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Exploring the proteasome system: A novel concept of proteasome inhibition and regulation

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1. Introduction

The proteasome system is the main protein disposal system in the cell for targeted protein degradation and counteracts protein synthesis by the ribosome. Proteasome function is essential for amino acid recycling and the generation of antigenic peptides for MHC class I presentation. Proteasome-mediated hydrolysis of more than 80% of all cellular proteins thereby determines their function in the cell. Accordingly, the activity of the proteasome is a key determinant of almost all cellular processes ranging from proliferation and cell survival to differentiation and immune responses, which makes the proteasome an effective therapeutic target for cancer treatment but also for non-malignant diseases such as cardiovascular, neurodegenerative, lung and autoimmune disorders (Ciechanover & Kwon, 2015; Drews & Taegtmeyer, 2014; Meiners, Keller, Semren, & Caniard, 2014; Morozov & Karpov, 2019; Zhang et al., 2020a). Numerous catalytic proteasome inhibitors have been developed in the past years, which inactivate the catalytic active sites of the proteasome and effectively block protein degradation of all proteasome complexes in the cell resulting in growth inhibition and apoptosis (Meiners, Ludwig, Stangl, & Stangl, 2008; Morozov & Karpov, 2018). While these inhibitors, e.g. the federal drug administration (FDA) approved drugs Velcade™, Kyprolis™, Ninlaro™, have shown promising results for the treatment of multiple myeloma, their efficacy for solid tumors is hampered by their pronounced cytotoxic side-effects due to broad inhibition of overall cellular protein degradation and emerging resistance (Manasanch & Orlowski, 2017; Robak, Drozdz, Szemraj, & Robak, 2018). Targeted inhibition of distinct subcellular proteasome complexes might represent an alternative strategy to overcome these limitations.

Indeed, the term "proteasome" refers to an entire proteasome system comprising multiple diverse proteasome complexes and not just a single enzymatic entity (FIG. 1). While all proteasome complexes contain the 20S catalytic core proteasome, they differ in their interaction with several activators and regulators. These regulators can be regarded as building blocks, which assemble to form proteasome super-complexes (FIG. 1A). The most abundant of these super-complexes in the cell is the 26S proteasome, which is assembled from the 20S core and one or two 19S regulatory particles that enable ubiquitin- and ATP dependent protein degradation. The 26S proteasome complex is at the heart of the ubiquitin-proteasome system. Other regulators of the proteasome include the proteasome activators (PA) PA28αβ, PA28γ, PA200, which all mediate ubiquitin-independent substrate degradation (Jiang, Zhao, & Qiu, 2018; Stadtmueller & Hill, 2011), the putative proteasome inhibitor PI31 and proteasome interacting proteins ECM29 or VCP/p97. Each of these regulators can potentially bind to the 20S core to form singly capped proteasome complexes or doubly capped ones forming so called hybrid proteasome complexes. This gives rise to a large variety of different proteasome complexes (FIG. 1B). The theoretical combination of all possible interactions of the 20S core with the different activators and regulators yields 56 possible proteasome complexes. While we lack systematic evidence about the existence and functional relevance of all of these complexes, we can envision that each of these different proteasome complexes has the potential to degrade specific proteins at distinct subcellular sites or to modulate proteasome function in a defined manner. Several predictions come with this building block model: i) assembly of proteasome complexes from their building blocks can be rapidly regulated according to cellular signals and needs; ii) proteasome super-complexes may provide specificity but also redundancy if required; iii) proteasomal protein degradation can be highly compartmentalized within the cell offering a novel level of subcellular regulation of proteasomal protein degradation; iv) defective assembly of proteasome complexes may occur under pathological conditions thereby contributing to disease onset and progression; v) proteasome complex assembly can be potentially targeted by small molecules to specifically interfere with the function of defined proteasome complexes in the cell. Thus, there is not one but many proteasome complexes representing a variety of drug targets for intervention (FIG. 2A). This offers a selective targeting strategy to inhibit the activity of distinct cellular proteasome complexes compared to the established broad catalytic proteasome inhibition (FIG. 2B) and opens an entirely new avenue for drug development. On a side note, this concept is paralleled by an emerging fine-tuning of ribosome form and function (Emmott, Jovanovic, & Slavov, 2019; Xue & Barna, 2012)

The aim of this review is to summarize the available evidence that supports a proteasome building block concept thereby providing a strong rationale for the defined targeting of distinct proteasome super-complexes in disease. We thereby hope to stimulate research on the regulation of the proteasome system under physiological and pathological conditions, which might ultimately lead to the development of tool compounds to study proteasome complexes in detail as well as of inno-

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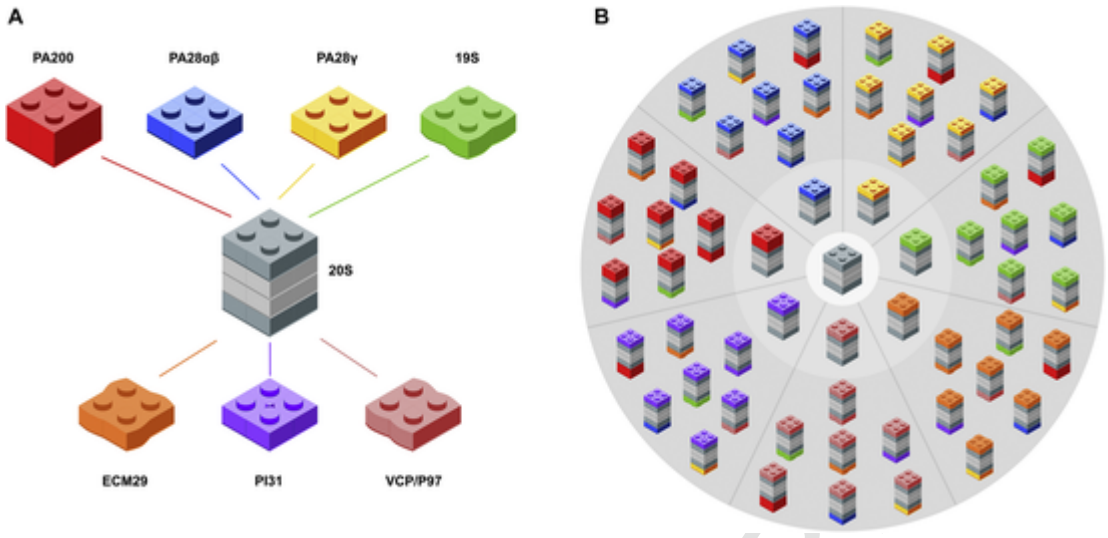

Fig. 1. Building block concept of the proteasome system.**A**) The 20S proteasome is symmetrically built of two outer rings consisting of alpha subunits and two inner rings built from beta subunits. Via its alpha ring surface it binds proteasome activators such as the 19S, PA28αβ, PA28γ or PA200 but also the proteasome inhibitor PI31 and the proteasome interacting proteins ECM19 or VCP/97. **B**) Multiple forms of proteasome super-complexes can assemble from the combination of 20S catalytic core, proteasome activators or regulators in form of singly or doubly capped homo- or heterotypic complexes. Admittedly, this is a theoretical consideration and the existence of some complexes has not been experimentally proven yet.

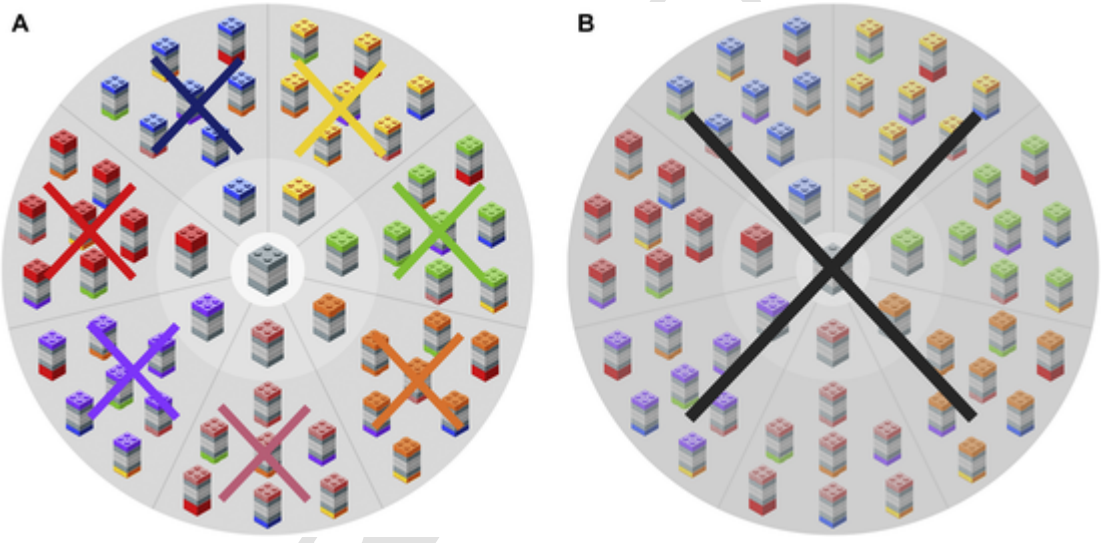

Fig. 2. Targeting of the proteasome system for drug development**A**) The activity of proteasome super-complexes can be potentially targeted specifically by small molecules that interfere with the assembly of defined complexes as indicated by the colored x. This would provide increased specificity and would most probably overcome the cytotoxic effects of broadly acting catalytic proteasome inhibitors (**B**).

vative therapeutic approaches beyond broad catalytic proteasome inhibition.

