International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
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ARTICLE TITLE	RECENT ADVANCES IN AUTOPHAGY AND VESICLE TRAFFICKING IN PANCREATIC DISEASES: MOLECULAR MECHANISMS AND SELECTIVE AUTOPHAGY PATHWAYS
DOI	https://doi.org/10.31435/ijitss.3(51).2026.6327
RECEIVED	18 May 2026
ACCEPTED	07 August 2026
PUBLISHED	14 August 2026
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RECENT ADVANCES IN AUTOPHAGY AND VESICLE TRAFFICKING IN PANCREATIC DISEASES: MOLECULAR MECHANISMS AND SELECTIVE AUTOPHAGY PATHWAYS

Jakub Motor *(Corresponding Author, Email: oliwiermotor@gmail.com)*
Medical University of Łódź, al. Tadeusza Kościuszki 4, 90-419 Łódź, Poland
ORCID ID: 0009-0008-3769-0101

Michał Hajt
University Clinical Center of the Medical University of Warsaw, ul. Banacha 1A, 02-097 Warszawa, Poland
ORCID ID: 0009-0001-6558-0902

Dastin Misiaszek
University Clinical Center of the Medical University of Warsaw, ul. Banacha 1A, 02-097 Warszawa, Poland
ORCID ID: 0009-0000-6932-9515

Anna Wolszczak
Samodzielny Publiczny Szpital Kliniczny im. prof. W. Orłowskiego, Czerniakowska 231, 00-416 Warszawa, Poland
ORCID ID: 0009-0006-7348-1185

Alicja Graczyk
Szpital Bielański im. ks. Jerzego Popiełuszki, ul. Cegłowska 80, 01-809 Warszawa, Poland
ORCID ID: 0009-0002-8684-0846

Weronika Martynowska
Samodzielny Publiczny Szpital Kliniczny im. prof. W. Orłowskiego, Czerniakowska 231, 00-416 Warszawa, Poland
ORCID ID: 0009-0003-6403-6926

Piotr Ciecierski
District Medical Center in Grójec, Piotra Skargi 10, 05-600 Grójec, Poland
ORCID ID: 0009-0005-7225-7918

Natalia Grabowska
Specjalistyczny Szpital Wojewódzki w Ciechanowie, Powstańców Wielkopolskich 2, 06-400 Ciechanów, Poland
ORCID ID: 0009-0007-9797-4416

Zofia Parol
University Clinical Center of the Medical University of Warsaw, ul. Banacha 1A, 02-097 Warszawa, Poland
ORCID ID: 0009-0007-0885-2637

ABSTRACT

Autophagy is a key lysosome-dependent degradation pathway essential for maintaining cellular homeostasis, particularly in the highly secretory pancreas. This review summarizes recent advances in autophagy, selective autophagy, and vesicle trafficking in pancreatic physiology and disease. We focus on the dual role of autophagy, which can support cellular protection and organelle quality control, but also contribute to pathology when dysregulated. We highlight emerging molecular mechanisms linking autophagy with vesicle trafficking systems, including membrane remodeling, organelle contact sites, and key regulators such as VMP1 and Beclin-1. In addition, we discuss the role of autophagy in pancreatic inflammation and cancer, emphasizing its context-dependent function. Finally, we outline recent translational approaches targeting autophagy-related pathways, including pharmacological and genetic strategies, with potential diagnostic and therapeutic relevance in pancreatic diseases.

KEYWORDS

Autophagy; Pancreas; Vesicle Trafficking; Selective Autophagy; Cellular Homeostasis; Pancreatitis; Pancreatic Cancer

CITATION

Jakub Motor, Michał Hajt, Dastin Misiaszek, Anna Wolszczak, Alicja Graczyk, Weronika Martynowska, Piotr Ciecierski, Natalia Grabowska, Zofia Parol. (2026) Recent Advances in Autophagy and Vesicle Trafficking in Pancreatic Diseases: Molecular Mechanisms and Selective Autophagy Pathways. *International Journal of Innovative Technologies in Social Science*. 3(51). doi: 10.31435/ijitss.3(51).2026.6327

Introduction

Cellular homeostasis depends on continuous turnover of proteins and organelles mediated mainly by the ubiquitin–proteasome system and autophagy. Autophagy is a lysosome-dependent process responsible for degradation of cytoplasmic components, including protein aggregates and damaged organelles, and is particularly important in the pancreas due to its high secretory activity **(Zhang et al., 2020; Zhou et al., 2024)**.

