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Review Article

Morpho functional features of proteasomes. Participation in pathological processes. Inhibitors of the ubiquitin-proteasome system as potential drugs

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Abstract

Proteasomes are multiunit proteases that are found in the cytosol. Their ubiquitous presence and high abundance in compartments reflects their central role in cellular protein metabolism. Research on the proteasome over the past quarter of a century has provided a deep understanding of its structure and function, which has greatly contributed to our understanding of cell life. However, many questions remain to be clarified.

This review considers the main processes and interactions of proteasomes in the cell. Particular attention is paid to the role of proteasomes in pathology.

Keywords: proteasome; cell; protein; apoptosis; proteasome subunit; protein complex

Introduction

The proteasome is a large (2.5 MDa) multisubunit protein structure that provides ubiquitin-mediated destruction of proteins with a defective or altered structure subject to hydrolysis [1, 2]. This complex is located in the cytoplasm of the cells of all organisms, which indicates their absolute significance [3]. Their sizes are similar to those of ribosomes, but they are not always referred to as organelles.

According to modern concepts, cellular proteasomes are ubiquitous: they are located both in the nuclear space and in the cytosol. They are associated with membranes, with their phospholipids, being perpendicular to the hydrophilic side of the membranes, formed by the polar parts of lipid molecules [4]. In the course of studies, trypsin resistance was found in some proteasomes, which indicates incomplete penetration of proteasomes into the membrane [5].

Proteasomes are found in various extracellular fluids: cerebrospinal, alveolar, and blood plasma. Moreover, proteasomes were identified in the cell culture medium. The proteasomes found in the intercellular space were called extracellular, and those found in blood plasma were called "circulating proteasomes" (circulating proteasome), or c-proteasomes (c-proteasome), sometimes they are called p-proteasomes (p-proteasome; from: plasma proteasome) [1,6]. Generally speaking, proteasomes are a component of blood plasma and are normally present in all healthy individuals. Thus, the concentration of c-proteasomes measured using enzyme immunoassay in healthy people is, according to some researchers, 300 ng/ml, and according to others, 2350 ng/ml. The difference is based on the fact that the first authors determined the concentration of only 20S proteasomes (core part), while other researchers measured the total presence and structure of 20S and 26S proteasomes. This difference can be explained by the different enzyme immunoassay methods used [7,8].

Structural and functional organization of the proteasome

The 26S proteasome is an energy production dependent structure. Provides specific degradation of proteins that are conjugated with ubiquitin. The study using electron microscopic methods made it possible to establish that the proteasome has a dumbbell shape. The central part is represented by the enzyme center (or core part). This complex is connected on both sides to PA700 (Protein Activator), complexes that regulate proteasome activity [9].

The basis of the proteasome is the 20S core particle, which consists of 14 pairs of subunits with a mass of 25 to 35 kDa. All subunits are combined into a single structure. Its mass is 750 kDa. The 20S component is a figure of rotation (cylinder) with a length of 16 nm and a radius of 6 nm. The 20S-component of the proteasome includes 7 pairs of α-components and 7 β-components. The study of the structure using X-rays of the 20S proteasome confirmed the organization of the proteasome subunits into the $(\alpha)_7(\beta)_7(\beta)_7(\alpha)_7$ complex. Two pairs of rounded formations form three invaginations of the structure with a radius of about 2.5 nm [10].

The central space – proteolytic – is formed by two b-rings facing "head to head", and is isolated from the two outer cavities formed by the other sides of the b-rings and a-rings by a gate 3 nm thick. The volume of the external space of the 20S-component of the «*Thermoplasm Acidophilic*» is about 60 nm^3, the volume of the space located inside the enzyme complex is about 84 nm^3, and its dimensions are comparable to a globular ~70-kDa protein. Proteolytically active sites are located in the inner cavity of the cylinder at the N-terminals of the β-component, and the entry of the protein to be hydrolyzed into the cavity of the enzyme complex is limited by the "gates" on both sides of the 20S-proteasome formed by the N-terminals of the a-subunits [11,12].

All proteasome subunits have the same spatial structure based on the increased similarity of the α and β amino acids. Oriented in three-dimensional space, the packing of components is a pair of non-parallel of 5 strands of the β-plate, which are located between pairs of twisted (curvilinear) α-components and three of the same on the opposite side. A distinctive feature between the β and α components of proteasomes is the presence of an additional nonlinear structure in the latter [13].

This structure is a complex of closely adjacent rings. The outer rings are formed by α-components, and the inner rings by β. Threonine, which is a component of the β-components of proteasomes, contributes to the destruction of bonds within protein molecules that are subject to hydrolysis [1,3].

