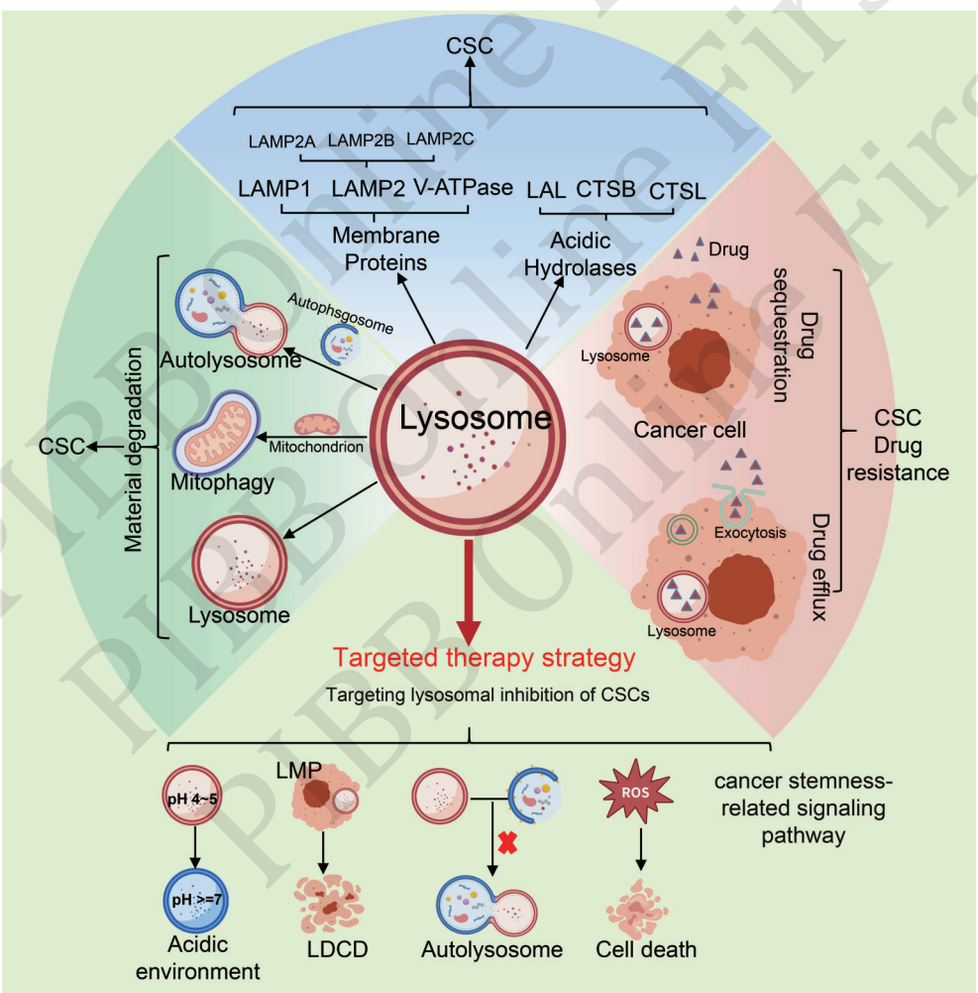
Graphical abstract



* This work was supported by grants from The National Natural Science Foundation of China (82360548), Basic Research Program of Science and Technology Department of Yunnan Province (202301ATO70466), and Yunnan "Xing Dian Ying Cai" Project (XDYC-QNRC-2022-0280).

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Received: December 28, 2025 Accepted: March 10, 2026

Abstract Cancer stem cells (CSCs) represent a distinct subpopulation of cells characterized by self-renewal capacity, differentiation potential, and critical roles in driving tumor progression, therapeutic resistance, recurrence, and maintenance of the tumor microenvironment. Targeting CSCs has emerged as a pivotal direction in cancer research, offering novel strategies to overcome drug resistance and prevent metastasis and relapse. Lysosomes, traditionally recognized as central organelles for intracellular degradation and recycling, are indispensable for cellular homeostasis. Dysregulation of lysosomal function is intimately linked to various diseases, including cancer. In tumors, aberrant lysosomal activity can promote malignant progression through mechanisms such as altering metabolic pathways, enhancing lysosomal exocytosis, modulating drug resistance, and interfering with autophagy-lysosomal pathways. Recent studies have underscored the involvement of lysosomes in regulating CSC properties. This review synthesizes findings on lysosomal regulation of CSCs through the following aspects. (1) Lysosomes exert complex and critical bidirectional control over CSC stemness maintenance through three degradation pathways that are dependent on their degradative function. I. The lysophagy pathway. This pathway exhibits dual roles. Activation can sustain CSC functions; for instance, in glioblastoma, hypoxia upregulates Gal-8 *via* the STAT3/HIF1α signaling axis to induce autophagy, supporting stem cell survival. In head and neck squamous cell carcinoma, degradation of GSK3β activates the Wnt pathway, enhancing stemness. Conversely, this pathway can suppress stemness by degrading stemness-related proteins such as BMI-1 and OCT4A, thereby impairing CSC self-renewal capacity. II. Mitophagy pathway. In non-small cell lung cancer stem cells, mitophagy-related mechanisms, such as the accumulation of mitochondrial DNA (mtDNA) activating the TLR9-Notch1-AMPK signaling axis, have been shown to promote CSC proliferation. III. Autophagosome-dependent lysosomal degradation pathway. This pathway directly regulates stemness-related proteins in a bidirectional manner. Enhanced degradative function can promote CSC properties, exemplified by the degradation of NUMB to activate Notch signaling. Conversely, attenuated degradative function can also enhance stemness by stabilizing oncoproteins (*e. g*., protecting Frizzled-1 from degradation to sustain Wnt signaling) or preventing the degradation of tumor suppressors (*e. g*., inhibiting Notch degradation). (2) Constituent proteins of lysosomes, including membrane proteins and luminal acid hydrolases, participate in regulating CSC stemness. Regarding membrane proteins, LAMP2A facilitates chaperone-mediated autophagy to maintain stemness in glioblastoma and ovarian cancer. V-ATPase, by maintaining an acidic luminal environment, promotes proliferation and drug resistance in glioma stem cells. Among hydrolases, cathepsins B and L are highly expressed in pancreatic and ovarian cancers and correlate with poor prognosis. Furthermore, targeting lysosomes to induce lysosomal membrane permeabilization (LMP) triggers lysosome-mediated cell death, presenting a potential therapeutic strategy for eradicating CSCs. (3) The acidic luminal environment, single-membrane structure, and the presence of transmembrane transporters (*e.g*., ABCA3) enable lysosomes to passively trap or actively uptake and sequester chemotherapeutic drugs. Subsequent drug extrusion *via* exocytosis confers drug resistance. In CSCs, this lysosome-mediated drug sequestration, often cooperating with autophagy, establishes multimodal drug resistance. Therefore, targeting lysosomal function represents a potential strategy to overcome therapy resistance. The central role of lysosomes in regulating CSC stemness and resistance positions them as highly promising therapeutic targets. Strategies aimed at disrupting lysosomal function to selectively eliminate CSCs include: inhibiting the lysosome-autophagy system using agents like IITZ or lovastatin; inducing lysosomal membrane permeabilization (LMP) with compounds such as hexamethylene amiloride to compromise membrane stability; and disrupting the acidic luminal environment using drugs like siramesine or the K/H transport compound 2. In conclusion, lysosomes critically regulate CSC stemness maintenance and drug resistance through degradative pathways, membrane protein functions, luminal hydrolase activities, and drug sequestration mechanisms. This redefines the lysosome from a traditional "waste disposal unit" to a "signal integration center" in CSCs. The duality and context-dependency of lysosomal function in CSCs offer novel insights into the heterogeneity observed across different tumors. Targeting lysosomal vulnerabilities—such as inducing LMP, disrupting acidity, or blocking autophagic flux—provides a strategy to bypass canonical CSC resistance mechanisms and directly trigger cell death. This establishes the lysosome as a key target to overcome CSC-mediated therapy resistance, paving the way for developing diverse candidate drugs and innovative combination therapies in oncology.

