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Review Article

Biological consequences of structural and functional proteasome diversity

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Abstract

Cell homeostasis and regulation of metabolic pathways are ensured by synthesis, proper folding and efficient degradation of a vast amount of proteins. Ubiquitin-proteasome system (UPS) degrades most intracellular proteins and thus, participates in regulation of cellular metabolism. Within the UPS, proteasomes are the elements that perform substrate cleavage. However, the proteasomes in the organism are diverse. Structurally different proteasomes are present not only in different types of cells, but also in a single cell. The reason for proteasome heterogeneity is not fully understood. This review briefly encompasses mammalian proteasome structure and function, and discusses biological relevance of proteasome diversity for a range of important cellular functions including internal and external signaling.

Keywords: Cell biology, Biochemistry, Molecular biology

1. Introduction

Most intracellular proteins are degraded by the ubiquitin-proteasome system (UPS) (Livneh et al., 2016). The proteasomes are multi-subunit protein complexes, responsible for protein breakdown. Thus, they represent central element of the UPS. Accumulating data indicate that cellular proteasome pool is more diverse and flexible than

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previously anticipated. A single cell can contain various forms of proteasomes differing by: structural and catalytic subunits; interaction with different regulators; posttranslational modifications of subunits (Dahlmann, 2016; Hirano et al., 2016). The repertoire of proteasome forms is dynamic and changes from tissue to tissue and even from cell to cell, presumably reflecting cellular function, state, condition and ongoing adaptation processes. Proteasome forms have different substrate preferences and generate specific sets of peptides. In fact, the significance of the spectrum of produced peptides could be underestimated. It may be important not only for the antigen presentation, but for the regulation of multiply intercellular events and even for cellular communication (Ferro et al., 2014). This article describes proteasome diversity in mammalian cells and discusses its biological meaning.

2. Main text

2.1. 20S proteasome

All cellular proteasomes are either 20S proteasomes or contain it as a principal part. The 20S proteasome (20S core particle) is a 700 kDa barrel-like hollow structure with dimensions 115 to 150 Å, composed of four stacked heptameric rings (Groll et al., 1997). Two outer rings are built of seven alpha subunits (α1-α7), while the two inner rings − of beta subunits β1-β7 (Groll et al., 1997; Livneh et al., 2016). Alpha subunits perform scaffolding function and prevent haphazard substrate entry into the proteasome. Their N-termini form «gates» that sequester proteasome interior, where protein degradation is performed by the beta subunits, three of which display proteolytic activities and cleave substrates via N-terminal threonine hydrolase-based mechanism (Groll et al., 1997).

20S proteasomes can differ by subunit composition; this might be considered as a first level of proteasome organization (Fig. 1). Different catalytic beta subunits within the 20S complex usually define major forms or subpopulations (Dahlmann, 2016) of 20S proteasomes (Supplementary Table).

Constitutive (standard, sP) 20S proteasome contain two β1 (Y) subunits, which has caspase-like, activity and perform cleavage after acidic amino acids, two β2 (Z) subunits, demonstrating trypsin-like activity (cleavage after basic amino acids), and two β5 (X) subunits with chymotrypsin-like activity (cleavage after hydrophobic residues) (Livneh et al., 2016). SPs constitute the basis of the proteasome pool in most cells of the body (Supplementary Table).

Immune cells, medullary thymic epithelial cells permanently and many other cells under conditions of oxidative stress, inflammation, cytokine stimulation, viral or bacterial infection assemble so-called ***immunoproteasomes*** (iPs). IPs contain pairs of IFN-γ-inducible catalytic ("immune") subunits β1i (LMP2), β2i (MECL-1) and β5i (LMP7) instead of β1, β2, β5, respectively (Ferrington and Gregerson, 2012).

