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Review

Mechanistic insights and therapeutic strategies for targeting autophagy in pancreatic ductal adenocarcinoma

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Abstract
Pancreatic ductal adenocarcinoma (PDAC) is characterised by early metastasis and resistance to anti-cancer therapy, leading to an overall poor prognosis. Macroautophagy (hereinafter referred to as autophagy) is a conserved cellular homeostasis mechanism that degrades various cargoes (e.g., proteins, organelles, and pathogens) mainly playing a role in promoting survival under environmental stress. Autophagy is an essential defense mechanism against PDAC initiation, acting on multiple levels to maintain cellular and tissue homeostasis. However, autophagy is also intimately involved in the molecular mechanisms driving PDAC progression, facilitating the adaptation of cancer cells to the tumor microenvironment's harsh conditions. In this review, we examine the complex role of autophagy in PDAC and assess the potential of modulating autophagy as a therapeutic strategy. By reviewing current research and clinical trials, we seek to elucidate how targeting autophagy can disrupt PDAC tumor survival mechanisms, enhance the efficacy of existing treatments, and ultimately improve patient outcomes.

Keywords Autophagy · Pancreatic cancer · PDAC · Cancer treatment · Immune response · Tumor microenvironment (TME)

1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) is recognized as one of the most lethal malignancies, with an alarming rise in incidence and mortality rates that currently position it among the leading causes of cancer-related deaths worldwide [1, 2]. Its exceptionally poor prognosis is largely attributed to the complex tumor biology, including genetic heterogeneity, dense stromal composition, and significant metabolic reprogramming that collectively fuel PDAC's aggressiveness and therapeutic resistance [3]. Notably, PDAC is often diagnosed at an advanced stage due to its asymptomatic nature during early development and lack of reliable early-detection biomarkers [4]. By the time symptoms manifest, most patients already present with metastasis or locally advanced disease, limiting eligibility for curative surgery to a small subset of cases [5, 6]. The tumor microenvironment (TME) in PDAC plays a substantial

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role in enhancing its malignancy and therapeutic recalcitrance. Characterized by dense desmoplastic stroma, immunosuppressive cell populations, and restricted vascularization, the TME limits drug delivery and supports the tumor's adaptive metabolic strategies [7–10]. Among the hallmarks of PDAC is the ability of cancer cells to exploit autophagy, macropinocytosis, and other nutrient-scavenging mechanisms, enabling them to thrive in the nutrient-deprived, hypoxic conditions characteristic of the PDAC tumor microenvironment, further complicating therapeutic interventions [11–13] The standard-of-care treatments, including chemotherapy and, in rare cases, surgical resection, offer limited survival benefits. Despite recent advancements in chemotherapeutic regimens such as FOLFIRINOX and gemcitabine with nab-paclitaxel, the median survival remains dismal, with a five-year survival rate persistently below 10% [14, 15]. Given the inadequate outcomes of current therapeutic strategies and the rising incidence of PDAC, there is an urgent need for novel approaches that not only target the tumor cells but also modify the TME to improve treatment efficacy and patient outcomes.

Autophagy is an evolutionarily conserved mechanism, induced by nutrient depletion or cell stress, that enables cells to degrade and recycle intracellular components, sustaining energy and removing damaged organelles, protein aggregates, and other cellular debris [16]. This process, mediated by autophagosomes that deliver cargo to lysosomes, is critical for cellular quality control and adaptation to stress, as it provides essential metabolites during nutrient scarcity [16]). Autophagy's functions extend beyond individual cells, influencing a wide array of cellular processes across different tissue types, from preserving endothelial cell homeostasis in cardiovascular systems to regulating protein balance in neurons, which is crucial for neural function and plasticity [17, 18]. In cancer, the role of autophagy is uniquely complex and context-dependent [19]. Autophagy is well-recognized for its tumor-suppressive functions, including the prevention of DNA damage, induction of cell death following chemotherapy, and clearance of damaged components that might lead to oncogenic transformation [20–23]. Autophagy can also act as a tumor promoter by sustaining cancer cell metabolism and survival under stress, while suppressing immune responses that would otherwise target tumor cells. In this regard, it has been documented that hepatic autophagy fosters immune tolerance in high-tumor-mutational-burden cancers by supporting regulatory T-cell function and dampening antitumor immune responses, thereby promoting tumor growth through metabolic and immune mechanisms [24]. Autophagy reduction leads to p62/SQSTM1 (Sequestome 1) [25] accumulation which may target RAD51 to proteasomal degradation thus altering Homologous Repair (HR) pathway of the DNA Damage Response (DDR), further linking autophagy inhibition to carcinogenesis [26]. On the other hand, p62/SQSTM1 can establish a cross-talk with NRF2 (nuclear factor erythroid 2-related factor 2), the master regulator of the cellular antioxidant response [27], and reduce oxidative stress and inflammation in some specific contexts, counteracting carcinogenesis [28]. Moreover, Beclin-1—essential for autophagosome formation—is also implicated in PDAC progression, with its expression associated with tumor progression and poor prognosis, which underscores its critical role in maintaining autophagic flux under stress [29] Additionally, host autophagy plays a critical role in providing metabolic support to tumors, as systemic deletion of Atg7 in mice reduces circulating arginine, impairs tumor growth, and reveals a metabolic vulnerability exploitable for therapy [30]. Furthermore, studies in Drosophila models show that tumors can induce non-cell-autonomous autophagy in the microenvironment and distant tissues, supplying essential nutrients for early tumor growth and invasion, which can be inhibited pharmacologically [31]. The autophagy process is intricately regulated by several kinases, among the most important being the mechanistic target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK). mTOR functions as a central inhibitor of autophagy; under nutrient-rich conditions, it suppresses autophagic processes to promote cell growth and proliferation [32]. Notably, the regulation of autophagy is influenced by the Gαq subunit, which modulates mTORC1 activity through interactions with p62, affecting both autophagy induction and termination during nutrient fluctuations [33]. In prolonged starvation, mTOR reactivation plays a critical role in terminating autophagy and restoring lysosome homeostasis by recycling autolysosomal products into proto-lysosomal structures, highlighting its dual role in nutrient sensing and cellular equilibrium [34]. Conversely, AMPK acts as an energy sensor, activating autophagy in response to low energy states by inhibiting mTOR and directly phosphorylating autophagy-related proteins like Ulk1 at Ser 317 and Ser 777, which is essential for autophagy induction under glucose starvation [35]. Beyond initiation, AMPK is also required for efficient autophagosome maturation and lysosomal fusion, as demonstrated by impaired autophagy progression in AMPK α1 knockout cells, which can be rescued by reintroducing AMPK α1 [36] Together, these pathways intricately coordinate autophagy to maintain cellular homeostasis under dynamic metabolic conditions.