2. The proteasome system: structure and function

In this chapter, we will introduce the proteasome system as composed of the 20S catalytic core and its canonical proteasome activators to emphasize the structural diversity of proteasome complexes which represents a prerequisite for the above outlined conceptual understanding of the regulation, fine tuning and dysregulation of the proteasome system. In Table 1, we provide the reader with an overview on the various gene and protein names of all components of the proteasome system according to the HUGO gene nomenclature committee (https://www.genenames.org/).

2.1. The 20S catalytic core proteasome

The 20s proteasome is evolutionary highly conserved (Fort, Kajava, Delsuc, & Coux, 2015). It is abundantly present as free 20S particles in the cytoplasma and nucleus of the cell (Fabre et al., 2013). The eukaryotic 20S particle has a barrel like structure with twofold symmetry consisting of seven outer alpha and seven inner beta rings (α7β7β7α7). These subunits assemble at stoichometric ratios from two preformed rings with the help of proteasome assembly chaperones (PAC) such as PAC1-4/PSMG1-4 and POMP1 (Kunjappu & Hochstrasser, 2014; Murata, Yashiroda, & Tanaka, 2009). All subunits including PACs are essential for cellular survival (Tanaka, Mizushima, & Saeki, 2012). Within this structure, the catalytic active sites are located on three distinct beta subunits, namely β1/PSMB6, β2/PSMB7 and β5/PSMB5, within the inner chamber of the barrel. These sites contain an N-terminal active site threonine residue which enables

Table 1
Proteasome nomenclature.

HGNC ID (gene)	Approved symbol	Approved name	Alternative protein names	Synonyms
HGNC:9530	PSMA1	Proteasome 20S subunit alpha 1		HC2,NU,PROS30,MGC14542,MGC14575,MGC14751,MGC1667,MGC21459,MGC22853,MGC23915
HGNC:9531	PSMA2	Proteasome 20S subunit alpha 2		MU,HC3,PMSA2
HGNC:9532	PSMA3	Proteasome 20S subunit alpha 3		HC8
HGNC:9533	PSMA4	Proteasome 20S subunit alpha 4		HC9,HsT17706
HGNC:9534	PSMA5	Proteasome 20S subunit alpha 5		ZETA
HGNC:9535	PSMA6	Proteasome 20S subunit alpha 6		IOTA,PROS27,p27K,MGC22756,MGC2333,MGC23846
HGNC:9536	PSMA7	Proteasome 20S subunit alpha 7		XAPC7,C6,HSPC,RC6-1
HGNC:22985	PSMA8	Proteasome 20S subunit alpha 8		MGC26605,PSMA7L
HGNC:9537	PSMB1	Proteasome 20S subunit beta 1		PMSB1,HC5
HGNC:9539	PSMB2	Proteasome 20S subunit beta 2		HC7-I
HGNC:9540	PSMB3	Proteasome 20S subunit beta 3		HC10-II,MGC4147
HGNC:9541	PSMB4	proteasome 20S subunit beta 4		HN3,PROS26
HGNC:9542	PSMB5	Proteasome 20S subunit beta 5		MB1
HGNC:9543	PSMB6	Proteasome 20S subunit beta 6		Y,DELTA
HGNC:9544	PSMB7	Proteasome 20S subunit beta 7		Z
HGNC:9545	PSMB8	Proteasome 20S subunit beta 8	LMP7	RING10,D6S216E,PSMB5i,beta5i
HGNC:9546	PSMB9	Proteasome 20S subunit beta 9	LMP2	RING12,beta1i,PSMB6i
HGNC:9538	PSMB10	Proteasome 20S subunit beta 10	MECL1	LMP10,MGC1665,beta2i
HGNC:9547	PSMC1	Proteasome 26S subunit, ATPase 1	Rpt2	S4,p56
HGNC:9548	PSMC2	Proteasome 26S subunit, ATPase 2	Rpt1	MSS1,S7,Nbla10058
HGNC:9549	PSMC3	Proteasome 26S subunit, ATPase 3	Rpt5	TBP1,TBP-1
HGNC:9551	PSMC4	Proteasome 26S subunit, ATPase 4	Rpt3	TBP7,S6,MGC8570,MGC13687,MGC23214,TBP-7
HGNC:9552	PSMC5	Proteasome 26S subunit, ATPase 5	Rpt6	SUG1,p45/SUG,TBP10,p45,S8,TRIP1,SUG-1
HGNC:9553	PSMC6	Proteasome 26S subunit, ATPase 6	Rpt4	p42
HGNC:9554	PSMD1	proteasome 26S subunit, non-ATPase 1	Rpn2	S1,P112
HGNC:9559	PSMD2	Proteasome 26S subunit, non-ATPase 2	Rpn1	S2,P97,TRAP2,MGC14274
HGNC:9560	PSMD3	Proteasome 26S subunit, non-ATPase 3	Rpn3	S3,P58
HGNC:9561	PSMD4	Proteasome 26S subunit, non-ATPase 4	Rpn10	S5A,AF-1,AF
HGNC:9563	PSMD5	Proteasome 26S subunit, non-ATPase 5		S5B,KIAA0072

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Table 1 (*Continued*)

HGNC ID (gene)	Approved symbol	Approved name	Alternative protein names	Synonyms
HGNC:9564	PSMD6	Proteasome 26S subunit, non-ATPase 6	Rpn7	S10,p44S10,KIAA0107
HGNC:9565	PSMD7	Proteasome 26S subunit, non-ATPase 7	Rpn8	S12,P40,MOV34
HGNC:9566	PSMD8	Proteasome 26S subunit, non-ATPase 8	Rpn12	S14,Nin1p,p31,HIP6,HYPF
HGNC:9567	PSMD9	Proteasome 26S subunit, non-ATPase 9	Rpn4	p27
HGNC:9555	PSMD10	Proteasome 26S subunit, non-ATPase 10		p28
HGNC:9556	PSMD11	Proteasome 26S subunit, non-ATPase 11	Rpn6	S9,p44.5,MGC3844
HGNC:9557	PSMD12	Proteasome 26S subunit, non-ATPase 12	Rpn5	p55
HGNC:9558	PSMD13	Proteasome 26S subunit, non-ATPase 13	Rpn9	p40.5
HGNC:16889	PSMD14	Proteasome 26S subunit, non-ATPase 14	Rpn11	POH1,pad1
HGNC:9568	PSME1	Proteasome activator subunit 1	PA28alpha	IFI5111
HGNC:9569	PSME2	proteasome activator subunit 2	PA28beta	
HGNC:9570	PSME3	Proteasome activator subunit 3	PA28gamma	Ki,PA28-gamma,REG-GAMMA,PA28G
HGNC:20635	PSME4	Proteasome activator subunit 4	PA200	KIAA0077
HGNC:9571	PSMF1	Proteasome inhibitor subunit 1	PI31	
HGNC: 3043	PSMG1	Proteasome Assembly Chaperone 1	PAC1	
HGNC: 24929	PSMG2	Proteasome Assembly Chaperone 1	PAC2	
HGNC: 22420	PSMG3	Proteasome Assembly Chaperone 1	PAC3	
HGNC: 21108	PSMG4	Proteasome Assembly Chaperone 1	PAC4	
HGNC: 20330	POMP	Proteasome Maturation Protein	UMP1	hUMP1, Proteassemblin

nucleophilic attack of the polypeptide bond. The cleavage specificity of the β1, β2 and β5 subunits is determined by their respective substrate binding pocket and confers distinct activities towards acidic (caspase-like activity), basic (trypsin-like activity), bulky and hydrophobic amino acids (chymotrypsin-like activity) (Arciniega, Beck, Lange, Groll, & Huber, 2014; Groll et al., 1997; Huber et al., 2012). These so called standard catalytic subunits form the standard 20S proteasome which is constitutively expressed in all cells. An alternative set of inducible (i) catalytic subunits, namely β1i/PSMB9, β2i/PSMB10 and β5i/PSMB8 replaces the constitutive active subunits in cells stimulated by Interferon (IFN)γ, IFNα, IFNβ or tumor necrosis factor α (Sijts & Kloetzel, 2011) forming the immunoproteasome. In immune cells, usually around half of the 20S proteasome content is constituted by immunoproteasomes (Fabre et al., 2014). These inducible subunits show distinct structural features in their β1i and β5i but not β2i substrate binding pockets resulting in slightly altered proteolytic activities (Huber et al., 2012) which may produce peptides whose C-terminus fit better into the MHC I antigen binding pocket for triggering effective $CD8^+$ T cell immune responses (Vigneron & Van den Eynde, 2014). An additional catalytic subunit is specifically expressed in the thymus, β5t/PSMB11 (t for thymus), playing a role in the positive selection of $CD8^+$ T cells in the thymus (Shigeo Murata et al., 2007; Nitta et al., 2010). Tissue specific expression of the α4s/PSMA8 subunit, namely in the testis, contributes to the cellular diversity of 20S proteasome particles (Kniepert & Groettrup, 2013; Uechi, Hamazaki, & Murata, 2014). It is most likely that cells contain multiple distinct forms of the

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20S proteasome consisting of a mix of catalytic beta and alpha subunits (Dahlmann, 2016; Kloss, Meiners, Ludwig, & Dahlmann, 2010; Schmidt et al., 2006). In addition, it is well feasible that the composition of the 20S determines its interaction with proteasome activators as suggested for the immunoproteasome, which has a higher affinity for PA28αβ (Fabre et al., 2015).

