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Autophagy and oxidative stress in solid tumors: Mechanisms and therapeutic opportunities

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Abbreviations: ADT, Androgen deprivation therapy; ADSL, Adenylosuccinate lyase; AKR1C1, Aldo-keto reductase family 1 member C1; AMPK, AMP-dependent protein kinase; AOOP, Advanced oxidative protein products; AORGs, Autophagy-related genes in gastric cancer; AR, Androgen receptor; ATO, Arsenic trioxide; ATG, Autophagy genes expression; BC, Breast cancer; BC HR+, Breast cancer with positive hormonal receptors; CAFs, Cancer-associated fibroblasts; Cav-1, Caveolin-1; CCS, Copper Chaperone for Superoxide Dismutase; CPE, Calotropis procera extract; CRC, Colorectal cancer; DCA, Dichloroacetate; DHM, Dihydromyricetin; DPP4, Dipeptidyl peptidase-4; ENOS, Endothelial nitric oxide synthase; ER, Endoplasmic reticulum; ER+, Estrogen receptor positive; ET, Endocrine therapy; GA, Gingerol acid; Gln, Glutamine; GLS1, Glutaminase 1; GSH, Glutathione; HCC, Hepatocellular carcinoma; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HNK, Hidroxil-Nor-Kavain; HO-1, Heme oxygenase-1 expression; ICD, Immunogenic cell death by damage-associated molecular patterns DAMPs; ICIs, Immune checkpoint inhibitors; IBD, Inflammatory bowel disease; IL-6, Interleukin-6; INOS, Inducible nitric oxide synthase; IRFA, Incomplete radiofrequency ablation; LC, Lung cancer; LRG1, Leucine-rich alpha-2-glycoprotein 1; MAOA, Monoamine oxidase A; MAPK, Mitogen-activated protein kinase; MDR, Multidrug resistance; MHC-I, Major histocompatibility complex class I; MMP-3, Metalloproteinase-3; MSI-H, Microsatellite instability-high; MtDNA, Mitochondrial DNA; NAC, N-acetylcysteine; NAFLD, Non-alcoholic fatty liver disease; NDUFS1, NADH, ubiquinone oxidoreductase subunit 1; NED, Neuroendocrine differentiation; NF-kB, Nuclear factor kappa B; NO, Nitric oxide; NOX4, NADPH oxidase 4; NSCLC, Non-small cell lung cancer; O_2^-, Superoxide anion; OH•, Hydroxyl radical; PAHs, Polycyclic aromatic hydrocarbons; PCa, Prostate cancer; PCSC, Prostate cancer stem cells; PR+, Progesterone receptor positive; REST, Repressor element 1-silencing transcription factor; RNS, Reactive nitrogen species; ROS, Reactive oxygen species; RPRD1A, Regulation of Polymerase II Transcription DNA Repair and Damage 1 A; SCLC, Small cell lung cancer; SFA, Sophflarine A; SESN1/2, Sestrin proteins 1 and 2; SOD, Superoxide dismutase; STL, Sertraline; TFRC, Transferrin receptor 1; TIPRL, TOR Signaling Pathway Regulator-Like Protein; TNBC, Triple negative breast cancer; TNF-α, Tumor necrosis factor-alpha; TOR, Target of rapamycin; 5-FU, 5-fluorouracil; $\Delta\Psi m$, Mitochondrial membrane potential.

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ABSTRACT

Cancer remains a leading cause of mortality worldwide, with solid tumors representing most cases. Autophagy and oxidative stress are two interconnected cellular mechanisms that influence tumor initiation, therapeutic response and disease progression. Autophagy plays a context-dependent role, functioning as a tumor suppressor by eliminating damaged organelles in early stages, while later supporting tumor survival under metabolic and therapeutic stress. Similarly, oxidative stress, characterized by an imbalance in reactive oxygen species (ROS), can drive tumorigenesis by promoting genomic instability and resistance to therapy but can also induce apoptosis in cancer cells. The crosstalk between autophagy and oxidative stress plays a pivotal role in shaping the tumor microenvironment, affecting immune evasion, drug resistance, and metabolic adaptation. Targeting these processes through pharmacological modulation presents both challenges and opportunities in cancer therapy. While autophagy inhibition can enhance chemotherapy efficacy by preventing tumor cell survival mechanisms, excessive oxidative stress induction may lead to cellular damage and systemic toxicity. This review explores the complex interplay between autophagy and oxidative stress in solid tumors, emphasizing their implications for cancer progression and treatment strategies. By understanding these mechanisms, novel therapeutic approaches, including combination therapies and precision medicine strategies, may be developed to improve patient outcomes.

1. Introduction

Nowadays, cancer is one of the leading causes of death in the world. According to GLOBOCAN 2022 estimates, approximately 20 million new cancer cases were diagnosed globally in 2022, with cancer-related deaths reaching around 9.7 million (Bray et al., 2024). These alarming statistics underscore the urgent need for continued research in oncology to gain a deeper understanding of the mechanisms driving their growth and progression (Bray et al., 2024). Solid tumors account for roughly 90 % of adult cancers and 60 % of childhood cancers (https://seer.cancer.gov/statfacts/html/aya.html, accessed 26/02/2025; https://seer.cancer.gov/statfacts/html/all.html, accessed 26/02/2025). Their high prevalence highlights the importance of gaining a deeper understanding of the mechanisms driving their growth and progression. Despite significant advancements, many aspects of tumor biology remain complex and incompletely understood. Recent studies have pointed to specific cellular processes that play pivotal roles in both the development and treatment resistance of these tumors. One such process is autophagy, which, along with oxidative stress, has emerged as a crucial factor influencing tumor behavior and response to therapies. However, many aspects of tumor biology remain complex and not fully understood while significant advancements have been made in cancer research.

Although numerous reviews have addressed the relationship between autophagy and oxidative stress in solid tumors, many focus on a specific cancer type, isolated molecular pathways, or partial aspects of this complex interaction. In contrast, this work provides an integrative and up-to-date perspective encompassing molecular mechanisms, their dual role in tumor promotion and suppression, and their impact on the tumor microenvironment across multiple cancer types, including breast, lung, prostate, colorectal cancers, and hepatocellular carcinoma. Furthermore, it thoroughly explores emerging therapeutic implications, emphasizing advances in modulators of autophagy and oxidative stress as strategies to overcome resistance to conventional treatments. This comprehensive approach facilitates the identification of unresolved questions within the literature and proposes an innovative conceptual framework that integrates molecular biology with clinical applications, thereby enhancing the rigor and translational relevance of this review.

Autophagy is a catabolic process in which the cell degrades its own components such as organelles, proteins and other molecules, particularly under conditions of nutrient deprivation or cellular stress (Hasan et al., 2022). This mechanism is crucial for maintaining the internal cellular homeostasis, as it also contributes to the elimination of the pathogens regulated by AMP-dependent protein kinase (AMPK), target of rapamycin (TOR) and growth factors such as insulin (Behrends et al., 2010). During this process, the substrates to be degraded are sequestered into double membrane vesicles called autophagosomes, which then fuse with lysosomes producing autolysosomes. In the autolysosomes, the substrates are degraded, generating products that could be used as energy sources for multiple cellular processes (Onorati et al., 2018). Autophagy plays a dual role in solid tumors, acting as a tumor suppressor in early stages by eliminating damaged components and reducing genomic instability, while promoting tumor progression in advanced stages by providing energy and nutrients under stress conditions like hypoxia and chemotherapy. Key signaling pathways, including AMPK and mTOR, regulate this process, influencing tumor cell survival. Autophagy also impacts immune responses, either enhancing antigen presentation or aiding immune evasion. In particular, secretory autophagy has emerged as a relevant mechanism in solid tumors, influencing tumor-immune interactions and offering novel clinical insights (Li and Zhao, 2025). Given its context-dependent effects, targeting autophagy selectively could improve cancer therapies (Jalali et al., 2025).

Oxidative stress, defined as an imbalance between the production of reactive oxygen species (ROS) and the efficacy of antioxidant defenses, is another hallmark of cancer (Ďuračková, 2010). During the endogenous metabolic reaction, aerobic cells produce ROS such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH•), and organic peroxides. The transfer of electrons to oxygen occurs in the mitochondrial membrane during the respiratory chain. Under hypoxic conditions, the respiratory chain could generate nitric oxide (NO) (Li et al., 2016). Oxidative stress plays a key role in cancer by promoting DNA damage, tumor growth, angiogenesis, and metastasis. It activates signaling pathways like PI3K/AKT and NF-κB, enhancing cell survival and therapy resistance (Iqbal, 2024). Additionally, it alters the tumor microenvironment, weakening immune responses (Iqbal, 2024). Targeting oxidative stress is a potential therapeutic strategy, either by increasing ROS to induce cancer cell death or reducing it to prevent tumor progression (Hayes et al., 2020; Reuter et al., 2010; Zhao et al., 2023).

Importantly, autophagy and oxidative stress are not independent phenomena but are intricately linked through a bidirectional regulatory relationship. Various stressors, including hypoxia or starvation, activate autophagy pathways that can raise ROS generation including superoxide and hydrogen peroxide (Redza-Dutordoir and Averill-Bates, 2021). This interplay has been extensively explored in hematological malignancies, offering mechanistic insights that may also be relevant to solid tumors (Cabrera-Serrano et al., 2025). Tumor initiation, growth, and possible therapeutic treatments all depend on the interaction between these processes, which each have a vital part to play in the development and progression of cancer (Chen et al., 2008). This review explores the intricate relationship between these processes, examining their dual

roles in tumorigenesis and their implications for therapeutic intervention. Notably, ongoing clinical trials targeting autophagy and ROS pathways highlight promising future strategies for cancer treatment (Pandey et al., 2024). In cancer biology, autophagy and oxidative stress are deeply interconnected, with their roles oscillating between protective and pathological depending on the tumor microenvironment.

2. Crosstalk between autophagy and oxidative stress in solid tumors

Autophagy and oxidative stress are two fundamental cellular processes that play a pivotal role in the development and progression of solid tumors. Autophagy, a tightly regulated lysosomal degradation pathway, is essential for maintaining cellular homeostasis by recycling damaged organelles and misfolded proteins (Hasan et al., 2022; Li et al., 2023; Taucher et al., 2022). This process maintains metabolic balance and prevents the accumulation of cytotoxic elements in cells. Conversely, oxidative stress results from an imbalance between the production of (ROS) and the efficacy of cellular antioxidant defenses, often culminating in DNA damage, genomic instability and cellular dysfunction (El Hout et al., 2020; Sharifi-Rad et al., 2020). The interaction between autophagy and oxidative stress can either suppress or promote tumor growth, depending on the context and stage of cancer development (Dong et al., 2023; Hasan et al., 2022; Taucher et al., 2022). Elevated ROS levels also activate various oncogenic pathways, such as the mitogen-activated protein kinase (MAPK) signaling pathway, and nuclear factor kappa B (NF-kB), promoting cancer development (Hasan et al., 2022). However, excessive ROS may induce cell death. This complex interaction contributes to the preservation of cellular stability and prevents the accumulation of alterations that could produce tumor development (Hasan et al., 2022).

2.1. Regulation of autophagy by oxidative stress

It is widely known that autophagy can be regulated by ROS through mTOR dependent pathways. When ROS levels are high it could produce the inactivation of PTEN by direct oxidation (Leslie, 2006), which increases the PIP3 levels, activating AKT and inhibiting mTORC1 signaling (Kma and Baruah, 2022). Other studies have shown that MAPK molecules such as JNK, p38 and ERK can also be regulated by ROS. As a result, these molecules play an important role in the activation of mTOR (Zhang et al., 2020; Zhou et al., 2015). MAPK/JNK is involved in the autophagy process through the direct phosphorylation of ULK1 or by promoting the autophagy key genes transcription like *BECN1* (He et al., 2018). In conclusion the accumulation of ROS could affect the autophagy pathway through MAPK/JNK/mTOR. In addition, ROS levels can also activate AMPK, which in turn induces autophagy. This process occurs when AMPK phosphorylates and activates ULK1 or inhibits mTORC1. It has been demonstrated that ROS can inhibit mTOR or activate the AMPK pathways, promoting autophagy in different tumor cell types, which directly impacts tumor progression (Zhao et al., 2017).

Additionally, transcription factors such as TFEB, HIF-1α, p53, NF-kB, FOXO3, ATF4 and NRF2, which are essentials for the regulation of the autophagy genes expression (ATG), are activated by higher ROS levels (Dong et al., 2023). Furthermore, Sarkar et al., 2011 investigated the role of nitric oxide (NO) in S-nitrosiler IKKβ and reducing its phosphorylation, preventing the phosphorylation of AMPK which affects the initiation of autophagy (Sarkar et al., 2011). Whereas reactive nitrogen species (RNS) have traditionally been considered to inhibit autophagy, some studies suggest that NO could induce this process. In breast cancer cells for example, nitro oxidative stress triggered autophagy rapid activation in response to DNA damage mediated by ATM, activating LKB1. As a result, AMPK/TSC1/2/mTOR pathway was inhibited, promoting autophagy induction (Tripathi et al., 2013).

2.2. Autophagy and oxidative stress as tumor suppressor

Autophagy as a tumor suppressor in early cancer development plays a protective role by mitigating oxidative damage and maintaining cellular integrity. Removal of damaged mitochondria by mitophagy reduces ROS generation, thereby limiting oxidative damage to DNA and proteins (Choi et al., 2012; Li et al., 2020; Yan and Li, 2018). Loss or downregulation of core autophagy genes, such as *BECN1* and *LC3*, has been linked to increased ROS accumulation and heightened tumor initiation risk (Nurdinov, 2020; Poillet-Perez et al., 2015). This suggests that autophagy may act as a barrier to early tumorigenesis by preventing ROS-induced mutations (Fig. 1).

Mitophagy is regulated by two principal pathways, NIX/BNIP3L and PARKIN (PARK2/PINK1). The NIX/BNIP3L pathway interacts with proteins such as GABARAP and GABARAPL1 to label defective mitochondria and directs it to its degradation in the autophagosome (Poillet-Perez et al., 2015). Furthermore, the PARKIN/PINK1 pathway facilitates the removal of dysfunctional mitochondria in response to membrane depolarization, induced by the increase of ROS levels (Youle and Narendra, 2011). It has been demonstrated that the elimination of damaged mitochondria through autophagy reduces ROS production, thereby limiting its impact on tumor progression (Poillet-Perez et al., 2015).

ATG proteins modulate inflammatory and immune signaling through both autophagy dependent and independent mechanisms. In the former, mitophagy reduces mitochondrial ROS, indirectly modulating immune sensors such as RIG-I and the NLRP3 inflammasome. In the latter, ATG proteins interact directly with immune signaling pathways, independent of their role in autophagosome formation (Levine and Kroemer, 2019). Additionally, redox homeostasis is supported by enzymatic (e.g., superoxide dismutase (SOD), catalase, peroxidases) and non-enzymatic (e.g., glutathione (GSH), thioredoxin) antioxidant systems, which detoxify species like superoxide (O_2^-) and hydrogen peroxide (H_2O_2) (Dorval and Hontela, 2003; Kern and Kehrer, 2005).

Furthermore, the p53 protein plays a role in the modulation of autophagy through the regulation of ROS levels (Maiuri et al., 2010; Rahman et al., 2022; Tang et al., 2015). Under oxidative stress conditions, basal p53 levels activate the expression of various antioxidants, such as, GPX1, MnSOD, ALDH4 and TPP53INP1, to mitigate oxidative damage (Budanov et al., 2010; Hu et al., 2010; Pani and Galeotti, 2011; Suzuki et al., 2010). This antioxidant function contributes to mTORC1 inhibition and autophagy induction (Budanov and Karin, 2008). Sestrin proteins (SESN1/2), transcriptional targets of p53, mediate this effect by activating AMPK and the TSC1/TSC2 complex, reinforcing autophagic flux and ROS detoxification (Budanov, 2011). In contrast, p53 can increase ROS levels. Duan et al. (2011), have shown that the silibinin can induce the autophagy cell death mediated by p53 through the activation of ROS-p38 and JNK pathways, as well as the inhibition of MEK/ERK and PI3K/AKT pathways (Duan et al., 2011). Thus, p53 plays a dual role in cancer by either preserving cellular homeostasis or initiating programmed cell death depending on the oxidative context.

2.3. Autophagy and oxidative stress as tumor promoter

Autophagy often switches to a pro-survival mechanism in established tumors. Cancer cells use autophagy to adapt to stressful microenvironmental conditions such as hypoxia, nutrient deprivation, and elevated ROS levels (Choi, 2012; Debnath et al., 2023; Yang et al., 2011). For example, hypoxia-induced autophagy enables tumor cells to withstand oxidative stress by degrading damaged components and providing metabolic substrates for survival. This paradoxical role highlights the adaptability of autophagy in cancer biology, where its modulation is context-dependent (Hasan et al., 2022; Hu et al., 2023).