Key words lysosome, cancer stem cells, drug resistance
DOI：10.3724/j.pibb.2025.0553 **CSTR**：32369.14.pibb.20250553

Cancer stem cells (CSCs), also referred to as tumor-initiating cells (TICs) or cancer-initiating cells (CICs), represent a distinct subpopulation of tumor cells endowed with self-renewal capacity and tumor-initiating potential. Their functional role in tumor biology, collectively termed "cancer stemness" encompasses critical biological behaviors such as tumor initiation, progression, metastasis, therapeutic resistance, immune evasion, and maintenance of the tumor microenvironment[1-3]. CSCs are characterized by a repertoire of representative markers, including cluster of differentiation 44 (CD44) [4], cluster of differentiation 133 (CD133) [5], cluster of differentiation 24 (CD24)[6], cluster of differentiation 90 (CD90)[7] , and aldehyde dehydrogenase (ALDH) [8] . In clinical identification of CSCs within solid tumors, carcinoembryonic antigen (CEA), cytokeratin 19 fragment (YFRA 21-1), and alpha-fetoprotein (AFP) expressed by CSCs[9] have also been employed as specific biomarkers.

The activation and maintenance of CSC functions are orchestrated by stemness-associated transcription factors and evolutionary conserved signaling pathways. Transcription factors such as sex determining region Y-box 2 (SOX2) [10], octamer-binding transcription factor 4 (OCT4) [11], myelocytomatosis oncogene protein (MYC) [12], krüppel-like factor (KLF) [13], nanog homeobox (Nanog) [14], forkhead box transcription factors (FOX) [15] , and runt-related transcription factor (RUNX) [16] have been implicated in sustaining CSC properties. Concurrently, signaling pathway including Wnt/β-catenin signaling pathway[17] , Notch signaling pathway[18] , Sonic Hedgehog signaling pathway[19], nuclear factor-κB (NF-κB) signaling pathway, JAK2/STAT3 signaling pathway, TGFβ/Smad signaling pathway[20], and Hippo/YAP signaling pathway[21] form a complex regulatory network that induces stemness gene expression, represses differentiation programs, and establishes autoregulatory loops to stabilize CSC phenotypes. Given the established role of CSCs as key drivers of tumor initiation and recurrence, elucidating these molecular mechanisms provides a theoretical foundation for developing CSC-targeted therapeutic strategies.

Lysosomes, bounded by a single lipid bilayer and enriched with acidic hydrolases, serve as the central organelle for intracellular degradation and recycling, thereby ensuring cellular homeostasis. Their degradative capacity depends on the acidic microenvironment sustained by vacuolar-type ATPases (V-ATPases), which ensures optimal enzymatic activity. Through autophagy, endocytosis, and phagocytosis, lysosomes degrade extracellular cargo-including apoptotic cells and pathogens-as well as intracellular substrates such as damaged mitochondria, endoplasmic reticulum, and lysosomes themselves. Proteins, nucleic acids, lipids, and carbohydrates delivered to lysosomes[22] are hydrolyzed into reusable or excretable products[23]. Thus, lysosomes are indispensable for eliminating toxic cellular components, removing worn-out organelles, and sustaining metabolic homeostasis. Beyond catabolism, lysosomes are integral to metabolic signaling, transcriptional regulation, immune responses, plasma membrane repair, and processes of adhesion and migration[24]. Dysregulation of lysosomal function is linked to pathological states, including lysosomal storage disorders (LSDs) [25] , which predispose to late-onset neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, and frontotemporal dementia (FTD) [26]. In cancer, lysosomal dysfunction facilitates malignant progression by reprogramming metabolism, enhancing lysosomal exocytosis, conferring chemoresistance, and enabling macromolecule recycling *via* the autophagy-lysosome axis[24]. Moreover, lysosomal activity has been implicated in stem cell quiescence, underscoring its relevance in stem cell biology[22]. This review will systematically summarize current advances regarding lysosomal structure and function in the regulation of cancer stemness, aiming to provide a conceptual framework for CSC-targeted therapeutic interventions through lysosomal modulation.

1 Lysosome−mediated degradation pathways in the maintenance of CSC stemness

Lysosomes, as the central degradative organelles within cells, play complex and critical roles in maintaining CSC stemness and drug resistance through multiple pathways (Figure 1).

1.1 The lysophagy pathway

Lysosomes participate in diverse forms of autophagy, including microautophagy, macroautophagy, and chaperone-mediated autophagy[26]. As a key mechanism for degrading intracellular components and sustaining cellular homeostasis, the autophagy-lysosome pathway is frequently dysregulated in CSCs and exhibits remarkable duality in stemness regulation across different tumor contexts.

Activation of the autophagy-lysosome pathway is an important mechanism for sustaining CSC function. In glioblastoma (GBM), the hypoxic microenvironment activates the STAT3/HIF1α signaling axis, which upregulates galectin-8 (Gal-8). Gal-8 interacts with the Ragulator-Rag complex on the lysosomal membrane, leading to mechanistic target of rapamycin complex 1 (mTORC1) inactivation, nuclear translocation of transcription factor EB (TFEB), and initiation of autophagy-lysosome biogenesis, ultimately supporting glioblastoma stem cell (GSC) survival[27]. Conversely, impaired autophagic flux triggers lysosome-mediated cell death, accompanied by mTOR inactivation and lysosomal dysfunction, thereby suppressing the expansion of patient-derived GSCs *in vitro*[28] . Under nutrient stress, the CSC marker CD133 promotes autophagosome-lysosome fusion, enhancing metabolic adaptability in glioma cells[29]. In head and neck squamous cell carcinoma (HNSCC), enhanced lysosomal biogenesis facilitates autophagic

degradation of glycogen synthase kinase 3 beta (GSK3β), stabilizing β-catenin and activating the Wnt/β-catenin pathway, which inhibits differentiation and reinforces CSC traits[30].

The autophagy-lysosome pathway has also been shown to suppress CSC stemness, highlighting its potential as a therapeutic target. In colorectal cancer, the small molecule QW24 degrades the stemness regulator B-cell-specific Moloney leukemia virus insertion site 1 (BMI-1) via this pathway, thereby impairing CSC self-renewal and inhibiting tumor growth and metastasis[31]. In inflammatory breast cancer (IBC), decorin (DCN) promotes the autophagic degradation of E-cadherin, negatively regulating the E-cadherin/EGFR/ERK axis and suppressing tumorigenicity and metastatic potential[32]. In colorectal cancer, Sox2-induced autophagy promotes cellular senescence, reducing proliferation and anchorage-independent growth[33]. In GBM, autophagy negatively regulates the Wnt/β -catenin pathway by altering β-catenin subcellular localization, thereby attenuating CSC traits[34]. In anaplastic thyroid carcinoma (ATC), capsaicin (CAP) activates calcium-dependent autophagy-lysosome degradation of OCT4A, suppressing CSC features[35].

