Biochimica et Biophysica Acta 1823 (2012) 138–144

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Cdc48/p97, a key actor in the interplay between autophagy and ubiquitin/proteasome catabolic pathways ☆

Catherine Dargemont *, Batool Ossareh-Nazari **

CNRS, UMR7592, Institut Jacques Monod, Univ Paris Diderot, Sorbonne Paris Cité, 75205 Paris, France

ARTICLE INFO

Article history:
Received 28 April 2011
Received in revised form 11 July 2011
Accepted 18 July 2011
Available online 23 July 2011

Keywords:
Cdc48
Autophagy
Ubiquitin
Proteasome

ABSTRACT

The AAA-ATPase Cdc48/p97 controls a large array of cellular functions including protein degradation, cell division, membrane fusion through its ability to interact with and control the fate of ubiquitylated proteins. More recently, Cdc48/p97 also appeared to be involved in autophagy, a catabolic cell response that has long been viewed as completely distinct from the Ubiquitine/Proteasome System. In particular, conjugation by ubiquitin or ubiquitin-like proteins as well as ubiquitin binding proteins such as Cdc48/p97 and its cofactors can target degradation by both catabolic pathways. This review will focus on the recently described functions of Cdc48/p97 in autophagosome biogenesis as well as selective autophagy. This article is part of a Special Issue entitled: AAA ATPases: structure and function.

1. Introduction

The Cdc48 chaperone, also called p97 or VCP in higher eukaryotes, is a phylogenetically highly conserved member of the AAA-ATPases family involved in many cellular functions including protein degradation, endoplasmic reticulum-associated degradation (ERAD), cell cycle progression, membrane fusion or DNA repair. It consists of a homohexamer, each monomer presenting two AAA cassettes that couple ATP-hydrolysis to conformational changes of the entire complex [1]. Ability to primarily interact with ubiquitined targets represents the second essential property of Cdc48/p97 [2]. Together, these characteristics are believed to support a "segregase" function for Cdc48/p97 that uses energy provided by ATP hydrolysis to segregate ubiquitinated substrates from protein complexes, cell membranes and chromatin and to release them for either proteasomal degradation or recycling [3–7]. The diversity of cellular functions controlled by Cdc48/p97 is mediated by its multiple cofactors structurally characterized by their Cdc48/p97-interacting domains. The UBX or UBX-like containing proteins form the largest family of Cdc48/p97 cofactors conserved from yeast to mammals. Although the precise function of some members of this family is currently unclear, the high conservation of the interaction surface allows all UBX proteins to bind the N-terminal domain of Cdc48/p97 [8–11] (Fig. 1). Other N domain binding cofactors that contain interaction motifs corresponding to short stretches of conserved amino-acids such as the BS1/SHP Box, the VIM (VCP-interaction motif) or the VBM (VCP-binding motif) were found so far in a limited number of cellular proteins. In contrast, proteins containing a PUB domain bind the 10 C-terminal residues of p97 [12–14] (Fig. 1). Interestingly, phosphorylation of tyrosine 805 by the c-src kinase prevents this interaction indicating that signaling pathway can modulate the recruitment of specific adaptors to Cdc48/p97 [13–15].

Cdc48/p97 cofactors can also be functionally classified into two families, substrate-recruiting factors and substrate-processing factors [16,17]. The first class of cofactors corresponds to adaptor proteins able to interact with both Cdc48/p97 and ubiquitin moiety on ubiquitinated substrates via dedicated domains. For example, Shp1 (mammalian p47), the major cofactor involved in the membrane fusion activity of Cdc48/p97 presents a combination of UBX, BS1/SHP Box and UBA domains [18]. Some of these adaptors also allow the targeting of Cdc48/p97 to specific cellular locations. In yeast, Ubx2, an integral ER protein recruits Cdc48/p97 and its major cofactors Npl4 and Ufd1 to the ER, stabilizes the interaction between Cdc48/p97, ERAD substrates and ubiquitin ligases and thus increases the efficiency of the ERAD pathway [19,20]. Processing factors associated with Cdc48/p97 act downstream of recruiting factors and mainly influence the fate of Cdc48/p97 substrates. They belong to two major families of enzymes, E3/E4 ubiquitin ligases such as the Ubiquitin chain elongating enzyme Ufd2 (UFD-2 in *Caenorhabditis elegans*, [21–23] and deubiquitylation enzymes (DUB) such as Ataxin3, VCIP135 or Ubp3 involved in ERAD

