Abstract:

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Seminar Title: Machines of Protein Destruction

In all domains of life, AAA+ family proteolytic machines eliminate unnecessary or damaged intracellular proteins and help to regulate biological circuits. The operation of these ATP-dependent machines depends upon a AAA+ ring hexamer with a central axial channel or pore, which engages an unstructured region of a target protein. Conformational changes in the ring, powered by cycles of ATP hydrolysis, pull on and eventually denature the substrate, and the unfolded polypeptide is subsequently translocated through the pore and into the chamber of an associated self-compartmentalized peptidase for degradation. AAA+ proteases can be used to create truncated proteins with biological activities that differ from the intact molecule, and AAA+ ring enzymes also function biologically to remodel macromolecular complexes. For ClpXP, the best studied AAA+ protease, ClpX is the AAA+ enzyme and ClpP is the peptidase. Recent single-molecule studies have revealed how ClpX unfolds model substrates, how it translocates them into ClpP, and how these activities differ for a protease in which ClpA, a double-ring AAA+ hexamer, replaces ClpX. This work, crystallographic studies, and biochemical experiments have led to detailed models of structure and function, which will be discussed.