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Lifelong companions

RNA helicases and their roles in RNA metabolism

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The life of an RNA molecule is complicated. Once a newly synthesized eukaryotic RNA has emerged from the RNA polymerase in the nucleus, it will be processed, spliced and exported into the cytoplasm. In prokaryotes, transcribed RNA is synthesized directly in the cytoplasm. RNA molecules that serve as mRNAs have to be kept devoid of local structures that are inhibitory for ribosome scanning and translation. Quite differently, structural and catalytic RNAs have to adopt a defined three-dimensional conformation to exert their biological function, and may assemble with other protein and/or RNA partners into complex functional units. Ultimately, RNA degradation by the so-called degradosome will end the RNA's life.

The high stability of folding intermediates containing duplex regions, and the comparatively low stabilization gained from tertiary contacts, leads to a rugged energy landscape of RNA folding, and stable kinetic traps impede formation of the correctly folded, functional structure. Removal or remodeling of unproductive RNA structures is thus an important element of all processes in RNA metabolism. In the cell, duplex separation and rearrangement of RNA and RNP structures is catalyzed by RNA helicases in an ATP-dependent reaction. RNA helicases are thus vital companions in the life of RNA.

RNA helicases are ubiquitous enzymes present in all kingdoms of life. Since their discovery in the 1980s, numerous studies have provided insight into their structure, function and mechanism. In this special issue on RNA helicases, 11 review articles provide an overview on the structures of RNA helicases, their various cellular functions and our current understanding of the underlying mechanisms. Two original research papers connect a helicase to quorum sensing, and dissect the annealing and strand displacement activities of a helicase that is part of the cold-shock response.

RNA helicases have been grouped into different helicase superfamilies, with the majority belonging to superfamily 1 (Upf-like helicases) or superfamily 2 (DEAD-box, DEAH-box, NS3/NPH-II, RIG-I-like, Ski2-like helicases). The minimal functional unit shared by these RNA helicases is the so-called helicase core that is formed by two RecA domains connected via a flexible linker. Ancillary domains can confer additional functions to the helicase core. From biochemical, structural and single molecule data, a picture of the catalytic cycle of the helicase core and of the mechanism of duplex destabilization has emerged. Andreou and Klostermeier[1] present an overview on the mode of action of the DEAD-box helicase core. They summarize the insight gained from studying a minimal DEAD-box helicase, the translation initiation factor eIF4A that consists of an isolated helicase core. The lessons learned on DEAD-box helicase mechanism are highlighted, and the limitations of eIF4A as a universal model for DEAD-box protein function in general, are discussed. The article by Russell et al.[2] summarizes the current knowledge on the molecular mechanism of RNA remodeling by DEAD-box helicases, with the splicing helicases Cyt-19 and Mss116 as selected examples. Both DEAD-box proteins consist of a helicase core, followed by a C-terminal α-helical region and a basic tail. Integrating insight from thermodynamic, kinetic and structural studies, contributions of regions outside the helicase core to interactions with RNA and to RNA unwinding are highlighted, and a model for a general chaperone activity of DEAD-box proteins is presented.

The review by König et al.[3] provides an overview of force- and fluorescence-based single molecule approaches. The folding pathway of a minimal form of the group II intron has been delineated with single-molecule FRET both in the absence and presence of Mss116. The insight into the inter-play of Mss116 and RNA, and of helicases and their RNA substrates in general is discussed. The role of Mss116 in RNA folding in vivo is illuminated in the contribution from Sachsenmaier and Waldsich.[4] Mutations in Mss116 that affect ATP binding and hydrolysis, RNA binding and unwinding, as well as splicing in vitro and in vivo are summarized, and the impact of Mss116 on the folding pathway of group II introns in vitro and in vivo are compared. Mss116 appears to play a dual role by stabilizing the core of the group II intron, and destabilizing inhibitory structural elements in the flanking exonic region. Interestingly, the role of Mss116 in assistance of folding of group I and group II introns may be different. In addition to duplex separation, some helicases also display an RNA annealing activity. Stampfl et al.[5] present results on the balance between unwinding and annealing activities for CsdA, and show that the thermodynamic stability of the duplex limits the rate of unwinding by CsdA.

