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Autophagy-Related Gene Expression Changes Are Found in Pancreatic Cancer and Neurodegenerative Diseases

Doaa M. Ali and Martin R. Berger

Abstract

Genetic alterations can cause cancer, including pancreatic cancer (PC) as well as certain neurodegenerative diseases. Our lab has recently identified genes that are modulated during pancreatic cancer liver metastasis, and some are known to have a role in neurobiology or neurodegenerative diseases. Autophagy or self-eating portrays the lysosomal-dependent degradation and recycling of protein aggregates and defective organisms in eukaryotic cells. Deregulation of autophagy as a cellular mechanism is common in neurodegenerative diseases as well as cancer and may represent a platform by which some genes can affect both disorders. This is exemplified for optineurin, which is an autophagy receptor that was found among genes with intensive modulation of expression in PC liver metastasis. Our results on this autophagy receptor draw the attention to the expression status of this and other autophagy genes in pancreatic cancer progression.

Keywords: pancreatic cancer, nervous system, neurodegenerative diseases, autophagy, optineurin

1. Introduction

Recent findings from microarray analyses of cancer cells have shown a growing list of genes with modulated expression, which are known to have importance in diseases other than cancer. This is in particular true for genes or gene families that have been identified to play a role in some neurodegenerative diseases or are a factor in cells of the nervous system, which may have a controlling role on the growth and development of cancer in general and of pancreatic cancer in particular. One cellular property, the alteration of which seems to be related to both types of diseases, is autophagy. In the lines below, we will discuss whether deregulation of autophagy could be a mechanism, which is in common between certain neurodegenerative diseases and pancreatic cancer, and thus may represent a link between two extremely different diseases.

2. Disrupted autophagy links cancer and neurodegenerative diseases

Autophagy is a Greek term that means self-eating and it portrays the lysosomal-dependent way of degrading and recycling cytosolic components in eukaryotic

cells. Autophagy is categorized into three different types, that is, microautophagy, macroautophagy, and chaperone-mediated autophagy (**Figure 1**), which are different in terms of their cargo and the mechanism of their occurrence [1, 2].

Micro-autophagy refers to the process where minute parts of the cytoplasm become sequestered and later on completely engulfed by lysosomal invaginations [3].

Chaperone-mediated autophagy is a selective pathway of autophagy, where proteins are targeted by the presence of a pentapeptide motif in the amino acid sequence of the substrate proteins, which is recognized by a chaperone protein. This complex is then delivered to the lysosomes for degradation in a receptor-dependent manner [2]. The motif should be accessible to the chaperone protein regardless of its position in the protein, but under normal conditions, it is concealed within the core when the protein is appropriately folded. Substrates for CMA are recognized by chaperones as heat shock cognate protein of 70 kD (hsp70) and cochaperones, which may be responsible for the unfolding of the protein before substrate-chaperone interaction can take place, but without direct interactions in some cases. Cochaperones include proteins PINK as hsp90, hsp40, and Bcl-2-associated athanogene 2 (Bag-1). Then, the substrates bind to the cytosolic tail of lysosome-associated membrane protein type 2A (LAMP-2A) and through its multimerization are translocated toward the lysosomal lumen, and this is seen as a limiting step for the pathway [2, 4, 5].

Macroautophagy, referred to below as autophagy, is the most widely investigated type of autophagy and entails the formation of what is called an autophagosome, which is a double membrane structure that is used to deliver cargos later through fusion to lysosomes or endosomes [6]. It is formed through several chronological steps starting from nucleation, elongation, to closure of a phagophore or isolation membrane that leads to the autophagosome formation. Proteins responsible to drive the autophagy process were basically discovered through analyzing the yeast genome and are named autophagy-related (ATG) proteins [6, 7].

Once stimulated, the autophagic process starts with the assembly of the initiation complex (ULK1 complex) and the nucleation complex (BECN1 complex) at the phagophore assembly site and this forms the basis for recruiting other ATG proteins and the elongation of the phagophore membrane [1]. ATG8/LC3 becomes bound to the inner and outer membrane of the phagophore following cleavage by the ATG4 protease and following conjugation to phosphatidylethanolamine (PE). Before

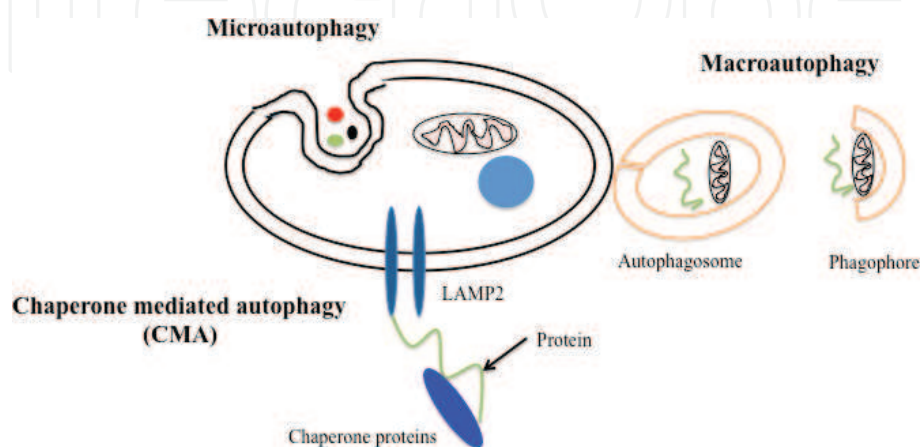


Figure 1.

