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Editorial

Non-coding RNAs, a real Next-Gen Class of Biomarkers?

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Over the past two decades, the concept of non-coding RNAs (ncRNAs) has changed radically, moving from “junk/black matter” to crucial regulatory molecules controlling two-third of the human transcriptional output. This change of perspective has been possible due to the evolution of high-throughput technologies together with improvements in the bioinformatics field, leading to the discovery that a large portion of the human genome is transcribed in functional ncRNAs.

Eukaryotic cells express a greater amount of ncRNAs compared to protein-coding mRNAs, supporting the idea that ncRNAs are far away to be inert molecules. In fact, ncRNAs can switch off/reduce the expression of multiple targets simultaneously, affecting entire signaling pathways within the cells. Thus, it is easy to imagine the great power these macromolecules have in controlling multiple biological processes. Accordingly, advances in the understanding of the molecular role of ncRNAs in both physiological and pathological conditions have significantly contributed to the identification of alternative molecular pathways that have started to influence the planning of secondary prevention strategies and the selection of new therapeutic modalities for human diseases. By reviewing recent literature on this topic, this special issue *"Clinical Utility of ncRNAs, a Next-Gen Class of Biomarkers"* further supports the pivotal role of ncRNAs in regulating both physiological and pathological mechanism and the significant ncRNAs aberrant expression in different human disorders, such as reproductive disorders [1] and cancer [2,3].

The term ncRNAs refers to a broad and heterogeneous group of molecules that differ for length, biological function, and cellular localization. According to their size, ncRNAs are classified into long-ncRNAs (lncRNA, > 200 nucleotides) and short-ncRNAs (< 200 nucleotides), that includes in turn microRNA (miRNA), short interfering RNAs (siRNA), piwi-interacting RNA (piRNA) and small nucleolar RNA (snoRNA), among the others. Among these classes of ncRNAs, miRNAs have been largely studied and established their role as the Next-Gen class diagnostic as well as prognostic biomarker, predominantly at preclinical stages. However, translating into clinical utility is very challenging due to the various reasons, including getting precise quantification of circulating miRNA and consistent of specific miRNA for a specific cancer type as well as tissue-type [4]. In contrast to miRNAs, lncRNAs are tissue-specific and can control gene expression at different levels such as epigenetic, transcriptional, post-transcriptional, generating small interfering RNAs and short-ncRNAs, acting as scaffold to create ribonucleoprotein complexes. This broad range of functions is also due to the peculiar ability of lncRNAs to directly interact with other macromolecules, such as DNA, RNA and protein.

It has recently emerged how lncRNAs crucially participate in carcinogenesis and the metastatic process. In addition, lncRNAs expression has been shown to change accordingly to the tumor stage and level of metastasis. All these findings, together with their tissue-specificity, highlights the advantages of using lncRNAs as next-generation biomarkers with great prognostic and predictive value. In this special issue, two reviews have deeply described the aberrant lncRNAs profiling characterizing both gastroesophageal [2] and breast cancers [3], two of the most important causes of cancer-related morbidity and mortality worldwide. Fanelli and collegeus [2] detailed the association between dysregulated lncRNAs with cancer initiation, progression and metastasis in gastroesophageal cancers. Interestingly, both reviews pointed out as the worst prognosis has been associated to malignancies overexpressing MALAT1 and HOTAIR, suggesting these lncRNAs (i) may be master regulators, whose dysregulation could be a first/necessary hit in the oncogenesis process; (ii) could be excellent biomarkers and targets for a future therapy.

As emerged by many recent data, besides their intracellular role of direct/indirect modulators of gene expression, ncRNAs stably circulate in the body fluids, preserving their ability to regulate mRNA target(s) of different tissues [2]. For clinical purposes, extracellular stability may arguably be the most useful property of ncRNAs. According to their different subtype, circulating ncRNAs appears to be stable by themselves (i.e. miRNAs) or require molecular modifications (methylation, adenylylation, capping) or transportation in extracellular vesicles to prevent their degradation (i.e., lncRNAs). Overall, the aberrant expression in pathological conditions, the ability to circulate in the body fluids and maintain paracrine functions, makes of ncRNAs optimal molecules to be used as (i) next-generation biomarkers of disease, with important impact on diagnosis, prognosis and evaluation of the efficacy of a therapy; (ii) new form of treatment, potentially able to restore the physiological conditions when ncRNAs profiling results dysregulated.

