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Review article

Mammalian proteasome subtypes: Their diversity in structure and function

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ABSTRACT

The 20S proteasome is a multicatalytic proteinase catalysing the degradation of the majority of intracellular proteins. Thereby it is involved in almost all basic cellular processes, which is facilitated by its association with various regulator complexes so that it appears in different disguises like 26S proteasome, hybrid-proteasome and others. The 20S proteasome has a cylindrical structure built up by four stacked rings composed of α- and β-subunits. Since the three active site-containing β-subunits can all or in part be replaced by immuno-subunits, three main subpopulations exist, namely standard-, immuno- and intermediate-proteasomes. Due to posttranslational modifications or/and genetic variations all α- and β-subunits occur in multiple iso- or proteoforms. This leads to the fact that each of the three subpopulations is composed of a variety of 20S proteasome subtypes. This review summarizes the knowledge of proteasome subtypes in mammalian cells and tissues and their possible biological and medical relevancy.

Contents

1. The proteasome-system

The proteasome is a multicatalytic proteinase present in all eukaryotic cells [1,2]. The 10 × 15 nm sized cylinder–or barrel-shape of a proteasome is built up by four stacked rings, two consisting of seven different α-subunit proteins and the other two of seven different β-subunits resulting in a subunit stoichiometry $\alpha_{1\text{-}7}$, $\beta_{1\text{-}7}$, $\beta_{1\text{-}7}$, $\alpha_{1\text{-}7}$. The molecular weights of the different subunits are in the range of 22–30 kD and thus sum up to a molecular mass of about 700 kD and a sedimentation coefficient 20S, which is why it was designated 20S proteasome (20Sprot). In eukaryotic 20S proteasomes three β-subunits catalyse the peptide bond hydrolysis. These active sites are directed to the central cavity encircled by the two adjacent β-rings. This necessitates that a substrate protein has to be inserted through a pore in the outer α-rings and then to be

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transported to this proteolytic chamber [3] (Fig 1).

Although the amino acid sequences of the α- and β-subunits as well as the shape and principal architecture of 20S proteasomes from different eukaryotic organisms are highly conserved, small species-specific differences were observed regarding their physicochemical properties, like pI values, molecular mass and specific activities [4–6].

In a mammalian cell proteasomes catalyse the degradation of a major part of cytosolic, nuclear and membrane proteins. This function is facilitated by association of 20S proteasomes to a variety of regulator complexes (reg) like 19S regulator, PA28αβ, PA28γ, PA200, EMC29, PI31 and thus they emerge in various disguises, known e.g. as 26S proteasome (19Sreg - 20Sprot), 30S proteasome (19Sreg - 20Sprot - 19Sreg), hybrid proteasome (19Sreg - 20Sprot - PA28), PA28-proteasome (PA28 - 20Sprot - PA28) complexes and others [7]. Proteasomes cooperate with another multi-component system, the ubiquitination-system, consisting of enzymes that attach poly-ubiquitin chains to proteins marking them as substrates to be degraded by proteasomes [8,9] especially by 26S and 30S proteasome complexes, where the 19S regulator binds ubiquitinated proteins and then catalyses their deubiquitination and defolding before they are translocated into the central cavity of the 20S proteasome [10]. The functions of the other regulators are only partly known [11–13]. The relative content of all these complexes has been estimated in HeLa cells by immunoprecipitation and Western blotting and it appears that about 40% of all 20S proteasomes exist in a regulator-free form, the rest is bound to PA28 and 19Sreg in different combinations [14]. A slightly higher percentage of 'free' 20S proteasomes was determined in U937 cells stimulated with interferon-γ [15], so this may vary between different types of cells. Recently, by using a newly developed form of electron cryotomography a census of 26S and 30S proteasomes was performed in neurons, which do not contain PA28, and classified about a quarter of all 20S-19Sreg complexes as 30S proteasomes, the rest as 26S proteasomes [16]. Considering the specific functions of the many different cells in a mammalian organism it is very likely that they all have their individual compositions of proteasome regulator complexes also due to the fact that not all regulators are present in all cells [17]. Nevertheless, the whole system of different proteasome–regulator complexes and of 'free' not-regulator-bound 20S proteasomes constitutes the total 20S proteasome population of a cell or tissue.

