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Review

Glycophagy: An emerging target in pathology

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ABSTRACT

Autophagy, a highly conserved self-digestion process, is initially regarded as non-selectively sequestering and degradation cytoplasmic contents. Nowadays, many kinds of selective autophagy have been found in response to various physiological cues such as mitophagy, reticulophagy and glycophagy. Glycophagy, as a selective autophagy, plays a crucial role in maintaining glucose homeostasis in many tissues including heart, liver and skeletal muscles. Moreover, glycophagy is highly regulated by many signal pathways like the cyclic AMP protein kinase A/protein kinase A, PI3K-Akt/PKB-mTOR and Calcium. Latest studies have demonstrated that glycophagy is triggered by STBD1, which tethers glycogen to membranes via binding itself to the cognate autophagy protein GABARAPL1. More importantly, glycophagy might act as a protective role in coping with the accumulation of glycogen-rich lysosomes in infant patients with Pompe disease. However, glycophagy might aggravate diabetic cardiomyopathy via FoxO1 signal pathway. In this review, we focus on some findings about the occurrence and development, as well as the regulatory mechanism of glycophagy. We also analyze the role of glycophagy in Pompe disease and diabetic cardiomyopathy. Targeting glycophagy may open a new avenue of therapeutic intervention to these diseases.

1. Introduction of glycophagy

Autophagy, a highly conserved self-digestion process, can degrade misfolded cytoplasmic proteins, damaged organelles, pathogenic organisms and superfluous cytosol. Autophagy facilitates maintaining protein and organelle quality at a low basal level. Furthermore, autophagy, as indicated by strong evidence, is associated with a large number of other functions such as metabolic regulation, growth & differentiation, and mobilization of various cellular energy store including carbohydrates, lipids and minerals when nutrient deficiency happens [1]. However, the defective or excessive autophagy, is subject to damaging or even killing other healthy cells due to enzymes leakage from lysosomes.

So far, autophagy has been recognized to have main types: macroautophagy, microautophagy and chaperone-mediated autophagy identified in mammals. Macroautophagy is characterized by the formation of autophagosomes, a double membrane-bound vesicle, which engulf organelles and cytoplasmic proteins. These autophagosomes subsequently fuse with lysosome in order to degradation the sequestered cargoes [2]. Compared to macroautophagy, microautophagy participates in the invagination of the lysosomal membrane itself resulting in firsthand engulfment of cargoes that are subsequently degraded in the lysosomal lumen [3]. It is well known that chaperone-mediated autophagy is different from macroautophagy and microautophagy. In the process of chaperone-mediated autophagy, proteins containing the KFERQ-like pentapetide motif can be recognized by the cytosolic chaperone heat shock cognate 70 kDa protein (Hsc70), then transported into the lysosomal lumen ultimately resulting in degradation of proteins [4]. These types autophagy regarded as non-selectively process, sequesters and degrades some cytoplasmic contents.

Unlike the process mentioned above, recently numerous researches have confirmed autophagy, as a process, capturing engulfment of specific cargoes, has a more selective role in response to various physiological cues [5]. As a result, the process evokes extensive research interesting. Up to now, many kinds of selective autophagy have been identified including glycophagy [6, 7], lipophagy [8, 9], RNautophagy [10], DNautophagy [11], ferritinophagy [12], reticulophagy [13–15], pexophagy [16], mitophagy [17], crinophagy [18–20], xenophagy [21, 22] and aggrephagy [23] (Table 1).

Glycophagy, a glycogen-specific autophagy, functions as degrading cell glycogen within autophagic vacuoles. It plays a key role in maintaining glucose homeostasis under conditions of demand for yielding of glucose such as in the heart, liver, and other organs of newborn animals [24]. Such process is involved in the sequestration of polysaccharide,

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Table 1
The diversity of selective autophagy species.

Types	Markers	Cargo	Regulation pathways	Reference
Aggrephagy	LC3-II, Alfy	Protein aggregates and inclusions	p62-Nrf2, NBR1	[23]
Crinophagy	HOPS	Superfluous peptide, Secretory granules	Prostaglandin E-2	[18–20]
DNautophagy	LAMP2C	DNA	Ubp3/Bre5	[11]
Ferritinophagy	NCOA4	Ferritin	/	[12]
Glycophagy	STBD1	Glycogen	cAMP, mTOR, Ca^{2+} Heterotrimeric G proteins GTPases	[6, 7]
Lipophagy	LIPA	Lipid droplets	FoxO1, PRDX1, ATGL	[8, 9]
Mitophagy	PINK1, Parkin	Damaged or superfluous mitochondria	Bnip3/Nix	[17]
Pexophagy	Atg36	Damaged or superfluous peroxisome	Dnm1,Vps1, Atg11, Atg30	[16]
Reticulophagy	Syntaxin 17, DFCP1	Damaged or superfluous ER	Syntaxin17/Atg14, Ypt1	[13–15]
RNautophagy	LAMP2C	RNA	Ubp3/Bre5	[10]
Xenophagy	CALCOCO2/NDP52	Bacteria, Viruses, and other Pathogens	AMPK, mTOR	[21, 22]

