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Review Article

Dual role of autophagy in bone metastasis: mechanistic insights and therapeutic targeting

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Abstract: Autophagy, a cellular degradation mechanism, plays a dual role in the progression and therapy of bone metastases in cancers, including prostate cancer. This review delves into the intricate roles of autophagy in both tumor suppression and progression, with a focus on its impact on bone metastasis and osteosarcoma (OS). Initially, autophagy acts as a tumor suppressor by eliminating damaged organelles and proteins, thus preventing tumor initiation. However, as cancer progresses, autophagy supports cancer cell survival under stress conditions, such as nutrient deprivation and hypoxia, and contributes to drug resistance. Specifically, in bone metastasis from breast and prostate cancers, autophagy facilitates tumor cell migration, invasion, and survival. The review also highlights the therapeutic potential of targeting autophagy in cancer treatment, especially in overcoming drug resistance in osteosarcoma, where autophagy modulation could reduce chemoresistance. By understanding the dual roles of autophagy in cancer and bone metastasis, new therapeutic strategies can be developed to target this process, offering hope for improved treatment outcomes in cancers prone to bone metastasis, including prostate cancer.

Keywords: Autophagy, bone neoplasms, osteosarcoma, neoplasm metastasis, drug resistance, prostate cancer

Introduction

Autophagy, an intracellular degradation process, is pivotal for maintaining cellular homeostasis and responding to various stressors [1, 2]. The complex role of autophagy in both the development and progression of cancer has become increasingly clear. It serves to prevent tumor initiation by eliminating damaged organelles and proteins, yet paradoxically supports cancer cell survival and fosters drug resistance as the tumor progresses [3-5]. Hence, modulating autophagy mechanisms presents a potential target in cancer therapy.

An epidemiological study on cancer bone metastasis reveals significant disparities in incidence rates across different cancer types, with breast and prostate cancers being the most common sources of bone metastasis [6, 7]. The ramifications of bone metastasis transcend survival implications, critically undermining patients' quality of life through a spectrum of bone-related complications, including pathological fractures and spinal cord compression [8, 9]. Emerging evidence suggests autophagy's substantial influence on the genesis and progression of bone metastases, potentially through its modulation of tumor cell migration, invasion, and survival mechanisms [10].

Osteosarcoma (OS), the most prevalent type of bone sarcoma, represents a group of malignant neoplasms characterized by osteoid matrix production [11]. OS predominantly spreads through the hematogenous route, with the lungs being the primary site for metastasis [12-14]. The inclusion of chemotherapy in the treatment regimen for localized OS has significantly improved prognoses, increasing survival rates up to 70%

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[15]. However, drug resistance, both inherent and acquired, poses a significant clinical challenge, with patients exhibiting poor response and refractory disease facing limited effective options in second- or third-line chemotherapy [16-18]. Chemotherapy primarily works by triggering apoptosis in cancer cells, yet it can also stimulate autophagy within these cells [19, 20]. Therefore, modulating autophagy in osteosarcoma (OS) cells to diminish their chemoresistance is a critical aspect of researching and developing innovative therapeutic approaches for OS.

Given the complex mechanisms of autophagy in cancer bone metastasis and osteosarcoma, involving various intracellular signaling pathways, a thorough understanding of these mechanisms is crucial for developing new therapeutic strategies. With advancing research into autophagy mechanisms, clinical exploration of autophagy-based therapeutic strategies has begun, which could potentially offer new directions for the treatment of cancer bone metastasis and osteosarcoma. This review will focus on the role and mechanisms of autophagy in cancer bone metastasis and osteosarcoma, exploring potential therapeutic strategies and providing a reference for future research and clinical applications.

Processes of autophagy

Molecular mechanisms of autophagy: insights into cellular self-digestion processes

Autophagy is a self-digestive process that plays a crucial role in cellular survival under conditions of external stress, hypoxia, and starvation [21-23]. It functions by clearing damaged organelles and long-lived proteins, thereby maintaining cellular homeostasis. The autophagic process encompasses macroautophagy, microautophagy, and chaperone-mediated autophagy, with macroautophagy being predominantly observed in the context of cancer [24-26]. Autophagosomes, double-membraned vesicles in the cytoplasm, are named based on their morphological characteristics and are regulated by a set of autophagy-related proteins (ATGs) [27, 28].

The autophagic process unfolds in four distinct steps. Initially, the formation of the phagophore is triggered by a complex composed of autophagy-related genes, including ATG1, ATG13, and ATG17, necessitating the involvement of the membrane protein ATG9 [29, 30]. The complex formation of Class III phosphatidylinositol 3-kinase (PI3K-III) and vacuolar protein sorting 34 (Vps34) with Beclin-1 (ATG6) further facilitates the development of the phagophore. Mitophagy, the selective autophagic degradation of mitochondria, begins with the interaction between B-cell lymphoma 2 (Bcl-2) and adenovirus E1B 19-kDa interacting protein 3 (BNIP3), which upon binding to Bcl-2, releases Beclin-1, leading to the formation of a Beclin-1-ATG14-PI3K-III complex [31, 32].

Subsequently, the assembly process within the phagophore is completed. ATG12 is covalently bonded to ATG5 through the action of ATG10, which is transported from ATG12 after being activated by ATG7 [33-35]. This ATG12-ATG5 conjugate promotes the elongation and closure of the phagophore to form the autophagosome [36-38]. The formation of the autophagosome also involves the conversion of LC3-I to LC3-II, mediated by ATG4. LC3, a mammalian homolog of yeast ATG8, is conjugated to phosphatidylethanolamine (PE) through the action of ATG7 and ATG3, resulting in LC3-II [38-40]. LC3-II becomes an integral part of the autophagosomal membrane. Finally, the autophagosome fuses with lysosomes to form a mature autolysosome, where the engulfed cytoplasmic proteins and organelles are degraded by lysosomal hydrolases.

This intricate process of autophagy illustrates the cell's sophisticated regulatory mechanisms in response to environmental changes, highlighting its vital role in cellular function and survival. Understanding the molecular intricacies of autophagy not only sheds light on basic cellular physiology but also opens avenues for therapeutic interventions in diseases where autophagy is dysregulated, such as cancer.