Structural analysis of 20S proteasomes indicates that the gate to the proteolytic chamber of 20S proteasomes is obstructed by the N-termini of the alpha rings of the 20S particle (M Groll et al., 2000; Groll et al., 1997; Huber et al., 2012; Schneider, Stark, Bourenkov, & Chari, 2016) thereby preventing uncontrolled protein degradation by 20S proteasomes. Activation of 20S proteolysis involves at least partial opening of the gate to allow entry of partially folded or unfolded proteins as discussed below (Kish-Trier & Hill, 2013). About 20% of all cellular proteins are potentially degraded by 20S proteasomes including mainly unfolded proteins with extended disordered regions (Baugh, Viktorova, & Pilipenko, 2009; Deshmukh, Yaffe, Ben-Nissan, & Sharon, 2019). In line with this finding, 20S proteasomes mediate degradation of intrinsically disordered proteins as well as of oxidatively modified and unstructured proteins (Davies, 2001; Myers et al., 2018; Raynes, Pomatto, & Davies, 2016). For the cell, such direct processing by 20S proteasome complexes may be favorable under conditions of oxidative and proteotoxic stress (Farout & Friguet, 2006). The 20S has also been shown to be involved in post-translational processing of proteins. Hydrolysis occurs at disordered regions within proteins that contain intrincically disordered regions such as the translation elongation initiation factors (eIF)3 and eIF4F, the transcription factors Y-box-1, p53, nuclear factor (NF) κB precursor p105, and the proteostasis regulators LC3 and hsp70 (as recently reviewed in (Deshmukh et al., 2019).

2.2. Proteasome activators

Several proteasome activators, i. e. the 19S regulator, PA28αβ, PA28γ, and PA200, have been described which bind to the alpha rings of the 20S proteasome and open the gate to the proteolytic chamber thereby facilitating protein or peptide degradation. These regulators can bind to only one end of the 20S or to both ends forming singly or doubly capped complexes, respectively (Fig. 1B). In addition, they may form hybrid complexes with mixed regulators binding to a single 20S catalytic core (Fig. 1B).

2.2.1. The 19S regulator

The 19S regulator binds to the 20S core and forms the 26S or 30S proteasome when attached to only one or to both ends, respectively. We will here use only the term 26S proteasome for the sake of simplicity. The 26S proteasome is at the heart of the ubiquitin-proteasome system as it mediates ubiquitin-dependent substrate degradation (Ciechanover, 2005). Together with free 20S proteasomes it represents the majority of proteasome complexes in the cell (Fabre, Lambour, Delobel, & Amalric, 2012). It is built of a base- and a lid-like structure (for details see (Bard et al., 2018). The base is composed of a ring of six ATPases as well as three additional non-ATPase subunits with structural and ubiquitin-binding properties. The ATPases mediate binding to the 20S core and drive ATP-dependent unfolding of substrates and conformational shifts required for 26S activation (Eisele et al., 2018; Finley, Chen, & Walters, 2015; Matyskiela, Lander, & Martin, 2013; Navon & Goldberg, 2001). The lid is composed of at least 9 subunits and associated ubiquitin-binding and deubiquitinating proteins (Bard et al., 2018). For details on the structure and dynamics of substrate degradation by the 26S proteasome the reader is referred to several recent excellent publications (Asano et al., 2015; Dambacher, Worden, Herzik, Martin, & Lander, 2016; de la Peña, Goodall, Gates, Lander, & Martin, 2018; Lander et al., 2012). Assembly of 26S proteasome complexes from the 20S core and 19S regulator depends on dedicated assembly chaperones (Funakoshi, Tomko, Kobayashi, & Hochstrasser, 2009; Kaneko et al., 2009; Shigeo Murata et al., 2009; Roelofs et al., 2009) but also on chaperones with broader specificity such as BAG6 (Akahane, Sahara, Yashiroda, Tanaka, & Murata, 2013). In particular, p28/PSMD10 and p27/PSMD9 serve as activating assembly factors in mammals (Kaneko et al., 2009; Lu et al., 2017) while Proteasomal ATPase-Associated Factor 1 (PAAF1) and S5b/PSMD5 appear to inhibit assembly of 26S complex formation (Levin, Minis, Lalazar, Rodriguez, & Steller, 2018; Park et al., 2005; Shim et al., 2012). The 26S proteasome also interacts with several E3 ubiquitin ligases and deubiquitinating enzymes which serve to fine-tune ubiquitin conjugation and thereby turnover of substrates at the 26S proteasome (Bard et al., 2018; Lee et al., 2016; Martinez-Fonts et al., 2020; Xie & Varshavsky, 2000). Most of the 19S subunits are essential for cell and organismal survival as demonstrated by several knockout mouse models (for details see (Tanaka et al., 2012)). The cell type-specific knockout of single subunits of the 19S subunits confirmed the essential nature of these subunits and established a causal link to the pathogenesis of neurodegeneration or acute lung damage (Bedford et al., 2008; Sitaraman et al., 2019; Ugun-Klusek et al., 2017).

For degradation by the 26S proteasome, all substrates need a targeting signal and an unstructured region. The targeting signal is constituted by ubiquitin moieties bound to the ubiquitin receptors Rpn1/PSMD1, Rpn10/PSMD4, and/or Rpn13 (Komander & Rape, 2012). An additional unstructured region in the substrate is required to engage with the ATPases of the 19S lid compartment, which then pull on the substrates, unfold it and translocate it into the catalytic 20S chamber (for details see (Bard et al., 2018)). The 19S regulator contains some deubiquitinating enzymes (DUB) such as the essential Rpn11/PSMD14 subunit, and the associated Usp14 and Usp37 proteins. These DUBs allosterically affect the activity of the ATPases, and the process of 20S gate opening to regulate substrate degradation (Bard et al., 2018).

2.2.2. PA28alpha/beta

The PA28alpha/beta (also named REGalpha/beta) proteasome activator is found only in higher eukaryotes (Fort et al., 2015) and formed by seven 28 kDa sized alpha or beta subunits also named PSME1 and PSME2, respectively. Both subunits are inducible by IFNγ and found usually coregulated with the immunoproteasome indicating a function for PA28αβ in MHC I antigen presentation (Cascio, 2014; Rechsteiner, Realini, & Ustrell, 2000). In mammals, PA28αβ is composed of four PA28α and three PA28β subunits which stimulates proteasome activity more effectively compared to homomeric PA28α or PA28β complexes (E. M. M. Huber & Groll, 2017; Realini et al., 1997). Structural data indicate that the PA28αβ is wide enough to accomodate small proteins and unstructured polypeptides and that it opens the 20S alpha gate upon binding to the 20S (Stadtmueller & Hill, 2011). Currently, there are no structural data available for mammalian 20S proteasome complexes making the prediction of the molecular function of these complexes difficult. *In vitro* data support the notion that PA28αβ functions as a molecular sieve to regulate hydrophilicity of peptides generated by proteasomal cleavage in order to improve production of MHC I compatible antigenic peptides (Rechsteiner et al., 2000). A recent study suggests that PA28αβ proteasome complexes might degrade specific substrates that contain a novel charge-dependent degradation signal enriched in basic and flexible amino acids (Kudriaeva, Kuzina, Zubenko, Smirnov, & Belogurov, 2019). In cells, PA28αβ not only binds to the 20S particle but also to 26S proteasomes and possibly regulates the subcellular localization of 26S proteasome complexes (Cascio, Call, Petre, Walz, & Goldberg, 2002). Of note, PA28αβ double knockout mice display only partial defects in MHC I antigen presentation and disease progression upon virus infection

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which indicates that PA28αβ is not essential for MHC I antigenic peptide generation in general but rather affects processing of distinct epitopes (Murata et al., 2001; Respondek et al., 2017; Yamano et al., 2008). These mice are protected from experimentally induced diabetes possibly due to altered immune responses (Yadranji Aghdam & Mahmoudpour, 2016). Cells lacking PA28αβ and PA28γ were more susceptible to oxidative stress (Pickering et al., 2010) suggesting a protective role for PA28αβ in the degradation of oxidatively modified proteins. Controversial effects have been observed upon knockout or overexpression of either PA28α or β which might be related to forced - and possibly unphysiological - formation of homomeric PA28α or PA28β complexes in the cell or due to some in phenotypes unrelated to the proteasome (Adelöf et al., 2018) such as Hsp90-dependent protein refolding (Minami et al., 2000).