This review article aims to critically examine the complex role of autophagy in PDAC and assess the potential of modulating autophagy as a therapeutic strategy. By reviewing current research and clinical trials, we seek to elucidate how targeting autophagy can disrupt PDAC tumor survival mechanisms, enhance the efficacy of existing treatments, and ultimately improve patient outcomes.

2 Autophagy in PDAC initiation

Numerous studies have assessed that autophagy plays a critical role in maintaining cellular homeostasis and that can act as a barrier to tumor initiation in several cancers including PDAC by preventing oxidative stress, genomic instability, and chronic tissue damage [37]. By removing damaged organelles, protein aggregates, and other harmful components, autophagy supports normal acinar pancreatic cell function and suppresses early oncogenic processes, highlighting its tumor-suppressive potential in the initial stages of PDAC development (Fig. 1).

Genetic studies have revealed that the loss of autophagy-related genes in pancreatic beta cells has profound consequences for cellular function and systemic health. Without autophagy, the clearance of damaged organelles, particularly mitochondria, is impaired, leading to mitochondrial dysfunction characterized by reduced energy production and heightened oxidative stress. This dysfunction is further exacerbated by the accumulation of misfolded and aggregated proteins, which overwhelm the cellular quality control mechanisms [38]. Autophagy prevents the accumulation of reactive oxygen species (ROS) (Fig. 1) by maintaining mitochondrial integrity and regulating antioxidant

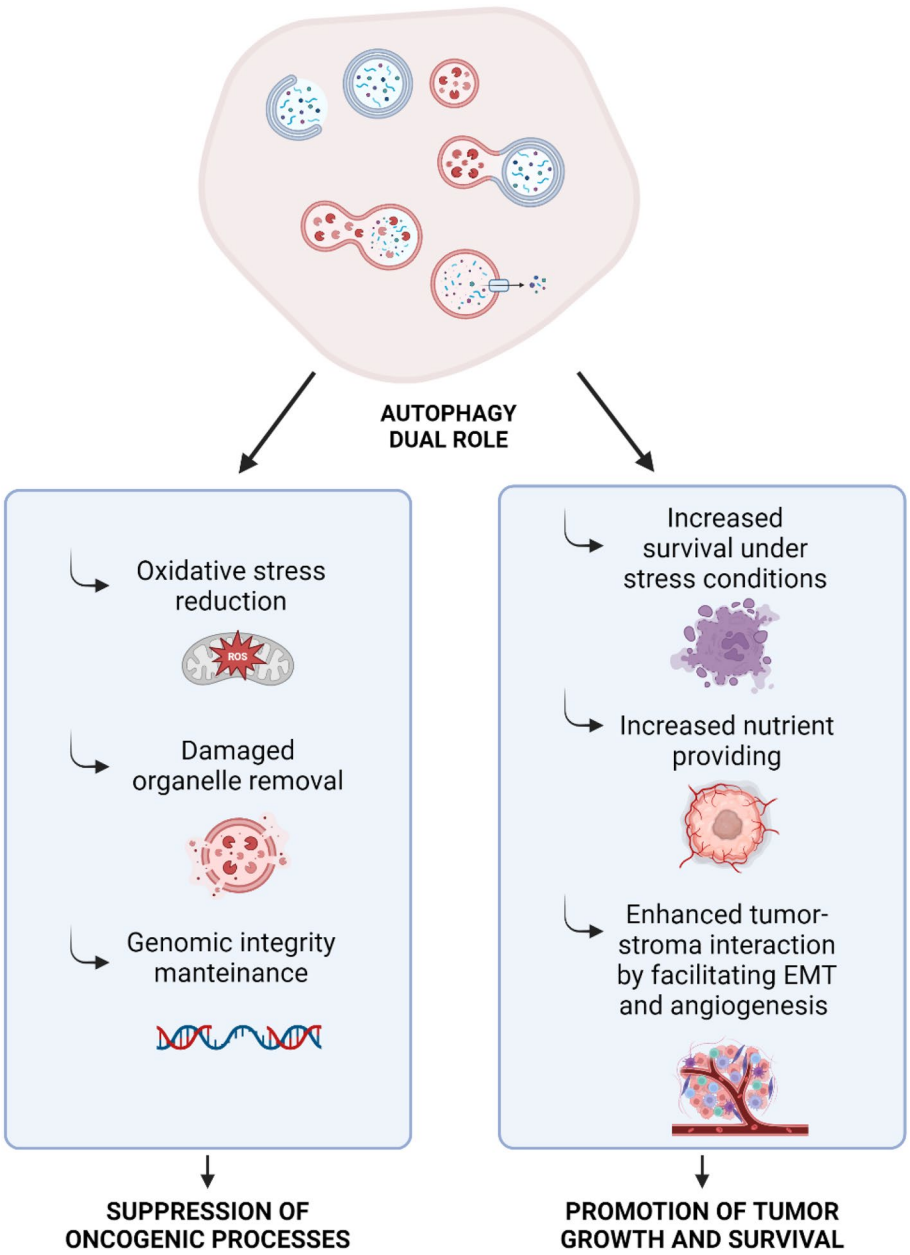

Fig. 1 The dual role of autophagy in PDAC initiation and progression, In the left part autophagy maintains cellular homeostasis by removing damaged organelles and proteins and by preventing oxidative stress, therefore preserving genomic integrity. These mechanisms act to suppress oncogenic processes. In the right part of the figure, autophagy promotes tumor growth and survival under stress conditions, by recycling intracellular components to fuel bioenergetic and biosynthetic pathways, while simultaneously modulating the tumor microenvironment (TME)

