Clinical Potential of miRNAs in Human and Infectious Diseases

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Abstract

MicroRNAs (miRNAs) are small non-coding RNA molecules that play critical roles in human disease. Several miRnome profiling studies have identified miRNAs deregulated in cancer and infectious diseases and miRNAs are also involved in regulation of the host response to infection. Thereby, the usage of miRNAs as biomarkers and potential treatments for both human and infectious diseases is under development. This review will provide insights into the contribution of miRNAs to pathogenesis and disease development and will present a general outline of the potential use of miRNAs as therapeutic tools.

Keywords: micro-RNA, cancer, infectious diseases, parasites, *Toxoplasma*, *Plasmodium*, *Theileria*.

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Introduction

Non-coding RNAs (ncRNAs) are functional RNAs transcribed from DNA, but not translated into protein, which play a role in regulating gene expression at the transcriptional and post-transcriptional levels. The best- [1–3] characterized short ncRNAs are the 18 to 25 nucleotide long microRNAs (miRNAs), first discovered in 1993 by Ambros et al. when they found the genetic locus of lin-4 in *Caenorhabditis elegans* and described its antisense complementarity to lin-14 [4]. This discovery led to a milestone in the research of small RNA biology and altered significantly longstanding dogmas that previously defined gene regulation.

miRNAs are transcribed by RNA polymerase II into primary miRNAs (pri-miRNA), which get processed in two steps by Drosha and Dicer into 70 nt precursor miRNAs (pre-miRNA), then into a 20 nt miRNA duplex, respectively. The first step takes place in the nucleus after which the pri-miRNA is transported by exportin-5 into the cytoplasm. One of the two strands of the 20 nt long miRNA duplex binds to the argonaute (AGO) and TNRC6 proteins to form the miRNA-loaded RNA-induced silencing complex (miRISC) (Figure 1). This complex is capable of silencing mRNAs bearing complete or partially similar complementary sequence to the miRNA seed region. The seed region of a miRNA is a 6–8 nt long sequence present at the 5′-region of the miRNA. This region defines miRNA targets, as any mRNA with a complete or partially complementarity sequence present, mostly, in the 3′-untranslated region (UTR) of the mRNA. After binding to its target, the miRISC complex provokes mRNA degradation through a variety of methods including mRNA deadenylation, cleavage and translation repression [5]. However, recent studies report that this class of non-coding RNAs can also play a role in positive regulation of the target mRNAs through transcript stabilization [6], promoting transcription [7], or translation stimulation [8].

miRNAs are key regulators in several biological processes ranging from development and metabolism to apoptosis and signalling pathways [9, 10]. Indeed, their profiles are altered in many human diseases and particularly in cancer [11, 12], making them attractive drug targets for disease treatment. Moreover, miRNAs are key mediators of the host response to infection, predominantly by regulating proteins involved in innate and adaptive immune pathways. The role of miRNAs in bacterial [13, 14], viral [15] and protozoan [16] infections is now well established. In this review, we synthesize our current understanding of the roles of miRNA in human cancer and infectious diseases with emphasis on their potential clinical applications.

