Unravelling the Enigma: 20S Proteasome and VAT ATPase - Partners in a Molecular Dance or Solitary Performers?

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Cellular proteins need to be removed for many reasons - they may be damaged, no longer required by the cell, or originate from a pathogen and therefore be harmful. Proteasomes are ubiquitous in bacterial, prokaryotic, and eukaryotic cells as they cleave faulty proteins back into their short peptide substituents for further recycling and regeneration.[1, 2] Denaturation of malfunctional proteins is performed by unfoldases[2] as they work in parallel with proteasomal units and function by unravelling proteins marked for degradation before being finally degraded.[3] These processes have been reported and exploited for decades and yet, important areas of the overall unravelling and degradation process remain unclear.

As such, to date it has been unachievable to visualise the complexation between two archaeal protein assemblies: ATP-dependent unfoldase called VAT (Valosine-containing protein-like ATPase) and the proteasome core particle 20S CP from *Thermoplasma acidophilum.* Unless artificial linking methods like chemical crosslinking are employed[4], these assemblies have not been caught forming a uniform 'machinery', despite their indisputable collaboration in protein degradation.

In this study, we focus on examining the interplay between VATΔN and the 20S proteasome, revealing a unique process of self-directed breakdown where VATΔN acts as both an unfolding agent and its own substrate for degradation by the 20S proteasome. Our results mark the first instance, to our knowledge, of observing the cryo-EM structure of tunnel-like patterns formed by interactions between VATΔN-VATΔN and 20S-20S.[5] This discovery challenges existing views on how protein degradation operates in archaea, offering fresh insights into the complex dynamics of proteolytic mechanisms within this realm.

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