

Foreword: non-coding RNAs as potential laboratory biomarkers

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ARTICLE INFO

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Key words:

microRNA, biomarker, diagnosis, preanalytics

FOREWORD

Since the discovery of non-coding RNAs, enormous information has been accumulated about the function of these molecules acting as fine-tuners of cellular processes in development, maintenance of homeostasis up to the generation of malignancies. The group of non-coding RNAs includes a large number of microRNAs (miRNAs), long non-coding RNAs (lncRNAs), small-nucleolar RNAs (snoRNAs) and circular RNAs (circRNAs), which are not translated into a protein, but regulate the translation of at least two-thirds of messenger RNAs (mRNAs) with chromatin modification and gene silencing. Furthermore, release of non-coding RNAs from donor cells and their uptake by recipient cells can provide additional intercellular signaling that may allow a direct regulation of gene expression in the recipient cells. Altered expression of non-coding RNAs have been implicated to the pathogenesis of diverse human diseases suggesting their potential to become diagnostic or prognostic molecular biomarkers in the near future.

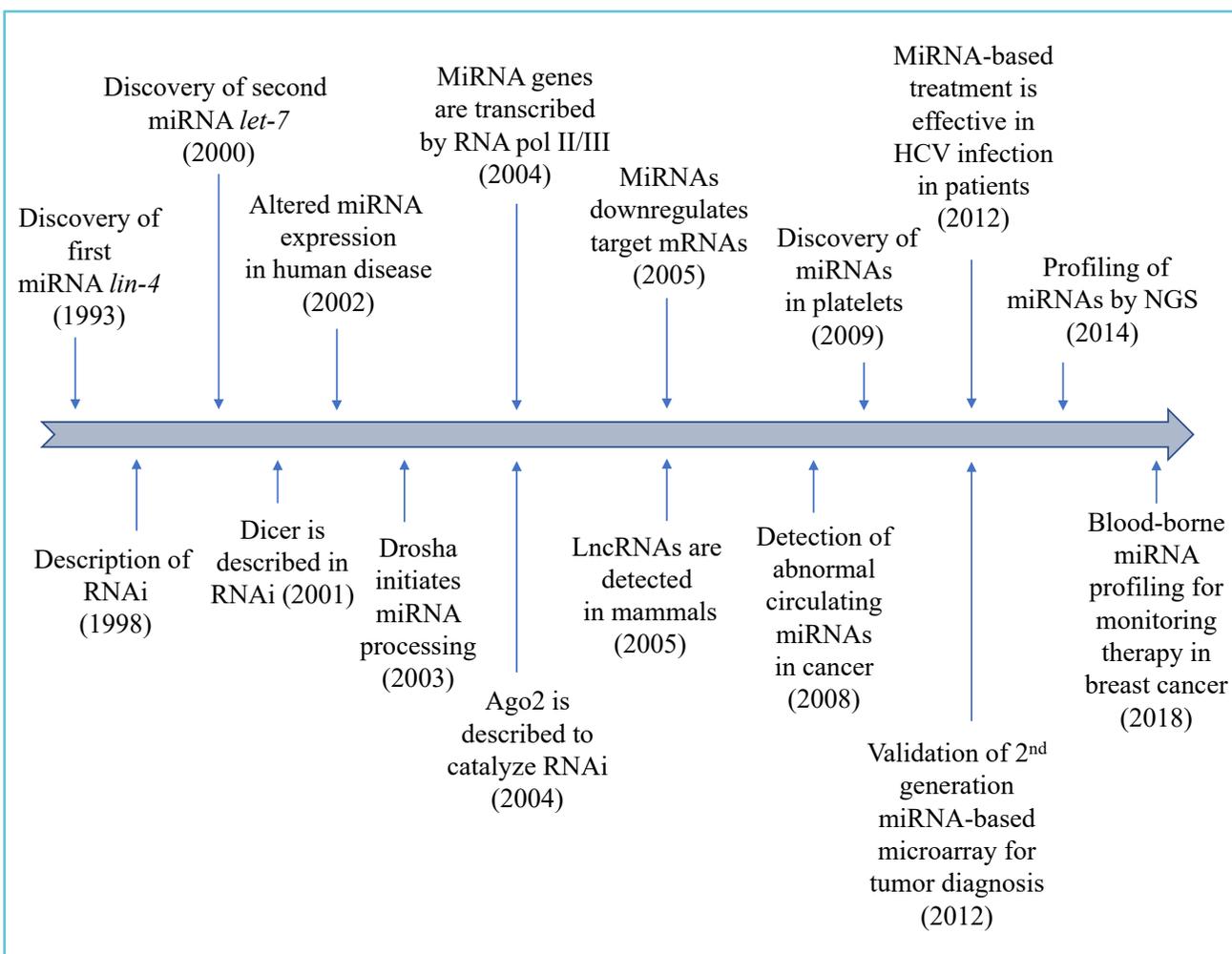
Among non-coding RNAs, miRNAs have been the most intensively investigated generating thousands of publications in this field each year. Compared to mRNAs, miRNAs are stable in human body fluids, such as blood

plasma, serum, urine or saliva due to the association with RNA-binding proteins (e.g. high-density lipoproteins) and housing in shed microvesicles. In addition, they are fairly viable even after repeated cycles of freeze-thawing and long-term frozen storage. Despite these facts, there are still many pre-analytical and analytical challenges for accurate detection of extracellular miRNAs in body fluids. For instance, sample preparation and handling need to be minimized, and special attention is required to avoid contaminations with cellular miRNAs potentially released from erythrocytes or platelets. The concentration of

cell-free miRNAs may be low and variable, thus equal volumes of specimens should be used for total RNA extraction. There is still no standardized methodology for the normalization of non-coding RNAs.

