FEBS Letters xxx (2013) xxx–xxx

journal homepage: www.FEBSLetters.org

Hypothesis

Formation of alternative proteasomes: Same lady, different cap?

Elah Pick *, Tali S. Berman

Department of Biology and Environment, University of Haifa at Oranim, Tivon 36006, Israel

ARTICLE INFO

Article history:
Received 26 October 2012
Revised 23 December 2012
Accepted 7 January 2013
Available online xxxx

Edited by Noboru Mizushima

Keywords:
26S proteasome
COP9 signalosome (CSN)
Cullin RING E3 ligases
P97
Ubiquitin
VAT

ABSTRACT

The 26S proteasome is thought to be a homogenous complex, consisting of a 20S proteolytic core and a 19S regulatory particle that is required for its activation.

Two groups have recently reported the activation of archeal 20S by a p97-related double-ring AAA+ ATPase complex, in a similar fashion to that reported for 19S. Since p97 is found in eukaryotes, the existence of a parallel setting in higher organisms is intriguing. Herein, we present supporting data and hypothesize that in eukaryotes, p97 and CSN form a promiscuous, hence hard-to-detect, "alternative cap", enabling the prompt and precise elimination of particular substrates.

© 2013 Published by Elsevier B.V. on behalf of the Federation of European Biochemical Societies.

1. Introduction

Rapid response of cells to environmental changes or stress is key for all domains of life. Adjustment to new circumstances requires alterations of the cellular environment through degradation of unneeded proteins by the 26S proteasome, a master regulator of cellular quality control [1]. The 26S proteasome is a mega complex, arranged in 2 major assemblages: the 20S core particle (CP), a barrel-shaped complex, which is composed of 4 stacked heptameric rings (α,β,β,α), forming a tightly sealed gated cylinder, and the 19S regulatory particle (RP), which caps the 20S CP and controls/activates the entrance into the proteolytic cavity. The 19S RP (also referred to as "cap") is divided into lid and base assemblies. The lid is composed of 9 subunits (Rpn3, 5–9, 11, 12, and 15) and has a deubiquitinase enzymatic activity essential for proteolysis (donated by Rpn11). The base includes 2 large solenoid-shaped subunits (Rpn1, 2), 2 ubiquitin receptors (Rpn10, 13), and a motor AAA+ ATPase ring, which comprises 6 distinct subunits (Rpt1–6), and is required for the unfolding of substrates, opening the gate, and translocating substrates into the 20S CP [2]. Recent cryo-electron microscopy studies have provided evidence that several lid subunits interact directly with the AAA+ motor domain within several Rpt subunits (Rpn7 with Rpt2/6; rpn5/6 with Rpt3) [3–7] and even with the 20S (i.e. Rpn6) [8], suggesting that the Rpt1–6 ATPases ring is more static than was thought and might be motivated through substantial conformational rearrangements achieved by incorporation of the lid into the 26S holocomplex [5]. Activation of the 20S by the 19S involves interactions with a binding pocket within the α ring of the 20S CP, causing extensive conformational changes in the 20S and resulting in gate opening [9].

The ubiquitin proteasome system (UPS) plays an essential role in a variety of fundamental cellular processes. Not surprisingly, multiple proteasome activators (PA) exist in addition to the well-studied default 19S RP configuration. Three proteasome regulators, PA28/11S, PA200/Blm10, and ECM29, were found to compete with the 19S RP on the α-ring activation-binding site, in a non-ATP-dependent manner [10]. The PA28/11S consists of heteroheptameric (α,β,γ) rings, is induced by interferon-γ, associated with the 20S, and involved in immune response [11]. PA200/Blm10 activates the 20S and has a role in spermatogenesis, DNA repair, and other pathways [12]. ECM29, functions as a chaperon and stabilizer of proteasome 20S–19S interactions, as well as a negative regulator, which suppresses gate opening and causes proteasome blockage [13–16]. However, because interaction with the 20S CP (upon a specific cellular function or stress) could be transient, the list of proteasome regulators in eukaryotes might be longer and difficult to predict. One thing is clear, the proteasome is not assembled as one homogenous entity, and the exact number of

Abbreviations: Hb-Y-X, hydrophobic-tyrosine-X motif; PA, proteasome activator; CSN, COP9 signalosome; CRL, Cullin RING E3 ligase; PAN, proteasome-activating nucleotidase; Ribophagy, Ribosome autophagy; UbD, ubiquitin-binding domain; DUb, deubiquitinationg enzyme; UPS, ubiquitin proteasome system

* Corresponding author. Address: Department of Biology and Environment, Faculty of Natural Sciences, University of Haifa, Oranim, 36006 Tivon, Israel. Fax: +972 4 9539608.