Abbreviations: ERAD, endoplasmic reticulum-associated degradation; IBMPFD, inclusion body myopathy, Paget's disease of bone and frontotemporal dementia; PMN, piecemeal microautophagy of the nucleus; PD, Parkinson disease

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* Correspondence to: C. Dargemont, Institut Jacques Monod, 15 rue Hélène Brion, 75205 Paris Cedex 13, France. Tel.: +33 1 57278032.

** Correspondence to: B. Ossareh-Nazari, Institut Jacques Monod, 15 rue Hélène Brion, 75205 Paris Cedex 13, France. Tel.: +33 1 57278033.

E-mail addresses: dargemont.catherine@ijm.univ-paris-diderot.fr (C. Dargemont), ossareh-nazari.batool@ijm.univ-paris-diderot.fr (B. Ossareh-Nazari).

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doi:10.1016/j.bbamcr.2011.07.011

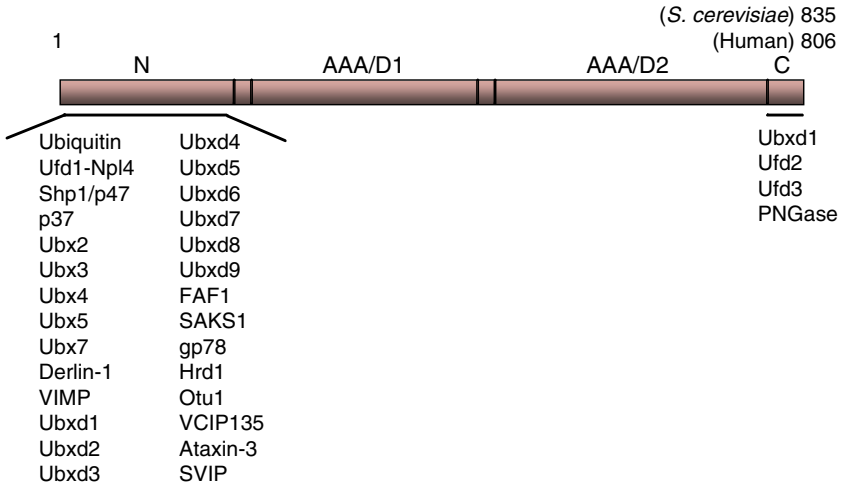

Fig. 1. Schematic molecular organization of Cdc48/p97. The binding domains of the different co-factors of Cdc48/p97 mentioned in Table 1 are indicated on the schematic representation of Cdc48/97.

[24,25], membrane fusion [26] or selective autophagy respectively [27]. Interaction of Cdc48/p97 with these opposing enzymatic activities led to the hypothesis of a "decision platform" role for Cdc48/p97 in the regulation of substrate ubiquitylation [28,29]. A concerted action of these enzymes has been proposed in either a "chain editing" model where a DUB can selectively cleave off certain types of ubiquitin chains from Cdc48/p97 substrates and thus control their fate, or a "proofreading" model where a DUB can control the length of ubiquitin chain conjugated to a Cdc48/p97 substrate (reviewed in ref. [30]).

Concomitantly to the characterization of an increasing number of Cdc48/p97 cofactors, a growing number of cellular functions appear to be controlled by Cdc48/p97. In particular, while the Proteasome System and autophagy have long been viewed as complementary degradation systems with no point of intersection, studies performed over the past 3 years clearly demonstrate that ubiquitin conjugation

Table 1
Cofactors of Cdc48/p97.