Three types of autophagy are distinguished: microautophagy, chaperone-mediated autophagy, and macroautophagy, with the latter involving autophagosome formation and delivery of cargo to lysosomes **(Parzych KR et al., 2014)**.Autophagy is closely integrated with vesicle trafficking, which controls membrane transport through Rab GTPases, SNAREs, and tethering factors to ensure precise vesicle fusion and cargo delivery **(Cohen et al., 2018)**.

Together, autophagy and vesicle trafficking form a coordinated network essential for membrane homeostasis, and their dysregulation contributes to pancreatic diseases, including inflammation and cancer.

1.Mechanisms of Autophagy in Pancreatic Cells

Autophagy is a highly conserved intracellular degradation pathway that maintains cellular homeostasis by removing damaged organelles, misfolded proteins, and other cytoplasmic components. In the pancreas, autophagy operates in acinar, ductal, and endocrine cells, and its regulation is tightly linked to both physiological adaptation and pathological processes **(Zhou Z. et al., 2024)**.

Physiological Regulation of Autophagy

1.1 Energy Deficiency and Stress Response

Autophagy was initially described as a survival mechanism activated under nutrient deprivation, allowing cells to recycle intracellular components to sustain energy homeostasis **(Wang F. et al., 2020)**. In long-term fasting studies, autophagy is induced in multiple digestive organs, leading to significant reductions in pancreatic mass (>20%) **(Chediack et al., 2012)**. In pancreatic β cells, fasting enhances the expression of 9cRA protein, which activates FoxO1, reduces oxidative stress, promotes autophagy, and decreases DNA damage via Atg7 induction **(Yoo et al., 2023)**. Furthermore maternal malnutrition similarly influences fetal

pancreatic autophagy: low-protein diets during pregnancy enhance neonatal autophagy and trigger ER stress in β cells **(Yang et al., 2020)**.

Interestingly, hypoxia does not universally activate autophagy in pancreatic cells. In islet β cells, hypoxia elevates ROS and downregulates autophagy-related proteins, a process reversible by the antioxidant NAC, suggesting a context-dependent protective role of basal autophagy. Likewise, pancreatic stellate cells maintain energy homeostasis under hypoxia without increasing autophagic flux, indicating reliance on alternative metabolic adaptations **(Wu et al., 2022)**

1.2 Lysosomal Maintenance

Lysosomes are essential for autophagic degradation. Fusion of autophagosomes with lysosomes enables the breakdown of damaged organelles and protein aggregates. Lysosomal membrane damage is sensed and repaired by galectins such as Gal-3 and Gal-9, maintaining lysosomal integrity and supporting pancreatic autophagy **(Sudhakar et al., 2020)**. LAMP-2, a major lysosomal membrane protein, is critical for lysosome biogenesis and autophagic flux; its depletion impairs autophagy and contributes to pancreatic dysfunction. In pancreatic cancer, Gal-3 deficiency decreases LC3 levels, reflecting its role in tumor-associated autophagy regulation **(Mareninova et al., 2015) (Sudhakar et al., 2020)**

1.3 ER and Mitochondrial Homeostasis

Pancreatic acinar cells exhibit high protein synthesis rates, producing large quantities of digestive enzymes within the ER and Golgi apparatus. Disruption of ER function results in accumulation of misfolded proteins, triggering ER stress and activation of the unfolded protein response (UPR**) (Zhu et al., 2019)**. Persistent ER stress induces ER-phagy, a selective autophagy mechanism mediated by receptors such as CCPG1, which interacts with ATG8 family proteins and RB1CC1/FIP200 to degrade excess ER components, attenuate UPR signaling, and protect pancreatic function. When ER-phagy fails to restore homeostasis, apoptotic pathways may be triggered. **(Smith and Wilkinson, 2018a; Smith and Wilkinson, 2018b; Smith et al., 2018)**

