Non-coding RNA Research 10 (2025) 41–54

Contents lists available at ScienceDirect

Non-coding RNA Research

journal homepage: www.keaipublishing.com/en/journals/non-coding-rna-research

Review Article

Recent advances in the development and clinical application of miRNAs in infectious diseases

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ARTICLE INFO

Keywords:
microRNAs
Infectious diseases
Biomarkers
Therapeutic targets

ABSTRACT

In the search for new biomarkers and therapeutic targets for infectious diseases, several molecules have been investigated. Small RNAs, known as microRNAs (miRs), are important regulators of gene expression, and have emerged as promising candidates for these purposes. MiRs are a class of small, endogenous non-coding RNAs that play critical roles in several human diseases, including host-pathogen interaction mechanisms. Recently, miRs signatures have been reported in different infectious diseases, opening new perspectives for molecular diagnosis and therapy. MiR profiles can discriminate between healthy individuals and patients, as well as distinguish different disease stages. Furthermore, the possibility of assessing miRs in biological fluids, such as serum and whole blood, renders these molecules feasible for the development of new non-invasive diagnostic and prognostic tools. In this manuscript, we will comprehensively describe miRs as biomarkers and therapeutic targets in infectious diseases and explore how they can contribute to the advance of existing and new tools. Additionally, we will discuss different miR analysis platforms to understand the obstacles and advances of this molecular approach and propose their potential clinical applications and contributions to public health.

1. Introduction

Basic research on diseases provides insight into the mechanisms of pathogenesis, enabling the development of novel strategies for disease control and more effective treatments. Regarding infectious diseases, pathogens employ a wide range of strategies to invade, survive and replicate within hosts. However, many host attempts to manage physiological, metabolic, and immunological disruptions fail due to pathogen-induced dysregulation [1,2]. These mechanisms involve the activation of intracellular signaling pathways and transcription factors. Reprogramming cellular transcripts allows the expression and modulation of immune-associated genes following disease onset. In this process, non-coding RNAs play key roles [3,4].

MicroRNAs (miRNAs) are small, non-protein encoding, endogenous single-stranded RNAs with approximately 22 nucleotides in length. Acting by repressing translation or by the degradation of target messenger RNAs (mRNAs), miRNAs are important regulators of gene expression in several biological processes, including cell proliferation, development, differentiation, apoptosis, and energy metabolism, as well as carcinogenesis [5–8]. These molecules correspond to approximately 1–2% of the known genome of eukaryotes and are considered key regulators of at least 60 % of human genes [9,10].

Several studies highlight the promising use of miRNA profiles as endogenous biomarkers to distinguish between diseased and healthy individuals, identify different disease stages, and serve as a screening tool for high-risk individuals [11–20]. Clinical trials investigating miRNAs as therapeutic targets have produced interesting results, such as Miravirsen for hepatitis C [21], MRX34 for advanced solid tumors [22], and Cobomarsen [23] for cutaneous T-cell lymphoma and ringworm. The modulation of miRNAs can be exploited as a monotherapy or to enhance the efficacy of conventional treatments [24–27].

This review aims to first characterize miRNAs and describe their roles in regulating gene expression, followed by exploring their potential as biomarkers and therapeutic targets in infectious diseases. Finally, we

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https://doi.org/10.1016/j.ncrna.2024.09.005
Received 25 March 2024; Received in revised form 6 August 2024; Accepted 1 September 2024
Available online 2 September 2024

discuss different platforms for miRNA analysis and examine the advances and challenges in their clinical applications.

2. The biogenesis of microRNAs

MiRNAs function by decreasing translational efficiency and/or mRNA levels [28,29]. They originate as primary miRNA (pri-miRNA) [30], which are initially transcribed as double-stranded sequences with a hairpin structure. These pri-miRNAs are cleaved by the Drosha/DGCR8 endonuclease complex, resulting in the formation of precursor miRNA (pre-miRNA). The pre-miRNAs are then transported to the cytoplasm via a binding protein named Exportin 5 [29,31]. In the cytoplasm, pre-miRNAs are further cleaved by the DICER endonuclease, forming mature double-stranded miRNAs [32,33]. Subsequently, these strands are separated, and the functional strand is incorporated into the RNA-induced silencing complex (RISC), which includes proteins such as including Argonaut 2 (AGO-2). When RISC binds to the 3′ untranslated region (3′ UTR) of a target mRNA, it triggers deadenylation by exonucleases (Fig. 1). This mechanism ultimately results in the regulation of gene expression [30,34,35].

The binding of the seed region of miRNAs to complementary sequences in the 3′ UTR of target mRNAs inhibits gene expression at the