E-mail address: elahpic@research.haifa.ac.il (E. Pick).

0014-5793/$36.00 © 2013 Published by Elsevier B.V. on behalf of the Federation of European Biochemical Societies.
http://dx.doi.org/10.1016/j.febslet.2013.01.014

Please cite this article in press as: Pick, E. and Berman, T.S. Formation of alternative proteasomes: Same lady, different cap? FEBS Lett. (2013), http://dx.doi.org/10.1016/j.febslet.2013.01.014

PA-complexes and their respective roles is thus far, shrouded in mystery (Fig. 1).

Whereas both 19S substructures (base and lid) are found only in eukaryotes, a base-like subcomplex composed of AAA+ ATPases is found in several prokaryotes, with a conserved evolutionary role in acceleration of selective proteolysis. A few examples are ARC (*Rhodococcus erythropolis*), or MPA (*Mycobacterium tuberculosis*) that activate bacterial orthologs of the 20S proteasome [10,17]. Other bacterial examples are ClpA, C, or X, all of which activate the ClpP protease [18]. In archea, a homohexameric ring that is located proximally to the catalytic 20S subcomplex is known as PAN (proteasome-activating nucleotidase) [19]. PAN exhibits the highest homology with the eukaryotic Rpt-ring of ATPases, and shares more than 40% of amino acid similarity with them [20]. Interestingly, PAN is absent in several archea and is not required for viability of other archea in which the 20S exists and is required for protein degradation.

2. New insights regarding proteasome activators based on studies in archea

Recent studies have suggested a regulatory network of proteasome AAA+ ATPases across the archea kingdom. Bioinformatics analysis suggests that PAN is not alone, and that the putative number of proteasome ATPases in archea varies between 1 and 5, including the double ring AAA+ ATPase Cdc48/p97/VAT (p97), which is conserved from archea to humans. Interactions between archeal p97 and 20S CP, and formation of active proteasomes were found so far in 2 organisms, *Thermoplasma acidophilum* and *Methanosarcina Mazei* [21–23]. These newly described assemblages are actively involved in translocation of substrates into the proteolytic cavity [21,22]. Using bioinformatics tools, Barthelme and Sauer [16] showed that p97 is the only 20S CP potential partner in ~15% of archea, and that both p97 and PAN exist in similar rates in the remaining ~85% of analyzed genomes [16]. Interactions between the 20S and p97 involve a similar, conserved C-terminal hydrophobic-tyrosine-X motif (Hb-Y-X), which is also found in PAN and the Rpt1–6 ring [24,25]. In all of these interactions, the core complex is activated through docking of the activator into the α-ring-binding pockets within the 20S (Fig. 2) [21,24–26]. Interestingly, the Hb-Y-X motif exists not only in other archeal but also in eukaryotic p97 enzymes, suggesting a common mechanism for activation of proteolysis and that p97 has the potential of forming active proteasomes [16]. These new data raise questions regarding the evolutionary conservation of this unconventional architectural design (Fig. 2).