Regulatory molecular mechanisms of autophagy: deciphering the control of cellular self-eating processes

Autophagy is a crucial intracellular clearance mechanism that aids cells in coping with external stresses, such as starvation, ischemia-hypoxia, oxidative stress, calcium homeostasis imbalance, and mitochondrial dysfunction, by removing damaged organelles and long-lived

proteins. The autophagic process is regulated by multiple signaling pathways, including key pathways influenced by mTOR (mammalian target of rapamycin), Beclin-1, and p53.

mTOR signaling pathway: mTOR is a pivotal regulator of cell growth and metabolism, belonging to the phosphatidylinositol kinase-related kinase (PIKK) family [41, 42]. It regulates cell growth, metabolism, and autophagy by sensing ATP, hormones, and amino acid levels. In the regulation of autophagy, mTOR acts as a negative regulator [43]. Studies have shown that the downstream ribosomal protein S6 (p70S6) of the mTOR signaling pathway inhibits autophagy, while rapamycin induces autophagy by inhibiting mTOR activity, thereby reducing the activity of p70S6 [44, 45]. There are two forms of mTOR: mTORC1 and mTORC2, with mTORC1 being most closely related to autophagy regulation and the focus of current research.

Beclin-1 signaling pathway: Beclin-1 is a key regulatory factor in the autophagic process, homologous to Atg6/Vps30 in yeast [46-48]. By forming a complex with Class III PI3K, Beclin-1 regulates the activity of other autophagy-related genes, promoting the formation and maturation of autophagosomes. The expression level of Beclin-1 is closely related to the survival and therapeutic response of cancer cells, making the Beclin-1-regulated autophagic process a potential target for cancer treatment [49-51].

p53 signaling pathway: p53 is a critical tumor suppressor gene that regulates cellular autophagy in multiple ways [52-54]. In the nucleus, p53 can upregulate the level of cellular autophagy; in the cytoplasm, however, p53 may inhibit autophagy. Thus, p53 plays a dual regulatory role in cellular autophagy, with its specific mechanisms requiring further investigation [55, 56].

Other signaling pathways: In addition to the aforementioned pathways, the PI3K signaling pathway, hypoxia-inducible factors (HIF), AMPK, REDD1, and Tsc1/Tsc2 also participate in regulating cellular autophagy. For example, hypoxic conditions can induce autophagy through HIF-dependent or -independent mTOR mechanisms to adapt to the stress caused by low oxygen on the endoplasmic reticulum and mitochondria.

The molecular mechanisms regulating cellular autophagy involve multiple signaling pathways and regulatory factors. These mechanisms work together, enabling cells to adapt to continuously changing internal and external environments. By delving deeper into these molecular mechanisms, not only can our understanding of the cellular autophagy process be enhanced, but new strategies for treating diseases such as cancer may also be developed (**Figure 1**).

The dual role of autophagy in cancer

Autophagy in tumor suppression

Autophagy, a self-degradative process within cells, plays a crucial role in suppressing tumorigenesis by eliminating misfolded proteins, damaged organelles, and reactive oxygen species (ROS), thereby mitigating chronic tissue damage and preventing tumor development, particularly in early tumorigenesis.

Maintenance of genomic integrity: Beclin-1, a tumor suppressor, induces autophagy by binding to and activating Vps34, exerting antitumor effects [57]. Studies have observed a monoallelic deletion of Beclin-1 in 40-75% of breast, ovarian, and prostate cancers, with an increased tumor incidence in Beclin-1+/- mouse models [48, 58]. Furthermore, frame-shift mutations in certain autophagy-related genes have been identified in gastric and colorectal cancers, contributing to tumorigenesis by deregulating autophagy [59]. The phosphatase gene PTEN, the first identified tumor suppressor gene with lipid phosphatase activity, upregulates autophagy by inhibiting the PI3K/Akt pathway [60, 61]. Consequently, mutations in the PTEN gene or activation of Akt suppress autophagy. Clinical studies have found PTEN gene mutations in samples from 135 patients with gastric, colorectal, and hepatocellular carcinomas, highlighting autophagy's role in limiting genomic damage and mutations, thus inhibiting early tumor development [62, 63].

Suppression of necrotic inflammation: Chronic inflammation is a significant factor in early tumor development. Inflammatory cytokines regulate autophagic responses by binding to specific receptors on the cytoplasmic membrane [64, 65]. Activation of oncogenes, due to increased oxidative stress, creates a pro-

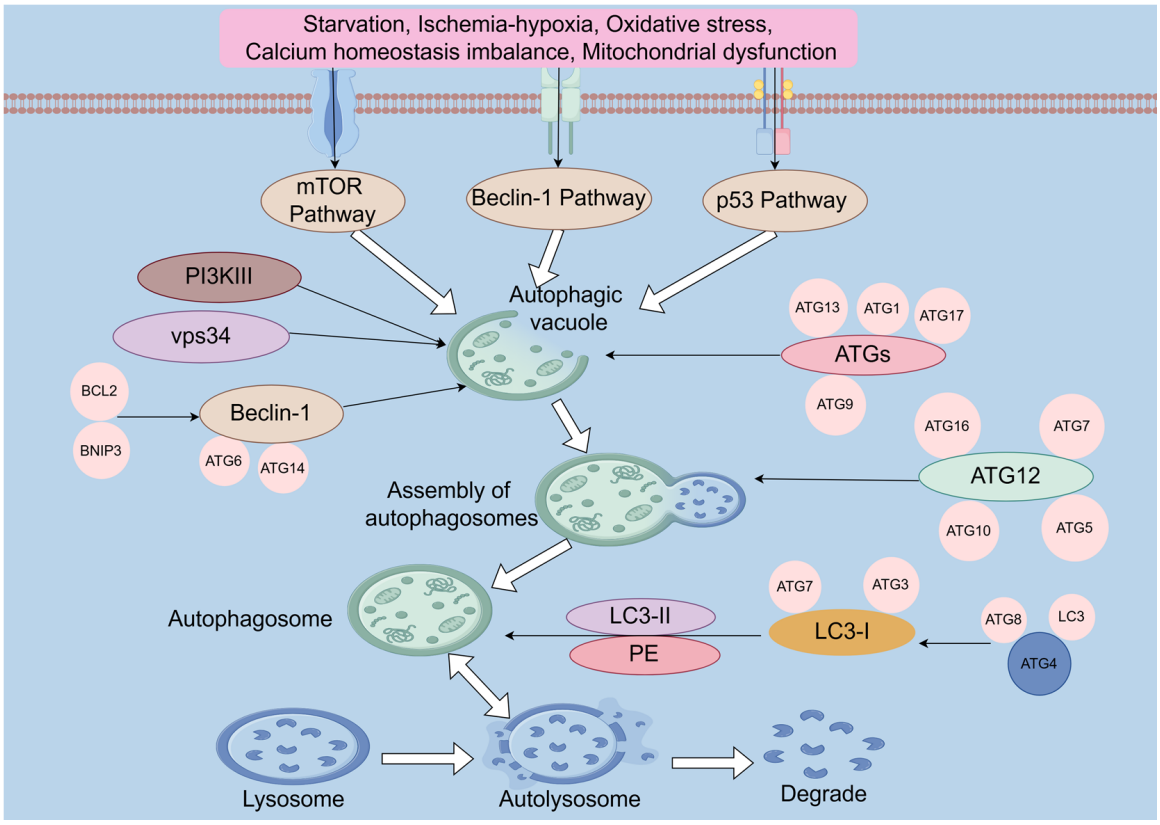

Figure 1. The occurrence and regulation process of autophagy. ATGs, autophagy-related proteins; Bcl-2, B-cell lymphoma 2; BNIP3, adenovirus E1B 19-kDa interacting protein 3; mTOR, mammalian target of rapamycin; PI3K-III, Class III phosphatidylinositol 3-kinase; PE, phosphatidylethanolamine; Vps34, vacuolar protein sorting 34. Created by Figdraw.com (https://www.figdraw.com).