Protein	Organisms	Functions	References
Substrate-recruiting cofactors			
Ufd1-Npl4 heterodimer	Yeast, metazoans	ERAD, OLE pathway, mitosis, protein degradation	[4,5,89–91]
Shp1/p47	Yeast, metazoans	ER membrane fusion, Golgi assembly, autophagosome biogenesis, protein degradation	[11,46,92]
p37	Mammalian	Membrane fusion	[93]
Ubx2	Yeast, metazoans	ERAD, protein degradation	[11,20]
Ubx3	Yeast	Unknown	[11]
Ubx4	Yeast	ERAD, UV-dependent turnover of RNA Pol II	[11,94,95]
Ubx5	Yeast	UV-dependent turnover of RNA Pol II	[11,95]
Ubx6	Yeast	Unknown	[11]
Ubx7	Yeast	Unknown	[11]
Derlin-1	Mammalian	ERAD	[96–99]
VIMP	Mammalian	ERAD	[99]
Ubxd1	Mammalian	ERAD	[8,12,100]
Ubxd2 (Erasin)	Mammalian	ERAD	[8,101]
Ubxd3	Mammalian	Unknown	[8]
Ubxd4	Mammalian	Unknown	[8]
Ubxd5 (Socius)	Mammalian	Reorganization of the actin cytoskeleton	[8,102]
Ubxd6 (Rep-8)	Mammalian	Unknown	[8]
Ubxd7	Mammalian	Degradation of HIF1α	[8]
Ubxd8 (ETEA)	Mammalian	Unknown	[8]
Ubxd9 (ASPL)	Mammalian	Glucose uptake	[8,103]
FAF1	Mammalian	Protein degradation, Apoptosis	[8,104]
SAKS1	Mammalian	Protein degradation	[8,105,106]
Substrate-processing cofactors			
Ufd2	Yeast, metazoans	E4 polyubiquitylation enzyme	[21,28,107]
Ufd3	Yeast, metazoans	Inhibitor of Ufd2,	[27,28]
gp78	Mammalian	E3 ubiquitin ligase	[108]
Hrd1	Mammalian	E3 ubiquitin ligase	[97,109]
Out1	Yeast	Deubiquinating enzyme	[28]
Ubp3-Bre5	Yeast	Deubiquinating complex	[27,110]
VCIP135	Mammalian	Deubiquinating enzyme	[26]
Ataxin-3	Mammalian	Deubiquinating enzyme	[24]
PNGase	Mammalian	Deglycosylase	[12]
HDAC6	Mammalian	Deacetylase (direct interaction with Cdc48/p97?)	[111]
SVIP	Mammalian	Negative regulator of ERAD	[112]

can target degradation by both catabolic pathways. Consequently, some ubiquitin-binding proteins such as Cdc48/p97 appear to play a major role in this interplay. This review will focus on the recently described functions of Cdc48/p97 and its cofactors in non-selective and selective autophagy.

2. Role of Cdc48/p97 in autophagosome formation

Autophagy is an evolutionarily conserved process in eukaryotes that eliminates longer-lived proteins, macromolecular assemblies as well as superfluous or damaged organelles. Autophagy is generally induced to maintain cell survival as a cellular response to various stress conditions such as periods of starvation or regression of retired tissues. There are three major types of autophagy, chaperone-mediated autophagy (CMA), macroautophagy and microautophagy. CMA has only been characterized in higher eukaryotes and allows selective degradation of cytosolic proteins in lysosome [31]. Macroautophagy is characterized by the de novo formation of a double membrane-bound compartment, the autophagosome, which engulfs cytoplasmic material and ultimately fuses with the vacuole or lysosome to allow the breakdown of its contents. Microautophagy refers to the direct uptake of cytosolic components by the vacuole/lysosome, through invagination of its limiting membrane (Fig. 2). Microautophagy is active during starvation, thereby compensating for the membrane flux caused by macroautophagy, and maintaining vacuolar homeostasis. So far, the yeast genetics allowed the identification of 35 AuTophagGy-related genes (ATG) referred to ATG1 to ATG 35 [32–35]. A subset of the ATG genes is involved in the formation of the autophagosome, and the corresponding gene products are referred to as the 'core' autophagy machinery. The core machinery consists in four functional groups: (1) Atg9 and its cycling factors (2) the phosphatidylinositol 3-kinase (PtdIns3K) complex (3) the ubiquitin like protein system (4) the proteins involved in the breakdown of autophagic bodies and the release of the degraded products back to the cytosol [33,36,37]. Atg8 (LC3 in mammalian cells) is a ubiquitin-like protein essential for the expansion of the autophagosome precursor, or phagophore, and the autophagosome formation [38]. Coupling of Atg8 to phosphatidylethanolamine (PE) by an ubiquitin-like conjugation system is required for Atg8 to mediate membrane fusion. Atg8-PE (LC3 II in mammalian cells) is initially located on the phagophore membrane. Upon completion of the autophagosome, Atg8 is released from the outer membrane by Atg4-mediated PE deconjugation while Atg8-PE on the inner membrane is delivered into the vacuole/lysosome where it is degraded [39–42].