2.2.3. PA28gamma

PA28γ(PSME3) is closely related to PA28αβ and its ancestor (Fort et al., 2015). It is also composed of seven 28 kDa large subunits but forms a homoheptameric complex. Currently, no structural data are available for PA28γ but due to the conserved activation loops it is supposed to form similar complexes as described above for PA28αβ. The distinct functions of PA28α and PA28γ are probably determined by unstructured homolog-specific inserts likely localized at the entrance pore of PA28 that characterize each PA28 isoform and may regulate substrate binding (J. Li & Rechsteiner, 2001). PA28γ is localized exclusively in the nucleus (Realini et al., 1997; Stadtmueller & Hill, 2011). PA28γ can complex to both the 20S and 26S particles but the majority of nuclear PA28γ is found as free complexes or in non-proteasome-bound structures (Welk et al., 2016) suggesting that PA28γ might also perform proteasome-unrelated functions or that this free PA28γ represents a reservoir from which PA28γ is rapidly recruited to the proteasome (Welk et al., 2016). In the nucleus, PA28γ plays a role in intranuclear dynamics by regulating nuclear bodies (Baldin et al., 2008; Cioce, Boulon, Matera, & Lamond, 2006; Zannini, Buscemi, Fontanella, Lisanti, & Delia, 2009), trafficking of splicing factors (Baldin et al., 2008) and chromatin dynamics (Jonik-Nowak et al., 2018; Zannini et al., 2009). Several studies also indicated that PA28γ in involved in the control of cellular proliferation as it mediates the degradation of specific nuclear substrates, such as the cyclin-dependent kinase inhibitors p16, p21 and p21, p53, c-myc, β-catenin, the steroid receptor co-activator-3 and the deacetylase SIRT1 (Chen, Barton, Chi, Clurman, & Roberts, 2007; Dong et al., 2013; Li et al., 2015; Li et al., 2015; Xiaotao Li et al., 2007; Zhang & Zhang, 2008). In line with mediating the degradation of important cell cycle inhibitors, PA28γ-/- mice exhibit growth retardation and mouse embryonic fibroblasts show increased apoptosis when compared to wild type cells (Murata et al., 1999). However, PA28γ is not essential for survival as these knockout mice are viable and fertile but prone to premature aging (Fort et al., 2015; Murata et al., 1999). PA28γ functions in several signal transduction pathways including NFκB (Sun et al., 2016; T. Xie et al., 2019; Xu et al., 2016a) and transforming growth factor (TGF)β signaling (Ali et al., 2013; Jiao et al., 2019). It also plays a critical role for protein homeostasis in response to oxidative stress (Pickering et al., 2010; Zhang et al., 2015), proteotoxic stress after proteasome inhibition (Welk et al., 2016) and genotoxic stress when it is recruited to DNA double-strand break sites for coordination of proteasome function in DNA repair (Levy-Barda et al., 2011). PA28γ also contributes to the regulation of autophagy (Dong et al., 2013; Jiang et al., 2019).

2.2.4. PA200

PA200 (or PSME4) is a 200 kDa large, monomeric proteasome activator that binds to the 20S but also forms hybrid complexes with the 26S proteasome (see FIG. 1B) (Blickwedehl et al., 2007; Dange et al., 2011; Ustrell, Hoffman, Pratt, & Rechsteiner, 2002). It is highly conserved among mammals and also found in yeast (known as Blm10) but not in Drosophila melanogaster (Fort et al., 2015; Ustrell et al., 2002). The only recently resolved structure of human PA200-20S proteasome complexes revealed some unexpected features of human PA200 (Toste Rêgo & da Fonseca, 2019): i) the yeast structure of Blm10 is significantly different from human PA200 (Stadtmueller & Hill, 2011); ii) binding to the 20S is mediated by the C-terminal HBYX motif and an extended PA200 loop; iii) PA200-induced opening of the alpha gate results in allosteric adjustments of the three active sites with a widening of the β2 pocket and slight narrowing of the β1 and β5 substrate binding pockets; iv) purified PA200-20S complexes accordingly show elevated trypsin-like activity and a slight decrease in the caspase-like and chymotypsin-like activities. This finding is in contrast to the observed activation of the caspase-like activity in bovine PA200 (Ustrell et al., 2002). Finally, the narrow PA200 entry pore was complexed with inositol phosphates, which copurified with PA200 and may represent endogenous regulators of PA200 function.

The yeast ortholog Blm10 of PA200 has been well studied and proposed to function in proteasome maturation and assembly (Fehlker, Wendler, Lehmann, & Enenkel, 2003; Marques, Glanemann, Ramos, & Dohmen, 2007) and maintenance of mitochondrial and genomic integrity (Doherty et al., 2012; Tar et al., 2014). The function of mammalian PA200-proteasome complexes is less clear. PA200 is mainly localized in the nucleus (Ustrell et al., 2002). It is ubiquitously expressed in different organs but is most abundant in testis (Ustrell 2002), heart and muscle tissue (www.proteinatlas.org). PA200-/- knockout mice are viable but show impaired male fertility. This phenotype has been attributed to the defective degradation of acetylated histones by PA200-proteasome complexes (Khor et al., 2006; Mandemaker et al., 2018; Qian et al., 2013). PA200 has also been suggested to function in glutamine homeostasis (Blickwedehl et al., 2012) and DNA repair (Blickwedehl et al., 2008; Ustrell et al., 2002). However, PA200-deficient mouse embryonic stem cells are not sensitive to irradiation-induced DNA damage (Khor et al., 2006) questioning this activity of PA200. The function of PA200 in mammalian cells thus remains quite enigmatic.

3. Regulation of the proteasome system

The regulated assembly of proteasome super-complexes from the 20S core particle, proteasome activating regulators and compartmentalized binding partners offers the cell a unique strategy to fine-tune proteasomal protein degradation according to cellular needs as outlined above (Fig. 1). We will here summarize available evidence supporting this regulatory building block concept focussing on the different levels of regulation such as transcriptional, posttranscriptional, posttranslational, assembly and disposal of proteasome super-complexes under physiological and pathological conditions. In addition, we will review the regulation of the proteasome system by interacting cellular and interfering viral proteins. These interacting proteins may also contribute to the fine-tuning of the assembly and function of proteasomal super-complexes in defined subcellular compartments. Moreover, they may provide an evolutionary conserved strategy to inhibit proteasome complex function under conditions of stress and in disease which could possibly be repurposed for therapeutic approaches.

3.1. Regulation of the 20S proteasome

The function of the 20S catalytic core proteasome is regulated on several levels starting from transcriptional and posttranscriptional regulation of proteasome subunits and assembly factors to localization, fine tuning by posttranslational modifications and disposal via the autophagy pathway (Deshmukh et al., 2019). We will here focus on available studies that describe regulation only of the 20S complex with-

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out any further regulators attached. However, there might be some overlap to regulatory mechanisms involving proteasome super-complexes as studies might not always clearly separate these entities.

3.1.1. Regulation of 20S proteasome formation

The 20S protasome is an abundant protein in the cell with a half-life of 5-15 days depending on the cell type (Hendil, 1988; Tanaka & Ichihara, 1989). Formation of 20S proteasome particles in the cell is a highly ordered process and tightly regulated by chaperones (Bai et al., 2014; Heinemeyer, Ramos, & Dohmen, 2004; Murata et al., 2009). It requires the concerted expression of at least 14 different subunits together with the proteasome assembly chaperones PAC 1-4/PSMG1-4 and POMP1 resulting in the stoichometric assembly of these subunits into the mature 20S particle which is a tedious, time and energy consuming process.

At least two transcription factors drive proteasomal gene expression in mammals, i. e. nuclear factor erythroid-derived 2 – related factor (NRF) 1 and NRF2, under conditions of enhanced proteasomal turnover such as oxidative stress, oncogenic proliferation and starvation (Digaleh, Kiaei, & Khodagholi, 2013; Koizumi, Hamazaki, & Murata, 2018; Walerych et al., 2016; Zhang et al., 2014). Due to the stoichometric nature of assembled 20S particles, the expressional regulation of rate-limiting alpha or beta subunits might also impact 20S formation as described for the α4/PSMA7 subunit (Li et al., 2015). In addition, regulation of the proteasome assembly factor POMP1 by microRNA-101 has been demonstrated to impair 20S assembly and activity, thereby suppressing tumor cell proliferation (Zhang et al., 2015). Unwanted fully assembled proteasome complexes are disposed by the autophagy-lysosomal system in a process only recently delineated and termed proteaphagy (Cohen-Kaplan et al., 2016; Dikic, 2017; Livneh, Cohen-kaplan, Cohen-Rosenzweig, Avni, & Ciechanover, 2016). The molecular signals governing of this process, however, are mainly unexplored.

3.1.2. Regulation of 20S activity

The closed conformation of the 20S can be opened by structural displacement of the obstructing N-termini of the alpha subunits to open the entrance into the proteolytic chamber. Such activation can be induced *in vitro* by addition of low amounts of sodium dodecyl sulfate (SDS) (B Dahlmann et al., 1993), by hydrophobic peptides (Dal Vechio, Cerqueira, Augusto, Lopes, & Demasi, 2013; Kisselev, Kaganovich, & Goldberg, 2002), basic proteins (Orlowski, 2001) or defined posttranslational modification of alpha subunits such as acetylation, phosphorylation or binding of poly-ADP-ribose as recently summarized in (Kors, Geijtenbeek, Reits, & Schipper-Krom, 2019). As outlined above, substrates of the 20S proteasome need to be unstructured either intrinsically or due to stress-mediated unfolding of proteins (Davies, 2001; Myers et al., 2018; Raynes et al., 2016). This makes the 20S proteasome ideally suited for the degradation of oxidatively modified, damaged and misfolded proteins at conditions of protein stress and aging (Kumar Deshmukh et al., 2019). Accordingly, the levels and activity of 20S proteasomes is increased at mild conditions of oxidative stress either by i) disassembly of the 26S proteasome into 19S regulators and 20S (Grune et al., 2011; Livnat-Levanon et al., 2014) or ii) redox modifications that open 20S particles (Silva et al., 2012). In addition, formation of immunoproteasomes, which potently degrade oxidatively modified proteins under certain conditions, might be favored (Kotamraju et al., 2006; Pickering, Linder, Zhang, Forman, & Davies, 2012; Raynes et al., 2016; Seifert et al., 2010). This is, however, still controversially discussed (Nathan et al., 2013). In contrast, severe oxidative stress induces several redox modifications of the 20S proteasome (Farout & Friguet, 2006; Jung, Höhn, & Grune, 2014; Kors et al., 2019) which mainly inhibit its proteolytic activity. 20S activity is also impaired by oligomeric and aggregated proteins contributing to the pathogenesis of neurodegenerative disorders (Bennett, Bence, Jayakumar, & Kopito, 2005). Pathogenic beta-sheet isoform prion protein (PrP) binds directly to the 20S and impairs the activity of all three peptidase activities of the proteasome (Homma et al., 2015). Amyloid β protein has been localized to the middle portion of 20S proteasome complexes possibly blocking the catalytic chamber and thereby 20S activity (Gregori, Hainfeld, Simon, & Goldgaber, 1997).