tumorigenic inflammatory microenvironment [66, 67]. Similarly, inhibiting autophagy in defective cancer cells increases cell death and pro-inflammatory cytokine secretion secretion (e.g., HMGB1), exacerbating inflammation [68]. As a central inflammasome regulator, autophagy prevents tissue necrosis, chronic inflammation, and genomic instability, thereby reducing cancer susceptibility [69, 70].

Reduction of p62/SQSTM1 accumulation: The multifunctional ubiquitin-binding protein p62/SQSTM1, involved in both the ubiquitin-proteasome and autophagy-lysosome degradation pathways, selectively degrades misfolded proteins [71, 72]. p62 directly interacts with LC3, inducing its autophagic degradation [73]. Lack of Atg expression or impaired autophagosome-lysosome fusion leads to significant p62 protein accumulation, causing cytotoxicity, oxidative stress, and DNA damage closely associated with tumor progression [74, 75].

Autophagy in tumor progression

In the later stages of tumor progression, environmental stresses such as limited angiogenesis, nutrient deprivation, and hypoxia induce autophagy. This process supports established tumors survive and grow by degrading cellular contents and macromolecules for recycling, thereby enhancing tumor invasiveness and metastasis. Additionally, as a cellular defense mechanism, autophagy reduces the clinical effectiveness of most anticancer treatments.

Prevention of cellular damage: Under stress conditions, autophagy protects cells by clearing damaged mitochondria, inhibiting DNA damage, maintaining genomic stability, and limiting inflammatory responses [76, 77]. Mitochondria are a primary source of ROS. A deficiency in ATG proteins leads to accumulation of damaged mitochondria, excessive ROS production, DNA damage, and genomic instability [78, 79]. Autophagy suppresses ROS-induced DNA dam-

age and provides nucleotides for DNA replication and repair through its recycling function.

Promotion of cell metastasis: During advanced tumor progression, autophagy facilitates dissemination of malignant cells in the circulatory system, enhances colonization in target organs/tissues, induces dormancy, and enables survival in new microenvironments, with upregulated autophagy levels observed during metastasis [80, 81]. Elevated autophagy levels have been confirmed in the metastasis of breast cancer, melanoma, hepatocellular carcinoma, and glioblastoma [82].

Resistance to radio- and chemotherapy: Most anticancer therapies, including radiotherapy, chemotherapy, histone deacetylase inhibitors (colon cancer), temozolomide/rapamycin (malignant glioma), γ-ray irradiation (breast/prostate/colon cancers), resveratrol (ovarian cancer), and tamoxifen (breast cancer/glioblastoma), can induce autophagy [83, 84]. As a pro-survival mechanism, autophagy drives treatment-resistant cancer cells into dormancy, promotes tumor relapse/metastasis, and diminishes therapeutic efficacy [85, 86]. Given autophagy's protective role, combining autophagy inhibitors with conventional therapies may improve clinical outcomes [87, 88].

The relationship between autophagy and bone metastasis in cancer

The bone microenvironment's influence on cancer cell autophagy

The bone microenvironment plays a pivotal role in the regulation of autophagy in cancer cells. Tumor cells within the bone microenvironment exhibit aberrant expression of bone development-related genes, altering cellular activities and promoting tumor progression [89]. Cytokines and growth factors in the bone microenvironment enhance cancer cell survival and drug resistance by activating autophagy pathways (e.g., upregulating LC3-II and p62/SQSTM1), thereby increasing treatment tolerance [90]. The bone matrix, acting as a fertile niche for cancer cells, provides physical support via the extracellular matrix (ECM) and regulates autophagy through bidirectional interactions [91]. Osteoblasts and osteoclasts critically modulate autophagy in the bone microenvironment. Osteoblast-derived RANKL (Receptor Activator of Nuclear Factor κB Ligand) promotes osteoclast formation and activity, indirectly influencing cancer cell autophagy [92, 93]. Osteoclasts release bioactive molecules (e.g., TGF-β, IGF-1) during bone resorption, which regulate autophagy pathways to support cancer cell survival and proliferation [94]. Intercellular communication within the bone microenvironment is essential for autophagy regulation. Osteoblasts, osteoclasts, and bone marrow stromal cells exchange materials and signals with cancer cells via exosomes and microvesicles, containing microRNAs (e.g., miR-21, miR-30a) and proteins (e.g., HSP90) that modulate autophagy-related gene expression and signaling [95-97].

Autophagy's regulatory role in cancer cell proliferation and migration during bone metastasis

During the process of bone metastasis, autophagy influences cancer cell proliferation by regulating intracellular energy metabolism and levels of reactive oxygen species (ROS), and tumor cells remove damaged mitochondria through autophagy within the bone microenvironment, thereby maintaining cellular energy balance and viability [98, 99]. However, excessive activation of autophagy might enhance the migratory capabilities of tumor cells, facilitating bone metastasis [100]. Moreover, the interaction between osteoblasts and osteoclasts within the bone microenvironment can also affect cancer cell migration by modulating autophagy. Secretions from osteoblasts, for example, can activate autophagy and promote tumor cell metastasis [101]. In some cancer types, the activation of autophagy may lead to cytoskeletal reorganization and enhanced cell adhesion, limiting tumor cell migration [102]. Furthermore, autophagy could suppress tumor invasion and bone metastasis through mechanisms such as inducing apoptosis or inhibiting epithelial-mesenchymal transition (EMT) [103]. This dual role of autophagy makes it a significant target in cancer treatment research.