Since the discovery that some genes of proteasome subunits are located in the chromosomal MHC-class II region and that their transcription can be regulated by interferon-γ resulting in formation of 20S proteasomes with slightly altered proteolytic activities, it became clear that 20S proteasomes exist in several subsets, which contain different combinations of the active site-containing β-subunits [18–24]. These subsets form three major 20S proteasome subpopulations, namely standard-, intermediate- and immuno-proteasomes (Fig. 2).

The chromatographic separation of the whole 20S proteasome populations purified from different rat tissues into their subpopulations revealed that each of the three subpopulations could be further subdivided into several types of proteasomes, which we called proteasome subtypes [25] (Fig. 2). Since then proteasome subtypes have been described in several publications [15,25–28], however, without paying attention that the term 'subtype' was always used with the same meaning. Therefore, in the following a conceptual classification of proteasome 'subpopulations' and proteasome 'subtypes' is given and the present knowledge about proteasome subtypes summarized to elucidate the heterogeneity of mammalian 20S proteasomes.

2. 20S proteasome subpopulations and cell-specific proteasomes

2.1. Standard- and immuno-proteasomes

The functions of proteasomal α-subunits are to form the substrate entrance pore with a regulatory gating mechanism [3], and to frame an antechamber between the α- and a β-ring, where a substrate entrapped can be kept in an unfolded state before being forwarded into the central proteolytic chamber [29]. Additionally, α-subunits form pockets for docking with the proteasome regulators (Fig. 1) [30]. Therefore the arrangement of subunits α1-α7 is highly conserved in mammalian proteasomes.

Similar to α-subunits the arrangement of the seven β-subunits

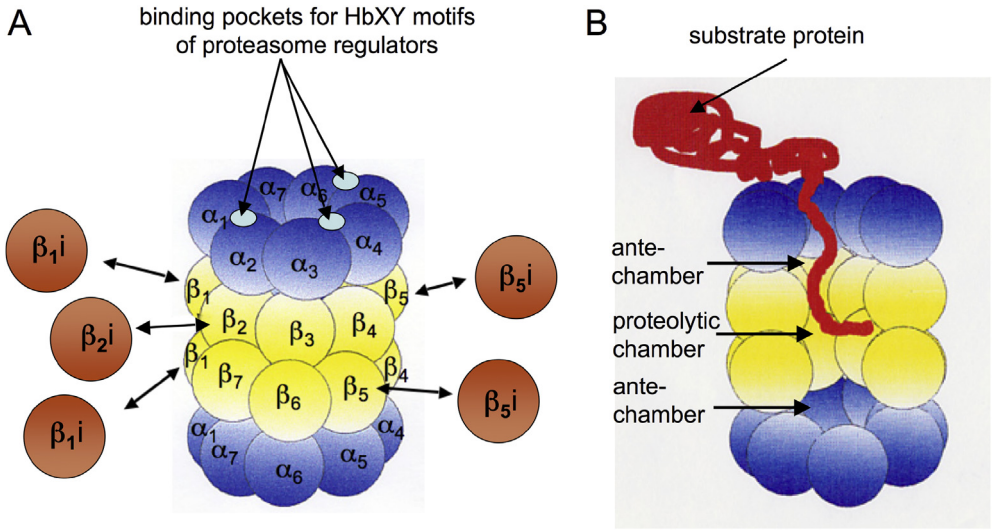

Fig. 1. Cartoon showing the arrangement of α- and β-subunits in the cylindrical-shaped 20S proteasome. Panel A: Standard subunits β1, β2, and β5 can be replaced by immuno-subunits β1i, β2i, and β5i to form immuno-proteasomes or in case of only partial substitution intermediate-proteasomes. HbYX C-terminal motifs of some proteasome regulators anchor in docking pockets between subunits α1-α2, α3-α4 and α5-α6. Panel B: Sliced model of 20S proteasome cylinder showing the antechambers between α- and β-subunit rings and the central proteolytic chamber formed by the two β-subunit rings. A substrate protein is threading through the entrance pore of the α-subunits into the central proteolytic chamber.