Extracellular matrix (ECM) of the tumor microenvironment plays a

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crucial role in the progression and metastasis of the cancer cells. Many cross-talks between cancer cell and components of ECM exist and are essential for tumor development and metastasis as D'Angelo and colleagues [5] elegantly described the significant role of lncRNAs in the functional cross-talk between cancer cells and the ECM. Notably, the changes in the expression of MALAT1 and HOTAIR in neoplastic cells seem to vary also according to the biological and structural changes of the tumor microenvironment. Thus, the evaluation of these lncRNAs potentially reflects also the presence of abnormal ECM, which is a hallmark of cancer to all effects. The important value of ncRNAs as a biomarker is not only limited to the oncology field, but it regards several disorders, as emerged from the work of Robles and colleagues [1] reviewed the importance of ncRNAs mainly miRNA, piRNA and lncRNA in modulating development of primordial germ cell specifications, spermatogenesis and oogenesis. Further described the putative clinical use of the testing of different ncRNA in reproductive disorders. Many ncRNAs altered during development of reproductive disorders, and these alterations in expression levels can be utilized as biomarkers for diagnosing the specific disorders. Also, the authors have pointed out how ncRNAs changes due to epigenetic factors (such as diet, stress and exercise), may have a direct negative impact in the offspring phenotype. This concept makes visible the great power exerted by the non-coding genome.

A further intriguing open question is the possible role of extra-genomic food-derived ncRNAs in the maintenance of the physiologic gastrointestinal *milieu* or in the establishment of human disease. In this regard, the review from Sundaram GM [6] raised the important question, if plant dietary miRNAs can modify the human transcriptome by passing through the gut, enter the systemic circulation and exert biological effects on animal physiology. The resistance of miRNAs to various degrading enzymes in the gut might be due to 2′-O-methylation of plant-derived miRNAs or through exosomes mediated/edible nanoparticles. This stability of ncRNAs during circulation was also discussed by Fanelli et al., [2] where they described the modifications such as methylation, adenylylation, capping or exosome-mediated circulation enhances the stability and bioavailability of ncRNAs. Despite of having controversial results on bioavailability of dietary miRNAs, Sundaram GM [5] discusses the idea of creating drugs based on ncRNAs is becoming more and more tangible. To make possible these next-generation drugs, it is necessary to find a solution that may allow an efficient absorption of ncRNAs in the gastrointestinal tract and prevent a systemic effect. In the next future, plants and bacteria could be genetically modified to produce a large amount of therapeutic ncRNAs (either miRNAs or lncRNAs) to be included in biological or artificial engineered-exosomes, allowing a correct absorption, transportation and a targeted delivery within the organism.

As concluding remarks of this special issue, data show the great potential of using ncRNAs as fascinating diagnostic, prognostic and predictive biomarkers. However, there is a side story that testifies that ncRNAs are not yet widely used in clinical practice. This is mainly due to the low levels of expression of ncRNAs in human tissues and body fluids, the complexity in the comprehensive analysis of the different ncRNA-altered molecular pathways and the difficulties in the choice of an adequate reference gene to normalize ncRNAs data. Nonetheless, still the ncRNAs as biomarkers leads advantageous because of detection through non-invasive techniques. In the future, the introduction of novel next-generation high-throughput technologies and more accurate characterization of the ncRNAs' biological mechanisms will lead to a definitive clinical introduction of these classes of molecules, which may represent an extraordinary source of novel therapeutic targeted approaches. Further, the expression levels of these lncRNAs might determine the stages of disease progression that will help in prescribing personalized medicine.

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Chiara Borga[1]
Surgical Pathology Unit, Department of Medicine (DIMED), University of Padua, Padua, PD, Italy

Syed M. Meeran[**,1]
CSIR-Central Food Technological Research Institute, Mysore, 570020, Karnataka, India
E-mail address: s.musthapa@cftri.res.in.

Matteo Fassan[*]
Surgical Pathology Unit, Department of Medicine (DIMED), University of Padua, Padua, PD, Italy
E-mail address: matteo.fassan@unipd.it.

[1] Equally contributed.
[**] Corresponding author. Principal Scientist & Associate Professor, AcSIR - Division of Biochemistry, CSIR-Central Food Technological Research Institute, Mysore, 570020, Karnataka, India.
[*] Corresponding author. Department of Medicine (DIMED), Surgical Pathology Unit, University of Padua, 35121, Padua, Italy.