Current clinical targeted therapies affecting the skeletal system

In the realm of oncological therapeutics, a diverse array of drugs has been developed targeting specific molecular pathways to inhibit cancer progression and metastasis, particular-

Table 1. Current clinical targeted therapies affecting the skeletal system

Drug	Status of Application	Target	Autophagy Activity	Mechanism	Reference
Denosumab	Clinical Routine	RANKL	Not Specified	Inhibiting osteoclast formation and activity, reducing bone resorption and metastatic tumor growth in bone	[104-107]
Vemurafenib	Clinical Application	BRAF in Melanoma	Not Specified	Affecting multiple pathways in cancer cells, potentially altering autophagy	[108]
Dabrafenib	Clinical Application	BRAF in Melanoma	Not Specified	Similar to Vemurafenib, affecting cancer cell pathways, potentially impacting autophagy	[108]
Erlotinib	Clinical Application	EGFR in NSCLC	Not Specified	Reducing SREs in bone metastasis, suggesting an impact on bone remodeling and possibly autophagy	[109]
Crizotinib	Clinical Application	ALK in NSCLC	Not Specified	May influence bone remodeling through its antitumor efficacy, indirectly affecting autophagy	[108]
Cabozantinib	Clinical Application	VEGFR2, AXL, MET	Not Specified	Reducing tumor-induced osteolysis, suggesting an effect on bone remodeling and autophagy	[110-112]
Everolimus	Clinical Trials	mTOR	Inhibition	Inducing osteoprotegerin expression and apoptosis of osteoclasts, potentially affecting autophagy	[113, 114]
Imatinib	Clinical Application	C-KIT, PDGFR	Dual Activity	Affecting osteoblast activity, potentially influencing autophagy through bone remodeling	[115, 116]

ly in bone. These drugs, while primarily focused on their direct anticancer effects, also exhibit potential implications for autophagy. Denosumab [104-107], a drug used in clinical routines, targets RANKL to inhibit osteoclast formation and activity. This action not only reduces bone resorption but also potentially impacts metastatic tumor growth within the bone. Although its direct effect on autophagy is not specified, the mechanism suggests a possible influence on cellular processes related to cancer progression.

Vemurafenib and Dabrafenib [108], both targeting BRAF in melanoma, are in clinical application and share a similar mechanism that affects multiple pathways in cancer cells, which could potentially alter autophagy. Similarly, Erlotinib [109] and Crizotinib [108], targeting EGFR and ALK in NSCLC respectively, are noted for their roles in reducing skeletal-related events and exhibiting antitumor efficacy, which may indirectly influence autophagy through effects on bone remodeling. Cabozantinib [110-112], with its targets including VEGFR2, AXL, and MET, is recognized for its capacity to reduce tumor-induced osteolysis. Moreover, Everolimus [113, 114], currently in clinical trials and targeting mTOR, is one of the few drugs explicitly noted for its autophagy inhibition activity. By inducing osteoprotegerin expression and promoting apoptosis of osteoclasts, it offers a clear link between its primary mechanism and potential effects on autophagy. Imatinib [115, 116], targeting C-KIT and PDGFR, exhibits dual activity that affects osteoblast activity and, consequently, may influence autophagy through its impact on bone remodeling. This dual activity provides an intriguing insight into the complex interplay between cancer therapeutics, bone metabolism, and autophagy (**Table 1**).

Autophagy-related medications for common cancers with bone metastasis

Bone metastases are predominantly linked with certain cancers, such as breast cancer (70%), prostate cancer (85%), lung cancer (40%), renal cancer (40%), and multiple myeloma (95%) [117]. The prevalent incidence of breast, lung, and prostate cancers contributes to more than 80% of metastatic bone disease cases [118]. This section reviews autophagy-modulating therapies for these cancers.

Breast cancer: Autophagy modulation has emerged as a strategy to enhance conventional breast cancer therapies. Autophagy inhibitors such as bafilomycin A1 (BafA1) and chloroquine (CQ) [119, 120] has demonstrated increased radiation sensitivity in breast cancer cells, highlighting the potential of targeting autophagy to overcome radioresistance. The PI3K/AKT pathway, known for its role in promoting tumor growth and survival, has been targeted by inhibitors such as ipatasertib and taselisib [121]. Hormonal therapies like tamoxifen [122], which have been the mainstay for treating estrogen receptor-positive (ER+) breast cancer,

stimulate autophagy, contributing to both cell survival and resistance mechanisms. Similarly, Lapatinib [123], a HER2/EGFR inhibitor, exhibits a dual role in autophagy regulation, where short-term treatment induces apoptosis through autophagy, whereas long-term treatment fosters protective autophagy, leading to resistance. Trastuzumab and its conjugate, trastuzumab emtansine (T-DM1) [124, 125], widely used in HER2+ breast cancer treatment, also interact with autophagy pathways, contributing to their cytotoxic effects. Overall, the strategic modulation of autophagy in breast cancer therapy offers a promising avenue for enhancing the efficacy of existing treatments and overcoming resistance. Further research and clinical trials are warranted to fully elucidate the mechanisms and optimize the therapeutic strategies involving autophagy modulators.

The exploration of phytochemicals as potential therapeutic agents in breast cancer treatment has unveiled a diverse array of natural compounds capable of modulating autophagy. These phytochemicals, derived from various plants, exhibit a wide range of molecular effects on breast cancer cells, including the induction or inhibition of autophagy, apoptosis induction, cell cycle arrest, and sensitization to traditional chemotherapy. Artemisinin and its derivatives [126-129], for instance, have been shown to up-regulate autophagy markers like Beclin-1 and LC3-II, enhancing the sensitivity of breast cancer cells to chemotherapy drugs such as epirubicin. Baicalein [130-133], another phytochemical, suppresses cell proliferation and triggers both apoptosis and autophagy by modulating the PI3K/AKT/mTOR pathway, demonstrating its potential as a chemosensitizer in breast cancer therapy. Britannin [134, 135] and gaillardin [136], by down-regulating autophagy markers, induce apoptosis, suggesting a role in suppressing autophagy to enhance cancer cell death. Celastrol [137-139], known for its antiproliferative activity, elevates the expression of autophagy markers, indicating its potential to induce autophagy as a mechanism of action against breast cancer cells. Cucurbitacin B [140-142] and curcumin [143-145] have been noted for their ability to induce autophagy through various mechanisms, including ROS-mediated DNA damage and inactivation of the PI3K/Akt/mTOR pathway, respectively. These mechanisms highlight the multifaceted roles of phytochemicals in targeting autophagy pathways to combat breast cancer. Icariin [146-148], paclitaxel [149-151], and resveratrol [152-154] exhibit dual activities in modulating autophagy, demonstrating the complexity of autophagy as a therapeutic target. Tetrandrine [155-157], thymoquinone [158-160], and tocotrienols [161-163] activate autophagy, contributing to decreased cancer cell viability and enhanced sensitivity to chemotherapy. Ursolic acid [164-166] emerges as a potent inducer of cytotoxic autophagy and apoptosis by affecting AKT signaling and glycolysis, underscoring the potential of natural compounds in overcoming resistance to conventional therapies (**Table 2**).