Taken together, the autophagy-lysosome pathway functions as a "double-edged sword" in CSC biology, with its ultimate effects determined by the tumor cellular context and microenvironment. This duality underscores its therapeutic potential while necessitating deeper mechanistic investigations into its complex regulatory networks.

1.2 The mitophagy pathway

Mitophagy is a lysosome-mediated selective process that eliminates damaged mitochondria, thereby ensuring mitochondrial quality control and cellular homeostasis[36]. This process is typically highly active in CSCs, suggesting its involvement in stemness regulation[37]. A study on non-small cell lung cancer (NSCLC) CSCs revealed that elevated mitophagy leads to the accumulation of mitochondrial DNA (mtDNA) within lysosomes. This accumulation activates the TLR9 signaling pathway, which, in a Notch1-dependent manner, initiates AMPK signaling to enhance mitochondrial metabolism, ultimately promoting CSC proliferation[38].

1.3 Lysosome−dependent degradation independent of autophagy

The activation and maintenance of CSC functions are orchestrated by stemness-associated transcription factors and signaling pathways. Lysosomes can directly degrade these stemness regulators independent of autophagosomes, thereby exerting bidirectional control over CSC stemness.

On one hand, enhanced lysosomal degradation promotes CSC traits. In breast cancer, the secreted toxin BFT-1 binds and stabilizes nucleotide-binding oligomerization domain 1 (NOD1), which cooperates with Cyclin-G-associated kinase (GAK) to phosphorylate protein numb homolog (NUMB). Phosphorylated NUMB undergoes lysosomal degradation, relieving its inhibitory effect on the NOTCH1-HEY1 axis and increasing the CSC population[39]. During metastasis, lysosomal degradation also acts as a driver. For example, high expression of lysosomal-associated transmembrane protein 5 (LAPTM5) recruits the E3 ubiquitin ligase WWP2, mediating ubiquitination and lysosomal degradation of BMP type 1 receptors (BMPR1A), thereby blocking anti-metastatic bone morphogenetic protein (BMP) signaling in the lung stroma and promoting lung-specific metastasis[40].

On the other hand, impaired lysosomal degradation stabilizes certain oncogenic proteins, thereby enhancing CSC stemness. In gastric cancer, MYC-driven activation of the mTOR and ERK pathways suppresses lysosomal biogenesis, impairing epithelial cell adhesion molecule (EPCAM) macropinocytosis-dependent degradation. Elevated EPCAM levels promote CTNNB1 accumulation on chromatin, sustaining Wnt pathway activation[41]. Similarly, in invasive breast CSCs, beta-1, 4-galactosyltransferase-5 (B4GalT5) modifies and protects Frizzled-1 from lysosomal degradation, continuously activating the Wnt/β-catenin signaling to maintain CSC traits[42]. In GBM, collapsin response mediator protein 5 (CRMP5) prevents Notch degradation, leading to persistent Notch activation and tumor proliferation[43]. Likewise, receptor tyrosine kinases (RTKs) evade lysosomal degradation, activating downstream JAK2/STAT3 signaling to drive GBM progression and therapy resistance[44]. In hepatocellular carcinoma (HCC) and advanced serous ovarian cancer, suppression of Notch1/Notch3 lysosomal degradation results in aberrant Notch activation, promoting CSC survival and proliferation[45]. In addition, the nuclear factor NF-κB pathway also plays an important role in tumor stemness and resistance[46-47]. In GSCs, glucose-regulated protein 78 (GRP78) inhibits the lysosomal degradation of beta-site amyloid precursor protein cleaving enzyme 2 (BACE2), activating NF-κB and C/EBPβ signaling to sustain stemness[48].

Conversely, lysosomal degradation can suppress CSC stemness. In HCC, Ku80 interacts with spalt-like transcription factor 4 (SALL4), competitively

disrupting the SALL4-OCT4 complex and promoting OCT4 lysosomal degradation, thereby inhibiting CSC self-renewal and metastasis[49]. In GBM, palmitoylation of Oct4A protects it from lysosomal degradation, enabling complex formation with SOX4 to enhance SOX2 transcriptional activity and sustain stemness[11]. In breast cancer, membrane-associated RING-CH8 (MARCH8) acts as a tumor suppressor by promoting the lysosomal degradation of CD44, thereby inhibiting metastasis and inducing cell death[50]. For receptor tyrosine kinases such as the epidermal growth factor receptor (EGFR), endocytic lysosomal degradation is critical for signal termination. In breast CSCs, ε-Sarcoglycan (SGCE) functions as a "molecular sponge" interfering with EGFR-c-Cbl interactions, suppressing EGFR lysosomal degradation, and maintaining CSC stemness[51]. In osteosarcoma, insulin receptor substrate4 (IRS4) induces hyperactivation of the PI3K/AKT pathway to promote proliferation and tumorigenesis. However, IRS4 phosphorylation at Ser859 by casein kinase 1γ2 (CK1γ2) triggers CHIP-mediated ubiquitination and subsequent lysosomal degradation, thereby suppressing AKT signaling and inhibiting tumor growth[52].

2 The role of lysosomal proteins in the regulation of CSCs

The functional integrity of lysosomes depends not only on their unique acidic lumen but also on a series of key proteins localized to the lysosomal membrane or lumen. These proteins (Figure 2) maintain lysosomal structure and degradative capacity while directly participating in the regulation of cancer