pathways, including sestrins and other redox modulators [39]. When autophagy is impaired, damaged mitochondria persist, becoming a major source of ROS and exacerbating oxidative stress, which damages cellular components and drives genomic instability. In addition, autophagy reduction significantly impairs insulin secretion, a critical function of beta cells, resulting in hyperglycemia and reduced beta cell mass. Hyperglycemia, in turn, contributes to systemic metabolic stress and chronic inflammation, both of which are established risk factors for pancreatic cancer, including PDAC [40]. Last but not least, hyperglycemia impairs Dendritic Cell (DC) formation and activation through ROS increase, which further lower the capacity of immune system to prevent carcinogenesis [41]. Additionally, autophagy plays a critical role in enabling beta cells to adapt to metabolic stress caused by high-fat diets. By maintaining cellular homeostasis, autophagy prevents the degeneration of pancreatic islets, thereby safeguarding their function and preserving glucose tolerance. In its absence, beta cells lose the ability to cope with such metabolic challenges, leading to glucose intolerance, systemic inflammation, and a heightened risk of pancreatic dysfunction. This highlights the protective role of autophagy in cellular quality control and in mitigating the metabolic dysfunction and chronic inflammatory states that contribute to cancer risk [42] In line with its protective role, impaired autophagy in the pancreas has been shown to drive the development of pancreatitis, a well-established precursor to PDAC [43]. As previously mentioned, impaired autophagy disrupts lysosomal degradation, leading to the accumulation of damaged organelles and proteins. In the pancreas, this dysfunction allows improper activation of trypsinogen into trypsin within acinar cells, causing cellular damage and triggering inflammatory responses that drive pancreatitis [44]. Defective autophagy amplifies acinar cell necrosis, which promotes tissue destruction and leads to chronic inflammation—a hallmark of pancreatitis. Chronic inflammation, in turn, creates a pro-tumorigenic environment by increasing the production of inflammatory cytokines and reactive oxygen species (ROS), which further damage cellular components and disrupt genomic stability. Over time, this cycle of cell damage, necrosis, and inflammation drives the formation of pancreatic intraepithelial neoplasia (PanIN), precancerous lesions that can progress to invasive PDAC [45]. Chronic pancreatitis becomes a fertile ground for oncogenic transformation, with sustained inflammation fueling mutations in genes like KRAS and p53, which are commonly implicated in PDAC [46]. In this context, it is important to highlight that oncogenic KRAS-driven inflammation, characterized by the activation of NF-κB and STAT3, is exacerbated by the loss of autophagy, which sustains cytokine production and perpetuates inflammatory feedback loops. Moreover, in the presence of oncogenic mutant p53 proteins, autophagy is inhibited in pancreatic cancer cells during early tumorigenesis, leading to increased ROS production and enhanced cell proliferation through a Sestrin-AMPK-dependent mechanism, which fosters a microenvironment conducive to PDAC initiation [47]. This interplay between mutant p53 and autophagy loss amplifies oxidative stress and disrupts cellular energy balance, fostering a microenvironment conducive to tumorigenesis [48, 49]. This interplay between autophagy, oxidative stress, and inflammation underscores its vital role in protecting against PDAC initiation and highlights the importance of maintaining functional autophagy in pancreatic tissues. By modulating these oxidative and inflammatory processes, autophagy preserves genomic integrity and prevents the onset of tumorigenic mutations that can initiate PDAC [50, 51].

3 Autophagy in PDAC progression

Autophagy is intimately involved in the molecular mechanisms driving PDAC progression, facilitating the adaptation of cancer cells to the tumor microenvironment's harsh conditions. Autophagy sustains PDAC growth by integrating multiple signaling pathways and transcriptional programs to maintain metabolic homeostasis and survival under nutrient and oxygen deprivation. Yang et al. demonstrated that autophagy promotes PDAC growth through both cell-autonomous and nonautonomous mechanisms, as demonstrated in a mouse model with reversible autophagy inhibition [52]. In this model, autophagy inhibition caused significant tumor regression, highlighting its critical role in tumor maintenance. Mechanistically, autophagy supports tumor cell metabolism by recycling intracellular components to fuel bioenergetic and biosynthetic pathways, while simultaneously modulating the tumor microenvironment (TME) to promote survival under stress conditions [53] (Fig. 1). Notably, autophagy also regulates stromal interactions and nutrient availability, remodeling the microenvironment into a supportive niche that sustains cancer cells' metabolic needs and survival [52]. As an example, the treatment of pancreatic cancer cells with Valproic Acid (VPA), which triggers both apoptosis and autophagy [54], has been shown to reduce dendritic cells (DCs) immune response by promoting the release of Prostaglandin (PG) E2 through endoplasmic reticulum (ER) stress and its transfer to DCs [55], inducing immune dysfunction. It is also important to remember that autophagy plays a crucial role in metastasis by enabling cancer cells to adapt to environmental challenges, such as nutrient scarcity and detachment from the extracellular matrix (ECM).

Autophagy can facilitate epithelial-mesenchymal transition (EMT)—a process where epithelial cells acquire mesenchymal traits to enhance migration and invasion—and help cancer cells evade anoikis and interact with stromal cells to establish metastases [56].

TGFB1-induced autophagy, regulated by SMAD4 status, exhibits dual roles in PDAC progression, highlighting the intricate interplay between genetic context and tumor behavior [57]. In SMAD4-positive PDAC cells, TGFB1-induced autophagy promotes cellular proliferation by limiting SMAD4's nuclear translocation, thereby modifying its tumor-suppressive functions. Conversely, in SMAD4-negative cells, TGFB1-induced autophagy drives increased migratory and invasive capabilities by activating the MAPK/ERK signaling pathway [57]. This dichotomy underscores the context-dependent nature of autophagy's tumor-promoting effects, revealing how it adapts to the molecular landscape of PDAC to facilitate either growth or metastasis. These findings suggest that targeting TGFB1-induced autophagy could require tailored strategies depending on the genetic and molecular profile of the tumor.

In addition to the mechanisms discussed above, several additional signaling pathways play pivotal roles in modulating autophagy in PDAC. Emerging evidence in pancreatic cancer indicates that metabolic substrates and diverse signaling cascades drive tumor progression by regulating autophagic flux. For example, a recent study by Cui et al. demonstrated that excessive fructose uptake via the transporter GLUT5 fuels PDAC cell survival under glucose-deficient conditions by providing both energy and biosynthetic precursors, while activating the AMPK–mTORC1 axis to inhibit autophagic cell death [58]. This work indicates that fructose-induced mTORC1 activation contributes to tumor progression and suggests that targeting fructose metabolism might offer a novel therapeutic approach. In parallel, research focusing on pancreatic beta-cells under hyperglycemic conditions has shown that chronic high glucose elevates autophagy levels, which in turn protect beta-cells from glucotoxicity and apoptosis; importantly, manipulation of AMPK activity can modulate this protective autophagy [59].

Further insights come from studies targeting key oncogenic signaling cascades. A comprehensive review on the PI3K/AKT/mTOR pathway in PDAC revealed that genetic aberrations frequently lead to pathway activation, positioning this cascade as a promising target for therapy, although clinical outcomes have so far been modest—patient stratification may be critical to improving efficacy [60]. Similarly, another investigation demonstrated that the Akt inhibitor MK-2206 significantly reduces pancreatic cancer cell viability and, when combined with gemcitabine, synergistically enhances cytotoxicity by inhibiting Akt phosphorylation and downstream survival signals [61]. In this frame, Additional work has established that activating mutations in PIK3CA can initiate pancreatic tumorigenesis, with murine models showing rapid PanIN formation and invasive cancer that are particularly sensitive to dual PI3K/mTOR inhibition; this underscores the potential of targeting aberrant PI3K signaling in a subset of PDAC [62]. Moreover, phospho-Akt overexpression has been correlated with poor patient prognosis and has been proposed as both a prognostic and predictive biomarker, since Akt inhibitors combined with gemcitabine exhibit enhanced efficacy in PDAC cells with high phospho-Akt levels [63].