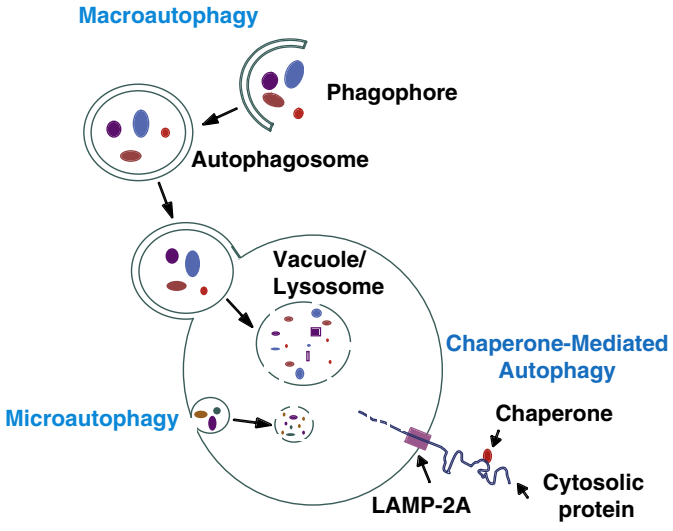

Fig. 2. Schematic presentation of autophagy. There are three major types of autophagy in eukaryotes. Macroautophagy, microautophagy and chaperone-mediated autophagy (CMA). Macroautophagy is characterized by formation of a double membrane vesicle called autophagosome that non-selectively engulf cytoplasmic components and delivers them to the vacuole/lysosome for degradation. Microautophagy involves sequestration and degradation of cytoplasmic components by invagination of the vacuole/lysosome membrane. CMA has only been characterized in higher eukaryotes. In this process, a chaperone protein binds to a specific cytosolic protein allowing its unfolding and translocation into the lysosome directly across the lysosome membrane via the lysosome-associated membrane protein type 2A, LAMP-2A.

The role of Cdc48/p97 in autophagosome maturation has been first identified in mammalian cells, in the context of the IBMPFD disease caused by mutations within the N-terminal and D1 domains of Cdc48/p97 [43]. Cells expressing the IBMPFD associated mutants of Cdc48/p97 display an increased level of the autophagosome markers, p62 and LC3 II. SiRNA-mediated knockdown of Cdc48/p97 also leads to the accumulation of p62, LC3 II and GFP-LC3 puncta. Cells with a decreased expression of Cdc48/p97 fail to degrade LC3 II upon nutrient-starvation induced autophagy, indicating that the Cdc48/p97 activity is required for autophagic protein degradation [44]. More precisely, Cdc48/p97 is necessary for autophagosome–lysosome fusion and formation of autolysosome [44,45]. The majority of autophagosomes accumulated in cells expressing Cdc48/p97 mutant forms contain ubiquitin, suggesting that Cdc48/p97 may be required for the autophagic degradation of ubiquitylated substrates [45]. However, the mechanisms responsible for the Cdc48/p97-mediated autophagosome/lysosome fusion are still unclear although the interaction of Cdc48/p97 with the ubiquitin-like domain of some autophagosome-associated proteins has been speculated [44].

