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Review

Create and preserve: Proteostasis in development and aging is governed by Cdc48/p97/VCP☆

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ABSTRACT

The AAA-ATPase Cdc48 (also called p97 or VCP) acts as a key regulator in proteolytic pathways, coordinating recruitment and targeting of substrate proteins to the 26S proteasome or lysosomal degradation. However, in contrast to the well-known function in ubiquitin-dependent cellular processes, the physiological relevance of Cdc48 in organismic development and maintenance of protein homeostasis is less understood. Therefore, studies on multicellular model organisms help to decipher how Cdc48-dependent proteolysis is regulated in time and space to meet developmental requirements. Given the importance of developmental regulation and tissue maintenance, defects in Cdc48 activity have been linked to several human pathologies including protein aggregation diseases. Thus, addressing the underlying disease mechanisms not only contributes to our understanding on the organism-wide function of Cdc48 but also facilitates the design of specific medical therapies. In this review, we will portray the role of Cdc48 in the context of multicellular organisms, pointing out its importance for developmental processes, tissue surveillance, and disease prevention. This article is part of a Special Issue entitled: Ubiquitin–Proteasome System. Guest Editors: Thomas Sommer and Dieter H. Wolf.

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1. Introduction

Protein degradation is vital for the regulation of protein homeostasis (proteostasis) and triggers a variety of processes including cell cycle progression and cellular signaling. Lysosomal proteolysis mainly affects macromolecular structures or entire organelles and depicts a rather coarse mechanism regarding the targeted substrates, albeit dedicated adaptor proteins can also mediate substrate specificity [1,2]. In contrast, the ubiquitin–proteasome system (UPS) represents the major selective proteolytic pathway in eukaryotic cells defining the degradation of specific substrate proteins. For its initiation a poly-ubiquitin chain is attached to target proteins by a catalytic cascade based on ubiquitin-activating (E1), ubiquitin-conjugating (E2), and ubiquitin-ligating enzymes (E3) [3]. In some cases ubiquitin chain elongation factors called E4 enzymes are required for efficient ubiquitylation [4,5]. Polyubiquitylated proteins are then degraded within the 26S proteasome, a multicatalytic protease complex localized both in the cytosol and the nucleus (Fig. 1) [6–8]. Of note, protein ubiquitylation does not necessarily result in proteasomal degradation at all times. Attachment of ubiquitin to one or multiple sites of a substrate protein as well as the length of the ubiquitin chain and the linkages in between ubiquitin molecules encode specificity towards distinct cellular pathways [9]. For instance, chains linked via the lysine 48 residue (K48) of ubiquitin represent the conventional signal for proteasomal degradation [6]. Conversely, modification with a single ubiquitin molecule or K63-linked chains, primarily triggers lysosomal degradation as well as non-proteolytic signaling pathways [10,11].

Downstream of the ubiquitylation reaction, tagged proteins are recognized by dedicated ubiquitin binding adaptors that eventually promote the delivery to the 26S proteasome [9]. A key factor involved in substrate recruitment, processing, mobilization as well as subsequent proteasomal transfer is Cdc48 [12], a ubiquitin-selective segregase. Cdc48 is a highly conserved and abundant protein in all eukaryotes (Cdc48 in yeast, CDC-48 in *Caenorhabditis elegans* (*C. elegans*), TER94 in *Drosophila melanogaster*, p97 or VCP in vertebrates, for simplicity referred to as Cdc48) that belongs to the ATPases associated with diverse cellular activities (AAA+) protein family [13]. ATP hydrolysis results in dramatic conformational changes of the homohexameric, barrel shaped Cdc48 complex [14,15]. These dynamic rearrangements seem to drive ubiquitin-directed disassembly of substrate complexes [16]. Thereby, Cdc48 generates mechanical forces to selectively mobilize