One key molecule as a tumor promoter is p-62 (also known as SQSTM1) (Katsuragi et al., 2015), which plays a key role in protein accumulation and the formation of inclusion bodies, which are

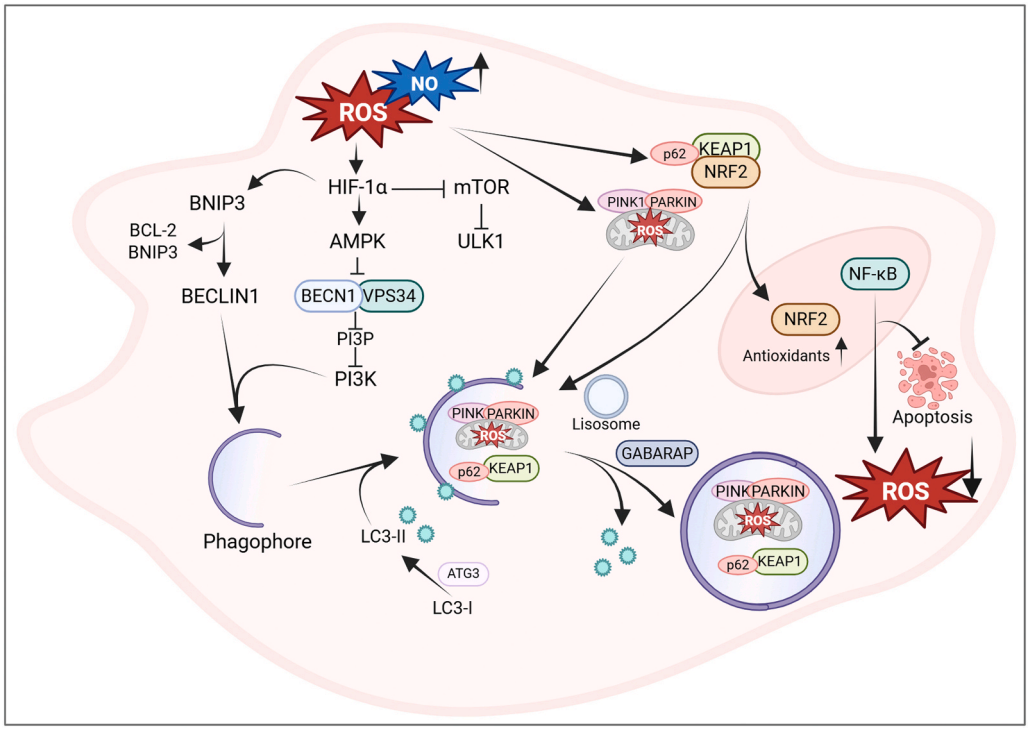

Fig. 1. Autophagy prevents tumorigenesis via BECN1 and LG3.

associated with diverse diseases (Stumptner et al., 1999; Zatloukal et al., 2002). For instance, in models lacking *ATG5* or *ATG7*, p62 aggregation promotes ROS accumulation and tumorigenesis (Takamura et al., 2011). This accumulation leads to increased ROS levels and promotes tumorigenesis, especially in cells with a defective autophagy. Specifically, p62 activates non canonical antioxidant pathway Nrf2, by competing with Keap1 and producing the translocation of Nrf2 to the nucleus, where it activates antioxidants genes (Jiang et al., 2015). However, excessive p62 accumulation also increases ROS levels, favoring tumor development. In addition, p62 can activate the NF-kB pathway, contributing to ROS production. Even so, when autophagy is impaired, p62 struggles to effectively activate the NF-κB pathway. While this might seem beneficial by reducing inflammation, the buildup of p62 also leads to increased oxidative stress, which can fuel tumor growth (Mathew et al., 2009).

Autophagy loss also disrupts mitochondrial homeostasis. Wei et al. (2011) have shown that in murine models with a mutation in FIP200, present abnormal mitochondria and an accumulation of healthy and dysfunctional mitochondria, in comparison with normal mice (Wei et al., 2011). The elimination of FIP200 in hematopoietic stem cells and neurons causes an accumulation of mitochondrial and ROS levels (Liu et al., 2010). Additionally, the accumulation of mitochondria with abnormal morphology has been identified in ATG7 -/- murine livers, in β pancreatic cells, in ATG5 -/- murine cardiac cells and Paneth cells with a mutation in ATG16L1 (reviewed in (Chavez-Dominguez et al., 2020)). This investigation shows that the dysfunction of autophagy produces an increase of intracellular ROS levels that could be associated with tumor development. Another study describes the association between autophagy and endoplasmic reticulum (ER) stress, highlighting their role in tumor development and treatment response, specifically in melanoma. In melanomas with $BRAF^{V600E}$ mutation, the oncogenic alteration induces chronic ER stress, increasing basal autophagy levels (Corazzari et al., 2015). $BRAF^{V600E}$ activates p38 which in turn stimulates the pathways IRE1/ASK1/JNK and TRB3 pathways. The phosphorylation of Bcl-XL/Bcl-2 by JNK releases Beclin1, a key regulator of autophagy, while TRB3 inhibits Akt/mTOR, increasing basal autophagy (Corazzari et al., 2015). Furthermore, ATG7 is essential for maintaining metabolic fitness in $BRAF^{V600E+}$ tumors and suggests that targeting autophagy may have therapeutic potential in this context (Strohecker et al., 2013). Autophagy also regulates ferroptosis—a form of iron-dependent oxidative cell death, by degrading protective factors such as lipid droplets, GPX4, ferritin, SLC40A1, CDH2 and BMAL1 (An et al., 2024). Reticulophagy, a subtype of autophagy directed toward the ER, similarly enhances ferroptotic susceptibility (Liu et al., 2022).

Liu (2023) have investigated the role of genes related to oxidative stress and autophagy in gastric cancer (OARGs) (Liu, 2023). The study analyzed 17 OARGs with prognostic value, identifying three different patterns, each with unique biological and immunological characteristics. Finally, they found a significant negative correlation between the OARG score (a method to evaluate the patterns in specific tumors) and the immune cells infiltration. These results provide a new point of view to predict the prognostic and immunotherapy response in gastric patients, moreover, to highlight oxidative stress and autophagy in its progression (Liu, 2023).

2.4. *Autophagy and oxidative stress in tumor microenvironment*

In the tumor microenvironment oxidative stress can mimic the effects of hypoxia, even in the presence of oxygen, leading to elevated ROS levels that damage DNA and drive genomic instability. This “bystander effect” also promotes aneuploidy in adjacent tumor cells ROS in the stroma trigger autophagy and mitophagy, generating recycled nutrients such as lactate and ketones that support tumor growth (Lisanti et al., 2010). Martinez-Outschoorn (2010) demonstrated that, in breast cancer, tumor cells can induce oxidative stress in neighboring stromal fibroblasts, triggering the autophagic degradation of caveolin-1 (Cav-1). This process, regulated by HIF-1α and NF-κB, promotes nutrient recycling in the microenvironment and confers resistance to apoptosis in adjacent cancer cells, thereby supporting tumor progression (Martinez-Outschoorn, 2010).

3. The role of autophagy and oxidative stress in selected solid tumors

3.1. Breast cancer

Breast cancer (BC) is the most common cancer among women globally, with incidence rates highest in North America, Northern Europe, and Oceania (Kelsey and Horn-Ross, 1993; Shimizu et al., 2012). Risk factors include demographic factors (age, race, socioeconomic status, and geographic location) and reproductive factors (early menarche, late menopause, nulliparity), as well as hormonal factors, genetics, and lifestyle. While BC is a multifactorial and complex disease, studies suggest that interactions between autophagy and oxidative stress may contribute to its initiation (Hasan et al., 2022; Poillet-Perez et al., 2015). In addition, the relationship between autophagy and ROS in BC appears to be context-dependent, with evidence indicating that these processes can also be involved in tumor suppression and disease progression (Table 1) (Hasan et al., 2022; Poillet-Perez et al., 2015).

In early-stage BC, autophagy functions as a tumor suppressor by removing ROS-damaged organelles and proteins, thereby maintaining genomic stability. Key mechanisms include Beclin-1 regulation, where monoallelic deletion (observed in ~50 % of BC) impairs autophagy, leading to ROS accumulation and mitochondrial dysfunction (Aita et al., 1999; Liang et al., 2006); mitophagy, whose defects (e.g., ATG5 or ATG7 deficiency) result in damaged mitochondria accumulation, exacerbating ROS levels and promoting mutagenesis (Hasan et al., 2022; Kongara and Karantza, 2012). Prolonged NRF2 activation can lead to reductive stress and proteotoxicity, highlighting the importance of maintaining redox balance (Dodson et al., 2015). In fact, in established tumors, autophagy shifts towards a pro-survival role, enabling metabolic adaptation by maintaining mitochondrial health in response to increased ROS and metabolic demands driven by oncogenic signaling (e.g., mutant Ras) (Lock et al., 2014). Autophagy also facilitates metastasis, as detached mammary tumor cells activate ROS-dependent PERK signaling to induce autophagy, enhancing survival during matrix detachment and lung colonization (Avivar-Valderas et al., 2011). ROS-activated pathways like TGF-β1 and NF-κB promote EMT, while autophagy meets the energy demands of invasion. Under hypoxia, ROS triggers autophagy, creating a feedback loop that sustains tumor growth (Galluzzi et al., 2015). For example, ROS induce the oxidation of ATG4 and ATM, which triggers (Kim et al., 2011; Li et al., 2010) autophagosome formation. In addition, ROS activate AMPK, which inhibits mTORC1 in a H_2O_2-dependent manner, subsequently leading to ULK1 and Raptor phosphorylation and further promoting autophagy. On the other hand, HIF-1α, which is stabilized under oxidative stress, has been shown to activate autophagy pathways, including the AMPK/mTOR signaling axis, highlighting the crucial role of ROS in modulating autophagic activity (Daskalaki et al., 2018; J. Li et al., 2022; Zhou et al., 2018). Therefore, understanding these mechanisms is vital for developing therapeutic strategies targeting the Keap1-Nrf2 and AMPK/mTOR pathways, but also TGF-β1- and NF-κB-induced pathways in various malignant diseases, including BC (Shan et al., 2024) (Fig. 2).

In advanced BC, autophagy shifts from a suppressive to a tumor supportive role, allowing cancer cells to adapt to harsh conditions such as hypoxia, nutrient deprivation, and oxidative stress (Fig. 1). Upregulation of autophagy-related proteins, including LC3B and ATG5, has been observed in BC cells resistant to therapies such as tamoxifen and taxanes, highlighting the role of autophagy in therapy evasion (Aqbi et al., 2018; Dwyer et al., 2024; Han et al., 2017). These findings emphasize the need for precision therapies that consider autophagy and oxidative stress, targeting these pathways in a context-dependent manner. This approach has emerged as a promising therapeutic strategy, with over 30 clinical trials investigating autophagy inhibition in combination with conventional cancer treatments.

In the metastatic scenario the interplay between autophagy and oxidative stress is also important. Autophagy supports the survival of

Table 1
Therapeutic strategies in BC.

Therapeutic strategies	Molecular mechanism	References
Preclinical study: **Simultaneous inhibition of the estrogen receptor, CDK4/6 and PI3K**	Favors cell cycle arrest, apoptosis induction and tumoral regression *in vitro* and *in vivo*	(Jhaveri et al., 2024)
Phase I/Ib study: **Inavolisib (PI3K inhibitor) + palbociclib (inhibitor of CDK4/6) + letrozole or fulvestrant (endocrine therapy)**	Reduction of PI3K/AKT biomarker expression in tumoral tissue	(Jhaveri et al., 2024)
Phase III study: **Inavolisib + palbociclib + fulvestrant in HR+ ,HER2- metastatic BC patients with PIK3CA mutation**	Significant improvement in progression-free survival	(Juric et al., 2024)
Preclinical study: **Autophagy inhibitors could enhance the effectiveness of lapatinib (HER2-targeted drugs)**	Targeted treatments to HER2 can induce autophagy as a resistance mechanism	(M. Wang et al., 2024)
***Preclinical study*:** **IC87114 drug (inhibitor of the p110δ PI3K isoform) in MCF−7 (BR HR+ cell line) and MDA-MB−231 (TNBC cell line)**	Decreases cell migration in spheroids.	(Di Donato et al., 2022)
Vps34-IN1 (inhibitor of Vps34, class III PI3K isoform)	Mediates autophagy phenomena and increases sunitinib and erlotinib drugs' efficacy	(Di Donato et al., 2022)
MitoQ, a derivative of Coenzyme Q10 that specifically targets mitochondria	Generates the degradation of Keap1 through autophagy, increasing the transcriptional activity of Nrf2 leading to the expression of antioxidant genes such as *p62*. The p62 protein is associated with Keap1 and activates Nrf2, producing a positive feedback loop that protects cells from oxidative damage	(Gonzalez et al., 2014)
REDD1 Modulation	REDD1 inhibits mTORC1, reducing cancer cell proliferation and linking to chemotherapy-induced reduced BC cell survival.	(Lan et al., 2013; Tirado-Hurtado et al., 2018; Zhidkova et al., 2022, 2020)
Pro-oxidants (Elesclomol, ATO)	Pro-oxidants such as elesclomol and arsenic trioxide (ATO) exploit BC cells' redox vulnerabilities by increasing ROS, overwhelming antioxidant defenses, and inducing apoptosis. Their efficacy is enhanced when combined with autophagy inhibitors. Elesclomol induces oxidative stress by disrupting mitochondrial	(Alli and Ford, 2012; Alzuwaidi and Khalil, 2019; Buccarelli et al., 2021; Chow et al., 2004; Kirshner et al., 2023; Li et al., 2023; Moomivand et al., 2024; Nagai et al., 2012; Nasrollahzadeh, 2020; Nooshinfar et al., 2016; Qu et al., 2010; Rajaram et al., 2024; Wang et al., 2023; Wang et al., 2011; Xia et al., 2014; Zhang et al., 2016)

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Table 1 (*continued*)

Therapeutic strategies	Molecular mechanism	References
	metabolism and copper homeostasis, leading to cuproptosis. ATO inhibits BC growth, promoting apoptosis and activating key apoptotic proteins.	
Mitophagy Targeting (PINK1, Parkin)	Targeting mitophagy-specific proteins, such as PINK1 and Parkin, addresses mitochondrial dysfunction in cancer, offering new therapeutic opportunities	(Dong and Zhang, 2024; Li et al., 2022; Narendra and Youle, 2024; Wang et al., 2023)

disseminated tumor cells in circulation and at secondary sites by reducing oxidative stress, allowing them to establish metastatic colonies. Targeting these processes therapeutically could reduce the metastatic potential of BC and improve long-term survival outcomes (Grandvallet et al., 2020; Wu and Sharma, 2023).

3.2. Lung cancer

Lung cancer (LC) is the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) accounting for approximately 85 % and 15 % of cases, respectively (Lemjabbar-Alaoui et al., 2015; Molina et al., 2008). LC is significantly influenced by various risk factors, with cigarette smoking being the predominant cause (Chen, 2023; Schwartz and Cote, 2016), although other contributors include aging, air pollution, radon, occupational exposures, and chronic lung diseases (de Groot et al., 2018). Tobacco smoke contains harmful chemicals, including polycyclic aromatic hydrocarbons (PAHs), nitrosamines, and heavy metals like cadmium (Hecht, 2011; Lemjabbar-Alaoui et al., 2015; Liu et al., 2009). These toxins generate excessive ROS, overwhelming the antioxidant defenses and leading to DNA damage, triggering mutations in key tumor suppressor genes like p53 and activating oncogenes like KRAS (Drosten and Barbacid, 2022; Luo et al., 2022; Suzawa et al., 2019). Moreover, tobacco smoke accelerates epigenetic changes, including DNA methylation and histone modification, which contribute to lung carcinogenesis (Seiler et al., 2020; Xie et al., 2021; Zong et al., 2019). On the other hand, air pollution, particularly fine particulate matter (PM2.5 and PM10), also plays a significant role in LC. These fine particles, often carrying toxic metals and chemicals, reach deep into the lungs, where they fuel chronic inflammation and oxidative stress. Studies have shown that prolonged exposure to PM2.5 increases LC risk by activating inflammatory pathways such as NF-κB and STAT3, which encourage tumor growth by stimulating the production of inflammatory molecules and new blood vessels (Deng et al., 2020; Grivennikov and Karin, 2010; Lim and Yoon, 2022; Liu et al., 2023; Zhao et al., 2021).