More recently Cdc48/p97 and its cofactor Shp1 have been identified as novel components of autophagosome biogenesis in yeast [46]. In *Saccharomyces cerevisiae*, starvation-induced macroautophagy monitored by vacuolar degradation of GFP-Atg8 was indeed blocked in both a *cdc48* thermosensitive strain at restrictive temperature and in *shp1Δ* cells. In addition, no accumulation of autophagic bodies could be observed in *shp1Δ* cells indicating that autophagosome biogenesis was affected. This effect of Cdc48/p97 and Shp1 on macroautophagy is mediated by the direct interaction of Shp1 with Atg8, preferentially in its PE-conjugated form. However this binding does not involved the ubiquitin-like domain of Atg8 nor the UBA domain of Shp1. More generally, the function of Cdc48/p97 and Shp1 in autophagosome biogenesis appeared independent of the function of these proteins in ubiquitin–proteasome system and the requirement of the segregase activity of the Cdc48/p97 complex to extract Atg8-PE prior delipidation has been speculated [46]. Although Cdc48/p97 has been involved in the fusion of the autophagosome with the lysosome in mammalian cells, it seems to be implicated in an early step of autophagosome formation in yeast. Whether it corresponds to two distinct functions of Cdc48/p97 mediated by distinct cofactors or to an evolutionary difference remains to be defined.

3. Cdc48/p97 regulates the selective autophagy

Although macroautophagy is generally considered as a non-selective or bulk autophagy, several forms of selective autophagy in which the target is specific have been reported both in yeast and higher eukaryotes [47]. That includes yeast specific cytoplasm-to-vacuole targeting (CVT) pathway, required for the transport of two vacuolar enzymes, aminopeptidase I (Ape1) and α-mannosidase (Ams1) [48,49]. Mitochondria and peroxisomes are degraded via processes known as mitophagy [50–53] and pexophagy [54,55]. Activation of the unfolded protein response in yeast induces a branch of macroautophagy that selectively targets the endoplasmic reticulum, so-called ER-phagy[56]. Non-essential portions of the nucleus are degraded by 'piecemeal microautophagy of the nucleus' (PMN) at nucleus–vacuole junctions [57]. Finally, a selective autophagic pathway for 60S ribosomal subunit degradation called ribophagy was recently described [27,58] (Fig. 3).

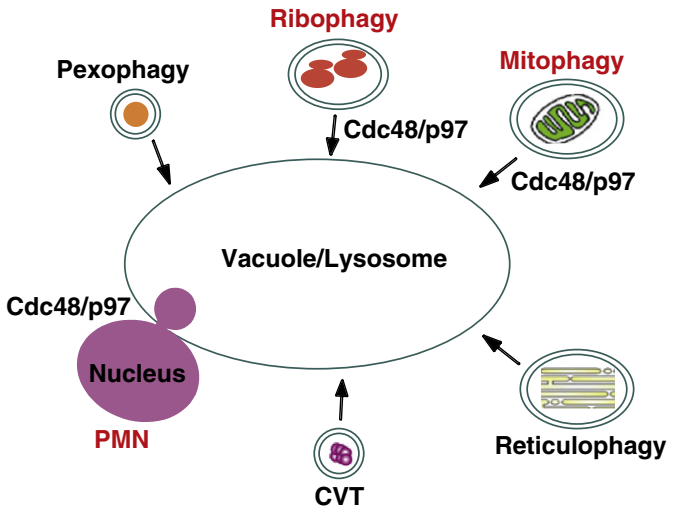

Fig. 3. Schematic presentation of selective autophagy. There are several forms of selective autophagy, including yeast specific cytoplasm-to-vacuole targeting (CVT) pathway, required for the transport of two vacuolar enzymes, aminopeptidase I (Ape1) and α-mannosidase (Ams1), mitophagy and pexophagy involved in the degradation of mitochondria and peroxisomes, ER-phagy selectively targets the endoplasmic reticulum, 'piecemeal microautophagy of the nucleus' (PMN) required for degradation of non-essential portions of the nucleus at nucleus–vacuole junctions and ribophagy, a selective autophagic pathway for 60S ribosomal subunit degradation. So far, the role of Cdc48/p97 has been shown in ribophagy, mitophagy and PMN.

