Review TRENDS in Cell Biology Vol.15 No.1 January 2005

Mobilizing the proteolytic machine: cell biological roles of proteasome activators and inhibitors

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Proteasomes perform the majority of proteolysis that occurs in the cytosol and nucleus of eukaryotic cells and, thereby, perform crucial roles in cellular regulation and homeostasis. Isolated proteasomes are inactive because substrates cannot access the proteolytic sites. PA28 and PA200 are activators that bind to proteasomes and stimulate the hydrolysis of peptides. Several protein inhibitors of the proteasome have also been identified, and the properties of these activators and inhibitors have been characterized biochemically. By contrast, their physiological roles – which have been reported to include production of antigenic peptides, proteasome assembly and DNA repair – are controversial. In this article, we briefly review the biochemical data and discuss the possible biological roles of PA28, PA200 and proteasome inhibitors.

Introduction

Proteasomes are large complexes that carry out crucial roles in many cellular pathways by degrading proteins in the cytosol and nucleus of eukaryotic cells to enforce quality control and to regulate many cellular processes [1]. The catalytic heart of these complexes, the 20S proteasome, has been highly conserved from yeast to humans, with simpler versions also found in some archaea and prokaryotes. The 20S proteasome is a barrel-shaped assembly of 28 protein subunits that possesses three distinct proteolytic active sites with different specificities (Figure 1). Together, the three active sites, present in the two central rings of β subunits, hydrolyze almost all peptide bonds, having trouble only with those bonds that follow glycine and proline. As revealed by structural studies performed by Huber and colleagues [2,3], the potentially catastrophic elimination of inappropriate substrates is prevented by sequestration of active sites within the hollow structure of the 20S proteasome. Substrates access the central catalytic chamber through axial ports in the end rings of α subunits [4], although in the absence of activators these channels are closed and proteasome activity is repressed (Figure 2).

Proteasomes are activated by protein complexes that bind to the end rings of α subunits (Figure 3). The best-known activator is PA700 [proteasome activator MW 700, also known as 19S or regulatory complex (RC)], which has been highly conserved from yeast to humans and binds to the 20S proteasome to form the 26S proteasome. PA700 is the only proteasome activator that is known to stimulate degradation of protein substrates, which it generally recognizes by a polyubiquitin modification and which it processes by an ATP-dependent mechanism. Thus, PA700 is thought to mediate most of the biological effects of the proteasome by facilitating substrate degradation. This biological role is well established, and PA700 and 26S proteasomes have been reviewed extensively elsewhere [5].

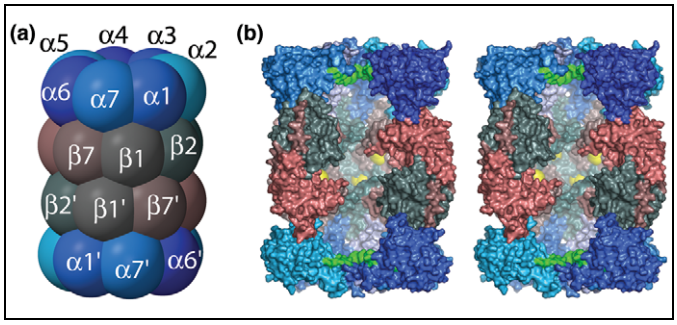

Figure 1. Architecture of the 20S proteasome. **(a)** Side view of the proteasome. Active sites are formed at the N-termini of β1, β2 and β5. The substrate preferences of these sites are: β1 – PGPH substrates; β2 – trypsin-like substrates; β5 – chymotrypsin-like substrates [3]. (Immunoproteasomes are the same as constitutive 20S proteasomes except that the constitutive catalytic subunits are replaced by inducible counterparts.) **(b)** Cutaway stereoview showing how the active sites (yellow) are sequestered within a central catalytic chamber. Substrates and products pass through an opening called the α-annulus (green) through the middle of the ring of α subunits [3].

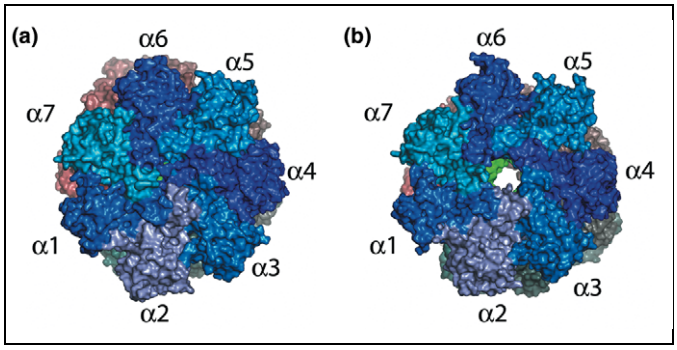

Figure 2. Proteasome entrance gate. **(a)** Top view of the proteasome in the closed conformation [3,64]. **(b)** Top view of the proteasome in the open conformation (as seen in complex with PA26) [9].

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Available online 8 December 2004

 0962-8924/$ - see front matter doi:10.1016/j.tcb.2004.11.003