The proteasome belongs to the class of N-terminal nucleophilic hydrolases (NTN hydrolases). The inhibition of the efficiency of hydrolysis leads to the replacement of the N-terminal threonine of β-subunits with serine. The proteasome contains 14 protease centers. Three of the seven β-subunits have threonine-protease enzyme centers of different substrate specificity, that is, each proteasome has 6 protease centers. The β_1 subunit has caspase-like activity, the β_2 subunit has trypsin-like activity, and β_5 has chymotrypsin-like activity [1,7,13].

The proteinase centers formed by β-subunits face the internal proteolytic cavity. Through the pore formed by the α-subunits, the substrate can access them.

Forms of existence of proteasomes can be different. This is due to their modifications after translation. The functions of proteasomes can differ even from a minimal change in the charge of their constituents. This phenomenon is due to the physical properties (hydrophobic, electrical, etc.) of biological molecules [1, 3]. There are a number of modifications of proteasome protein molecules after the completion of the translation process, such as sumoylation, N^{α}-myristylation, N^{α}-methylation, succinylation, and others. Baker's yeast 26S proteasomes are currently the most studied type of modification of proteasome molecules due to the convenience of laboratory experiments (studying properties, obtaining mutations) on this substrate [14, 15].

The detection of ubiquitinated proteins and their preparation for degradation in the 20S catalytic proteasome occurs due to the proteasome regulatory complexes. This preparation consists of selecting and connecting with the object, releasing ubiquitin, unfolding and transporting the object to the part of the proteasome where hydrolysis will be performed (20S component). The sizes of protein molecules that are products of proteolysis are determined by the functioning of proteasome channels. The release of peptide residues of protein molecules, as a rule, occurs slowly. This is important for further effective proteolysis, which will be carried out by cytoplasmic enzymes [7,8].

The 26S proteasome is responsible for the breakdown of cellular peptide molecules. It destroys up to 90% of cellular proteins. The 20S component, which is the core part, is an isolated compartment. The core part consists of enzymatic centers that carry out proteolysis. Only those peptide molecules that are connected to four ubiquitin molecules can penetrate into the core part of the proteasome, which is usually closed. Entering the proteasome channel, the protein molecule loses its tertiary and secondary structures, breaking down with the formation of short peptides that leave the channel on the other side. The ubiquitin molecule does not enter the proteasome channel, and after the destruction of the protein, it is attached to the next protein molecule to be hydrolyzed – the so-called protein destruction due to the combination with ubiquitin [1,5]. Until 2004, it was believed that all unnecessary cellular proteins were hydrolyzed by lysosome proteases.

Methods For Studying Proteasomes

Various sources describe methods for isolating and purifying intracellular proteasomes. In fact, they can all be combined into one of two approaches: a biochemical method, which relies on the separation of proteins using stepped salting out, ultracentrifugation and chromatographic techniques, and purification by affinity binding on a sorbent. Each of the approaches has its own advantages and disadvantages. The main advantage of the affinity purification method is the speed of obtaining purified proteasomes: it takes several hours instead of several days [16].

Peptide affinity purification was generated by labeling the Rpn11 proteasome subunit with an HTBH polypeptide sequence that carries two sequences of six histidines (H), a TEV protease cleavage site (T), and a biotin-like sequence (B). The peptide binds strongly to avidin, which makes it possible to isolate proteasomes on an avidin carrier, followed by elution from the carrier using TEV protease cleavage [2,16].

For the extraction of the 26S component, there is a gel filtration method. However, the impossibility of pure extraction of the 26S component can be considered a disadvantage of this method. In addition, there is a method of ultracentrifugation. However, when using this method, the 26S-component remains in a mixture with the 20S-component, which makes ultracentrifugation unsuitable for analytical scientific research [1,7,8].

Functions Of The Proteasome

The lifetime of protein molecules in a cell is mainly determined by the proteasomes. Peptide molecules with an abnormal structure, antigens, etc. undergo hydrolysis in proteasomes. Proteasomes play an important role in regulating the activity of the immune system, as well as in all vital processes of tissue cells throughout the body (mitosis, tumor growth, and programmed cell death) [17]. That is, proteolysis inside the cell is not a mechanical process of peptide degradation, but part of the main factors that regulate the vital activity of cells.

Proteins cyclins regulate the sequential change of phases of the cell cycle. All phases of the cell cycle have their own regulator. This is what the 26S proteasomes provide. Some cyclins are known to contain regions concentrated with glutamic acid, serine, proline, and trionine as a recognition mark, while a number of others contain a conserved fragment of nine amino acids, which is usually located at a distance of 40 amino acid residues from the N-terminus. A regulatory peptide, identified by a label, is bound to the ubiquitin chain by its fragment and is cleaved by the 26S proteasome. It is clear that a failure in its work will lead to a stop of the cell cycle at one or another phase [16].