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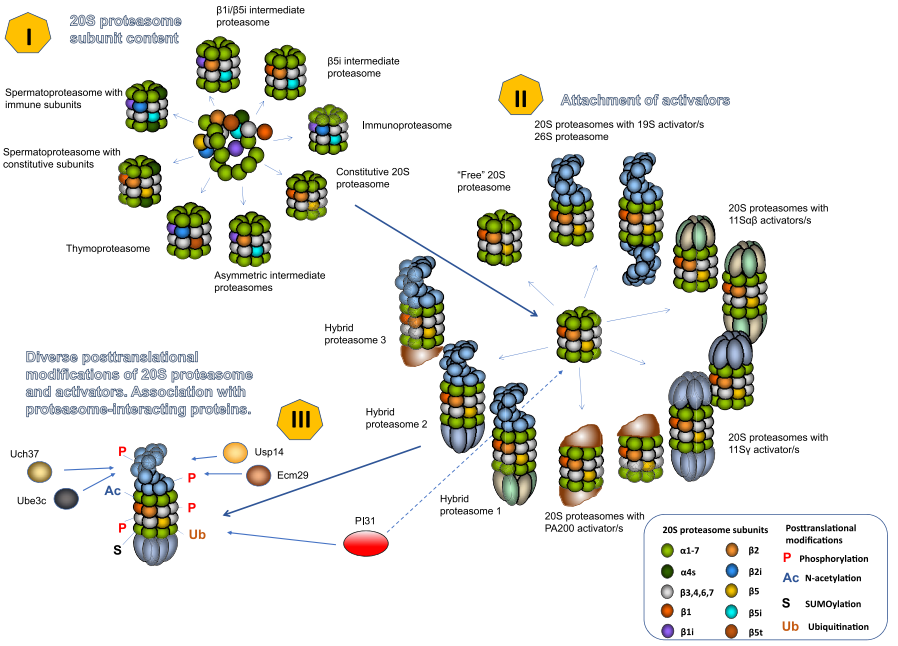

Fig. 1. Principal levels of proteasome organization. I. 20S proteasome subunit composition. Based on the composition of catalytic subunits proteasomes are divided into constitutive (2β1, 2β2, 2β5), immunoproteasomes (2β1i, 2β2i, 2β5i), intermediate proteasomes (2β1, 2β2, 2β5i), (2β1i, 2β2, 2β5i), intermediate proteasomes with assymetric subunits (for instance 2β1, 2β2, 1β5,1β5i), thymoproteasomes (2β1i, 2β2i, 2β5t). Spermatoproteasomes have unique α4s subunit. II. Binding of activator/s. Proteasomes can be found without an activator ("free"), or can carry either one or two 19S, 11Sαβ, 11Sγ and PA200 activators and likely PI31 (a proteasome inhibitor rather than activator). Hybrid proteasomes carry two different regulators. It worth mentioning that recent findings indicate preferential association of particular 20S proteasome subpopulations with particular regulators (Fabre et al., 2015). III. Post-translational modifications of proteasomes. Subunits of 20S proteasomes, as well as the regulators, can undergo different post-translational modifications including: P-phosphorylation, U-ubiquitination, S-SUMOylation, A-N-acetylation, M-myristylation, G-N-glycosylation, R-poly-ADP ribosylation, etc. (Hirano et al., 2016). For the sake of simplicity not all of the possible post-translational modifications of proteasome subunits are shown. 26S Proteasomes can associate with additional proteins that affect catalytic activity and processivity of the complex. Here PI31, Usp14, Uch37, Ube3c and Ecm29 are shown.

Not all iPs contain entire set of immune subunits and proteasomes bearing immune and constitutive catalytic subunits simultaneously exist (Guillaume et al., 2010). These are ***intermediate proteasomes*** (intPs).

It should be noted that intPs are present in normal conditions in various cells and tissues, including liver, heart and kidney (Supplementary Table). IntPs contain combinations of paired immune and constitutive beta-subunits, thus six types of intermediate 20S complexes can be theoretically formed. The presence of two major types is well established. The first type contains 2β1/2β2/2β5i catalytic subunit set and the second type − 2β1i/2β2/2β5i (Guillaume et al., 2010). Since each 20S proteasome contain two copies of single beta subunit, combinations with one constitutive and one immune cannot be excluded. Indeed, β1 and β1i were found in the same 20S complexes isolated from IFN-γ stimulated HeLa cells (Klare et al., 2007). In

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addition, proteasomes containing β5 and β5i subunits simultaneously were detected in IFN-β-treated mouse insulinoma cells (Freudenburg et al., 2013). Accordingly, existence of 13 different subtypes of intermediate 20S proteasomes was proposed (Klare et al., 2007). Although, some of these subtypes are unlikely to be formed or maybe detected only in specific conditions, this creates another sublevel of 20S proteasome organization – ***asymmetrical 20S proteasomes***.