LAMP2C: lysosomal-associated membrane protein 2c; PRDX1: peroxiredoxin 1; NCOA4: nuclear receptor co-activator 4; DFCP1: double FYVE domain-containing protein; PINK1: PTEN-induced putative kinase 1; HOPS: *Humulus lupulus* L; CALCOCO2: calcium-binding and coiled-coil domain2; NDP52: nuclear dot protein 52; PRDX1: peroxiredoxin 1; Ubp3: The Ubiquitin-Specific Protease Subfamily; Bnip3: Bcl-2/adenovirus E1B 19-kDa interacting protein; Ypt1: *Saccharomyces cerevisiae* yeast protein two 1protein; Dnm1: dynamin 1; Vps1: Vacuolar protein sorting 1; NBR1: neighbor of BRCA1 (breast cancer early-onset 1) gene 1; Alfy: PI3P-binding Autophagy-linked FYVE domain protein.

which is subsequently degraded via lysosomal acid a-glucosidase (GAA) [25]. The breakdown of glycogen mediated lysosomal triggers liberation of free α–glucose that can be rapidly used by starving neonatal cells. Emerging evidence indicate that the alteration of glycophagy is involved in some diseases such as Pompe disease [26] and diabetic cardiomyopathy [27]. Here, we will provide a brief review to describe the occurrence and regulation mechanism of glycophagy, as well as the important role of glycophagy in Pompe disease and diabetic cardiomyopathy.

2. The occurrence and development of glycophagy

The occurrence of glycophagy is an intricate process. Mostly information concerning glycophagy stems from studies on neonatal animals [6, 28]. At birth, the level of blood glucose declines soon due to the interruption of trans-placental energy supply. However, the gluconeogenic mechanisms for more and more yielding glucose are not yet completely established [29]. As we know that, glycogen acts as an effective means of energy storage, both cytoplasm and autophagic vacuoles are two spatially distinct pools of cellar glycogen. Moreover, ultimately the glycogen in autophagic vacuoles, is degraded into non-phosphorylated glucose because of the autophagic lysosomes containing enzyme activities, including glycogen-hydrolyzing GAA. GAA is synthesized in the rough endoplasmic reticulum (ER), which is essential for the trafficking of the enzyme through the Golgi complex to the lysosomes. Similarly, cytosolic glycogen is degraded into phosphorylated glucose (glucose-1-phosphate) by glycogen phosphorylase. The hydrolytic degradation of glycogen in the autophagic vacuoles is an important alternative for the phosphorolytic degradation of polysaccharide in the cytosol of hepatocytes, muscle fibers and cardiomyocytes to keep survival during the period of neonatal starvation [30, 31]. Thereafter, glycophagy occurrence in tissues acts as a mechanism of glucose homeostasis. Except for the neonatal condition, the activity of glycophagy is also activated in varied conditions such as in phlorizin treatment [32], isolated embryonic hepatocytes [33] and hypoxia [34]. Overall, glycophagy plays an important role in sustaining the glucose homeostasis, although the mechanism of glycogen trafficked to the lysosome was unclear in the past decades.

Until recently, researches have suggested that the starch-binding domain-containing protein 1(STBD1) is a novel mediator of glycophagy. STBD1, also termed Genethonin-1, is emerging as a cargo receptor for anchoring glycogen to lysosomes during the process of glycophagy [35, 36]. STBD1, initially isolated from human skeletal muscle library, is widely expressed in liver, heart and muscle tissues [37]. Additionally, STBD1 contains an N-terminus Atg8-interacting-motif for mediating membrane anchorage via interaction with the autophagosome-forming Atg8 family proteins, and a C-terminal CBM20 domain for binding glycogen and glycogen-associated proteins including Laforin, GS (glycogen synthase) and GDE (glycogen debranching enzyme) [37, 38]. Moreover, STBD1 includes an N-terminal 24 amino acid hydrophobic stretchwhich permits itself to be linked with a cellular membrane structure-possibly pertaining to the lysosomal organelles or ER [37, 39]. Amazingly, recent studies have revealed that there is an interplay between STBD1 and γ-aminobutyric acid receptor-associated protein like 1 (GABARAPL1), a member of the Atg8 family [35, 37]. GABARAPL1 may be regarded as the preferred physiological binding partner due to strictly co-distributed with STBD1 in cells [35]. Based on proceeding information, the process, where STBD1 tethers glycogen to membranes via binding itself to the cognate autophagy protein GABARAPL1, is termed glycophagy.

3. Signal pathways involved in glycophagy

3.1. Cyclic AMP/PKA pathway

Glycophagy is mainly induced by the cyclic AMP (cAMP)/protein kinase A signal pathway. A mounting number of studies have suggested that cAMP increases the formation of autophagic vacuoles and facilitates the degradation of glycogen inside these organelles, which acts as a response to the demand for vast production of glucose [40–42]. Hypoglycemia happens approximately 2–3 h after birth because of the interrupt of maternal nutrient supply, whereas the gluconeogenic mechanisms are not yet fully established.. For neonatal animals adapt to their postnatal environment, increasing concentration of plasma glucagon induces glucose production to cope with hypoglycemia. The process increases cAMP and protein kinase A, consequently resulting in the activation of phosphorylase [43]. Cyclic AMP also triggers gene transcription, and stimulates liver glucose 6-phosphatase [24, 44]. Cyclic AMP and cyclic AMP elevating agents like glucagon and adrenalin, stimulate glycophagy in liver, heart, and skeletal muscles, whereas the agents of cAMP-antagonizing such as propranolol and parenteral glucose contribute to opposite changes [45, 46]. These results have indicated that the signal pathway of cyclic AMP (cAMP)/protein kinase A plays a crucial role in the progress of glycophagy.

3.2. PI3K-Akt/PKB-mTOR signal pathways

Glycophagy is also regulated by the PI3K-Akt/PKB-mTOR signal