Mitochondrial quality control in pancreatic cells is similarly maintained through mitophagy, which can proceed via PINK1-dependent or PINK1-independent mechanisms **(Zhao et al., 2020)**. In the PINK1-dependent pathway, dysfunctional mitochondria accumulate PINK1 on the outer membrane, which autophosphorylates and recruits Parkin, initiating ubiquitination of mitochondrial proteins and recruitment of autophagy receptors such as OPTN and NDP52. Feedback loops involving phosphorylated ubiquitin and ATG8 family proteins further regulate the process. However, basal mitophagy in most tissues appears largely PINK1-independent, with compensatory mechanisms particularly evident in pancreatic islets, highlighting tissue-specific regulation of mitochondrial autophagy. **(Zhou Z et al., 2024)(Padman et al., 2019)**

1.4 Autophagy Activation and Mechanistic Steps

Autophagy can be initiated under basal conditions or rapidly activated in response to cellular stressors such as nutrient deprivation, oxidative stress, ER stress, or pathological stimuli. Five key events define autophagy progression: (1) initiation, (2) nucleation and phagophore formation, (3) elongation and cargo encapsulation, (4) fusion of autophagosomes with lysosomes to form autolysosomes, and (5) degradation of cargo within autolysosomes. Experimental models demonstrate that inhibition of autophagy sensitizes pancreatic cells to injury, resulting in increased vacuolization, inflammation, and cellular damage, highlighting its protective role **(Xia L et al., 2020)(Kuo CJ et al., 2018).**

Autophagy Under Pathological Condition

Autophagy dysregulation is closely associated with pancreatic disease. In acinar cells, imbalances in autophagy can lead to oxidative stress, ER stress, zymogen accumulation, and cell death. Genetic studies confirm that loss or overactivation of autophagy exacerbates pancreatic injury. For instance, deficiencies in autophagy-related genes impair clearance of digestive enzymes and enhance susceptibility to pancreatitis, while proper autophagy limits enzyme-mediated damage and inflammation **(Wang Q. et al., 2022) (Zhou Z et al., 2024)**

In pancreatic β cells, autophagy contributes to maintenance of metabolic homeostasis and stress adaptation. ER stress induced by misfolded IAPP impairs autophagy, promoting β-cell dysfunction and diabetes progression. Controlled activation of autophagy, for example via VMP1–BECN1 interactions, can reduce oxidative stress, apoptosis, and ER stress, highlighting its therapeutic potential **(Zhou Z. et al., 2024)**. However, under severe or prolonged stress, excessive autophagy can exacerbate tissue injury, reflecting a context-dependent duality **(Xia L et al., 2020)**.

Although autophagy is critical in pancreatitis and pancreatic cancer, detailed discussion of its role in inflammation and tumor progression is provided in dedicated sections later in this work. Briefly, impaired autophagic flux contributes to accumulation of autophagosomes, pathological zymogen activation, and lysosomal dysfunction in pancreatitis **(Mareninova O. A. et al., 2020)**. In pancreatic cancer, autophagy can act as a tumor suppressor during early stages but may support tumor survival under stress in established disease, interacting with oncogenic Kras signaling and metabolic pathways **(Iovanna J. L. et al., 2017)**.

2.Selective Autophagy and Zymophagy:

Selective autophagy is a highly regulated intracellular degradation pathway that enables the targeted removal of specific cellular components, in contrast to non-selective autophagy. This process plays a fundamental role in maintaining cellular homeostasis, particularly under stress conditions, by ensuring the precise elimination of damaged or superfluous cellular constituents **(Vargas et al., 2023)**. Mechanistically, selective autophagy depends on efficient cargo recognition systems, which are frequently mediated by ubiquitination, allowing specific substrates to be marked for degradation. This process involves the recruitment of autophagy receptors, such as p62/SQSTM1 and NBR1, which act as molecular bridges by binding both ubiquitinated cargo and components of the autophagosomal membrane, particularly LC3 family proteins **(Kumar AV et al., 2022)**. In addition, interactions with core autophagy-related (ATG) proteins are essential for the formation and maturation of autophagosomes, thereby ensuring the specificity and efficiency of cargo sequestration and degradation **(Vargas et al., 2023)**.

