In the recent years, a huge number of human transcripts have been found in the human genome that do not encode for proteins, which have been named non-coding RNAs (npcRNAs) containing secondary structures or short regions highly conserved within mammalian sequences.

Long RNAs (antisense RNA, structured RNA, and long interspersed ncRNAs) and small RNAs (miRNAs, siRNAs, snoRNAs) have shown to exert many roles: functioning as regulators of other mRNAs, at transcriptional and post-transcriptional level, controlling protein ubiquitination and degradation, regulating epigenetic marks and affecting chromosome structure. One group of npcRNAs that is well-characterized, at the biochemical level, is represented by miRNAs. This group comprises a large class of small npcRNAs (~22-nucleotide RNAs) acting through base pairing to partially complementary sites in the 3’ untranslated regions (3’UTR) of the targeted messenger RNA.

Circular RNAs, competing endogenous RNAs (ceRNAs) acting as RNA sponges, natural antisense RNAs (NAT), enhancer RNAs (eRNAs), and RNA decoys are further expanding the wide array of functionalities exerted by ncRNAs. In the last case, as example, Growth Arrest Suppressor 5 (GAS5) forms a structured RNA that is a decoy for the glucocorticoid receptor (GR), mimicking the DNA structure of the GR element (GRE).

Long noncoding RNAs (lncRNAs) have emerged as key players in regulating various fundamental cellular processes. Many of the mechanisms that modify the 3’ UTRs, or that affect differential splicing, make use of RNA regulation, antisense RNAs, and may involve RNP complexes. Many human ncRNAs have been characterized in terms of function or expression profiles. HOTAIR, described in detail in the review by Ge Shan, is a structured RNA that assemble several proteins to form an epigenetic regulation complex: it assembles Polycomb Repressive Complex (PRC) proteins and determines the silencing of specific genes. Terminal differentiation induced ncRNA (TINCR) destabilises ALU elements in mRNAs through the RNA binding protein Staufen 1 binding to polypurine tract.

Thus, proteins involved in the functioning of ncRNAs are highly varied: RNA binding proteins, ribonucleoprotein complexes, alternative splicing proteins, alternative polyadenylation proteins, chromatin remodeling complexes, and gene activation and repression complexes (PRC) and enzymes positioning or eliminating histone marks. Then, it is clear that the changes determined in several diseases and in cancer are caused non only by mutated genes but also by epigenetic deregulation and by alternative spliced genes and alternative polyA tails that evade microRNA recognition. Concerning miRs, the varied presence of Argonaute family of proteins and the link with diseases are well detailed in more than one review in this special issue.

In this thematic issue, Ge Shan’s paper provides an overview of several examples in small and long RNAs; Yangchao Chen introduces the recent topic of circular RNAs; Charles Lawrie presents the deregulated pathways involving miRNAs in myeloma malignancies, while George Calin classifies leukemias according to epigenetic deregulation, oncomiRs and loss of antioncomiRs; Massimo Mallardo reviews the mechanism of infectivity in RNA viruses; Marek Sanak describes a unique microRNA differently expressed in neutrophils in healthy individuals and in Granulomatosis with Polyangitiis patients; finally two papers describe the circulating miRNAs protected by exosomes that are released by cancer cells and can be found in bodily fluids. Sonia Melo gives a detailed overview on circulating miRNAs, and Valeria Mezzolla proposes a method to group glioma and differentiate them from other malignancies based on the most representative circulating miRNAs. This field is a promising means to ensure novel approaches to treatment and more effective therapies exploiting ncRNAs.

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