The 20S particle is activated by gate opening upon binding of the 19S, PA200 or PA28s regulators. The ATPase subunits of the 19S regulator and PA200 possess a C-terminal HbYX motif (Hb: hydrophobic residue, Y: tyrosine, X: variable), which is able and in some cases even sufficient to induce 20S gate opening (Kish-Trier & Hill, 2013; Smith et al., 2007; Stadtmueller & Hill, 2011). In contrast, PA28 regulators do not posses a HbYX motif but rather open the 20S gate by insertion of an activation loop (Förster, Masters, Whitby, Robinson, & Hill, 2005; Whitby et al., 2000). Of interest, some of these activators show preferential binding to either constitutive or imunoproteasome 20S core particles with PA28αβ, for example, binding preferentially to immunoproteasomes (Fabre et al., 2015, 2014). The reason for this is presently unclear. Of note, some recently discovered mutations in the PSMB4 and PSMA3 genes display altered binding affinities of 20S particles to their regulators (Brehm et al., 2015). Association of 20S particles to their activators and regulators is also regulated by post-translational modifications as discussed below.

3.1.3. Regulation of 20S localization

20S proteasome function might also be regulated by its subcellular localization. 20S proteasomes have been early shown to diffuse freely between cyto- and nucleoplasm in mammalian cells and change according to cell cycle phase depending on the cell type (Brooks et al., 2000; Fabre et al., 2012; Palmer, Mason, Paramio, Knecht, & Rivett, 1994). 20S proteasomes can also associate with membranes such as the ER (Brooks, Murray, Mason, Hendil, & Rivett, 2000; A. V. Gomes, 2006). Only recently, a specialized 20S proteasome was identified in mammalian neurons that is located at the plasma membrane and modulates neuronal function by ejecting peptide products into the extracellular space (Ramachandran & Ramachandran & Margolis, 2017). In addition, active 20S complexes are present in the extracellular compartment such as the alveolar space of the lung (Stephan Urs Sixt, Beiderlinden, Jennissen, & Peters, 2007). Under acute respiratory distress, the amount of extracellular 20S proteasomes was dramatically increased while its activity was impaired and its composition altered (S U Sixt et al., 2012; Stephan Urs Sixt et al., 2009). Active release of proteasomes has been observed for various cell types including primary and cancer cells and appears to be mediated by extracellular vesicle release (Burkhardt Dahlmann, 2016; Kulichkova et al., 2017).

3.1.4. Mutations in the 20S proteasome

Several mutations in 20S proteasome subunits, mainly in the immunproteasome subunits LMP7 and LMP2, have been described in the past years (as reviewed in (Aldrin V Gomes, 2013; McDermott, Jacks, Kessler, Emanuel, & Gao, 2015). Diseases associated with these mutations have been grouped into Proteasome Associated Autoinflammatory Syndromes (PRAAS) (Torrelo, 2017). These diseases are extremely rare autosomal recessive genetic disorders and characterized by severe autoinflammation and early onset of diseases caused by decreased levels and activity of proteasome complexes. The recently described mutations in the assembly factors POMP1 and PAC2 interfere with the assembly of 20S proteasome complexes (de Jesus et al., 2019; Poli et al., 2018). For further information, the reader is referred to the summaries provided by Gomes and McDermott (Gomes, 2013; McDermott et al., 2015).

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3.2. Regulation of the 26S proteasome

Similar to the 20S and according to its housekeeping function in the degradation of unwanted, old and damaged proteins 26S proteasomes are highly abundant both in the cytoplasm and nucleus of the cell constituting between 0.1 and 1% of the cellular protein content (Brooks, Fuertes, et al., 2000; Princiotta et al., 2003). Accordingly, small changes in 26S abundance and activity will have a major impact on cellular protein turnover.

3.2.1. Regulation of 26S proteasome formation and assembly

Similar to the 20S proteasomal subunits, 19S subunit expression is concertedly regulated via the stress-related transcription factors NRF1 and NRF2 (Koizumi et al., 2018). Transcriptional activation of 26S proteasomes is observed under conditions of growth stimulation by epidermal growth factor and activation of the mammalian target of rapamycin (mTOR) pathway (Liu, Rogers, Murphy, & Rongo, 2011; Yinan Zhang et al., 2014), upon oncogenic activation via mutant p53 (Walerych et al., 2016) and at conditions of immune cell activation (Arata et al., 2019; Rieckmann et al., 2017). Formation of 26S proteasome complexes can also be regulated on the level of single subunit availability such as observed for the 19S DUB PSMD4 (Cai et al., 2019; Lin, Chang, Wu, Huang, & Lee, 2016) or PSMD3 (Fararjeh et al., 2019). Reducing individual 19S subunit levels increases the amount of free 20S and lowers 26S proteasome activity which is associated with proteasome inhibitor resistance (Acosta-Alvear et al., 2015; Shi et al., 2017; Tsvetkov et al., 2015, 2016). However, lower levels of single 19S subunits impair 26S proteasome activity and reduce survival of cancer cells (Tsvetkov et al., 2018).

An additional way of 26S proteasome regulation encompasses the assembly of the 26S from 19S regulators and 20S core components which can be fine-tuned on the level of assembly chaperones (Rousseau & Bertolotti, 2018). As already mentioned above, the 19S regulatory particle is built upon the 20S core particle in a complex process. The four regulatory particle assembly chaperones (RACs) S5b/PSMD5, p27/PSMD9, p28/PSMD10 and PAAF-1 are involved in the base assembly of the 19S. A decrease in the levels of these proteins leads to diminished 26S proteasome assembly and activity although none of the RACs is essential for cell survival (Kaneko et al., 2009; Rousseau & Bertolotti, 2016). Of note, p28/PSMD10 has independently been identified as the oncoprotein gankyrin which regulates cyclin-dependent kinase 4 and the tumor suppressors Rb and p53 thereby promoting oncogenesis (Wang, Jiang, & Zhang, 2016). The 19S subunit S5b/PSMD5 rather acts as an inhibitor of 26S proteasome assembly and activity when overexpressed in the cell. Mice overexpressing S5b displayed signs of premature aging and reduced life span which was accomanied by reduced proteasome activity (Shim et al., 2012). S5b/PSMD5 deficiency, on the other hand, increased proteasome activity and extended the life span of flies in a Drosophila neuropathology model (Shim et al., 2012). Levels of S5b were decreased in intestinal tumors while 26S proteasome activity was upregulated. Overexpression of S5b in these cancer cells lead to the inhibition of 26S proteasomes and the accumulation of polyubiquitinated proteins (Levin et al., 2018). The 19S subunit RPN6/PSMD11 is also crucial for the assembly of 26S proteasome complexes (Pathare et al., 2012). Partial knockdown of this subunits diminishes amount and activity of 26S proteasome complexes whereas overexpression of RPN6 induces 26S proteasome assembly and activity (Semren et al., 2015; Vilchez et al., 2012).

Disposal of non-wanted 26S proteasomes is mediated by autophagosomal proteaphagy as mentioned above for the 20S proteasome (Cohen-Kaplan et al., 2016; Cohen-Kaplan, Ciechanover, & Livneh, 2017; Livneh et al., 2016). In addition, disassembly of the 26S proteasome takes place under conditions of oxidative stress (Livnat-Levanon et al., 2014; Segref et al., 2014; Yu et al., 2019) or cigarette smoke (Kammerl et al., 2019) possibly due to posttranslational modifications that disrupt 19S and 20S interacting interfaces (see below). Inhibition of 26S activity may also be mediated by interaction with oligomeric proteins such as tau or mutant huntingtin smiliar to the above described effects on the 20S proteasome (Bennett et al., 2005; Hipp et al., 2012; Myeku et al., 2016). A recent structural study resolved the interaction between poly-Gly-Ala aggregates and 26S proteasome complexes *in situ* demonstrating that these oligomeric protein aggregates stabilize a transient substrate-processing conformation of the 26S proteasome and stall the activity of 26S proteasomes similar like a "chocked substrate" (Guo et al., 2018).