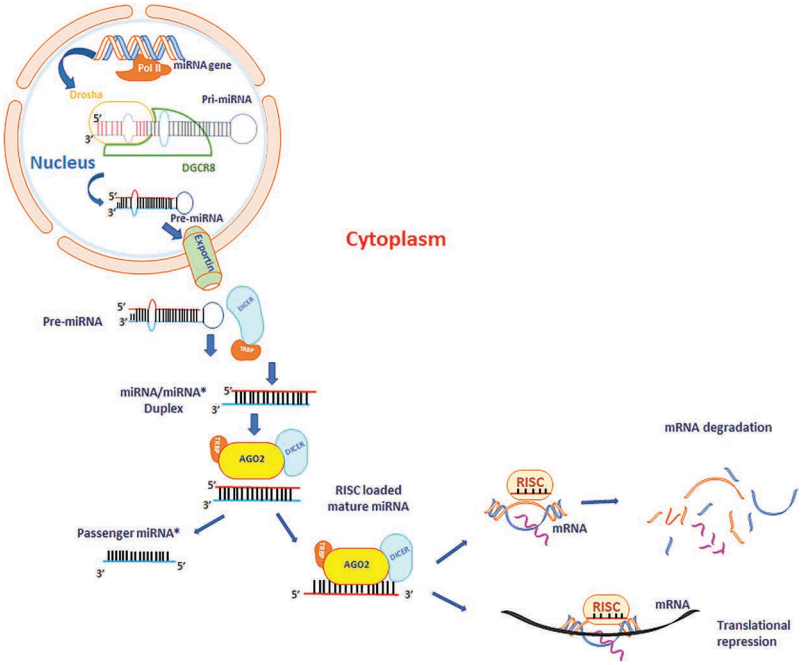

Figure 1 miRNA biosynthesis pathway. miRNA biogenesis begins with the generation of the primary transcript (pri-miRNA) by polymerase II/III. Pri-miRNA is then processed in the nucleus into precursor miRNA (pre-miRNA) by RNase III (Drosha) and DiGeorge critical region gene 8 (DGCR8). The pre-miRNA is exported to the cytoplasm by Exportin5 and cleaved by RNase III called Dicer together with its catalytic partner TAR-binding protein (TRBP) to produce the mature miRNA duplex. Finally, one strand of the mature miRNA duplex (either the 5p or 3p strands) is loaded into the Argonaute (AGO) proteins to form a miRNA-induced silencing complex (miRISC), which binds to target mRNAs to induce cleavage or translation inhibition.

miRNA and Cancer

Increasing evidence supports a role for miRNAs dysregulation in the occurrence of multiple human diseases, particularly cancer [17–21]. Many miRNAs have been found altered in various cancers [22] and can function either as oncogenes, or tumour suppressors. miR-21 is one of the earliest identified oncogenic miRs and the most frequently up-regulated in tumours. It is highly expressed in a number of malignancies such as glioblastomas, breast, colon and pancreatic cancer [23]. miR-21 targets PTEN [24], promoting invasion and migration, as well as tumorigenesis by inhibiting the negative regulators of the Ras/MEK/ERK pathway [24]. Moreover, the

miR-17-92 cluster promotes tumours in different human cancers such as breast, lung, colon, stomach, and pancreatic cancers [23, 25]. In addition, miR-155 was found associated with the majority of solid and hematopoietic malignancies [26, 27]. miR-155 gene is overexpressed in several solid tumour such as breast cancer [28, 29], pancreatic ductal adenocarcinoma [30] and lung cancer [31], where it is considered a marker of poor prognosis.

Even though some miRNAs are increased in cancer, many others are repressed and are therefore considered as tumour suppressor. For example, miR-15a and miR-16-1 are lost in Chronic Lymphocytic Leukaemia (CLL) and multiple myeloma, and let-7 is lost in lung and breast cancers [29]. miR-34 is a p53 responsive miRNA family that is down-regulated in several tumours such as non-small cell lung cancers [32] and pancreatic cancers [33]. In myelodysplastic syndrome, miR-146a and miR-145 were downregulated [34]. Many of miR-200 family members (miR-200a, miR-200b, miR-200c, miR-141, and miR-429) are downregulated in human cancer cell lines and tumours, and they play an important role in the suppression of epithelial-to-mesenchymal transition (EMT) and tumour cell adhesion, migration, invasion, and metastasis by repressing the expression of key mRNAs (ZEB1 and ZEB2, β-catenin) involved in EMT [35].

The role of microRNAs in cancer depends on the mRNA that's targeted, and whether the transcripts when translated or not act as oncogenes or tumour suppressors. Interestingly, some miRNAs may have dual functions as both tumour suppressors and oncogenes [36] depending on the cellular context. For example, miR-29a has been described to function as a tumour suppressor in CLL and lung cancer, and as an oncogene in breast cancer [36]. Also, miR-125b can have both oncogenic and tumour suppressive effects. miR-125b can target mRNAs encoding anti-apoptotic, pro-apoptotic and pro-proliferative factors, metastasis promoters and metastasis inhibitors [37, 38]. Therefore, the balance of expression of different miR-125b targets determines the function fulfilled (oncogene/tumour suppressor) by miR-125b within an individual tumour.