These findings underscore the potential of phytochemicals as adjunctive or alternative therapies in breast cancer treatment, offering new avenues for overcoming drug resistance and enhancing therapeutic outcomes through the modulation of autophagy.

Prostate cancer: In the realm of urological system cancer therapies, particularly focusing on prostate cancer (PC), the modulation of autophagy through small-molecule compounds represents a promising therapeutic strategy. BML-275 [167, 168], also known as Dorsomorphin, serves a dual role by inhibiting AMPK and mTOR, leading to autophagy inhibition and activation, respectively, and demonstrating antitumor activities in PC models. Metformin [169], a well-known AMPK activator, has been shown to induce autophagy in PC, highlighting its potential beyond its traditional use in treating diabetes. The classical autophagy inhibitor 3-MA [170, 171] and the ULK1 inhibitor SBI-0206965 [172] demonstrate the therapeutic potential of autophagy inhibition in PC by disrupting autophagy-dependent processes and inducing apoptosis. The ATG4B inhibitors such as 21f [173] and DHA [174], show efficacy in inhibiting autophagy, leading to cell death in PC.

Marchantin M [175] display the inhibition of autophagy-mediated epithelial-mesenchymal transition (EMT) and activation of PERK/eIF2α-associated autophagy in PC. NCL1 [176], an LSD1 inhibitor, activates autophagy in PC, offering a novel approach to targeting autophagy regulation. Further research and clinical trials are essential to fully understand the therapeutic potential and mechanisms of these small-molecule compounds in modulating autophagy for cancer therapy (**Table 3**).

Table 2. Autophagy-related medications for breast cancer

Drug	Application Status	Target	Tumor or cell Type	Autophagy Activity	Mechanism	Reference
BafA1	Research	Autophagosome	Breast cancer	Inhibition	Enhancing radiation-induced death in breast cancer cells by likely modulating endoplasmic stress and mTOR pathway	[119]
Chloroquine (CQ)	Clinical Application	Autophagosome	Breast cancer	Inhibition	Boosting radiation sensitivity by suppressing TAK1; improving cytotoxicity of chemotherapy in resistant tumors	[119, 120]
Ipatasertib	Preclinical & Clinical Trials	PI3K/AKT	Breast cancer	Induction	Induces autophagy in TNBC, enhancing antitumor activity of PI3K/AKT suppressors in combination with CQ	[121]
Taselisib	Preclinical & Clinical Trials	PI3K/AKT	Breast cancer	Induction	Similar to Ipatasertib, inducing autophagy in TNBC, potentiating antitumor effects of chemotherapy with CQ	[121]
Tamoxifen	Clinical Application	ER	Breast cancer	Induction	Induces autophagy in ER+ breast cancer cells, potentially contributing to cell survival and resistance	[122]
Lapatinib	Clinical Application	HER2/EGFR	Breast cancer	Dual Activity	Short-term treatment induces apoptosis via autophagy; long-term treatment leads to protective autophagy	[123]
Trastuzumab	Clinical Application	HER2	Breast cancer	Not Specified	Autophagy plays a significant role in the cytotoxic effects of trastuzumab and T-DM1 on HER2+ breast cancer cells	[124, 125]
Artemisinin	Research	Beclin-1, P21	MCF-7, MDA-MB-231	Up-regulation	Inducing autophagy by up-regulating Beclin-1 and P21, leading to increased sensitivity to chemotherapy and apoptosis	[126-129]
Baicalein	Research	PI3K/AKT, mTOR	MCF-7, MDA-MB-231	Activation	Suppressing cell proliferation and triggers apoptosis and Inducing autophagy by modulating the PI3K/AKT/mTOR pathway	[130-133]
Britannin	Research	ATG1, ATG4, ATG5	MCF-7	Inhibition	Inducing apoptosis and inhibits autophagy by down-regulating autophagy markers such as ATG4, ATG5, Beclin1, and LC-III	[134, 135]
Celastrol	Research	LC3 A/B, p62	MCF-7	Activation	Exhibits antiproliferative activity and inhibits colony formation by elevating expression of autophagy markers LC3 A/B, p62, and Beclin-1	[137-139]
Cucurbitacin B	Research	LC3 II, p-mTOR	MCF-7	Activation	Decreasing cell viability and inducing DNA damage and autophagy by up-regulating LC3 II and inhibiting p-mTOR, p-Akt, and p62 expressions	[140-142]

Curcumin	Research	PI3K/Akt/mTOR	MCF7, MDA-MB-231	Activation	Sensitizing MDR breast cancer cells to cisplatin and inducing apoptosis and autophagy by down-regulating CCAT1 and inactivating the PI3K/Akt/mTOR pathway	[143-145]
Gaillardin	Research	ATG1, ATG4, ATG5	MCF-7	Inhibition	Inducing apoptosis and inhibiting autophagy by down-regulating autophagy markers such as ATG1, ATG4, ATG5, Beclin1, and LC-III	[136]
Icariin	Research	CDK2, CDK4	MCF-7, MDA-MB-231	Dual Activity	Inducing cell cycle arrest and apoptosis through suppression of autophagy in TAM-resistant cells and enhances autophagy in other contexts	[146-148]
Paclitaxel	Research	Beclin1	BT474	Inhibition	Inhibiting tumor growth by reducing the expression of Beclin1	[149-151]
Resveratrol	Research	AKT, mTORC1	MDA-MB-231, MCF-7	Dual Activity	Sensitizing breast cancer cells to talazoparib and inducing apoptosis by suppressing AKT signaling and inhibiting autophagy flux	[152-154]
Tetrandrine	Research	PI3K/AKT/mTOR	MDA-MB-231, MCF-7	Activation	Blocks cell proliferation and stimulating autophagy and apoptosis by elevating Beclin1, LC3-II/LC3-I and reducing p62/SQSTM1	[155-157]
Thymoquinone	Research	Beclin-1, LC3	MCF-7, MDA-MB-231	Dual Activity	Inhibiting autophagy and cell migration in some contexts, while in others, it increases autophagic vesicles and sensitizes cells to PTX	[158-160]
Tocotrienols	Research	Beclin-1, LC3B	MCF-7, MDA-MB-231	Activation	Decreasing cancer cell viability by increasing markers of both early and late phase autophagy	[161-163]
Ursolic acid	Research	PI3K, AKT	MCF-7, MDA-MB-231	Activation	Inducing cytotoxic autophagy and apoptosis by diminishing AKT signaling and affecting glycolysis	[164-166]