3.2.2. Regulating 26S proteasome function by posttranslational modifications

The formation and activity of 26S proteasome complexes is also regulated via post-translational modifications. Recent phosphoproteomic screens revealed that 26S proteasome components are dynamically phosphorylated under physiological and pathological conditions as reviewed recently in detail (Guo, Huang, & Chen, 2017). Phosphorylation of 19S subunit RPT3/PSMC4 was shown to induce 26S/30S proteasome activity by enhancing substrate translocation during cell cycle progression (Guo et al., 2015). Reversible phosphorylation of Rpn1 regulates 26S assembly and function (X. Liu et al., 2020). In addition, the assembly promoting 19S subunit RPN6/PSMD11 was shown to be regulated by protein kinase A (PKA) mediated phosphorylation activating both 26S proteasome assembly and activity (Lokireddy, Kukushkin, & Goldberg, 2015; Verplank, Lokireddy, Zhao, & Goldberg, 2019). Other post-translational modifications such as O-linked beta-N-acetylglucosamine (O-GlcNAc)-ylation, carbonylation or ubiquitination have also been described to regulate 26S proteasome assembly and activity for a recent summary see (Kors et al., 2019).

3.2.3. Regulation of 26S proteasome subcellular localization

Emerging evidence indicates defined subcellular sites of 26S proteasome activity such as at the primary cilium (Gerhardt et al., 2015; Gerhardt, Leu, Lier, & Rüther, 2016; Liu et al., 2014), at neuronal dendrites (Bingol & Schuman, 2006) and at the ER (Albert et al., 2019). Upon protein stress, 26S proteasome complexes are also specifically recruited to localized stress granules which may also contain aggregated proteins where they contribute to the resolution of protein stress by degrading misfolded and defective proteins (Johnston, Ward, & Kopito, 1998; Kopito, 2000; Protter & Parker, 2016; Turakhiya et al., 2018). A recent study demonstrated that upon hyperosmotic stress proteasomes and ubiquitinated proteins are able to condensate into membrane-less organelles in the nucleus in a phase-separation process (Yasuda et al., 2020). Extracellular 26S has also been recently detected in exosomal vesicles, its function, however, is not clear (Bec et al., 2019).

3.3. Regulation of PA28alpha/beta-proteasome complexes

Regulation of PA28αβ-proteasome complexes is mainly driven by the transcriptional activation of PA28αβ complexes via cytokines such as IFNγ (Groettrup et al., 1995). Both, PA28α and β subunits can also be transcriptionally activated by lipopolysaccharides (LPS) (Ossendorp et al., 2005). PA28αβ subunits are upregulated in dendritic cell maturation (Macagno et al., 1999). It is unclear whether other cytokines such as type I interferons or TNFα, which are able to induce immunoproteasome gene expression, regulate PA28αβ in a similar way. Induction of PA28αβ has been observed under conditions of oxidative stress via transcriptional activation by the antioxidant transcription factor NRF2 (Pickering et al., 2010; Pickering et al., 2012; Pickering &

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Davies, 2012). Similarly, PA28αβ expression is elevated in the retina and kidney glomeruli of diabetic mice which might also be related to glucose-induced oxidative stress (Aghdam, Gurel, Ghaffarieh, Sorenson, & Sheibani, 2013). Upon embryonic stem cell differentiation PA28αβ is induced, which is associated with the degradation of carbonylated proteins (Hernebring et al., 2013). PA28αβ is overexpressed in different types of cancers (reviewed recently in (Morozov & Karpov, 2019) but reduced in its expression by ethanol or NO and in parkinson disease (Bousquet-Dubouch et al., 2009; McNaught, Jnobaptiste, Jackson, & Jengelley, 2010; Tsihlis et al., 2012). Beyond transcriptional regulation, PA28αβ is phosphorylated on several serine residues which seems to be required for its ability to activate the 20S proteasome activity (Li, Lerea, & Etlinger, 1996). Physical association of PA28β with N-α-acetyltransferase 10 has been shown to inhibit PA28αβ-mediated activation of 26S proteasome activity (Min et al., 2013). Similarly, the intracellular signaling adaptor 14-3-3ζ binds to PA28α thereby impairing assembly of PA28αβ-containing proteasome complexes (Gu et al., 2018). Up to date there is no evidence for regulation of PA28αβ by miRNAs or genetic variances (SNPs or mutations).

3.4. Regulation of PA28gamma-proteasome complexes

Regulation of PA28γ takes place on the transcriptional level via the transcriptional activators p53 and NFκB (Ali et al., 2013; Wan et al., 2014; Xu et al., 2016a, 2016b) but apparently does not involve NRF1 and NRF2 (Sha & Goldberg, 2014; Walerych et al., 2016). In addition, PA28γ is negatively regulated on the post-transcriptional level by several microRNAs, which all act as tumor suppressors and suppress oncogenic cell proliferation (Sanchez et al., 2013; Y. Shi et al., 2015; Xiong et al., 2014). In line with this oncogenic role, PA28γ has been found to be overexpressed in multiple different cancers, including lung cancer (He et al., 2012; Okamura et al., 2003; Wang et al., 2011; Zhang, Gan, & Ren, 2012). In aging, PA28γ is downregulated which accords well with the premature aging phenotype of PA28γ knockout mice (Li et al., 2013). Similarly, PA28γ expression is impaired in neurodegenerative diseases while overexpression of PA28γ improved survival in neuronal model cells (Seo, Sonntag, Kim, Cattaneo, & Isacson, 2007) and the disease phenotype in a Huntington disease mouse model (Jeon, Kim, Jang, Isacson, & Seo, 2016). Only recently, PA28γ was shown to alter processing of MHC I antigenic peptides and counteract induction of the immunoproteasome suggesting that it plays a role in autoimmunity (Yao et al., 2019).

PA28γ is also modified by posttranslational modifications including phosphorylation by the ataxia-telangiectasia mutated protein kinase, which regulates the recruitment of PA28γ-26S proteasome complexes to the sites of DNA damage (Levy-Barda et al., 2011). In addition, PA28γ is phosphorylated by DNA damage checkpoint kinase 2 in the process of DNA repair (Magni et al., 2014; Zannini et al., 2009) and by MEKK3, the function of which is unknown (Hagemann, Patel, & Blank, 2003). PA28γ is also regulated by sumoylation, which mediates translocation into the cytosol and alters its function (Wu et al., 2011; Zannini et al., 2009). Acetylation of PA28γ promotes the assembly of PA28γ heptamers and thus regulates its protein degrading activity (J. Liu et al., 2013). The activating effects of PA28γ on peptide degradation by the 20S proteasome is also regulated by its association with PIP30 (Fam192A) (Jonik-Nowak et al., 2018).

3.5. Regulation of PA200-proteasome complexes

Regulation of PA200-proteasome complex function is still a matter of debate and has not been systematically studied. On the transcriptional level PA200 is regulated upon proteotoxic stress after proteasome inhibition by the transcription factor NRF1 (Sha & Goldberg, 2014). We have recently shown that PA200 is also transcriptionally induced by transforming growth factor (TGF) β (Welk et al., 2019). On the posttranscriptional level, PA200 is regulated by miRNA29b via its 3'UTR region (Wang et al., 2017). PA200-proteasome complexes accumulate on chromatin structures when cells are challenged with ionizing radiation. Silencing of PA200 in these cells impaired their survival suggesting a crucial role for PA200 in DNA damage responses (Blickwedehl et al., 2008; Ustrell et al., 2002). Dysregulation of PA200-proteasome complexes in disease has only recently been described by our lab. We observed elevated levels of PA200 in lungs of patients with idiopathic pulmonary fibrosis as well as in experimental models of fibrosis of the lung and kidney (Welk et al., 2019). Enhanced formation of PA200-proteasome complexes was induced upon TGFβ-induced myogenic differentiation. Knockdown experiments of PA200, however, revealed an adaptive function of PA200 in myofibroblast activation (Welk et al., 2019). Protein atlas data analysis indicates that increased RNA expression of PA200 in tumors might be associated with poor prognosis in liver and endometrial cancers based on TCGA data (www.proteinatlas.org).

3.6. Proteasome interacting proteins

Proteasome interacting proteins (PIPs) bind the 20S proteasome or proteasome activators and may affect the activity and/or localization of proteasome complexes with potentially functional consequences. Below we focus on three well-known proteasomal interacting proteins, i.e. proteasome inhibitor (PI) 31, ECM29 and valosin-containing protein (VCP)/p97, which have been demonstrated to regulate proteasome function in the cell.

3.6.1. Proteasome inhibitor PI31

PI31 (Proteasome Inhibitor of 31 kDa) is an endogenous cellular proteasome inhibitor, which inhibits proteasomal hydrolysis of small synthetic substrates and large unfolded proteins (Xiaohua Li, Thompson, Kumar, & Demartino, 2014). DeMartino reported the inhibitory function of PI31 located within the proline-rich carboxyl-terminal domain (McCutchen-Maloney et al., 2000). Structural information on how PI31 interacts with the proteasome is currently missing. PI31 affects the interaction of the proteasome with PA28 and the 20S proteasome (Zaiss et al., 1999). Overexpression of PI31 impaired assembly of immunoproteasomes and interfered with the generation of immunoproteasome-dependent MHC I epitopes (Zaiss, Standera, Kloetzel, & Sijts, 2002). Recent studies reported that PI31 forms a dimer and interacts with E3 ubiquitin ligases in Drosophila (Bader et al., 2011; Kirk et al., 2008). PI31 might serve as an adaptor for axonal transport of proteasomes in Drosophila (Liu et al., 2019) regulating longevity and locomotor ability (Merzetti et al., 2017). Regulation of PI31 by ADP-ribosylation is still controversial (Cho-Park and Steller, 2013; Li et al., 2014).