Schematic representation of the three different types of autophagy showing the underlying difference in the mechanisms, microautophagy by invaginations of the lysosomes, macroautophagy through the formation of autophagosomes, and CMA with the targeted protein recognized by chaperones and delivered to the lysosomes through the LAMP2 protein.

closure, all ATGs dissociate and are recycled except for ATG8/LC3, which is located on the outer membrane. This protein is recycled after closure with the assistance of ATG4, while lysosomal enzymes in the autophagosome lumen degrade the ATG8/LC3 attached to the inner membrane.

Autophagosomes later unite with late endosomes and lysosomes to proceed for degradation [1]. LAMP proteins again control the fusion step and protect against degradation of the lysosomal membrane [1, 8].

Autophagy can be either selective or nonselective. During the selective process, specific cargos as aggregated proteins, damaged mitochondria, excess peroxisomes, and invading pathogens undergo degradation after being recognized via autophagy receptors. These autophagy receptors have the ability to recognize degradation signals on cargo proteins and also bind LC3/GABARAP proteins on the forming autophagosome. Among the identified autophagy receptors are p62/SQSTM1 (p62/Sequestosome 1), OPTN (optineurin), NBR1 (neighbor of BRCA1), and NDP52 (nuclear dot protein 52 kDa). All of them possess an ubiquitin-binding domain and LC3-interacting regions (LIRs) [9, 10].

Autophagy is a highly conserved process in mammals and is strictly regulated. One of the major regulators is mTOR through its complex 1 (mTORC1) and its activation exerts an inhibitory effect on autophagy induction. A similar effect is shown with PI3 kinases class I, whereas PI3 kinase class III activity is required for autophagosome formation. Starvation and amino acid depletion result in stimulation of the process. Other regulatory and autophagy inducers are based on an increase in cytosolic calcium, inhibition of inositol triphosphate, or starvation-induced autophagy [6, 11, 12]. Starvation also positively regulates autophagy by activation of AMPK that directly phosphorylates ULK1 or by inhibition of mTORC1 activity, or through inhibitory phosphorylation of nonautophagic BECN1 complexes [1]. Oxidative stress [13], DNA damage [14], and hypoxia [15] are all among the cellular mechanisms that can induce autophagy.

Autophagy has several cellular functions; it provides nutrients, eliminates damaged proteins and organelles, combats against invading microorganisms/pathogens, and in general keeps the homeostasis and balance in cells [1]. Because of its important role and significant cellular implications, defects or deregulation of this process was detected in different human diseases [1]. Infections and pathogens modulate autophagy according to their requirements to secure their survival in host cells. Certain steps of autophagy are hindered in neurodegenerative disorders and proteinopathies are a feature of these disorders. Autophagy is cytoprotective in cardiovascular tissue under physiological conditions, but it is induced in many cardiovascular diseases and is also deregulated in cancer, diabetes, and immune disorders [1].

2.1. Role of autophagy in cancer

In cancer, autophagy can either inhibit or promote cancer development and progression, and this varies according to the genetic lesions, tumor type, and stage. Combating mutagenic reactive oxygen species (ROS) accumulation, DNA damage, genomic instability, and oncogenic proteins are part of the protective functions of autophagy against tumor induction, as they induce autophagy when initiated [16, 17].

With regard to its onco-stimulatory role, downregulation of some autophagy-related genes, as Beclin-1 or ATG5, results in reduced growth of metastatic carcinoma cell lines, while that of ATG7 will promote apoptosis of colon cancer cells. Autophagy also permits tumors to resist stress and apoptotic signals and is connected in advanced cancer to poor prognosis and invasiveness. It increases ATP levels that support cell survival during hypoxia and starvation. Thus,

autophagy keeps healthy cells away from malignant transformation through maintaining the cellular homeostasis, but after tumor establishment, it may result in increased tumor progression and invasiveness [16, 17]. Autophagy supports tumor development through improving resistance of cells to endogenous apoptotic signals as well as resistance to chemotherapy and maintains the cancer stem cell compartment [17].

Pancreatic tumors show an elevated level of basal autophagy, more than any other epithelial cancer. The role of autophagy in PDAC needs to be clarified; as some investigations and the effect of anticancer drugs that generate ROS and induce autophagy give rise to the idea that autophagy is protective against cancer and stimulates apoptotic cancer cell death following treatment [18]. On the other hand, a number of reports suggested the role of autophagy in PDAC development. Autophagy was anticipated to be the cellular mechanism responsible for cancer development and progression from pancreatitis to overt carcinogenesis in the presence of K-ras mutations. Different observations supported a harmful role of autophagy, as being strongly induced in the inflammatory process. Inhibition of tumor development was observed after using the autophagy inhibitor chloroquine. Finally, LC3 is overexpressed in pancreatic cancer and downregulation of autophagy genes significantly reduces the growth and colony formation of PDAC cells in vitro [19, 20].