Table 3. Autophagy-related medications for prostate and lung cancer

Drug	Application Status	Target/Pathway	Tumor Type	Autophagy Activity	Mechanism	Reference
BML-275 (Dorsomorphin)	Preclinical	AMPK inhibitor, mTOR inhibitor	PC	Inhibition/ Activation	Inhibiting autophagy via AMPK; Induces mitochondria-mediated apoptosis and autophagy via mTOR	[167, 168]
Metformin	Clinical	AMPK activator	PC	Activation	Activating AMPK-induced autophagy by binding to PEN2	[169]
3-MA	Preclinical	PI3K inhibitor	PC	Inhibition	Suppressing ATG5-dependent autophagy and autophagy-dependent exocytosis by inhibiting PI3K	[170, 171]
SBI-0206965	Preclinical	ULK1 inhibitor	PC	Inhibition	Inhibiting autophagy, PPP flux, and ROS clearance, inducing apoptosis	[172]
21f	Preclinical	ATG4B inhibitor	PC	Inhibition	Reducing LC3II/I levels and p62 degradation, inhibiting cellular autophagy	[173]
Docosahexaenoic acid (DHA)	Preclinical	ATG4B inhibitor	PC	Inhibition	Inhibiting ARSI-induced autophagy through mitochondrial dysfunction	[174]
Marchantin M	Preclinical	20S proteasome inhibitor	PC	Inhibition	Activating PERK/eIF2 associated autophagy by inhibiting the 20S proteasome	[175]
Sunitinib	Clinical	RTK inhibitor	RCC	Activation	Inducing autophagy by activating ERK1/2 and inhibiting mTOR/ p70S6K	[231]
NCL1	Preclinical	LSD1 inhibitor	PC	Activation	Activating autophagy by inducing H3K4me2 accumulation at the P21 promoter	[176]
Dihydroartemisinin (DHA)	Research	MAPK, mTOR/HIF-1	NSCLC	Activation/ Inhibition	Inducing excessive autophagic cell death via HMGB1/MAPK signaling; Inhibits mitophagy to decrease radiation resistance; Induces ROS-dependent apoptosis	[177, 178]
Curcumin	Research	PI3K/Akt/mTOR, IP3R, miR-192-5p	NSCLC	Activation	Initiating autophagy by causing mitochondrial damage; Triggers apoptosis via calcium overload and caspase-3 activation	[179-181]
Baicalein	Research	MAP4K3/mTORC1/TFEB, PI3K/Akt/NF-kB	NSCLC	Activation	Regulating autophagy via MAP4K3 inhibition; Induces apoptosis by downregulating Bcl-2 and caspase-3 proform; Enhances chemosensitivity to cisplatin	[182-184]
Ginsenosides	Research	ATF4-CHOP-AKT1-mTOR, PI3K/Akt, PINK1-Parkin	NSCLC	Activation	Enhancing autophagy flux and induces autophagic cell death; Promotes apoptosis and mitophagy via ROS and PINK1-Parkin activation	[185-188]

Lung cancers: In the quest to combat non-small cell lung cancer (NSCLC), researchers have explored various natural compounds for their potential therapeutic effects. Dihydroartemisinin (DHA) [177, 178], a derivative of artemisinin, has demonstrated a multifaceted approach in NSCLC treatment. It has been shown to initiate excessive autophagic cell death via HMGB1/MAPK signaling and inhibit mitophagy to decrease radiation resistance, thereby enhancing the therapeutic effect against NSCLC. Moreover, DHA induces ROS-dependent apoptosis, showcasing its potential as a comprehensive anticancer agent. Curcumin [179-181], derived from Curcuma longa, is recognized for its anti-inflammatory and antioxidant properties. In NSCLC, Curcumin has been found to initiate autophagy by causing mitochondrial damage and triggering apoptosis through calcium overload and caspase-3 activation. Its ability to modulate the PI3K/Akt/mTOR pathway further underscores its therapeutic potential in NSCLC by enhancing autophagy and promoting apoptosis. Baicalein [182-184], a flavonoid from Scutellaria baicalensis roots, exhibits anti-tumor activity by regulating autophagy and apoptosis. It directly binds to and inactivates MAP4K3, leading to TFEB-dependent autophagy and tumor growth inhibition. Baicalein also induces apoptosis by down-regulating Bcl-2 and caspase-3 proform, and it enhances NSCLC chemosensitivity to cisplatin through the PI3K/Akt/NF-kB pathway. Ginsenosides [185-188], key constituents of ginseng, have been studied for their anticancer effects, which include cell cycle arrest, apoptosis, and autophagy induction. They enhance autophagy flux and induce autophagic cell death in NSCLC cells through ATF4-CHOP-AKT1-mTOR axis activation. Ginsenosides also promote apoptosis and mitophagy via ROS and the PINK1-Parkin signaling pathway, highlighting their role in NSCLC therapy.

By targeting various signaling pathways, these compounds not only inhibit tumor progression but also enhance the sensitivity of cancer cells to conventional treatments, offering a promising avenue for future therapeutic strategies against NSCLC. Further clinical research and trials are essential to validate these preclinical findings and to determine the efficacy and safety of these compounds in human subjects (**Table 3**).

The interaction between autophagy and osteosarcoma

Autophagic activity in osteosarcoma cells

Autophagy, a cellular self-degradation process, plays a crucial role in osteosarcoma cells. Studies have shown that autophagic activity is significantly enhanced in osteosarcoma cells, closely associated with tumor initiation and progression. Specifically, autophagy facilitates tumor cell survival and proliferation by maintaining intracellular homeostasis through the clearance of damaged organelles and proteins. For instance, autophagy-related genes such as Beclin1 and LC3B are found to be highly expressed in osteosarcoma patients, correlating with poor prognosis [189]. Moreover, research has identified that Sirt1 promotes autophagic activity in osteosarcoma cells by regulating the phosphorylation of histone H3, potentially influencing tumor progression [190]. Therefore, autophagy serves not only as a mechanism for osteosarcoma cells to adapt to microenvironmental stress but also as a vital support for tumor cell survival.