It should be emphasized that there are forms of proteasomes specific for a particular tissue (Kniepert and Groettrup, 2014). For example, ***thymoproteasomes*** (tPs) are found exclusively in cortical thymic epithelial cells (Murata et al., 2007). These proteasomes contain unique catalytic β5t subunit together with immune subunits β1i and β2i (Murata et al., 2007). Spermatocytes, spermatids and sperm express another tissue-specific form of 20S proteasome – ***spermatoproteasome*** (spPs) (Qian et al., 2013; Uechi et al., 2014). The hallmark of these proteasomes is a unique α4s subunit (Supplementary Table). According to Qian et al. spermatoproteasome contain only immune catalytic subunits (Qian et al., 2013), although experimental results presented by the authors and by others (Uechi et al., 2014) indicate presence of constitutive beta subunits in the α4s-containing proteasomes.

Incorporation of immune subunits or β5t affects proteasome activity and a repertoire of peptides generated by proteasomes. In contrast to β1, β1i subunit displays rather chymotrypsin-like activity and structural data indicates that β5i "prefers" to cleave after different hydrophobic residues than β5 (Huber et al., 2012). Conversely, the β5t subunit demonstrates 60–70% reduced cleavage after hydrophobic residues comparing to β5 (Murata et al., 2007) and tPs produce a set of unique peptides comparing with iPs (Sasaki et al., 2015). At the same time, recent study by Mishto et al. demonstrated that iPs and constitutive proteasomes generate identical peptides, however the frequency of specific cleavage-site usage might change significantly between these forms of proteasomes (Mishto et al., 2014). Taken together, it can be deduced that all the above-mentioned forms of 20S proteasomes containing various combinations of catalytic subunits, display altering proteolytic activity and produce peptide sets that differ quantitatively, but also in at least some cases – qualitatively (Guillaume et al., 2010; Kincaid et al., 2011; Mishto et al., 2014; Sasaki et al., 2015; Toes et al., 2001). Since quantitative differences are frequently determinative in biological systems and for the sake of simplicity, we will further refer peptide sets produced by different 20S proteasome forms as altered. In addition, presence of different beta subunits, as well as α4s, likely, influences interactions of 20S proteasomes with regulators (Fabre et al., 2015; Qian et al., 2013).

2.2. Proteasome regulators

Besides "free" 20S proteasomes there are 20S proteasomes with attached regulator/s. Among those there are activators. Reversible attachment of activators to either one or

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both alpha-subunit rings of 20S proteasomes is another level of proteasome organization, that contributes to overall heterogeneity and functionality of proteasomes (Fig. 1, Supplementary Table). In fact, bound activators increase the proteolytic activity of the 20S proteasome via promoting alpha-gate opening and influence substrate specificity of the complex. Several proteasome activators are briefly described below.

The ***19S proteasome activator*** (RP/PA700) is a ~150−160 Å high and ~180−200 Å wide protein complex with MW ~700 kDa, composed of at least 19 subunits (Huang et al., 2016; Liu and Jacobson, 2013). The 19S regulator is a sole regulator that binds ubiquitinated proteins, deubiquitinates, unfolds and translocates them into the activated 20S proteasome for degradation (Liu and Jacobson, 2013). The 20S proteasomes with one or two attached 19S regulators are both frequently termed "**26S proteasomes**".

The ***11Sαβ activator*** (PA28αβ, REGαβ) is a 60 to 90 Å heteroheptamer composed of four alpha and three beta subunits, each having MW of ~28 kDa (Huber and Groll, 2017). When the activator is bound to the 20S proteasome, it increases all catalytic activities of the latter. The 11Sαβ is found predominantly in the cytoplasm. The activator is assumed to facilitate cleavage of peptides, rather than proteins (Cascio, 2014) and increase double cleavages of the polypeptide substrates (Dick et al., 1996). However, recent findings indicated that it stimulates degradation of oxidized proteins (Pickering and Davies, 2012). Expression of 11Sαβ is induced by IFN-γ and up-regulated in the immune cells and tissues (Cascio, 2014). Interestingly, 11Sαβ is frequently associated with iPs and is engaged in antigen presentation (de Graaf et al., 2011; Fabre et al., 2015; Raule et al., 2014).

The ***11Sγ activator*** *(PA28γ, REGγ)* is a homoheptamer. It is composed of identical 29,5 kDa subunits and has predominant nuclear localization (Mao et al., 2008). 11Sγ was shown to increase exclusively the trypsin-like activity of the 20S proteasome (Gao et al., 2004) and facilitate ubiquitin and ATP-independent hydrolysis of several regulatory proteins, as well as of oxidized proteins (Pickering and Davies, 2012).

