

Keynote lectures

KN-1 Crystal structures of amino acids: investigations into CSD

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After the discovery of X-ray diffraction by crystals, amino acids were among the first organic compounds to have their solid state structures investigated. After a short introduction dealing with the early history of crystal structure determination, this keynote will present the main results of a systematic review of more than 3500 entries for alpha-amino acids in the Cambridge Structural Database. This includes an overview of various experimental techniques and conditions, a classification of amino acid structures, and a discussion of their acid-base properties leading to a series of different protonation states. For each such state essential structural elements are described, especially hydrogen bonding preferences and coordination to metal ions. Finally, the concepts of polymorphism and phase transitions as the result of extreme temperatures or pressures are discussed, with reference to recent work.

Keywords: amino acid, crystal structure, database, hydrogen bonding, polymorphism, metal complexes

KN-2 Keeping muscle proteins in shape: The moonlighting function of the UNC-45 chaperone

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Muscle development and function rely on the correct assembly of contractile units called the sarcomeres. Their main components, thin (actin) and thick (myosin) filaments are organized in a precisely ordered, quasi-crystalline protein framework that mediates muscle contraction. Although the overall architecture of the sarcomere has been studied in detail, little is known about its complicated assembly process. In particular, the mechanism of myosin incorporation into thick filaments is poorly understood.

The UCS (UNC-45/CRO1/She4) chaperones play an evolutionarily conserved role in promoting myosin-dependent processes including cytokinesis, endocytosis, RNA transport and muscle development. To investigate the protein machinery orchestrating myosin folding and assembly, we performed a comprehensive analysis of *Caenorhabditis elegans* UNC-45. Our structural and biochemical data demonstrate that UNC-45 can form linear protein chains offering multiple binding sites for co-working chaperones and client proteins. Accordingly, Hsp70 and Hsp90, which bind to the TPR domain of UNC-45, could act in concert and with defined periodicity on captured myosin molecules. We thus propose that UNC-45 represents a novel type of filament assembly factor that is capable of coupling myosin folding with myofibril formation.

As for the assembly, also the degradation of muscle myosin is relatively little understood. The U-box containing E3 ligase UFD-2, which is one of the most abundant proteins in embryonic cardiomyocytes, is implicated in this process. New data from our lab reveal the molecular mechanism of UFD-2 in myosin homeostasis. We show that UFD-2 employs UNC-45 as an adaptor protein to target and ubiquitinate the muscle myosin in a highly specific manner. These data suggest that UNC-45 is situated at the interface of myosin folding and degradation pathways. On one side, it interacts with its partner chaperones Hsp70 and Hsp90 to fold and assemble myosin molecules. On the other side, UNC-45 can team up with UFD-2 to ubiquitinate and quality-control damaged myosin proteins. Accordingly, UNC-45 is a central player in the triage system channeling myosin molecules into refolding and ubiquitination pathways, thereby determining the fate of the myosin protein in different cellular situations.

Keywords: protease, chaperone, filament assembly, myosin, UNC-45, UFD-2