All the above evidence clearly highlights the involvement of miRNA in various cancers, and underscores how identification of specific regulators of miRNAs will be important in developing new anti-cancer therapeutic agents.

miRNA and Infectious Diseases

Many studies have documented the role of miRNAs in infection and immunity. For example, let-7 was identified as a modulator of the macrophage

immune response to infection with *Mycobacterium tuberculosis* via targeting the NF-κB inhibitor A20 [39]. miR-146b, miR-16, let-7a1, miR-145, and miR-155 expression were significantly altered following *Listeria monocytogenes* infection in epithelial cells [40]. *Pseudomonas aeruginosa* infection enhanced miR-762 and miR-155 expression to downregulate expression of immune response genes [41, 42]. Besides the role of miRNAs in bacterial infectious diseases, many studies have demonstrated the importance of miRNAs in viral infections. It is known that DNA viruses can encode miRNAs that regulate their replication and pathogenesis through targeting of host, as well as viral mRNAs [15]. Viruses can additionally manipulate host cell miRNA levels either by increasing the expression of host miRNAs that favour viral replication, or by expressing proteins that antagonize host miRNAs, which play a role in host immunity [43]. For instance, numerous host miRNAs such as miR-196, miR-296, miR-351, miR-431 and miR-448 are dysregulated in hepatitis C virus (HCV)-infected hepatocytes, as a result of type I interferon (IFNα/β) production [44]. Furthermore, miRNAs can also play a key role in parasite infection. A large body of work has demonstrated that parasites promote modifications in the cell host miRnome, underscoring the importance of miRNAs in parasite-host interactions. For instance, *Toxoplasma gondii* specifically modulates expression of important host miRNAs during infection [45] with around 14% of host miRNAs in primary human foreskin fibroblasts found to be altered 24 h after infection [46]. NF-κB signalling and transactivation by STAT3 binding was demonstrated to regulate a subset of miRNAs (miR-30c-1, miR-125b-2, miR-23b-27b-24-1, and miR-17$\sim$92 cluster genes) that were induced following *T. gondii* infection of human macrophages. These miRNAs are mainly involved in regulating an anti-apoptosis response following *T. gondii* infection [47]. Another study highlighted two immune-modulatory miRNAs, miR-146a and miR-155, important for the infected host cell response to *T. gondii* challenge. Both miRNAs were co-induced in the brains of mice challenged in a strain-specific manner with *Toxoplasma*. Mice challenged with the *T. gondii* cystogenic (type II) strain showed an exclusive and significant induction of miR-146a partly mediated by the rhoptry kinase ROP16 [48]. miR-146a deficiency led to better control of parasite burden in the gut and most likely also early parasite dissemination into brain tissue, resulting in the long-term survival of mice. By contrast to *T. gondii*, the *Plasmodium falciparum* genome lacks orthologues of Dicer and Argonaute, crucial enzymes in miRNAs biogenesis [49, 50]. Moreover, sequencing and bioinformatics analysis of small RNA libraries from *P. falciparum*-infected erythrocytes

did not identify parasite-specific miRNAs [51]. However, in haemoglobin S (HbS) erythrocytes a role for host miRNAs in the resistance of these mutant red blood cells to infection provoked malaria has been reported [16]. This study provided the first data on human miRNAs regulating *Plasmodium* gene expression and suggested the possibility of miRNAs being able to translocate into malaria parasites. Around 100 different human miRNAs were taken up by the parasite with a particular enrichment of miR-451 and let-7i in parasitized HbAS and HbSS erythrocytes. Integration of miR-451 into transcripts of the *P. falciparum* regulatory subunit of cAMP-dependent kinase Protein Kinase A (PKA-R) was shown. The gene coding for *Plasmodium* PKA-R is crucial to parasite survival [52] and suppression of its expression mediated by miR-451 was related to an increased number of gametocytes (the sexual forms infectious to mosquitoes). Furthermore, LaMonte et al. confirmed that human miRNA transferred into the parasite formed chimeric fusions with *P. falciparum* mRNA via impaired ribosomal loading, resulting in translational inhibition, eventually impairing parasite biology and survival. However, it's not yet known what determines the specific enrichment of a particular miRNA, or its incorporation into specific parasite mRNAs [50, 51, 53]. Moreover, Extracellular Vesicles (EVs) derived from *P. falciparum*-infected red blood cells (iRBC) contain miRNAs that can modulate target gene expression in recipient host cells and multiple miRNA species in EVs were identified bound to AGO2 forming functional complexes [54]. Furthermore, *P. falciparum* can take up micro-vesicles containing AGO2 and miRNA from infected RBC [55]. In addition, a recent study investigated alterations in plasma miRNA levels mediated by *P. vivax* showing down-regulation in the levels of miR-451 and miR-16 in *P. vivax* malaria patients [56]. The expression profiles of miRNAs have also been studied in models of experimental malaria. Changes in liver miRNAs were investigated in mice infected with *P. chabaudi* [57], and a recent study reported an infection-induced significant up-regulation of miR-155 in liver infected with Genetically Attenuated Parasites (GAP) [58]. miR-155 plays a crucial role in *Plasmodium*-infected liver, as ectopic administration of miR-155 (AAV-155) reduced the number of GAP injections necessary to immunize mice against *P. chabuadi* malaria.