PA200 is another proteasome activator with nuclear localization. It is a monomeric 200 kDa phosphoprotein that forms a hollow, asymmetric dome-like structure of about ~100 × 60 Å (Ortega et al., 2005; Savulescu and Glickman, 2011). *In vitro* it increases all 20S proteasome catalytic activities, but mainly − the caspase-like activity. PA200 was assumed to stimulate degradation of peptides rather than entire proteins (Ustrell et al., 2002). Though, it was shown to promote ATP- and ubiquitin-independent degradation of acetylated histones during spermatogenesis and in the course of DNA damage repair in somatic cells (Qian et al., 2013).

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The 20S proteasomes can bind activators to both alpha-rings and hence, complexes bearing one activator, two identical, or two different activators can be formed (Fig. 1). The latter represent ***hybrid proteasomes.*** To date, hybrid proteasomes with 19S-20S-11Sα/β, 19S-20S-11Sγ and 19S-20S-PA200 architecture have been described (Blickwedehl et al., 2008; Bochmann et al., 2014; Hendil et al., 1998; Ustrell et al., 2002).

Besides activators proteasomes interact with hundreds of other proteins (Fabre et al., 2015). Some of these proteins were shown to regulate proteasome function and thus, can be also considered as proteasome regulators. Among them: PI31 — a putative proteasome inhibitor (McCutchen-Maloney et al., 2000); Usp14, Uch37 a deubiquitinating enzymes and a ubiquitin ligase Ube3c, these three represent 19S complex subunits that temporarily associate with the activator (Kuo and Goldberg, 2017; Leggett et al., 2002); and Ecm29 (Leggett et al., 2002) (Fig. 1, Supplementary Table).

Mutations in proteasome subunits, as well as post-translational modifications (PTMs) of proteasome subunits and regulators additionally contribute to the proteasome diversity (Fig. 1) (Dahlmann, 2016; Hirano et al., 2016). Most frequent PTMs are: phosphorylation, ubiquitination, SUMOylation, N-acetylation, myristylation, glycosylation, poly-ADP ribosylation, carbonylation, nitration, glycoxidation as well as modification with lipid peroxidation products (Fig. 1) (Guo et al., 2017; Hirano et al., 2016; Hohn and Grune, 2014; Xu et al., 2009). Such modifications affect proteasome assembly, stability, activity, interactions with other proteins and substrates, localization, and sensitivity to proteasome inhibitors (Gohlke et al., 2014; Guo et al., 2016; Hohn and Grune, 2014; Jarome et al., 2013; Kloss et al., 2010; Lokireddy et al., 2015; VerPlank and Goldberg, 2017; D. Wang et al., 2013; Xu et al., 2009). Assuming various PTMs of proteasome subunits, it was predicted that 5×10^{15} subtypes of only 20S proteasomes can be theoretically found (X. Wang et al., 2011). However, such estimations are almost impossible to confirm experimentally.

2.3. Implications of proteasome diversity

Why the world of proteasomes is so diverse? Currently there are several clues.

First, **proteasomes with different regulators have diverse substrate specificities.** Indeed, proteins destined for degradation and tagged with ubiquitin can be specifically recognized, unfolded and broken down only by proteasomes with the 19S regulator. In addition, 26S proteasomes can degrade certain proteins even without ubiquitination (Baugh et al., 2009). Interestingly, 26S complexes lacking Usp14 perform hydrolysis of such substrates more efficiently, comparing to the proteasomes with the attached enzyme (H. T. Kim and Goldberg, 2017).

https://doi.org/10.1016/j.heliyon.2018.e00894

At the same time, the main function of "free" 20S proteasomes is supposed to be the degradation of oxidized, damaged proteins, and of native proteins with intrinsically disordered regions (Baugh et al., 2009; Ben-Nissan and Sharon, 2014; Raynes et al., 2016). This has critical implications for maintenance of normal cellular metabolism and for adaptation to various stresses.

The 11Sαβ and 11Sγ regulators additionally facilitate hydrolysis of oxidized proteins by the 20S proteasomes (Pickering and Davies, 2012). Furthermore, binding of 11Sγ and PA200 promotes ubiquitin-independent hydrolysis of several regulatory proteins and acetylated histones, respectively (Qian et al., 2013) (Supplementary Table).