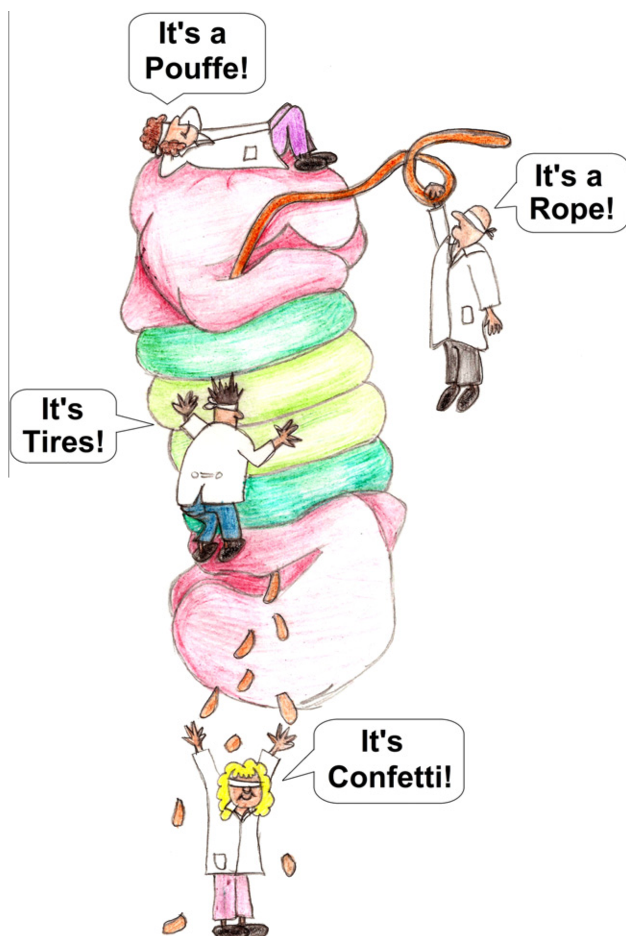

Fig. 1. Understanding proteasome function and regulation. Similar to the story about the blindfolded scientists who described an elephant differently according to the organ they held, the role and control systems of the proteasome are not fully understood in the scientific world.

3. p97 as a Proteasome activator: supporting information

Could it be that the eukaryotic p97 replaces the 19S and directly promotes selective protein degradation? In eukaryotes, p97 ATPase functions in a plethora of pathways with an important role in preparing proteins for degradation through the 2 key degradation apparatuses: the proteasome and the lysosome [27]. It participates in a wide range of cellular processes including cell-cycle regulation, response to DNA damage, ER degradation, and autophagy [28]. Together with its counterparts, p97 binds to polyubiquitinated substrates and uses ATP to unwind them. If required, p97 also functions to extract clients out of membranes or chromatin, and to eventually facilitate their degradation [29].

The eukaryotic p97 interacts with substrates that are covalently attached to a poly-ubiquitin chain through an array of p97-binding factors, such as the Ufd1/Npl4 counterparts that are required for extraction of substrates from chromatin and membranes, or members of the UbX family that harbor a ubiquitin-binding domain (UbD) and connect between p97 and substrates. Additionally, p97 also binds to an array of deubiquitinating enzymes (DUbs) such as the ovarian tumor protein Otu1, atx3 that regulates the degradation of misfolded ER proteins, Yod that is included in ER disclosure, or the Ubp3/Bre5 factors in budding yeast that are involved in ribosome autophagy (ribophagy) [30–33]. Interactions between 2 enzymes such as a DUb and an unfoldase (p97), could be explained by the need for recycling of client proteins. Yet, in addition to interactions with DUbs, the mammalian p97 interacts also with the proteasome [34], and may have the potential to play a role of PA, and to enable a prompt degradation of ubiquitinated proteins in situ. p97 and the 19S-RP have common characteristics: both include a molecular ATPase engine, interact with ubiquitin shuttles and with deubiquitinating enzymes, and both are involved in the regulation of proteolysis. Proteasome activation by p97 might explain the involvement of this molecule in the precise and rapid degradation of a wide array of proteasome substrates. Nevertheless, suggesting that eukaryotic p97 serves as an "alternative base" that activates the 20S-CP is unimaginable, because interactions between p97 and the eukaryotic proteasome have so far been confirmed only through the 19S and not directly with the 20S [29,34].

Finley and Matouschek have suggested 2 models that may explain the contribution of p97 to the eukaryotic proteasome [23]. The first model suggests that p97 was initially an integral part of the degradation machinery, however, the eukaryotic 19S took over the 20S-binding site, and interactions between p97 and the

Download English Version:

https://daneshyari.com/en/article/10870998

Download Persian Version:

https://daneshyari.com/article/10870998

Daneshyari.com