Proteasome

Characteristics

A protein that carries a K48 polyubiquitin chain. It can be recognized by the so-called 26S proteasome and degraded in it.

The 26S proteasome is a common type of proteasome found in our cells. It consists of two basic parts [1]:

1. 20S proteasome, i.e. the **core particle**, which has the shape of a cylinder and in which the proteolysis of PDG itself takes place;
2. 19S proteasome or **regulatory particle**, which is also called PA700.

Main particles

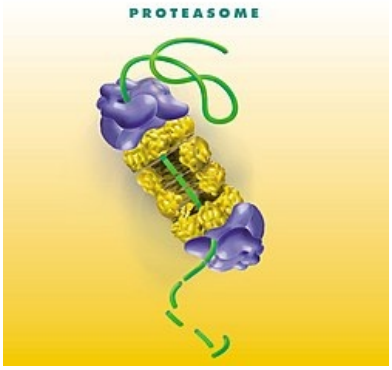
The 20S proteasome consists of a total of four rings. The two outer ones are formed by seven *α units* and the two inner ones by seven *β subunits* . The active protein-cleaving sites are in the β rings and face the inside of the 20S proteasome cylinder, namely:

- β1 subunit with caspase-like activity ;
- β2 subunit with trypsin -like activity ;
- β5 subunit with chymotrypsin-like activity.

In addition to the normal 20S proteasome, inducible proteasomes also exist in our cells. These have other active sites (β1i, β2i and β5i), which are called immunoproteasomes or mixed proteasomes. They play a role in the immune response of cells to foreign substances [2]. A very special type of proteasome exists in the thymus, the so-called **thymoproteasome**. They contain a β5t subunit with unusual catalytic activity. Their role is related to the positive selection of CD8+ T cells[3].

Regulatory particles

Regulatory particles bind to the outer, i.e. α, ring of the 20S proteasome. In addition to the 19S proteasome, these can also be other complexes, such as PA28 or PA200, or even proteins that reversibly attach to the 20S proteasome in substoichiometric amounts[4]. Although the organization of proteasomes varies dynamically, it has been shown that the 26S proteasome remains intact during protein degradation[5].



Proteazom

The regulatory particle of the 26S proteasome (PA700) contains two basic, interconnected regions: the **base** and the **lid**. In the base we can find six different AAA+ ATPases and another four subunits. Its main mission is to regulate entry into the interior of the 20S proteasome[6]. The lid contains nine non-ATPase subunits [7] and its basic function is the deubiquitination of ubiquitinated proteins by the JAMM domain DUB Poh1 before their entry into the interior of 26S proteasomes[8].

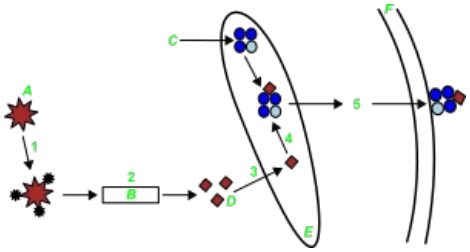
Degradation of non-ubiquitinated proteins

A typical protein, degraded in a eucaryotic cell by the proteasome, must be ubiquitinated. However, according to recent findings, about 20% of all proteins cleaved by proteasomes in eukaryotic cells may not have ubiquitin labeling. Such proteins contain poorly ordered sites in their structures, which serve as a non-specific signal for degradation in proteasomes without the need for ubiquitination of the given protein[9].

Degradation of ubiquitinated proteins

We will focus on the mechanism of degradation of ubiquitinated PDGs in 26S proteasomes.

Some subunits from the base (ubiquitin receptors) and also some proteins that only transiently associate with 26S proteasomes play a key role in the recognition of the ubiquitinated protein[10]. If the ubiquitinated protein is already bound to the 26S proteasome, its polyubiquitin chain can be variously cleaved by the proteasome and resynthesized by deubiquitinases and ubiquitin ligases[11]. It has also been shown that the reduction in the intensity of the degradation of ubiquitins themselves in the proteasome is related to the activity of a specific DUB, called Ubp6, which is not a constant subunit of the 26S proteasome[12].



Individual steps

- Before PDG degradation itself, the polyubiquitin chain is usually cleaved en bloc (as a whole, at once) by **Poh1** and further removed by other DUBs[13].
- The unfolding of the protein into the primary structure and its movement into the opening of the proteasome is then associated with the hydrolysis of ATP by AAA+ ATPases [14].
- The unfolded protein can be "stored" in the α rings if the β rings are still occupied by the degradation of the previous PDG[15]. Proteins can enter the 20S proteasome from both sides[16]. Degradation continues as long as the resulting oligopeptides are not small enough to spontaneously diffuse out[17].
- As soon as the oligopeptides get out of the 26S proteasomes, they are further cleaved in the cell by other peptidases to amino acids that can be used for further protheosynthesis[18], or are used within the immune system as antigens [19].

