The Architecture of the Anbu Complex Reflects an Evolutionary Intermediate at the Origin of the Proteasome System

Highlights

- The crystal structure of the bacterial proteasome homolog Anbu has been solved
- The dodecameric architecture reveals unique features compared with classical proteasomes
- Bioinformatic analysis places Anbu at the root of the proteasome family

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In Brief

Fuchs et al. present the first experimental study of a new bacterial proteasome homolog called Anbu. The *Pseudomonas aeruginosa* Anbu structure, combined with bioinformatic analyses, allows the authors to draft an evolutionary scenario in which Anbu represents an ancestral proteasome precursor at the origin of self-compartmentalization.
The Architecture of the Anbu Complex Reflects an Evolutionary Intermediate at the Origin of the Proteasome System

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SUMMARY
Proteasomes are self-compartmentalizing proteases that function at the core of the cellular protein degradation machinery in eukaryotes, archaea, and some bacteria. Although their evolutionary history is under debate, it is thought to be linked to that of the bacterial protease HslV and the hypothetical bacterial protease Anbu (ancestral beta subunit). Here, together with an extensive bioinformatic analysis, we present the first biophysical characterization of Anbu. Anbu forms a dodecameric complex with a unique architecture that was only accessible through the combination of X-ray crystallography and small-angle X-ray scattering. While forming continuous helices in crystals and electron microscopy preparations, refinement of sections from the crystal structure against the scattering data revealed a helical opening structure in solution, contrasting the ring-shaped structures of proteasome and HslV. Based on this primordial architecture and exhaustive sequence comparisons, we propose that Anbu represents an ancestral precursor at the origin of self-compartmentalization.

INTRODUCTION
The proteasome is a ubiquitous nano-machine for protein degradation in eukaryotes and archaea (Maupin-Furlow, 2012). It is a ~670 kDa barrel-shaped complex of four stacked rings (Kish-Trier and Hill, 2013), each composed of seven identical (archaea) or distinct (eukaryotes) subunits. The outer rings consist of catalytically inactive α subunits, whereas the inner rings are composed of proteolytic β subunits. α and β subunits are similar in sequence and structure, and are thought to have emerged by the duplication of a proto-β subunit.

The proteasome can act by itself as a 20S proteasome (Pickering and Davies, 2012a), or its α subunits may interact with various regulators that affect its choice of substrates (Forouzan et al., 2012; Fort et al., 2015). The proteasome’s most prominent function, targeted protein degradation, requires interaction with hexameric unfoldases of the AAA+ ATPase with diverse cellular functions (Bar-Nun and Glickman, 2012), which can also act as chaperones on their own (Benaroudj and Goldberg, 2000). In recent years, experiments have also emphasized the significance of the proteasome’s ATP-independent functions (Ben-Nissan and Sharon, 2014), such as the degradation of oxidized proteins through interaction with PA28αβ (Pickering and Davies, 2012b) or the degradation of acetylated histones through interaction with PA200 (Qian et al., 2013).

The proteasome is absent from bacteria, barring some branches of Actinobacteria (Lupas et al., 1994; Maupin-Furlow, 2012) and Nitrospirae (De Mot, 2007). While one theory attributes the occurrence of the proteasome in actinobacteria to horizontal gene transfer (HGT) (Gille et al., 2003), another argues that the original proteasome evolved in an ancestral actinobacterium, from where it was inherited by archaea and eukaryotes (Cavalier-Smith, 2006). Both theories, however, assume (Bochtler et al., 1999) that the proteasome as such evolved from its simpler and widely distributed bacterial homolog HslV (heat shock locus V). This homolog, unlike the proteasome, is a homomeric assembly of just two stacked hexameric rings (Bochtler et al., 1997) and thus lacks the antechamber constituted by the α subunits. Despite this, HslV is similar to the proteasome in its ability to interact with an unfoldase of the AAA+ superfamily, HslU, which recognizes intrinsic features of misfolded proteins (Gur et al., 2011). HslU and proteasomal unfoldases, however, belong to different clades of AAA+ ATPases (Ammerburg et al., 2006) and use different interfaces for interaction with their respective proteolytic machinery (Sousa et al., 2000; Yu et al., 2010), suggesting that they were recruited independently. While several studies indicate that HslU is not always bound to HslV (Azim et al., 2005) and possesses chaperone-like activities on its own (Seong et al., 2000), HslV has not been shown to function in the cell on its own in an ATP-independent manner. Unlike the essential, constitutively expressed eukaryotic proteasome, the non-essential heat-shock-induced HslV complements a set of other unrelated self-compartmentalizing proteases, such as FtsH, Lon, and Clp, under stress conditions (Gur et al., 2011; Kanimori et al., 1997).

In 2008, a novel bacterial β subunit homolog, termed Anbu (ancestral β subunit) was identified (Valas and Bourne, 2008). It was proposed that Anbu, not HslV, gave rise to the proteasome, and that this event took place in actinobacteria. This interpretation was, however, questioned as Anbu, unlike other self-compartmentalizing proteases, is not associated with an AAA+ ATPase on the genomic level, but frequently co-occurs in an...
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