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Mechanisms and Functional Diversity of Macromolecular Remodeling by ATP-Dependent Motors

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Members of the AAA+ protein family (ATPases associated with a variety of cellular activities) play essential roles in most fundamental processes, such as DNA replication, DNA repair, recombination, transcription, splicing, peroxisome biogenesis, bacteriochlorophyll biosynthesis, protein unfolding, degradation, and biological motility. In partnership with diverse macromolecules, these molecular motor proteins are involved in cellular events of high complexity. They use common structural and operational principles to perform mechanochemical work in cells, including protein unfolding prior to degradation, remodeling of macromolecular complexes, solubilization of aggregates, and translocation of nucleic acids and proteins.

Most AAA+ ATPases assemble into ring-shaped hexamers with an axial channel that can be used to translocate substrates. The large size, conformational heterogeneity, and dynamics of these ATP-dependent motors had made it challenging to address their specific roles, detailed mechanisms, and regulation, as well as the sequence of conformational changes that take place during the motor's catalytic cycle. Some of these challenges have been overcome in the recent years. Therefore, the Journal of Molecular Biology is assembling a collection of eight reviews and one communication that illustrate important advances in the field.

- Ferdos Abid Ali and Alessandro Costa review the role of the Minichromosome Maintenance (MCM) helicase, a hetero-hexameric AAA + ATPase in which the non-catalytic N-terminal DNA-interacting collar might destabilize and unwind the DNA double helix for duplication in the eukaryotic replisome. The reconstitution of DNA replication *in vitro* has established the succession of events that lead to the replication origin activation by the MCM. Although recent studies have started to elucidate the structural basis of duplex DNA unwinding,

how the MCM converts the energy derived from ATP hydrolysis into motion to translocate on DNA remains unclear and a matter of debate [1].

- Zev Bryant and colleagues focus their review on the essential role of DNA gyrase in compacting the genome and solving topological challenges associated with replication and transcription. DNA gyrase is a molecular motor that harnesses the free energy of ATP hydrolysis to perform mechanical work on DNA. Gyrase remodels the bacterial chromosome by introducing negative supercoils. The authors present the current understanding of mechanochemical coupling in this essential molecular machine, with a focus on recent diverse biophysical approaches that have revealed details of molecular architectures, new conformational intermediates, structural transitions modulated by ATP binding, and the influence of mechanics on motor function. Recent single-molecule assays have also illuminated the reciprocal relationships between supercoiling and transcription, an illustration of mechanical interactions between gyrase and other molecular machines at the heart of chromosomal biology [2].
- Chromatin remodeling and modulation of nucleosome function play a vital role during repair of DNA double-strand breaks. Brendan D. Price and colleagues review the steps involved in this process. The latter is dependent on the rapid reorganization of the surrounding chromatin structure by remodeling complexes and involves transient accumulation of repressive complexes including NuRD. The repressive chromatin is subsequently dismantled by dynamic exchange of the histone variant H2A.Z by NuA4. Acetylation of the H4 tail by the NuA4–Tip60 complex shifts the chromatin to a more open structure. H2A.Z removal then promotes chromatin ubiquitination and recruitment of additional double-strand break repair proteins to the break [3].
- In eukaryotic cells, Cdc48 (alias p97 or VCP) plays roles in a puzzling array of cellular functions, including cell cycle regulation, DNA replication, transport processes, immune signaling, reassembly of nuclear and Golgi membranes, and protein degradation by autophagy and the ubiquitin proteasome system (UPS). The ability of Cdc48 to remodel, unfold, or disassemble various proteins and their complexes is thought to underlie each of these diverse activities and require Cdc48's interaction with a large number of adaptor proteins. Dominik Barthelme and Robert T. Sauer review possible mechanisms that have been proposed to explain how Cdc48 might couple ATP hydrolysis to forcible unfolding, dissociation, or remodeling of cellular substrates. [4].
- The ATP-dependent motor Hsp104 couples ATP hydrolysis to disassembly and reactivation of proteins trapped in soluble pre-amyloid oligomers, disordered protein aggregates, and stable amyloid or prion conformers in yeast. Upon ATP hydrolysis, a peristaltic pumping motion likely drives directional substrate translocation through the central Hsp104 channel. Elizabeth A. Sweeny and James Shorter discuss advances revealed by small-angle x-ray scattering that grew our structural understanding of Hsp104 and how Hsp104 deconstructs Sup35 prions. Contrasting to previous assumption, recent studies highlight the

importance of the N-terminal domain in enabling the full repertoire of Hsp104 activities [5].

- Dynein is a large microtubule-based motor complex that requires tight coupling of ATP hydrolysis with the generation of mechanical force and track-binding activity. Because of the separation of the microtubule-binding domain from the nucleotide-binding sites, this process requires a long-range, two-way communication. To investigate the structural changes that occur in the dynein stalk region to produce two different, low-affinity and high-affinity, interaction modes with microtubules, Genji Kurisu and colleagues compare currently available X-ray structures. The authors discuss the basis of the transition from the low-affinity to the high-affinity coiled-coil registry and propose a modified open zipper model of two-way communication along the long stalk coiled coil [6].
- Meiotic clade AAA ATPases include four family members, Vps4, spastin, katanin, and fidgetin. Their function is to disassemble specific polymeric protein structures, with Vps4 disassembling the endosomal sorting complexes required for transport (ESCRT)-III polymers that are central to the many membrane-remodeling activities of the ESCRT pathway, and spastin, katanin, and fidgetin, affecting multiple aspects of cellular dynamics by severing microtubules. These motors share a common domain architecture that features an N-terminal microtubule-interacting and trafficking domain followed by a single AAA ATPase cassette. Meiotic clade AAA ATPases appear to disassemble their polymeric substrates by translocating subunits through the central pore of their hexameric ring. Nicole Monroe and Christopher P. Hill discuss recent mechanistic studies investigating the potentially coordinated disassembly and microtubule-severing functions of these AAA ATPase [7].
- *N*-ethylmaleimide-sensitive factor (NSF) forms a 20S supercomplex with and consequently disassembles soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complexes in conjunction with soluble *N*-ethylmaleimide-sensitive factor attachment protein. NSF is essential in protein and hormone secretion and neurotransmitter release in eukaryotes. Based on recent structures of NSF and the 20S supercomplex at atomic or near-atomic resolution, Minglei Zhao and Axel T. Brunger review recent insights into the molecular mechanism and energy requirements of NSF [8].
- The members of the myosin superfamily are enzymes that function in active transport processes, cytoplasmic contractility, and mechanosensing in both physiological and pathological processes. They are regulated by allosteric mechanisms that determine the stimulation or inhibition of myosin motor activity and enable precise timing and spatial aspects of myosin function at the cellular level. Sarah M. Heissler and James R. Sellers review the molecular basis of post-translational regulation of eukaryotic myosins from different classes across species by allosteric intrinsic and extrinsic effectors [9].

Abbreviations used:

MCM	minichromosome maintenance
NSF	<i>N</i> -ethylmaleimide-sensitive factor

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