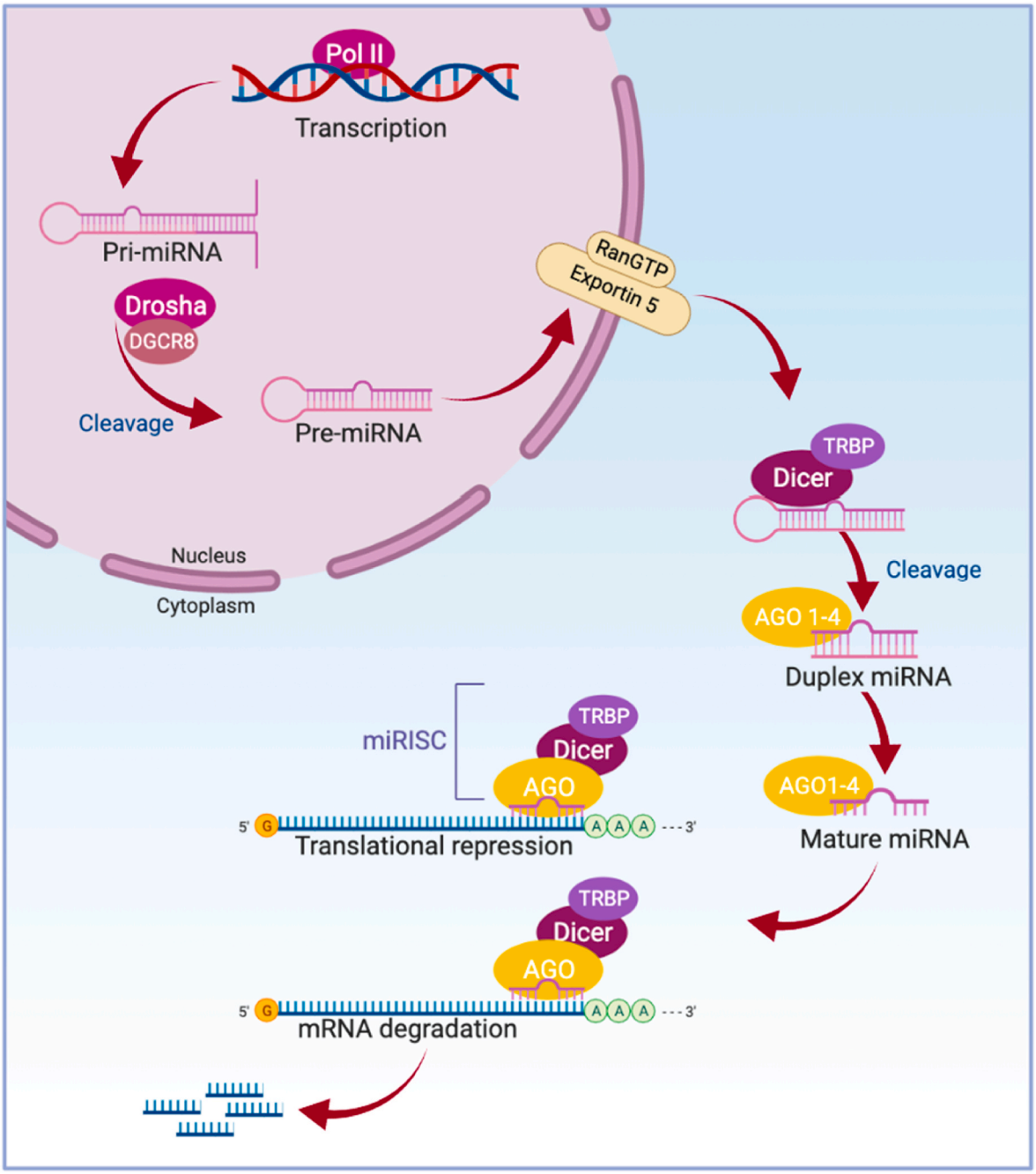

Fig. 1. Biogenesis of microRNAs. The biogenesis of miRNAs begins with transcription of primary miRNA (pri-miRNA) by RNA Polymerase II, followed by cleavage of pri-miRNA by DROSHA endonuclease, forming a precursor miRNA (pre-miRNA). The pre-miRNA is transported to the cytoplasm by the exportin 5 complex. In the cytoplasm the pre-miRNA is cleaved by another endonuclease, DICER, forming a miRNA duplex. The strands are separated by argonaut complex, and the single strand is considered the mature miRNA, which together with the RNA-induced silencing complex (RISC), binds to the target mRNA leading to repression of translation or degradation of mRNA. Created with BioRender.com.

post-transcriptional level [5]. Different approaches for analyzing miRNAs aim to predict the potential to inhibit target genes by considering factors such as base pair similarity, algorithmic predictions, and conservation of target sites. Additionally, these methods assess the association of target genes with different biological processes and diseases [36]. Since many miRNAs are conserved across different species, they play crucial roles in development and the regulation of homeostasis. Indeed, without miRNAs, animals and plants would be unable to survive or reproduce [37,38]. The recognition of miRNAs as key post-transcriptional regulators has led to significant clinical applications.

3. Clinical application of miRNAs

3.1. Treatment and therapy

Several studies have suggested that miRNAs can be used to modulate biological processes for medical interventions in the treatment of different human conditions. However, nonspecific actions or biological compensation can occur in both miRNA-mediated therapies and conventional treatments. To address or minimize these limitations, preclinical validation can be conducted using *in silico, in vitro* and *in vivo* assays [26,39].

Specific sequences known as miRNA mimics and antagomirs have been designed to either induce or inhibit target gene expression by imitating the action of miRNAs. Preliminary *in silico* analysis aids in identifying these sequences and predicting their binding potential. Additionally, *in vivo* studies are crucial for optimizing existing delivery systems and developing new, more efficient ones. Ensuring efficient miRNA delivery is fundamental due to the potential degradation of their structure by nucleases and other proteins [40–43].

The Clinicaltrials.gov (https://clinicaltrials.gov/) website provides a comprehensive record of miRNAs currently under investigation in preclinical and clinical trials (Table 1). One notable example is the use of miR-122 to treat HCV infection [21]. This research has resulted in the development of Miravirsen, a locked nucleic acid (LNA) that binds with high affinity to the complementary 5' end of miR-122. MiR-122 is crucial for the stability of the HCV genome by forming a protective complex that shields it from nucleolytic degradation or from host immune responses [44]. Miravirsen binds and inactivates miR-122, leading to a reduction in circulating HCV viral load [21,45]. Additionally, studies on miR-34a in tumors [22] have contributed to the development of MRX34, a potent treatment for different types of solid tumors (NCT02862145 and NCT01829971). MRX34 has also shown promise as a therapeutic candidate for Multiple Myeloma [22,46].

Artificial miRNAs (amiRNAs) have also emerged as an alternative to mimic miRNAs for achieving long-lasting gene silencing in specific tissues. They consist of a target-specific siRNA insertion within a scaffold based on a natural pri-miRNA. Currently, a clinical trial testing an amiRNA to treat Huntington's disease is in the recruitment phase (NCT04120493). This genetic disorder is fatal due to neurodegenerative complications caused by the mutant huntingtin protein (HTT), which leads to the gradual degeneration of neurons and progressive impairment of motor coordination [47]. AMT-130 is an amiRNA designed to degrade both wild-type and mutant human huntingtin protein. The strategy involves administering AMT-130 via a viral vector that binds to cell receptors, is internalized by neurons, and is processed as a regular miRNA. *In vitro* and *in vivo* assays have demonstrated the efficacy of this approach, suggesting that it is specific, broad-spectrum and safe [48,49].

Collectively, these studies pave the way for the development of miRNA-based tools for disease treatment, demonstrating their effectiveness, stability and safety.

Table 1
miRNAs as targets for clinical trial at https://clinicaltrials.gov.

NCT Number	miRNA	Mode of action	Conditions	Phases	Study Type
NCT01200420	miR-122	Anti-miR	HCV	Phase 2	Interventional
NCT01646489	miR-122	Anti-miR	Hepatitis C| Chronic Hepatitis C	Phase 1	Interventional
NCT01727934	miR-122	Anti-miR	Hepatitis C	Phase 3	Interventional
NCT02452814	miR-122	Anti-miR	HCV	–	Observational
NCT02508090	miR-122	Anti-miR	Chronic Hepatitis C	–	Observational
NCT03713320	miR-155	Anti-miR	Mycosis Fungoides| Cutaneous T-Cell Lymphoma	Phase 2	Interventional
NCT03837457	miR-155	Anti-miR	Mycosis Fungoides| Cutaneous T-Cell Lymphoma	Phase 2	Interventional

NCT numbered trials are registered at ClinicalTrials.gov.

