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Special Focus Hfq

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In all domains of life, non-coding RNAs (ncRNAs) play a central role in cellular biology. In bacteria, the systematic discovery and analysis of ncRNAs revealed a large repertoire of regulatory transcripts, which among other characteristics is responsible for the high adaptability of prokaryotes. Bacterial ncRNAs can be simplistically categorized by their way of biogenesis: into *cis*-encoded and *trans*-encoded transcripts. Additionally, they can be classified according to their mode of function as *cis*- or *trans*-acting molecules. A special group of trans-encoded and *trans*-acting ncRNAs are so-called Hfq-binding small RNAs (sRNAs). These short (50–300 nt) and structurally diverse transcripts function at the post-transcriptional level and often recognize entire sets of mRNA targets to ultimately regulate their stability and/or translation. Several studies have confirmed the widespread distribution and sequence conservation of sRNAs and the identification of entire sRNA-regulated networks established their central role in regulation of bacterial gene expression.

The growing understanding of sRNA function not only opened an exciting new field of RNA research, it also drew attention on a long-known RNA-binding protein: the ring-shaped, homo-hexameric (L)Sm protein Hfq. Hfq was discovered in the early 1960s as a host factor required for Qβ-phage replication and in the following decades a plethora of other cellular functions were described: Hfq was shown to function in polyadenylation-mediated mRNA degradation and in regulation of gene expression especially under adaptive growth conditions. However, the central role of Hfq in bacterial RNA metabolism and the associated pleiotropic effects of *hfq* inactivation, made it difficult to address specific questions in vivo.

The key finding that the biological function of sRNAs depends on Hfq, finally explained many of its pleiotropic effects on bacterial gene expression. In this context, Hfq directly interacts with sRNAs and is essential for their cellular stability. Furthermore, Hfq facilitates sRNA/mRNA base-pairing as it interacts with both the sRNA and the respective mRNA target. In parallel, important insights into Hfq and sRNA biology came from the biochemical and structural characterization of Hfq/RNA complexes: in vitro, Hfq binds various nucleic acid substrates and soon two independent RNA binding sites, proximal and distal, with different sequence-specificity were described on opposite surfaces of the ring, showing that Hfq can interact with RNA in a sequence specific manner using its different surfaces.

Despite the growing understanding of Hfq biochemistry and biology, a major question in the field remained: How does Hfq specifically recognize sRNAs, despite their structural diversity? An intriguing solution was recently provided by binding experiments and structural data showing that Hfq specifically recognizes a common feature of bacterial sRNAs, namely the uridine-rich 3′ end. This element results from Rho-independent transcription termination and is found at the end of most Hfq-binding sRNAs. These in vitro observations were supported by in vivo data showing that the uridine-rich 3′-end is required for sRNA stability and function in the cell. Combined, these results ultimately suggested a new sRNA binding model where Hfq directly recognizes the uridine-rich sRNA 3′end on its proximal surface and additionally interacts with sequences in the sRNA body via a new RNA binding site on the lateral surface of the hexamer.

Therefore, the main purpose of this Special Focus on Hfq is the discussion of the recent findings in Hfq biochemistry and the new sRNA binding model in the broader context of Hfq function in the cell. The contributing authors analyze whether and how the new sRNA binding model is consistent with previously published results and what future questions there are to address. The first review introduces the structure and RNA binding properties of Hfq, describes the current sRNA binding model and discusses how the combined in vitro observations could correlate with sRNA function in vivo.[1] In vitro, the high stability and slow dissociation rates of Hfq/sRNA complexes were a long time in contrast with the in vivo situation where sRNAs exert their effects on gene expression on a minute time scale. The "active sRNA cycling model" provided a solution to this paradox and is the main topic of the second review by E. Gerhart Wagner.[2] The manuscript summarizes how Hfq interacts with multiple, competing RNA species present in the cell and discusses how recent findings could be incorporated into the cycling model.

The general mechanisms of bacterial RNA turnover and the role of Hfq in these processes are the main topic of two additional reviews: the third review by Katarzyna J. Bandyra and Ben F. Luisi provides an overview over the major enzymatic activities and their complexes in bacterial mRNA degradation and particularly addresses the mechanism of sRNA-mediated mRNA degradation.[3] The fourth review by Eliane Hajnsdorf and Phillipe Regnier gives a systematic overview of the enzymes involved in polyadenylation-mediated RNA decay and suggests a model for the interplay of Hfq, poly-(A) polymerase I and the exonuclease PNPase at the 3′ ends of RNAs resulting from Rho-independent termination.[4]

Hfq belongs to the conserved (L)Sm protein superfamily the members of which are generally involved in RNA metabolism

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in all domains of life. Consequently, the increasing understanding of Hfq biology and its RNA binding properties can provide insights into the functions of (L)Sm proteins. Therefore, the implications of the recent findings in Hfq research are also discussed in the context of the (L)Sm superfamily. The fifth review by Carol J. Wilusz and Jeffrey Wilusz compares the relations and differences of bacterial Hfq proteins with the eukaryotic Sm and LSm complexes.[5] The sixth review by Cameron Mura analyzes the archeal branch of (L)Sm proteins (SmAPs).[6] Although the current knowledge of SmAPs is rather limited, the phylogenetic relations to eukaryotic and bacterial homologs suggest that SmAPs may represent a missing link for the further understanding of the RNA biology of (L)Sm proteins.

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