The role of autophagy in osteosarcoma drug resistance

Autophagy plays a dual role in the drug resistance of osteosarcoma. While autophagy can protect cells by eliminating intracellular toxic substances, it may also promote resistance to chemotherapy drugs in certain contexts. For example, chemotherapeutic agents like Doxorubicin can induce autophagy in osteosarcoma cells, a response closely linked to the development of drug resistance [191]. Furthermore, miR-331-3p has been found to promote chemotherapeutic resistance by regulating the autophagy process, highlighting the significant regulatory role of autophagy in the drug tolerance of osteosarcoma cells [192]. Therefore, therapeutic strategies targeting autophagy, such as the application of autophagy inhibitors, may offer new insights and approaches to overcoming osteosarcoma resistance. By modulating autophagic activity, it is hoped that the sensitivity of osteosarcoma patients to chemotherapy can be enhanced, thereby improving treatment outcomes.

Adjusting autophagy in osteosarcoma treatment strategies

The modulation of autophagy in osteosarcoma therapy involves a diverse range of pharmacological inhibitors and inducers targeting various components of the autophagy pathway. Inhibitors like LY294002 [193], 3-MA [193, 194], and Wortmannin [193] act on early stages of autophagy by targeting the PI3K pathway, thereby improving the chemosensitivity of OS cells. Late-stage inhibitors such as Chloroquine and Hydroxychloroquine [195, 196] target the fusion of autophagosomes with lysosomes, leading to cell death independent of autophagy. The use of specific VPS34 inhibitors like Spautin-1 [197] and SAR405 [198], as well as ATG4B inhibitors NSC185058 [196] and NSC377071 [196], demonstrates the potential of targeting specific autophagy-related proteins for therapeutic benefits in OS. Verteporfin is noted for its ability to disrupt early autophagic processes, induce lysosomal instability, and inhibit autophagic flux, presenting a multifaceted approach to inhibiting autophagy at multiple levels [199]. Bafilomycin A1 targets lysosomal acidification, a crucial step for autophagosome maturation, and has shown cytotoxic effects in OS cells when combined with other inhibitors, highlighting its role in hindering the autophagy process [200]. NBDHEX and MC3181 [201], both acting through JNK activation, lead to autophagic impairment and subsequent cell death, underscoring the potential of targeting the JNK pathway as a means to disrupt autophagy and promote cancer cell death in OS.

Conversely, inducers of autophagy, such as EGCG [202, 203], Rapamycin [204], and its analogs Temsirolimus [205], aim to increase tumor autophagy, thereby reducing tumor growth and inducing cell death. Metformin [206] and PF-06409577 [207], which activate AMPK, represent another strategy for inducing autophagy, with the latter showing more potent effects than traditional activators.

This comprehensive approach to modulating autophagy in osteosarcoma therapy highlights the complexity of targeting autophagy for therapeutic benefits. Given the dual role of autophagy in cancer - both suppressive and promotive - it is imperative to carefully consider the context in which autophagy modulation is applied. Future research should focus on elucidating the precise mechanisms of action of these drugs, optimizing their delivery and efficacy, and evaluating their safety and therapeutic potential in clinical trials.

It's evident that natural products offer a diverse arsenal against osteosarcoma, targeting various pathways to inhibit tumor growth, induce apoptosis, and modulate autophagy. Oridonin [208-210] stands out for its ability to induce mitochondria-mediated apoptosis and modulate several signaling pathways, including p38 MAPK, JNK, and PPAR-γ, while also inhibiting Akt and Nrf2 pathways, highlighting its potential as a multifaceted anti-cancer agent. Wogonin [211-213] and Oleuropein [214-216] also demonstrate significant anti-cancer properties through ROS production and anti-proliferative effects, respectively, though the specific role of autophagy in their mechanisms remains to be further elucidated.

Evodiamine [217-219], with its capacity to induce mitochondrial apoptosis and arrest cell-cycle progression via the inactivation of key signaling pathways like PTEN/PI3K/Akt and Wnt/β-catenin, offers another promising avenue for osteosarcoma treatment. Parthenolide's [220-222] ability to suppress NF-κB activity and induce autophagy through ROS generation makes it a valuable candidate for further research, especially considering its potential to prevent metastasis and enhance radiosensitivity.

Shikonin [223, 224] and Berberine [225-227] both exhibit potent anti-cancer effects, with Shikonin inducing apoptosis and necroptosis and Berberine inhibiting cell migration and enhancing the effects of cisplatin. Triptolide's [228-230] multifunctional approach, affecting apoptosis, autophagy, and angiogenesis through a variety of pathways, underscores the complex interplay between these processes in cancer treatment and the potential of natural products to offer comprehensive therapeutic strategies (**Table 4**).

These findings underscore the potential of natural products as valuable candidates for osteosarcoma treatment, either as standalone therapies or in combination with conventional treatments, to overcome resistance and reduce side effects. Further research is needed to fully

Table 4. Autophagy-related medications for osteosarcoma

Drug	Application Status	Target	Tumor Type	Autophagy Activity	Mechanism	Reference
LY294002	Preclinical	PI3K	OS	Inhibitor	Inhibiting PI3K, increasing chemosensitivity in combination with cisplatin	[193]
3-MA	Preclinical	PI3K-III, PI3K-I	OS	Inhibitor	Transient inhibition of PI3K-III and permanent inhibition of PI3K-I, improving OS cell sensitivity to chemotherapy	[193, 194]
Wortmannin	Preclinical	PI3KIII, PI3K-I	OS	Inhibitor	Permanently inhibiting PI3KIII and transiently inhibits PI3K-I, also affects mTOR	[193]
NSC185058	Preclinical	ATG4B	OS	Inhibitor	Suppressing LC3 lipidation, inhibits autophagy in OS cells in vivo, suppresses tumor growth	[196]
NSC377071	Preclinical	ATG4B	OS	Inhibitor	May suppress ATG4B activity by regulating the mTOR pathway or PI3K pathway down-regulation	[196]
Chloroquine (CQ)	Preclinical	Autophagosomes and lysosomes	OS	Inhibitor	Deacidifies and blocks the fusion of autophagosomes with lysosomes, triggering lysosomal lysis and cell death	[195, 196]
Hydroxychloroquine (HCQ)	Preclinical	Autophagosomes and lysosomes	OS	Inhibitor	Similar to CQ, interferes with critical biological processes independent of autophagy	[195, 196]
Spautin-1	Preclinical	VPS34	OS	Inhibitor	Enhancing degradation of VPS34 complexes, synergistic anti-tumor effects with rapamycin	[197]
SAR405	Preclinical	VPS34	OS	Inhibitor	Potently inhibiting VPS34, enhances celecoxib-mediated suppression of cell viability	[198]
Verteporfin	Preclinical	Multiple levels of autophagy	OS	Inhibitor	Disrupting early autophagic processes, induces lysosomal instability, inhibits autophagic flux	[199]
Bafilomycin A1	Preclinical	Lysosomal acidification	OS	Inhibitor	Inhibiting lysosomal acidification, combined with other inhibitors shows cytotoxic effects in OS cells	[200]
NBDHEX	Preclinical	JNK activation	OS	Inhibitor	Triggering autophagic impairment and cell death by JNK activation	[201]
MC3181	Preclinical	JNK activation	OS	Inhibitor	Similar to NBDHEX, triggers autophagic impairment and cell death	[201]
EGCG	Preclinical	p38/MAPK, PI3K/AKT	OS	Inducer	Inhibiting DOX-induced pro-survival autophagy, partially inhibits self-renewal capacity of OSCs	[202, 203]
Rapamycin	Preclinical	mTORC1	OS	Inducer	Forms complex with FKBP12, resulting in RAPTOR dissociation and mTORC1 inactivation	[204]
Temsirolimus	Preclinical	mTORC1	OS	Inducer	Water-soluble analog of rapamycin, increases tumor autophagy and reduces tumor growth	[205]
Metformin	Preclinical	AMPK activation	OS	Inducer	Indirectly activating AMPK, promoting inactivation of mTORC1 Complex	[206]
PF-06409577	Preclinical	AMPK subunits	OS	Inducer	Binds selectively to AMPK subunits, more potent effects than traditional activators	[207]