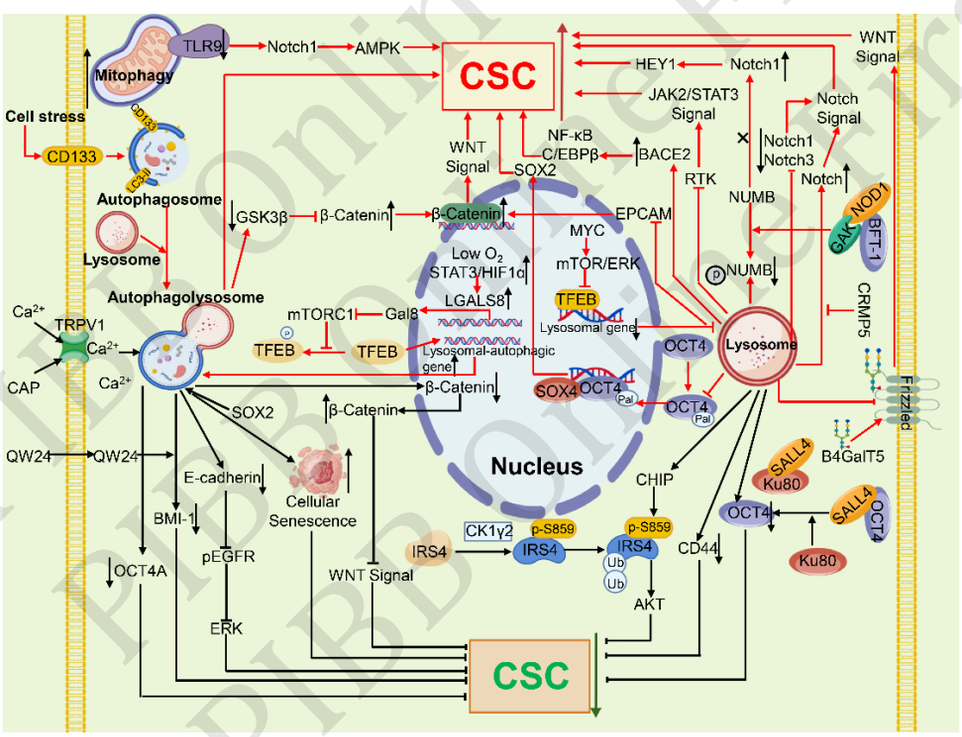

Fig. 1 Lysosome-mediated degradation pathways in the maintenance of CSC stemness

Lysosome-mediated degradation pathways (lysophagy pathway, lysosome-dependent degradation independent of autophagy and mitophagy pathway) regulate tumor stemness-related signaling pathways by degrading key protein factors, thereby promoting (in red) or inhibiting (in black) the characteristics of tumor stem cells. CSC: cancer stem cell; CD44: cluster of differentiation 44; CD133: cluster of differentiation 133; SOX2: sex determining region Y-box 2; OCT4: octamer-binding transcription factor 4; MYC: myelocytomatosis oncogene protein; NF-Kb: nuclear factor kappa B; mTORC1: mechanistic target of rapamycin complex 1; TFEB: transcription factor EB; GSK3β: glycogen synthase kinase 3 beta; BMI-1: B-cell-specific moloney leukemia virus insertion site 1; NOD1: nucleotide-binding oligomerization domain 1; NUMB: protein numb homolog; BMPR1A: BMP type 1 receptors; EPCAM: epithelial cell adhesion molecule; B4GalT5: beta-1, 4-galactosyltransferase-5; CRMP5: collapsin response mediator protein 5; SALL4: spalt-like transcription factor 4; EGFR: epidermal growth factor receptor; IRS4: insulin receptor substrate4; CK1γ2: casein kinase 1γ2; Gal-8: galectin-8; NOTCH1: neurogenic locus notch homolog protein 1; HEY1: hairy/enhancer-of-split related with YRPW motif protein 1; TLR9: Toll-like receptor 9; AMPK: AMP-activated protein kinase; ERK: extracellular signal-regulated kinase; RTK: receptor tyrosine kinases; BACE2: beta-site amyloid precursor protein cleaving enzyme 2; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; C/EBPβ: CCAAT/enhancer-binding protein beta; Ku80: Lupus Ku autoantigen protein p80; SOX4: sex determining region Y-box 4; CHIP: C-terminus of Hsc70-Interacting Protein; ERK: extracellular signal-regulated kinase. Created with BioGDP.com.

stem cell (CSC) properties.

2.1 Lysosomal membrane proteins

The lysosomal membrane provides the structural basis for lysosomal function and is enriched with highly glycosylated proteins, which protect them from degradation by acidic hydrolases within the lumen[53]. Beyond this protective role, lysosomal membrane proteins are central to organelle stability, substrate transport, and signal transduction. Key representatives include lysosome associated membrane protein (LAMP-1, LAMP-2), and Vacuolar-type H+-ATPase (V-ATPase), which regulate lysosomal biogenesis, acidification, and metabolite transport, respectively[54-55].

2.1.1 LAMP1

LAMP1 is one of the most abundant lysosomal membrane proteins. It participates in lysosomal exocytosis[56] and plays an important role in intracellular lipid transport[57]. In astrocytic glioblastoma tissues, GSCs were found to be enriched with lysosomes, and LAMP1 showed significant colocalization with the CSC marker CD133[58]. This observation suggests that lysosomes and their membrane proteins may be deeply involved in maintaining CSC stemness, offering a potential therapeutic strategy for targeting CSCs. However, current clinical data do not demonstrate a correlation between LAMP1 expression levels and overall survival, and its prognostic value remains to be clarified.

2.1.2 LAMP2

LAMP2 exists in three isoforms-LAMP2A, LAMP2B, and LAMP2C-each contributing to cellular homeostasis through distinct mechanisms.

LAMP2A serves as the receptor and translocation channel for chaperone-mediated autophagy (CMA), a selective autophagic pathway that does not involve autophagosome formation. Instead, proteins are directly delivered into the lysosomal lumen via interactions between heat shock cognate protein 70 (Hsc70) and LAMP2A[59-60]. In GBM, high LAMP2A expression significantly enhances CSC activity, whereas its knockdown suppresses CSC traits[61]. In ovarian CSCs, TFEB upregulates OCT4 and LAMP2A, thereby promoting CSC maintenance through CMA regulation[62].

LAMP2B primarily regulates autophagosome-lysosome fusion in cardiomyocytes[63]. In cancer, LAMP2B is highly expressed in colorectal cancer cells[54], and has been linked to sunitinib resistance in renal cell carcinoma[64]. Although direct evidence of its role in CSC regulation is lacking, LAMP2B has been extensively studied in exosome biology, where it is exploited for targeted drug delivery[54]. For instance, in acute myeloid leukemia (AML), exosomes carrying miR-34c-5p selectively target leukemia stem cells (LSCs), effectively eliminating them[65].

LAMP2C functions as a receptor in RNautophagy and DNautophagy (RDA), mediating ATP-dependent binding and lysosomal degradation of RNA and DNA[66]. Although less studied in cancer, LAMP2C expression in melanoma has been shown to induce cell cycle arrest, apoptosis, and necrosis, thereby suppressing tumor cell proliferation. Its role in other tumor types remains unclear.

2.1.3 V-ATPase

V-ATPase is a core protein complex responsible for maintaining the acidic environment (pH 4 – 5) of the lysosomal lumen. Composed of V1 and V0 domains, it hydrolyzes ATP to pump protons into the lysosome, directly influencing lysosomal degradation and signaling[67]. In CSCs, V-ATPase plays a critical role: its inhibition suppresses tumor sphere formation and epithelial-mesenchymal transition (EMT), thereby attenuating CSC malignancy[68]. Enrichment of V-ATPase subunits has been observed in GSCs and in patients with poor prognosis[69]. Inhibition of V-ATPase activity in GSCs induces reactive oxygen species (ROS) production and mitochondrial damage, suppressing tumor growth both in vitro and in vivo[70]. Moreover, V-ATPase contributes to chemoresistance by actively exporting chemotherapeutic drugs into the extracellular space[71].

2.1.4 Other lysosomal transmembrane proteins

Beyond classical lysosomal proteins, other lysosomal transmembrane proteins also play important roles in CSC regulation. High expression of lysosome-associated protein transmembrane 4B-35 (LAPTM4B-35) correlates with poor overall survival and biochemical recurrence-free survival in prostate cancer patients, suggesting its potential as a prognostic marker[72]. In CSCs, LAPTM4B stabilizes Yes-associated protein (YAP) by preventing its ubiquitin-mediated degradation. YAP, in turn, binds cAMP responsive element binding protein 1(CREB1) to transactivate LAPTM4B transcription, forming a positive feedback loop that sustains CSC stemness[73]. Another lysosomal protein, LAMP5, has been implicated in tumor progression; its knockdown suppresses ALDH activation and reduces tumor sphere formation[74]. In colorectal cancer, lysosomal proteins RAB5/7 and LAMP1/2 have been identified as potential CSC therapeutic targets, with RAB5/7 inhibition effectively eliminating CSCs and disrupting tumor lesions[75].

