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Review

Proteolytic and non-proteolytic roles of ubiquitin and the ubiquitin proteasome system in transcriptional regulation☆

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ABSTRACT

The ubiquitin proteasome system (UPS) regulates perhaps the most intriguing balance in all of biology: how cells control protein function and malfunction in order to regulate, and eventually eliminate, the old and error prone while simultaneously synthesizing and orchestrating the new. In light of the growing notion that ubiquitination and the 26S proteasome are central to a multiplicity of diverse cellular functions, we discuss here the proteolytic and non-proteolytic roles of the UPS in regulating pathways ultimately involved in protein synthesis and activity including roles in epigenetics, transcription, and post-translational modifications. This article is part of a Special Issue entitled The 26S Proteasome: When degradation is just not enough!

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1. The ubiquitin proteasome system

Work in the late 1930s by Schoenheimer indicated the cellular pool of proteins is in a "dynamic state" involving constant synthesis and degradation [1]. We now know the process of protein degradation is carried out by the ubiquitin proteasome system (UPS) and that it plays a critical role in the maintenance of cellular homeostasis. Ubiquitination is the term applied to the enzymatic cascade that covalently attaches ubiquitin, a 76 amino acid protein, to a substrate protein. The 26S proteasome is itself a multi-subunit complex known as the 'master regulator' of protein degradation. The role of ubiquitin and the 26S proteasome in protein turnover was comprehensively described in the 1970s and early 1980s [2,3] and in the last two decades the ubiquitin proteasome pathway has been demonstrated to play crucial roles in cellular activities as diverse as cell cycle regulation, DNA damage repair, signal transduction, membrane trafficking, neural development, and transcription. While it is well accepted that changes in the proteolytic function of the UPS lead to deregulation of cellular function and disease development, recent studies have introduced non-proteolytic functions of the UPS and have demonstrated an equally significant impact on cellular function and disease. Here, the ubiquitin pathway and the 26S proteasome are discussed with emphasis on recent findings indicating non-proteolytic roles for components of the UPS in regulating transcription including diverse functions in epigenetics, transcription, and post-translational modifications.

1.1. The ubiquitin pathway

The process of protein ubiquitination and degradation was first identified by Aron Ciechanover, Avram Hershko, and Irwin Rose for which they received the Nobel Prize in Chemistry [4]. Ubiquitin, initially termed adenosine triphosphate (ATP) dependent proteolysis factor 1 (APF-1) [5], is a highly conserved, 8.5 kD, 76 amino acid protein which is ubiquitously expressed in eukaryotic cells [4,6–11]. Although cells have multiple copies of ubiquitin genes arranged in tandem with no intronic sequences, ubiquitin proteins are expressed as monomers [12]. However once attached to target substrates, ubiquitin contains a unique propensity to form multimeric chains [4,6–11].

Ubiquitination is a multi-step process involving the covalent addition of ubiquitin molecules to lysine residues within target proteins. Substrate ubiquitination is mediated by an ATP-dependent enzymatic cascade involving an ubiquitin-activating enzyme (E1), an ubiquitin-conjugating enzyme (E2), and an ubiquitin-ligase (E3) [3,4,13,14]. E1 is encoded by a single highly conserved gene with two isoforms, E1a and E1b [15]. Both E1 isoforms lack specificity for target proteins, but are essential for cellular function as inactivation of E1 is lethal [16]. By comparison, there are more than 50 genes encoding for E2 and more than 500 genes encoding for E3 [17,18], and, as each E2 can interact with multiple E3s, numerous E2/E3 combinations make possible increased substrate specificity [18].

To initiate substrate ubiquitination, the C-terminal glycine residue of free ubiquitin is activated by the E1 ubiquitin-activating enzyme.

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Ubiquitin activation involves the formation of an ubiquitin-adenylate intermediate, the release of PP_i, transfer of ubiquitin-adenylate to a cysteine residue in E1 via a thiolester bond, and subsequent release of AMP [3,13,14]. Activated ubiquitin is transferred to a cysteine residue on the E2 ubiquitin-conjugating enzyme via a thiolester bond [3,4,13,14]. Transfer of activated ubiquitin from E2 to target proteins is frequently orchestrated by an E3 ubiquitin ligase which recognizes the target substrate and catalyzes transfer via an isopeptide bond between the C-terminal glycine residue of ubiquitin and the ε-amino group of an internal lysine residue of the substrate [3,4,13,14].

The product of this enzymatic cascade is a mono-ubiquitinated protein. Mono-ubiquitination has been linked to roles in transcription via regulation of histones and transcription factors [19–23] and to various cellular functions including receptor transport, viral replication, cell cycle regulation, protein localization, and DNA repair [20,24–28]. Consecutive addition of ubiquitin molecules to internal lysine residues of substrate conjugated mono-ubiquitin leads to the formation of poly-ubiquitin chains [29].