A role for miR-155 in the virulence of *Theileria annulata*-transformed leukocytes has been described to involve miR-155-mediated suppression of De-Etiolated Homolog 1 expression that diminishes c-Jun ubiquitination [59]. An increase in c-Jun levels led to an augmentation in BIC transcripts that contain miR-155, explaining how a positive feedback-loop

contributes to the growth and survival of *Theileria*-infected leukocytes [59]. Further, a recent study characterized the cargo of extracellular vesicles (EV) from a control non-infected bovine lymphosarcoma cell line (BL20) and BL20 infected with *T. annulata* (TBL20) by comparative mass spectrometry and microRNA (miRNA) profiling. The study revealed an enrichment of infection−associated proteins essential to migration and extracellular matrix digestion in EV from TBL20 cells compared with BL20 controls. They proposed that EV and their miRNA cargo play an important role in the manipulation of the host cell phenotype and the pathobiology of *Theileria* infection [60]. Furthermore, we have shown that infection of macrophages with *T. annulata* induced upregulation of miR-126-5p levels to directly target and suppress a cytosolic scaffold protein called JNK-Interacting Protein-2 (JIP-2), so liberating JNK1 to enter the nucleus and phosphorylate c-Jun [61]. This activates AP-1-driven transcription of the gene (*mmp9*) coding for Matrix Metallo-Proteinase 9 that promotes tumour dissemination. In addition, we showed that variation in miR-126-5p levels depends on the tyrosine phosphorylation status of AGO2, which is regulated by Grb2-recruitment of PTP1B [61].

Taken altogether, the above demonstrates the importance of miRNAs in the host response to pathogen infection and strongly argues that a reprogramming of miRNA expression could have a regulatory function in the pathogenesis of various infectious diseases and this could potentially generate a new therapeutic approach.

Clinical Relevance and Therapy

miRNAs levels were found to be dysregulated and associated with various infectious and human diseases. Numerous studies have shown altered miRNA profiles in multiple cancer types [62–65]. In view of these data miRNAs have been proposed as candidate biomarkers of different types of cancer [66–71]. As an example, increased miR-126 levels can predict patient survival, especially for patients with digestive or respiratory system cancers [72]. Moreover, miRNAs are considered very attractive in terms of drug development, as they possess unique characteristics i.e. they are small with known sequences and are often conserved among species. This has led to their use as therapeutic agents [73, 74]. miRNA-based therapeutics is divided into miRNA mimics and inhibitors of miRNAs (also known as antimiRs). Different strategies are currently applied in preclinical development to restore the tumour suppressive function of miRNAs (using miRNA mimics), or to suppress oncomiRs (using

antimiRs). miRNA mimics are synthetically derived oligonucleotide duplexes that mimic the function of a naturally occurring miRNA counterpart [75]. By contrast, antimiRs are chemically modified antisense oligonucleotides, which sequester the mature miRNA inhibiting their binding to their cellular target mRNAs leading to de-repression of direct targets [76]. Several miRNA-targeted therapeutics have reached clinical development. For instance, the mimic of miR-34 has reached phase I clinical trials (NCT01829971) for treating cancer. Administration of lipid nanoparticle-encapsulated miR-34 mimics showed promising activity in mouse models of liver [77], prostate [78] and lung [79] cancer. In addition to miR-34, other miRNAs have shown exploitable clinical relevance. For example, miR-26a expression is highly reduced in patients with HCC compared to the normal controls. Importantly, adeno-associated virus-mediated expression of miR-26a in murine models with HCC resulted in significant tumour reduction [80]. miR-200c has been also tested in preclinical studies. In a xenograft model of lung cancer, administration of liposomal nanoparticles loaded with miR-200c increased the sensibility of lung cancer cells to radiation and markedly longer survival compared with controls [81]. Moreover, a role of miR-15a and miR-16-1 in therapeutic development for CLL has been described [82]. Overexpression of the miR-15/16 cluster using viral vectors in a MEG-01 subcutaneous model of leukaemia reduced significantly tumour volume and growth [82]. Further, miR-10b appears to be a promising anti-metastasis agent. Silencing of miR-10b by a miR antagonist in mice bearing highly metastatic cells significantly suppressed formation of lung metastases [83]. Cholesterol-anti-miR-221 has been demonstrated to be an efficient therapeutic agent for patients with advanced HCC. Intravenous administration of chol-anti-miR-221 in an orthotopic mouse model blocked HCC and promoted mouse survival [84]. Nanoliposomes carrying anti-miR-630 in a xerograph model of ovarian cancer reduced considerably tumour growth and metastasis [85].