2.2 Acidic hydrolases

The lysosomal lumen contains more than 60 hydrolases, including proteases, nucleases, glycosidases, peptidases, sulfatases, and lipases, which directly execute lysosomal degradation. Cathepsins are representative hydrolases, classified by substrate specificity into serine proteases (*e. g*., cathepsins A and G), aspartic proteases (*e. g*., cathepsins D and E), and cysteine proteases (*e. g*., cathepsins B, C, F, H, K, L, O, S, V, X/Z, and W)[76]. These enzymes not only degrade macromolecules but also regulate diverse physiological and pathological processes, including cell growth, phagocytosis, apoptosis, immunity, secretion, and signal transduction[24, 77-78].

In CSCs, aberrant expression and activity of acidic hydrolases are closely associated with the malignant phenotype. For example, cathepsin B (CTSB) is highly expressed in pancreatic CSC-like cells (P-CSLCs) and serves as a biomarker for poor prognosis in pancreatic cancer patients[79]. Cathepsin L (CTSL) is overexpressed in ovarian cancer tissues and negatively correlates with patient survival; its knockdown significantly suppresses proliferation, invasion, and tumorigenicity *in vivo*[80]. In mesenchymal stem cells (MSCs), lysosomal acid lipase (LAL) regulates the synthesis and secretion of cytokines and chemokines, playing a key role in MSC-mediated tumor growth and metastasis[81].

Under normal conditions, acidic hydrolases are strictly confined within the lysosomal membrane. Once lysosomal integrity is compromised, hydrolase leakage into the cytoplasm triggers lysosome-dependent cell death (LDCD), a distinct form of programmed cell death[82]. In GBM stem cells, expression of the cysteine protease inhibitor SerpinB3 effectively suppresses LDCD, thereby maintaining CSC stemness[83]. This mechanism suggests that targeting LDCD may represent a promising strategy for CSC eradication. However, not all lysosomal damage leads to LDCD, as cells possess multiple pathways to recognize and manage damaged lysosomes, thereby maintaining cellular homeostasis. Upon lysosomal damage, cells initiate a damaged lysosome recognition mechanism, which identifies and transmits signals either by sensing leaked ions or by recognizing the ectopic exposure of lipids and glycoproteins on the lysosomal membrane[84]. Subsequently, cells proceed to repair damaged lysosomes, whereas irreparable lysosomes are eliminated, and the synthesis of new lysosomes is re-regulated[85]. This process involves the remodeling of multiple intracellular biological processes, such as protein translation, metabolism, and energy regulation[86]. These biological processes not only regulate the repair of damaged lysosomes but also trigger a series of stress responses, enabling cells to adapt to adverse environments and restore cellular homeostasis[87]. Lysosomal-dependent cell death (LDCD) is influenced by the number of damaged lysosomes and the extent of lysosomal content leakage. When a large-scale leakage of lysosomal contents occurs into the cytoplasm, it leads to fatal cytoplasmic acidification, resulting in massive hydrolysis of cytoplasmic components and cell necrosis, thereby triggering LDCD[85].

3 Lysosomes as key mediators of CSC–induced drug resistance

CSCs are recognized as central drivers of chemoresistance and disease relapse, and accumulating evidence indicates that lysosomes play a pivotal role in these resistance mechanisms (Figure 3). Lysosomes contribute to drug resistance primarily by sequestering chemotherapeutic agents and facilitating their efflux from the cell. The acidic interior of lysosomes creates a significant osmotic gradient relative to the cytoplasm, which promotes the passive diffusion of weakly basic, lipophilic, or amphipathic small-molecule chemotherapeutic drugs across the lysosomal membrane. Once inside the acidic lumen, these drugs become trapped, thereby reducing their cytotoxic effects on target cells[24]. Additionally, lysosomes can actively uptake chemotherapeutic drugs through transporters embedded in their membrane, such as ABC transporters, leading to intraluminal sequestration[88-89]. Beyond sequestration, lysosomes also expel chemotherapeutic agents via exocytosis, a process that contributes to drug resistance. This mechanism has been observed in various cancers, including undifferentiated pleomorphic sarcoma[90] and leukemia[91]. Recent studies have revealed that in hepatocellular carcinoma (HCC) patients, those with higher lysosome-related risk scores (LRRS) often present with more advanced clinical stages, stronger stemness features, and greater chemoresistance[92], suggesting a close association between lysosomal gene expression, CSC stemness, and therapy resistance. Mechanistic studies further reveal that in cisplatin-resistant oral CSCs, lysosomal activity and autophagosome-lysosome fusion are markedly enhanced, whereas inhibition of lysosomal function or blockade of autophagy significantly reduces the CSC subpopulation[93], underscoring the functional contribution of lysosomes to CSC-

