



# Non-coding RNAs: the silent regulators of health and diseases

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## Abstract

Non-coding RNAs (ncRNAs) like miRNAs, siRNA, lncRNAs, circRNAs, piRNAs, snoRNAs, snRNAs etc. form a collective group of RNAs that is instrumental to the various functions of the genome. With the advent of cutting-edge molecular biology tools and techniques, scientists have unearthed several mechanisms through which these ncRNAs act. Although our understanding may still be limited, yet scientists have been able to establish ncRNAs as major regulators of genetic inter-plays that dictate various pathophysiological conditions. This special issue of Molecular Biology Reports features a collection of research and review articles on ncRNAs and their involvement in different pathophysiological conditions that include different types of cancers. It is expected that this special issue will motivate researchers in the field to delve deeper into the world of ncRNAs and attempt to develop new diagnostic and therapeutic interventions for challenging clinical conditions.

**Keywords** Non-coding RNAs · miRNA · siRNA · lncRNA · piRNA · ncRNA

## Introduction

Disease has been traditionally considered as any deviation that negatively impacts the structural and/or functional integrity of living organisms. This structural and functional integrity and any associated deviations are guided by various pathophysiological mechanisms, which in turn are orchestrated by a complex interplay between genes and their products. While the human genome contains approximately three billion nucleobase pairs arranged in specific sequences, majority of these genetic sequences are known to be non-coding in nature and do not lead to synthesis of any protein products. In fact, close to 90% of the human genome is labeled as “junk” or “dark” and is devoid of any functional role [1, 2]. While the findings from the Encyclopedia of DNA Elements (ENCODE) project attempted to assign biochemical functions to > 80% of the genome [3], these findings have been criticized by many researchers. The major criticism of the findings of the ENCODE project resides in the C-value paradox, which reflects upon the lack of correlation between genome size and organismal complexity [4].

Furthermore, the lack of scientific data assigning functional role to majority of the non-coding regions of the genome strengthen the proposition that this majority may actually be junk [5]. Whether the major portion of the genome is “junk” or not is therefore a matter of larger debate. However, it is known that this “dark” portion of the genome is home to several regulatory genetic elements. Among these genetic elements lies a heterogeneous group of RNA molecules that is collectively known as “non-coding RNAs” (ncRNAs).

The “ncRNAs” as a group has been found to host several functionally important RNA molecules that include microRNAs (miRNAs), small interfering RNA (siRNA), long ncRNAs, circular RNAs (circRNAs), piwi-interacting RNA (piRNAs), small nucleolar RNAs (snoRNAs), small nuclear RNA (snRNAs) etc. [6], besides the more abundant transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs). Majority of these small non-coding RNA molecules have been found to have key regulatory roles in guiding the various physiological and pathological processes by regulating transcription and translation of genes in living systems. This special issue is aimed to provide a broad overview of the current and ongoing research in the field of non-coding RNAs. It provides a broad perspective on the role of miRNAs, lncRNA, circRNAs and piRNAs in health and diseases.

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## Non-coding RNAs and cancers

The ncRNAs, being a part of the host genetic machinery, are known to influence various pathophysiological mechanisms of the body through their targets, which include genes or other RNA molecules. Although all clinical conditions of the body are guided by these signaling mechanisms; cancerous conditions are amongst the most critical ones that are guided by changes in genes like abnormalities, mutations and alterations etc. Several of the research and review articles in this special issue are therefore focused on cancer. Dayakar et al., for example have highlighted the importance of anomalous genetic and epigenetic regulations of miRNA-genes in malignant conditions [7]. They have further discussed the role of miRNAs in influencing drug responses in cancer therapeutics. In another article, Roy et al. have reviewed the role of ncRNAs in lung cancer and progression [8]. The role of ncRNAs and their cross-talks in triple negative and quadruple negative breast cancer have been discussed in another article. In the field of prostate cancer, the work by Bozgeyik et al. demonstrates that functional restoration of miR-19a and miR-421 in prostate cancer may benefit prostate cancer patients [9]. In another work, Arsalan et al. illustrate the regulatory role the long non-coding RNA, TP73-TP73-AS1 axis in prostate cancer [10]. This special issue has also touched upon the impact of ncRNAs on rare malignancies like osteosarcoma.

## Non-coding RNAs and stem cells

The cancer stem cell hypothesis has put forward a new perspective to re-visit cancer pathogenesis. According to this hypothesis, cancers arise from a small group of stem cell like cells which are responsible for tumor initiation and growth. One of the articles in this special issue reports the altered expression of several miRNAs, piRNAs and mRNAs in PIWIL2-reprogrammed fibroblast cells (PIWIL2-iCSCs)—lab-designed cancer stem cell-like cells [11]. PIWIL2 is recognized as a cancer–testis antigen (CTA) and is known to be involved in genesis and/or maintenance of cancer stem cells [12]. ncRNAs are also known to play important instrumental roles in maintenance, regulation and differentiation of normal stem cells as well. In this special issue, Li et al. describe two lncRNAs, MALAT1 and LINC00657 that are upstream to miR-214-3p/BMP2 as regulators of osteogenic differentiation of mesenchymal stem cells [13].

## Non-coding RNAs in COVID-19

The ongoing COVID-19 pandemic has ravaged the world for the last 2 years and this definitely hasn't gone unnoticed in this Special Issue. A pilot study from Brazil reports differential expression of plasmatic miRNAs in patients with COVID-19 and healthy volunteers [14]. In this study the researchers have identified 18 miRNAs that are differentially expressed in COVID-19 cases when compared with healthy controls. The key miRNAs identified (miR-4433b-5p, miR-6780b-3p, miR-6883-3p, miR-320b, miR-7111-3p, miR-4755-3p, miR-320c, and miR-6511a-3p) in this study were found to be involved in PI3K/AKT, Wnt/ $\beta$ -catenin, and STAT3 signaling pathways. Interestingly, similar pathways have been reported to be significantly associated signaling pathways in SARS-CoV2 infection in a bioinformatics analysis conducted by our lab on publicly available datasets [15]. The findings of this new study urge the need for further study on a larger number of participants.

ncRNAs are thus re-defining our understanding of molecular regulation of health and diseases. This special issue attempts to bring together a bouquet of articles underlining the role of ncRNAs in various pathophysiological conditions and thus emphasizes the need to investigate ncRNAs in greater depths. The power to manipulate ncRNAs in a focused manner with minimal off-target effects will usher a new therapeutic arena of the future.

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**Code availability** Not applicable.

## Declarations

**Conflict of interest** The author has no relevant financial or non-financial interests to disclose.

**Ethical approval** This article does not contain any studies with human participants or animals performed and hence ethical approval was not required for the work.

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