2.2. Role of autophagy in neurodegenerative diseases

Autophagic removal of proteins and damaged organelles is vital for the appropriate function of neurons, not only under pathological conditions, but also at baseline level under normal circumstances, as denoted by some studies [21].

Autophagosomes are very rarely detected in healthy neurons owing to the fact that the brain has a very low level of basal autophagy, or because the robust efficiency of the autophagy processes prevents the autophagosomes from accumulation [21, 22].

Dysfunction in autophagy affects the neuronal function and results in the occurrence of neurodegenerative diseases [23].

Induction of autophagy was anticipated to be an early stress response in axonal dystrophy and to contribute to axon remodeling [24]. Autophagy was shown to play a role in controlling microtubule dynamics and axon regeneration. Autophagy induction encouraged neurite growth, lessened the inhibitory effects of myelin, and reduced the formation of retraction bulbs after axonal injury in cultured cortical neurons [25].

Neurodegeneration is associated with deterioration of cognitive capabilities as well as motor functions with progressive damage to the nerve structure and functions. Alzheimer's, Parkinson's, amyotrophic lateral sclerosis, and Huntington's diseases represent the most famous neurodegenerative diseases [26]. They share in common the accumulation of toxic misfolded protein aggregates, as extracellular amyloid protein (A β) plaques and intracellular accumulation of tau protein in Alzheimer's disease, α -synuclein and ubiquitin in Parkinson's disease, and mutant Huntingtin protein in Huntington's disease [26]. Defective mitochondria, generating excessive reactive oxygen species (ROS), represent another feature of neurodegenerative diseases, as ROS harm the cellular constituents including DNA, lipids, and proteins [26]. The misfolded proteins are responsible for neuronal damage and death, and hence autophagy becomes a crucial target for the management of neurodegenerative diseases [27].

Recent studies revealed that alterations in autophagy-related genes trigger neurodegenerative diseases [28].

In Alzheimer's disease, transmembrane amyloid precursor protein (APP) is processed by β - and γ -secretases, which thus produce A β peptide [28, 29]. Autophagosomes show γ -secretase activity and represent a possibly active compartment for the production of A β and contribute to its deposition in affected neurons in Alzheimer's disease [30]. Dysfunction of Presenilin-1, associated with familial Alzheimer's disease, hinders proteolysis in autolysosomes and results in accumulation of A β peptides in autophagosomes [28]. Beclin-1 deficiency impedes the autophagic clearance of APP as an autophagy substrate, and it increases the pathology of Alzheimer's disease [31].

Huntington's disease is an inherited neurodegenerative disease and shows a range of declining motor, behavioral, and cognitive functions. Mutations in the huntingtin (HTT) gene are associated with cytosine-adenine-guanine (CAG) expansion, encoding a polyglutamine (polyQ) at the N-terminus of the gene [32]. This mutation affects the interaction of huntingtin with other proteins leading to all the neuropathological changes observed in the disease [33]. Huntingtin protein was shown to function as a scaffold protein for selective macroautophagy through interaction with autophagy pathway components; it cooperates with the autophagy receptor p62 and enables its connection with the essential autophagosome element LC3 and with ubiquitinated substrates. Huntingtin also binds to ULK1, the initiator kinase for autophagy, and this interaction liberates ULK1 from the negative regulation exerted by mTOR [34].

Parkinson's disease (PD) is a common progressive neurological disorder characterized by tremors, bradykinesia, rigidity, and loss of postural reflexes. The disease is caused by the loss of dopaminergic neurons in the *substantia nigra* [28, 35]. Different stages of Parkinson's disease showed deregulation of autophagy with the aggregation of α -synuclein in 'Lewy bodies.' Disrupted mitophagy is a major mechanism in the pathogenesis of the disease through mutations of PINK1 and PARKIN, which are essential for mitochondrial biogenesis and recycling [36]. Physiologically, PINK1 is a target of the ubiquitin-proteasome system after it has been processed by the mitochondrial protease presenilin-associated rhomboid-like (PARL). In depolarized mitochondria, this process is inhibited and PINK1 accumulates on the outer mitochondrial membrane, autophosphorylates, and recruits Parkin to damaged mitochondria. Parkin is an enzyme 3 (E3) ubiquitin ligase, and it was suggested that its ubiquitinated proteins recruit the autophagy receptor p62 to be integrated in an autophagosome for the autophagy degradation of damaged mitochondria (mitophagy) [28].