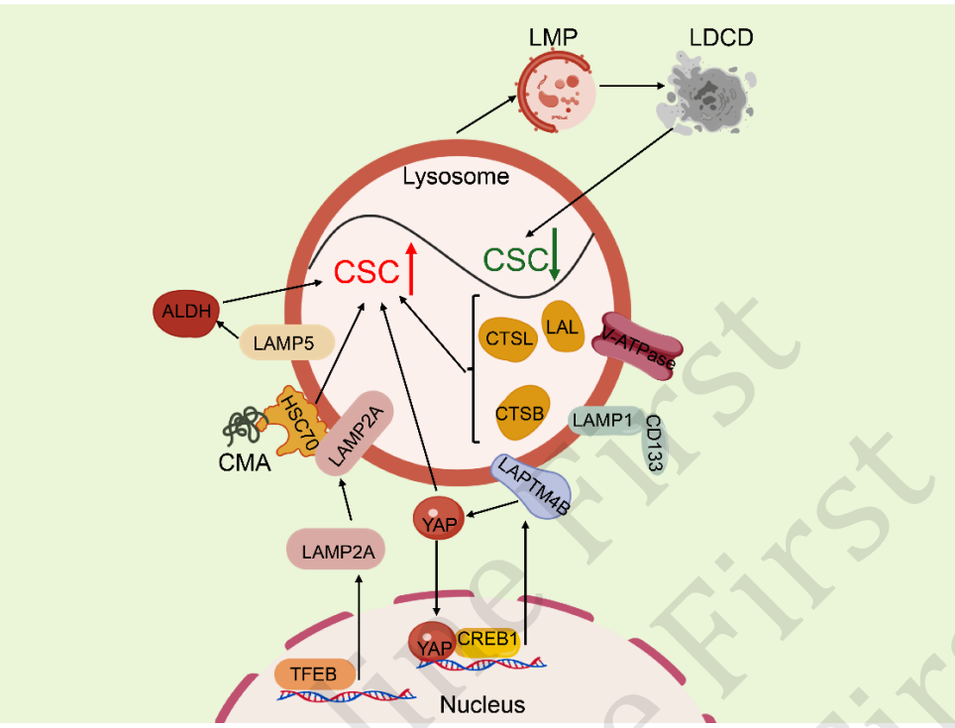

Fig. 2　Regulation of lysosomal proteins in CSC

Lysosomal proteins, including lysosomal membrane proteins (LAMP2A, LAMP1, LAMP5, LAPTM4B, and V-ATPase) and lysosomal acid hydrolases (CTSB, CTSL, ALA), can directly promote cancer stemness or promote it by regulating related signaling pathways (red). Furthermore, disrupting lysosomal stability leads to lysosome-dependent cell death (LDCD), thereby inhibiting cancer stemness (green). CSC: cancer stem cell; LAMP2A: lysosome-associated membrane protein 2 isoform A; LAMP1: lysosome-associated membrane protein 1; LAMP5: lysosome-associated membrane protein 5; LAPTM4B: lysosome-associated protein transmembrane 4B; V-ATPase: vacuolar-type ATPase; ALA: lysosomal acid lipase; CTSB: cathepsins B; CTSL: cathepsin L; CMA: chaperone-mediated autophagy; LMP: lysosomal membrane permeability; LDCD: lysosome-dependent cell death; TFEB: transcription factor EB; YAP: Yes-associated protein; CREB1: cAMP responsive element binding protein 1. Created with BioGDP.com.

mediated drug resistance. In multidrug-resistant (MDR) leukemia stem cells, high expression of the lysosomal membrane transporter ATP-binding cassette transporter A3 (ABCA3) sequesters drugs within the lysosomal lumen, preventing their interaction with intracellular targets and thereby inducing resistance[94]. Lysosomes can also internalize and proteolytically activate heparanase, which regulates autophagy and enhances chemoresistance in tumor cells[95].

Autophagy, as a critical survival mechanism under stress conditions, plays an important role in tumor resistance to radiotherapy and chemotherapy. Inhibition of autophagy has been shown to restore treatment sensitivity and promote tumor cell death. For instance, in CD44+CD24+ colorectal cancer stem cells, high expression of Cdx1 activates autophagy and enhances paclitaxel resistance[96]. The autophagy-lysosome pathway occupies a central position in CSC-mediated resistance. In HCC cells, the long noncoding RNA, nuclear enriched abundant transcript 1 variant 1 (NEAT1v1) regulates the expression of gamma-aminobutyric acid receptor associated protein (GABARAP), a key protein in autophagosome-lysosome fusion, thereby activating autophagy and conferring radio resistance[97]. Similarly, in studies of breast cancer MCF-7 cells and their CSCs exposed to ultra-high dose rate FLASH irradiation, CSCs exhibited lower levels of apoptosis, necrosis, and pyroptosis compared with parental cells, but displayed higher lysosomal activity and autophagy, suggesting that CSCs may enhance radioresistance through lysosome-mediated autophagy[98].

However, the role of the autophagy-lysosome pathway in resistance is highly context-dependent. In sorafenib-resistant HCC cells, transactivation response element RNA-binding protein 2 (TARBP2) undergoes degradation via the autophagy-lysosome pathway, thereby stabilizing the CSC marker Nanog and promoting resistance[99]. In contrast, in colorectal

CSCs (CD44+/CD133+), although autophagy levels are higher than in parental cells, irradiation does not further activate autophagy, and inhibition of autophagy does not alter radiosensitivity[100]. These findings indicate that the contribution of the autophagy-lysosome pathway to CSC-mediated resistance varies across tumor types and microenvironments, necessitating model-specific mechanistic investigations.

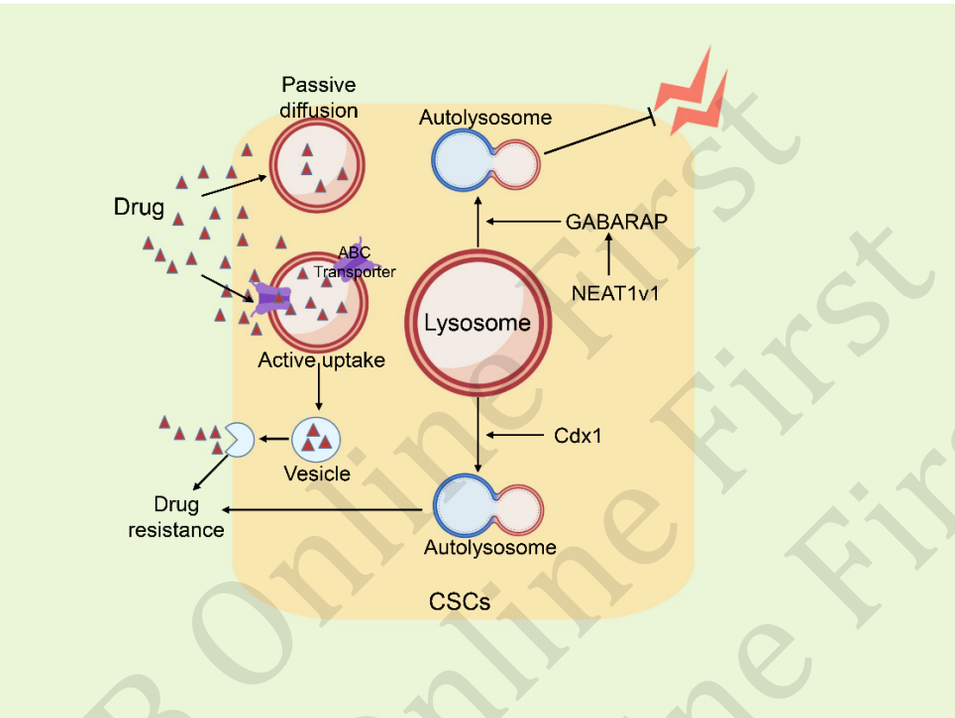

Fig. 3 Lysosomes as key determinants of CSC drug resistance

Lysosomes primarily contribute to drug resistance by sequestering and effluxing drugs: drugs enter lysosomes through passive diffusion or active transport, leading to their sequestration. Additionally, lysosomes can expel drugs from tumor cells via exocytosis. In cancer stem cells (CSCs), lysosomes also play a role in resistance to radiotherapy and chemotherapy through the autolysosome pathway, which helps CSCs evade the cytotoxic effects of these treatments. ABC transporter: ATP-binding cassette transporter; NEAT1v1: nuclear enriched abundant transcript 1 variant 1; GABARAP: gamma-aminobutyric acid receptor associated protein; Cdx1: caudal type homeobox 1. Created with BioGDP.com.

4 Pharmacological strategies targeting lysosomes to suppress CSC stemness

Lysosomes play multiple roles in maintaining the stemness of tumor stem cells, making them a highly promising therapeutic target. Currently, various intervention strategies targeting lysosomes have shown promising results in research, mainly through mechanisms such as inducing lysosomal membrane permeability and disrupting its intraluminal environment, interfering with the autophagy-lysosomal system, and regulating key signaling pathways. The targeted drugs involved are summarized in Table 1.