3.6.2. ECM29

ECM29 is a 200 kDa HEAT repeat protein that serves as an adaptor for tethering the 26S and 20S proteasome complexes to specific subcellular compartments (Wang et al., 2017; Wang et al., 2017). In mice, ECM29 is particularly highly expressed in brain and testis, while at lower level in liver, and almost undetectable in heart or kidney (Gorbea, Goellner, Teter, Holmes, & Rechsteiner, 2004b). In nascent axons, ECM29 was shown to bridge 26S proteasomes to the molecular motor protein dynein and it is crucial for active retrograde axonal transport in neurons (Hsu et al., 2015). ECM29-proteasome complexes localize to the centrosome and the secretory compartment (Gorbea et al., 2004b, 2010). It recruits the 26S proteasome to specific endosomes to degrade vesicle-associated signaling proteins (Gorbea et al., 2010). It may also play a role in synaptic plasticity and the selec-

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tive degradation of misfolded neuronal proteins such as in neurodegenerative diseases (Hsu et al., 2015). Binding of ECM29 might also compete with the 19S for binding to the 20S and thereby facilitate 26S disassembly and freeing of 20S particles. This has been suggested as a regulatory mechanism in oxidative stress (Xiaorong Wang, Chemmama, et al., 2017). In line with this notion, the binding of ECM29 to the proteasome is regulated by stress such as toxins, ethanol and oxidative stress (Gorbea, Goellner, Teter, Holmes, & Rechsteiner, 2004a; Xiaorong Wang, Yen, Kaiser, & Huang, 2010). In contrast, ECM29-deficient mouse embryonic fibroblasts are more resistant to oxidative stress and display stabilized 26S proteasome complexes (Haratake, Sato, Tsuruta, & Chiba, 2016).

3.6.3. VCP/P97

The ATP-driven valosin-containing protein (VCP)/p97 acts as a molecular chaperone and ATP-dependent unfoldase. It assists in membrane-associated protein degradation of ubiquitin-labeled substrates by the proteasome or autophagy pathway, endosomal sorting and in chromatin remodeling (reviewed in (Meyer, Bug, & Bremer, 2012; van den Boom & Meyer, 2018). VCP/p97 directly associates with the 20S proteasome (Barthelme, Chen, Grabenstatter, Baker, & Sauer, 2014) and possibly functions in an antagonistic manner to the proteasome inhibitor PI31 in order to maintain the activity of proteasome (Clemen et al., 2015). Binding of VCP/p97 to the 20S proteasome complex is regulated by methylation (Wang et al., 2019). VCP/p97 plays an important role under conditions of cellular stress. It retrotranslocates misfolded ubiquitinated proteins from the ER and mitochondria into the cytosol for ER-associated degradation (ERAD) and mitochondria-associated degradation (MAD), respectively. It is involved in protein quality control at the ribosome and helps to degrade cytosolic proteins (van den Boom & Meyer, 2018). Depending on its cofactor binding, it localizes to different subcellular localizations, which may fine-tune proteasome activity at subcellular membranes (Ballar et al., 2007; Wang et al., 2011).

3.7. Regulation by viral proteins

Interfering with cellular proteasome function is a well-known survival strategy for different viruses to ensure their intracellular replication, propagation and escape from the immune system (Ehrlich, 1995; Loureiro & Ploegh, 2006). While proteasome function is required for viral replication (Ma et al., 2010; Wang, Sun, Volk, Proesch, & Kern, 2011), the proteasome also degrades viral proteins into antigenic peptides for MHC class I mediated antigen presentation to activate $CD8^+$ T cell-mediated killing of infected cells (Sijts & Kloetzel, 2011). Accordingly, viral survival strategies aim at the inhibition of proteasome function to prevent efficient adaptive immune recognition of infected cells while maintaining proteasome function for viral replication. The first proteasome regulating viral protein was identified in human immunodeficiency virus (HIV)-1. The HIV-1 Tat protein binds to the 20S proteasome and inhibits its activity (Seeger, Ferrell, Frank, & Dubiel, 1997). Binding of Tat also interferes with the formation of PA28αβ-proteasome complexes (Seeger et al., 1997). In contrast, Tat binds to the 19S regulator and assembled 26S proteasome causing activation of the complex *in vitro* (Seeger et al., 1997). The Hepatitis B Virus X protein (HBX), a critical protein for hepatitis B virus infection, was shown to interact with two subunits of the 26S proteasome and inhibits the activity of both 26S and 20S proteasome (Hu, Zhang, Doo, Coux, & Goldberg, 1999). A HBX-derived peptide was also able to compete with PA28αβ for the binding to the 20S α4/PSMA7 subunit resulting in impaired activation of 20S proteasomes by PA28αβ (Stohwasser, Lehmann, Henklein, & Kloetzel, 2003). The Epstein-Barr virus (EBV) -encoded nuclear antigen 1 protein contains a Gly-Ala repeat, which impairs the unfolding of substrates by the 26S proteasome (Zhang & Coffino, 2004). In addition, during activation of the EBV lytic cycle in Burkitt's lymphoma cells, the chymotrypsin- and caspase-like activities of the proteasome are downregulated and expression of several proteasomal subunits is differentially regulated (De Leo, Matusali, Arena, Di Renzo, & Mattia, 2010).

Viral proteins also specifically regulate expression and function of the nuclear proteasome activator PA28γ, which plays a role in replication of viruses such as Human T-cell leukemia virus type 1 (HTLV-1) (Ko et al., 2013) and Hepatitis C virus (HCV) (Moriishi et al., 2003). In PA28γ gene knockout mice degradation of HCV is impaired but improves hepatic steatogenesis and hepatocarcinogenesis (Moriishi et al., 2007) as well as insulin resistance (Miyamoto et al., 2007). At the same time, PA28γ is required for cellular proliferation and is thus hijacked by the virus to ensure cell survival required for virus replication (Kwak, Tiwari, & Jang, 2017; Yeom, Jeong, Kim, & Jang, 2018).

Taken together, different virus strains have developed various strategies to inhibit, modulate and hijack the proteasome system to ensure ongoing virus replication but to escape immune recognition. This may represent an evolutionary conserved strategy to modulate and fine-tune distinct functions of the proteasome system which might be exploited for therapeutic approaches.

4. Inhibition of the proteasome system

As outlined above, both inhibition or activation of proteasome function can be a potentially useful therapeutic targeting strategy depending on the disease. Activation of the proteasome system might be favorable in diseases such as neurodegenerative disorders (summarized in (Jones & Tepe, 2019)). Recent chemical screens aiming at the activation of proteasome activity in cells have identified several small molecules, which activate proteasome activity ranging from kinase inhibitors, activators of the mTOR pathway to natural compounds that activate NRF2 (Leestemaker et al., 2017; Wedel, Manola, Cavinato, Trougakos, & Jansen-Dürr, 2018; Zhou et al., 2019). Similarly, activation of single proteasome super-complexes can be envisioned as a therapeutic concept. Enhancement of proteasome activity was previously achieved by the overexpression of single proteasome activators such as PA28αβ or PA28γ or by posttranslational modification of proteasome components contributing to protective effects in cardiac and neurodegenerative disease models (for a recent summary see (Kors et al., 2019)). In addition, proteasome activity can be activated by activator peptides that contain sequences and the HBYX motif derived from the proteasome activators PA200 or the 19S ATPase subunit RPT5 (Smith et al., 2007; Witkowska et al., 2017).

Here, we will focus on different strategies to inhibit proteasome function either by catalytic inhibition of the 20S proteasome, which will indiscriminately affect all proteasome complexes in the cell (FIG. 2B), or by interfering with the assembly and specific function of proteasome super-complexes (FIG. 2A).

4.1. Inhibition of the 20S proteasome

The development of proteasome inhibitors targeting the proteolytic active sites of the 20S proteasome core complex has largely influenced proteasome research and also cancer therapy (Kisselev, van der Linden, & Overkleeft, 2012; Manasanch & Orlowski, 2017; Kisselev et al., 2012). In 2003, bortezomib (Velcade®) was approved by the FDA as the first 20S proteasome inhibitor initially for third-line treatment of relapsed and refractory mantle cell lymphoma but then as a first-line treatment of newly diagnosed multiple myeloma patients (Mohan, Matin, & Davies, 2017). The second-generation inhibitor carfilzomib (Kyrpolis®) was approved in 2012 for the therapy of multiple myeloma and demonstrated reduced side-effects compared to bortezomib (Herndon et al., 2013). Since then, a variety of catalytic in-

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hibitors have been developed that reversibly or irreversibly bind to the catalytic active sites of the 20S proteasome with different active-site specificities (Manasanch & Orlowski, 2017; Park, Miller, Jun, Lee, & Kim, 2018; Thibaudeau & Smith, 2019). As multiple recent reviews have covered these developments in full depth, we would like to refer the interested reader to these excellent summary articles for details on the pharmacology and clinical use of these inhibitors (Ettari et al., 2018; Park et al., 2018; Thibaudeau & Smith, 2019). Importantly, most of the available proteasome inhibitors bind to catalytic sites of the proteasome via a common mechanism involving the nucleophilic addition of the catalytic Thr1 hydroxyl group to the inhibitor analogously to the nucleophilic attack of peptides for degradation. Both, the composition of side chains and of the pharmacophore defines the specificity of the inhibitor to the proteolytic site (Beck, Dubiella, & Groll, 2012; Screen et al., 2010). The currently approved proteasome inhibitors do not discriminate between standard and immunoproteasome active sites and thereby have broad activity against non-immune and immune cells. They have proven an effective strategy for treatment of multiple myeloma and are currently tested for other hematologic and non-hematologic malignancies (Manasanch & Orlowski, 2017). A major ongoing effort now aims to develop small molecule inhibitors that target defined catalytic sites of the standard 20S or immunoproteasome (Ettari et al., 2018). In particular, novel immunoproteasome inhibitors are currently developed as therapeutics for the treatment of autoimmune diseases, and first phase II clinical trial are on their way (as recently summarized in (Zhang et al., 2020b)).

