Therapeutic Implications of Targeted Cancer for Autophagy Modulation by RNA-Binding Proteins and Mitochondrial Genes in Tumor Pathogenesis

Qintao Li*

[1]Southern University of Science and Technology, School of Biological Sciences, ShenZhen, China

*Corresponding author. Email: liqintao666@gmail.com

Abstract. Autophagy is a highly conserved lysosomal degradation pathway that plays a crucial and multifaceted role in maintaining cellular homeostasis. It is a process by which cells sequester damaged organelles, misfolded proteins, and other cytoplasmic components within double-membraned autophagosomes. This review explores how neurodegenerative disease-associated genes (hnRNPA1, hnRNPA2B1, CHCHD10, DAO, Pfn1), originally linked to autophagy dysregulation in neurons, critically influence autophagy in cancers. We present evidence showing that these genes modulate autophagic flux via LC3-II/LC3-I ratio and p62/SQSTM1 dynamics in a tissue-specific manner. In glioblastoma, hnRNPA1 knockdown inhibits autophagosome maturation, exacerbating chemoresistance; in breast cancer, CHCHD10 mutations disrupt mitochondrial turnover, driving metastasis. Conversely, DAO knockout elevates autophagy, suppressing hepatocellular carcinoma growth. We further discuss therapeutic strategies targeting these pathways, including CRISPR-based gene editing and small-molecule inhibitors. This mechanistic convergence between neurodegeneration and oncology highlights novel targets for precision cancer therapy.

Keywords: Autophagy, cancer, RNA-binding proteins, mitochondrial genes, targeted therapy

1 Introduction

Autophagy constitutes a fundamental cellular process essential for cellular homeostasis, involving the sequestration of damaged organelles, misfolded proteins, and cytoplasmic components within double-membraned autophagosomes. These structures subsequently fuse with lysosomes, enabling enzymatic degradation and recycling of macromolecules[1]. Key molecular markers facilitate autophagy monitoring: (i) LC3-I to LC3-II conversion, where LC3-II incorporation into autophagosomal membranes indicates autophagosome formation, and (ii) p62/SQSTM1 degradation, whose accumulation signifies impaired autophagic flux [1]. The functional duality of autophagy in disease pathogenesis is increasingly evident. In neurodegenerative disorders like

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amyotrophic lateral sclerosis (ALS), impaired autophagy promotes toxic protein aggregation and neuronal death [2]. Conversely, in cancer, autophagy exhibits context-dependent roles: during tumor initiation, it suppresses carcinogenesis by eliminating oncogenic protein aggregates; in established or metastatic tumors, it sustains cancer cell survival under metabolic stress (e.g., hypoxia, nutrient deprivation) and confers therapy resistance [3].

Recent research reveals an unexpected mechanistic link: genes primarily associated with neurodegeneration (hnRNPA1, hnRNPA2B1, CHCHD10, DAO, Pfn1) critically regulate autophagy in cancers. These genes modulate autophagic flux through shared molecular pathways yet elicit tissue-specific effects, presenting novel targets for therapeutic intervention (Tissue-specific autophagy responses to gene modulation are shown in Table 1). This review synthesizes current evidence on how neurodegeneration-associated genes govern autophagy in tumor pathogenesis and discusses emerging strategies for targeted cancer therapy.

2 Mechanistic Convergence

2.1 hnRNPA1 and hnRNPA2B1: RNA-Binding Proteins Orchestrating Autophagic Flux

hnRNPA1 and hnRNPA2B1 are part of the cell's "splicing machinery"—they help process RNA to make proteins. But they also do something else: they stabilize the genetic instructions (mRNA) for autophagy-related genes like ATG5 and BECN1, which are critical for starting autophagy [4]. In cancer, their roles depend on where the tumor is. In glioblastoma (a type of brain cancer), if hnRNPA1 is removed, the LC3-II/LC3-I ratio drops by 60%. This gums up the autophagy process, making tumor cells resistant to temozolomide, a common chemotherapy drug. Without proper autophagy, the drug can't trigger cell death [5]. In breast cancer, too much hnRNPA2B1 causes problems. It stabilizes the mRNA for HIF-1α—a protein that thrives in low-oxygen conditions—ramping up autophagy. This extra autophagy helps cancer cells spread to other parts of the body [6].

2.2 CHCHD10: Keeping Mitochondria in Check

Mitochondria are the cell's powerhouses, but when they break down, they release harmful substances. CHCHD10 is a protein that keeps mitochondria healthy by maintaining their structure and helping the cell clear out damaged ones through a process called mitophagy (a specialized form of autophagy controlled by the PINK1/Parkin pathway) [7].

In ovarian cancer, mutations in CHCHD10—like the G66V mutation—throw this system off. Damaged mitochondria build up, leaking reactive oxygen species (ROS) that damage DNA. Over time, this genetic chaos helps tumors grow and resist drugs like cisplatin [8].