Collectively, these studies highlight a multifaceted regulatory network in PDAC wherein metabolic inputs, such as fructose and high glucose, converge with signaling pathways—including the AMPK/mTOR, ULK1, and PI3K/Akt axes—to modulate autophagy. A thorough understanding of these interconnections has the potential broadens our insight into the metabolic and molecular drivers of pancreatic cancer progression and to provide a compelling rationale for the development of combination therapies that target these pathways to overcome therapeutic resistance.

At the molecular level, a report by Perera et al. has demonstrated that autophagy induction in PDAC is orchestrated by the MiT/TFE transcription factors (MITF, TFE3, and TFEB), which serve as master regulators of lysosomal biogenesis and nutrient scavenging pathways [64]. These transcription factors are decoupled from their normal cytoplasmic regulatory mechanisms in PDAC, allowing their nuclear translocation and activation of a gene network essential for heightened lysosomal catabolic function. This process is highly relevant in the context of cancer progression as it ensures a continuous supply of intracellular amino acids, enabling PDAC cells to sustain metabolic reprogramming critical for survival and proliferation in nutrient-deprived conditions. Thus, by linking autophagy to enhanced lysosomal activity and metabolic adaptability, the MiT/TFE-driven program underscores the centrality of autophagy in maintaining the aggressive growth of PDAC [64]. This mechanism seamlessly integrates with autophagy's broader roles in modulating the tumor microenvironment and supporting metastatic progression, further demonstrating its multifaceted contributions to PDAC progression.

Mutations in key oncogenic drivers, such as RAS and p53, significantly contribute to autophagy induction in PDAC [65] Plac8, a gene activated by these mutations, has been shown to enhance lysosome-autophagosome fusion, a critical step for maintaining the efficient turnover of intracellular components [66]. In contrast to its inhibitory role in early tumorigenesis, mutant p53 can contribute to autophagy induction in advanced PDAC stages, as seen with Plac8, which enhances lysosome-autophagosome fusion to support metabolic homeostasis under nutrient stress. This stage-specific

shift underscores the context-dependent nature of mutant p53's effects on autophagy, transitioning from suppression to promotion as PDAC progresses. By facilitating this process, Plac8 supports metabolic homeostasis, ensuring a continuous supply of nutrients necessary for pancreatic cancer survival and proliferation under nutrient-deprived conditions. Additionally, LC3, a critical component of autophagosome formation, is upregulated in PDAC cells, facilitating autophagy activation via the EGFR/MEK/ERK and HGF/c-MET/Akt/mTORC1/HIF-1α axes, supporting tumor survival under nutrient deprivation [67, 68]. This dual mechanism, involving both Plac8 and LC3, highlights the intricate link between primary oncogenic mutations and autophagy induction, suggesting a framework where metabolic reprogramming and autophagic activity are deeply interwoven in PDAC progression. Such findings point to autophagy not merely as a survival strategy but as a downstream effector deeply embedded within tumor-promoting networks driven by oncogenic key mutations like RAS and p53 [66]. Together with the MiT/TFE transcriptional regulation of lysosomal biogenesis, these mechanisms might represent a coordinated adaptation orchestrated by genetic mutations to sustain tumor growth. While this interplay highlights promising therapeutic avenues, further research is necessary to fully elucidate the extent to which these processes operate synergistically and whether targeting them could effectively disrupt PDAC progression.

Caprin-1, a protein found significantly upregulated in advanced pancreatic cancer, plays a pivotal role in activating autophagy by interacting with ULK1 and modulating its phosphorylation status [69]. This autophagic activation, is not merely a metabolic adaptation but extends its influence into immune modulation, as evidenced by the increased presence of tumor-associated macrophages (TAMs) and CD4 + T cells in Caprin-1-high PDAC tissues. These immune cells foster an immunosuppressive microenvironment, enabling PDAC cells to evade immune surveillance. However, additional research is necessary to determine which specific subtypes of CD4 + T cells are primarily attracted and to clarify the precise roles they play in remodeling immunosuppressive characteristics. Thus, the dual role of Caprin-1 in promoting tumor growth and immune suppression highlights its significance in autophagy-driven tumor progression, presenting a promising target for disrupting cancer growth and enhancing anti-tumor immunity. In a complementary mechanism, autophagy has been shown to sustain PDAC growth by facilitating glycolysis and promoting resistance to therapeutic interventions, particularly under conditions of nutrient scarcity and hypoxia [70]. Table 1 summarizes the key autophagy-modulated molecules involved in PDAC progression.

4 Autophagy, immune response and metabolic reprogramming in PDAC

A groundbreaking study led by Kimmelman's team has shown that autophagy promotes immune evasion in PDAC by degrading MHC-I molecules via a Neighbor of BRCA1 (NBR1)-dependent pathway, reducing their surface expression and impairing antigen presentation to cytotoxic T cells [71]. Notably, autophagy inhibition restores MHC-I surface levels, enhances CD8 + T cell responses, and synergizes with dual checkpoint inhibitors, offering a potential therapeutic strategy against PDAC. Further underscoring the role of autophagy in immune evasion, Immunity Related GTPase Q (IRGQ) has been identified as a regulator of MHC-I quality control, mediating its degradation through interactions with GABA Type A Receptor Associated Protein Like 2 (GABARAPL2) and LC3B. Loss of IRGQ allows misfolded MHC-I to accumulate on the cell surface, promoting CD8 + T cell activity and enhancing immune responses, which could improve survival outcomes, as observed in hepatocellular carcinoma models [74]. Together, these findings highlight the intricate role of the autophagy-lysosome pathway in suppressing immune responses and demonstrate the potential for autophagy inhibition to restore immune surveillance in PDAC, further linking autophagy to both metabolic flexibility and immune evasion in the tumor microenvironment.