Of note, the contribution of single active sites to cellular protein degradation is still incompletely understood (Kisselev, Akopian, Woo, & Goldberg, 1999; Meiners et al., 2008). Only the recent progress in the development of cell permeable site-specific inhibitors of either the standard or immunoproteasome catalytic sites will help to obtain a more systematic and detailed understanding of these activities for cellular protein degradation and their possible use in disease treatment (Cromm & Crews, 2017; Ettari et al., 2018; Alexei F. Kisselev & Groettrup, 2014). This has been exemplarily shown for the application of a selective caspase-like active site inhibitor which sensitizes tumor cells to the inhibition of the chymotrypsin-like site (Britton et al., 2009). The combination of site-specific inhibitors with defined specificity for β1, β2, β5, β1i, β2i, and β5i active sites with the recently developed unique method to identify substrates of the proteasome might help to answer this important question (de Bruin et al., 2014; Geurink et al., 2010, 2013; Kisselev et al., 2012; Wolf-Levy et al., 2018).

4.2. Inhibition of proteasome super-complexes

It is evident that the different proteasome super-complexes as depicted in Fig. 1 potentially have defined functions in the cell. Defined inhibition of distinct proteasome super-complexes may thus represent a promising therapeutic strategy to interfere with their specific substrates degradation activities under pathological conditions (Fig. 2A). Specific inhibition could be achieved by the development of small molecules that inhibit protein-protein interactions to interfere with the formation or stability of the super-complexes as suggested previously by Gaczynska and Osmulski (Gaczynska & Osmulski, 2015). This targeting strategy is different from the small molecule based inhibition of single 19S subunits such as ubiquitin receptors, DUB or ATPases (Muli, Tian, & Trader, 2019). These compounds influence protein degradation by inhibiting for example binding of ubiquitinated proteins to the respective 19S receptors RPN10 and RPN13, impeding activity of deubiquitinases such as USP14, UCH37 and RPN11, or blocking ATPase activity of the 19S base subunits (as recently summarized by (Muli et al., 2019)).

In principle, one can envision small molecules that competitively interfere with the binding of proteasome activators or regulators to the 20S core particle similar to the above-described viral proteins. In Table 2, we give an overview on the available molecules. This concept has previously been exploited by using regions of the HIV-1 Tat2 protein which are homologous to the C-terminal region of PA28α as minimal peptide inhibitors to compete with the binding of PA28αβ to the 20S proteasome (Jankowska et al., 2010; Witkowska, Karpowicz, Gaczynska, Osmulski, & Jankowska, 2014). HbYX-based small peptides such as the HbYX-containing C-terminal fragment of PI31 can be used as minimal units to compete with the binding of proteasome activators or modulators. However, this approach resulted in a non-specific activation of the 20S catalytic core due to alpha gate opening and not in specific inhibition of proteasome super-complex formation (Gaczynska & Osmulski, 2015). Of note, the mTOR inhibitor rapamycin and other rapamycin-derived structures, i.e. pipecolic esters, have been identified as proteasome inhibitors that bind to the alpha gate of the 20S core, destabilize it and obstruct 19S binding thereby preventing 26S proteasome formation (Giletto, Osmulski, Jones, Gaczynska, & Tepe, 2019; Osmulski & Gaczynska, 2013).

An additional mode of regulating super-complex formation and stability is the non-competitive binding of small molecules to the 20S or proteasome activator to allosterically disrupt or destabilize proteasome super-complexes. So far, only few small molecules have been identified as possible inhibitors, among them two small proline and arginine rich peptides, i.e. PR39 and PR11 (Gaczynska & Osmulski, 2015; Giżyńska et al., 2019). These peptides interact with the C-terminus of the α7/PSMA3 subunit of the 20S core and possibly interfere with the gate-opening dynamics thereby destabilizing the interaction with proteasome regulators (Gaczynska & Osmulski, 2015). Peptide mimetics of the N-terminal coiled-coil region of 19S ATPase subunits, such as RPT5, have been shown to interfere with 26S proteasome function and identify these ATPases as potential targets for 26S proteasome inhibition (Inobe & Genmei, 2015). A promising small compound is TCH-165 which binds to the α1/α2 intersubunit pocket of the 20S core particle to prevent the binding of the 19S RPT3 subunit and inhibit assembly of 26S proteasomes (Njomen, Osmulski, Jones, Gaczynska, & Tepe, 2018). While TCH-165 is targeting the 20S core particle, other small molecules may target the 19S subunits of the proteasome to interfere with 26S proteasome formation. One small molecule (cjoc42) has been identified which inhibits the activity of p28/gankyrin, one of the 19S regulatory particle assembly chaperones (Chattopadhyay et al., 2016). Cjoc42 is suggested to bind the RPT3/PSMC4 subunit to prevent the interaction of gankyrin with the 19S. However, this mode of action has not been experimentally confirmed yet. Another small molecule (TXS-8) has recently been discovered which binds to RPN6 and disrupts 26S proteasome assembly (Tian & Trader, 2020). This probe might represent an interesting scaffold to develop further peptoid inhibitors that interfere with 19S/20S assembly. Of note, specific targeting of PA28- or PA200-containing proteasome complexes has not been described at all and remains to be further explored.

In summary, while the therapeutic potential of specific targeting of proteasome super-complexes is evident, only few approaches and molecules have been described so far. Specific targeting of the interaction interfaces of proteasome activators or regulators with the 20S catalytic core by small molecules that interfere with protein-protein-interactions may harbour a great potential for drug development and open a new road for innovative therapeutic strategies.

5. Conclusion and outlook

It is evident that the proteasome system is far more complex than the originally described ubiquitin-proteasome system whose identification was awarded the Nobel Prize in chemistry in 2004. The detailed understanding of how single components of the proteasome system, i.e.

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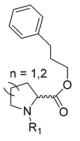
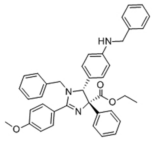
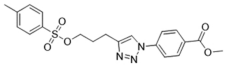
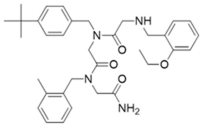
Table 2
Inhibitors of proteasome super-complex formation

Name	Primary target	Structure	Effect	References
HIV Tat2	α ring of the 20S proteasome	RKKRRQRRQDPI	Competes with PA28αβ for 20S binding	(Jankowska et al., 2010; Witkowska et al., 2014)
PR11	α7 subunit of the 20S proteasome	RRR-PRPP-*YLPR*-OH	Destabilizes interaction with proteasome regulators	(Gizyńska et al., 2019)
Peptide mimetics	19S ATPases RPT4 and RPT5	EIRIFRSELQRLSHELNVMLEKIKDLKEKIKNNRQLP	Interfere with 26S assembly and ATPase function	(Inobe & Genmei, 2015)
PR39	α7 subunit of the 20S proteasome	RRRPRPPYLPRPRPPPFFPPRLPPRIPPGFPPRFPPRFP	Selectively inhibits proteolytic degradation of polypeptide chains, ie. IκBα and HIF-1α	(Anbanandam, Albarado, Tirziu, Simons, & Veeraraghavan, 2008)
Pipecolic esters	α ring of the 20S proteasome		Inhibit 26S proteasome assembly	(Giletto et al., 2019)
TCH-165	α1/α2 intersubunit pocket of the 20S proteasome		Inhibits 26S proteasome assembly	(Njomen et al., 2018)
cjoc42	RPT3 of the 19S regulator		Inhibits binding of gankyrin to the 19S	(Chattopadhyay et al., 2016; Kanabar et al., 2020)
TXS-8	RPN6 of the 19S regulator		Inhibits 26S proteasome assembly	(**Kanabar et al.**, 2020)

distinct proteasome super-complexes, function, what substrates they degrade and how they are regulated under physiological and pathological conditions is mandatory for any future therapeutic considerations. The outlined building block concept offers a starting point for a more systematic analysis of proteasome species and super-complexes. The identification of tool compounds, i.e. small molecules that specifically interfere with the assembly or activity of defined proteasome super-complexes, would be a first and major step towards the molecular dissection of the function of proteasome super-complexes in health and disease similar to the development of the first proteasome inhibitors in 1992 (Vinitsky, Michaud, Powers, & Orlowski, 1992) which might then be extended to the development of new therapeutic agents.

Declaration of Competing Interest

The authors declare no conflict of interest.

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