2.3 DAO: A Metabolic Switch for Autophagy

DAO (D-amino acid oxidase) is best known for breaking down D-serine, a molecule that affects brain cell activity. In the brain, it regulates autophagy by controlling D-serine levels [9]. But in liver cancer, it plays a different role: when DAO is missing, autophagy revs up—specifically, the LC3-II/LC3-I ratio jumps by 1.8 times. This extra autophagy targets and breaks down c-Myc, a protein that drives cancer growth, slowing the tumor [10].

2.4 Pfn1: Moving Autophagosomes Where They Need to Go

Pfn1 (profilin-1) helps shape the cell's internal "skeleton" made of actin, which is crucial for moving things around inside the cell—including autophagosomes. For autophagy to finish, autophagosomes need to merge with lysosomes, and Pfn1 helps this happen. Mutations like E117G mess up this actin-based movement, stopping the merge [11]. In pancreatic cancer, losing Pfn1 puts the brakes on autophagy. This actually helps: without autophagy to rescue them, cancer cells become more sensitive to gemcitabine, a key chemotherapy drug [12].

Table 1. Tissue-Specific Autophagy Responses to Gene Modulation

Gene	Tumor Type	Autophagy Change	Functional Outcome
hnRNPA1 KD	Glioblastoma	↓ LC3-II/I;↑ p62	Chemoresistance
hnRNPA2B1 OE	Breast cancer	↑ Autophagic flux	Metastasis promotion
CHCHD10 Mut	Ovarian cancer	Impaired mitophagy	Cisplatin resistance
DAO KO	Hepatocellular carcinoma	↑LC3-II/I	Tumor suppression

3 Tissue-Specific Autophagy in Tumors

3.1 Brain Tumors vs. Cancers Elsewhere

Glioblastoma, a brain tumor, survives in a tough environment—there's not much oxygen or nutrients. To cope, it relies on constant, baseline autophagy to recycle materials. But if hnRNPA1 is missing, autophagy slows, and p62 builds up. This p62 clumps with other proteins, creating harmful aggregates that fuel tumor growth [5].

In breast or liver cancer, things are more variable. For example, different versions (isoforms) of hnRNPA2B1 in breast cancer or DAO in liver cancer can either speed up or slow down autophagy, depending on the tissue [6, 10].

3.2 Autophagy Shifts with Tumor Stage

Autophagy's role changes as a tumor progresses. Early on, in liver cancer, DAO-driven autophagy keeps tumors in check by breaking down Nrf2, a protein that helps cancer cells survive stress [10].When tumors start to spread (metastasize), CHCHD10 problems take center stage. Damaged mitochondria leak DNA, which triggers the cGAS-STING pathway—a signal that ramps up autophagy to help cancer cells survive the journey to new tissues [13].

4 Targeting Autophagy for Cancer Therapy

4.1 Editing Genes to Fix Autophagy

CRISPR-Cas9, a gene-editing tool, can tweak autophagy genes to fight cancer. In glioblastoma, turning up hnRNPA1 levels with CRISPR "activation" (CRISPRa) restores autophagy, making tumors sensitive to temozolomide again[14].Another approach uses RNA interference (RNAi) to quiet genes. In lung cancer, silencing DAO with short hairpin RNA (shRNA) slows down protective autophagy, making tumors more vulnerable to immunotherapy drugs that block PD-1 [15].

4.2 Small Molecules to Tune Autophagy

Drugs that target specific proteins are also in the works. Proflinide compounds block mutant Pfn1 from clinging to actin, letting autophagosomes merge with lysosomes again [11]. Mito-CP conjugates stabilize faulty CHCHD10 in ovarian cancer, fixing mitochondrial health and boosting mitophagy [8].

4.3 Combinatorial Strategies

Exploiting autophagy modulation to enhance other therapies holds significant potential:

Overcoming Chemoresistance: Combining autophagy inhibitors (CQ/HCQ) or targeted agents (like PFN1i) with chemotherapy (e.g., gemcitabine in PDAC) exploits cancer cell dependency on autophagy under treatment stress [3, 12].

Enhancing Immunotherapy: Silencing DAO or inhibiting protective autophagy primes tumor cells for immune recognition. This augments the efficacy of immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1) by reducing autophagy-mediated antigen masking and T-cell exhaustion [15].

Targeting Metabolic Vulnerabilities: Inducers of mitochondrial stress (e.g., complex I inhibitors) combined with CHCHD10 stabilizers (Mito-CP) or mitophagy modulators could exploit mitochondrial dysfunction in specific cancers [8].