3.1. Cdc48/p97 and ribophagy

Under nitrogen starvation, mature ribosomes are degraded in yeast by ribophagy, that allows a degradation of the 60S ribosomal subunits faster than degradation of cytoplasmic components by non-selective autophagy. Ribophagy is monitored in vivo using Rpl25 and Rpl5 ribosomal proteins as markers. Starvation induces degradation of GFP-tagged Rpl25 or Rpl5 and accumulation of the GFP signal in the vacuole [58]. To characterize the factors responsible for such a process, a collection of mutants was screened for defects in vacuolar accumulation of Rpl25-GFP upon starvation. This approach led to the identification of the deubiquitylating complex Ubp3-Bre5 as a critical ribophagy component that, interestingly, requires the catalytic activity of this complex. Recently, Ubp3-Bre5 has been shown to form a tripartite complex with Cdc48/p97 and its cofactor Ufd3, a non-essential ubiquitin binding protein containing a PUL domain [27,59,60]. Ufd3 competes with the E4 ubiquitin ligase for interaction with Cdc48/p97 and consequently is believed to limit the rate of polyubiquitylation of bound substrates [28]. Cdc48/p97 not only regulates the fate of some Ubp3-Bre5 specific substrates, but is also required for the Ubp3-Bre5 dependent ribophagy [27,61]. Indeed, the starvation-induced vacuolar degradation of Rpl25-GFP is inhibited in both a thermosensitive mutant of *cdc48* as well as in *ufd3Δ* cells. Similarly to Ubp3-Bre5, Cdc48/p97 and Ufd3 do not participate to degradation of 40S ribosomal subunits. Although Cdc48/p97, Ufd3 and Ubp3-Bre5 are essential components of ubiquitin–proteasome system, the proteolytic activity of the proteasome is not involved in the ribophagy pathway. It has thus been proposed that efficient ribophagy requires Ubp3-Bre5-Ufd3-Cdc48/p97 dependent deubiquitylation of specific target(s) prior to vacuolar degradation [27]. In agreement with such a hypothesis, the Rsp5 ubiquitin ligase displays a synthetic ribophagy defect with loss of Ubp3 [62] (Fig. 4). Whether targets of Ubp3-Bre5-Ufd3-Cdc48 belong to the ribosome itself, to the ribophagy machinery or both, whether deubiquitylation only or dynamic ubiquitylation/deubiquitylation cycles are required for efficient ribophagy still remain open questions.

3.2. Cdc48/p97 and mitophagy

Mitophagy is required for the turnover of mitochondria as well as elimination of damaged or dysfunctional mitochondria. Mitophagy is also implicated in developmental processes as it allows the removal of undamaged mitochondria during maturation of reticulocytes and adapts the amount of mitochondria to the cell energy requirements [63–65]. Studies in yeast allowed to identify several mitochondrial proteins required for mitophagy including Atg32, the mitochondrial receptor, Atg11, the adaptor that mediates recruitment of mitochondria to the phagophore assembly site and Atg33, Uth1 or Aup1, probable sensors for age or redox stress [66–71]. In mammalian cells, the mitochondrial dysfunction is associated with a group of neurodegenerative pathologies, including Parkinson's disease (PD). Loss-of-function mutations in the PARK2 gene represent the most common cause of the familial form of PD [72]. The PARK2 gene product, Parkin is a ubiquitin ligase that contains a ubiquitin like domain and two Ring finger domains [73–75]. Although essentially located in the cytosol, Parkin is selectively recruited to the depolarized/damaged mitochondria and mediates engulfment of dysfunctional mitochondria by autophagosomes prior elimination [76]. Localization of Parkin to mitochondria is mediated by the PINK1 protein, a serine/threonine kinase located in the outer