Chronic inflammation, triggered by infection or long-term exposure to pollutants, contributes to LC development (Budisan et al., 2021), creating a microenvironment rich in ROS and RNS, which further damage DNA and proteins. Pro-inflammatory cytokines such as tumor

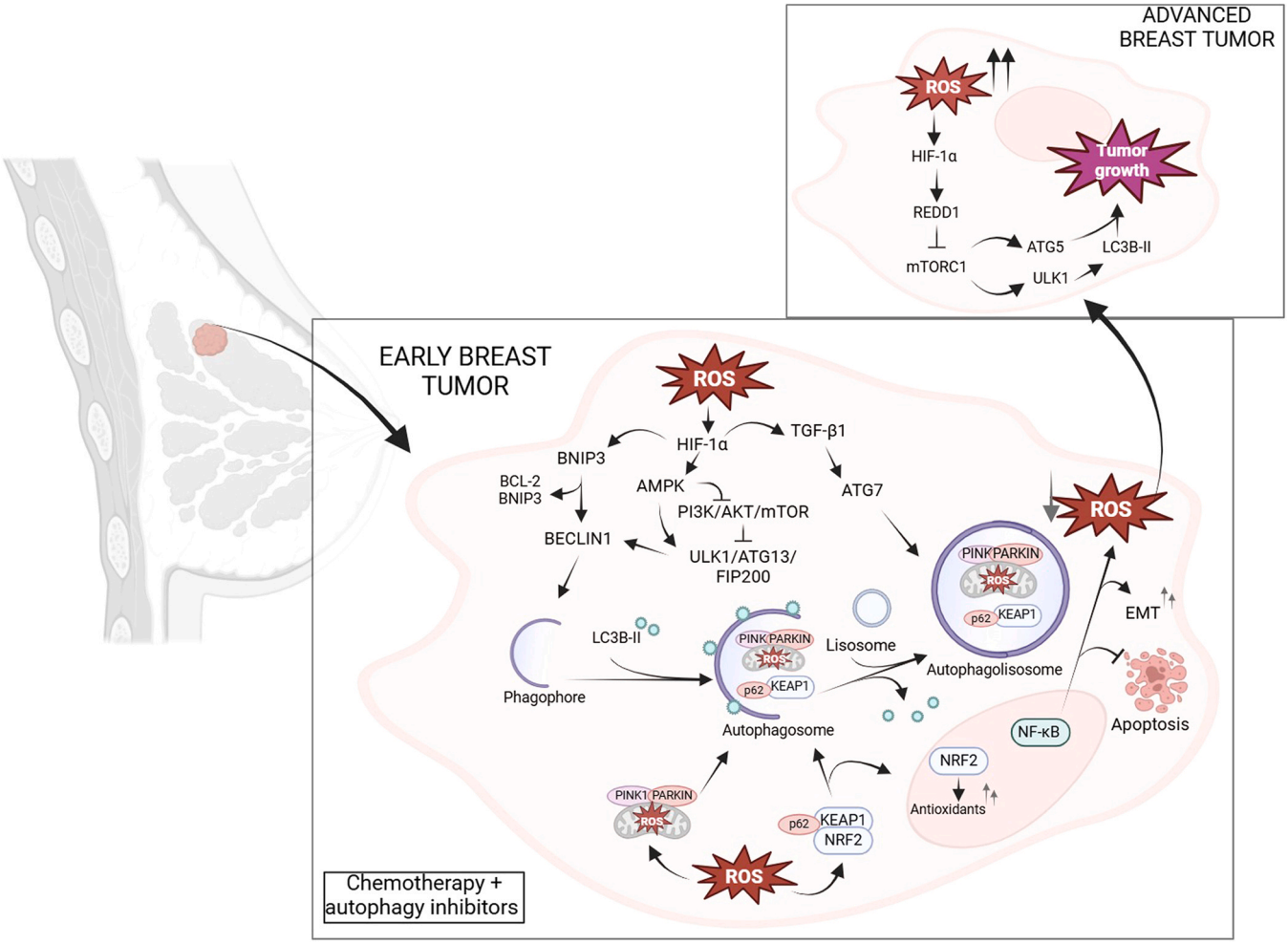

Fig. 2. Molecular pathways involved in determining early and advanced BC.

necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are upregulated in such environments and promote cancer cell proliferation and survival through the PI3K/AKT/mTOR and JAK/STAT signaling pathways (Deng et al., 2020; Rasková, 2022; Shang et al., 2017; Wu and Zhou, 2010).

Exposure to carcinogens also induces changes in the tumor microenvironment characterized by immune evasion and angiogenesis. Air pollutants such as benzene and formaldehyde contribute to these changes by exacerbating oxidative stress and impairing immune surveillance (Shankar et al., 2019; Xiong et al., 2024).

In the past few decades, our understanding of the biology and progression mechanisms of the disease has significantly improved. It has become clear that autophagy and ROS can regulate each other to influence the initiation and progression of LC. These processes initially promote cancer through oxidative stress and DNA mutations, while at later stages, they can induce apoptosis (ArulJothi et al., 2022). Autophagy is differentially regulated in NSCLC and SCLC. While NSCLC often shows upregulation of autophagy-related genes, SCLC exhibits a mixed autophagy profile, with both up- and down-regulated genes compared to normal tissue, possibly reflecting different tumor microenvironments and metabolic needs (Shen et al., 2022; Wang et al., 2023; Zinn et al., 2013). These findings highlight the need for subtype-specific approaches when targeting autophagy in LC therapies (Filomeni et al., 2015).

In NSCLC, the AKR1C1 (Aldo-keto reductase family 1 member C1) is overexpressed and is associated with a poor prognosis (Zhu et al., 2018). AKR1C1, directly interacts with SQSTM1, producing its oligomerization and promoting autophagy, contributing to cancer cells' drug resistance. Under oxidative stress conditions, the ARK1C1-SQSTM1 complex stabilizes a signaling loop that involves AKR1C1, SQSTM1, and Nrf2, increasing antioxidant defense mechanisms of tumor cells (Chang et al., 2022). Autophagy also maintains mitochondrial homeostasis during EMT, especially under TGF-β1 stimulation, supporting ATP production and energy balance (Hwang et al., 2022), while its inhibition reduces mesenchymal marker expression at the protein level, without affecting mRNA levels, suggesting a post-transcriptional control (Alizadeh et al., 2018). Furthermore, its inhibition decreases ATP production, affecting mitochondrial function, which activates AMPK and alters protein translation (Hwang et al., 2022). The PI3K/AKT/mTOR axis, a central regulator of autophagy and cell growth, has been identified as a key therapeutic target in NSCLC (Tan, 2020; Yip, 2015). Dual inhibitors of PI3K and mTOR not only suppress autophagy but also disrupt oncogenic signaling pathways, thereby enhancing the efficacy of chemotherapy and immunotherapy (Huang et al., 2020; Shimizu et al., 2023). Targeting upstream regulators such as AMPK could also selectively impair autophagy in cancer cells without compromising its homeostatic functions in normal tissues (Wang et al., 2020; Yuan et al., 2023) (Fig. 3).

In SCLC, the activation of the PI3K/AKT/mTOR signaling pathway is associated with radiotherapy resistance and poor prognosis in particular in those patients carrying RAS mutations (Chen et al., 2020). Inhibiting this pathway accelerates G6PD degradation via HSC70-mediated autophagy, disrupting NADPH production and glutathione regeneration, thus enhancing oxidative damage and apoptosis, particularly when combined with radiation (Deng et al., 2023). This reduction of G6PD levels typically helps tumor cells survive oxidative stress damage by generating NADPH and reduced GSH. The inhibition of G6PD reduces cancer cell viability, migration and colony formation and increases oxidative stress damage and induces apoptosis when combined with radiotherapy (Deng et al., 2023). In addition, in cisplatin-resistant LC cells, G6PD suppression reverses drug resistance by altering redox homeostasis (Hong et al., 2018) and triggers immunogenic cell death, enhancing the efficacy of immunotherapies in LC models (Nakamura

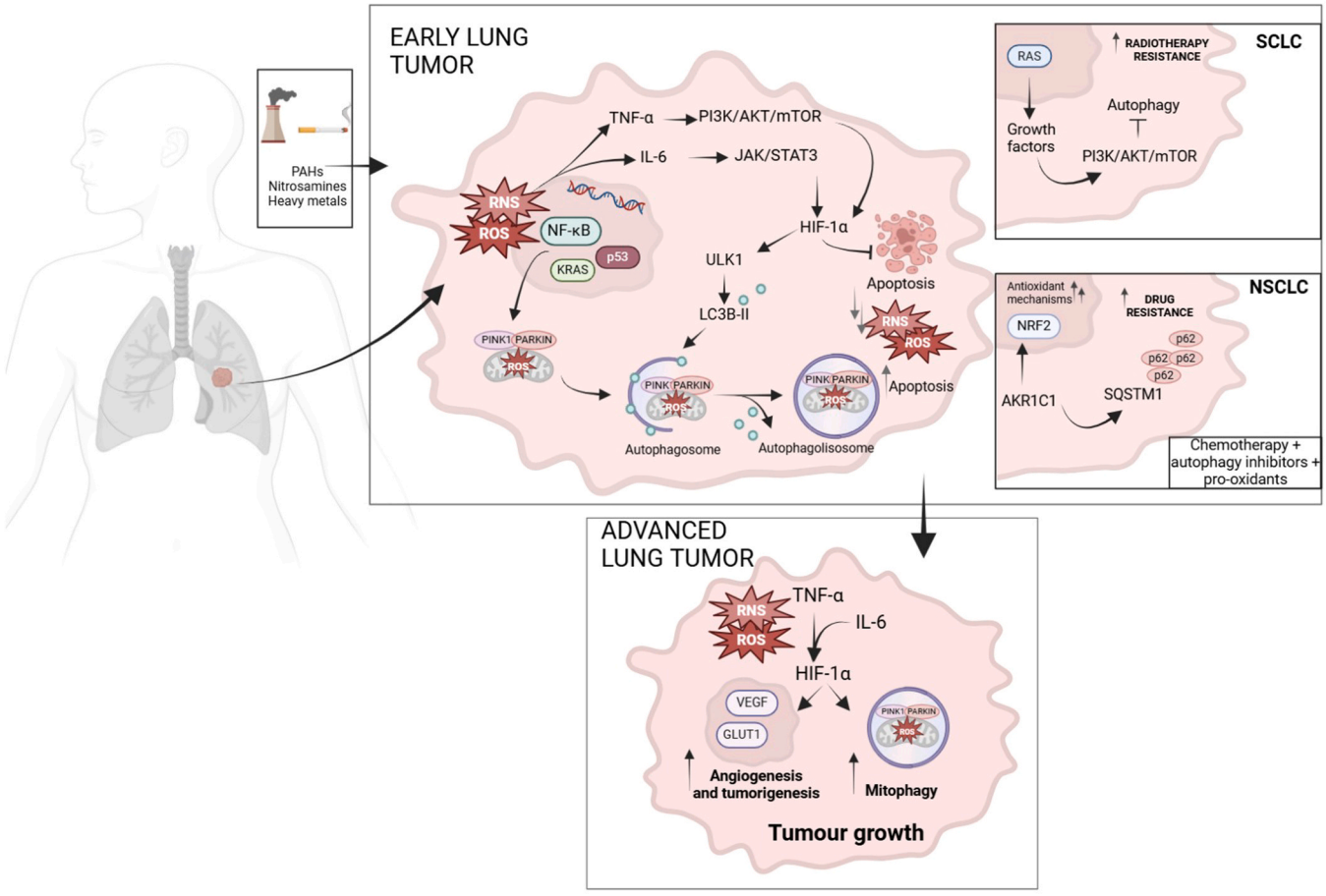

Fig. 3. Molecular pathways involved in determining early and advanced LC.

et al., 2024). Hu et al. (2023) also demonstrated that the activation of Copper Chaperone for Superoxide Dismutase (CCS) through H3K27 acetylation reduces oxidative stress in LC cells, promoting autophagy and inhibiting cellular apoptosis (Hu et al., 2023). Inhibition of CCS increases ROS levels, thereby enhancing oxidative stress and reducing cell survival. Furthermore, CCS inhibition suppresses autophagy and activates apoptosis by increasing the expression of the pro-apoptotic gene BAX and decreasing the expression of the anti-apoptotic gene Bcl-2. CCS inhibition also plays a role in tumoral microenvironment and immune response in LC (Zhou et al., 2024) (Fig. 3).

Tumor cells under oxidative stress can suffer mitochondrial dysfunction, which is associated with a reduction in the number of mitochondrial DNA (mtDNA) copies (Scheid et al., 2021). This stress is also induced by the transfer of mtDNA from stromal cells to tumor cells, resulting in the restoration of mitochondrial function and the promotion of tumor progression (Tan et al., 2015). ROS induce mitophagy in cancer-associated fibroblasts (CAFs), leading to the release of mtDNA and facilitating communication between CAFs and tumor cells through autophagy and oxidative stress. Additionally, tumor-derived exosomes play a crucial role in CAF activation and tumor progression by transferring molecules like miRNAs, which reprogram CAFs to a cancer-promoting phenotype (Zhou et al., 2024).

The role of autophagy in drug resistance is particularly well documented. Increased autophagic activity in LC cells has been shown to mitigate the cytotoxic effects of chemotherapeutic agents such as cisplatin and paclitaxel (Chen et al., 2018; Ornatowski et al., 2020). Similarly, during radiotherapy, which generates lethal levels of ROS, cancer cells upregulate autophagy-related genes such as LC3B and ATG7 to limit oxidative damage and maintain mitochondrial integrity (Chen et al., 2018; Shadab et al., 2020; Zinn et al., 2013). Autophagy inhibitors such as CQ and HCQ have also shown efficacy in preclinical models, particularly when combined with chemotherapy or immunotherapy (Zinn et al., 2013). These agents increase oxidative stress in cancer cells by preventing the removal of damaged mitochondria, thereby pushing them towards apoptosis (Chen et al., 2018; Takano et al., 2023). In addition to HCQ, novel inhibitors SBI0206965, targeting specific autophagy-related proteins such as ULK1, are being developed to improve therapeutic precision and minimize off-target effects (Ghazi et al., 2024; Tang et al., 2017) (Fig. 3).

3.3. Prostate cancer (PCa)

Prostate cancer (PCa) is the second most frequently diagnosed malignancy and a leading cause of cancer-related mortality in men worldwide (Bergengren et al., 2023). Its global incidence has risen over the past two decades, driven by population aging, advancements in diagnostic techniques, and increased screening efforts (Rawla, 2019). Although mortality rates have declined, PCa remains the sixth leading cause of cancer-related death globally. Established risk factors include age, ethnicity, and family history, while environmental influences also contribute significantly (Bergengren et al., 2023). Additional potential risk factors include smoking, diet, physical activity, certain medications, and occupational exposures (Bergengren et al., 2023). The widespread adoption of prostate-specific antigen (PSA) screening, along with advanced diagnostic tools such as MRI and novel biomarkers, has shaped PCa epidemiology and detection strategies (Pernar, 2018). PCa is a highly heterogeneous disease, ranging from indolent to aggressive forms (Adamaki and Zoumpourlis, 2021). Autophagy and ROS play a pivotal role in PCa initiation and progression (Wang et al., 2016), with their interplay influencing tumor behavior in a context-dependent manner (Kongara and Karantza, 2012).

On the pro-tumorigenic side, androgen receptor (AR) signaling induces autophagy, promoting PCa cell proliferation and survival (Ashrafizadeh et al., 2022). Autophagy can act as a pro-survival mechanism, especially in response to chemotherapy, with autophagy induction by NPRL2 leading to resistance against drugs like everolimus and docetaxel (Luo et al., 2020). Similarly, recent evidence shows that modulation of autophagy and oxidative stress also mediates resistance to bortezomib in prostate cancer, further highlighting the role of these processes in therapeutic response (Zafeiropoulou et al., 2024). NPLR2 modulates mTOR signaling and the response to stress conditions. Its overexpression inhibits mTOR, favoring autophagy and promoting the survival of tumor cells in hostile environments. Cells with high *NPRL2* expression are less sensitive to this treatment, while NPRL2 inhibition enhances the therapeutic response by promoting apoptosis. This suggests that NPRL2 may be modulating lysosomal acidification, a key process in the late phase of autophagy (Ashrafizadeh et al., 2022; Chen et al., 2019). Mesenchymal stem cells secrete TGF-β1 which regulate Nox4 and promotes PCa progression by generating ROS and activating fibroblasts which produces tumor microenvironment remodeling and facilitates cancer cell migration and invasion (Sampson et al., 2018). Furthermore, Nox4 influences autophagy, promoting cell survival under adverse conditions and modulating communication between stromal and epithelial cells. Its interaction with TGFβ1 creates a feedback loop that reinforces stromal activation and contributes to tumor progression, consolidating its position as a central regulator of oxidative stress and tumor dynamics in PCa (Sampson et al., 2018). Oxidative stress regulates gene expression in CAFs. Hydrogen peroxide promotes changes in the expression of growth factors, adhesion molecules and metalloproteinases, facilitating the conversion of fibroblasts to active myofibroblasts, enhancing invasive cancer growth and metastasis (Cat et al., 2006). CAF becomes resistant to chemotherapy and radiotherapy, contributing to tumor relapses. In addition, ROS increases Matrix Metalloproteinase-3 (MMP-3) expression in PCa cells by miR-128, suggesting an interaction between oxidative stress and metalloproteinases regulation (Hsieh et al., 2017) (Fig. 4).