Proteasomes are also found in cancer cells. They can serve medicine as antitumor agents due to their ability to lead to apoptosis of malignant cells [18].

There are different points of view about extracellular proteasomes. For example, some scientists believe that the accumulation of proteasomes in the extracellular space is primarily associated with the need to "clear the territory" – getting rid of peptides concentrating in the extracellular space and activation of precursor proteins secreted by the cell, as well as antigen processing. Other researchers believe that the presence of proteasomes in the extracellular space is the cause of cell disorders and acts as a diagnostic marker of diseases. Still others consider extracellular proteasomes as a possible prognostic parameter in the outcome of diseases [1,13].

Modifications of the proteasome molecule that occur after the completion of the translation process are an important factor determining enzymatic activity, the ability to bind to a certain substrate, the location of the proteasome in the cell cytoplasm, and the preservation of the optimal structure of the molecule. A detailed study of proteasome molecules has not yet been completed and is a field for further research [1,8].

The role of proteasomes in pathology Involvement in the development of neurodegenerative diseases.

The main distinguishing feature of these diseases is the dysfunction and death of cells of the brain and spinal cord, as well as the formation of large aggregates in the cytoplasm, which are formed by proteins with an abnormal structure [19]. In many cases, aggregates contain ubiquitin and proteasomes. The functional relationship between proteasomes and ubiquitin is currently the object of close study in the pathogenesis of neurodegenerative diseases. The danger to cell life of proteasome inclusions is also an open question. It has been suggested that the cause of the formation of these bodies in neurodegenerative diseases are disturbances in the functioning of the ubiquitin-proteasome system [1]. Several groups of researchers have found that proteasome inhibitors induce the formation of inclusion bodies and death of neurons through programmed cell death in neuronal cell cultures. In addition, it turned out that in neurons with Parkinson's disease, the enzymatic activity of proteasomes is reduced. However, protein aggregates that lead to changes in the functional work of proteasomes have now been studied. Thus, it was possible to establish a link between the development of the disease and dysfunction of the ubiquitin-proteasome system only for some types of hereditary diseases (Parkinson's and Alzheimer's) [1,14,19].

Involvement of proteasomes in carcinogenesis. It has been established that during the development of Krebs carcinoma, a significant decrease in 26S proteasomes is observed compared to normal tissues [20].

An increase in the content of ubiquitated forms of the Bax peptide was noticeable in prostate cancer with high expression of the anti-apoptotic peptide Bcl-2. This leads to a decrease in its content in the cell, inhibition of apoptosis of malignant cells and an increase in the risk of death according to the Gleason score. Inhibition of the ubiquitin-proteasome protein cleavage pathway by the PSI inhibitor promotes the induction of apoptosis in human mesothelioma cells [19].

Under in vitro conditions, it has been found that the level of ubiquitated peptides is increased in renal cell carcinoma cells. Mutations in the VHL gene in von Hippel-Lindau syndrome lead to renal carcinoma. One of the elements of the E3 ligase of the ubiquitin system is encoded by the VHL gene. The HIF family of transcriptome factors is degraded by the E3 ubiquitin ligase. These factors, with a lack of oxygen in the tissues, significantly increase the production of factors that promote vascular growth, for example, vascular endothelial growth factor. An increase in the expression of angiogenic factors and the progression of kidney cancer are associated with impaired ubiquitin-proteasome destruction of HIF family proteins in E3 ligase mutations. In breast cancer, violations of the gene encoding E3 ligase are often detected [1,11,13,19].

In addition, proteasomes play a significant role in the development of viral and autoimmune diseases.

Inhibitors of the ubiquitin-proteasome system as potential drugs. Disruption of some components of the ubiquitin-proteasome system is most likely the cause of various diseases. Related to this is the relevance of the search for specific inhibitors of this system. However, the ubiquitin-proteasome complex is a vital component of a normal cell. The least specific suppressors of the activity of the ubiquitin-proteasome system are the suppressors of the enzymatic activity of the 20S proteasome and E1. Most of the used suppressors of 20S proteasome activity are aimed at suppressing their chymotrypsin-like activity. In terms of chemical structure, most activity suppressors are short peptides that interact with catalytic residues in the active site. Peptide boronates are highly specific suppressors of 20S proteasome activity [21].