3.2. The potential of miRNAs as biomarkers

In recent years, the search for new biomarkers has significantly intensified, driven by remarkable technological advancements that have enhanced the precision and reliability of their selection. Among the various biomarkers being explored, miRNAs have emerged as promising candidates due to their non-invasive nature, enabling their potential use in diagnosing and predicting the progression of numerous conditions. This stands in contrast to certain proteins, which can be challenging to access and require considerable time for analysis [50].

One notable advantage of miRNAs is their detectability in various human body fluids, further underscoring their potential as biomarkers. Studies have confirmed the abundance and specificity of miRNAs across different tissues and pathological conditions, establishing their suitability for diagnostic purposes [51–53]. More recently, numerous studies have highlighted the significance of circulating miRNAs in several infectious diseases. Initially focused primarily on cancer [54], research has expanded to demonstrate the potential of miRNAs as diagnostic tools for a wide range of conditions, including infections [55–58], immunological and metabolic disorders [59], cardiovascular diseases [60], and more (Table 2).

Another significant advantage of miRNA profiles is their detectability early in the course of a disease, even before treatment begins.

Table 2
microRNAs as potential biomarkers of infectious diseases.

miRNA (s)	Expression profile	Disease	Ref
miR-19a-3p, miR-19b-3p, and miR-92a-3p	Up	Covid-19	[65]
miR-150 and miR- 146b-5p	Down	Human immunodeficiency virus (HIV)	[66]
miR-150	Down	Human immunodeficiency virus (HIV)	[67]
miR-122, miR-21, and miR-34a	Up	Hepatitis C	[68]
miR-149, miR-638, and miR-491	Up	Hepatitis C	[69]
miR-122	Up	Hepatitis C	[70]
miR-361-5P, miR- 889, and miR-576-3p	Down	Tuberculosis	[57]
miR-144	Up	Tuberculosis	[57]
miR-378, miR-483-5p, miR-22 and miR-29c	Up	Tuberculosis	[71]
miR-101 and miR-320b	Down	Tuberculosis	[71]
miR-16 and miR-451	Down	Malaria	[72]

This early detection holds promise as a potential indicator of different disease outcomes [61]. Additionally, specific miRNA profiles have been identified for different stages of the same disease, offering the possibility of modulating these profiles and restoring homeostasis [62].

The ability of miRNAs to serve as diagnostic tools across various diseases underscores their clinical potential and highlights their role as valuable biomarkers [63,64]. By examining the altered profiles of circulating miRNAs, researchers and healthcare professionals can gain insights into disease onset, progression, and potential therapeutic interventions. Continued research in this field holds promise for enhancing disease management and patient outcomes.

4. Expression of miRNAs in infectious diseases

4.1. Tuberculosis

Tuberculosis (TB), a global health concern caused by the airborne bacterium *Mycobacterium tuberculosis* (MTb), primarily infects the lungs. Astonishingly, approximately one-fourth of the world's population is affected by MTb, resulting in a significant disease burden. Each year, around 10 million people fall ill with TB, and 1.3 million people die from this disease, making it the world's leading cause of infectious death [73].

Upon infection, MTb has the remarkable ability to persist within macrophages for an extended period, evading host immune responses and establishing a foothold for disease progression. This prolonged intracellular survival of MTb within macrophages ultimately leads to the formation of granulomas - organized aggregates of immune cells aimed at containing the infection. Unfortunately, granuloma formation can also neutralize defense mechanisms, creating an environment conducive to the pathogen's persistence [73].

Several studies have identified an association between miRNAs and tuberculosis, revealing specific miRNAs that play crucial roles in regulating the immune response during infection. Notably, miR-21, miR-146a, and miR-155 have emerged as key regulators, showing increased expression in patients with active tuberculosis compared to healthy controls. These miRNAs can play diverse roles, such as controlling infection [74], favoring Mtb survival [75] or having a dual function of supporting the pathogen while promoting better cellular function, thereby enabling a more effective immune response [76–78].

One such miRNA, miR-21, is upregulated in peripheral blood mononuclear cells (PBMCs) and targets Bcl-2 and TLR4 in MTb-infected macrophages, leading to impaired anti-TB immunity [74,79]. Similarly, miR-146a promotes mycobacterial survival in macrophages by suppressing nitric oxide production, which is essential for antimicrobial activity [75]. Conversely, miR-155 sustains macrophage survival, creating an environment conducive to bacterial replication [78]. Additionally, miR-155 subverts autophagy by targeting ATG3 in human dendritic cells, inhibiting a crucial mechanism for controlling tuberculosis. Intriguingly, silencing miR-155 during MTb infection restores ATG3 levels and rescues autophagy, presenting a novel approach to counter tuberculosis [80].

Several studies have highlighted the involvement of miRNAs in regulating critical processes such as phagosome maturation and autophagy, which are pivotal in controlling the spread of Mycobacterium tuberculosis (MTb) infection. MiR-33 is one such miRNA induced during MTb infection, playing a role in reprogramming autophagy and host lipid metabolism [81]. Additionally, miR-27a and miR-144 have been identified as regulators that downregulate autophagosome formation and maturation in patients with active tuberculosis [82,83]. In contrast, miR-20b is downregulated during MTb infection, resulting in increased inflammation and pyroptosis of alveolar cells in mice via the NLRP3/caspase-1/IL-1β pathway [84]. The involvement of these miRNAs in phagosome maturation and autophagy provides detailed insight into the immunological mechanisms controlling MTb propagation. This understanding can lead to the development of new therapeutic strategies aimed at enhancing these defense pathways, offering novel approaches for clinical application.

Biomarker research in tuberculosis has identified several miRNAs with potential diagnostic value. *In silico* analysis has revealed that miR-223 and miR-448 are downregulated in the plasma of patients with active tuberculosis compared to healthy controls, indicating their ability to distinguish these patients during infection. These miRNAs participate in regulatory networks that interfere with interferon signaling pathways, suggesting their involvement in the immune response against tuberculosis [85].

In the context of tuberculous meningitis, the most severe form of the disease, a study identified four miRNAs — miR-126, miR-130a, miR-151a, and miR-199a — that can distinguish tuberculous meningitis from viral meningitis. These miRNAs were found to be downregulated in PBMCs from tuberculosis patients compared to those with viral meningitis, highlighting their potential as diagnostic tools [86]. Importantly, these miRNAs play roles in protecting the blood-brain barrier, modulating neutrophil-mediated inflammation, inhibiting macrophage activation, regulating Th1-mediated immunity, and producing pro-inflammatory cytokines [86].

