Current role of non-coding RNAs in the clinical setting

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ABSTRACT
Non-coding RNAs (ncRNAs) have long been considered as “junk” material of the human genome until functional studies have exposed them as critical regulators of gene expression in both physiological and pathological conditions. Mounting evidences have also shown that ncRNAs may serve as diagnostic markers for several disorders, predictor for drug responses, and targets for new therapeutic approaches. In this mini-review, we discuss the state of the art of non-coding RNAs in drug development and their involvement in conventional treatments response.

1. Introduction
Approximately the 98% of human genome is transcribed in non-coding RNA (ncRNA) while less than 2% consists of protein-coding genes [1]. ncRNA were initially considered as “junk” material while recent studies underlined their role in the regulation of gene expression [2]. The functional importance of the non-coding portion of the genome has emerged, indeed, as a key element during both physiological conditions and diseases [3].

Non-coding RNAs (ncRNAs) are a big family of ribonucleic acids composed by several categories of long and short RNA such as microRNAs (miRNA), transcribed ultraconserved regions (T-UCRs), small nucleolar RNAs (snoRNAs), PIWI-interacting RNAs (piRNAs), circular RNAs (circRNAs), large intergenic non-coding RNAs (lincRNAs), and long non-coding RNAs (lncRNAs) [4–6]. MicroRNAs and long non-coding RNAs represent the two most studied non-coding RNAs, whose involvement in human diseases, including cancer, has been extensively demonstrated [7,8]. miRNAs are a class of small molecules of 19–25 nucleotides that are able to modulate the expression of at least one third of protein-coding genes [9]. Mature miRNAs recognize specific mRNA targets based on sequence complementarity. Specifically, mature miRNAs are incorporated into active miRNA-induced silencing complex (RISC) [10]. Within this complex, specific proteins orient miRNA for interaction with target messenger RNA, which can happen at the 3’ untranslated region (UTR) or to the open reading frame (ORF) depending on the degree of base pairing complementarity between miRNA and mRNA [11]. Gene silencing mediated by the RISC occur either via reduced mRNA translation or degradation of the target. Moreover, due to the shortness of the miRNA-mRNA binding site (6–8 base pairs), each miRNA is able to target multiple different mRNA [12]. For this reason, they are involved in multiple cellular processes such as proliferation, apoptosis, and differentiation both in physiological conditions and diseases. In cancer, miRNAs act either as oncogenes or tumorsuppressors based on the nature of their targets [13–15]. Several genomic alterations have been proposed to explain the aberrant expression of miRNAs in tumor tissues, including DNA point mutations, chromosomal aberrations, epigenetic mechanisms and alterations of miRNA processing machinery [16]. LncRNAs are another representative group of transcripts with no protein coding capacity, longer than 200 nucleotides, and involved in several biological processes [17]. For example, it is reported in literature their contribution to X-chromosome inactivation in mammals, or to epigenetic modifications at specific genomic regions thought the recruitment of chromatin remodeling complexes [18,19]. Moreover, the association between lncRNA dysregulation and carcinogenesis has been also described [20].

On this ground, the understanding of ncRNAs function in cancer and other pathological conditions is crucial to the development of novel therapeutic targeted approaches. In the present review, we discuss the current role of ncRNAs focusing our attention on their emerging employment in the clinical setting.

2. ncRNAs targeted therapies
Deregulated ncRNAs, mainly miRNAs, are emerging as suitable targets for novel anticancer therapeutic approaches either alone or in
combination with current therapies [16,21,22].