As a consequence, variable normalization methods are applied in different studies, such as small endogenous nucleolar RNAs (e.g. RNU-43) as reference genes, or external “spike-in” synthetic oligonucleotides (e.g. cel-miR-39), or one specific (mi)RNA, or global mean normalization when hundreds of miRNAs are simultaneously profiled. Sometimes these circumstances can

Figure 1 Key findings in the non-coding RNA research with miRNA-based diagnostic and therapeutic implications from 1993 up to present time*



* *lncRNA*: long non-coding RNA; *RNAi*: RNA interference; *NGS*: new generation sequencing.

make difficult the comparison of results. This is one reason why a wider miRNA profile prefers to be evaluated in patient samples in contrast to the analysis of individual miRNA. For such, new miRNA panels are now commercially available to observe “miRNA signatures”. The milestones of 25-year-old evolution of non-coding RNA research are depicted in Figure 1.

This special issue of the eJIFCC incorporates a series of manuscripts that summarize the recent issues of non-coding RNAs as non-invasive biomarkers in various clinical conditions, especially focusing on cell-free miRNAs in different human diseases.

In the first manuscript, Bonneau *et al.* raised the question whether circulating miRNAs could be a reality in near clinical practice for diagnostic and therapeutic aspects. The authors reviewed the latest issues on miRNA-based laboratory diagnostics in malignancies, age-related diseases, and abnormal heart and liver function. In addition, some new therapeutic products are represented for liver disease, fibrotic disorders and cancers.

Sepsis is still a demanding clinical condition and early (differential) diagnosis and evaluation of prognosis are a must for these patients. Szilágyi *et al.* summarized the most important intracellular miRNAs with their function in Toll-like receptor mediated signaling in immune cells as well as platelets along with those circulating miRNAs, which have been recently reported to be valuable in sepsis.

In the last couple of years, a number of miRNA-related manuscripts have been published in the field of endocrine neoplasms, such as pituitary adenomas. Here, Butz and Patócs reviewed the current knowledge on circulating and tissue specific miRNAs in thyroid, adrenal, pituitary and neuroendocrine malignancies for diagnostic and prognostic implications.

Congenital heart diseases (CHD) are the most common type of birth anomalies, with high

morbidity and mortality rates. Hence, a better understanding of the function of miRNAs in the pathomechanism of CHD may propagate their application for laboratory analysis to improve the diagnosis and prognosis of these patients. Nagy and her colleagues gave an overview about altered expression of miRNAs in different subtypes of CHD.

Coronary artery disease (CAD) is one of the leading cause of death worldwide. Several former studies reported that certain circulating miRNAs have substantial diagnostic and prognostic values for CAD. Melak *et al.* described the most suitable miRNAs as potential biomarkers in CAD with those circumstances that may limit utility or interfere with their levels.

The first evidence about abnormal miRNA expression in relation to a disease was reported in chronic lymphocytic leukemia in 2002. Since then, several hematological disorders have been investigated for profiling circulating miRNAs. In this issue, Getaneh *et al.* summarized the clinical values of miRNAs in the subtypes of B-cell non-Hodgkin lymphoma in terms of diagnostic and prognostic implications.

Among cell-free nucleic acids, circulating miRNAs have been considered promising tools for the diagnosis of pregnancy associated conditions like preeclampsia, fetal growth restriction and gestational diabetes. These prenatal tests, which are still in the experimental phase, were also reviewed by Dr. Nagy.

Beside circulating miRNAs, lncRNAs have been also confirmed to be involved in the pathogenesis of cancers and inflammatory diseases. Kelemen and her colleagues summarized the role of exosomal lncRNAs as potential biomarkers in chronic inflammatory diseases, such as rheumatoid arthritis and psoriasis as well as in different types of cancer.

In case of rare diseases, profiling of tissue specific miRNAs can also assist the differential di-

agnosis. Zilahi *et al.* described five specific tissue miRNAs (myomiR) that are associated with the development of polymyositis in an original article.

In conclusion, we are learning about more and more aspects of the diagnostic application of non-coding RNAs, but we should note that these

results may be incorporated into the area of therapeutic implications. Based on preliminary data, the modulation of certain miRNA function by specific mimics or inhibitors may result in beneficial effects in hepatitis C infection, or in cancer. However, it is a far-reaching story, and is still under intensive (pre)clinical investigation.