The two autophagy receptors previously linked to xenophagy, nuclear dot protein 52 kDa (NDP52) and optineurin (OPTN), were identified in a recent study to be the primary receptors for PINK1- and Parkin-mediated mitophagy. In this study, PINK1 recruits these two autophagy receptors, but not p62, to activate mitophagy directly, independent from Parkin. Upon their recruitment to mitochondria, NDP52 and OPTN recruit other autophagy components as ULK1, DFCP1, and WIP1, thus revealing a function for these autophagy receptors upstream of LC3. While PINK1 begins mitophagy in the absence of Parkin, mitophagy is significantly boosted in the presence of Parkin [37].

Amyotrophic lateral sclerosis is a deadly progressive neurodegenerative disease characterized by the degeneration and deterioration of motor neurons. Beside the association of several genes in ALS, it has been reported that mutations in the Sigma-1 receptor (SigmaR1) are related to the autosomal recessive familial form of ALS [28, 38]. SigmaR1 controls calcium transport and its reduced expression can lead to the increased release of calcium from ER, the depolarization of mitochondrial membrane potential, and apoptosis. It reduces autophagic flux and autophagic degradation [28, 39]. Recent exome sequencing studies identified TANK-binding

kinase 1 (TBK1) as an important protein in both sporadic and familial ALS. TBK1 phosphorylates OPTN [40], and it was reported that a mutation of OPTN is also associated with ALS [41]. Furthermore, neuron-specific Atg5 and Atg7 knockout mice are associated with motor defects [42]. Beclin-1, the major player in the autophagic initiation process, has been shown to promote ALS by interacting with superoxide dismutase 1 (SOD1) and its downregulation was associated with aggregation of amyloid- β tau tangles, which are indicators of Alzheimer's disease (AD).

3. Link between autophagy and the nicotinic cholinergic system

The role of neurology genes in the progression and metastasis of cancer in general has been emphasized recently. In many reviews, Hildegard M. Schuller established the theory that modulation of the autonomic nervous system is responsible for driving cancer development, progression, and resistance to chemotherapy not only in non-small-cell lung cancer and pancreatic ductal adenocarcinoma but also in other cancers [43–48].

She anticipated the different modifiable risk factors of PDAC development, including smoking, chronic psychological stress, and habitual ingestion of alcohol, to act mostly via the sensitization ($\alpha 7$ nAChR) and desensitization ($\alpha 4$ nAChR) of nAChRs that drive the expression of proteins, which regulate the synthesis and release of catecholamines and GABA and result in the hyperactivity of Gs-mediated cAMP signaling [47]. $\alpha 7$ nAChR activation is responsible for the production of stress neurotransmitters, which are known to promote cancer features, as well as of serotonin, dopamine, and glutamate, while the desensitization of $\alpha 4$ nAChR is the main reason for reduced GABA levels, which is known to be a protective neurotransmitter [45]. This is believed to disturb the normal equilibrium and homeostasis of the signaling neurotransmitters in favor of cancer development, progression, and reduced responsiveness to treatment [44].

A link between the nicotinic cholinergic system and autophagy can be thought as follows: in one study, nicotine hindered the macrophage clearance of mycobacterium tuberculosis via inhibition of autophagosome formation in infected T helper cells and macrophages [49]. In another study, nicotine enhanced the proteasome activity and the total protein ubiquitination as well as autophagy as was proven by the occurrence of autophagic vacuoles and increased MAP LC3-II at protein level. These mechanisms help in the downregulation of connexin 43 and limit the communication in endothelial cells based on the involvement of nAChR $\alpha 4\beta 2$ and $\alpha 3\beta 2$, but not $\alpha 7$ [50]. Jeong et al. have shown that melatonin's neuroprotective effects against prion-mediated neural damage are owing to the activation of autophagy as an outcome of $\alpha 7$ nAChR regulation [51].

4. Modulated expression of some neurologic genes in PDAC with special reference to autophagy

Our lab has identified a group of genes, which are modulated during pancreatic cancer liver metastasis [52]. The microarray data are derived from ASML rat PDAC cells that were reisolated from rat liver after they had been implanted intraportally and colonized the rat liver for various periods of time. These genes were arranged according to their fold change versus control cells (more than threefold modulation of expression) at early, intermediate, advanced, and final stages of metastasis, and the resulting genes were investigated by the Ingenuity Pathway Analysis program [53]. Among these genes, a subgroup was identified to have a dual role in

neurobiology and cancer metastasis. Thus, from ca. 30,000 genes, as found in a microarray experiment, 14 genes were selected as most promising. They are shown in **Table 1**. Data describing these genes are retrieved from the NCBI database [54].

From this list, some genes attracted our attention, including the autophagy receptor OPTN as well as MAOA/MAOB and CAV1.

What attracted our interest in this group of genes was that they share certain roles in cancer and neurology, and some were reported to have some direct or indirect link to autophagy.