On the anti-tumorigenic side, ROS-induced oxidative stress can trigger autophagic cell death in PCa cells, with agents like inactivated Sendai virus (HVJ-E) has been shown to exerting anticancer effects via ROS-dependent autophagic cell death (Qian et al., 2018). For instance, HVJ-E induces autophagy in PCa cells through the activation of the PI3K/Beclin-1 pathway, favoring cell death. Modulators such as rapamycin increase apoptosis mediated by the virus, while CQ does not alter the anticancer effects. Moreover, this virus generates ROS in tumor cells, activating MAPK (JNK and p38) pathways, which are associated with cytotoxicity and apoptosis (Gao et al., 2014; Qian et al., 2018). Additionally, downregulation of DNM1L/DRP1 induces autophagy, leading to inhibited proliferation. DRP1 is positively regulated by AR signaling and modulates the VDAC-MPC complex, which regulates mitochondrial pyruvate import, promoting the growth and survival of PCa cells. Moreover, microenvironmental stress, such as hypoxia and oxidative stress, activates adaptive stress responses, including autophagy, which are closely linked to mitochondrial functions. Under low oxygen conditions, mitochondrial fragmentation mediated by DRP1 is associated with higher ROS levels, enhancing cell survival. The inhibition of DRP1, combined with autophagy inhibition, increases cell death in PCa (Lee et al., 2020). At the molecular level, AR signaling regulates autophagy-related genes such as *TFEB, ATG4B, ATG4D, ULK1, and ULK2*, while *GABARAPL1*, modulated by androgen, plays a key role in autophagy and cell proliferation (Ashrafizadeh et al., 2022). Furthermore, during ER stress, upregulation of ERN1/IRE1 activates autophagy to restore homeostasis. ERN1/IRE1, along with other proteins such as ATF6 and CHOP, is overexpressed in tumor cells due to miR-200c-3p activation. miR-200c-3p plays a significant role in autophagy regulation and the ER stress response, inducing an increase in LC3-II expression and the accumulation of LC3 puncta, while its inhibition blocks autophagy induced by starvation. This suggests that miR-200c-3p can enhance survival mechanisms through autophagy activation and the IRE1 pathway in PCa (Sohn, 2018) (Fig. 4).

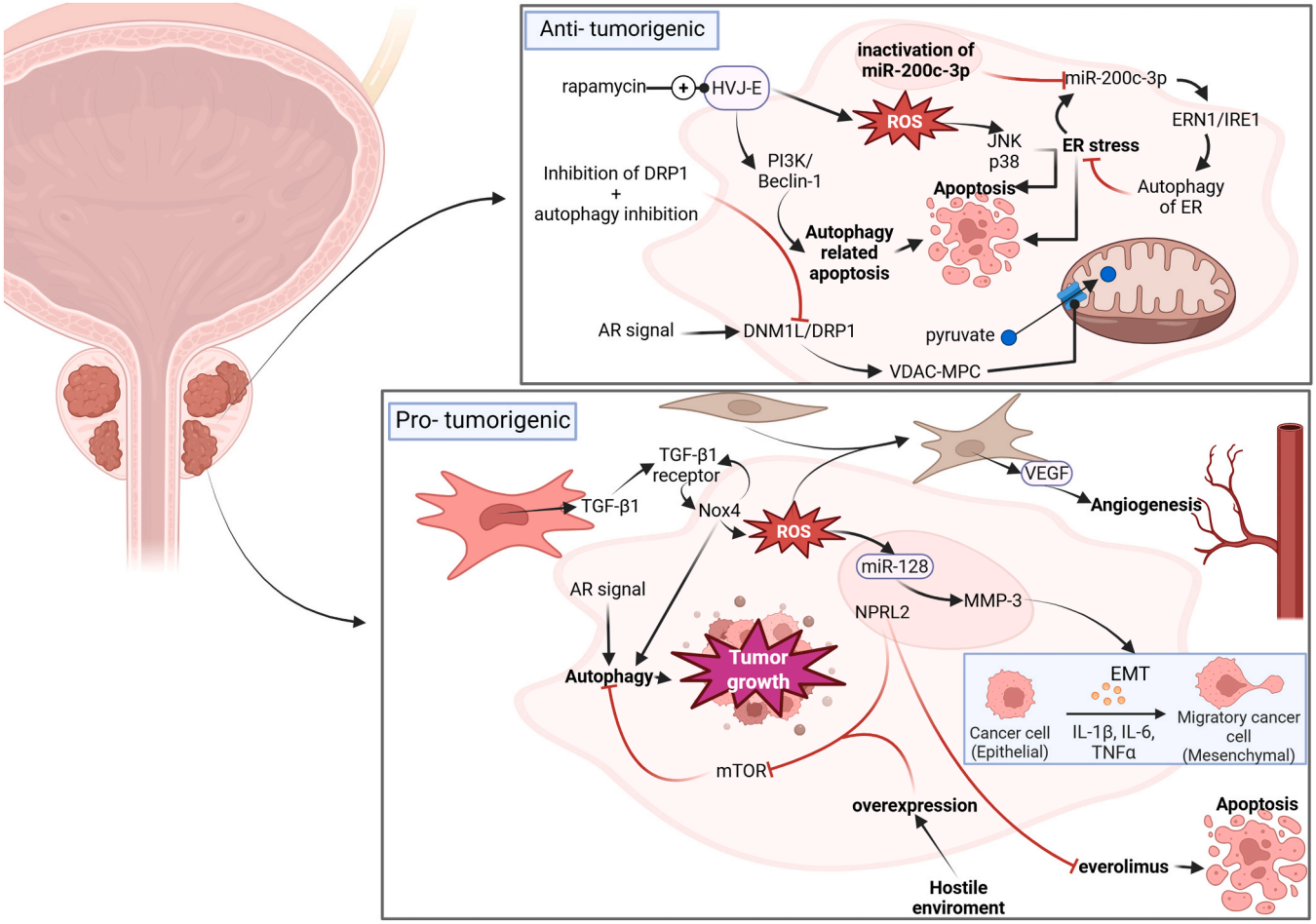

Fig. 4. Molecular pathways involved in determining early and advanced PCa.

3.4. Colorectal cancer

Colorectal cancer (CRC) is the third most prevalent cancer in developed countries and the second leading cause of cancer-related morbidity and mortality worldwide in both men and women (Lauzier et al., 2019; Siegel et al., 2013). According to GLOBOCAN 2022 data, there were approximately 1.926 million new CRC cases and 903,859 deaths globally (Bray et al., 2024). Despite significant advancements in diagnosis, surgery, and treatment, approximately 40 % of CRC patients succumb to the disease (Guo et al., 2024). While CRC incidence is rising globally, especially in developing countries adopting Western lifestyles, mortality rates have decreased in developed nations due to improved screening and treatment options. Risk factors for CRC include age, genetic predisposition, gastrointestinal disorders, and lifestyle factors such as obesity, physical inactivity, red meat consumption, alcohol intake, and smoking (Sawicki et al., 2021). While the molecular mechanisms underlying CRC progression are still being elucidated, growing evidence highlights a dynamic interplay between autophagy and oxidative stress in regulating tumor initiation, progression, treatment resistance, and metastasis.

On one hand, ULK1 is a key regulator in autophagy initiation and its expression increases in CRC progression. In CRC, ULK1-driven autophagy promotes clearance of cytotoxic components in hypoxic, nutrient-deprived environments (Zou et al., 2015). In addition, the AMPK/ULK1 axis is involved in the treatment response of oridonin, a natural compound belonging to the ent-kaurane diterpenoids, in CRC cells. In DLD-1 colon cancer cells, oridonin increases AMPK phosphorylation while decreasing mTOR and ULK1 phosphorylation in a concentration-dependent manner, promoting autophagy and apoptosis (Bu et al., 2020). AMPK inhibition reversed cytotoxicity and reduced apoptosis, confirming its key role in this process. Furthermore, in animal models, oridonin significantly reduced tumor growth, with changes in AMPK, mTOR, and ULK1 levels like those observed in vitro, supporting the importance of the AMPK/mTOR/ULK1 pathway in regulating cell death in CRC (Bu et al., 2020). Liu et al. (2019) have demonstrated that autophagy plays a survival role when CRC cells are treated with the inhibitor of PI3K/mTOR denominated NVP-BEZ235 so blocking autophagy by AMPK/ULK1 inhibition enhances the treatment response (Liu et al., 2019). Ras mutations lead to the uncontrolled activation of several signaling pathways, such as the Raf-MAPK, MEK-ERK, and PI3K-Akt pathways. This alteration in Ras also increases superoxide production through the activation of NOX1 in the MAPK pathway. Oncogenic KRAS allows cells to evade apoptosis through the MAPK, PI3K, and Rac1 pathways. Furthermore, oncogenic Ras initiates an antioxidant program that helps the tumor grow, facilitating its adaptation to the environment, proliferation, and resistance to cell death (Catalano et al., 2025; Ternet and Kiel, 2021). ERK regulates autophagy and oxidative stress in CRC. When ERK is inhibited, both autophagy and apoptosis are induced in CRC cells. Additionally, inhibiting ERK leads to an increase in ROS levels, which activates autophagy, potentially protecting the cells from treatment effects (Mi et al., 2021).

ROS play a crucial role in the activation of ferroptosis. In CRC cells, the loss of p53 is associated with increased activity of DPP4 (dipeptidyl peptidase-4) on the plasma membrane, which facilitates lipid peroxidation mediated by NOX and promotes ferroptosis. In an antagonistic role, p53 protects against ferroptosis in CRC by promoting the translocation of DPP4 to the nucleus, where it forms a complex with p53. This complex blocks the formation of the DPP4-NOX link, preventing lipid

peroxidation and ferroptosis, thus enhancing tumor cell survival (Zhang et al., 2018). Nrf2, activated under oxidative stress, supports antioxidant defense, regulates iron metabolism, and influences mitophagy, glycolysis, and mitochondrial function through the Keap1–Nrf2 axis, ultimately affecting metastasis (Hu et al., 2024). Overexpression of adenylosuccinate lyase (ADSL) activates Nrf2 and promotes proliferation in ROS-rich environments (Hu et al., 2024; Taha-Mehlitz et al., 2021).

In the tumor microenvironment, CAFs activate autophagy in response to oxidative stress induced by tumor cells, promoting migration and tumor invasion through the positive regulation of leucine-rich alpha-2-glycoprotein 1 (LRG1) via the IL-6/STAT3 axis (Zhong et al., 2021). CAFs also show higher levels of autophagy metabolites and Cav-1, and when these cells are treated with oxidative stress inhibitors autophagy and proliferation levels decrease and IDH2 and Cav-1 expression levels are restored in fibroblast. Therefore, CAFs in the tumor microenvironment undergo metabolic reprogramming, which supports tumor proliferation. Through glycolysis, CAFs generate high-energy metabolites (such as pyruvic acid and lactate) that are supplied to growing tumor cells or used to maintain their own elevated autophagy state. Enhanced autophagy in CAFs also contributes to the tumorigenic effects of CAFs (Zhou et al., 2017).

Chronic inflammation in inflammatory bowel disease (IBD) increases CRC risk through ROS production (Roessner et al., 2008). This inflammatory environment activates tumorigenic pathways, including NF-κB and cyclooxygenase-2, and releases proinflammatory mediators like TNF-α and IL-6 (O'Connor et al., 2010). These processes contribute to carcinogenesis by increasing oxidative stress, promoting DNA mutagenesis, anti-apoptotic pathways, and creating a supportive environment for tumor growth and metastasis (O'Connor et al., 2010; Shahgoli et al., 2024). The link between chronic inflammation and CRC underscores the importance of controlling inflammation and implementing regular screenings (Shahgoli et al., 2024) (Fig. 5).

3.5. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide, driven by risk factors such as chronic hepatitis B and C infection, alcohol abuse and non-alcoholic fatty liver disease (NAFLD) (Llovet et al., 2021; Samant et al., 2021). NAFLD, particularly in its progressive form, non-alcoholic steatohepatitis (NASH), is marked by hepatic lipid accumulation, chronic inflammation, and fibrosis, all of which contribute to a pro-tumorigenic microenvironment in the liver. These pathological alterations promote oxidative stress, DNA damage, and compensatory hepatocyte proliferation, thereby fostering malignant transformation. In addition, metabolic dysfunction and insulin resistance associated with NAFLD activate oncogenic signaling pathways and impair immune surveillance, further facilitating hepatocarcinogenesis (Divella et al., 2019; Scholten, 2024). Oxidative stress plays a central role in HCC progression by inducing genomic instability, modulating transcriptional activity, altering key signaling cascades, and reshaping the tumor microenvironment.

Genetic changes in hepatocellular carcinoma include oxidative DNA damage, hypomethylation, and abnormal microRNA expression. Several signaling pathways, Keap1/Nrf2/ARE, PI3K/AKT/mTOR, Wnt/β-catenin, and Notch, play dynamic roles in HCC, influencing tumorigenesis, therapy resistance (Yuanyuan Li et al., 2023), and metabolic reprogramming through stage-specific mechanisms.

Genetic changes include oxidative DNA damage, hypomethylation, and abnormal miRNA expression. Keap1/Nrf2/ARE, PI3K/AKT/mTOR,

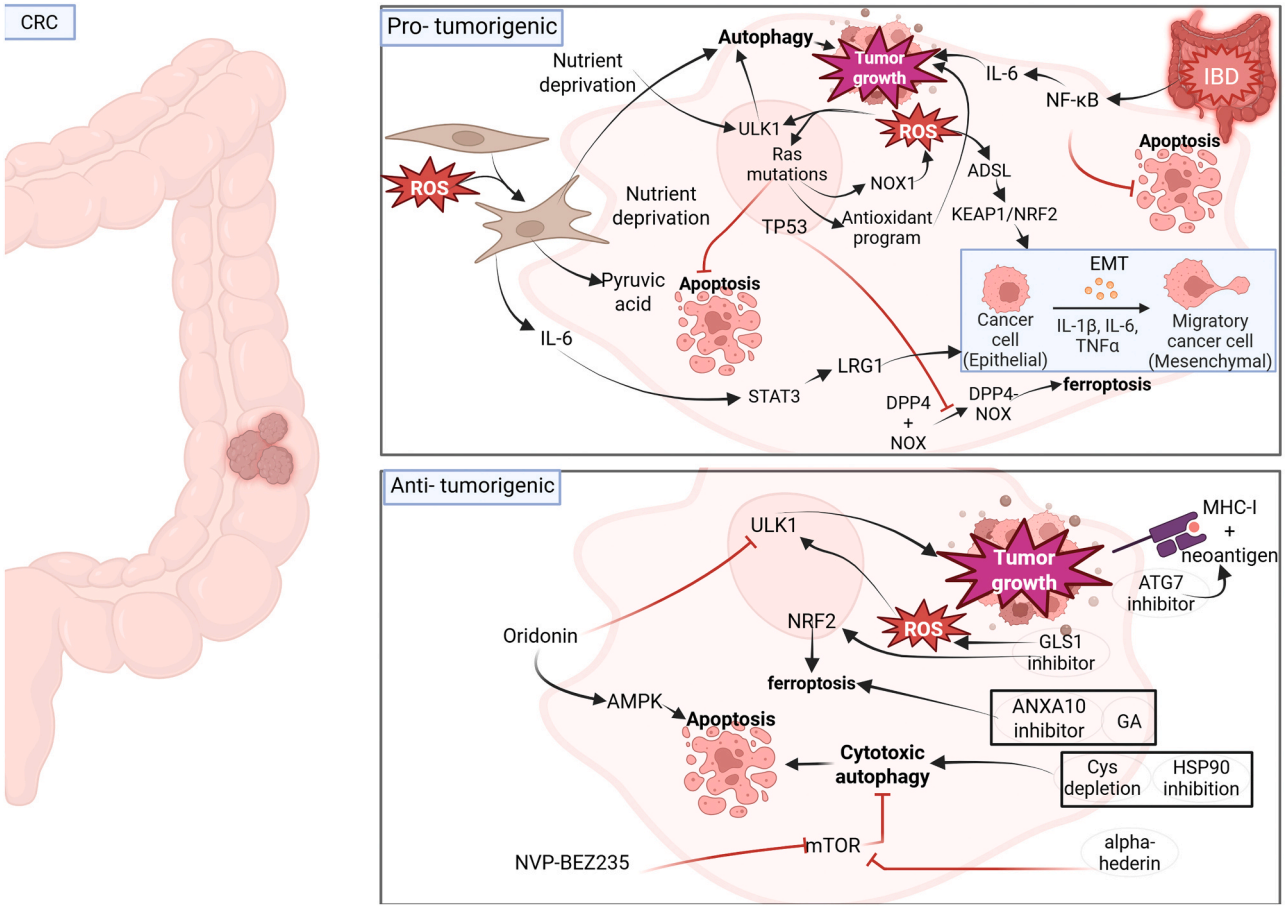

Fig. 5. Molecular pathways involved in determining early and advanced CRC.