Suppressors of 20S proteasome activity have an adverse effect on cells up to destruction by programmed cell death. Under long-term influence of suppressors of 20S proteasome activity, they turn out to be toxic for cells and lead to their death as a result of apoptosis. However, proliferating cells are more sensitive to these substances. Paying attention to this fact, as well as to the anti-angiogenic effect of inhibitors, it can be seen that these substances should be effective in the fight against cancer. One of the proteasome suppressors, bortezomib (bortezomib, PS-341, pyrazinylcarbonyl Phe-Leu-boronate, Velcade) has found its application [1,22]. Bortezomib is a strong suppressor of chymotrypsin-like and partially trypsin-like activity of the proteasome. After studying the antitumor activity of bortezomib in vitro and in vivo, its clinical trials began. It has become known that bortezomib in general does not show an effect as a monodrug in the treatment of solid tumors, but shows good results in the case of multiple myeloma and other hematological diseases [23].

Currently, a search is underway for new proteasome suppressors that are likely to overtake bortezomib and its derivatives in terms of their effectiveness. A highly specific suppressor, salinosporamide A (NPI-0052), was recently obtained from marine bacteria. A distinctive feature of this suppressor from bortezomib is its irreversible binding to all enzyme sites of the proteasome. NPI-0052 inhibits the proteasome and NF-κB better than bortezomib when used at equal concentrations, which has been proven in in vitro studies. While in the course of clinical studies in patients with chronic lymphocytic leukemia, NPI-0052 has a more powerful apoptogenic effect of isolated lymphoid cells. In addition, NPI-0052 induces apoptosis in multiple myeloma cells resistant to bortezomib and other drugs [1,24].

A more effective method compared to the suppression of the activity of the 20S proteasome is the search and application of inhibitors of E3 ligases and specific protein-substrate-E3 interactions. Several approaches can be distinguished. The first approach is to use peptides similar to the part of the protein-substrate to which the E3 ligase binds as E3 suppressors. It was shown that the phosphopeptide corresponding to the N-terminal region of IκB protects the whole peptide from degradation by

proteasomes, and microinjections of this phosphopeptide inhibit the activation of NF-κB in cells. The second approach is to search for small molecules that will specifically inhibit the active sites of E3 or the sites of their binding to the substrate [1,25]. The selection and appropriate modification of these compounds is greatly facilitated when the structures of the substrate-E3 settling complexes are known. Using the example of the search for inhibitors of the p53-Mdm2 interaction, we can consider the results of applying this approach. Examination of a large library of small molecules revealed the HLI-98 family whose members inhibited Mdm2 autoubiquitination in vitro. Despite the fact that these molecules also inhibited other E3 ligases, and even E2 at high concentrations, they were able to induce apoptosis in transformed cells, with virtually no poisoning effect on normal cells. This study demonstrated that inhibition of E3, in particular Mdm2, can be considered as an alternative approach in the treatment of cancer. Currently, several more specific low-molecular-weight suppressors of the p53-Mdm2 interaction are known [1,21,24].

Nutlins were the first to be discovered. They are derivatives of cis-imidazoline and are able to displace p53 from the complex with Mdm2. Nutlins bind to the hydrophobic cavity Mdm2, to which lateral branches of three p53 amino acids are usually attached, and do not allow binding to Mdm2. Treatment with nutlins leads to the accumulation in cells of p53 and the products of the genes that it activates (for example, p21 and p27). The effect of nutlin-3 is the apoptosis of cancer cells with wild-type p53, while in normal cells it slows down growth while maintaining viability. As it turned out later, in addition to p53-Mdm2, nutlins inhibit other protein-protein interactions. In particular, the HIF1α peptide binds to the same Mdm2 site as p53, so nutlin-3 destroys this interaction as well. Nutlins may have a therapeutic effect on p53 mutant cancer cells: sensitivity to many drugs in such cells is increased. The goal of a number of ongoing studies is to investigate the effect of suppressors of p53-Mdm2 activity (RITA, MI-63). It has been established that their effects are similar to those of nutlins. Some of the mechanisms of peptide ligases are listed below. In human papillomavirus, aptamer proteins interact with viral peptides, causing apoptotic elimination of HPV16-positive tumor structures, without affecting healthy cell structures [1,25].

To date, the ligase suppressors SCFSkp2, CpdA (Compound A) have been discovered and studied in detail; they prevent the incorporation of Skp2 into the enzyme. CpdA induces cell cycle arrest and SCFskp2- and p27-dependent cell death, acting predominantly on cancer cells [1,23,24].

In general, the use of substances that modify the activity of the ubiquitin-proteasome system for therapeutic purposes is very promising. First of all, they are used in the fight against malignant tumors, however, given that disturbances in the well-coordinated work of the ubiquitin-proteasome system also occur in other diseases, it can be assumed that soon the scope of suppressors of this system in medicine will be expanded [1,26].

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