Two are the main strategies that can be used for targeting miRNAs: the first involves the inhibition of miRNAs function while the second leads to their restoration. The inhibition of miRNAs function is intended to target oncogenic miRNAs by: (i) antisense oligonucleotides (ASOs) that bind miRNAs leading to miRNAs degradation (Locked nucleic acids (LNAs), anti-miRNA oligonucleotides (AMOs), antagonirs represent the three main classes); (ii) miRNAs sponges, constructs with multiple miRNA binding sites, able to prevent the interaction between miRNAs and their natural targets; (iii) small-molecules that regulate miRNAs expression at transcriptional level; (iv) miRNAs' masking, through the employment of molecules complementary to 3′-UTR of specific miRNAs leading to the inhibition of downstream target effects [23–25]. The second approach is referred to as “miRNA replacement therapy” and aimed at targeting miRNAs that act as tumor suppressors, which are typically downregulated in cancer. This approach foresees the re-introduction of miRNAs in order to restore a loss of function through miRNA mimics or the employment of viral construction containing miRNAs coding genes [26,27]. Nevertheless, there are two main challenges in the development of miRNA-based treatment. At first, there is the necessity to get a tissue-specific delivery and to obtain a sufficient cellular uptake of synthetic oligonucleotides in order to allow a constant miRNA inhibition. In addition, the low biological stability of miRNAs in body fluids or tissue represent another hurdle that has been overcome through the employment of locked nucleic acid (LNA) constructs [22]. In fact, miRNAs, as unmodified oligonucleotides, are rapidly degraded by nucleases, thus requiring the dosing of elevated amount of drug. Similar methods have been used for other ncRNAs such as long ncRNAs, albeit it seems to be more difficult as compared to miRNAs. Indeed, due to InRNA complex secondary structures new bioinformatic tools are necessary to design new inhibitors. Some strategies have been proposed for long ncRNAs-based treatment hoping to translate their potential benefits into the clinical practice [28,29].

3. miRNAs therapeutic development status

New therapeutic approaches against cancer and other diseases have been developed through the employment of miRNA mimics or anti-miRNAs in vivo aimed at modulating specific miRNAs targets. On this ground, several miRNA carriers have been proposed for delivery either through local injection or systemically. Here, we summarized the current status of miRNA-based therapies development highlighting relevant ongoing phase I and phase II trials (Table 1).

3.1. miR-122

It is well known in literature the capacity of miR-122 to favor the replication of the hepatitis C virus (HCV) RNA genome [30]. In particular, miR-122 binds the non-coding region of the HCV viral RNA promoting its stability and protection from degradation [31]. Of note, an efficacious delivery to the liver of a LNAs (Locked Nucleic Acids) construct targeting miR-122 was associated to reduction of the viral load in chronic HCV patients treated with RG-101 (hepatocyte targeted N-acetylgalactosamine conjugated anti-miR-122 oligonucleotide) [32,33]. Phase I and II trials were than conducted with success and allowed additional phase II research studies [34]. In particular, Mirvirasen ([β-d-oxo-locked nucleic acid-modified phosphorothioate antisense oligonucleotide targeting the liver-specific microRNA-122) demonstrated antiviral activity against hepatitis C virus and no cytotoxicity, albeit nucleotide changes in the HCV 5′UTR associated with miravirsen resistance were identified [35]. Another study provided evidences regarding the reduction of viral load in chronic HCV patients treated with RG-101 (hepatocyte targeted N-acetylgalactosamine conjugated anti-miR-122 oligonucleotide) [36].

3.2. miR-34

Physiologically, miR-34 acts as tumor suppressor down-regulating the expression of several oncogenes such as MYC, MET, WNT 1/3 as well as genes implicated in tumor immune invasion such as CD274 [37–40]. In vitro studies showed that the introduction of miR-34a mimics leads to a significant reduction of cell proliferation, invasion, migration of cancer cells and have a synergistic effect in combination with anticancer drugs [41–43]. Notably, in vivo administration of miR-34a mimics was shown to block metastasis formation and accordingly increase survival [44,45]. On this ground, a phase I study assessed the clinical activity and safety of MRX34, a liposomal miR-34a mimic in patients with advanced solid tumors providing partial responses [46,47]. However, the trial was terminated due to immune related adverse events.

3.3. miR-16

miR-16 is an important member of the miR-15 family acting as tumor suppressor gene and playing critical role in the regulation of proliferation, apoptosis, differentiation and angiogenesis [48]. Mimics of miR-16 have entered in phase I trials in patients with non-small cell lung cancer (NSCLC) and malignant mesothelioma. In particular, in the first human, open-label, dose-escalation phase 1 trial, patients with a confirmed diagnosis of malignant pleural mesothelioma were treated with TargomiR drug called MesomiR-1 (bacterially derived minicells loaded with miR-16-based mimic and targeted to EGFR) showing acceptable safety and activity [49].

3.4. miR-29

miR-29 is an anti-fibrotic miRNA that is able to inhibit the expression of extracellular matrix genes such as COL1A1, COL1A2 and COL3A1. In cutaneous scars and keloids, miR-29 is repressed leading to the upregulation of its targets [50]. One phase I clinical trial for miR-29 mimic (MRG-201) was initiated in order to treat patients with keloid and scar tissue. This study aimed at investigating the safety, tolerability and activity of remlarsen (MG-201) in affected subjects.