Abbreviations: AAA, ATPase associated with diverse cellular activities; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; AMPK, adenosine monophosphate activated kinase; Cdc48/CDC-48, cell division cycle protein 48; DUB, de-ubiquitylating enzyme; ERAD, endoplasmic reticulum-associated degradation; HD, Huntington's disease; IBMPFD, inclusion body myopathy with Paget's disease of bone and frontotemporal dementia; MAD, mitochondria-associated degradation; MJD, Machado–Joseph disease; OMM, outer mitochondrial membrane; polyQ, extended poly-glutamine stretch; STUbL, SUMO-targeted ubiquitin ligase; TLS pol, translesional DNA polymerases; TOR, target of rapamycin; UBX, ubiquitin regulatory x; UPS, ubiquitin–proteasome system; VCP, valosin-containing protein

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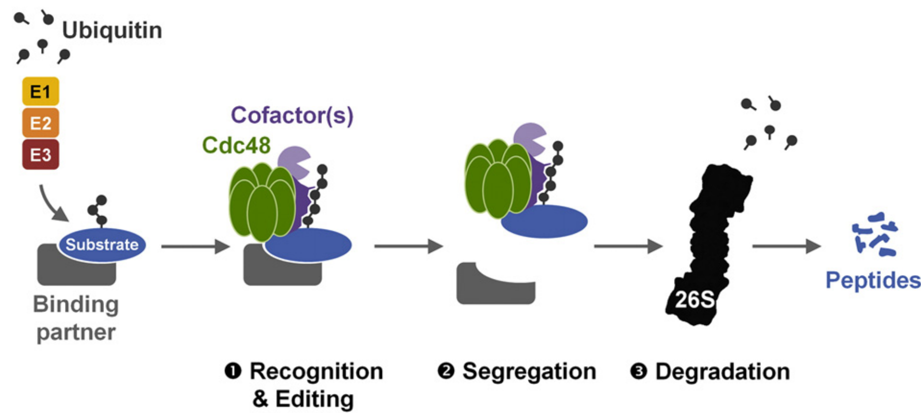

Fig. 1. Mechanistic model for the ubiquitin-selective chaperone Cdc48. Substrate proteins (blue) are earmarked by covalent attachment of ubiquitin chains by E1, E2, and E3 enzymes (yellow, orange, red). ❶ Cdc48 hexamers (green) cooperate with dedicated cofactors (lilac) in substrate recognition and together with E3/E4 or de-ubiquitylating (DUB) enzymes in ubiquitin chain editing. ❷ The chaperone activity of Cdc48 is required to mobilize substrate proteins from binding partners (light gray) such as protein complexes, membranes, or chromatin. ❸ After segregation of client proteins from their binding partner, substrates are optionally transferred to the 26S proteasome (dark gray) for degradation. See text for further details and references.

substrates out of multimeric protein complexes, usually followed by proteasomal degradation (Fig. 1) [17]. In addition, Cdc48 acts in segregating proteins out of multisubunit complexes or from immobile structures without promoting subsequent proteolysis of the substrate (Fig. 1) [18–20]. Although the exact mechanistic requirement for Cdc48 is unclear and could even be context-specific, protein unfolding at least partially might be a common mechanism [17,21,22].

Initially characterized biochemically [23], Cdc48 was soon linked to the UPS [24] and implicated in the maintenance of cellular proteostasis. Moreover, Cdc48 emerges as a pivotal regulator of lysosomal proteolysis through autophagic and endosomal trafficking (Fig. 2) [25]. Besides the rather broad function in protein turnover, a variety of cellular pathways [26,27] controlling cell cycle progression, transcription, DNA damage response, endoplasmic reticulum (ER)-associated degradation (ERAD), and mitochondria-associated degradation (MAD) are governed by Cdc48 (Fig. 2) [26–29]. The coordination of these diverse cellular pathways is defined by alternative cofactors forming individual Cdc48 complexes (Figs. 1 and 2) [26,30,31]. Depending on their activities, Cdc48 binding partners are subdivided into substrate recruiting and substrate processing cofactors [32]. The recruiting factors p47 and Ufd1/Npl4 compose distinct Cdc48 core complexes that determine substrate specificity and handling [33,34]. Processing factors such as E3 and E4 enzymes [4], or de-ubiquitylating enzymes (DUBs) associate with Cdc48 to define the topology of ubiquitin chains by chain editing on substrate proteins (Fig. 1) [35,36].