Additionally to the role of miRNAs in cancer, many studies have shown their implication in the host response to infection raising the potential for new miRNA-based diagnostics [86] and therapies [87] for infectious diseases. For instance, miR-122 is known to upregulate the replication of the hepatitis C virus (HCV) RNA genome promoting its stability [88]. The systematic administration of 16-nt, unconjugated LNA (locked nucleic acid)-antimiR oligonucleotide complementary to the 5′-end of miR-122 markedly reduced the infection load and liver damage in mouse models of HCV infection [89]. Furthermore, Hock et al., found [90] enhanced bacterial killing of mice infected with non-typeable *Haemophilus influenza* [91]. Moreover,

administration of exosomes containing miR-146a and miR-155 enhanced mice inflammatory responses to endotoxin *in vivo* [92]. In addition, inhibition of miR-146a in Enterovirus 71-infected mice by intraperitoneal injection of an anti-miR-146a significantly improved their survival by restarting the production of interferon gamma I. Furthermore, intragastric delivery of anti-miR-128 in *Salmonella enterica*-infected mice promoted survival and suppressed infection [93].

Finally, *Plasmodium* transcripts have shown to be targeted by host miRNAs translocating into the parasite [16]. LaMonte et al. pointed out that translocation of sickle cell erythrocyte miRNAs into *P. falciparum* inhibited parasite mRNA translation and contributed to malaria resistance [16]. miRNAs have also been found to regulate virulence of *Theileria*-infected leukocytes. Modulation of miR-126-5p expression by either a mimic or an antimiR regulated the metastatic potential of *Theileria*-infected leukocytes [61].

Conclusion

Overall, the use of miRNA-based therapies has shown great therapeutic potential for cancer and infectious diseases (Figure 2). So far, many approaches using either miRNA mimics, or miR-inhibitors have made their way into clinical trials. With advance in knowledge of RNA interference (RNAi) and the progress of RNAi technologies, miRNAs will in the near

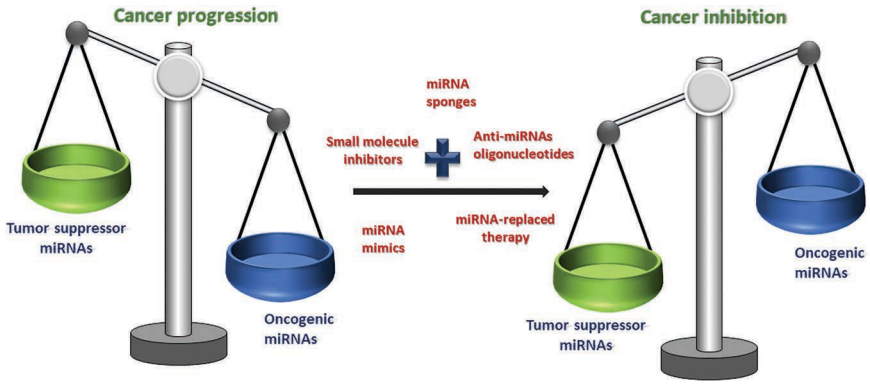

Figure 2 miRNAs in cancer therapy: Inhibition of onco-miRs function by using anti-miR oligonucleotides (AMOs), small molecule inhibitors and miRNA sponges, and enhancing the expression of anti-onco-miRs through gene therapy or delivery of miRNA mimics can serve as therapeutic approach against cancer.

future become very helpful new biomarkers and effective therapeutic tools routinely used in the clinic.

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