Wnt/β-catenin, and Notch pathways play a dynamic role in HCC, influencing tumorigenesis, therapy resistance (Yuanyuan Li et al., 2023), and metabolic reprogramming through stage-specific mechanisms. The Keap1/Nrf2/ARE pathway intersects with autophagy in HCC through p62-mediated mechanisms (Orrù et al., 2020), where phosphorylated p62 sequesters Keap1, stabilizing Nrf2 and driving antioxidant and detoxification responses. Autophagy deficiency exacerbates this effect by accumulating p62-Keap1 aggregates, leading to sustained Nrf2 activation, which supports tumor progression. In early HCC, Nrf2 or Keap1 mutations predominate, while in advanced stages, p62 accumulation replaces mutations as the primary driver of Nrf2 activation (Lau et al., 2010). During oxidative stress, modifications to Keap1 allow Nrf2 to translocate into the nucleus, where it binds to the antioxidant response element (ARE) and activates the expression of antioxidant genes (Yuanyuan Li et al., 2023). Furthermore, Nrf2 promotes immune evasion by upregulating immunosuppressive cytokines such as IL-10 and TGF-β, improving the tumor microenvironment and reducing the effectiveness of immune checkpoint inhibitors (ICIs) (Gan et al., 2024; Raghunath et al., 2018). In this way, Nrf2 activation is linked to multidrug resistance (MDR) and poor prognosis (Yuanyuan Li et al., 2023). Another sign of poor prognosis is given by PI3K/AKT/mTOR which, altered by mutations in EGFR, promotes tumor progression. FOXO 3 acts as a tumor promoter in HCC, where its overexpression induces both oxidative stress and tumorigenesis. Although FOXO3 regulates both the production and the deletion of ROS, its activation in hepatocytes favors cell damage and malignant transformation. It is observed that FOXO3 activates the signalization pathway Akt/mTORC2 promoting a positive feedback loop which maintains its activation. Moreover, FOXO3 increases the PPP pathway and its relationship with NADPH/NADP+ protecting cells from oxidative stress (Yang et al., 2021).

Likewise, the overproduction of endothelial and inducible nitric oxide synthases (eNOS and iNOS) raises NO levels, which disrupts normal autophagy. This happens because NO interferes with the binding of BECN1 and VPS34 while strengthening the interaction between Bcl-2 and BECN1, ultimately pushing cancer cells toward apoptosis (O'Connor et al., 2010). Silica nanoparticles, however, affect the NO/NOS system by blocking the PI3K/AKT/mTOR pathway. As a result, eNOS activity drops while iNOS activity increases significantly, leading to inflammation, autophagy activation, and eventually, endothelial dysfunction (Duan et al., 2014).

Hypoxia-induced autophagy is mediated by HIF-1α and its downstream targets BNIP3 and BNIP3L, which regulate BCL-2 interactions (Nakamura et al., 2024). In addition, the Wnt/β-catenin signaling pathway plays a crucial role in regulating autophagy in HCC (Zhao, 2024). Under nutrient stress, β-catenin interacts with LC3 for autophagic degradation, suppressing autophagosome formation and inhibiting the expression of p62, reducing its activity and supporting cellular adaptation (Petherick et al., 2013). Autophagy can degrade β-catenin, promoting cellular adaptation to metabolic stress and creating a feedback loop where β-catenin inhibits autophagy. In HCC, Wnt/β-catenin-mediated suppression of autophagy may support tumor growth, while autophagy activation can enhance β-catenin degradation and potentially inhibit tumor progression (Inagawa et al., 2002). This pathway also contributes to drug resistance and metastasis in HCC. Targeting autophagy or modulating the Wnt/β-catenin signaling axis could offer promising therapeutic strategies to improve treatment outcomes in HCC. In addition, USP8, an ubiquitin ligase, is associated with ferroptosis resistance in HCC. USP8 stabilizes β-catenin, which upregulates GPX4 and its depletion of USP8 reduces GPX4 levels, promoting ferroptosis (Tang, 2023) (Fig. 5).

In primary hepatocellular carcinoma (HCC) tumors, the *RPRD1A* gene (Regulation of Polymerase II Transcription DNA Repair and Damage 1 A) is overexpressed and correlates with aggressive clinicopathological characteristics. Its function involves disrupting the interaction between TRIM21 and p62, thereby blocking ubiquitination and enhancing Keap1 sequestration. This leads to the stabilization of NRF2, helping to reduce cellular damage caused by ROS and promoting HCC progression. Additionally, RPRD1A regulates the cell cycle and upregulates Wnt/β-catenin signaling. Therefore, the RPRD1A–TRIM21–p62 axis may represent a novel therapeutic target in HCC cells (Feng et al., 2021). Inflammation is a major cause of ROS production in chronic liver disease. Pro-inflammatory cytokines such as TNF-α and IL-6 exacerbate oxidative damage by inducing NADPH oxidase activity and disrupting mitochondrial function (Cichoż-Lach and Michalak, 2014; Liang et al., 2016; Singh et al., 2017; Tang et al., 2022; Vachliotis and Polyzos, 2023). Chronic liver diseases, including viral hepatitis B and C, NAFLD and alcohol-induced liver injury, are often associated with sustained ROS production due to persistent inflammation, mitochondrial dysfunction and lipid peroxidation (Che et al., 2023; Cichoż-Lach and Michalak, 2014; Sharma et al., 2023) (Fig. 6).

Mitochondrial dysfunction, characterized by ultrastructural lesions, altered dynamics, and impaired respiratory chain activity, plays a crucial role in the pathogenesis of these conditions (Mansouri et al., 2018; Zhang et al., 2022). Persistent ROS production, primarily from mitochondrial NADH and NADPH oxidases, leads to lipid peroxidation and depletion of antioxidant mechanisms. This oxidative stress disrupts redox balance, modulates inflammatory pathways, and contributes to disease progression, including fibrosis, cirrhosis, and HCC (Shimizu et al., 2012).

4. Therapeutic potential

Autophagy and oxidative stress are crucial factors in the initiation, progression, and treatment of solid tumors. Their therapeutic value lies in modulating these processes and leveraging their interactions to improve cancer treatment strategies (Yang et al., 2011). In established tumors, autophagy often promotes cell survival under stress conditions, leading to treatment resistance. On the other hand, modulating oxidative stress offers several therapeutic approaches, such as pro-oxidant therapies, antioxidant enzyme inhibition or targeted therapies (Gorrini et al., 2013).

4.1. *Breast cancer therapeutic potential*

BC can be classified in three principal types: tumors with positive hormonal receptors (BC HR+) characterized by a higher expression of estrogen and/or progesterone levels (ER+ and/or PR+); BC; breast cancer positive HER2 positive that overexpress the oncogene ERBB2; and triple negative breast cancer (TNBC), which lacks both hormonal receptors and HER2 overexpression. These subtypes have differences in terms of aggressiveness, therapeutic response, progression risk and tendency to develop metastases in specific organs (Prat and Perou, 2011). The dysregulation of the PI3K/AKT/mTOR pathway is involved in endocrine resistance in patients with BC HR+ . It is observed that the overactivation of the growth factor signaling pathway, including PI3K/AKT/mTOR, contributes to resistance to endocrine therapy (ET) and CDK4/6 inhibitors. The interaction of these pathways plays a crucial role in the treatment response of breast cancer. In preclinical studies the simultaneous inhibition of the estrogen receptor, CDK4/6 and PI3K has demonstrated synergistic effects, favoring the cell cycle arrest, apoptosis induction and tumoral regression in both, in vitro and *in vivo* models (Jhaveri et al., 2024). A phase I/Ib clinical trial showed that the treatment with inavolisib, a PI3K inhibitor administered daily, in combination with palbociclib, an inhibitor of CDK4/6 and endocrine therapy (letrozole or fulvestrant), resulted in a reduction in the expression of PI3K/AKT biomarker in tumoral tissue, confirming the efficacy of this treatment (Jhaveri et al., 2024), ClinicalTrials.gov identifier: NCT03006172). Another clinical trial in phase III, INAVO120, is evaluating the combination of inavolisib, palbociclin and fulvestrant in HR+ , HER2- metastatic BC patients with PIK3CA mutation. The preliminary results of this study have demonstrated a significant

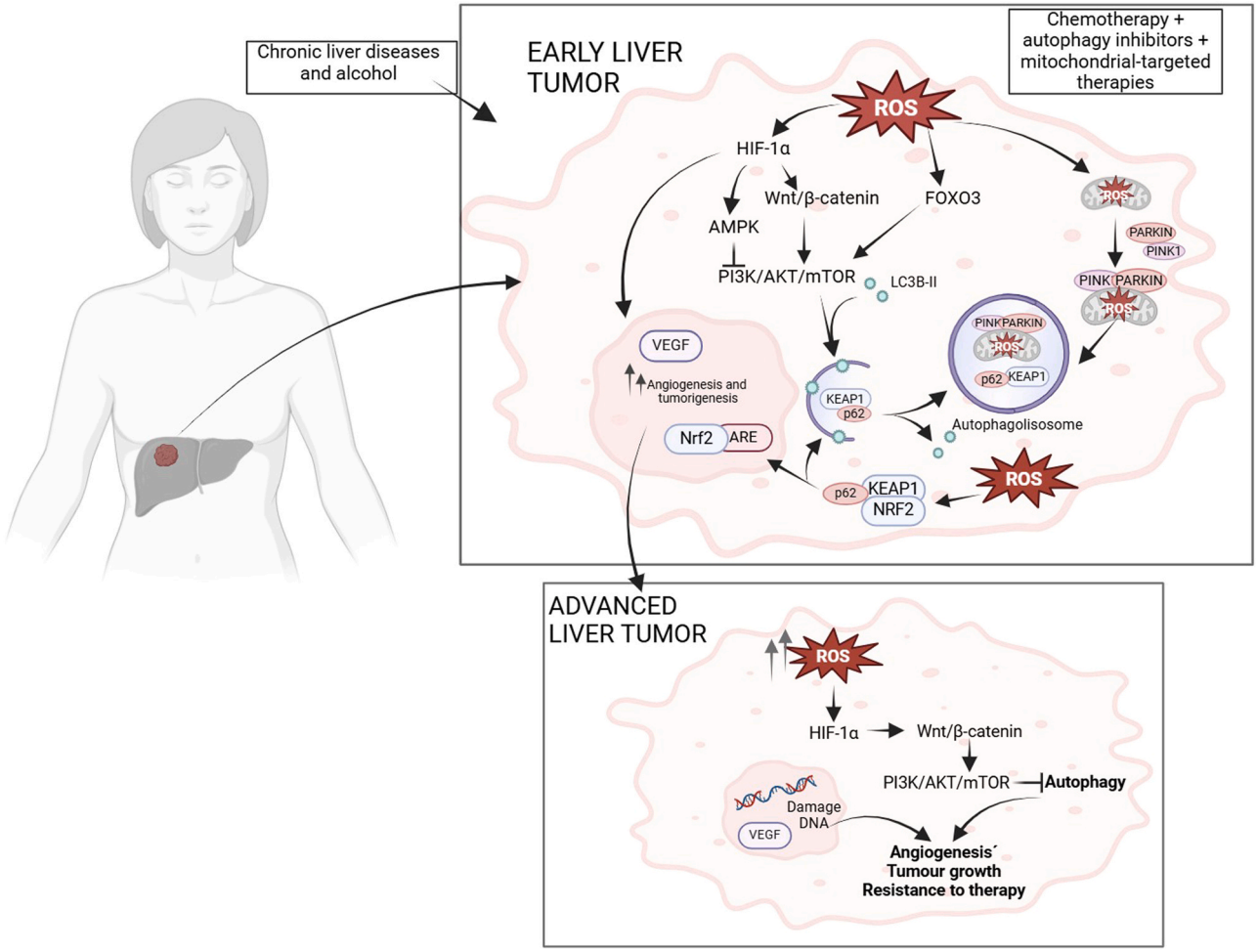

Fig. 6. Molecular pathways involved in determining early and advanced HCC.

improvement in progression-free survival (ClinicalTrials.gov identifier: NCT04191499) (Juric et al., 2024).

Additionally, autophagy contributes to drug resistance in HER2 + BC by HER2 + protected autophagy mechanism. HER2 is a transmembrane tyrosine kinase receptor belonging to the epidermal growth receptor family. Its overexpression triggers excessive activation of various signaling pathways, including MAPK, JAK/STAT, RAS/MEK/ERK and PI3K/AKT/mTOR, promoting proliferation and differentiation of tumor cells. Evidence suggests that the HER2 receptor inhibits autophagy interacting with Beclin-1, moreover, the activation of Beclin-1 signaling pathway induces mTORC1 activation, a key inhibitor in autophagy. It has been reported that the HER2-targeted treatments can induce autophagy as a resistance mechanism, and its inhibition may enhance the drug response (M. Wang et al., 2024).

Di Donato et al. (2022) investigated the role of the p110δ PI3K and Vps34 isoforms (Di Donato et al., 2022). The p110δ isoform is involved in the proliferation and cell migration modulation and its inhibition with the IC87114 drug decreases cell migration in spheroids of both the MCF-7 (BR HR+ cell line) and MDA-MB-231 (TNBC cell line). In contrast, Vps34, a class III PI3K kinase regulates autophagy and influences cancer development. Its inhibition with Vps34-IN1 increases sunitinib and erlotinib drug's efficacy, showing synergistic effects in the cell migration and proliferation. Vsp34 belongs to class III PI3K, and its pharmacological inhibition mediates vesicle transport and autophagy phenomena (Di Donato et al., 2022).

MitoQ, a derivative of Coenzyme Q10 that specifically targets mitochondria. It has antioxidant properties but, paradoxically, it also induces the production of ROS in cells. The increased ROS levels trigger a protective response that involves autophagy. MitoQ generates the degradation of Keap 1 through autophagy, which activates the Keap1/Nrf2 pathway. The deletion of Keap 1 increases the transcriptional activity of Nrf2 leading to the expression of antioxidants genes such as p62, protecting cells from oxidant damage. The p62 protein is associated with Keap1 and activates Nrf2, producing a positive feedback loop that protects cells from oxidative damage. Autophagy inhibition produces an accumulation of p62 and the activation of Nrf2, producing to the tumor cells a defense against chemotherapeutic agents. Therefore, inhibiting Nrf2 could be a potential strategy to improve the function of chemotherapeutic drugs (Gonzalez et al., 2014).

Various studies have explored the role of REDD1 in growth regulation, differentiation, stress response, survival and cellular metabolism. Its main function is to inhibit the mTORC1 complex, which consists of the serine/threonine mTOR kinase and the Raptor protein. mTORC1 is activated by mitogens and nutrients, coordinating key cellular processes, including autophagy (Zhidkova et al., 2022). Hypoxia, energy stress, oxidative stress, glucocorticoids, or specific pharmacological activators have been shown to upregulate REDD1, leading to mTORC1 inhibition and reduced cancer cell proliferation. Furthermore, the increased REDD1 expression following chemotherapy has been linked to lower BC cell survival. In HER2-positive and triple-negative BC, tumor cell proliferation and survival in hypoxic environments are associated with REDD1 downregulation and HIF-1α stabilization (Lan et al., 2013; Tirado-Hurtado et al., 2018; Zhidkova et al., 2020).

Pro-oxidants such as elesclomol and arsenic trioxide exploit the redox vulnerabilities of BC cells by selectively increasing ROS (Alli and Ford, 2012; Qu et al., 2010), overwhelming antioxidant defenses, and

inducing apoptosis (Kirshner et al., 2023). Their efficacy is further enhanced when combined with autophagy inhibitors, revealing a promising dual-targeting strategy (Yang Li et al., 2023). Elesclomol induces oxidative stress by disrupting mitochondrial metabolism and copper homeostasis, leading to ROS accumulation and cuproptosis, a copper-dependent cell death pathway (Nagai et al., 2012). It also targets cancer stem-like and drug-resistant cells, including cisplatin-resistant populations, by elevating ROS levels beyond their antioxidant capacity (Buccarelli et al., 2021). Similarly, arsenic trioxide (ATO) inhibits BC growth by downregulating Notch-1 signaling, reducing Bcl-2 and NF-κB levels, and promoting apoptosis (Xia et al., 2014). It exhibits dose-dependent cytotoxicity in triple-negative (MDA-MB-231), ER+ (MCF-7), and HER2 + (SKBR-3) BC cells (Alzuwaidi and Khalil, 2019; Chow et al., 2004; Rajaram et al., 2024; Wang et al., 2011). ATO also upregulates p53 expression, inhibits cell migration and invasion while down regulating Bcl-2 (Zhang et al., 2016), and activates key apoptotic proteins, including caspases and cytochrome C (Alzuwaidi and Khalil, 2019), which further contribute to apoptosis induction (Chow et al., 2004). Combining elesclomol or ATO with autophagy inhibitors like bafilomycin A1 or CQ prevents ROS clearance (Wang et al., 2023), leading to excessive oxidative damage and increased apoptosis. Additionally, ATO synergizes with tetrandrine or miR-27a modulation, further suppressing antioxidant defenses and metastatic potential (Zhang et al., 2016). Furthermore, the combination of ATO and BIBR1532, an hTERT inhibitor, synergistically inhibits BC cell proliferation by targeting the hTERT and NF-κB pathways (Nasrollahzadeh, 2020). Likewise, it has been shown that the combination of ATO, carboplatin, and cyclophosphamide induces synergistic effects in promoting apoptosis and autophagy in triple-negative BC cell lines (Moomivand et al., 2024). Similarly, dichloroacetate (DCA) potentiates ATO's cytotoxicity by targeting cancer cell metabolism and downregulating c-Myc and HIF-1α (Sun et al., 2011). Melatonin also enhances ATO-induced apoptosis in MCF-7 cells by increasing p53 activity and the Bax/Bcl-2 ratio while suppressing survivin, c-Myc, and hTERT expression (Nooshinfar et al., 2016).