Selective autophagy encompasses several specialized subtypes that target distinct cellular structures. These include:

1. mitophagy: responsible for the removal of damaged mitochondria
2. ER-phagy, which mediates the turnover of endoplasmic reticulum
3. aggrephagy, which eliminates protein aggregates
4. xenophagy, which targets invading pathogens.

Each of these pathways utilizes specific receptors and regulatory mechanisms, reflecting the versatility and adaptability of selective autophagy in response to diverse cellular challenges **(Germain et al., 2024)(Zhao Q et al., 2026)**. Functionally, selective autophagy is essential for maintaining cellular integrity through the quality control of organelles, the removal of misfolded or damaged proteins, and the adaptation to metabolic and environmental stress. By regulating these processes, selective autophagy contributes not only to physiological homeostasis but also to the modulation of disease states. Dysregulation of selective autophagy has been implicated in a wide range of pathological conditions, including cancer, neurodegenerative disorders, and metabolic diseases, highlighting its critical role in both health and disease **(Vargas et al., 2023)(Bharath LP et al., 2021)**.

Zymophagy - as a specialized form of selective autophagy in pancreatic acinar cells:

Zymophagy is a specialized subtype of selective autophagy primarily described in pancreatic acinar cells, where it functions as a protective mechanism under pathological conditions. This process is responsible for the recognition and sequestration of activated zymogen granules and the degradation of prematurely activated digestive enzymes, such as trypsin **(Wang Q. et al., 2022)(Vaccaro et al., 2022)**. Under physiological conditions, digestive enzymes are stored as inactive zymogens and are only activated in the intestine. However, during pathological states, such as pancreatitis, premature intracellular activation of these enzymes can lead to autodigestion of pancreatic tissue. Zymophagy acts as a cellular defense mechanism by selectively targeting enzyme-containing vesicles and delivering them to lysosomes for degradation, thereby limiting pancreatic injury **(Wang et al., 2019; Vaccaro et al., 2022)**.

At the molecular level, an early step in zymophagy involves the ubiquitination of zymogens. The E3 ubiquitin ligase TRIM33 has been shown to mediate the ubiquitin modification of trypsin, promoting the activation of zymophagy (Wang Q. et al., 2022). Following ubiquitination, trypsin interacts with vacuole membrane protein 1 (VMP1), a key regulator of autophagy initiation, and is subsequently sequestered to prevent enzymatic damage. VMP1 functions in coordination with BECN1/Beclin1 to orchestrate the execution of this pathway **(Vaccaro et al., 2008; Grasso et al., 2009; Wang S. et al., 2022).**

VMP1 was initially identified in rats with experimental acute pancreatitis and has since been extensively studied as a critical mediator of zymophagy. Under physiological conditions, VMP1 expression induces autophagy but does not trigger zymophagy or pancreatitis. Experimental evidence indicates that VMP1 is essential for autophagosome formation, as its knockdown inhibits autophagy induced by rapamycin or nutrient

starvation. In pathological contexts, such as acute pancreatitis, VMP1 undergoes relocalization from the basal region of acinar cells to areas enriched in zymogen granules). This redistribution is associated with the activation of zymophagy and contributes to the clearance of activated enzymes. **(Dusetti et al., 2002) (Vaccaro et al., 2008) (Grasso et al., 2011)**.

Functional studies further support the protective role of VMP1-mediated zymophagy. In pancreatic acinar-specific transgenic mice (ElaI-Vmp1), reduced inflammation and necrosis were observed following caerulein-induced pancreatitis compared to wild-type animals **(Grasso et al., 2011)**. In contrast, deletion of VMP1 in acinar cells leads to rapid tissue inflammation and impaired cellular responses to prematurely activated zymogens, resulting in pancreatic damage and pancreatitis. Notably, VMP1 deficiency induces inflammatory changes more rapidly than the deletion of other autophagy-related genes, such as Atg5 or Atg7, highlighting its critical and non-redundant role in this pathway **(Wang S. et al., 2022)**.