1.2. The 26S proteasome

The 26S proteasome is an approximately 2.5 MDa complex composed of more than 31 subunits which was partially purified from rabbit reticulocytes by Hough et al., was characterized by Waxman and colleagues as a high molecular weight alkaline protease, and was later renamed the 26S proteasome [30,31]. The 26S is composed of a 20S core particle capped on one or both ends by 19S regulatory particles (RP) or PA700 (Fig. 1) [32–34]. The 19S and 20S sub-complexes exist as the 26S complex or as independent complexes in both nuclear and cytoplasmic compartments [35]. Discrepancies exist regarding the nomenclature assigned to the 26S, which was originally named based on sedimentation coefficients as measured by density–gradient centrifugation [32]. Yoshimura and colleagues have shown that the sedimentation coefficient of the 26S proteasome in solution is "30S" according to physicochemical calculations [36]. The difference may be due to the "26S" proteasome containing one 19S regulatory particle on one end of the 20S core while the "30S" proteasome contains two 19S regulatory particles, one on each end of the 20S core [32]. For the remainder of this review, '26S' will be used to describe the functional proteasome with a 19S regulatory particle on one end of the 20S core.

1.3. The 20S core

The 20S core particle is a 670 kDa complex composed of 28 subunits and is the proteolytic center of the proteasome [37]. This hollow cylindrical structure is composed of two heptameric rings of α subunits and two heptameric rings of β subunits with an α_{1-7} β_{1-7} β_{1-7} α_{1-7} structure [38,39]. The α-subunits in the outer rings of the 20S core serve to recognize and direct poly-ubiquitinated substrates into the proteolytic center. The N-terminus of the α_2, α_3 and α_4 subunits forms a gate that protects the opening to the proteolytic center. Binding of the regulatory 19S particle to the 20S core triggers a conformational change in the N-terminus of the α_2, α_3 and α_4 subunits which opens the gate and allows passage of proteins into the proteolytic center [40]. Each of the α-subunits has a highly conserved YRD-motif (Tyr8-Asp9-Arg10) which functions as a hinge and is essential for opening and closing of the gate.

Poly-ubiquitinated proteins targeted for degradation are processed by deubiquitinating enzymes (DUBs) prior to being channeled into the proteolytic core [12]. The DUBs remove the poly-ubiquitin tag from the substrate to prevent "clogging" of the small proteolytic chamber (13 Å) by the poly-ubiquitin chain [12]. Although the 20S proteolytic core has two β rings with seven β subunits in each ring, only three β-subunits: β_1, β_2 and β_5, which reside in each of the two β rings, are proteolytically active. The result of protein degradation via the 26S proteasome are peptides with average lengths of 8–12 amino acids and free ubiquitin that is recycled in the ubiquitination process by the E1 activating enzyme [40].

1.4. The 19S regulatory particle (PA700)

The 20S core particle is capped on one or both sides by a 19S regulatory particle to form an active proteasome. The 19S regulatory

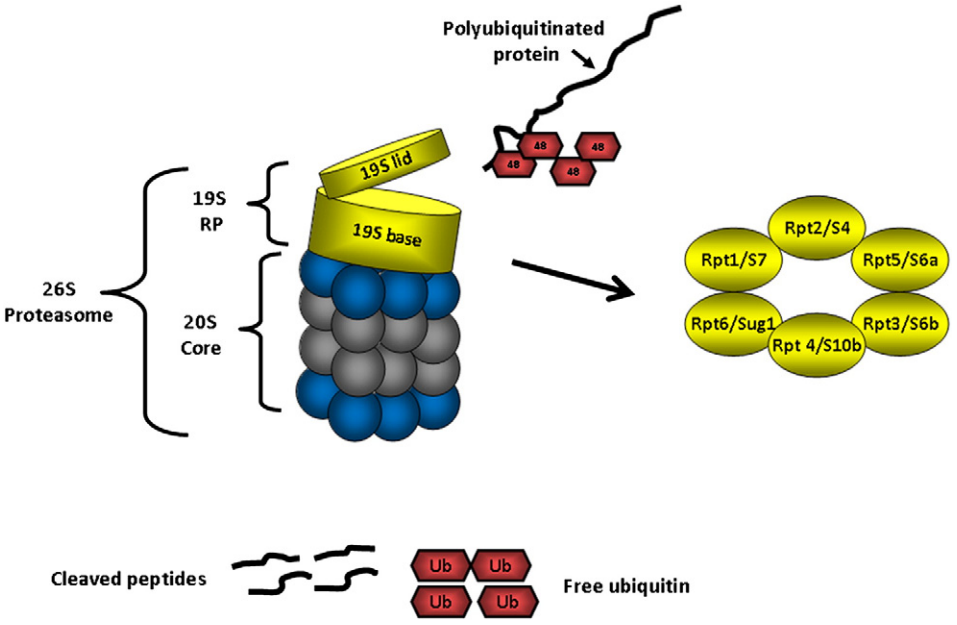

Fig. 1. The 26S proteasome. The 26S proteasome is composed of a 20S proteolytic core and a 19S regulatory particle (RP). The 20S core particle is the proteolytic center of the proteasome and is a 670 kDa complex composed of 28 subunits. The core is a hollow cylindrical structure composed of two heptameric rings of α subunits and two heptameric rings of β subunits (αββα). Capping one or both ends of the 20S core are 19S regulators. The 19S regulatory particle, (RP) also known as "PA 700" or "proteasome activator 700," is a large complex of approximately 700 KDa. The 19S is composed of a "base" component and a "lid" component with nine non-ATPase subunits (Rpn3, Rpn5–9, Rpn11, Rpn12 and Rpn15) in the lid and four non-ATPase (Rpn1, Rpn2, Rpn10 and Rpn13) and six ATPase subunits (Rpt1-6) in the base. Polyubiquitinated proteins are recognized and unfolded by the 19S ATPases and are translocated to the 20S core. Within the 20S core, proteins are cleaved into peptides and free ubiquitin is released.

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