RNA structure, maturation, interactions and functions

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RNAs play central roles in the fundamental processes of life and control of gene expression, and are also used as markers and therapeutic drugs in various pathologies, including cancer. The discovery of catalytic RNAs in the early 1980s entirely changed our view on the cellular functions of numerous cellular RNA molecules. This breakthrough led to a remarkable increase in knowledge on the folding of RNA molecules and their functional activities. Later on, the development of high-throughput sequencing techniques has allowed the identification of many new small and long non-coding RNAs (ncRNAs) in all life domains, the study of which uncovers wholly unexplored aspects of genome functioning.

The biannual meeting of Structure, Interaction, Function and Reactivity of RNA group (SifrARN) is one of the important events organized by the French Society for Biochemistry and Molecular Biology (SFBBM). Every two years the SifrARN meeting brings together over 250 french and european researchers working in RNA-related fields. The goal of the SifrARN meeting is to promote discussions between RNA specialists, molecular biologists, biochemists, biophysicists and chemists to exchange on federative topics dealing with the importance of RNA in the cell. This congress offers a privileged access for young scientists, students and post-docs, to present their work and meet experts in the field. At the occasion of the 11th SifrARN meeting that took place in Nancy from the 6th to the 8th of November 2018, a special issue of BIOCHIMIE was planned and a call for contributions was launched. This Special Issue is intended to provide latest insides on ncRNP synthesis and function, RNA/protein interaction, RNA modification and mRNP synthesis. It brings together 12 comprehensive reviews and reports, written by European specialists in the field.

The first part of the Issue is dedicated to ncRNAs synthesis, post-transcriptional modifications and functions. In prokaryotes, ncRNAs play multiple roles in the host-pathogen relationships, in the control of homeostasis and in the adaptation of organisms to stresses and infections. Among these ncRNAs, the antisense RNAs (asRNA) act as cis-regulatory elements via perfect base-pairing with their mRNA target. The review by **Lejars et al.** exhaustively describes the mode of action of asRNAs in bacteria and archaea. They also describe methods to characterize new asRNAs and discuss the challenges that lay ahead to analyze their functions.

Small nucleolar RNAs (snoRNAs) represent an abundant group of archaeal and eukaryotic ncRNAs which function predominantly as RNA modification guides, directing site-specific 2'-O-ribose methylations and pseudouridylations of rRNAs and snRNAs. Recently, snoRNAs have also emerged as potential players in human oncogenesis, both as potent oncogenes as well as tumor suppressors. In

their review, **Abel and Rederstorff** give an overview of the current knowledge in the field and discuss the mechanism used by snoRNAs to regulate tumorigenesis.

Many of ncRNAs are not only present inside of the cells, but also secreted in the growth media, or in bloodstream in human and animal body. This fraction of extracellular RNAs (collectively called exRNAs) may be present in nanometric lipidic particles or associated to soluble RNPs in plasma or serum. In their study, **Galvanin et al.** performed thorougful characterization of human exRNAs by deep sequencing. The results clearly show that isolation of lipid nanoparticles (frequently called exosomes) by precipitation-based commercial kits leads to substantial contamination by soluble RNPs. Purer preparations can be obtained by either size-exclusion chromatography or by extensive proteinase K and RNAse treatment. Such pure nanoparticles mostly contain non-human RNA species issuing from human microbiota.

Circular RNAs (circRNAs) are covalently closed RNA circles found in all domains of life. Our knowledge of the synthesis, expression, regulation and functions of these circRNAs is still severely limited. Some of circRNAs can act as sponges for miRNAs or proteins to modulate gene expression. The biogenesis of circRNAs has been mostly described as back-splicing of exons from a single pre-mRNA. In addition, a second pathway for circRNA formation has been described in archaea and is reviewed by **Becker et al**. This pathway includes a ligation step catalyzed by RNA ligases belonging to Rnl3 families. The authors also provide an overview of the current data on archaeal circRNA transcriptomes. Some cytoplasmic circRNAs are translated into peptides whose functions are still enigmatic. How translation initiation can occur is still not clear. Two alternative cap-independent mechanisms are reviewed in **Diallo et al**.: the presence of an internal ribosome entry site (IRES) or a N^6-methyladenosine (m^6A) residue, which both allow the recruitment of the 40S ribosomal subunit.