The overexpression of the well-known mitochondrial enzyme MAOA, linked with many psychiatric illnesses, was shown to be associated with prostate cancer. MAOA caused neuroendocrine differentiation of prostate cancer cells through

	Gene symbol	Summary
Upregulated genes		
Receptor (G protein–coupled) activity modifying protein 1	Ramp1	Expression is increased in the striatum after repeated L-DOPA administration in a rat model of Parkinson's disease.
Activating transcription factor 3	Atf3	Expression is rapidly upregulated in response to nerve injury.
Aristaless-like homeobox 3	Alx3	Preferential methylation of this gene's promoter is associated with advanced-stage neuroblastoma.
Sortilin-related VPS10 domain-containing receptor 2	Sorcs2	These genes are strongly expressed in the central nervous system.
MAP/microtubule affinity-regulating kinase 4	Mark4	Expression is a potential marker for cancer, and the protein may also play a role in Alzheimer's disease.
Chloride intracellular channel 6	Clic6	Elevated expression is correlated with poor prognosis in human gliomas.
Downregulated genes		
Caveolin 1, caveolae protein	Cav1	The protein helps in coupling integrins to the Ras-ERK pathway and in promoting cell cycle progression.
Neuritin 1	Nrn1	The encoded protein promotes neurite outgrowth suggesting its role in promoting neuritogenesis.
Monoamine oxidase A/B	MaoA/MaoB	They have an important role in the metabolism of neuroactive and vasoactive amines in the central nervous system and peripheral tissues.
5-hydroxytryptamine (serotonin) receptor 6, G protein–coupled	Htr6	This receptor is thought to regulate cholinergic neuronal transmission in the brain.
Ly6/neurotoxin 1	Lynx1	It has the capacity to enhance nicotinic acetylcholine receptor function in the presence of acetylcholine.
Calcium channel, voltage-dependent, beta 4 subunit	Cacnb4	Certain mutations in this gene have been associated with idiopathic generalized epilepsy (IGE) and juvenile myoclonic epilepsy (JME). Multiple transcript variants for different isoforms have been found.
Optineurin	Optn	Optineurin plays a role in normal-tension glaucoma and adult-onset primary open angle glaucoma.

Table 1.
Genes with modulated expression.

activation of autophagy, ROS production, and downregulation of repressor element-1 silencing transcription factor (REST) [55].

However, at mRNA level, MAOA was not measurably expressed in our panel of human PDAC cell lines. Another aspect, which prevented further experiments, was that the irreversible MAOA-inhibiting drug clorgyline halted the proliferation of BXPC3 cells only at very high concentrations, which rendered further studies of this gene unpromising.

Deficiency of the caveolae protein CAV1 stimulates the basal and inducible autophagy as a cell survival mechanism under starvation. This is a recently described function of CAV1 and lipid rafts in breast cancer development via modulation of lysosomal function and autophagy [56]. Another study reported that CAV1 regulates autophagy positively under oxidative stress and cerebral ischemic injury. CAV1 deficiency limited localization of Beclin-1 (BECN1) to the mitochondria and eliminated LC3 foci formation in response to hydrogen peroxide in the brain of CAV1 knockout mice [57]. CAV1 is related to tumorigenesis and metastasis. CAV1 overexpression in PDAC is associated with poor clinical outcome, as well as chemo- and radioresistance [58]. Moreover, signs of premature neuronal aging and degeneration are evident in CAV1 knockout mice together with increased A β , P-tau, and astrogliosis [59].

The gene optineurin (OPTN), which is an autophagy receptor, was also among the genes listed in **Table 1**. Since OPTN has an important role in many neurodegenerative diseases as well as a function as an autophagy receptor, thus linking autophagy in cancer and neurodegenerative diseases, a comprehensive overview of this gene is given as well as an outline of the expression of other autophagy genes in PDAC.

5. Optineurin

OPTN is linked to many neurodegenerative diseases including normal tension glaucoma, primary open-angle glaucoma [60], as well as amyotrophic lateral sclerosis [41].

The OPTN gene is located on chromosome 10p13 and translates into a protein of 67-kDa. The mRNA consists of 16 exons; the first 3 are noncoding, while the coding exons give rise to a protein composed of 577 amino acids [61, 62]. OPTN was found to be head to head oriented with the gene coiled-coil domain containing 3 (CCDC3) with a distance of about 98-kb between their 5'UTRs [63]. OPTN has a half-life of around 8 h and its degradation engages the ubiquitin proteasomal system as its level increases following exposure to a proteasome inhibitor, but not to autophagic or lysosomal inhibitors [64].

OPTN encompasses several domains: an NF- κ B-essential molecule-like domain, leucine zipper motif, coiled-coil motifs, an ubiquitin-binding domain (UBD), an LC3-interacting region, and a carboxyl (C)-terminal C₂H₂ type of zinc finger [65, 66].

As a cytoplasmic protein [60], OPTN colocalizes together with myosin VI and Rab8 around the Golgi complex and in vesicles at the plasma membrane [67]. It shows a high level of expression in certain tissues such as retina, brain, heart, skeletal muscle, placenta, testis, and kidney [68].