It should be emphasized that different substrates also differently affect functional state and structure of proteasomes. For instance, ubiquitinated but not non-ubiquitinated proteins were shown to stimulate association of 26S proteasomes with Usp14 and Ube3c, which in the presence of attached ubiquitin-conjugates induce conformational changes of the proteasome, increase its activity and processivity (Huang et al., 2016; Kuo and Goldberg, 2017; Matyskiela et al., 2013; Peth et al., 2009). However, the same substrate can mediate opposite effects on different forms of the proteasomes (Morozov et al., 2016, 2017).

Second, having different activity profiles and cleavage preferences **different 20S proteasome forms generate altered peptide repertoires** (Guillaume et al., 2010; Kincaid et al., 2011; Mishto et al., 2014; Sasaki et al., 2015; Toes et al., 2001), which are broadened by regulators such as 19S and 11Sαβ (de Graaf et al., 2011; Emmerich et al., 2000; Raule et al., 2014). This is highly relevant **for antigen presentation** (Fig. 2) (Vigneron and Van den Eynde, 2014). Through enhanced generation of peptides with hydrophobic C-terminus, due to elevated chymotrypsin-like activity, iPs and likely intermediate proteasomes produce peptides compatible with major histocompatibility complex class I (MHCI) more efficiently than constitutive 20S proteasomes (Kincaid et al., 2011; Mishto et al., 2014; Toes et al., 2001). Moreover, different 20S proteasomes contribute to the immune recognition through altered production of spliced peptides (peptides generated from non-sequential residues of the same protein) (Dalet et al., 2011), which can constitute up to a quarter of presented epitopes (Liepe et al., 2016; Vigneron et al., 2004). Concordantly, iPs and intermediate proteasomes are abundant in immune cells (Guillaume et al., 2010) and elevated in nonimmune cells during inflammation (Ferrington and Gregerson, 2012) (Supplementary Table). Another example is unique low affinity T cell receptor ligands produced by thymoproteasomes that are optimal for the positive selection of T cells (Sasaki et al., 2015) and it is noteworthy that the tPs eventually determine the functional state of the mature lymphocytes (Takada et al., 2015). While thymoproteasomes are not found elsewhere except thymus, high amounts of iPs and especially intPs revealed in various nonimmune cells in normal conditions (Guillaume et al., 2010) are not fully understood. Thus, **other roles of different proteasomes in cell metabolism cannot be excluded**.

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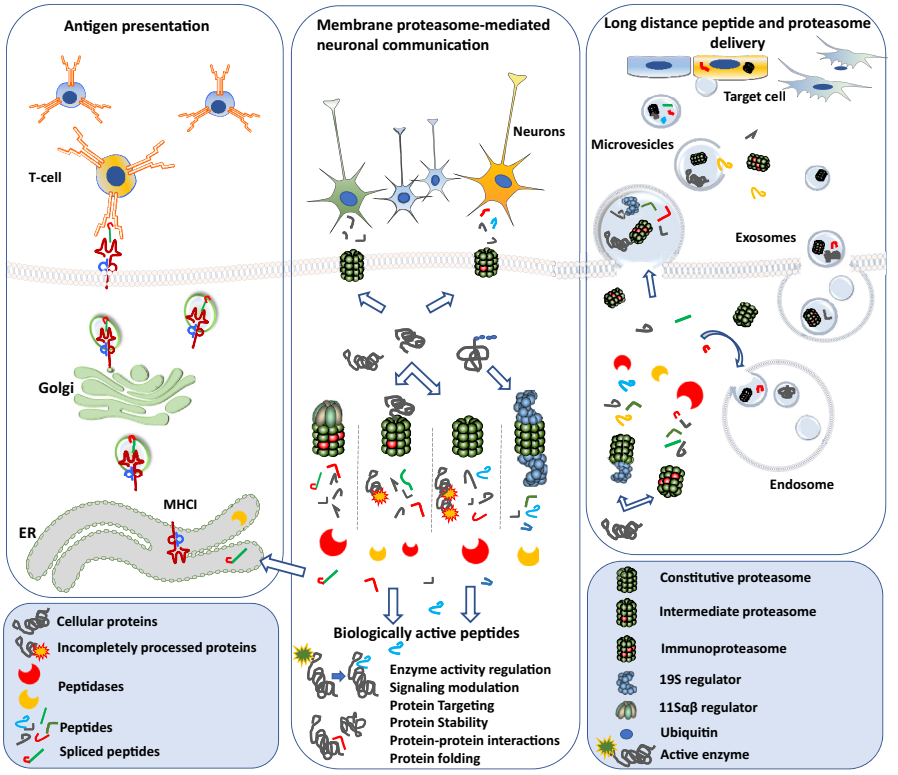