These findings emphasize the significance of miRNAs in fine-tuning the host immune response to MTb infection (Fig. 2), particularly in regulating autophagy and controlling inflammation. Understanding the precise roles of these miRNAs offers important insights into the molecular mechanisms underlying tuberculosis pathogenesis and identifies potential targets for therapeutic interventions. Continued research in this field holds promise for developing novel strategies to enhance host defense mechanisms and improve outcomes in tuberculosis management.

4.2. Leprosy

Leprosy is a chronic infectious disease caused by the bacterium *Mycobacterium leprae*. It is characterized by nerve damage, which leads to a wide range of clinical manifestations and can result in deformity and disability. *M. leprae* is an intracellular parasite that primarily resides in the peripheral nervous system and has a slow replication rate. This results in a long incubation period and a gradual progression of the disease. Leprosy remains a significant public health concern, with over 200,000 new cases reported globally each year. In Brazil alone, 27,864 cases have been documented, accounting for 93 % of all cases in the Americas and 13.7 % of the worldwide total [87–89].

Leprosy is classified into different clinical forms, including tuberculoid (TT) and lepromatous (LL), with an intermediate group that encompasses borderline tuberculoid (BT), borderline borderline (BB), and borderline lepromatous (BL) presentations. These classifications are based on the clinical and immunological characteristics observed in affected individuals [90].

The immune response in leprosy involves two distinct reactions: type 1 (R1) and type 2 (R2), associated with different clinical forms and immune profiles. Type 1 reactions (R1) typically occur in TT, BT, and BB forms. These reactions feature a strong cellular immune response against *M. leprae,* marked by T cell activation and the production of pro-inflammatory cytokines, such as interferon-gamma (IFN-gamma) and tumor necrosis factor-alpha (TNF-alpha), which help control the infection and cause tissue inflammation [91,92]. Conversely, type 2 reactions (R2) are common in BL and LL forms, where the cellular immune response against *M. leprae* is reduced or absent, and humoral immunity is increased. R2 reactions involve a shift to a Th2-type immune response, with cytokines such as interleukin-4 (IL-4) and interleukin-10 (IL-10) that promote antibody production and suppress cellular immunity, potentially worsening the disease and causing tissue damage [91,92].

The expression of specific miRNAs in biopsies from active leprosy lesions has been investigated, highlighting their potential diagnostic and discriminatory roles. Studies have identified a panel of miRNAs, including miR-101, miR-196b, miR-27b, and miR-29c, which show differential expression in leprosy patients compared to healthy controls.

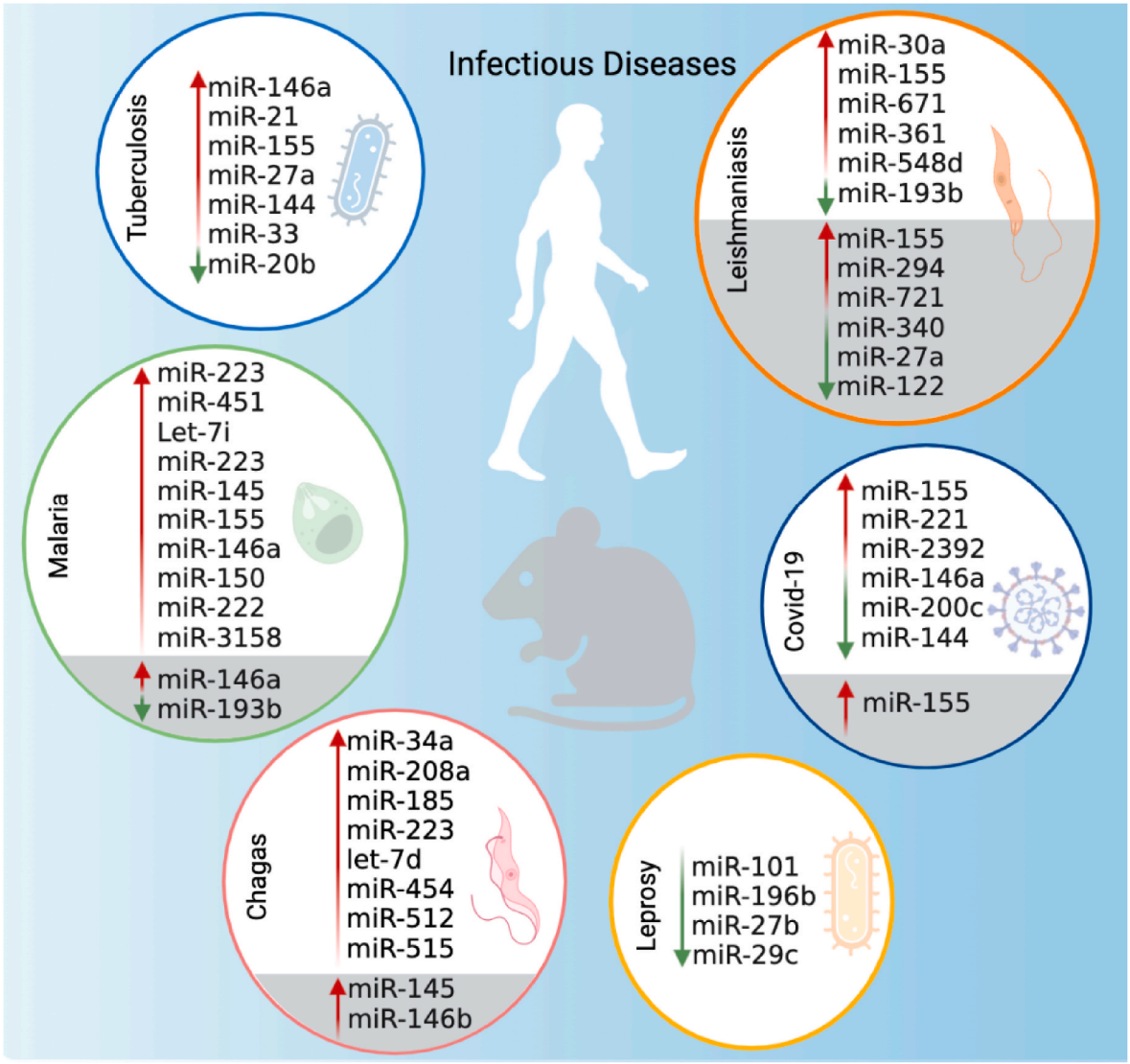

Fig. 2. Regulation of miRNAs of great significance in infectious diseases in humans and mice. Summary of the expression profile of miRNAs for Tuberculosis, Malaria, Leprosy, Leishmaniasis, COVID-19 and Chagas in human (white) and mice (grey), as discussed in the main text. The miRNAs up-regulated are symbolized by red arrows and the down-regulated by green arrows. Created with BioRender.com.