Most of the initial research on Cdc48 function was conducted *in vitro*, cultured cells, or in yeast. These studies deeply strengthened the understanding of Cdc48 on the molecular level. However, single cell studies bear a natural limitation as developmental and tissue-specific functions cannot be considered. Especially with respect to the complexity of age-related diseases, studying multicellular organisms is inevitable. Since Cdc48 is conserved from archaea to humans, it is conceivable to take advantage of the different model organisms at hand and to address pursuing issues concerning tissue functionality. Here, we highlight the physiological relevance of Cdc48 activity in the development of multicellular organisms and delineate its vital function in cellular proteostasis mechanisms and tissue maintenance in the context of development and aging.

2. Create: Cdc48 function in development

2.1. Proliferation and reproduction

2.1.1. Gametogenesis

In sexually breeding organisms the availability of haploid gametes is a prerequisite for propagation of genetic information to the next generation. In the course of gametogenesis DNA duplication is followed by two consecutive rounds of chromosome segregation in meiotic divisions I and II, respectively. After fertilization haploid sperm and oocyte fuse and give rise to a diploid zygote generating a new organism. To ensure reliable reproduction meiotic divisions are tightly regulated, which involve ubiquitin-mediated protein turnover [37]. Sasagawa and colleagues identified a critical function of Cdc48 during meiotic cell division in *C. elegans* [38]. In fact, complete downregulation of *cdc48* by RNAi results in the formation of one-celled embryos arrested with aberrant chromosomes during the first meiotic division. Now, it was uncovered that restriction of the *C. elegans* Aurora-B kinase AIR-2, to defined domains between homologous chromatids is essential for chromosomal integrity and meiotic progression [39]. The two meiotic divisions, usually occurring in succession, appear to be executed simultaneously in the absence of Cdc48. This defect in meiotic timing might be explained by an expansion of AIR-2 activity to ectopic chromosome regions and excessive phosphorylation of histone H3 [39] as well as other AIR-2 substrates, which presumably causes unscheduled release of cohesion between chromosomes.

Intriguingly, Aurora-B has initially been identified as a Cdc48 substrate in mitotic chromosome segregation using *Xenopus* egg extracts [18]. In this context Aurora-B is removed from chromatin late in mitosis, promoting chromatin decondensation and reformation of the nucleus. In yeast cells Cdc48 restricts Aurora-B/Ilp1 kinase activity but not chromatin association implicating explicit mechanistic differences in between species [41,48]. While a role of Cdc48 in Aurora-B regulation is conserved in principle in yeast and human cells [40,48], the mitotic regulation of AIR-2 in nematodes is still controversial [18,42,43]. Surprisingly, removal of AIR-2 from mitotic chromatin depends on the related AAA-ATPase CDC-48.3 (AFG2 in human or Drg1 in yeast), however, it does not require Cdc48. Drg1 ATPase activity facilitates ribosome maturation in yeast by segregation of cytoplasmic shuttling factors from the pre-60S particle [44,45]. The mechanistic function of CDC-48.3 and whether it is linked to ubiquitin-mediated processes have not been revealed so far [46] and will be tempting to address in future studies.

2.1.2. Proliferation

Originally, Cdc48 has been identified in a screen for yeast mutants that are defective in cell cycle progression [47], which has been further substantiated just recently [41]. Although our knowledge of Cdc48 function is steadily increasing, its role in cell cycle regulation remains unclear. Cell division comprises the faithful replication of DNA and accurate distribution of sister chromatids to the daughter

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