Fig. 2. Established and possible implications of proteasome diversity. *Central column middle.* Different proteasome forms degrade different proteins, produce altering sets of canonical (Guillaume et al., 2010; Kincaid et al., 2011; Mishto et al., 2014; Sasaki et al., 2015; Toes et al., 2001) and spliced peptides (Dalet et al., 2011), as well as may have varying efficacy in generation of functional cleavage products. *Central column bottom.* Some peptides generated by proteasomes are not processed immediately to the single amino acids and might be implicated in regulation of enzymes activity, signaling, protein targeting, protein stability, protein-protein interactions and folding (Ferro et al., 2014). *Left column.* Immune and intermediate proteasomes increase generation of peptides suitable for MHCI presentation, ensuring more efficient immune recognition of infected or cancer cells by circulating CD8+ T-lymphocytes. *Central column top.* 20S proteasome integrated into the neuronal membrane produce extracellular biologically active peptides from intracellular proteins, thus mediating communication between neurons (Ramachandran and Margolis, 2017). It was shown that some of membrane-associated 20S proteasomes contain β5i subunit, indicating at least possible presence of intermediate proteasomes. Therefore, different 20S complexes by producing altered peptide sets can mediate different signals. *Right column.* Proteasomes and generated peptides can also participate in long distance extracellular communication. Different forms of the proteasomes and bioactive peptides can be packed into exosomes and microvesicles along with other proteins (Bochmann et al., 2014; Lai et al., 2012). During trafficking in the exosomes, proteasomes can also cleave co-packed proteins into the biologically active peptides. Upon delivery to a target cell, the peptides and proteasomes can fulfill biological function. Extracellular vesicle (EV) cargo might be also released into the extracellular space. Thus, EVs likely represent a source of extracellular proteasomes and certain peptides. Some proteasome subpopulations and regulators are omitted on the image for the sake of simplicity. Star indicates the functional activity.

Along these lines, the 20S proteasomes were demonstrated to perform incomplete proteolysis and generate stable protein products from precursor-protein. These products might have important biological activity, for example: eIF3a and eIF4G subunits of translation initiation factors (Baugh and Pilipenko, 2004), p50 (NF-κB

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family member), Δ40p53 (Moorthy et al., 2006; Olshina et al., 2018; Solomon et al., 2017) (Fig. 2). Generation of a 30 kDa fragment from Hsp70 following incubation with 20S proteasome was observed (Morozov et al., 2017). The functional activity of this fragment is unknown. However, considering data reported in (Baugh et al., 2009), more examples of stable incompletely processed proteins can be expected and it cannot be ruled out that **structural differences of 20S subpopulations affect the size and efficacy of generation of such functional cleavage products, as well as overall substrate turnover rates.** Indeed, decreased levels of NF-κB p50 subunits were observed in β5i-deficient cells (Opitz et al., 2011). On the other hand, 26S proteasomes with immune 20S cores were demonstrated to be more efficient in degradation of ubiquitinated substrates than standard 26S complexes (Ebstein et al., 2013; Seifert et al., 2010). Although there is a certain contradiction between these results with data reported by Nathan et al. (2013), Ips were shown to degrade certain substrates faster than constitutive proteasomes in a more recent study (Mishto et al., 2014). Interestingly, different processing rates of several transcription factors by constitutive and iPs were discussed as a possible reason to explain altered expression of 8104 genes in dendritic cells with knocked out immunoproteasome subunits (de Verteuil et al., 2014). Indeed, Ips are involved in several important biological processes including: survival and expansion of T cells (Moebius et al., 2010); maintenance of normal retinal function (Hussong et al., 2011) and pluripotency of human embryonic stem cells (Atkinson et al., 2012); skeletal muscle differentiation (Cui et al., 2014) and cytokine production (Muchamuel et al., 2009). Moreover, iPs facilitate degradation of oxidized proteins and maintain cellular homeostasis during stress (Pickering et al., 2010; Yun et al., 2016). Recent study by St-Pierre and coauthors highlight the role of Ips in adaptation of medullary thymic epithelial cells characterized by high levels of protein synthesis to proteotoxic stress (St-Pierre et al., 2017). In addition, iPs were proposed to be involved in production of peptides which participate in cell-cell interactions in order to maintain nervous system plasticity in mice lacking β2-microglobulin (Lyupina et al., 2013).

