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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,

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.