Using these miRNAs, researchers were able to distinguish between healthy individuals and leprosy patients with 80 % sensitivity and 91 % specificity, suggesting their potential as diagnostic biomarkers for leprosy [93]. Moreover, this set of miRNAs has shown promise in distinguishing between lepromatous and tuberculoid forms of leprosy, with a sensitivity of 83 % and a specificity of 80 %. This underscores the potential of miRNA profiling as a tool for identifying different clinical forms of the disease and their reactional states [93,94].

In a study, researchers identified several differentially expressed miRNAs between lesions of leprosy patients with TT and LL forms. Among these miRNAs, miR-21 stood out for its specific expression in lepromatous lesions. Notably, miR-21 targets the vitamin D-dependent antimicrobial pathway, inhibiting the expression of CAMP and DEFB4A, essential peptides in antimicrobial defense mechanisms. The upregulation of miR-21 by M. *leprae* suggests it may be a mechanism employed by the bacterium to evade host antimicrobial responses [95].

The identification of specific miRNA panels capable of accurately diagnosing leprosy and distinguishing between its different forms holds significant clinical potential. These panels could enable early detection, prompt treatment initiation, and effective monitoring of treatment progression (Fig. 2). However, further research and validation studies are required to confirm the clinical applicability and reliability of these miRNA panels in larger patient cohorts and diverse populations.

4.3. *Malaria*

Malaria, caused by Plasmodium parasites, continues to be a major global health challenge, impacting approximately 1 billion people in 85 countries. Each year, malaria leads to an estimated 249 million cases worldwide, with approximately 608,000 deaths [96,97].

Initially malaria triggers excessive production of inflammatory cytokines like TNF-α and IFN-γ, which aim to control the parasite but can also lead to severe malaria. In advanced cases, the infection affects red blood cells, causing anemia and metabolic acidosis. Additionally, severe malaria can damage vital organs such as the brain, lungs, liver, and kidneys [98,99]. Efforts to control malaria include prevention through vector control measures, early diagnosis, and prompt treatment. Research into novel biomarkers and therapeutic targets, such as miRNAs, is essential for improving disease management and outcomes (Fig. 2). Identifying specific molecular markers associated with malaria progression can lead to more targeted interventions and better patient care.

Interestingly, individuals with sickle cell anemia exhibit a certain level of resistance to the malaria parasite *Plasmodium falciparum*, although the exact mechanism has remained elusive. Recent studies have highlighted the potential role of a specific miRNA, miR-451, in this phenomenon. It has been observed that miR-451 is translocated to the malaria parasite during infection of sickle cell anemia erythrocytes. This translocation appears to confer resistance to *P. falciparum* within these cells. Inhibition of miR-451 in HbSS erythrocytes, the sickle cell variant, has been found to increase susceptibility to *P. falciparum* infection. This suggests that miR-451 plays a crucial role in the inherent resistance to malaria observed in individuals with sickle cell anemia [100]. Further research is needed to elucidate the precise molecular pathways and targets influenced by miR-451 in the context of malaria resistance in sickle cell anemia [100].

Recent studies have investigated the expression of specific miRNAs in circulating microvesicles of mice infected with *Plasmodium berghei (P. berghei)*. These investigations revealed alterations in the expression of miR-146a and miR-193b, both implicated in inflammation and immune responses. During *P. berghei* infection, miR-146a is up-regulated, while miR-193b is down-regulated in circulating microvesicles. These changes in miRNA expression suggest their involvement in the development of neurological complications associated with severe malaria. MiR-146a is known to regulate inflammatory responses by targeting molecules such as Toll-like receptors (TLRs), which are key components of the innate immune system [101].

On the other hand, miR-193b is downregulated during infection and plays a role in immune regulation, particularly through the transforming growth factor beta 2 (TGFβ2) signaling pathway. TGFβ2 is involved in regulating various cellular processes, including immune responses and tissue homeostasis. Therefore, the regulation of miR-146a and miR-193b may significantly impact inflammatory processes, thereby contributing to the severity of malaria [101].

In patients infected with *Plasmodium vivax*, several miRNAs, including miR-223, miR-145, miR-155, have been found to be upregulated in plasma compared to healthy controls [102]. MiR-223 is known to modulate immune responses by regulating cellular activation, particularly in the polarization of macrophages into M1 and M2 phenotypes. This upregulation in *P. vivax*-infected patients suggests its involvement in immune modulation during malaria [103]. MiR-145, on the other hand, is associated with attenuating inflammation. In the context of sepsis, miR-145 levels are significantly downregulated, but its upregulation has been shown to attenuate lipopolysaccharide (LPS)-induced inflammation and sepsis-induced lung injury, partly through the TGFBR2/Smad3 signaling pathway. This suggests that miR-145 may play a protective role in mitigating inflammation-associated complications during malaria infection [104].

In patients with cerebral malaria, miR-155 levels are increased. MiR-155 is involved in infection control and neuroinflammation and negatively regulates blood-brain barrier integrity and T cell function [105]. Experimental models of cerebral malaria have shown that pretreatment with an inhibitor of miR-155 improves survival and helps preserve blood-brain barrier integrity.

These findings suggest that miR-223, miR-145, and miR-155 may play crucial roles in the immune response, modulation of inflammation, and malaria pathogenesis. Further research is necessary to elucidate the specific mechanisms and precise roles of these miRNAs in malaria infection. Understanding their regulatory functions could lead to novel therapeutic strategies for managing malaria and its associated complications [106].

In a study by Gupta et al. [107], children with severe malaria exhibited higher plasma levels of miR-3158 and miR-4497 compared to those with uncomplicated malaria. Interestingly, both miRNAs showed a positive correlation with the expression of histidine-rich protein 2 (HRP2), a protein produced by *P. falciparum* during the blood cycle and commonly used as an infection biomarker [108].

This study also identified plasmatic miR-3158 as a promising biomarker of cerebral malaria [107]. The expression levels of miR-3158 were associated with the mortality rate in patients with cerebral malaria and were linked to brain hypoxia pathways, indicating its potential involvement in the disease's pathogenesis. These findings suggest that miR-3158 and miR-4497 may serve as valuable biomarkers for assessing malaria severity and complications. The correlation between these miRNAs and HRP2 levels highlights their potential as indicators of active infection. Additionally, the association of miR-3158 expression with mortality and brain hypoxia pathways underscore its relevance as a prognostic marker and its possible role in the pathophysiology of cerebral malaria [107].