Concordantly, an exciting role of 20S proteasomes was recently revealed in neurons (Ramachandran and Margolis, 2017). It has been shown that 40% of 20S proteasomes in mouse neurons are tightly associated with plasma membrane (neuronal membrane proteasomes (NMPs)) and are exposed to the extracellular space (Ramachandran and Margolis, 2017) (Fig. 2). NMPs are capable to degrade intracellular proteins and directly release generated peptides into the extracellular space. By this they regulate target-neuron function through induction of calcium signaling with the involvement of NMDA receptors. Hence, these **20S proteasomes mediate crosstalk between neurons** (Ramachandran and Margolis, 2017). Interestingly, a fraction of the NMPs was represented by iPs or at least intermediate proteasomes (Ramachandran and Margolis, 2017). Thus, **proteasome form diversity can contribute to the spectrum and quantity of bioactive peptides produced by**

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NMPs, mediating potentially differing signals. At the same time many issues regarding NMPs remain unresolved. What peptides are generated by NMP? Which intracellular proteins they are deriving from? Do these proteins represent entire cellular proteome or a particular population? How different stresses affect presence and function of membrane-integrated proteasomes? What kind of proteasomes with β5i (intermediate, iPs, or both) are associated with neuronal membranes? Do these and constitutive proteasomes mediate different effects on target neurons via generated peptides? And vice versa, could these proteasomes degrade extracellular proteins and release bioactive peptides into the cytosol?

In fact, peptide-signals produced by different proteasomes can also have biological activity inside the cells (Fig. 2). Current concept implies that most of the generated peptides should be immediately degraded by peptidases (Reits et al., 2003), with the rare exception (less than 1%) of those that are eventually exposed on a membrane in complexes with MHCI (Yewdell, 2003). However, hundreds of relatively stable intracellular peptides were reported in different cells (Ferro et al., 2014; Fricker et al., 2012; Gelman et al., 2011). Many of these peptides are not produced from most abundant or least stable proteins, indicating that their generation might not be haphazard (Gelman et al., 2011). These peptides can participate in: modulation of signal transduction, protein-protein interactions, regulation of enzyme function, protein targeting and stability, stress response, host defense from pathogens (Ferro et al., 2014; Russo et al., 2012). Thus, it is reasonable that **proteasome diversity contributes to the spectrum and quantity of bioactive intracellular peptides**. Currently, however, there are very few described examples and we need more proofs of biological effects mediated by stable peptides generated by different proteasomes. Nevertheless, a peptide deriving from Rpt2 subunit of 19S regulator was found significantly increased in lysates of IFN-γ treated HeLa cells. It was predicted to be generated by iPs. The peptide was shown to stimulate proteasome activity in cellular lysates and potentiate β5i subunit expression in conditions of IFN-γ stimulation (Monte et al., 2017). Interestingly, several other UPS proteins were proposed as sources of bioactive peptides, for instance HECT E3 ubiquitin ligases (Candido-Ferreira et al., 2016) and ubiquitin, fragments of latter possessing antimicrobial activity, were found in amniotic fluid of pregnant women (J. Y. Kim et al., 2007). This indicates that some bioactive peptides are active within cells, while others can function outside. For example, hemopressins which are involved in cellular communication (Gelman et al., 2013). How these peptides are secreted is not clear, since they are produced from cytoplasmic non-secretory proteins. Generation of such peptides by NMPs could be one explanation. Otherwise, peptides may be secreted inside the extracellular vesicles (EVs). These are produced by different cell types and mediate intercellular communication by transporting their cargo to nearby or distant recipient cells inducing various biological effects (Raposo and Stoorvogel, 2013; Ridder et al., 2014, 2015) (Fig. 2). EVs include exosomes formed in cytoplasm, microvesicles that

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directly bud from the cellular membrane and apoptotic bodies. EVs can be constantly produced by cells; however, their release is frequently stimulated by stress and inflammation, or increased in cancer cells. The cargo of vesicles is diverse and is composed of mRNA, miRNA, proteins, peptides and lipids (Raposo and Stoorvogel, 2013). Thus, **bioactive peptides generated by different proteasomes in one cell can be packed into the extracellular vesicles and delivered to another cell** (Fig. 2).