The article by Cordin and Beggs[6] highlights the roles of RNA helicases in pre-mRNA splicing. RNA helicases are required during various steps of spliceosome assembly and dissassembly, and in rearrangements that allow for the two transesterification reactions. The review summarizes the current knowledge on the regulation of activity for this class of RNA helicases, and their interactions with other proteins that link splicing to transcription, processing and transport of mRNAs.

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The review by Martin et al.[7] gives an overview about RNA helicases involved in ribosome biogenesis in bacteria and in eukaryotes. These RNA helicases remodel the secondary structure of RNA in ribosome assembly intermediates, such that ribosomal proteins can bind. In addition, RNA helicases release snoRNPs from pre-ribosomes. snoRNAs target RNA-modifying enzymes to the modification site on the RNA.

Members of the Ski2-like helicases, involved in mRNA processing, splicing and degradation, are in the focus of the review by Johnson and Jackson.[8] Apart from the canonical helicase core formed by two RecA domains, Ski2-like helicases comprise a winged helix and so-called ratchet domain, and form ring-shaped structures. Via interactions with other proteins, they are integrated into large functional units. The authors present and compare recent structures of Mtr4 and Ski2, highlight their differences and discuss the implications for the role of these helicases in activating eukaryotic exosomes for RNA degradation. Hardwick and Luisi[9] summarize the current picture of the functional interactions of RNA helicases with RNases in bacterial, archaeal and eukaryotic RNA degradation. The role of different helicases in feeding RNA into RNA degradation pathways, and the implications for regulation and RNA quality control in the cell are discussed.

Due to their multitude of functions, RNA helicases contribute to the general well-being of bacteria and eukaryotic cells, and play an even more important role under stress conditions. RNA helicases are upregulated during the cold-shock response, implicating them in life below the temperature optimum, but also in response to oxidative stress and pH changes. The article by Owttrim[10] discusses the role of RNA helicases in the general stress response in bacteria. Interestingly, the helicase RhlB normally found in the RNA degradosome is replaced by DeaD during the cold shock response, exemplifying that the tasks of individual helicases within functional networks may be dependent on growth conditions. Oun et al.[11] present their recent findings on the role of *Staphylococcus aureus* CshA in controlling the stability of a certain mRNA involved in cell density sensing, connecting this DEAD-box helicase to quorum sensing.

In-line with their vital role in a variety of cellular processes, RNA helicases are implicated in infection and disease. The article by Fuller-Pace[12] summarizes the current knowledge on the role of RNA helicases in transformation, tumorigenesis and cancer. The precise mechanisms by which helicase malfunction causes cancer are often ill-defined. This is exemplified by the RNA helicase DDX3 that, depending on the functional context, can act as an oncoprotein or as a tumor suppressor protein.

While cellular RNAs play key roles in many metabolic and regulatory processes, the presence of certain RNA molecules can be an indicator of imminent danger. Foreign RNAs can invade cells as part of the infection by RNA viruses. RIG-I-like helicases sense foreign RNAs by acting as conformational switches that are activated by RNA duplexes in foreign RNAs. RIG-I-like helicases interface with signaling cascades, ultimately triggering the innate anti-viral immune response of the cell. The current picture of RNA sensing and signaling by RIG-I, and by duplex-RNA-activated helicases in general, is summarized by Luo et al.[13]

The collection of articles in this issue reflects the versatility of RNA helicase functions. Due to their prominent role in key cellular processes, and their implication in infection and disease, the high interest in the molecular mechanism of RNA helicases and their functional interaction with partners in different pathways is maintained. While the common principles of their mechanisms are now emerging, for many helicases, the natural substrates are still unknown. Future investigations that outline individual features tailoring helicases for specific tasks, and that unravel the cellular interplay of helicases with other factors, will further our understanding of this versatile and fascinating enzyme family.

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