Relationships between RNA modification profile and availability/intake of micronutrients are discussed in the review by **Mosca et al**. Recent discoveries clearly point out the dynamic and regulated character of RNA modifications, such modulation is observed not only under stress, but also when the nutritional status changes. Many micronutrients, like vitamins and other low molecular weight compounds may serve as cofactors or even substrates for RNA modification enzymes. Thus, modulation of the diet has a direct impact on the biogenesis of various RNA modifications. This interplay between vitamins and cofactors is reviewed and discussed in the review.

RNA modifications are widespread in all life domains and present in almost any RNA species. However, the exact mapping of modified nucleotides was only performed for a limited number of model organisms. In the research article from **Antoine et al.**, authors describe their results on the mapping of tRNA modifications in pathogenic bacteria *S. aureus*. Using combination of 2D gel electrophoresis and nano liquid chromatography/mass-spectrometry, 25 out of 40 tRNA species were isolated and various RNA modifications present in these species were analyzed. Development of this approach also opens a way for quantification of tRNA modifications under stress and infection.

The second part of the Special Issue is dedicated to analysis of RNA/protein interactions and RNP assembly. In many cases, the assembly and processing of large messenger RNP (mRNP) and ncRNP complexes require a dynamic series of RNA structural rearrangements. Getting the grips on RNA structure in association with their partners is a major challenge to understand gene regulation by RNAs. RNA K-turn motifs are universally conserved protein binding platform. For instance, Snu13 binding to K-turn motifs within box C/D snoRNAs is a pre-requisite for the assembly of the box C/D RNP. **Chagot et al.** describe the structure of the free or Snu13-bound U14 C/D snoRNA k-turn motif obtained by NMR. They show that the structure of the k-turn motif is stabilized upon Snu13 binding.

DEAD-box RNA helicases play central roles in the metabolism of many RNAs and RNPs, promoting their synthesis, folding, function, degradation and disassembly. **De Bisschop et al.** describe extensive *in vitro* study of biochemical properties of DDX3, a RNA helicase involved in numerous physiological processes including HIV-1 infection. They have identified HIV-1 full length RNA as a biological substrate which strongly stimulates DDX3 ATPase activity. They further demonstrated that the interaction between DDX3 and HIV-1 RNA relies both on specific RNA determinants and on the disordered N- and C-terminal regions of the protein.

The structure of the complexes of RNA and proteins are often difficult to obtain by X-ray Crystallography. **Dégut et al**. describe a new method to trap RNA and protein partners in a covalent complex, based on a modified reactive RNA which is then able to react with a cysteine residue of the protein to form a disulfide bridge. Such trapping in a covalent intermediate allows the subsequent use of the full range of common crystallogenesis tools.

Understanding how RNPs are produced in a functional state in the cells, and how their quality and their amounts are controlled are essential issues in the field. Defects in RNP assembly lead to severe human pathologies. Many factors are dedicated to the biogenesis of RNPs: they chaperone free subunits, increase the assembly specificity, control the quality of the produced particles, transport subunits, etc. However, even in the most studied cases, how RNP assembly is catalyzed and regulated is still poorly understood. This is especially the case concerning the biogenesis of one universally conserved ncRNP, the Signal Recognition Particle or SRP, reviewed by **Massenet**. SRP is crucial for targeting most transmembrane and secretory proteins to the endoplasmic reticulum. SRP assembly takes place largely in the nucleolus and the reason why is unclear. Remarkably, apart from the Survival of Motor Neuron (SMN) complex, only very few factors required for SRP biogenesis have been identified so far.

All central processes of gene expression, from mRNA biogenesis to translation, localization and degradation, revolve around mRNPs. Studies of mRNP components and dynamics are crucial to apprehend how mRNPs organize and regulate the fate of mRNAs. The review by **Thore et al**. summarizes the recent advances in the understanding of the 3'-end mRNA maturation process with a special focus on recognition of the polyadenylation site. The molecular interaction between the Cleavage and Polyadenylation Specificity Factor (CPSF) and the consensus polyadenylation site is extensively described.

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