Alternatively, or in addition, bioactive peptides can be produced inside the vesicles, through degradation of cargo proteins. Experimental data favors that some exosomes and microvesicles contain 20S proteasomes and possibly 26S proteasomes (Bochmann et al., 2014; Jia et al., 2017; Lai et al., 2012). These proteasomes are active and their concentration was estimated as 1 ng per 1000−1300 microvesicles (Bochmann et al., 2014). Importantly, proteasomes are not ubiquitous component of the EVs and what determines their presence in the EVs is largely unknown. At the same time EVs, originating from different cells contain different proteasomes: T-cells are secreting largely iPs (Bochmann et al., 2014), mesenchymal stem cells − proteasomes containing both immune and constitutive subunits (Lai et al., 2012), while only standard proteasomes are released from human leukemia K562 cells (Kulichkova et al., 2017). In exosomes from tumor-associated macrophages (TAMs), intermediate proteasomes containing β5i likely reside (Zhu et al., 2015). The presence of different proteasomes in EVs secreted from different cells probably reflects the major proteasome populations expressed in these cells. Hence, we can speculate that **EVs-mediated intercellular communication can contribute to the bioactive peptide and also a proteasome exchange between cells.** Although direct experimental evidences that exosomal proteasomes can enter a different cell to perform any function are lacking, it was demonstrated that extracellular vesicles can fuse with the membrane of target cells (Prada et al., 2016; Prada and Meldolesi, 2016) and proteasome-containing exosomes are efficiently internalized by the recipient cells (Jia et al., 2017). Along these lines, EVs from bone marrow-derived mesenchymal stem cells were shown to induce resistance of multiply myeloma cells to proteasome inhibitor bortezomib (Wang et al., 2014). Moreover, it was proposed that uptaking of TAM-derived exosomes containing active 20S proteasomes facilitates degradation of denatured or misfolded proteins in recipient cells supporting cell viability in the tumor microenvironment (Zhu et al., 2015). In addition, recent findings indicate that proteasome activity inside the EVs regulate autoimmune response to the EVs cargo proteins and allograft inflammation in mice (Dieude et al., 2015). Another characteristic example: proteasomes in exosomes deriving from hepatitis B virus-replicating cells were reported to modulate cytokine production in recipient monocytes (Jia et al., 2017).

Finally, bioactive peptides and proteasomes can be released from vesicles becoming a source of extracellular proteasomes. These are free floating catalytically active 20S

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proteasomes with unknown function found in concentration of 250 ng per ml of human serum (Fig. 2) (Bochmann et al., 2014; Kulichkova et al., 2017; Zoeger et al., 2006). In a recent paper Dianzani et al. demonstrated that these proteasomes are capable to degrade osteopontin, an important pleiotropic cytokine to produce biologically active peptides that stimulate migration of endothelial cells and lymphocytes (Dianzani et al., 2017). It can be expected, and this is proposed by the authors, that different extracellular proteasome forms e.g. iPs or intPs originating from the same or different cells, would produce altered set of osteopontin-derived signaling molecules, mediating different biological effects.

3. Conclusions

Recent investigations of cellular proteasome heterogeneity revealed that different forms of proteasomes can be simultaneously present in a single cell. However, the reasons of such diversity remain obscure. By performing protein hydrolysis different proteasome forms generate specific sets of peptides and proteolysis products. The breadth of biological meaning of this spectrum we are now only beginning to address. Based on the accumulating evidences, we suppose that, along with well established functions, proteasomes may represent modulators of a global signaling network, which rests on the diversity and amount of cleavage products generated by different proteasome forms. This can give additional nontrivial rationale for the elevation of iPs and intPs in healthy tissues and in several pathologies including cancer. All that rises questions concerning a role of a particular proteasome form in various biological processes in healthy and diseased organism. When, and what for it is assembled? Does it generate specific peptides, are these peptides stable and do they have biological function? What is the role of EV-mediated transport of proteasomes? What are the roles of extracellular proteasomes and, since there are different forms of proteasomes outside cells, do they have specific substrates and process them with different efficacy? Besides, putative role of different 20S proteasome forms in regulation of cellular metabolism indicates that special care should be taken when not only broad, but also subunit-specific proteasome inhibitors are used as drugs to treat various pathologies. Future investigations are necessary to answer these challenging questions and to shed more light on the intriguing issue of proteasome diversity.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Competing interest statement

The authors declare no conflict of interest.

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