5 Challenges and Perspectives

5.1 Delivery and Specificity Hurdles

Delivering therapies to tumors is tricky, especially in the brain. For example, nanoparticles carrying siRNA to target hnRNPA1 in glioblastoma need to get through the blood-brain barrier. Researchers are trying to coat these nanoparticles with molecules that "trick" the barrier into letting them pass, or using focused ultrasound to temporarily open the barrier [14]. To know if therapies are working, doctors need to track autophagy in living tumors. FRET biosensors—proteins tagged with glowing markers like GFP and RFP—can help. In autophagosomes, both markers glow, but in lysosomes, GFP fades, leaving RFP. The ratio of red to green light shows how well autophagy is working. Imaging tools like intravital microscopy let scientists watch this in real time [16]. Autophagy doesn't work alone, so combining treatments might be more effective. For example, DAO inhibitors could team up with immunotherapy: by slowing protective autophagy, they make cancer cells easier for the immune system to spot and attack [15]. Similarly, blocking autophagy with drugs like chloroquine might make chemotherapy more powerful in advanced tumors[3].

5.2 Monitoring Autophagic Flux In Vivo

Accurate assessment of autophagy modulation in vivo is essential for treatment guidance. Genetically encoded sensors (e.g., GFP-LC3-RFP) enable real-time visualization. Upon autophagosome formation, both fluorophores fluoresce; after lysosomal fusion and acidification, GFP is quenched while RFP persists. The RFP/GFP ratio quantifies autophagic flux. Intravital Microscopy allows longitudinal, real-time imaging of autophagy dynamics within living tumors using fluorescent reporters (e.g., LC3-GFP, mCherry-p62) [16].Non-Invasive Imaging (Clinical Translation): Developing PET tracers targeting LC3, p62, or lysosomal components is an active area of research to monitor autophagy in patients.

5.3 Addressing Context Dependence and Resistance

The dual role of autophagy demands sophisticated patient stratification and combination design. Identifying predictive biomarkers is crucial to select patients most likely to benefit from specific autophagy-targeting strategies. Multi-omic analyses (genomics, transcriptomics, proteomics) of tumors will refine this stratification. Tumors may activate compensatory survival pathways (e.g., alternative protein degradation like ubiquitin-proteasome system, metabolic rewiring) upon autophagy inhibition. Sequential or adaptive therapy regimens, and combinations targeting multiple vulnerabilities simultaneously, will be key. Leveraging the Neurodegeneration-Cancer Nexus: Further exploration of shared mechanisms (e.g., stress granule dynamics regulated by hnRNPs, mitochondrial quality control pathways like PINK1/Parkin beyond CHCHD10) will uncover novel targets and deepen understanding of context specificity.

5.4 Clinical Trial Considerations

Future trials should incorporate: Robust PD Biomarkers: Mandating pre- and post-treatment tumor biopsies (or advanced imaging/liquid biopsies) to confirm target engagement and modulation of autophagic flux.

Rational Combinations: Prioritizing combinations based on strong preclinical synergy and mechanistic understanding (e.g., DAO silencing + anti-PD-1).

Patient Selection: Enriching trials using molecular biomarkers predictive of autophagy dependency or specific pathway dysregulation (e.g., CHCHD10 mutations, high HIF-1α/hnRNPA2B1 in hypoxic tumors).

Monitoring Metabolic Adaptation: Tracking tumor metabolism (e.g., via FDG-PET or hyperpolarized MRI) alongside autophagy modulation.

6 Conclusion

The discovery that key genes implicated in neurodegenerative pathologies (hnRNPA1, hnRNPA2B1, CHCHD10, DAO, Pfn1) critically regulate autophagy in cancer represents a paradigm shift in understanding tumor pathogenesis. These genes exert profound, yet highly tissue-specific and stage-dependent, effects on autophagic flux—influencing processes ranging from chemoresistance in glioblastoma to metastatic progression in breast cancer and mitochondrial genome instability in ovarian cancer. This mechanistic convergence between neurodegeneration and oncology unveils a rich landscape of novel therapeutic targets. Strategies leveraging CRISPR-based gene editing, RNAi, and small molecules (Proflinide compounds, Mito-CP) offer promising avenues to normalize dysregulated autophagy for therapeutic benefit. Success, however, hinges on resolving critical translational challenges: developing sophisticated delivery systems capable of penetrating biological barriers like the BBB; creating reliable methods for real-time monitoring of autophagic flux in patients; and designing rational combinatorial regimens that account for the dynamic, context-dependent nature of autophagy in tumors.

Future research must prioritize the identification of robust predictive biomarkers to guide patient selection and the implementation of longitudinal monitoring strategies within clinical trials. Despite the challenges, exploiting the shared autophagy regulatory machinery between neurodegeneration and cancer holds immense potential for ushering in a new era of precision oncology, where therapies are tailored not only to the tumor type but also to its specific autophagic dependencies and stage of progression.

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