Collectively, these findings demonstrate that VMP1-mediated zymophagy represents an important protective mechanism in pancreatic acinar cells, facilitating the removal of activated zymogens and thereby preventing cellular damage, inflammation, and the progression of pancreatic disease **(Wang Q. et al., 2022; Vaccaro et al., 2022)**.

3. VMP1 and Autophagosome Formation:

Vacuole membrane protein 1 (VMP1) is an endoplasmic reticulum (ER)-resident multi-pass transmembrane protein that plays a central role in autophagy regulation and inter-organelle communication. VMP1 functions as a key regulator of membrane dynamics and autophagosome biogenesis, particularly under stress conditions associated with pathological states, including pancreatic diseases. VMP1 acts early in autophagosome formation by coordinating the assembly of core autophagic machinery at ER-derived membrane platforms. A critical aspect of this function is its direct interaction with Beclin-1 (BECN1), a central component of the class III phosphatidylinositol 3-kinase (PI3K) complex. Specifically, the C-terminal autophagy-related domain of VMP1 (VMP1-AtgD) binds to the BH3 domain of BECN1, enabling the recruitment and activation of the PI3K complex at the phagophore assembly site. This interaction promotes local production of phosphatidylinositol-3-phosphate (PI3P), which is essential for the recruitment of downstream autophagy factors, including ATG16L1 and LC3, thereby facilitating phagophore nucleation and expansion **(Molejon et al., 2013)**. Beyond initiation, VMP1 also regulates the structural dynamics of autophagosome formation sites. Autophagosome biogenesis occurs at specialized ER subdomains, such as omegasomes and mitochondria-associated membranes (MAM), where VMP1 transiently localizes. Importantly, VMP1 controls the dissociation of ER–isolation membrane contacts, a necessary step for proper autophagosome maturation. Loss of VMP1 leads to prolonged ER–membrane association, aberrant PI3P signaling, and impaired autophagic flux, indicating defects in later stages of autophagosome formation **(Zhao YG et al., 2017) (Calvo-Garrido J. et al., 2014)**

In addition to its role in autophagy, VMP1 functions as a broader regulator of membrane contact sites between the ER and other organelles. VMP1 deficiency results in excessive contacts between the ER and mitochondria, lipid droplets, and endosomes, suggesting that VMP1 acts as a negative regulator of membrane tethering. These alterations are associated with defects in organelle morphology, including mitochondrial swelling and cristae disruption, which further contribute to cellular dysfunction **(Zhao et al., 2017)**.

Mechanistically, VMP1 modulates these processes in part through regulation of calcium homeostasis at ER membranes. By influencing local Ca^{2+} dynamics, VMP1 facilitates membrane detachment and prevents excessive organelle coupling. Disruption of this regulatory mechanism leads to abnormal membrane contact persistence, affecting lipid exchange, organelle integrity, and vesicular trafficking pathways. The physiological relevance of these mechanisms has been confirmed in vivo using conditional knockout models. Neuron-specific deletion of VMP1 results in severe neurodegeneration, characterized by progressive motor deficits, loss of dopaminergic neurons, and accumulation of α-synuclein-positive inclusions. At the cellular level, VMP1 deficiency leads to impaired autophagic flux, evidenced by accumulation of LC3- and p62-positive structures and defective autophagosome–lysosome fusion. These phenotypes are accompanied by pronounced alterations in ER and mitochondrial morphology, highlighting the essential role of VMP1 in maintaining organelle homeostasis and proteostasis. **(Wang P. et al., 2021) (Wang P. et al., 2020)**

VMP1 plays a signicant role as a multifunctional regulator that integrates autophagy initiation with membrane remodeling and inter-organelle communication. Through its direct interaction with Beclin-1 and its role in controlling ER-associated membrane dynamics, VMP1 ensures proper autophagosome formation and maintains cellular homeostasis. In the context of pancreatic diseases, where autophagy and vesicle trafficking are tightly interconnected, VMP1 emerges as a critical molecular link between stress signaling, membrane remodeling, and selective autophagy pathways.