Preclinical studies have offered promising strategies for improving the therapeutic potential in breast cancer treatment, demonstrating that autophagy inhibitors enhance the cytotoxic effects of pro-oxidants in BC models (Wang et al., 2023). Another resistance-overcoming strategy involves CAT suppression, as elesclomol sensitizes resistant BC cells by reducing CAT expression, a key antioxidant enzyme responsible for neutralizing hydrogen peroxide (Glorieux and Calderon, 2018). This reduction lowers the threshold for ROS-induced apoptosis, particularly in cells that have adapted to oxidative stress. Clinically, a potential strategy to overcome treatment resistance is the combination of ROS-inducing agents with chemotherapy (e.g., elesclomol + paclitaxel) (Kirshner et al., 2008), metabolic modulators (e.g., ATO + dichloroacetate, 2-deoxy-D-glucose or 3-bromopyruvate) (Modica-Napolitano et al., 2024), autophagy inhibitors (e.g., ATO + CQ) (Wang et al., 2023), or antioxidant pathway inhibitors (e.g., elesclomol + N-acetylcysteine (NAC)) presents a potential strategy to overcome treatment resistance.

On the other hand, dysregulated mitophagy in BC cells leads to excessive ROS accumulation, driving both tumorigenesis and metastasis (Dong and Zhang, 2024; Wang et al., 2023). Targeting mitophagy-specific proteins, such as PINK1 and Parkin, is an emerging area of research and offers new therapeutic opportunities to address mitochondrial dysfunction in cancer (Li et al., 2022; Narendra and Youle, 2024). These findings underscore the therapeutic potential of targeting both ROS and autophagy pathways to improve BC treatment outcomes (Table 1).

4.2. Lung cancer therapeutic potential

The therapeutic potential of targeting autophagy and oxidative stress in LC is an area of significant interest, as these processes play critical roles in cancer cell survival, progression, and treatment resistance. Jeon, S. J. et al. (2019) have shown that TOR Signaling Pathway Regulator-Like Protein (TIPRL) binds to eIF2α and promotes its phosphorylation, thereby activating the eIF2α-ATF4 pathway (Jeon, 2019). As a result, tumor cells increase their ability to resist metabolic stress, promoting survival and contributing to tumor progression through autophagy activation. In contrast, TIPRL deletion decreases the autophagy flux, reducing the tumor cell survival and increasing the cell death. The combination of metabolic and ER stress induction with autophagy inhibition through TIPRL deletion could present a potential therapeutic target to treat LC (Jeon, 2019). Likewise, autophagy inhibition by CQ or specific autophagy inhibition potentiate T CD8 + infiltration and increase MHC-I expression molecules on tumor cell surface, thereby enhancing immunotherapy efficacy. Consequently, tumor growth is reduced. This process boosts the immune response through increasing tumor antigen exposure to T cells and activating the adaptive immune response (Guo et al., 2022) (Table 2).

Wiel C. et al. (2019) have demonstrated long-term supplementation with antioxidants including N-acetylcysteine and vitamin E, can enhance KRAS-related LC metastasis (Wiel et al., 2019). These antioxidants produce the stabilization of BACH1, activating glycolysis genes like hexokinase 2 and GAPDH, which promote metastasis. Inhibiting BACH1 reduces glycolysis and prevents antioxidant-induced metastasis. BACH1 plays a key role in metastasis under oxidative stress conditions and may serve as a potential therapeutic target for LC (Wiel et al., 2019).

Natural products are also under investigation; Red ginseng, specifically the Rg3-extract, has been demonstrated to promote apoptosis and mitophagy in lung tumor cells, through the activation of ROS and PINK1-Parkin signaling pathway (Nakamura et al., 2024). A ginsenoside metabolite, Compound K, induces apoptosis through autophagy in A549 and H1975 cells through AMPK/mTOR pathways and JNK. Therefore, in cisplatin treatment, Rh2 ginsenoside enhances apoptosis by autophagy inhibition, which reduces drug resistance in LC (Qin et al., 2024). Luo D. et al. (2023) discovered a novel alkaloid derivative from *Sophora flavescens* roots denominated Sophflarine A (SFA) (Luo et al., 2023). SFA induces ROS accumulation leading to autophagy activation by inhibiting PI3K/Akt/mTOR pathway. Additionally, ROS promotes NLRP3 inflammasome activation, triggering piroptosis and cancer cell death. Furthermore, SFA reduces metastasis blocking epithelial-mesenchymal transition and suppressing angiogenesis. These findings suggest that SFA can be a drug candidate for the treatment of LC (Luo et al., 2023). Rhabdothermin E is an ent-kaurene diterpenoid. The mechanism action of rhabdotermin E involves ROS accumulation which activates p38/MAPK/JNK pathway, promoting both apoptosis and ferroptosis. Moreover, it reduces GSH and GPX4 levels while increasing lipid peroxidation, confirming its ability to induce ferroptosis through SLC7A11/GPX4 pathway. In murine models, rhabdothermin E decreases tumor growth more effectively than treatments like cisplatin. In addition, it reduces the expression of tumor proliferative index Ki67 (tumor proliferation indicator) expression and increases Bax/Bcl-2 ratio, favoring apoptosis. These findings highlight the strong antitumor potential of rhabdothermin E, making it a promising therapeutic candidate for LC (Jin et al., 2024). Another study has shown that the synergistic effect of cisplatin with ginkgetin, a metabolite derived from *Ginkgo biloba*, enhances the cytotoxicity in LC cells, specifically NSCLC with wild EGFR both in vitro and in vivo. Ginkgetin, a flavonoid from *Ginkgo biloba*, enhances cisplatin cytotoxicity in NSCLC by promoting ROS accumulation and ferroptosis. It inhibits SLC7A11 and GPX4, disrupting redox homeostasis and sensitizing cells to lipid peroxidation, without affecting healthy lung tissue (Lou et al., 2021). Since resistance to apoptosis and restoration of redox balance are factors limiting the effectiveness of DDP, induction of ferroptosis and disruption of redox homeostasis by ginkgetin offer a promising strategy to improve the efficacy of this drug in the treatment of NSCLC (Lou et al., 2021). Another natural compound that may offer a new therapeutic option for LC is celastrol (a natural compound belonging to the triterpenoids family), either alone or in combination with TRAIL. Celastrol inhibits autophagic flux, enhancing

Table 2
Therapeutic strategies in LC.

Therapeutic strategies	Molecular mechanism	References
***Preclinical study:* TIPRL deletion + metabolic and ER stress induction could present a potential therapeutic target**	Decreases the autophagy flux, reducing the tumor cell survival and increasing the cell death	(Jeon, 2019)
***Preclinical study:* Autophagy inhibition by CQ or specific autophagy inhibition enhance immunotherapy efficacy**	Potentiates T CD8 + infiltration and increase MHC-I expression molecules on tumor cell surface,	(Guo et al., 2022)
***Preclinical study:* BACH1 inhibitors**	Reduce glycolysis and prevents antioxidant-induced metastasis, since long-term supplementation with antioxidants including N-acetylcysteine and vitamin E, produce the stabilization of BACH1, activating glycolysis genes like *HK2* and *GAPDH*, which promote metastasis	(Wiel et al., 2019)
***Preclinical study:* Red ginseng, Rg3-extract and ginsenoside metabolite, Compound K**	Promotes apoptosis and mitophagy through the activation of ROS, PINK1-PARKIN, AMPK/mTOR pathways and JNK	(Nakamura et al., 2024; Qin et al., 2024)
***Preclinical study:* Novel alkaloid derivative from *Sophora flavescens* roots denominated Sophflarine A (SFA)**	Induces ROS accumulation that inhibits PI3K/Akt/mTOR pathway leading to autophagy activation, and activates NLRP3 inflammasome, triggering piroptosis and cancer cell death, SFA also blocks epithelial-mesenchymal transition and suppresses angiogenesis	(Luo et al., 2023)
***Preclinical study:* Rhabdothermin E, an ent-kaurane diterpenoid, with no previously reported antitumor potential**	Induces ROS accumulation that activates p38/MAPK/JNK pathway, reduces Ki−67 expression, increases Bax/Bcl−2 ratio, promoting both apoptosis and ferroptosis through SLC7A11/GPX4 pathway. In murine models, tumor growth decreases more effectively than treatments like cisplatin	(Jin et al., 2024)
Preclinical study:* Synergistic effect *in vitro* and *in vivo* of cisplatin + ginkgetin, a metabolite derived from *Ginkgo biloba	Enhances the cytotoxicity in NSCLC cells with wild EGFR by inducing ROS accumulation which activates p38/MAPK/JNK pathway and triggers apoptosis and ferroptosis	(Lou et al., 2021)
***Preclinical study:* Celastrol (a natural compound belonging to the triterpenoids family)**	Inhibits autophagic flux, increases ROS levels and decreases mitochondrial membrane potential, contributing to cell death, enhancing apoptosis. The combined treatment of TRAIL and celastrol increases cell death compared to the individual treatments, moreover, celastrol elevates LC3-II and p62 levels and potentiates caspase 3 and 8 activation, which are correlated with apoptosis	(Nazim et al., 2019)

apoptosis mediated by TRAIL pathway. The combined treatment of TRAIL and celastrol increases cell death compared to the individual treatments, moreover, celastrol elevates LC3-II and p62 levels and potentiates caspase 3 and 8 activation, which are correlated with apoptosis induction. Additionally, autophagy inhibition by celastrol increases ROS levels and decreases ΔΨm (mitochondrial membrane potential), contributing to cell death (Nazim et al., 2019).

Clinical trials are currently investigating the combination of autophagy inhibitors with immune checkpoint inhibitors, such as anti-PD-1/PD-L1 antibodies, in NSCLC. Preliminary results indicate that autophagy inhibition enhances immunotherapy efficacy by promoting tumor cell death and reversing immune suppression in the tumor microenvironment (Gao and Chen, 2021; Guo et al., 2022; Li et al., 2024). Furthermore, the integration of pro-oxidants with autophagy inhibitors is another promising avenue. By simultaneously increasing ROS levels and blocking the protective effects of autophagy, this dual-targeting approach could induce synergistic cytotoxicity in LC cells while sparing normal tissues (Shimizu et al., 2023; W. Wang et al., 2022).

Pro-oxidants such as elesclomol and arsenic trioxide selectively exploit the elevated ROS vulnerability of cancer cells, inducing apoptosis with minimal toxicity to normal cells (You and Park, 2012). Preclinical studies have shown that combining pro-oxidants with autophagy inhibitors further sensitizes LC cells to oxidative damage, highlighting the potential of dual-targeting strategies (Kaminskyy et al., 2012; Wang et al., 2024). Conversely, antioxidants like NAC may protect normal tissues from therapy-induced oxidative damage, improving tolerance during radiotherapy (Shin et al., 2020). For example, N-acetylcysteine (NAC) has been shown to protect normal lung tissue during radiotherapy while maintaining the efficacy of cancer treatment (Moldeus et al., 1986; Sala, 1993). However, the use of antioxidants in cancer therapy remains controversial, as they may also protect tumor cells from ROS-mediated cytotoxicity.

4.3. PCa therapeutic potential

The interplay between autophagy and ROS presents significant therapeutic potential in PCa (Dong et al., 2023). The activation of autophagy by chemotherapeutic agents, such as docetaxel, plays a crucial role in promoting drug resistance in PCa. Increased expression of NPRL2 and BECN1 has been linked to autophagy-induced resistance, whereas mTOR pathway activation counteracts this effect by suppressing autophagy and improving docetaxel efficacy. Additionally, TGF-β1 stimulates autophagy and reduces the effectiveness of docetaxel. Inhibiting TGF-β1 secretion can prevent autophagy activation, thereby enhancing the drug's impact on PCa cells. KLF5, a transcription factor downregulated by docetaxel via the AMPK–mTOR–p70S6K axis, suppresses autophagy and sensitizes cells to therapy. Similarly, AMPK activation under androgen deprivation induces protective autophagy, promoting cell survival (Jia et al., 2019; Wang et al., 2018; Yu, 2021) (Table 3).

Ramos-Torres et al. (2016) investigated the effect of capsaicin in PCa cells, showing that this substance has an antiproliferative and cytotoxic effect, specifically in PC-3 cells, insensitive to androgens. Capsaicin also inhibits PI3K/Akt/mTOR pathway, which is overexpressed in PCa and increases LC3-II levels. However, it also produces an accumulation of p62, suggesting that capsaicin inhibits the autophagy pathway. Capsaicin also generates ROS, contributing to apoptosis when autophagy is inhibited, supporting its use as a potential PCa therapy (Ramos-Torres et al., 2016). Another study has shown the effects of Hydroxyl-Nor-Kavain (HNK), a natural anticancer agent, on autophagy in PCa cells. Autophagy induced by HNK plays a protective role in the cells, due to autophagy inhibition increases apoptosis in cells treated with HNK and it inhibits mTOR and AKT phosphorylation. In addition, ROS also plays a significant role in autophagy induction by HNK. However, autophagy inhibition with antioxidant substances does not affect apoptosis induced by HNK. Treatment with HNK induces protective autophagy in PCa cells, and inhibiting autophagy could enhance HNK's anticancer effect, highlighting the therapeutic potential of this natural agent (Hahm et al., 2014). Mukha et al. (2021) demonstrated that autophagy and oxidative stress play a key role in PCa

Table 3
Therapeutic strategies in PCa.

Therapeutic strategies	Molecular mechanism	References
Preclinical study: Capsaicin	Inhibits PI3K/Akt/mTOR, increases LC3-II, but also accumulates p62, suggesting autophagy inhibition. Generates ROS. Induces cytotoxicity and apoptosis in androgen-insensitive PC−3 cells, especially in combination with autophagy inhibitors	(Ramos-Torres et al., 2016)
Preclinical study: Hydroxyl-Nor-Kavain (HNK)	Induces protective autophagy, inhibits mTOR/AKT phosphorylation, increases ROS. Enhances apoptosis when autophagy is inhibited, improving therapeutic potential	(Hahm et al., 2014)
Preclinical study: CB−839 (Glutamine Metabolism Inhibitor)	Inhibits glutamine metabolism, increasing ROS and DNA damage. Induces autophagy as a survival mechanism. Sensitizes PCa cells to radiotherapy; combination with autophagy inhibitors (e.g., CQ) enhances oxidative stress and promotes apoptosis	(Mukha et al., 2021)
Preclinical study: Metformin	Downregulates MYC and GLS1, inhibits autophagy, and increases oxidative stress. Acts as a radiosensitizer, enhancing the effects of radiotherapy	(Mukha et al., 2021)
Preclinical study: Monoamine oxidase A (MAOA) inhibitors	Generates ROS, inhibits apoptosis (reduces p53 activation), and induces mitophagy. Inhibiting MAOA suppresses autophagy and promotes apoptosis, making it a potential therapy for castration-resistant PCa	(Lin et al., 2017)
Preclinical study: Sertraline (STL)	Induces ROS, mitochondrial dysfunction, autophagy and apoptosis. Inhibits PCa stem cell (PCSC) markers and EMT. Reduces PCa cell proliferation, migration, and stemness	(Chinnapaka et al., 2020)
Preclinical study: Calotropis procera extract (CPE)	Modulates autophagy, reduces ROS, increases p27 (cell cycle inhibitor), and inhibits NF-kB. Reduces PCa cell viability and migration; autophagy effects are cell type dependent. Preclinical study (clinical trials ongoing): PT−112. Generates mitochondrial stress via ROS, alters mitochondrial respiration, induces autophagy and immunogenic cell death (ICD). Reduces PCa cell viability and migration; autophagy effects depend on cell type. Selectively induces tumor cell death, enhances mitochondrial damage, and stimulates immune response	(Singh et al., 2024)
Preclinical study: PT−112 in PCa cells	PT−112 induces mitochondrial stress and ROS production, activates autophagy, and promotes immunogenic cell death (ICD) via DAMPS release, enhancing tumor cell targeting	(Soler-Agesta et al., 2024)
Preclinical study: miRNA-based therapies (tumor-suppressing/promoting miRNAs, siRNAs)	miRNAs regulate autophagy in cancer cells. miRNA replacement or inhibition strategies may suppress tumor progression by targeting autophagy-related pathways	(Ashrafizadeh et al., 2022; John Clotaire et al., 2016)
Preclinical study: Combating resistance to androgen deprivation therapy (ADT)	In prostate cancer, increased autophagic flux enables cancer cells to degrade AR inhibitors and sustain AR signaling, contributing to resistance against ADT	(Elshazly and Gewirtz, 2023; Nguyen et al., 2014; Quan, 2020)

radioresistance through glutamine (Gln) metabolism (Mukha et al., 2021). Tumor cells rely on Gln to maintain redox balance, by glutathione production (GSH), which reduces ROS levels and protects against DNA damage. Gln metabolism inhibition with drugs such as CB-839 increases ROS levels, accumulation of DNA damage and enhances cells sensibility to radiotherapy. However, PCa cells activate autophagy like a pro-survival mechanism in response to Gln inhibition, leading to cellular adaptation and therapy resistance. Therefore, autophagy inhibition by ATG 5 inhibition or with CQ, enhances the radiosensitizer effect of Gln inhibition, increasing oxidative damage and promoting cell death. Furthermore, metformin, an antidiabetic drug, shows a radiosensitizer effect through downregulation of MYC and GLS1 expression, autophagy inhibition and increasing oxidative stress in tumor cells. The combination of Gln inhibitors and autophagy inhibitors can enhance the radiotherapy efficacy in PCa by promoting oxidative damage and reducing the tumor cell resistance to treatments (Mukha et al., 2021). Monoamine oxidase A (MAOA), a target gene of repressor element 1-silencing transcription factor (REST), plays a crucial role in autophagy activation and apoptosis inhibition, specifically in androgen deprivation-induced neuroendocrine differentiated PCa cells. MAOA generates ROS that inhibit apoptosis by reducing p53 activation, while simultaneously activating autophagy through mitophagy induction. These mechanisms are essentials for PCa progression due to autophagy activation and apoptosis inhibition contribute to cell survival and treatment resistance. In addition, the study highlights that MAOA regulation by REST and its relationship with oxidative stress are key factors in autophagy activation and neuroendocrine differentiation (NED) in PCa cells. MAOA inhibition could be a therapeutic strategy for advanced PCa patients, including those resistant to castration and chemotherapy (Lin et al., 2017).