It interacts with itself to form homo-oligomers [69] and also with other molecules such as Ras-related protein 8 (Rab8) [70], huntingtin [71], myosin VI [72], transferrin receptor [68], LC3/GABARAP [62], polo-like kinase 1 [73, 74], TBK1 [75], as well as metabotropic glutamate receptor, transcription factor IIIA, serine/threonine kinase receptor-interacting protein 1, CYLD lysine 63 deubiquitinase (cylindromatosis, CYLD), and HECT (homologous to the E6-AP carboxyl terminus) domain and ankyrin

repeat containing E3 ubiquitin protein ligase 1 (HACE1) [65]. The structure of OPTN and some interactions are shown in **Figure 2**.

OPTN plays different roles under physiological conditions including membrane trafficking, maintenance of the Golgi apparatus, exocytosis, protein secretion, cell division control, regulation of NF-κB, and host defense against pathogens [61, 62, 65, 67].

Its antiviral preventive response was based on its ability to regulate the interferon response in a cell cycle-dependent manner owing to its nuclear translocation together with deubiquitinating enzyme CYLD during the G2/M phase of the cell cycle, which abolishes the inhibitory effect it exerts on TBK1. As a result, the TBK1 activity is increased with enhanced interferon production [76].

The overexpression of OPTN was demonstrated to be protective against H₂O₂-mediated cell death, a function, which is compromised by a mutated form of OPTN (E50K), resulting in cells that are less fit to survive under stress conditions [70].

Beside all the above stated roles, OPTN is considered as a disease-linked gene. Mutations of OPTN or its altered expression are associated with multiple diseases including normal tension glaucoma and primary open-angle glaucoma [60] as well as plenty of neurodegenerative diseases including amyotrophic lateral sclerosis [41], ubiquitin-positive intraneuronal inclusions in ALS with dementia, basophilic inclusions in the basophilic type of ALS, neurofibrillary tangles and dystrophic neurites in Alzheimer's disease, Lewy bodies and Lewy neurites in Parkinson's disease, ballooned neurons in Creutzfeldt-Jakob disease, glial cytoplasmic inclusions in multiple system atrophy, and Pick bodies in Pick's disease with unknown significance [77]. Reduced OPTN expression in humans might increase the risk of developing Crohn's disease [78] and dispose to the occurrence of Paget's disease by enhancing osteoclast differentiation, as OPTN is a recently identified regulator of bone resorption [79].

The OPTN protein was identified as a selective autophagy receptor such as the multidomain scaffold/adaptor protein p62/sequestosome-1 (p62/SQSTM-1) and nuclear domain 10 protein 52 (NDP52) in terms of binding to polyubiquitinated cargoes and brings them to autophagosomes via its LC3-interacting region [65, 80–82]. In this context, it can help cells to get rid of pathogens as salmonella [80], defective mitochondria [82], and misfolded protein aggregates [83] or can have a role in tumor suppression [81].

The role of OPTN in autophagy can also be independent from ubiquitination [65], where it can distinguish several protein aggregates through its C-terminal coiled-coil domain [84].

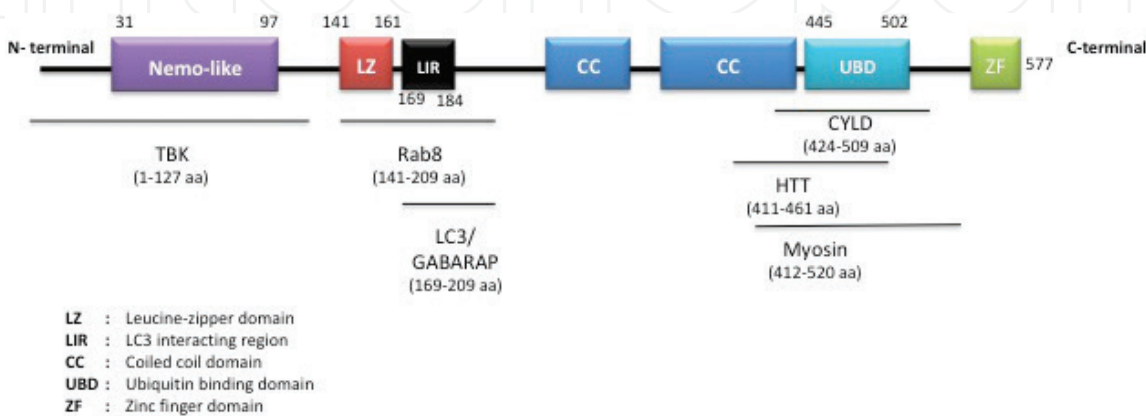


Figure 2.
Graphic illustration of OPTN structural domains and the localization of these domains relative to its amino acid sequence as well as some of its interacting proteins.