4. Vesicle Trafficking and Membrane Dynamics:

Recent studies increasingly demonstrate that autophagy is tightly integrated with intracellular vesicle trafficking systems, forming a coordinated network that regulates membrane remodeling, cargo delivery, and organelle homeostasis. At the molecular level, autophagosome biogenesis depends on dynamic contributions from multiple membrane sources, including the endoplasmic reticulum (ER), ER–Golgi intermediate compartment (ERGIC), endosomes, and recycling vesicles **(Mizushima N et al., 2020)**. Notably, ERGIC-derived membranes have been shown to support LC3 lipidation, directly linking early secretory pathway trafficking with autophagosome formation **(Ge et al., 2015)**. During the early stages of autophagy, phagophore nucleation occurs at specialized ER subdomains enriched in phosphatidylinositol-3-phosphate (PI3P), often referred to as omegasomes. The local production of PI3P by the class III PI3K complex is essential for the recruitment of downstream autophagy machinery and spatial organization of membrane assembly. Vesicle trafficking pathways ensure a continuous supply of membrane material required for phagophore expansion, highlighting the functional integration between canonical trafficking routes and autophagy **(Brier et al., 2019)**.

A key point of convergence between autophagy and vesicle trafficking is the regulation of membrane fusion events. Autophagosome maturation requires sequential fusion with endosomes and lysosomes, forming intermediate structures such as amphisomes **(Amaravadi et al., 2019)**. These processes are mediated by conserved trafficking regulators, including Rab GTPases and SNARE proteins, which coordinate vesicle docking and membrane fusion. This underscores that core components of vesicular transport machinery are repurposed to drive autophagic flux. **(Lamb et al., 2013)**.

Beyond vesicular transport, membrane contact sites (MCS) have emerged as critical platforms coordinating autophagy and inter-organelle communication. Contact sites between the ER and other organelles, including mitochondria and endosomes, facilitate lipid exchange and signaling required for autophagosome formation. These structures provide spatial organization for membrane remodeling and contribute to the regulation of autophagic membrane dynamics. **(Nascimbeni et al., 2017)** Importantly, lipid signaling plays a central role in integrating autophagy with vesicle trafficking. PI3P not only defines nascent autophagic membranes but also regulates endosomal trafficking and membrane identity. Dysregulation of PI3P turnover leads to aberrant membrane structures, persistent recruitment of autophagy-related proteins, and impaired autophagic flux, linking signaling defects with trafficking abnormalities **(Brier et al., 2019)**.

Disruption of the coordination between autophagy and vesicle trafficking pathways has been increasingly recognized as a major driver of cellular dysfunction. Impaired vesicle transport can block autophagosome–lysosome fusion, leading to accumulation of LC3- and p62-positive structures and defective cargo degradation. Conversely, defective autophagy feeds back on vesicular systems by altering endosomal maturation, Golgi organization, and secretory flux. These bidirectional interactions position autophagy as a central regulator of intracellular logistics rather than an isolated degradative pathway. **(Lamb et al., 2013) (Mizushima N et al., 2020)**

In highly secretory tissues such as the pancreas, the integration of autophagy with vesicle trafficking is particularly critical. Pancreatic acinar cells rely on tightly regulated membrane dynamics for efficient enzyme secretion, making them especially vulnerable to disruptions in these pathways. Dysregulation of autophagy–trafficking coordination contributes to impaired zymogen granule handling, accumulation of damaged organelles, and altered secretory processes. In acute pancreatitis, these defects are associated with vacuolization, ER stress, and defective degradation of intracellular components **(Zhang et al., 2024, Zhu et al., 2024**).

In pancreatic cancer, autophagy and vesicle trafficking are frequently reprogrammed to support tumor cell survival and metabolic adaptation. Enhanced autophagic activity sustains mitochondrial function and nutrient recycling, while coordinated trafficking pathways ensure efficient turnover of cellular components. This interconnected network represents a key adaptive mechanism in pancreatic ductal adenocarcinoma (PDAC) and highlights autophagy as a potential therapeutic target **(Ferretti GDS et al., 2024)**.