Maintaining the acidic environment of lysosomes is crucial for cell survival, and intervening in the acidic environment of lysosomes can be used as a therapeutic approach. Siramesine, as a lysosomal unstable drug, has shown cytotoxic ability against glioblastoma cells in both *in vitro* and *in vivo* experiments[101]. However, although Siramesine exhibited significant inhibitory effects in vitro in cell lines, these effects could not be replicated in organotypic spherical brain slice culture models or in mouse xenograft models of glioblastoma, suggesting that the in vivo mechanism of action of Siramesine warrants further investigation. Meanwhile, some studies have speculated that the blood-brain barrier (BBB) may prevent Siramesine from reaching tumor cells *in vivo*. However, existing research has shown that Siramesine can cross the BBB in mice following both oral and subcutaneous administration [102], indicating that the BBB may be implicated in impaired drug delivery[103]. In ovarian cancer CSCs, a

novel small molecule K/H transporter compound 2 induces lysosomal damage and apoptosis by interfering with the acidic environment of lysosomes, while simultaneously inhibiting autophagy, thereby selectively enhancing the toxicity to chemotherapy-resistant ovarian CSCs[104]. These findings suggest that the compound can enhance the cytotoxic effects of other chemotherapeutic agents on tumor cells, indicating the potential for developing novel therapeutic strategies. For instance, resistance to the anti-CSCs agent salinomycin can occur in tumor cells due to drug efflux mediated by ABC transporters[105]. However, the use of newly developed molecules to induce K/H transport offers the potential to achieve more effective CSC eradication while circumventing drug resistance. Tambjamine analogs, as anion carriers, can disrupt cellular ion homeostasis, leading to mitochondrial dysfunction and lysosomal deacidification, and kill lung CSCs through a necrotic pathway[106]. Lysosomal-dependent cell death (LDCD) is also an effective strategy for targeting CSCs[82, 107]. The cationic amphiphilic drug hexamethylene amiloride (HMA) can induce LDCD in various tumor cells, including those of the lung, colon, pancreas, brain, liver, prostate, and bladder, inhibiting tumor cell viability and spheroidization[108]. This study reveals the promising prospects of CAD-based therapeutic strategies targeting lysosomes for cancer treatment. Furthermore, other CADs have demonstrated similar effects; for example, Siramesine has been shown to induce LMP and tumor-selective cell death[109]. However, clinical efficacy data for the aforementioned LMP-targeting agents remain lacking[110]. Therefore, elucidating the molecular mechanism by which HMA targets lysosomes and developing more potent CADs represent critical directions for future research in this area. The neuronal nitric oxide synthase (NOS1) inhibitor ARL-17477 reduces membrane permeability after protonation within lysosomes, leading to lysosomal dysfunction, disrupting the autophagy-lysosomal pathway, and inhibiting tumor growth[111]. In this study, ARL-17477 demonstrated significant inhibition of transplanted tumor growth in mice, and the animals maintained good health throughout the treatment period. However, due to the lack of additional in vivo and clinical data to support these findings, ARL-17477 can only be regarded as a potential candidate for cancer therapy at this stage.

The autophagy-lysosomal system, as a regulatory system for cellular homeostasis, has become an important target for cancer treatment[112]. In triple-negative breast cancer, autophagy inhibitors IITZ-01 and IITZ-02 can specifically accumulate in lysosomes, causing lysosomal alkalization and impaired lysosomal enzyme maturation, thus exerting anticancer effects by inhibiting autophagy[113]. Statins have been extensively investigated as potential anticancer agents, with studies reporting that statin therapy reduces cancer-related mortality and improves survival rates in patients with glioblastoma[114]. In glioblastoma multiforme (GBM), lovastatin triggers autophagy initiation by inhibiting the Akt/mTOR signaling pathway, while interfering with the interaction between LAMP2 and dynein, impairing the fusion of autophagosomes and lysosomes, leading to impaired autophagy flux and promoting apoptosis[115]. However, this study has limitations. In terms of clinical research, no data is available to indicate the effect of lovastatin on chemotherapy. Among existing reports, only one registered Phase II clinical trial (NCT02029573) has been identified, evaluating the efficacy and safety of atorvastatin combined with radiotherapy and temozolomide in patients with glioblastoma. Although the trial was scheduled for completion in 2016, no findings have been published to date. Therefore, further experiments and clinical data are warranted to validate the anticancer effects of statins. Salinomycin (SAL) interferes with autophagy flux by inhibiting cathepsin activity without altering the integrity of lysosomal compartments, inhibiting the spheroidization ability of breast CSCs, and inducing apoptosis[116]. Although autophagy-lysosome targeted therapy holds great promise, autophagy plays a dual role in tumor cells. In the early stages of tumor development, autophagy can suppress tumors by maintaining genomic stability or by inhibiting inflammation. However, in later stages, it can promote tumor progression by providing nutrients for cancer cells[117]. This bifunctional nature complicates the determination of the optimal timing for intervention. Currently, there is a lack of reliable biomarkers to accurately assess the stage of lysosome-dependent tumor progression a patient is in. Therefore, when targeting the autophagy-lysosome pathway, factors such as tumor type, tumor malignancy grade, and drug resistance need to be considered. These limitations represent key challenges in the clinical translation of lysosome-targeted therapies.

ROS and autophagy regulation are also potential therapeutic targets. Studies have shown that ROS-induced stress survival in tumor cells depends on lysosomal function[118]. In breast cancer, the combination of kaempferol and verapamil (KV) can promote increased ROS, leading to lysosomal

degradation, Ca ion release, and decreased chemotherapy resistance, resulting in autophagic cell death[119]. Furthermore, linoplastin and melatonin inhibit TFEB expression and oligomerization, activate apoptosis signals, suppress GSC proliferation, and induce the expression of DNA damage markers (cleavage-PARP and γ -H2AX), thus inhibiting the formation of GSC tumor spheres[120].

In addition, some drugs regulate tumor stemness-related signaling pathways by modulating the lysosomal degradation pathways. In breast cancer, methyl 2-cyano-3, 12-dioxane-1, 9(11) -diene-28-olate (CDDO-Me) can induce the degradation of the Wnt receptor complex (LRP6/FZD7) *via* the ubiquitin-lysosomal pathway, inhibiting Wnt/β -catenin signaling and ultimately suppresses the stemness phenotype of breast cancer cells[121]. In uveal melanoma (UM), the photosensitizer verteporfen promotes the degradation of YAP protein via the lysosomal pathway, significantly inhibiting the migration, invasion, and tumor stem phenotype of UM cells[122] . In triple-negative breast cancer (TNBC), the AXL-PYK2-PKCα axis was found to maintain TNBC stemness through the regulators Oct4 and Nanog. Inhibition of PKCα can induce the degradation of AXL *via* the endosome-lysosomal pathway, suggesting that combined targeting of this signaling axis may eliminate CSCs and overcome drug resistance[123].

A comprehensive review of the mechanisms underlying various lysosome-targeting agents for CSC inhibition reveals that most studies remain at the cellular level, and in vivo investigations are largely confined to mouse models, such as inhibiting the growth of xenograft tumors, with a notable lack of clinical experimental data. This can be attributed to the complex in vivo environment. The core challenge of *in vivo* lysosome-targeted therapy lies in achieving precise and efficient drug delivery into lysosomes. This is not only a frontier in basic research but also a critical determinant of whether such therapies can successfully translate into clinical practice. The evolution of cancer therapy has been marked by a shift from broad-spectrum cytotoxic drugs towards precision medicine, with ongoing research into strategies that target specific moieties within tumor cells to achieve therapeutic effects[124]. Lysosomes have emerged as a such therapeutic target. Initial lysosome-targeting strategies primarily focused on utilizing lysosomes as intracellular drug depots. These approaches include designing nanoparticles that release drugs within the acidic lysosomal environment to overcome tumor cell resistance[125]. Such strategies aim to inhibit tumors primarily by increasing the intracellular concentration of anticancer agents and reversing drug resistance. With the advancement of nanotechnology, nanoparticle-based drug delivery systems (NDDSs) have emerged as a promising approach, with organelle targeting being a key mechanism of action. NDDSs can facilitate the specific transport of drugs to organelles, including lysosomes[126]. For instance, in hepatocellular carcinoma, pH-sensitive nanocarriers have been employed to deliver doxorubicin to the lysosomes, achieving lysosome-targeted tumor inhibition[127]. In conclusion, lysosome-targeted therapeutic strategies hold significant promise for cancer treatment. However, their successful clinical translation hinges on continued breakthroughs in critical areas and relies on the persistent efforts of numerous researchers.