Regulation of protein activity

Some proteins are not completely degraded by 26S proteasomes, but are actually activated. This happens by degrading other proteins that are bound to them and inhibit them. A typical example is the activation of the so-called nuclear factor-κB (NF-κB), which normally occurs in the cytoplasm in a complex with its inhibitor I-κB. Once this I-κB is ubiquitinated and degraded, NF-κB translocates to the nucleus and triggers the transcription of the relevant genes[20]. The function of 26S proteasomes is not only connected with the regulation of the amount of a given protein in the cell, but also with the regulation of the activity of various proteins. This implies that the UPS plays a key role in many therapeutically relevant processes, such as inflammatory diseases, neurodegenerative processes, muscular dystrophies , viral infections or carcinogenesis [21]_[22].

Links

Související články

- Proteins
- Degradation of proteins
- Degradative system of the cell
- Ubiquitination
- Deubiquitination
- History of the ubiquitin-proteasome system
- Proteasome inhibitors
- Translation

External links

- Proteazom (česká wikipedie)
- Proteasome (anglická wikipedie)

References

1. BEDFORD, Lynn – PAINE, Simon – SHEPPARD, Paul W. , et al. Assembly, structure, and function of the 26S proteasome. *Trends Cell Biol* [online]. 2010, vol. 20, no. 7, p. 391-401, Available from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2902798/?tool=pubmed>. ISSN 0962-8924 (print), 1879-3088.
2. STREHL, Britta – SEIFERT, Ulrike – KRÜGER, Elke. , et al. Interferon-gamma, the functional plasticity of the ubiquitin-proteasome system, and MHC class I antigen processing. *Immunol Rev* [online]. 2005, vol. 207, p. 19-30, Available from <https://www.ncbi.nlm.nih.gov/pubmed/16181324>. ISSN 0105-2896.
3. MURATA, Shigeo – TAKAHAMA, Yousuke – TANAKA, Keiji. Thymoproteasome: probable role in generating positively selecting peptides. *Curr Opin Immunol* [online]. 2008, vol. 20, no. 2, p. 192-6, Available from <https://www.ncbi.nlm.nih.gov/pubmed/18403190>. ISSN 0952-7915.
4. DEMARTINO, George N – GILLETTE, Thomas G. Proteasomes: machines for all reasons. *Cell* [online]. 2007, vol. 129, no. 4, p. 659-62, Available from <https://www.ncbi.nlm.nih.gov/pubmed/17512401>. ISSN 0092-8674.
5. KRIEGENBURG, Franziska – SEEGER, Michael – SAEKI, Yasushi. , et al. Mammalian 26S proteasomes remain intact during protein degradation. *Cell* [online]. 2008, vol. 135, no. 2, p. 355-65, Available from <https://www.ncbi.nlm.nih.gov/pubmed/18957208>. ISSN 0092-8674 (print), 1097-4172.
6. LI, Xiaohua – DEMARTINO, George N. Variably modulated gating of the 26S proteasome by ATP and polyubiquitin. *Biochem J* [online]. 2009, vol. 421, no. 3, p. 397-404, Available from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2872633/?tool=pubmed>. ISSN 0264-6021 (print), 1470-8728.
7. SHARON, Michal – TAVERNER, Thomas – AMBROGGIO, Xavier I. , et al. Structural organization of the 19S proteasome lid: insights from MS of intact complexes. *PLoS Biol* [online]. 2006, vol. 4, no. 8, p. e267, Available from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1523230/?tool=pubmed>. ISSN 1544-9173 (print), 1545-7885.
8. VERMA, Rati – ARAVIND, L – OANIA, Robert. , et al. Role of Rpn11 metalloprotease in deubiquitination and degradation by the 26S proteasome. *Science* [online]. 2002, vol. 298, no. 5593, p. 611-5, Available from <https://www.ncbi.nlm.nih.gov/pubmed/12183636>. ISSN 0036-8075 (print), 1095-9203.
9. BAUGH, James M – VIKTOROVA, Ekaterina G – PILIPENKO, Evgeny V. Proteasomes can degrade a significant proportion of cellular proteins independent of ubiquitination. *J Mol Biol* [online]. 2009, vol. 386, no. 3, p. 814-

