Wonderful World of Nucleic Acids

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The annual Gliwice Scientific Meetings (GSM) conferences are special occasions to celebrate spectacular discoveries and achievements in molecular biology, and nucleic acids particularly. GSM 2023 marked the 70th Anniversary of the Watson-Crick double helix structure for DNA [1]. Studies on DNA have a long history, which started in 1869 when Johann Friedrich Miescher discovered a new substance in the nucleus of living cells. The substance he called nuclein, but he always had it contaminated with proteins and, in some publications, the isolate he called the nuclein-acidic protamine [2]. The purification was done by Richard Altman, who separated proteins from nuclein and invented the term nucleic acid in 1890. The discovery of DNA as a chemical substance by Friedrich Miescher, followed by its basic chemical analysis demonstrated its participation in the structure of chromosomes. More than 70 years later Oswald Avery discovered that DNA was the genetic material, and then Erwin Chargaff showed that DNA molecule contains the same numbers of some bases (the number of adenines equal to the number of thymines and, similarly, the number of guanines to the number of cytosines). These discoveries, along with X-ray studies conducted by Maurice Wilkins and Rosalind Franklin, allowed James Watson and Francis Crick to propose the double-stranded structure of DNA molecules [1]. The double helical structure provided a hint as to how DNA could be self-replicating and genetic information stored and read [3]. The next discoveries of mRNA by Sidney Brenner, Francois Jacob, and James Watson; mechanisms in the protein synthesis by Francois Jacob, and Jacques Monod; the genetic code first letter phenylalanine encoded by poly(U) by Heinrich Matthaei and Marshall Nirenberg; the ribosomes the synthetically active, membrane-free particles by George Palade and Howard M. Dintzis [4]; the nucleosome, basic structure of DNA-protein complex in eukaryotes by Ada and Donald Olins [5] and many others opened a new era in science. Fitting nucleosomal strings into a small space in the cell nucleus, the implementation and copying of genetic information requires higher-order structures of the nucleosome chains and the possibility of their fast changes if needed. Studies on chromatin have the same long history as DNA. At Miescher times chemists and cytologists worked separately and cytologists coined their conclusions based on staining biological preparations for microscopical studies (by chemists they were called "guild of dyers") [6]. Only after the emergence of new techniques, such as fluorescence, confocal, and super-resolution microscopy, along with the development of antibody labeling techniques, it became possible to localize nucleic acids and proteins in structures within the cell, observe time changes in living cells and the impact of nuclear organization in space on genome functions [7].

Another molecule whose functions are related to the formation of double-stranded structures is RNA. In the beginning, RNA was recognized as a relatively simple, single-stranded molecule but today we know that RNAs create double-stranded complicated, and three-dimensional structures within the same molecule and with other molecules and these interactions are crucial for complexes of proteins with RNA function (Fig. 1).

RNA carries out a broad range of functions, from translating genetic information into the molecular machines and structures of the cell to regulating the activity of genes during development, cellular differentiation, and changing environments. RNA is a unique polymer. Like DNA, it can bind with great specificity to either DNA or another RNA through complementary base pairing and it can also bind specific proteins or small molecules. Contrary to DNA, RNA is an unstable molecule that is sensitive to degradation both through elevated temperatures

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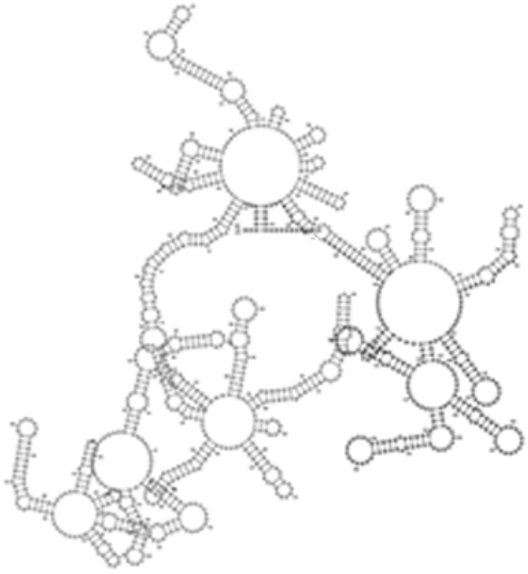

Figure 1. The example of double stranded structures which may form single stranded RNA molecule of reporter gene mRNA.