Speculatively, these findings suggest that autophagy acts as a central node connecting metabolic adaptation and immune evasion in PDAC. The interplay between autophagy-driven metabolic reprogramming and immune modulation positions is as a critical mechanism that sustains the tumor's ability to proliferate and evade therapy. Targeting these autophagy-mediated pathways could offer a twofold therapeutic advantage: disrupting the metabolic resilience of PDAC cells while simultaneously restoring immune surveillance. In the case of CAR-T cell-based therapy, as antigens on cancer cell surface recognized by T cells may undergo degradation through autophagy, its inhibition may increase expression of antigens and enhance CAR-T cell-mediated cancer killing. Moreover, cytokine release syndrome induced by CAR-T cell therapy may be ameliorated by autophagy inhibition, with beneficial effects for patients. However, it should be considered that, some chemotherapies require induction of autophagy to release ATP from dying tumor cells and that it acts as "find me signal" for DCs, stimulating their activity [75]. Moreover, loss of autophagy in cancer cells has been reported to reduce the efficacy of radiotherapy in immunocompetent mice, again due to reduction of ATP release[76]. From these findings, it emerges that, autophagy may play different roles, in both the tumor and its microenvironment,

Table 1 Overview of key autophagy-modulated molecules involved in PDAC progression

Autophagy-modulated molecule	Role in PDAC progression	Autophagy regulation mechanism	References
p62/SQSTM1	Genomic instability	Regulation of proteasome-dependent degradation	[26]
Beclin-1	Tumor progression, poor prognosis	Essential for autophagosome formation	[29]
ULK1	Initiates autophagy, potential synergy with AMPK	Phosphorylation by AMPK promotes autophagosome formation	[35]
MiT/TFE transcription factors	Survival and proliferation	Reprogramming of lysosomal metabolism	[66]
Plac8	Survival under nutrient-deprived conditions	Enhancing of autophagosome-lysosome fusion	[66]
LC3	Supports tumor survival under nutrient deprivation	Facilitates autophagy activation via EGFR/MEK/ERK and HGF/c-MET/Akt/mTORC1/HIF-1α pathways	[67, 68]
Caprin-1	Tumor growth and immunosuppression	ULK1 activation	[69]
MHC-I	Immune evasion	Degradation through NBR1-dependent pathway	[71]
UGDH	Cell proliferation through hyaluronic acid synthesis	Degradation through p62-dependent pathway	[72]
ATG5	Correlates with poor prognosis, enhances autophagic flux	Key component of autophagosome elongation	[73]
IRGQ	An autophagy receptor regulating MHC-I quality control	Interacts with GABARAPL2 and LC3B	[74]

The table summarizes their roles, the autophagy regulation mechanisms involved, and the corresponding references that support these findings

and thus therapeutic strategies must be carefully designed to avoid unintended consequences, such as exacerbating immune suppression or enhancing alternative survival pathways. Future studies should explore combination therapies that inhibit autophagy alongside approaches that boost anti-tumor immunity, leveraging these insights to disrupt PDAC progression comprehensively.

In addition to deeply affect immune regulation, autophagy also profoundly influences metabolic adaptation and resilience in pancreatic cancer. Beyond supporting glycolysis and biosynthetic pathways under nutrient scarcity, autophagy allows cancer cells to circumvent therapeutic pressures through additional metabolic strategies. In this context, it has been reported that PDAC cells can adapt to autophagy inhibition by increasing hyaluronic acid (HA) synthesis via the enzyme UDP-glucose dehydrogenase (UGDH), promoting tumor growth even under compromised autophagic activity [72]. Moreover, emerging evidence reveals that ATG7, a key autophagy-related gene, contributes to PDAC progression through mechanisms that extend beyond its role in canonical autophagy. ATG7 hemizygosity enhances tumor progression by altering succinate metabolism, thereby promoting invasion and metastasis despite partially retained autophagic capacity [77]. These findings indicate that ATG7 serves as a multifunctional regulator of tumor progression, coupling metabolic alterations with invasive potential. Additionally, ATG5, another key autophagy-related gene, has been shown to be highly expressed in PDAC, correlating with poor prognosis and supporting tumor progression through enhanced autophagic flux [73]

It is important to mention that autophagy plays a pivotal role in maintaining glutamine metabolism, a critical factor for anaplerosis of the TCA cycle in pancreas cancer cells. Under metabolic stress, PDAC cells induce macropinocytosis-associated autophagy to sustain intracellular glutamine levels, ensuring continuous fueling of the TCA cycle and survival under nutrient-deprived conditions [13]. This dependency on glutamine metabolism offers another potential target for therapeutic intervention in this terrible disease.

The melanoma-associated antigen MAGEA6 provides a striking example of the temporal regulation of autophagy in PDAC. During the early stages of tumor development, MAGEA6 induction by epigenetic regulation suppresses autophagy, thereby promoting tumor growth. However, in later stages, MAGEA6 degradation facilitates the reactivation of autophagy, enabling the tumor to meet its heightened metabolic demands and adapt to stressors such as nutrient scarcity and immune surveillance. This dynamic shift in MAGEA6 expression underscores its role in early tumorigenesis as well as in the promotion of survival and progression in advanced disease [78].

5 PDAC and stroma fibrosis

A defining feature of PDAC is its dense, fibrotic stroma and nutrient-deprived, hypoxic environment, which together create a metabolic bottleneck for tumor cells [79]. To overcome these challenges, PDAC cells exploit autophagy as a key survival mechanism. This process sustains tumor cell metabolism by recycling intracellular components to generate essential nutrients, such as amino acids and lipids, that fuel anabolic processes and mitochondrial function [80]. For instance, recent findings have revealed that autophagy in PDAC maintains iron homeostasis by regulating the labile iron pool and mitochondrial activity, which are critical for sustaining energy production through the tricarboxylic acid (TCA) cycle[81]. Notably, cancer-associated fibroblasts (CAFs) within the PDAC stroma can provide bioavailable iron to cancer cells, further enhancing their resistance to autophagy inhibition therapies. This stromal-cancer interaction underscores the complexity of targeting autophagy in PDAC, as stromal contributions extend beyond iron homeostasis. In this context, it has been shown that pancreatic stellate cells (PSCs), others key stromal component, secrete alanine via autophagy, providing an alternative carbon source that fuels the TCA cycle and lipid biosynthesis in PDAC cells, reducing their reliance on scarce nutrients like glucose [82]. This metabolic interaction between stromal and cancer cells displays a broader network in which autophagy directly supports cancer cell survival and proliferation, further emphasizing the key role of autophagy in tumor dynamics. Consequently, the pro-tumorigenic functions of autophagy in PDAC—as a metabolic driver for both cancer cells and the stroma—pose significant challenges for therapeutic interventions. The capacity of autophagy to sustain PDAC under extreme metabolic stress, promote chemoresistance, and enable metabolic crosstalk between tumor and stromal cells makes it a critical target for therapy. However, its systemic importance in maintaining cellular homeostasis highlights the need for carefully designed strategies to selectively inhibit autophagy in cancer while minimizing adverse effects on normal tissues. Figure 2 illustrates how autophagy regulates the microenvironment in a pro-tumor manner in PDAC. It highlights mechanisms such as MHC-I degradation for immune evasion and interactions with stromal components, including PSCs and CAFs, which support PDAC metabolism and mitochondrial function.