5. Autophagy and Inflammation in Pancreatitis:

The interplay between autophagy, inflammatory signaling, and immune cell activation represents a central axis in the initiation, amplification, and resolution of both acute and chronic pancreatitis. Contemporary evidence positions autophagy not merely as a degradative pathway but as a key regulator of sterile inflammation, linking intracellular stress responses with extracellular immune activation in pancreatic tissue injury. At the earliest stages of pancreatitis, acinar cell injury triggers the release of damage-associated molecular patterns (DAMPs), including mitochondrial DNA, HMGB1, and protease-activated signaling

molecules. These signals activate pattern recognition receptors (PRRs) on resident macrophages and infiltrating immune cells, initiating NF-κB-dependent transcriptional programs and inflammasome assembly. Importantly, impaired autophagy amplifies this response by failing to clear damaged mitochondria, thereby increasing ROS production and mitochondrial DAMP release, which are potent activators of the NLRP3 inflammasome. **(Gukovskaya AS et al., 2012) (Ding WX et al, 2024)**.

Recent mechanistic studies have further clarified that defective autophagic flux is a hallmark of both acute and chronic pancreatitis. In pancreatic acinar cells, genetic or functional disruption of autophagy-related genes (e.g., ATG5, ATG7, LAMP2) leads to accumulation of LC3- and p62-positive structures, defective lysosomal degradation, and enhanced trypsinogen activation, which collectively exacerbate inflammatory signaling and tissue injury. These defects also result in sustained ER stress and mitochondrial dysfunction, reinforcing inflammatory amplification loops within pancreatic tissue **(Zhang et al., 2024; Zhu et al., 2024)**.

A key molecular intersection between autophagy and inflammation is the regulation of inflammasome activity. Autophagy normally acts as a negative regulator of NLRP3 inflammasome activation by removing damaged mitochondria and degrading inflammasome components. However, once inflammasomes are activated, autophagy can paradoxically facilitate the secretion of IL-1β and IL-18, thereby contributing to propagation of inflammatory signaling under pathological conditions. This dual regulatory role underscores the context-dependent nature of autophagy in pancreatic inflammation **(Ding WX et al, 2024)**. In addition to intracellular effects, autophagy also modulates immune cell function within the pancreatic microenvironment. Macrophage polarization is strongly influenced by autophagic status: impaired autophagy promotes pro-inflammatory M1 macrophage infiltration, while dysregulated autophagy in adipose tissue macrophages has been shown to exacerbate systemic inflammation in severe pancreatitis models **(Ling et al., 2025).** Moreover, neutrophil recruitment and NET formation are also indirectly regulated by autophagy-dependent control of inflammatory cytokine release, further linking autophagy to innate immune activation in pancreatic injury **(Chen et al., 2025)**.

More recent reviews emphasize that mitophagy represents a particularly important protective mechanism in pancreatitis. By selectively removing damaged mitochondria, mitophagy limits ROS production, inflammasome activation, and acinar cell death. Conversely, impaired mitophagy contributes to persistent mitochondrial dysfunction and sustained inflammatory signaling, thereby worsening disease severity. Importantly, vesicle trafficking pathways are tightly integrated with autophagy-dependent inflammatory regulation. Disruption of autophagosome–lysosome fusion or endo-lysosomal trafficking leads to accumulation of dysfunctional autophagic vacuoles, which act as intracellular danger platforms sustaining inflammatory signaling. This highlights that autophagy-related membrane trafficking defects directly contribute to inflammatory amplification in pancreatitis rather than serving only as downstream consequences of cell injury.**(Zhu et al., 2024; Ding et al., 2024)**