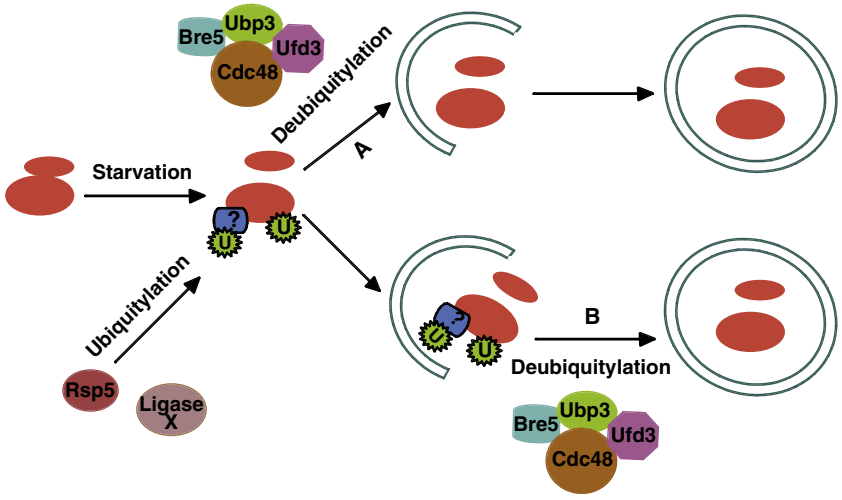

Fig. 4. Model for the role of Cdc48/p97 and its cofactors in ribophagy. Upon starvation, ubiquitylation of ribosome or ribosome associated protein(s) by Rsp5 and yet to be identified other ligase(s) may provide a signal for ribophagy. The Ubp3-Bre5-Ufd3-Cdc48/p97 complex may be required for deubiquitylation this (these) substrate(s) to allow either sequestration of ribosome in the autophagic membranes (A) or completion of autophagosome formation (B).

mitochondrial membrane, and encoded by the PARK6 gene also associated with familial form of PD [77–80]. In functional mitochondria, PINK1 located in the mitochondrial membrane is proteolytically cleaved into a cytosolic fragment that can be degraded by the proteasome [77,81,82]. The PINK1 cleavage depends on the mitochondrial voltage and is thus inhibited by loss of membrane potential leading to accumulation of PINK1 on the impaired mitochondria and recruitment of Parkin [80]. Parkin then promotes the ubiquitylation and proteasomal degradation of mitofusins, large GTPases anchored in the membrane and responsible for mitochondrial fusion [83]. Damage-induced loss of mitofusins prevents fusion of dysfunctional to unaffected mitochondria, and targets them to the autophagy pathway. Interestingly, overexpression of a dominant-negative form of Cdc48/p97 prevents Parkin-mediated mitofusins degradation as well as elimination of depolarized mitochondria, indicating that Cdc48/p97 is required for mitophagy [84]. However a general defect of the Ubiquitin/Proteasome degradation system in this experimental condition rather than a specific involvement of Cdc48/p97 cannot be formally excluded. Whether Cdc48/p97 and Parkin directly interacts to promote ubiquitin-degradation of mitofusins remains unclear. By analogy to its function in ERAD, Cdc48/p97 has been proposed, together with cofactors, to extrude mitofusins and other ubiquitylated proteins from the damaged mitochondrial membrane and target them for degradation by the proteasome [84–86].

3.3. Cdc48/p97 and other types of selective autophagy pathways

Besides the role of Cdc48/p97 in the ribophagy and the mitophagy processes, Cdc48/p97 has also been reported to favor PMN. Indeed the vacuolar degradation of GFP-Osh1, a micronucleophagic marker is not only inhibited in a thermosensitive mutant of *cdc48/p97* but also in *shp1Δ* cells, suggesting that Cdc48/p97 together with its cofactor Shp1 are required for PMN [46]. A role of Cdc48/p97 has been proposed in the formation of perinuclear aggresomes and in the autophagic clearance of protein aggregates, a function likely mediated by its cofactor HDAC6 [87,88]. In contrast Cdc48/p97 does not participate to the CVT pathway [46]. A complete overview of the Cdc48-dependent autophagic processes including pexophagy or ER-phagy still remains to be determined in order to precise the involvement of this chaperone in each step of this catabolic function.

4. Concluding remarks

Molecular mechanisms responsible for the different autophagic pathways are far from being fully characterized and understood. However, as illustrated in this review, Cdc48/p97 already appears as a major actor involved in distinct general or selective autophagic processes. In most cases so far, Cdc48/p97 acts as a ubiquitin-dependent chaperone, as it does for classical cellular functions, and already represents a key factor in the crosstalk between autophagy and ubiquitin/proteasome catabolic pathways. Interestingly, a segregase activity of Cdc48/p97 to extract the PE-linked ubiquitin-like Atg8 from membranes has been speculated [46], suggesting that Cdc48/p97 may contribute more generally to ubiquitin-like-mediated functions and thus opening new avenues in the knowledge of this intriguing chaperone.

Acknowledgments

We are grateful to A. Babour and A. Buchberger for critical reading of the manuscript. This work was supported by the Association for Research against Cancer.

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