Together, miR-223, miR-145, miR-155, miR-3158, and miR-4497 have significant potential as biomarkers and therapeutic targets in malaria. Their involvement in immune response modulation, inflammation control, and disease pathogenesis offers promising avenues for novel interventions. Further research is essential to fully understand the mechanisms through which these miRNAs function and to develop targeted therapies that can improve malaria management and patient outcomes.

4.4. Leishmaniasis

Leishmaniasis is a disease caused by *Leishmania* parasites, transmitted by infected sandflies [109]. It is a significant public health issue in developing countries, with about 1 billion people at risk and 12 million currently infected. Approximately 2 million new cases and 70, 000 deaths occur annually [110]. The host's immune response to the parasite can lead to chronic inflammation, as the parasite evades immune defenses, resulting in persistent infection [111,112].

Research has shown that *Leishmania* parasites can modify the miRNA profile in human cells. By altering the host cell's miRNA profile, *Leishmania* can potentially shape the immune response, creating a favorable environment for its survival and proliferation. This discovery enhances our understanding of the intricate interactions between host and parasite in leishmaniasis [113,114].

In the context of *Leishmania donovani* infection in human macrophages, it has been observed that the expression of miR-30a increases over time. This up-regulation of miR-30a is associated with a reduction in parasite load, achieved through the regulation of autophagy [115]. These findings indicate that miR-30a could be a promising target for developing new strategies to control the parasite and combat leishmaniasis. On the other hand, *in vivo L. donovani* infection decreases the expression of miR-122 in the liver, a miRNA critical for maintaining hepatic homeostasis. The reduction in miR-122 expression creates a favorable environment for parasite survival [116]. This observation highlights the parasite's ability to manipulate miRNA expression, enabling its own survival and proliferation within the host during visceral leishmaniasis [117].

Through *in silico* analysis of co-cultured $CD4^+$ T cells with *L. donovani*-infected macrophages from mice, dysregulated miRNAs were identified using next-generation sequencing. The study found 11 upregulated and 9 downregulated miRNAs associated with cellular immune responses and the Th1/2 dichotomy. The upregulated miRNAs targeted transcription factors associated with the Th1 phenotype, while the downregulated miRNAs directed cells towards Th2 populations, suggesting that there is a predominance of a Th2 response in donovani infection modulated by miRs [118].

Other studies on the treatment of two *L. infantum* strains with antimonial drugs have also explored miRNA expression. These studies observed an increase in miR-155 during *L. infantum* infection in mouse cells, which contributes to resistance against conventional treatments [119]. Additionally, mice deficient in miR-155 develop less severe diseases caused by *L. guyanensis*, highlighting the potential clinical importance of miRNAs during cutaneous leishmaniasis [120].

Regarding CL, infection of mouse macrophages with *L. amazonensis* increases the expression of miR-294 and miR-721, which are involved in

L-arginine and NOS2 metabolism, thereby promoting parasite proliferation [121]. Additionally, *L. amazonensis* modulates Toll-like receptor (TLR) signaling by altering the expression of let-7e in murine macrophages, enabling the parasite to subvert the host immune response and enhance its survival and persistence [121]. In THP1 lineage macrophages infected with *L. mexicana*, five miRNAs have been identified that inhibit cell death and maintain parasite survival, contributing to the evasion of host immune responses and the establishment of chronic infection [122]. Surprisingly, supernatants enriched with neutrophil extracellular traps (NETs) contain miRNAs that can modulate TNF-α production in macrophages infected with *L. amazonensis*. These findings reveal a novel role for NETs in cellular communication, transferring miRNAs from neutrophils to neighboring cells [123].

Few studies have sought to define the miRNA profile during *L. major* infection in human macrophages. Among these, one study identified 64 miRNAs with significant modulation upon infection. Notably, miR-210 exhibited increased expression in a HIF-1α-dependent manner and was implicated in stress response and signal transduction [113]. Conversely, let-7a was found to be down-regulated at both 24- and 48-h post-infection in human macrophages exposed to *L. major*. This down-regulation was associated with an increase in cellular apoptosis and necrosis leading infection control, once *Leishmania* is known to inhibit cell death to ensure its survival [124,125].

Similarly, *L. major* infection in a mouse peritoneal macrophage cell line resulted in decreased miR-340 expression, promoting parasite survival. This effect occurs because miR-340 knockdown led to increased expression of its targets, IL-10 and TGF-β1, immune regulatory cytokines. Furthermore, transfection of infected macrophages with miR-340 reduced macrophage infectivity, suggesting that miR-340 may be a promising new therapeutic agent for the treatment of cutaneous leishmaniasis [126].

Our research team made a groundbreaking contribution by being the first to investigate the expression profile of miRNAs in lesions of patients with CL caused by *L. braziliensis*. We identified a crucial triad consisting of miR-193b, miR-671, and their target gene TREM-1, which were associated with the healing time. Intriguingly, these associations were observed exclusively in patients whose lesions healed during the initial treatment cycle, up to 59 days after diagnosis. This suggests that the axis miR-193b, miR-671, and TREM-1 holds potential as a prognostic indicator for CL [127]. Another notable finding by Lago et al. demonstrated an induction of miR-361 in *L. braziliensis* lesions. This specific miRNA targets granzyme B and TNF genes, both associated with therapeutic failure and prolonged healing time. This discovery highlights the potential influence of miR-361 in the pathogenesis of CL and its implications for treatment outcomes [128].

More recently, the interplay between cytokines and miRNAs in regulating the host's immune response through the activation of inflammasome during CL was elucidated [129]. This study showed an increased expression of miR-7-5p, miR-133a, miR-146b, miR-223-3p, and miR-328-3p, as well as elevated cytokine levels of IL-1β, IL-6, and IL-17 in patients with CL compared to the healthy controls. These results suggest that these circulating molecules that can help in the diagnosis, prognosis and treatment of leishmaniasis [129].

Regarding parasite control, it was demonstrated that miR-548d is involved in parasite growth and inflammation in CL caused by *L. braziliensis* [130]. This discovery opens exciting avenues for precision medicine and the development of novel treatment strategies for CL.

Overall, these reports contribute to our understanding of the complex immune dynamics and regulatory mechanisms in leishmaniasis (Fig. 2). However, to our knowledge, there are no studies testing the efficacy of miRNAs in experimental models of leishmaniasis. This proof of concept has now become necessary to demonstrate that miRNAs can be used *in vivo* as a therapeutic strategy against leishmaniasis.

4.5. Chagas disease

Chagas disease, a neglected tropical disease caused by the parasite *Trypanosoma cruzi (T. cruzi),* progresses through acute and chronic phases, often manifesting as cardiac, digestive, or a combination of both forms. Cardiomyopathy is the most common presentation. Globally, around 6 million people are infected, and the disease is endemic in 21 Latin America countries, with approximately 30,000 new cases and 12,000 deaths reported annually [131,132].