Other authors have investigated the impact of the antidepressant sertraline (STL) on PCa stem cells (PCSC), highlighting its potential as a treatment in PCa. STL inhibits growth and metastasis of PCSC, decreasing cell viability in various PCa cell lines. Moreover, STL reduces cell proliferation and migration of PCSC, through inhibiting EMT markers, such as TCF8 and LEF1. STL's cytotoxicity is associated with apoptosis induction and ROS generation, besides, STL induces cell cycle arrest in the G0 phase and activates mitochondrial dysfunction, contributing to cell death. Oxidative stress plays a significant role in this process, as ROS generation and the use of STL negatively regulates stem cell marker expressions including ALDH1 and anti-apoptotic proteins such as TCTP. Furthermore, STL induces autophagy in PCSC, and the combination of STL with antioxidants suggests that apoptosis induction is mediated by ROS. STL acts on PCSC through oxidative stress, apoptosis activation and autophagy, affecting PCSC mark expression, and could be a potential therapy to advanced PCa (Chinnapaka et al., 2020).

Natural compounds as leaf extract of *Calotropis procera* (CPE), reduce cell viability, division, and migration of PCa cells, both androgen-

sensitive and androgen-independent. CPE treatment in cells increases p27 protein expression, producing inflammatory inhibition and cell cycle regulation, additionally, it also reduces NF-kB activation. Furthermore, CPE decreases ROS levels, which in turn reduces cell viability and migration in PCA cells. The effect of CPE on autophagy requires further study; in PC-3 cell type, autophagy activation is associated with increased levels of p62, LC3B and Beclin-1, in contrast, in another 22Rv1 cell type, treatment with CPE decreases Beclin-1 and LC3-II expression, suggesting autophagy inhibition. Thus, the effects of autophagy depend on the cell type. Therefore, CPE inhibits proliferation and migration in PCa cells by autophagy modulation and reducing ROS levels. It could be a new therapy to PCa but more studies are needed to fully understand the role of autophagy (Singh et al., 2024).

Soler-Agesta et al. (2024), have shown the anticancer effects of PT-112 in PCa cells. PT-112 generates mitochondrial stress by ROS production, modifying mitochondrial membrane potential, mitochondrial respiration and mitochondrial morphology. In addition, PT-112 activates autophagy and generates immunogenic cell death by DAMPS (ICD) in tumor cells and does not affect to not tumor cells. Mitochondrial stress and DAMPs release are correlated due to the ATP release, with PT-112 promoting ICD that could enhance mitochondrial damage, cell death and apoptosis. Autophagy, influenced by mitochondrial stress is also involved in the ICD induction, and the ribosome biogenesis altered by PT-112 could also be involved in autophagy regulation contributing to the selective targeting of tumor cells by PT-112 (Soler-Agesta et al., 2024).

miRNA-based approaches, including tumor-suppressing and tumor-promoting miRNAs, regulating autophagy in PCa, and miRNA replacement therapy and siRNAs could be employed to modulate autophagy and suppress PCa progression (Ashrafizadeh et al., 2022; John Clotaire et al., 2016). Resistance to androgen deprivation therapy (ADT), the cornerstone of PCa treatment, is often associated with increased autophagic flux. Cancer cells use autophagy to degrade androgen receptor (AR) inhibitors and maintain AR signaling, allowing them to escape therapy-induced cell death (Elshazly and Gewirtz, 2023; Nguyen et al., 2014; Quan, 2020).

4.4. Colorectal cancer therapeutic potential

Autophagy and ROS play crucial roles in the development and progression of CRC. Wang et al. (2023) showed that ANXA10, overexpressed in BRAF-mutant CRC, suppresses ferroptosis by reducing Fe^{2+} accumulation and enhancing transferrin Receptor 1 degradation (TFRC). ANXA10 inhibition increased ferroptosis and autophagic flux, accompanied by SQSTM1 accumulation, indicating a regulatory role in both processes (Wang et al., 2023). Other authors have explored the role of glutaminase 1 (GLS1), a key enzyme in Gln metabolism, in the growth and migration of CRC cells. GLS1 is upregulated in CRC and promotes proliferation and migration by converting Gln to glutamate, lowering ROS levels, and upregulating NRF2. GLS1 inhibition increased ROS and decreased NRF2, impaired autophagy, and suppressed tumor growth, suggesting it as a dual regulator of redox and autophagic balance (Liu et al., 2021) (Table 4).

Zhang et al. (2024) demonstrated that ATG7 suppression can enhance T CD8 + cells activation, offering a novel mechanism to immunotherapy in CCR (W. Zhang et al., 2024). This effect occurs by ROS/NF-kB pathway activation, which increases the expression of major histocompatibility complex class I (MHC-I) on the cell membrane. Moreover, the authors showed that the combination of an ATG7 inhibitor with atorvastatin, a drug belonging to the statin class, used primarily to reduce cholesterol and triglyceride levels in the blood, which inhibits HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase (HMGCR) could be a potential therapeutic target. Consequently, the simultaneous inhibition of ATG7 and cholesterol regulation can enhance the immunotherapy response in patients with colorectal cancer and microsatellite instability-high (MSI-H) (Zhang et al., 2024). Gingerol

Table 4
Representative Therapeutic Strategies Investigated in CRC.

Therapeutic strategies	**Molecular mechanism**	**Ref.**
***Preclinical study:* ANXA 10 inhibition**	Induces ferroptosis by increasing Fe^{2+} levels and reducing TFRC degradation; enhances autophagic flux and SQSTM1 accumulation	(Wang et al., 2023)
***Preclinical study:* GLS1 inhibition**	Disrupts glutamine metabolism, increases ROS, reduces Nrf2 expression, and alters autophagy, suppressing CRC cell growth and migration	(Liu et al., 2021)
***Preclinical study:* ATG7 inhibitor + atorvastatin**	Activates ROS/NF-kB signaling, increasing MHC-I expression and enhancing CD8 + T-cell activation. Atorvastatin, an inhibitor of HMGCR, improves immunotherapy response	(Zhang et al., 2024)
***Preclinical study:* Gingerol acid (GA)**	Induces ferroptosis by increasing lipid peroxidation, GSH depletion, and ROS/ Fe2 + accumulation. Ferroptosis inhibitors prevent GA-induced cell death.	(Xiao et al., 2024)
***Preclinical study:* Cysteine depletion + mTOR/autophagy inhibition**	Cysteine is crucial for tumor growth and redox balance. Its depletion activates autophagy via the mTOR/ ULK pathway. The combination enhances treatment response	(Lin et al., 2024)
***Preclinical study:* KRAS mutation and mitophagy**	KRAS G12/13 mutations increase autophagic flux. Activating mutant KRAS induces mitophagy and mitochondrial fission via AKT phosphorylation (S473) and ROS generation, leading to cancer cell death	(Iskandar et al., 2024)
***Preclinical study:* Heat shock protein 90 (HSP90) JD−02 inhibition**	Disrupts protein homeostasis, induces G0/G1 arrest, apoptosis, and autophagy via ROS/SRC signaling. Preclinical/clinical studies: Immune checkpoint inhibitors (ICIs, anti-PD−1/ CTLA−4 antibodies) + autophagy inhibition (CQ/ HCQ). Restore immune surveillance. Autophagy inhibition enhances antigen presentation and T-cell infiltration, boosting ICI response	(Liu and Sun, 2021; Wang et al., 2022)
Preclinical study: Conventional chemotherapy and radiotherapy	Induce cytotoxicity through ROS generation. However, cancer cells, especially cancer stem cells—activate antioxidant mechanisms that reduce treatment efficacy	(Lyons et al., 2023)
***Preclinical study*: Emerging therapies (photodynamic, sonodynamic, radiodynamic)**	Utilize targeted ROS generation to induce cell death. Nevertheless, adaptive mechanisms in cancer cells reduce the effectiveness of ROS-based drugs like 5-FU and oxaliplatin	(Levy and Thorburn, 2011)
***Preclinical study:* α-hederin**	Increases ROS production through the activation of the AMPK pathway, inhibition of mTOR and leads to autophagic cell death in cancer cells	(Sun et al., 2019)

(*continued on next page*)

Table 4 (*continued*)

Therapeutic strategies	**Molecular mechanism**	**Ref.**
Preclinical study: **Cucurbitacin CC 90003**	Promote ROS generation and induces autophagy	(Zhang et al., 2012)
Preclinical study: **Hydroperoxy fatty acid 13 (S)-HpODE**	Generate ROS, which leads to BAX activation and BCL−2 inhibition	(Biswas et al., 2023)
Preclinical study: **Dimethyl fumarate**	Induces glutathione depletion, ROS generation, and MAPK activation, which leads to necroptosis induction	(Han et al., 2018)
Preclinical study: **Oleanolic acid**	Promote ROS generation leading to G1/S cell cycle arrest and inhibition of cell proliferation	(Guo et al., 2017)
Preclinical study: **Cucurbitacin E**	Promote ROS generation and impede tumor growth by arresting the cell cycle at the G2/M phase	(Zhang et al., 2012)
Preclinical study: **CNN16, Psoralidin, Alantolactone, TPEN, Graphene oxide, CopA3, Extracts from marine invertebrates**	Induce the generation of ROS or ROS accumulation causing DNA damage	(Arslan et al., 1985; da Silva et al., 2022; Dey and Kang, 2021; Ding et al., 2016; Krasteva et al., 2019; Ruiz-Torres et al., 2019; Sun et al., 2022)
Clinical trial: NCT02106806	Analyzes the oxidative stress (SOD, GPx, MDA, Isoprostane, Vitamin C, Vitamin E) during cycles of chemotherapy in patients after surgery for CRC, with or without oral zinc supplementation	(Zhang et al., 2024)

acid (GA), an active compound of ginger, inhibits CRC progression by targeting the SLC7A11 protein and promoting its ubiquitin-mediated degradation, thereby inducing ferroptosis. GA treatment decreases significantly programmed CRC cellular proliferation both in vitro and in vivo, without showing toxic effect in vital organs. The mechanism consists of GA trigger ferroptosis in CRC cells by lipid peroxidation, GSH exhaustion and ROS and Fe2 + accumulation. Additionally, treatment with apoptosis inhibitors and autophagy don't protect significatively against induced cell death by GA, while ferroptosis inhibitors did, suggesting that ferroptosis is key in the antitumor action of GA. In summary, this study shows that GA promotes ferroptosis in CRC and suggests that it may be a promising candidate for targeted treatment of colorectal cancer (Xiao et al., 2024). On the other hand, cysteine is a key metabolite in CRC and is overexpressed in tumor cells. It has been demonstrated that cysteine is essential for tumor growth, and the inhibition of cysteine transporters reduces cysteine levels and can induce ferroptosis. ATF4, a transcription factor, regulates the expression of cysteine transporters in response to microenvironment tumor stress, such as hypoxia and oxidative stress. Cysteine is utilized for the GSH synthesis, allowing CRC cells to maintain ROS levels in a favorable balance to the tumor growth. Combining cysteine depletion with mTOR or autophagy inhibitors enhances tumor cell sensitivity and may overcome redox adaptation (Lin et al., 2024).

Furthermore, it has been demonstrated that G12/13 mutations in the KRAS gene in CRC increase autophagic flux in response to cellular stress. Pharmacological activation of mutant KRAS stimulates both mitophagy and mitochondrial fission, a process mediated by AKT phosphorylation at S473 and ROS generation, ultimately leading to the death of mutant KRAS-driven cancer cells. However, the relationship between AKT signaling, mTORC1, and mitophagy remains debated. AKT phosphorylation at S473 by mTORC2 is essential for mitophagy and mitochondrial fission to occur following drug-induced activation of mutant KRAS (Iskandar et al., 2024). Lan et al. (2024) identified JD-02 as a novel heat shock protein 90 (HSP90) inhibitor that binds to the ATP-binding site in the N-terminal domain, leading to protein destabilization and degradation. In CRC cells, JD-02 induces G0/G1 cell cycle arrest, apoptosis and autophagy primarily through the generation of ROS and modulation of Hsp90/SRC signalling axis. The combination of JD-02 with CQ, significantly enhances apoptotic cell death, suggesting that autophagy acts as a cytoprotective mechanism in this context (Lan et al., 2024). In line with thisN-acetylcysteine (NAC) has shown to inhibit autophagy and apoptosis by modulating the ROS/JNK/Bcl-2 axis in liver injury models (Wang et al., 2014) and the AMPK/mTOR pathway in macrophages (Lin et al., 2020; Su et al., 2024). Given that both pathways are involved in CRC progression and chemoresistance, these mechanisms are likely conserved. Moreover, NAC has been reported to reduce inflammation-associated tumorigenesis in murine CRC models by suppressing NF-κB activity and oxidative DNA damage, thereby reducing tumor burden and dysplasia severity. However, its effects are dose- and context-dependent. For example, under conditions of high ER stress, NAC may paradoxically inhibit autophagy, impair cellular adaptation and promote apoptosis (Xiang et al., 2016). Therefore, while NAC shows promise as an adjuvant to modulate redox balance and autophagy in CRC, further studies are needed to delineate its precise therapeutic window and mechanism of action in this cancer type. Taken together, these results highlight that autophagy inhibitors may enhance the efficacy of JD-02 treatment, especially when combined with autophagy inhibitors such as CQ or NAC (Lan et al., 2024).

On the other hand, combination therapies integrating ICIs with autophagy inhibitors are advancing in CRC research. ICIs, such as anti-PD-1 and anti-CTLA-4 antibodies, restore immune surveillance but are often limited by the immunosuppressive CRC microenvironment. Combining ICIs with autophagy inhibitors, such as CQ or HCQ, disrupts tumor-induced immune evasion and enhances antigen presentation and cytotoxic T-cell infiltration, thereby increasing the therapeutic potential of ICIs (Liu and Sun, 2021; Wang et al., 2022). This dual-targeting strategy overcomes immune resistance and exploits autophagy vulnerabilities.

Conventional CRC therapies, including chemotherapy and radiotherapy, derive their cytotoxicity from ROS generation (Lyons et al., 2023). However, elevated detoxification mechanisms in cancer cells, particularly cancer stem cells, can lead to therapy resistance. Emerging approaches such as photodynamic, sonodynamic, and radiodynamic therapies aim to harness ROS for therapeutic benefit (Lyons et al., 2023). While this adaptive mechanism allows cancer cells to mitigate oxidative damage, it also contributes to therapy resistance by reducing the efficacy of ROS-inducing chemotherapies such as 5-fluorouracil (5-FU) and oxaliplatin (Levy and Thorburn, 2011).

4.5. *Hepatocellular carcinoma therapeutic potential*

Autophagy and ROS play a crucial role in HCC progression, influencing both tumor development and therapeutic responses. Sorafenib, a chemotherapeutic drug for HCC, exerts its effects through the production of O_2^- (superoxide anion). Sorafenib induces ROS generation, specifically O_2^-, in tumor and endothelial cells which produce irreversible cellular damage such as cell death or inhibition of proliferation. O_2^- is produced by NADPH oxidase, which is activated by sorafenib and mediated by VEGF, contributing to ROS production and tumor hypoxia. In patients, the concentration of advanced oxidative protein products (AOPP) in serum, a marker of oxidative stress, is correlated with sorafenib efficacy. A serum AOPP level of $\geq$ 0.2 μmol/L is a good predictor of patient survival and treatment response 7 (Coriat et al., 2012). Additionally, it has been observed that the combination of Agrimol B with sorafenib, inhibits the growth and proliferation of HCC cells, inducing both apoptosis and autophagic cell death. Specifically, Agrimol B, a compound derived from *Agrimonia pilosa Ledeb,* induces autophagic cytotoxic in HCC by negatively regulating NADH: ubiquinone oxidoreductase subunit 1 (NDUFS1) which produces an accumulation of

mitochondrial ROS (Dong et al., 2024).