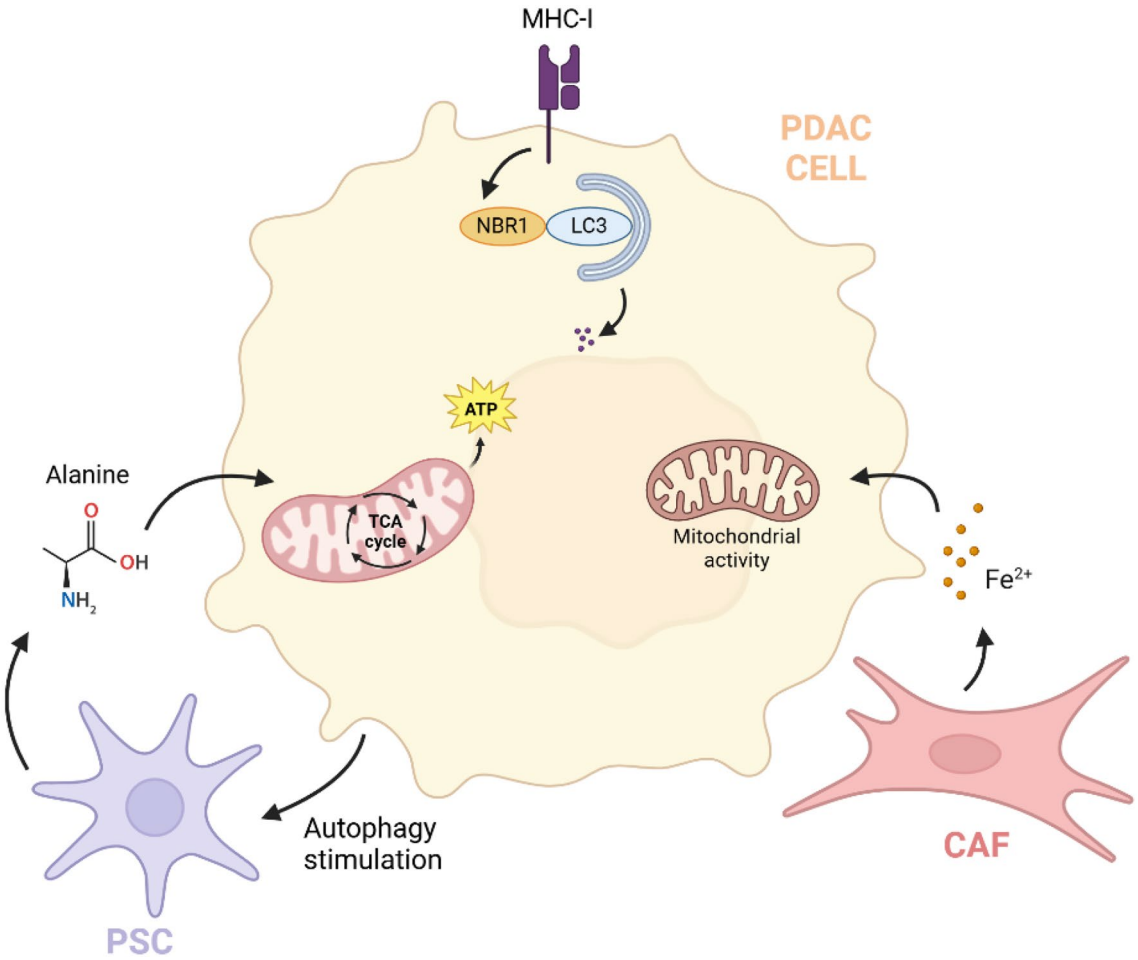

Fig. 2 Autophagy can regulate the microenvironment in a pro-tumor manner. PDAC cells can promote immune evasion by degrading MHC-I molecules via a NBR1-dependent autophagy pathway, reducing antigen presentation events. Furthermore, PDAC cells can interact with the stroma: they stimulate autophagy in pancreatic stellate cells (PSCs) inducing alanine secretion, which is important for tricarboxylic acid (TCA) cycle and lipid biosynthesis. In addition, cancer-associated fibroblasts (CAFs) can provide iron to PDAC cells; iron homeostasis is regulated by autophagy and contributes to the mitochondrial function

6 Innovative strategies to target autophagy in pancreatic cancer

6.1 Strategies based on nanomaterials

The integration of nanotechnology into pancreatic cancer treatment offers promising strategies to address one of the most aggressive and therapy-resistant cancers. Among these innovations, targeting autophagy, that represents a key survival mechanism for PDAC cells, has gained attention due to its critical roles in metabolic reprogramming, therapeutic resistance, and immune evasion. By exploiting this vulnerability, autophagy-modulating therapies aim to disrupt the tumor's adaptive mechanisms [83]. Nanoparticles present several unique advantages in this context. They enable precise drug delivery [84, 85], allow for the co-delivery of synergistic therapeutics [86–88], and facilitate penetration through the dense stromal barriers characteristic of PDAC [89–91]. These capabilities make nanoparticles highly suitable for enhancing the efficacy of autophagy-targeted treatments. Recent advancements demonstrate the potential of combining nanoparticles with autophagy-focused approaches to address key therapeutic challenges, including drug resistance, poor drug distribution, and tumor heterogeneity. Such innovations pave the way for more effective strategies in PDAC therapy.

Building on these developments, co-delivery strategies targeting autophagy-related pathways represent a transformative approach for PDAC therapy. Mesoporous silica nanoparticles that co-encapsulate palbociclib (a CDK4/6 inhibitor) and hydroxychloroquine (an autophagy inhibitor) have shown remarkable potential, achieving synergistic

efficacy in PDAC mouse models. This combination was observed to disrupt tumor growth and improving drug delivery within tumors, enabling both autophagy inhibition and cell cycle arrest. Notably, the addition of a Bcl inhibitor further enhanced therapeutic outcomes, illustrating the power of multi-targeted formulations to overcome PDAC's resistance to treatment [92]. Similarly, pH-responsive nanoparticles that co-deliver gemcitabine and chloroquine (CQ) have demonstrated superior results in combating PDAC progression and metastasis. These innovative "nanobombs" release CQ specifically in the acidic environment of the tumor, where it suppresses autophagy in cancer cells and neighboring support cells within the tumor microenvironment. This strategy is important as it amplifies the cytotoxic effects of gemcitabine and can alter the tumor-supportive environment, reducing proteins linked to metastasis, such as MMP-2 and paxillin, and decreasing fibrosis. These effects highlight the potential of such systems to disrupt both the tumor's growth and its ability to spread [93].