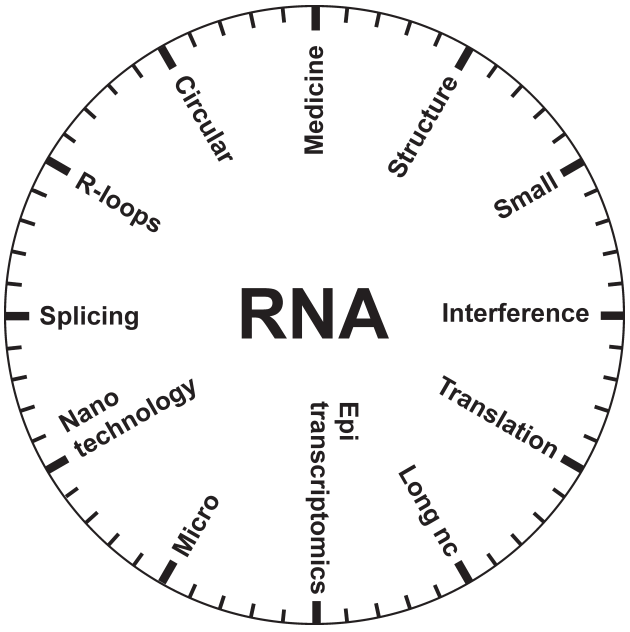

Figure 2. RNA clock showing different activities of RNA molecules some which are used as tools in scientific experiments, biotechnology and medicine.

and by RNases. RNA has both specific structural as well as catalytic properties. RNA can catalyze chemical reactions. Some RNAs possess intrinsic enzymatic activity and can directly catalyze RNA modification reactions. These catalytic RNAs include certain self-splicing RNA transcripts, joining amino acids to make proteins, ribozymes, and RNase P, an RNAzyme that maturates the 5′ end of tRNA precursors [8].

30 years ago in the December 1993 issue of the Cell, Victor Ambros described the first microRNA and Gary Ruvkun regulation of gene expression by these tiny RNA molecules [9,10]. MicroRNAs, ca 22 nt long are cut off from longer transcripts, associate with a protein (Argonaute), and base-pair specifically to mRNAs to inhibit their translation. A single miRNA can regulate the activity of hundreds of protein-coding genes and each mRNA can be targeted by many different miRNAs. Therefore, miRNAs have a big impact on the development and physiology of the cells and whole organisms.

Studies on RNA are flourishing. New RNAs are discovered, new structures are identified, new biological function list is growing, and new RNA nanotechnologies are being developed. RNA, in one form or another, touches nearly everything in a cell and it is also a tool for research and medicine. The outcome was that big pharma companies proposed simple, efficient, and flexible technologies to deliver nucleic acid drug tools into the cells and organisms. These technologies are based entirely on various properties of RNA (Fig. 2).

The RNA drugs face the challenges of targeting mRNA to specific tissues and giving substantial and lasting benefits without excessive side effects. For the last 30 years, this approach was not very practical due mainly to an mRNA's short half-life and inefficient *in vivo* delivery.

Tailoring mRNA medicine to a disease means tweaking the structures of the mRNA itself and the lipid nanoparticle used to ferry it through the body. Once injected into the cell, mRNA translates into a specific viral protein that trains the immune system to recognize the virus. mRNA vaccines are faster, cheaper, more adaptable, and easier to mass production than traditional vaccines. The main reasons for low interest in mRNA as a therapeutic were the lability of RNAs, immunogenicity, low level, and transient translatability, and difficulty of working with fragile RNA. These difficulties have been overcome after incorporating modified nucleosides, which efficiently reduced immunogenicity and significantly increased its translation.

This special issue of the Polish journal Advances in Biochemistry/Postępy Biochemii is dedicated to the 70th anniversary of the discovery of the double helix of DNA but it is also a tribute to two recently deceased professors, Mieczysław Chorąży and Ronald Hancock, scientists who spent their lives studying nucleic acids and who made a significant contribution in the development of Polish and world science.

Professor Chorąży organized the Department of Tumour Biology in Gliwice and was one of the first in Poland who developed research in the molecular biology field but, in his life, he also spent a lot of time trying to improve the functioning of science, health care or even municipal services in Poland. He was a great organizer, and he liked teamwork but as the head of the Department of Tumour Biology, he rarely personally conducted experiments.

Ronald Hancock had a completely different character. His passion and life was scientific work itself, he liked to work alone and until the end of his life, at the age of 89, he carried out experiments himself. He finished his stud-

ies and obtained a Ph.D. degree at Cambridge University in England, later, as a professor, he worked in laboratories in the United States, Switzerland, and Canada and last year in Gliwice in Poland. There, he gave lectures at the Silesian University of Technology and he could continue his experimental work on chromatin structure and the influence of entropic forces on cellular complexes, in the Biotechnology Centre.

It is worth noting that since the second half of the twentieth century DNA and RNA research gradually brought together scientists working sometimes in completely different scientific or technical disciplines. Research on nucleic acids is not only the study of the structure and interactions of chemical molecules, but above all, deciphering the enormous amount of information contained in biological structures, the understanding of which requires specialists and methods used in mathematics, computer science, control and system engineering, and many other fields that have previously been developed separately. The era of enthusiasts experimenting alone with nucleic acids seems to have approached an end. On the other hand, however, to discover truly new elements of the reality around us, we will always need enthusiasts who are concentrated on secrets of the Nature and less concerned about money and careers.

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