Although research on the miRNA expression profile during *T. cruzi* infection is still limited, existing studies offer significant insights into the complex molecular mechanisms involved in the disease. There is a notable upregulation of miR-145 and miR-146b in infected cardiomyoblasts, which correlates with a reduction in parasite burden. This observation suggests that these miRNAs could be crucial in the host's defense mechanism, potentially by modulating immune responses or interfering with the parasite's life cycle [133].

The upregulation of miR-145 and miR-146b might influence various cellular pathways, such as inflammation, apoptosis, and cellular proliferation, which are pivotal in the context of infection. For example, miR-146b is known to be involved in the regulation of the immune response and inflammation, possibly helping to control the inflammatory processes associated with *T. cruzi* infection. Similarly, miR-145 has been implicated in cell differentiation and apoptosis, processes that could limit the parasite's replication and spread [133].

Furthermore, these findings underscore the potential therapeutic implications of targeting specific miRNAs. Modulating the levels of miR-145 and miR-146b could emerge as a novel strategy to enhance host immunity and reduce parasitic load, offering a complementary approach to existing treatments [133].

Recent findings emphasize the importance of placenta-specific miRNAs, miR-512 and miR-515, in Chagas disease. MiR-512 promotes trophoblast differentiation by inhibiting c-FLIP, while miR-515 inhibits this differentiation by suppressing hGCM-1. During *T. cruzi* infection, miR-512 levels increase, and miR-515 levels decrease, indicating a potential placental defense mechanism against the parasite. These miRNAs are crucial in mediating the placenta's susceptibility to *T. cruzi*, affecting trophoblast turnover and defense responses [134].

In a study on patients with Chronic Chagas Cardiomyopathy (CCM), the expression levels of six circulating miRNAs (miR-34a, miR-208a, miR-185, miR-223, let-7d, and miR-454) were evaluated. Among these, only miR-223 was associated with improved markers of myocardial function. This association was particularly notable in the left atrium area, in the end-systolic and end-diastolic volumes of the left ventricle, suggesting that miR-223 could serve as a circulating biomarker for heart failure in individuals with CCM [135]. Furthermore, an in-depth analysis of the target genes regulated by miR-223 revealed signaling pathways involving receptor tyrosine kinases, indicating a potential mechanism by which low levels of miR-223 contribute to the progression of CCM. These findings enhance our understanding of the molecular basis of CCM and identify potential therapeutic targets.

Despite recent advances, no miRNA candidate has yet been identified as a biomarker or therapeutic target for pre-clinical studies in Chagas disease. Further research is needed to uncover miRNAs with the potential to diagnose or treat Chagas disease.

4.6. SARS-CoV-2

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, emerged as a public health threat in December 2019 and was declared a pandemic by the World Health Organization in March 2020. The disease exhibits a wide range of clinical manifestations, from asymptomatic to severe cases requiring intensive care [136]. To date, there are 776 million confirmed infections and over 7 million deaths [137].

SARS-CoV-2 can modulate the host's miRNA profile, influencing the host's response to infection and impacting disease progression.

Additionally, miRNAs play a crucial role in regulating viral replication [138–141]. Blocking miR-155 has been shown to mitigate the severe lung cytokine storm induced by SARS-CoV-2. Researchers delivered anti-miR-155 via intranasal injection to SARS-CoV-2-infected mice, successfully suppressing miR-155 expression. This intervention improved survival rates and clinical outcomes, reducing proinflammatory cytokines while increasing antiviral and anti-inflammatory cytokine responses in the lungs. These findings suggest that anti-miR-155 treatment is a promising therapeutic strategy for combating the detrimental effects of the lung cytokine storm associated with SARS-CoV-2 infection [142].

Similarly, COVID-19 patients exhibit a marked increase in the expression of miR-155 in peripheral blood mononuclear cells (PBMCs). This upregulation shows a negative correlation with the expression of SOCS-1, a critical negative regulator of cytokine signaling pathways. The inverse relationship between miR-155 and SOCS-1 suggests that miR-155 may play a significant role in the modulation of the immune response during COVID-19 infection. By downregulating SOCS-1, miR-155 potentially exacerbates the cytokine dysregulation often observed in COVID-19 patients, contributing to the heightened inflammatory response and immune imbalance. This miRNA's involvement in the regulation of immune signaling pathways highlights its potential as a target for therapeutic interventions aimed at reducing the severe inflammatory responses associated with the disease [143].

Another study highlighted the involvement of specific circulating miRNAs in the inflammatory response seen in critically ill COVID-19 patients. Specifically, miR-146a was downregulated, while miR-221 and miR-155 were upregulated. The upregulated miRNAs showed a positive correlation with key components of inflammation, including increased neutrophil counts, suggesting their potential role in modulating the inflammatory cascade associated with severe COVID-19. Moreover, pathway enrichment analysis of the target genes regulated by these miRNAs revealed a strong association with pathways related to inflammation, immune response, vascular diseases, and metabolic disorders. This suggests that SARS-CoV-2 may interfere with these pathways by modulating the expression of these specific miRNAs. The dysregulation of these miRNAs could contribute to the aberrant immune response and dysregulated inflammatory processes observed in critically ill patients with COVID-19 [144].

In a groundbreaking study utilizing transcriptomic analysis, researchers identified miR-2392 as a key regulator driving COVID-19 responses. This miRNA promotes inflammation, glycolysis, and hypoxia, processes known to contribute to COVID-19 pathogenesis. The study confirmed these findings in patients, showing elevated levels of miR-2392 in the blood and urine during COVID-19 compared to healthy controls. *In vivo* and *in vitro* experiments further demonstrated that increased miR-2392 levels induce biological responses similar to those seen in COVID-19 infection. These findings strongly suggest that miR-2392 plays a crucial role in the pathophysiology of COVID-19 [145]. Consequently, pharmacological inhibition of miR-2392 is proposed as a potential antiviral therapy for COVID-19. By targeting and suppressing miR-2392 activity, it may be possible to disrupt viral assembly, attenuate inflammatory responses, and mitigate metabolic dysregulation associated with the disease [145].

Another promising application of miRNAs is their use as markers for disease progression in COVID-19, with miR-200c emerging as a particularly promising indicator. Researchers measured its circulating levels in hospitalized patients at admission and seven days later. Remarkably, miR-200c exhibited a time-dependent increase that correlated with disease severity, regardless of whether patients were in ICU or non-ICU settings. These findings suggest that miR-200c has significant potential as a reliable predictive marker for assessing COVID-19 severity [146]. Additionally, the study observed a noteworthy trend in recovered patients: miR-200c expression decreased following recovery, suggesting that its levels align with disease status. This dynamic expression pattern underscores the potential utility of miR-200c as a marker for monitoring disease progression and recovery in COVID-19 patients [146].