Expanding therapeutic possibilities for pancreatic cancer, RNA-based nanoparticles represent a groundbreaking approach to modulating autophagy while simultaneously addressing critical challenges such as drug resistance and tumor heterogeneity. Unlike traditional small-molecule inhibitors or chemotherapy agents, RNA-based nanoparticles leverage the specificity of gene-targeted interventions to directly regulate autophagy-associated pathways. This precision offers a complementary advantage to broader nanoparticle strategies, such as co-delivery systems, by addressing genetic drivers of therapeutic resistance.

For instance, chimeric peptide nanoparticles targeting plectin-1 have successfully delivered miR-9, a microRNA that downregulates eIF5A2, a key autophagy regulator. This approach inhibited autophagy, enhanced doxorubicin efficacy, and triggered significant apoptosis in PDAC models, demonstrating the utility of RNA-based platforms in fine-tuning cellular processes for therapeutic gain [94]. Similarly, nanoparticles delivering miR-212 achieved remarkable results by downregulating USP9X, another gene critical to autophagy regulation. This intervention not only improved sensitivity to doxorubicin but also induced substantial apoptosis in PDAC cells, further highlighting the potential of RNA-based therapeutics to enhance chemotherapeutic outcomes while minimizing off-target effects [95].

In addition to RNA-based nanoparticles, magnetic nanoparticles (MNPs) combined with hyperthermia (MH) have emerged as promising tools in pancreatic cancer therapy, offering unique advantages in modulating autophagy and overcoming dense stromal barriers. Magnetic hyperthermia uses alternating magnetic fields to heat tumor tissues selectively via MNPs, enhancing drug delivery and disrupting the stromal matrix [96–98]. Beyond its physical effects, MH has also been linked to the induction of autophagy-associated cell death in lung [99], and gastric cancer [100], sensitizing cells to chemotherapy.

Interestingly, functionalized MNPs, such as those conjugated with gemcitabine, have demonstrated a dual mechanism: (i) controlled drug release in the tumor's reductive microenvironment and (ii) localized heat generation through MH. This combination induces ROS production, autophagy activation, and enhances drug penetration, ultimately promoting significant tumor cell death [101]. Notably, recent work has shown that the cytotoxic response to magnetic hyperthermia using gemcitabine- and NucAnt-conjugated nanoparticles depends strongly on the intrinsic sensitivity of pancreatic cancer cells. Differences in ROS production and activation of stress pathways (such as ERK1/2 and JNK) determine treatment efficacy, enabling significant cell death at much lower drug doses in certain phenotypes [102]. Similarly, MH has demonstrated significant potential in cancer therapy by stimulating immune responses and reducing tumor cell viability. Specifically, optimized for nanoparticle biodistribution and magnetic field conditions, MH effectively raises localized tumor temperatures, disrupting cellular homeostasis and triggering the release of tumor antigens and danger-associated molecular patterns (DAMPs). This process activates immune cells, such as dendritic cells and cytotoxic T cells, while also inducing direct tumor cell death through thermal stress. These effects position standalone MH as a valuable partner to autophagy-targeted therapies, enhancing their efficacy by creating a more immunogenic and vulnerable tumor microenvironment [103]. Additional evidence indicates that hyperthermia can synergistically enhance the efficacy of conventional chemotherapeutics, including gemcitabine, 5-fluorouracil, and cisplatin in PDAC cell lines, reducing drug resistance and improving tumor cell kill [104]. Furthermore, triple-modal strategies that combine hyperthermia, radiation therapy, and chemotherapy have demonstrated promising survival benefits in unresectable locally advanced PDAC patients, highlighting the translational potential of hyperthermia-based approaches [105].

Recent advances also highlight the versatility of multicore magnetic nanoparticles, which exhibit enhanced heating properties in hyperthermia applications. By combining hyperthermia with functionalization of MNPs using chemotherapy drugs or tumor-suppressive microRNAs, researchers demonstrated a profound reduction in tumor cell viability across various cancer models, particularly in PDAC. Thus, these modified MNPs can improve drug delivery efficiency and leverage heat to potentiate anti-tumor activity, achieving optimal results in pancreatic cancer cells compared to other tumor types. Importantly, these effects were amplified when hyperthermia was combined with chemotherapy and

gene regulation, offering a highly personalized therapeutic strategy for aggressive cancers [106] Importantly, precise in vivo temperature modulation during hyperthermia, achieved through controlled field intensity adjustments, has paved the way for safer and more effective treatments, reducing risks associated with overheating or tissue damage [107]. Notably, the combination of gemcitabine-conjugated MNPs with hyperthermia revealed phenotype-dependent cytotoxicity in PDAC cell lines, allowing for significantly reduced drug doses to achieve therapeutic efficacy. This dual strategy minimizes systemic toxicity while maximizing localized tumor control, further highlighting the potential of MNPs as a targeted and efficient platform for PDAC therapy [102]. Together, these findings emphasize the promise of integrating hyperthermia with functionalized MNPs to enhance therapeutic outcomes in pancreatic cancer. In the clinical setting, MNP-based hyperthermia therapies represent a promising avenue for addressing the unique challenges of pancreatic cancer, particularly the dense tumor stroma that impedes drug delivery. Clinical trials involving this approach have already established the feasibility of using MNPs in combination with hyperthermia to treat solid tumors like glioblastoma and prostate cancer, paving the way for similar applications in PDAC [83] Thus, the ability of MH to selectively disrupt the extracellular matrix of PDAC tumors provides a critical advantage, enhancing the permeability of the stroma and allowing deeper penetration of chemotherapeutic agents. It is important to highlight that this localized heating approach could also directly induce tumor cell death while sparing surrounding healthy tissues, offering a safer alternative to traditional systemic therapies. Therefore, the integration of MNP-based hyperthermia with current chemotherapy regimens could address the therapeutic resistance typical of pancreatic cancer by improving drug delivery efficiency and synergistically amplifying cytotoxic effects. As ongoing clinical developments refine the application of MNPs, including optimizing magnetic field conditions and nanoparticle formulations, this technology holds substantial promise for translating into effective PDAC therapies tailored to improve patient outcomes.