The role of OPTN in autophagy extends beyond being an autophagy receptor, as OPTN also plays a role as an autophagy inducer. Overexpression of OPTN in its wild type or mutated E50K forms, or its upregulation by cytokine treatment, was linked to elevated LC3-II levels in retinal ganglion cells, while the level of the proteasome activity marker PSMB5 (proteasome regulatory β 5) was reduced denoting induction of autophagy [64]. In vivo results confirmed the induction of autophagy and the reduction of ubiquitin proteasome pathway upon the injection of wild type and E50K OPTN transfected vectors in rat eyes [85].

Mutation or altered expression of OPTN may result in many diseases as glaucoma, ALS, other neurodegenerative diseases [65], or even cancer [81] owing to the implication of mitochondrial dysfunction and protein aggregation [65]. Mutations in both autophagy receptors p62 and OPTN in Paget’s disease of the bone may attribute to an autophagy-related mechanism of developing this disease [65].

An overview of the RNA-seq data generated by the Cancer Genome Atlas (TCGA) revealed high expression of the OPTN gene across several cancer types (reported as median number fragments per kilo-base of exon per million reads (FPKM)) and was based on mRNA expression in cancer tissues (see **Figure 3**). In this regard and with data retrieved from the Protein Atlas website [86, 87], pancreatic cancer represents the tumor with the second highest OPTN expression and is topped only by renal cancer.

Prompted by this result, we analyzed the expression of autophagy genes and autophagy receptors in PDAC in a TCGA cohort with a sample size of 179. Most of the autophagy genes were above average genomic expression, represented by >7.5 log2 rsem (RNA-seq by expectation maximization) except for ATG10, which was below average. OPTN was second highest expressed of all autophagy genes, preceded only by SQSTM1 (**Figure 4**).

Based on these findings, we reasoned that OPTN might be involved in important mechanisms associated with cancer as well as with neurodegenerative diseases that require further analysis.

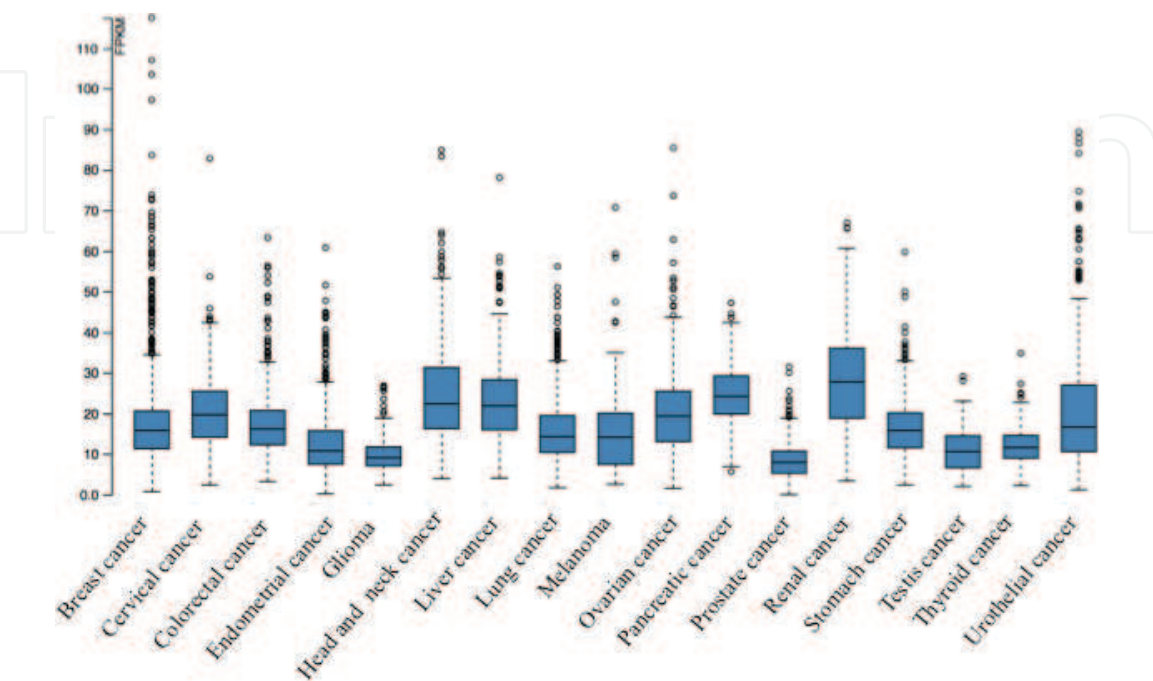


Figure 3. Overview of the RNA-seq data in TCGA of 17 cancer cohorts showing the highest OPTN expression in renal cell carcinoma followed by PDAC (expressed in terms of median FPKM) [86–88].