Oridonin	Preclinical	p38 MAPK, JNK, PPAR-γ, Akt, Nrf2 pathways	OS	Inducer	Inducing mitochondria-mediated apoptosis, ROS production, inhibits Akt and Nrf2, activates p38 MAPK, JNK, and PPAR-γ	[208-210]
Wogonin	Preclinical	ROS, STAT3, PRX5	OS	Inducer	Inducing ROS production leading to apoptosis, inhibits STAT3 and PRX5, affects MMP-9 expression in CSCs	[211-213]
Oleuropein	Preclinical	Not specified	OS	Implied	Anti-proliferative properties, role in autophagy induction unclear, used in combination therapy	[214-216]
Evodiamine	Preclinical	PTEN/PI3K/Akt, Wnt/β-catenin	OS	Not specified	Inducing mitochondrial apoptosis, cell-cycle arrest, inactivates PTEN/PI3K/Akt and Wnt/β-catenin pathways	[217-219]
Parthenolide	Preclinical	NF-κB, JNK, ROS	OS	Inducer	Suppressing NF-κB, activates JNK, induces caspase-independent cell death and autophagy via ROS production	[220-222]
Shikonin	Preclinical	ROS, ERK, RIP1, RIP3	OS	Not specified	Inducing apoptosis and necroptosis, increases ROS and activates ERK, suppresses MMP13, enhances effects of doxorubicin	[223, 224]
Berberine	Preclinical	MMP2, p53, MAPK signaling	OS	Not specified	Inhibiting cell proliferation, migration, and colony formation, induces cell-cycle arrest and apoptosis, enhances effects of cisplatin	[225-227]
Triptolide	Preclinical	Fas/FasL, caspases, Wnt/β-catenin, DUSP1	OS	Inducer	Reducing cell viability, induces apoptosis and autophagy, suppresses angiogenesis, enhances sensitivity to chemotherapy	[228-230]

understand their mechanisms of action, optimize their delivery, and evaluate their efficacy and safety in clinical settings.

Future perspectives and directions in autophagy-related cancer therapies

Given the critical role of autophagy in both promoting and suppressing cancer, particularly in the context of bone metastasis and osteosarcoma, future research should concentrate on several key areas to advance our understanding and therapeutic capabilities.

(1) Precision targeting of autophagy: The dual role of autophagy in cancer highlights the need for precision targeting, where autophagy can be modulated based on the cancer stage, type, and specific patient genetics. Developing biomarkers that can accurately predict the autophagic flux in tumor cells and its impact on patient prognosis is crucial. This approach will enable clinicians to tailor autophagy-modulating therapies to individual patients, maximizing efficacy while minimizing potential adverse effects. (2) Combination therapies: The interplay between autophagy and various signaling pathways, such as mTOR, Beclin-1, and p53, suggests that combination therapies targeting these pathways alongside autophagy could be particularly effective. Future research should explore the synergistic effects of combining autophagy modulators with existing chemotherapeutics, targeted therapies, and immunotherapies. This strategy could potentially overcome drug resistance and improve treatment outcomes in bone metastasis and osteosarcoma patients. (3) Novel autophagy inhibitors and activators: The development of new autophagy-modulating agents is imperative. The current review highlights several preclinical compounds with promising effects on autophagy modulation. Future efforts should focus on optimizing these compounds for better specificity, potency, and safety profiles. Additionally, the discovery of novel autophagy regulators through high-throughput screening and computational modeling could provide new therapeutic candidates. (4) Clinical trials: There is a pressing need to translate preclinical findings into clinical applications. Designing clinical trials that specifically target autophagy in cancer patients, particularly those with bone metastasis and osteosarcoma, will be essential. These trials should aim to assess not only the efficacy and safety of autophagy-modulating therapies but also their impact on quality of life and long-term outcomes. (5) Mechanistic studies: Despite significant advances, the precise mechanisms by which autophagy influences cancer progression and treatment response remain incompletely understood. Future research should aim to elucidate these mechanisms in greater detail, exploring the role of autophagy in cancer stem cells, the tumor microenvironment, and metastatic niches. Understanding these aspects could reveal novel therapeutic targets and strategies to inhibit cancer progression. (6) Interdisciplinary approaches: Combining insights from cell biology, oncology, pharmacology, and computational biology will be crucial in advancing our understanding of autophagy in cancer. Interdisciplinary research efforts can accelerate the identification of biomarkers, the development of novel therapeutics, and the design of effective treatment strategies.

In summary, the complex role of autophagy in cancer, especially in the context of bone metastasis and osteosarcoma, presents both challenges and opportunities for therapeutic intervention. By focusing on precision targeting, combination therapies, novel autophagy modulators, clinical translation, mechanistic studies, and interdisciplinary approaches, future research can pave the way for more effective and personalized cancer treatments.

Conclusion

In conclusion, the dual nature of autophagy in cancer, particularly in bone metastasis and osteosarcoma, highlights its potential as a therapeutic target. Despite its complex role in both suppressing and promoting tumor growth, strategies that modulate autophagy offer promising avenues for enhancing treatment efficacy and overcoming drug resistance. Future research should focus on the selective targeting of autophagy pathways to leverage its beneficial effects against cancer, paving the way for more effective and personalized treatment approaches.

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Disclosure of conflict of interest

None.

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