6. Autophagy in Pancreatic Cancer:

Pancreatic ductal adenocarcinoma (PDAC), driven predominantly by oncogenic KRAS mutations, remains one of the most aggressive malignancies, with a 5-year survival rate of approximately 9% (Siegel et al., 2019). Its development is shaped by a complex interplay of genetic alterations, chronic inflammation, metabolic stress, and profound remodeling of intracellular degradation pathways, including autophagy **(Li et al., 2021)**. Autophagy exerts a context-dependent role during pancreatic tumorigenesis. In early stages, it functions as a tumor suppressor by maintaining cellular homeostasis, limiting oxidative stress, and preventing the accumulation of damaged organelles. Disruption of core autophagy genes such as ATG5 or ATG7, as well as lysosomal dysfunction (e.g., LAMP2 deficiency), leads to acinar cell degeneration, fibrosis, and chronic inflammation **(Gukovskaya et al., 2017)**. In particular, ATG7-deficient models exhibit impaired autophagic flux, increased endoplasmic reticulum stress, and enhanced acinar-to-ductal metaplasia (ADM), a precursor to pancreatic intraepithelial neoplasia (PanIN) and PDAC. These findings indicate that basal autophagy protects against inflammation-driven transformation. **(Antonucci et al., 2015)** As tumorigenesis progresses, autophagy becomes upregulated and functionally reprogrammed to support tumor growth. Increased autophagic activity has been observed in PanIN lesions, and PDAC cells rely on autophagy to sustain metabolic demands under nutrient-limited and hypoxic conditions. Autophagy supplies essential metabolites through lysosomal degradation, thereby maintaining mitochondrial function and cellular bioenergetics. This metabolic dependence is closely linked to oncogenic KRAS, which promotes autophagy to support anabolic growth and survival **(Yang et al., 2011)**. Selective autophagy pathways, particularly mitophagy, further contribute to tumor progression by preserving mitochondrial quality and limiting excessive reactive oxygen species (ROS)

production. Disruption of these processes leads to mitochondrial dysfunction and impaired tumor fitness, highlighting the importance of organelle-specific autophagy in PDAC biology **(Perera et al., 2015)**.

Autophagy also plays a critical role in shaping the inflammatory and immune landscape of PDAC. At early stages, impaired autophagy promotes inflammatory signaling through the accumulation of damaged mitochondria and activation of innate immune pathways. In contrast, in established tumors, autophagy contributes to immune modulation by regulating antigen presentation and cytokine signaling, thereby facilitating immune evasion and tumor persistence **(Li et al., 2021; Yamamoto et al., 2020)**. Importantly, autophagy is tightly integrated with vesicle trafficking and lysosomal function. Defects in autophagosome - lysosome fusion or endo-lysosomal dynamics lead to the accumulation of autophagic intermediates and altered signaling outputs, linking membrane trafficking defects with tumor-promoting processes **(Mizushima N et al., 2020).**

In summary, autophagy plays a dual and stage-dependent role in PDAC, acting as a tumor-suppressive mechanism during early disease while supporting metabolic adaptation, mitochondrial homeostasis, and immune modulation in advanced cancer.

7.Translational and Therapeutic Perspectives:

Autophagy has emerged as a clinically relevant target in pancreatic diseases due to its central role in regulating cellular metabolism, stress adaptation, and organelle homeostasis. Translational research in this field increasingly focuses on three main areas: pharmacological modulation, genetic targeting, and biomarker development. In pancreatic ductal adenocarcinoma (PDAC), elevated basal autophagy supports tumor growth by sustaining mitochondrial metabolism and enabling survival under nutrient-limited conditions, making autophagy inhibition a promising therapeutic strategy **(Yang et al., 2011, Zhou et al., 2024)**. Pharmacologically, the most advanced approaches involve lysosomal inhibitors such as chloroquine (CQ) and hydroxychloroquine (HCQ), which block autophagic flux and have been evaluated in clinical trials in combination with chemotherapy **(Wolpin et al., 2014)**. However, their limited specificity has driven the development of more selective agents targeting early stages of autophagy, including ULK1 and the class III PI3K complex (VPS34), which regulate autophagy initiation and membrane nucleation. Importantly, therapeutic stress itself can induce cytoprotective autophagy, and its inhibition has been shown to sensitize tumor cells to conventional treatments, supporting combination strategies **(Kocaturk NM et al., 2018)**.

At the diagnostic level, autophagy-related proteins such as LC3-II and p62/SQSTM1 are widely used as markers of autophagic flux, while emerging evidence suggests that autophagy-associated gene signatures may serve as biomarkers of disease progression and therapeutic response in PDAC **(Li et al., 2021)**. Given the close integration of autophagy with vesicle trafficking and lysosomal function, components of these pathways are also being explored as complementary biomarkers. Overall, autophagy represents a promising but complex therapeutic target in pancreatic diseases. Its effective clinical exploitation will require precise, context-dependent strategies that integrate pharmacological inhibition, genetic insights, and biomarker-guided patient stratification.

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