proportion of cellular proteins independent of ubiquitination. *J Mol Biol* [online]. 2008, vol. 386, no. 3, p. 827-27, Available from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2649715/?tool=pubmed>. ISSN 0022-2836 (print), 1089-8638.
10. VERMA, Rati – OANIA, Robert – GRAUMANN, Johannes. , et al. Multiubiquitin chain receptors define a layer of substrate selectivity in the ubiquitin-proteasome system. *Cell* [online]. 2004, vol. 118, no. 1, p. 99-110, Available from <https://www.ncbi.nlm.nih.gov/pubmed/15242647>. ISSN 0092-8674.
11. CROSAS, Bernat – HANNA, John – KIRKPATRICK, Donald S. , et al. Ubiquitin chains are remodeled at the proteasome by opposing ubiquitin ligase and deubiquitinating activities. *Cell* [online]. 2006, vol. 127, no. 7, p. 1401-13, Available from <https://www.ncbi.nlm.nih.gov/pubmed/17190603>. ISSN 0092-8674.
12. HANNA, John – MEIDES, Alice – ZHANG, Dan Phoebe. , et al. A ubiquitin stress response induces altered proteasome composition. *Cell* [online]. 2007, vol. 129, no. 4, p. 747-59, Available from <https://www.ncbi.nlm.nih.gov/pubmed/17512408>. ISSN 0092-8674.
13. KOULICH, Elena – LI, Xiaohua – DEMARTINO, George N. Relative structural and functional roles of multiple deubiquitylating proteins associated with mammalian 26S proteasome. *Mol Biol Cell* [online]. 2008, vol. 19, no. 3, p. 1072-82, Available from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2262970/?tool=pubmed>. ISSN 1059-1524 (print), 1939-4586.
14. STRIEBEL, Frank – KRESS, Wolfgang – WEBER-BAN, Eilika. Controlled destruction: AAA+ ATPases in protein degradation from bacteria to eukaryotes. *Curr Opin Struct Biol* [online]. 2009, vol. 19, no. 2, p. 209-17, Available from <https://www.ncbi.nlm.nih.gov/pubmed/19362814>. ISSN 0959-440X (print), 1879-033X.
15. SHARON, Michal – WITT, Susanne – FELDERER, Karin. , et al. 20S proteasomes have the potential to keep substrates in store for continual degradation. *J Biol Chem* [online]. 2006, vol. 281, no. 14, p. 9569-75, Available from <https://www.ncbi.nlm.nih.gov/pubmed/16446364>. ISSN 0021-9258.
16. HUTSCHENREITER, Silke – TINAZLI, Ali – MODEL, Kirstin. Two-substrate association with the 20S proteasome at single-molecule level. *EMBO J* [online]. 2004, vol. 23, no. 13, p. 2488-97, Available from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC449772/?tool=pubmed>. ISSN 0261-4189.
17. KÖHLER, A – CASCIO, P – LEGGETT, D S. , et al. The axial channel of the proteasome core particle is gated by the Rpt2 ATPase and controls both substrate entry and product release. *Mol Cell* [online]. 2001, vol. 7, no. 6, p. 1143-52, Available from <https://www.ncbi.nlm.nih.gov/pubmed/11430818>. ISSN 1097-2765.
18. VABULAS, Ramunas M – HARTL, F Ulrich. Protein synthesis upon acute nutrient restriction relies on proteasome function. *Science* [online]. 2005, vol. 310, no. 5756, p. 1960-3, Available from <https://www.ncbi.nlm.nih.gov/pubmed/16373576>. ISSN 0036-8075 (print), 1095-9203.
19. KLOETZEL, Peter M. Generation of major histocompatibility complex class I antigens: functional interplay between proteasomes and TPPII. *Nat Immunol* [online]. 2004, vol. 5, no. 7, p. 661-9, Available from <https://www.ncbi.nlm.nih.gov/pubmed/15224091>. ISSN 1529-2908.
20. RAPE, Michael – JENTSCH, Stefan. Productive RUPture: activation of transcription factors by proteasomal processing. *Biochim Biophys Acta* [online]. 2004, vol. 1695, no. 1-3, p. 209-13, Available from <https://www.ncbi.nlm.nih.gov/pubmed/15571816>. ISSN 0006-3002.
21. RUBINSZTEIN, David C. The roles of intracellular protein-degradation pathways in neurodegeneration. *Nature* [online]. 2006, vol. 443, no. 7113, p. 780-6, Available from <https://www.ncbi.nlm.nih.gov/pubmed/17051204>. ISSN 0028-0836 (print), 1476-4687.
22. SCHWARTZ, Alan L – CIECHANOVER, Aaron. Targeting proteins for destruction by the ubiquitin system: implications for human pathobiology. *Annu Rev Pharmacol Toxicol* [online]. 2009, vol. 49, p. 73-96, Available from <https://www.ncbi.nlm.nih.gov/pubmed/18834306>. ISSN 0362-1642.