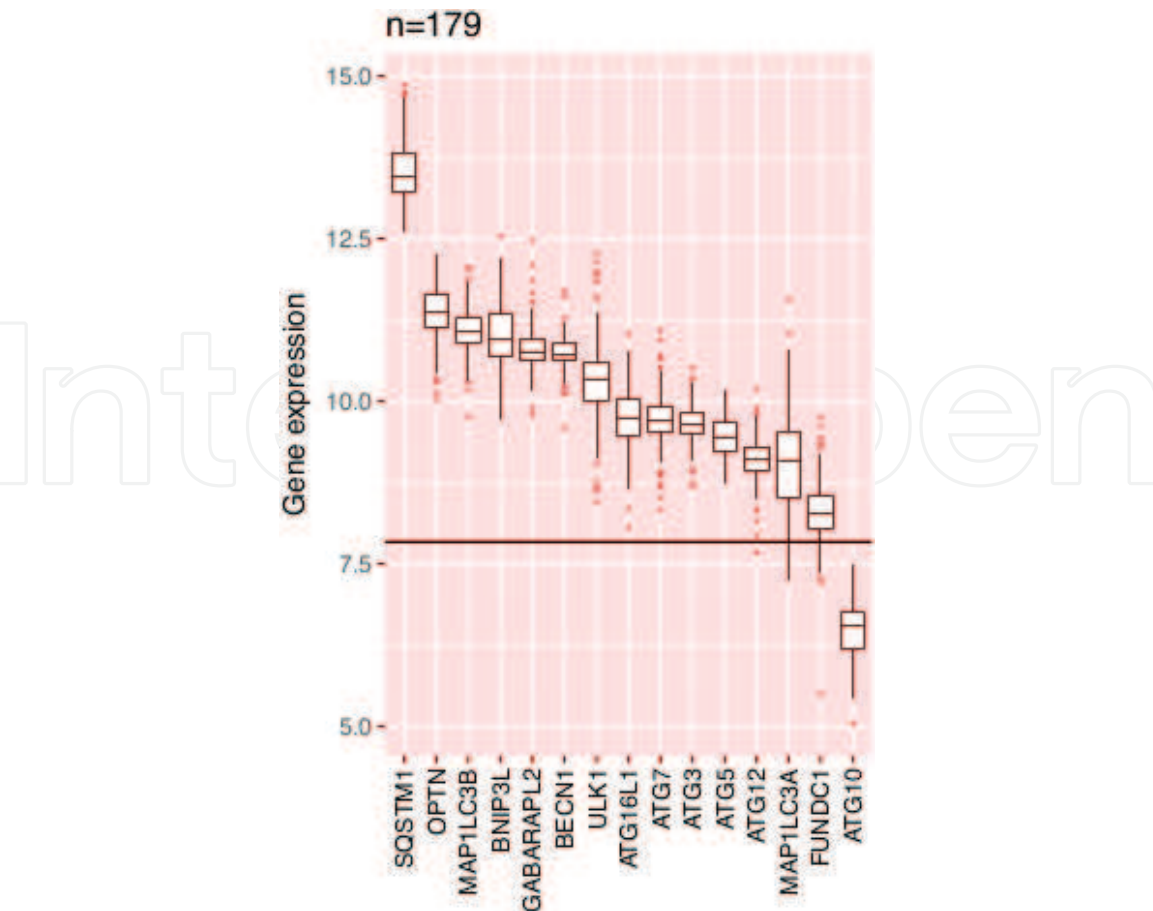


Figure 4.
Expression of autophagy-related genes and receptors in a PDAC cohort with a sample size of 179 patients showing high expression of all autophagy-related genes ($> 7.5 \log_2 \text{rsem}$) except for ATG10.

6. Conclusions

In summary, autophagy represents a link between the nervous system and cancer in general as well as pancreatic cancer in particular. The modulated expression of autophagy-related genes in cancer and neurodegenerative diseases highlights the importance of this mechanism and suggests further studies on their regulation and effective targeting. Autophagy is a new background for certain genes in cancer as well as in neurology, and understanding this process may well serve as a platform for understanding the pathogenesis of these diseases in different organs. In addition, there seems to be a special role for OPTN in different neurodegenerative diseases as well as cancer and this protein could well be a target in cancer treatment. The link between nicotinic acetylcholine receptors and autophagy still requires further studies to be properly delineated.

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Conflict of interest

The authors have no conflicting interests.

Acronyms and abbreviations

OPTN	Optineurin
PDAC	pancreatic ductal adenocarcinoma
CMA	chaperone-mediated autophagy
ATG	autophagy-related protein
BECN1	Beclin-1
ULK1	Unc-51 like autophagy activating kinase
MAP1LC3A	microtubule-associated protein 1 light chain 3 alpha
MAP1LC3B	microtubule-associated protein 1 light chain 3 beta
GABARAPL2	GABA type A receptor-associated protein like 2
SQSTM1	sequestosome 1
BNIP3L	BCL2-interacting protein 3 like
BNIP3	BCL2-interacting protein 3
FUNDC1	FUN14 domain containing 1

Author details

Doaa M. Ali^{1,2} and Martin R. Berger^{1*}

1 Toxicology and Chemotherapy Unit, German Cancer Research Centre (DKFZ), Heidelberg, Germany

2 Department of Pharmacology and Experimental Therapeutics, Medical Research Institute, Alexandria University, Egypt

*Address all correspondence to: m.berger@dkfz.de

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