3.5. miR-155

MiR-155 acts as an oncogene in both solid and hematological tumors by inhibiting many target genes (e.g., BCL2, SOX, VHL), which are

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Table 1

| miR name | Drug name | Therapeutic agent | Delivery system | Disease under investigation |
|----------|-----------|-------------------|-----------------|-----------------------------|
| miR-122  | Mirvirasen| Anti-miR           | LNA-modified antisense inhibitor | Hepatitis C virus (HCV) |
| miR-34   | MRX34     | AntimiR miR-mimic | LNP*            | Advanced solid tumor (lymphoma, melanoma, renal cell carcinoma, liver cancer, lung cancer) |
| miR-16   | MesomiR-1 | miR-mimic         | EnGeneC delivery vehicle | Malignant pleural mesothelioma |
| miR-29   | MRG-201   | miR-mimic         | Cholesterol-conjugated miRNA duplex | Keloid and scar tissue |
| miR-155  | MRG-106   | Anti-miR           | LNA-modified antisense inhibitor | T-cell lymphoma (mycosis fungoides subtype) |

*LNP*: lipid nanoparticles.
involved in crucial cellular events such as apoptosis [51–53]. In vivo preclinical studies showed impressive results in terms of survival extension and absence of toxicity in a mouse model of lymphoma treated with pHLP-antiIL-15 (pH low insertion peptide) [54]. On this ground, a phase 2 trial is ongoing to study the efficacy and safety of the LNA-modified antisense inhibitor cobomarsen (MRG-106) for the treatment of patients affected by cutaneous T-cell lymphoma (mycosis fungoides subtype).

3.6. miRNAs and drug efficacy

The efficacy of cancer treatments such as targeted therapies and chemotherapy is hampered by the emergence of intrinsic or acquired drug resistance. While intrinsic resistance is pre-existent, acquired resistance is specifically induced by the cancer treatment, yet both due to alternative transcriptional or translational cell states to which miRNAs can contribute [55]. The understanding of the mechanisms leading to resistance is therefore mandatory in order to develop more effective therapies. Recent studies highlight the role of miRNAs in promoting drug resistant in different cancers type [56–58]. Moreover, researchers have shown evidences regarding the relation between miRNAs and the resistance to tyrosine kinase-targeted therapies [59].

In particular, promising studies underlined the role of miRNAs as predictor of drug response in lung, colorectal cancer and renal cell carcinoma. Of note, in colorectal cancer patients’ cohorts, low expression of miR-31-3p was associated with improved outcome and prolonged benefit from anti-EGFR treatment [60–62]. The potential role of miR-31-3p for the selection of patients undergoing anti-EGFR therapy has been also confirmed recently by another group [63]. The role of miRNA as valid predictive marker was also confirmed in metastatic renal carcinoma where 4 miRNAs (miR-425-5p; miR-193-3p, let-7d and miR-31-3p) were identified as significantly associated with patient response to tyrosine kinase inhibitors treatment [64,65].

On this ground, combined treatments using conventional drug and new miRNAs inhibitor or mimics may help limiting the resistance to selected treatments [66].

4. Conclusion and future directions

Literature regarding the role of ncRNAs as critical regulators of gene expression in many diseases has rapidly expanded. As it stands, ncRNAs rapidly became attractive candidates for the development of novel therapeutic approaches. However, only few miRNAs therapeutic have successfully moved into clinical trials and this because several issues need to be taken into account when designing miRNA-based therapies: (i) the identification of the best miRNA target/set of targets to hit for each pathological condition, (ii) avoid toxic and off-targets effects, (iii) the employment of high stability and successful delivery system.

Recently, other ncRNAs such as lncRNAs or circRNAs are emerging as potential druggable molecules involved in cancer [67,68].

In summary, the number of non-coding RNA transcripts of the human genome with a presumed functional role in shaping pathological conditions, (ii) avoid toxic and off-targets effects, (iii) the need to be taken into account when designing miRNAs-based therapies:

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In summary, the number of non-coding RNA transcripts of the human genome with a presumed functional role in shaping pathological conditions has rapidly increased. The characterization of mechanisms through which ncRNAs exert their function will likely lead to significant improvement of cancer diagnosis and treatment.

Potential competing interests

The authors have no competing interests to declare.

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