Together, these findings position nanoparticles and hyperthermia as innovative and promising tools for pancreatic cancer therapy, leveraging their capacity to modulate autophagy, enhance drug delivery, and activate anti-tumor immune responses. However, several limitations remain [108]. The biodistribution of nanoparticles often results in off-target accumulation, raising concerns about systemic toxicity and reduced therapeutic efficacy [109]. Furthermore, achieving consistent tumor specificity is challenging due to the heterogeneity of PDAC tumors and the dense stromal barrier that limits nanoparticle penetration. To advance this promising platform, further optimization of nanoparticle formulations, including surface functionalization and targeting moieties, is necessary to improve their pharmacokinetic profiles[110]. Additionally, the scalability and reproducibility of nanoparticle synthesis must be addressed to ensure clinical feasibility and regulatory approval [111]. Addressing these challenges will be key to realizing the full potential of magnetic nanoparticles and hyperthermia in pancreatic cancer therapy.

7 Innovative therapies based on medicinal chemistry

In addition to nanoparticles, various metal-based coordination complexes have been explored for their ability to modulate autophagy in pancreatic cancer therapy. For instance, iron-based coordination trimers, for instance, have shown promise in enhancing gemcitabine's therapeutic effects by inducing oxidative stress, increasing ROS production, and downregulating the mTOR pathway—a critical regulator of autophagy and metabolism—thereby sensitizing PDAC cells to treatment [112]. Similarly, oxidovanadium (IV) complexes demonstrate selective cytotoxicity in PDAC cells by inducing ROS production, cell cycle arrest, and autophagy via the p53/p21 pathway. Although p53 is commonly mutated in PDAC, this autophagy induction may reflect a stress response that surpasses the cytoprotective capacity of autophagy, triggering autophagic cell death. Alternatively, oxidovanadium may engage residual wild-type p53 or p53-independent pathways, contributing to its cytotoxic effects [113]. In another study, terpyridine-metal complexes further illustrate this approach by generating oxidative stress, disrupting redox balance, and triggering autophagy-associated cell death alongside apoptosis in pancreatic cancer cells. Their selective toxicity and ability to alter key cellular pathways position them as promising candidates for anticancer therapy [114]. Moreover, platinum-based coordination complexes have shown efficacy in other cancers by modulating oxidative stress and pathways like MAPK, demonstrating mechanisms that could be explored in pancreatic cancer for inducing autophagy and enhancing tumor cell death [115]. Additionally, palladium (II) complexes have shown significant binding affinity with DNA and biomolecules, inducing autophagy and apoptosis selectively in pancreatic cancer cells, with reduced toxicity in normal cells [116]. Recent studies on metal complexes targeting MMPs have demonstrated that such compounds can regulate the expression and activity of MMP-2 and MMP-9—enzymes critically involved in extracellular matrix remodeling and tumor cell migration [117]. Although direct evidence in PDAC remains limited, these findings suggest

that metal-based coordination complexes may similarly modulate the stromal microenvironment, potentially reducing stromal rigidity and facilitating enhanced drug penetration and tumor cell death.

Collectively, these findings clearly underscore that the field of material science and coordination chemistry represent a transformative approach in pancreatic cancer therapy, particularly by leveraging the modulation of autophagy, a key adaptive mechanism that sustains PDAC survival under metabolic and therapeutic stress that is over exacerbated may lead cell death. The integration of nanoparticles, with their precision in drug delivery and ability to co-deliver synergistic agents, has unveiled new therapeutic paradigms that disrupt tumor resilience. Moreover, metal-based nanomaterials and coordination complexes add a novel dimension by inducing oxidative stress, altering redox balance, and downregulating pivotal pathways like mTOR and MAPK, thereby exploiting autophagy as both a target and a vulnerability. Additionally, these agents hold the promise of modifying the tumor microenvironment to overcome stromal barriers, facilitating enhanced drug penetration and ultimately improving therapeutic efficacy in PDAC. However, these findings also provoke a deeper question: could the selective induction of autophagy under controlled conditions be harnessed not just to enhance therapeutic efficacy but to drive tumor cells into a state of irreversible metabolic collapse? This possibility highlights the need for a nuanced understanding of autophagy's dual roles in cancer, where modulation—whether as suppression or hyperactivation—could represent a turning point in therapeutic strategies.

The integration of these technologies with emerging concepts in immunotherapy or multi-modal treatments could further enhance outcomes, suggesting that autophagy-modulating nanomaterials are not merely adjuncts but pivotal components in reprogramming the tumor microenvironment. These innovations demand a deliberate focus on scalability, clinical feasibility, and addressing off-target effects, as they hold the promise of reshaping pancreatic cancer treatment by turning the tumor's inherent adaptive mechanisms against itself.

8 Conclusions

These studies highlight autophagy as a critical defense mechanism against PDAC initiation, functioning at multiple levels to preserve cellular and tissue homeostasis. Autophagy suppresses key early tumorigenesis factors, such as oxidative stress and chronic inflammation, thereby reducing the risk of malignant transformation. Its role in systemic processes, including beta cell adaptation and inflammation control, underscores its importance in pancreatic health. However, impaired autophagy can promote a pro-tumorigenic environment, significantly elevating cancer risk in individuals predisposed to chronic pancreatitis or metabolic dysfunction. While autophagy's tumor-suppressive functions are clear, the exact molecular mechanisms remain incompletely defined, warranting further research to harness its protective potential effectively in preventive strategies. Conversely, autophagy also plays a pivotal role in PDAC progression by enhancing metabolic flexibility, enabling cancer cells to adapt to the harsh tumor microenvironment. It regulates pathways critical for tumor proliferation and metastasis, including hyaluronic acid synthesis, glutamine metabolism, and succinate balance, and contributes to immune evasion mechanisms, complicating therapeutic intervention. Targeting autophagy therapeutically is challenging due to its dual and context-dependent roles; preserving its early protective functions while inhibiting its tumor-promoting activities at later stages remains complex. Combining autophagy inhibition with complementary strategies, such as disrupting metabolic dependencies or immune evasion mechanisms, may effectively counter PDAC progression [118]. Exploiting heightened autophagic activity through chemotherapeutics that overstimulate autophagy beyond its protective threshold could selectively trigger cancer cell death [119]. The stage-specific role of mutant p53 in regulating autophagy—initially suppressive during early tumorigenesis and later supportive of tumor survival—further emphasizes the need for precision in therapeutic targeting. Agents like oxidovanadium exploit this duality to induce autophagy-mediated cancer cell death, but further studies are essential to optimize these approaches. Moreover, the intrinsic duality of autophagy—serving both as a survival mechanism and as a trigger for cell death when excessively activated—warrants a cautious, well-monitored approach to clinical translation, with further mechanistic studies needed to delineate and mitigate potential off-target effects.

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Declarations

Competing interests The authors declare no competing interests.

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