5 Conclusion and future directions

As a central hub for intracellular degradation and signaling regulation, lysosomes play a critical role in the establishment and maintenance of CSC stemmness. Current studies have not only revealed a direct association between lysosomal degradative functions and CSC phenotypes, but have also begun to elucidate the complex mechanisms by which lysosomes influence CSC fate through modulation of key signaling pathways such as Notch and Wnt/β -catenin. Moreover, lysosomal function is closely linked to malignant behaviors including drug resistance and metastasis, making lysosome-targeted strategies-such as autophagy inhibitors and lysosomal destabilizing agents-highly promising for reversing stemness and enhancing therapeutic sensitivity.

Nevertheless, several important scientific questions remain to be addressed. First, how lysosomes precisely regulate the stability and activity of specific signaling molecules and transcription factors to influence CSC stemness requires further mechanistic investigation. Second, the efficacy and specificity of current lysosome-targeted therapeutic strategies (*e. g*., autophagy modulators and interventions targeting lysosomal membrane stability) remain limited, underscoring the urgent need to develop more selective drug delivery systems and rational combination therapies. In addition, the role of lysosomes in mediating intercellular interactions within the tumor microenvironment and their functions in immune regulation represent critical directions for understanding tumor heterogeneity and advancing combined immunotherapeutic approaches.

With the deepening understanding of lysosomal

Table 1 Targeting lysosomes to suppress CSCs

Target	The main targeted drugs	Cancer types	Study outcomes	References
Autophagy-lysosome	IITZ-01 IITZ-02	Triple-negative breast cancer	Disruption of lysosomal acidity impairs lysosomal enzymatic activity and integrity， leading to autophagy inhibition	［113］
	Lovastatin	Glioblastoma multiforme	Blocking the Akt/mTOR signaling cascade triggers autophagy initiation， whereas concomitant inhibition of LAMP2 and dynein disrupts the autophagosome-lysosome fusion machinery， thereby compromising autophagic flux	［115］
	GNS561	Hepatocellular carcinoma （HCC） and colorectal cancer （CRC）	Inhibition of autophagy triggers lysosome-dependent cell death，thereby eradicating tumor masses and cancer stem cell （CSC） subsets	［128］
	Lys05 （a chloroquine analog）	Chronic myeloid leukemia （CML）	Lysosome-targeted autophagy inhibition facilitates the maturation of leukemia stem cells （LSCs）， thereby decreasing the in vitro LSC population	［129］
Autophagy-lysosome pathway genes	Vorinostat，melatonin	Glioblastoma	Suppressing TFEB expression and oligomerization triggers apoptotic signaling cascades， leading to reduced proliferation of glioma stem cells （GSCs）. This process concomitantly induces the expression of cleaved PARP and p-γH2AX， resulting in a marked reduction in both the formation efficiency and the size of GSC tumorspheres	［120］
	Silaromycin	Glioblastoma	Destabilization of the lysosomal membrane results in lysosomal membrane permeabilization （LMP） and subsequent release of cathepsins， which in turn trigger cathepsin-dependent cell death pathways	［130］
Lysosomal membrane stability	Kaempferol，verapamil	Breast cancer	An increase in reactive oxygen species （ROS） within the cellular milieu promotes lysosomal breakdown and calcium ion release，which subsequently trigger autophagy-induced cell death， ultimately resulting in significant inhibition of tumor growth	［119］
	Hexamethylene amiloride	Lung， colon， pancreatic，brain， liver， prostate， and bladder tumors	Facilitating lysosomal membrane permeabilization enhances the susceptibility of tumor cells to lysosome-dependent cell death （LDCD）， which in turn reduces cellular viability and markedly impairs tumorsphere formation	［108］
Cathepsins	Salinomycin	Breast cancer	By inhibiting the lysosomal activity of cathepsins， autophagic flux in cancer cells is effectively suppressed	［116］
V-ATPase	Omeprazole	Rhabdomyosarcoma	By inhibiting V-ATPase activity， lysosomal acidification is impaired， which in turn potentiates the cytotoxic effects of doxorubicin on rhabdomyosarcoma cancer stem cells （CSCs）	［131］
	Bafilomycin A1	Ovarian cancer	By inhibiting V-ATPase activity， autophagy is suppressed， which markedly reduces the self-renewal potential of ovarian cancer stem cells （OCSCs） and diminishes their chemoresistant phenotype	［132］

biology and its role within CSC regulatory networks, it is reasonable to anticipate that novel interventions targeting lysosomal pathways will provide new theoretical foundations and practical avenues for overcoming current therapeutic bottlenecks and achieving more precise cancer treatment.

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溶酶体：肿瘤干性与耐药的关键调控者*

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摘要　肿瘤干细胞（cancer stem cells，CSCs）是一类具有自我更新能力、分化潜能且能够驱动肿瘤进展、耐药、复发和维持肿瘤微环境的关键细胞亚群。靶向CSCs可以克服肿瘤耐药、防止复发和转移，是当前肿瘤研究的重要方向，为肿瘤治疗提供新的策略。溶酶体作为细胞内物质降解与回收的核心细胞器，在维持细胞稳态中不可或缺，其功能异常与包括癌症在内的多种疾病密切相关。在肿瘤中，溶酶体功能异常可通过改变代谢途径、增强溶酶体胞吐作用，调控肿瘤耐药以及干扰自噬溶酶体途径等机制促进肿瘤恶性进展。近年研究表明，溶酶体还参与调控肿瘤干细胞特性。本文综述了溶酶体通过介导物质降解途径（溶酶体自噬途径、线粒体自噬途径和不依赖自噬体的溶酶体降解途径）及其关键结构蛋白（溶酶体膜蛋白、酸性水解酶等）在肿瘤细胞干性调控和肿瘤耐药中发挥关键作用，并深入探讨靶向溶酶体策略（如溶酶体不稳定药物）在消除肿瘤细胞干性，进而抗肿瘤中的应用前景。通过阐明溶酶体在调控肿瘤细胞干性中的作用机制，旨在为未来肿瘤治疗策略的开发提供新的理论依据与研究方向。

关键词　溶酶体，肿瘤干性，肿瘤耐药

中图分类号　Q291，R73　　**DOI**：10.3724/j.pibb.2025.0553　　**CSTR**：32369.14.pibb.20250553

* 国家自然科学基金（82360548），云南省科学技术厅基础研究计划项目（202301ATO70466）和云南省“兴滇英才”项目（XDYC-QNRC-2022-0280）资助。

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收稿日期：2025-12-28，接受日期：2026-03-10