Oxaliplatin treatment induces autophagy in HCC cells, by autophagosomes generation and the accumulation of LC3-II. However, survival oxaliplatin-treated cells have shown higher metastatic potential. Inhibiting autophagy with CQ and 3-methylamphetamine enhances cell death induced by oxaliplatin both *in vivo* and *in vitro* suggesting that autophagy contributes to tumor cell survival treated with oxaliplatin. Drug resistance to platinum compounds can be correlated with reduced ROS, and autophagy helps to delete damaged proteins and organelles generated by ROS. Inhibiting autophagy combined with oxaliplatin increases ROS generation and potentiate treatment cytotoxicity (Ciccarone et al., 2019).

Xu et al. (2021) investigated the role of URI1, a protein overexpressed in HCC cells exposed to irradiation, which appears to inhibit radiotherapy-induced apoptosis. URI1 reduces ROS levels induced by irradiation, suggesting that URI1 can protect tumor cells against oxidative stress and contributes to HCC radioresistance. Furthermore, URI1 activates autophagy to eliminate excess ROS and maintain redox balance, thereby protecting cells from oxidative damage. This process is regulated by AMPK/FOXO3 signalization pathway, where URI1 promotes AMPK and FOXO3 activation, favoring autophagy. These findings suggest that modulating the URI1 pathway could enhance radiotherapy treatments in HCC (Xu et al., 2021).

Dihydromyricetin (DHM), a natural flavonoid, induces apoptosis in a concentration-dependent manner, reducing cellular proliferation without affecting normal hepatic cells. This effect is correlated with a decrease in ROS production in HCC cells, disrupting redox balance, blocking ROS-mediated transduction signals and promoting apoptosis. Additionally, DHM decreases GSH levels and ATP in tumor cells, while inducing heme oxygenase-1 expression (HO-1) which further favors apoptosis. ROS imbalance plays a key role in the apoptosis process induced by DHM, as even a small amount of ROS production is essential for cancer cell growth and that an imbalance in the cellular environment can trigger cell death in HCC cells (Liu et al., 2014).

Another molecule with potential interest for HCC therapy is FDX1, which plays a crucial role in cellular metabolism and HCC progression. FDX1 converts Cu^{2+} to Cu^{1+} and it is involved in diverse tumoral process, including proliferation, migration and tumor cell invasion. Its deficiency provokes metabolic alterations in mitochondria generating oxidative stress and activating mitophagy by PINK1/Parkin pathway. Additionally, FDX1 interacts with the PI3K/AKT pathway, which is associated with autophagy in malignant tumors, promoting HCC progression when its expression is low. From a therapeutic perspective, FDX1 is a tumor suppressor, and its activation can represent a potential strategy against HCC. Currently, diverse options to enhances its function are being explored which involve: 1) the use of copper ionophores as elesclomol, drugs that induce its expression (CX-5461, temozolomide or erlotinib among others), and 2) strategies for redox balance regulation through ROS scavengers. Moreover, FDX1 role in immunomodulation suggests that its combination with immunotherapy could improve treatment response and patients' survival (Sun et al., 2024). On the other hand, patients treated with incomplete radiofrequency ablation (iRFA), a therapy used for HCC, can achieve outcomes comparable to surgical resection when the tumor diameter is < 1 cm. However, HCC recurrence after this treatment remains a major challenge and is associated with poor prognosis, however HCC recurrence after this treatment remains a major challenge and is associated with poor prognosis. In the short term, after treatment, ROS levels increase and have a pro-survival effect. NADPH oxidase (NOX4), located in mitochondria, plays an important role in mitochondrial ROS production induced by thermal stress. This ROS increase activates mitophagy dependent on PINK1, promoting the deletion of damaged mitochondria and avoiding apoptosis. NOX4 inhibitors reduce mitochondrial ROS, highlighting its key role in response to thermal stress. Additionally, the transcription factor Nrf2 is activated in response to oxidative and thermal stress, promoting metabolic reprogramming and increased glycolysis and the regulation of key genes like PINK1. Nrf2 could also be involved in ferroptosis resistance after iRFA, although this aspect requires further investigation (Peng et al., 2023).

Caryophyllene oxide, a chemical compound found in essential oils, increased ROS formation and reduced intracellular antioxidants such as NRF2, HO-1, GPX4, and NQO1, which protect cells from ferroptosis. Additionally, caryophyllene oxide increased Fe^{2+} levels, promoting lipid peroxidation and cellular damage. It also regulated ferritinophagy by enhancing NCOA4 and LC3 II expression, facilitating ferritin autophagy and reducing FTH1 levels, thus contributing to ferroptosis (Xiu et al., 2022). (Table 5)

Table 5
Therapeutic strategies in HCC.

Therapeutic strategies	**Molecular mechanism**	**References**
***Clinical study:* Sorafenib**	Induces ROS (O2-) via NADPH oxidase activation, leading to tumor hypoxia and cellular damage. Serum advanced oxidative protein products (AOPP) levels correlate with treatment efficacy	(Coriat et al., 2012)
***Preclinical study:* Agrimol B**	Inhibits NDUFS1, leading to mitochondrial ROS accumulation and autophagic cytotoxicity. Enhances apoptosis and autophagy when combined with sorafenib	(Dong et al., 2024)
***Preclinical study:* Oxaliplatin + autophagy inhibitors (CQ, 3-MA)**	Induces autophagy (LC3-II accumulation) and autophagy inhibition increases ROS, enhancing oxaliplatin cytotoxicity	(Ciccarone et al., 2019)
***Preclinical study:* URI1 inhibition**	URI1 overexpression reduces ROS and promotes autophagy via AMPK/FOXO3, contributing to radiotherapy resistance. Inhibiting URI1 may improve radiotherapy efficacy.	(Xu et al., 2021)
***Preclinical study:* Dihydromyricetin (DHM)**	Induces apoptosis by disrupting redox balance, reducing ROS, ATP, and GSH, and increasing HO−1 expression	(Liu et al., 2014)
***Preclinical study:* FDX1 activation**	Regulates Cu^{2+} to Cu^{1+} conversion, affecting metabolism, oxidative stress, and mitophagy (PINK1/Parkin pathway). Low FDX1 promotes HCC progression. Therapeutic approaches include copper ionophores and redox balance regulators	(Sun et al., 2024)
***Preclinical/clinical study:* Incomplete radiofrequency ablation (iRFA) + NOX4/Nrf2 inhibition**	iRFA-induced ROS activates NOX4, leading to mitophagy (PINK1-dependent) and ferroptosis resistance via Nrf2. NOX4 inhibition reduces mitochondrial ROS and may improve outcomes	(Peng et al., 2023)
***Preclinical study:* Caryophyllene oxide**	Caryophyllene oxide promotes ferroptosis by increasing ROS and Fe^{2+} levels, reducing key antioxidants, and enhancing ferritinophagy through NCOA4 and LC3 II upregulation, leading to ferritin degradation	(Xiu et al., 2022)

5. Challenges and future directions

5.1. Therapeutic targeting and challenges in autophagy modulation

The modulation of autophagy is a promising approach in cancer therapy, targeting its dual role in tumor biology. However, this approach often causes unintended toxicity in normal tissues, although inhibiting autophagy can suppress its pro-survival functions in cancer cells. The optimal balance between risks and benefits requires further study to minimize side effects while maximizing therapeutic efficacy (Taucher et al., 2022). Developing selective inhibitors that target autophagy specifically in malignant cells without affecting normal cells remains a major challenge (Lim and Murthy, 2020). Identifying robust biomarkers to predict which patients will benefit most is critical for establishing this selectivity (Taucher et al., 2022). Notably, candidate biomarkers such as LC3, p62, and Nrf2-regulated genes offer promising avenues for patient stratification and monitoring autophagic and oxidative stress activity in tumors.

5.2. Complex interactions between autophagy, oxidative stress, and tumor biology

Autophagy's role in cancer is context-dependent, acting as either tumor suppressor or promoter based on tumor type, stage, and genetics (Debnath et al., 2023). This duality complicates therapy development and underscores the need for detailed understanding of autophagy's function in specific cancer contexts. The interplay between autophagy and oxidative stress is complex and dynamic, involving feedback loops and signaling pathways. Oxidative stress can stimulate or be attenuated by autophagy, forming a balance that influences cancer progression and treatment response (Debnath et al., 2023; Taucher et al., 2022). Targeted research is essential to dissect these interactions and refine therapies.

5.3. Exploration of combination therapies

Combining autophagy modulators with chemotherapy, radiotherapy, or novel targeted therapies shows synergistic potential to improve efficacy (Lim and Murthy, 2020). For instance, co-targeting autophagy with oxidative stress may enhance therapeutic outcomes by reducing cellular ROS levels and increasing cancer cell death. Furthermore, since autophagy shapes the tumor immune microenvironment, integrating autophagy modulation with immunotherapy is promising. Understanding these interactions could open the way to novel combination regimens optimizing immune response and suppressing tumor growth.

5.4. Advancing research tools and methodologies

Progress in this area depends on better experimental tools. Advanced genetic models are needed to clarify the role of specific ATGs in cancer progression and resistance to therapy (Lim and Murthy, 2020). Improved imaging techniques that allow real-time visualization and quantification of autophagy in living tissues will support characterization of its dynamic response to therapy (Taucher et al., 2022).

5.5. Considerations for antioxidant therapies in cancer treatment

The use of antioxidants in cancer therapy adds another layer of complexity. Antioxidants may interfere with chemotherapeutic agents that rely on oxidative mechanisms to induce cancer cell death (Jiang et al., 2023; Marioli-Sapsakou and Kourti, 2021). Therefore, antioxidant supplementation must be carefully balanced to avoid counterproductive effects. Antioxidants can protect normal cells but potentially promote cancer cell survival and recurrence (Jiang et al., 2023; Singh et al., 2018). However, antioxidant doses affect cells differently. Low doses may protect healthy and tumor cells, while high doses may stop tumor growth. Finding the best dose for treatment while avoiding cancer cell survival remains a challenge (Singh et al., 2018). Effects vary across cancer types and treatments (Marioli-Sapsakou and Kourti, 2021; Singh et al., 2018).

5.6. Future directions

To fully harness autophagy modulation in cancer therapy and improve patient outcomes while reducing risks, future research should focus on overcoming key challenges. Firstly, it is crucial to develop personalized strategies that tailor autophagy and oxidative stress modulation based on individual tumor characteristics and genetic profiles. Additionally, exploring the synergistic effects of combining autophagy modulators with traditional chemotherapies or targeted therapies could enhance treatment efficacy. Reliable biomarkers need to be identified to predict and monitor the efficacy of therapies based on autophagy and oxidative stress modulation. Moreover, the discovery of new compounds that selectively modulate autophagy or oxidative stress pathways in cancer cells is key to developing more effective treatments. A deeper understanding of the molecular mechanisms underlying the interplay between autophagy, oxidative stress, and cancer progression is also required. This will enable the design of more specific and effective therapies. Furthermore, determining the optimal timing for autophagy modulation in different cancer types and stages is crucial to maximizing therapeutic benefit. Finally, investigating the tumor microenvironment's role in these processes is crucial to improve treatment response. Together, these research efforts are vital to advance autophagy modulation as a cancer therapeutic strategy.

6. Conclusions

Autophagy and oxidative stress play crucial and often contradictory roles in the development and progression of solid tumors. While autophagy can act as a protector mechanism by eliminating damaged organelles and reducing cellular damage, it can also promote tumor cell survival under stress conditions promoting drug resistance. On the other hand, oxidative stress, characterized by the production of ROS, can induce cellular damage and apoptosis. However, it is a double-edged sword, and it can also stimulate tumor cell proliferation and adaptation.

In solid tumors such as BC, LC, CRC, PCa or HCC, the interaction between autophagy and oxidative stress influences the progression and resistance to chemotherapy and immune evasion. From a therapeutic perspective, regulation of autophagy and oxidative stress is a key strategy to enhance the efficacy of cancer treatments. Autophagy inhibition has been explored to increase tumor susceptibility to chemotherapy and radiotherapy, at the same time, oxidative stress modulation by antioxidants or prooxidants substances can be used to induce tumor programmed cell death. However, due to the complexity of these processes and their dual roles, a personalized approach is necessary to determine whether their activation or inhibition would be more beneficial for each specific cancer type.

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Declaration of Competing Interest

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José Manuel Sánchez-Maldonado: PhD. Researcher with expertise in molecular oncology. He has co-authored multiple studies and meta-analyses on autophagy-related biomarkers in cancer. His work focuses on the role of oxidative stress in tumour progression and therapeutic response, with ongoing contributions to collaborative cancer research projects.

Lucía Ruiz-Durán: Early-career researcher focusing on the molecular mechanisms that drive tumor growth and therapy resistance in solid cancers. Her work involves the analysis of signaling pathways and cellular stress responses, with an emphasis on autophagy and oxidative stress. Lucía actively participates in scientific meetings to strengthen her expertise in translational oncology and biomarker discovery.

Francisco Jiménez-Romera: Francisco is involved in cancer research, focusing on the molecular mechanisms driving tumour progression. He participates in translational projects aimed at identifying novel biomarkers and therapeutic targets in solid tumours. Francisco has gained experience presenting his work at national and international conferences, contributing to the scientific community as a promising early-career researcher.

Francisco José García-Verdejo: MD, PhD. Medical Oncology Specialist, with a primary focus on solid tumours. He leads and participates in phase II and III clinical trials, contributing to the development and evaluation of novel therapeutic strategies in oncology. He is also involved in functional studies aimed at understanding molecular mechanisms underlying tumour biology, including pathways relevant to autophagy and oxidative stress. His work bridges clinical practice and translational research to improve patient outcomes in solid cancers.

Carmen González-Olmedo: PhD. Researcher specializing in cancer metabolomics. She has extensive experience in managing research projects and her recent work includes studies on metabolomics biomarkers in breast and colorectal cancer, and the interplay between autophagy and oxidative stress in solid tumours, contributing to advances in personalized cancer therapy.

Aina Cardús: Clinical researcher with expertise in the integration of clinical research with patient care, advancing the development of innovative therapies in oncology.

Leticia Díaz-Beltrán: PhD. Researcher leading projects in liquid biopsy, NGS, and multi-omics in cancer. Her work focuses on identifying metabolomic and miRNA biomarkers for diagnosis, prognosis, and treatment response, with significant contributions to scientific literature and precision oncology.

Juan Francisco Gutiérrez-Bautista: PhD. Researcher with extensive experience in translational immunology and oncology. His work focuses on tumour biology, especially mechanisms involving autophagy and oxidative stress, as well as immune responses relevant to cancer progression. He has contributed to multiple research projects and publications bridging molecular pathways with clinical implications in solid tumours.

Yolanda Benavente: PhD. Senior researcher with an extensive publication record in cancer epidemiology, with a particular focus on environmental and genetic risk factors for cancer.

Fernando Gálvez-Montosa: MD, PhD. Medical oncologist with expertise in tumour autophagy. His research elucidates how alterations in autophagy influence cancer progression and therapy resistance. He has contributed to defining autophagy as a therapeutic target.

José Antonio López-López: MD. Medical Oncology Specialist primarily focusing on digestive, lung, and head and neck cancers. He holds expert qualifications in Immuno-Oncology and Medical Oncology, reflecting a strong clinical foundation in cancer treatment. He is actively engaged in multidisciplinary oncology care and research, contributing to advancing therapeutic approaches in solid tumours.

Paloma García-Martín: MD. Clinician and researcher with a strong focus on cancer biology and translational oncology. Her work centres on understanding mechanisms underlying tumour progression and treatment response, contributing to studies that aim to improve patient outcomes.

Eva María Pérez: MD. Clinical researcher with expertise in translational research. Her work focuses on the integration of clinical practice with advanced molecular tools, such as liquid biopsy, next-generation sequencing, and other omics technologies, to identify diagnostic and prognostic biomarkers for personalized treatment in cancer.

Juan José Rodríguez-Sevilla: MD, PhD. Clinical researcher leading projects on immune evasion in cancer, particularly NK and T-cell dysfunction. He has published in high-impact journals and his work contributes to understanding immune mechanisms in tumour progression.

Delphine Casabonne: PhD. Epidemiologist with expertise in environmental and genetic cancer risk factors. Her research includes the influence of viral infections, lifestyle, and anthropometrics on cancer development, contributing to large-scale studies and international consortia.

Pedro Sánchez-Rovira: MD, PhD. Renowned oncologist and expert in breast cancer. He has led over 50 clinical trials and several translational projects in tumour genomics and circulating tumour cells, contributing to major oncology journals and shaping clinical research in solid tumours.

Fernando Jesús Reyes-Zurita: PhD. Researcher in drug development targeting cancer pathways, with a focus on oxidative stress and autophagy. He has authored numerous publications and is involved in preclinical studies exploring new therapeutic strategies.

Juan Sainz: PhD. His research focuses on the genetic and molecular mechanisms underlying cancer development and progression. He has extensive experience in the study of cellular stress responses, such as autophagy and oxidative stress, and their roles in tumour initiation, immune evasion, and therapy resistance. Dr. Sainz actively participates in several international consortia on colorectal, pancreatic, and prostate cancer, where he integrates genomic, transcriptomic, and proteomic data to identify biomarkers and therapeutic targets. His work bridges basic and translational research, contributing to precision oncology through multi-omic and systems biology approaches.