In a recent breakthrough, researchers identified the significant role of miR-144 in the severity and mortality of COVID-19. This miRNA is downregulated in the plasma of hospitalized COVID-19 survivors compared to those who were discharged. This observation suggests that miR-144 expression could serve as an indicator of disease severity and prognosis. By measuring seric miR-144, clinicians may gain valuable insights into potential outcomes and overall prognosis for COVID-19 patients. Furthermore, miR-144′s ability to differentiate between COVID-19 patients and healthy individuals, as well as among different disease severities, highlights its potential as a diagnostic and prognostic tool. MiRNAs, such as miR-144, offer non-invasive and easily accessible biomarkers that could aid in early detection and accurate [147].

Additional research is essential to advance the application of miRNAs in the management of COVID-19. To the best of our knowledge, no studies have yet tested miRNAs as a therapeutic or diagnostic tool for COVID-19 [147]. However, the potential of miRNAs to serve as biomarkers and therapeutic targets holds promise for improving disease outcomes. Understanding and harnessing the specific roles of miRNAs could revolutionize the early detection, monitoring, and treatment of COVID-19, ultimately contributing to better patient care and management.

5. Platforms to analyze miRNAs

The evaluation of interactions between miRNAs and their target genes typically involves examining the pairing between the miRNA seed region with the 5′ and 3′ untranslated regions (UTRs) of the target mRNA. However, this binding is not always as effective, posing a challenge, as animal miRNAs often establish imperfect links with their target sites [9,148]. Different computational approaches have been widely used to indicate pairing strength (Fig. 3). The essential steps for studying miRNAs and comprehending the biological processes they influence include computational identification, prediction of miRNAs and their targets, analysis of canonical pathways, and experimental validation [149–151].

MiRBase (miRBase 21) is the leading online database for miRNA sequences and analysis (http://mirbase.org/). This tool can catalog, name, annotate, and characterize miRNA gene sequences, in addition to identify miRNAs in different species, either at their precursor and mature structure through deep sequencing data. Currently, miRBase is in version 22 and has described miRNAs in 271 organisms, with 48,860 different mature miRNA sequences where 1917 are described in humans.

The tool provides extensive information on published miRNAs, their 3p and 5p sequences, the chromosomes they are located, literature references, experimentally predicted and validated miRNAs, along with literature-oriented annotation. Considering the number of annotations for each miRNA, they can be classified as high confidence. This designation considers at least 10 readings that map each of the two mature sequences (-5p and -3p) of a given miRNA. Alternatively, it should have at least 5 readings mapped for each arm and at least 100 mapped readings in total [149,152,153]. The discovery of high confidence miRNAs highlights the potential participation of this transcript in certain biological contexts, since it is supported by the notes deposited in the database.

Some miRNA tools are designed to predict the potential targets of the miRNAs, moreover, it is possible to select molecules and predict the miRNAs that they can be targeted. Among these databases are: TargetScan [151], DIANA-microT [154], miRDB [155] and miRWalk2.0 [156,157]. In addition, there are target tools with some experimental support, such as DIANA-TarBase [158] and miRTarBase [159]. In addition to others that can contribute to the prediction of canonical pathways involving miRNAs and its targets, such as mirPath [160], Kyoto Encyclopedia of Genes and Genomes (KEGG) [161] and EnrichmiR [162].

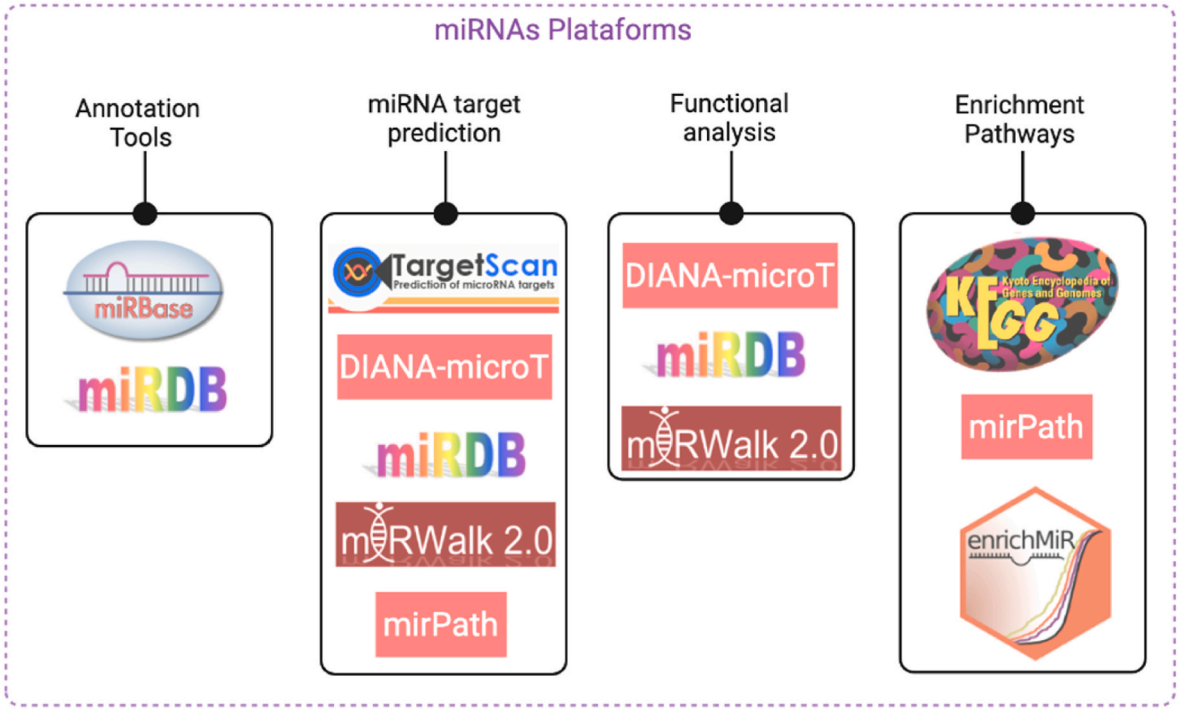

Fig. 3. Tools for predicting targets-associated microRNAs for their targets and pathways.

TargetScan is one of the most used miRNAs targeting platforms in literature. This database predicts biological targets based on the degree of conservation of the miRNAs (conserved, poorly conserved and non-conserved miRNAs), in addition to their interaction with the target via the seed region based on a statistical model that predicts the effects of binding at canonical sites. It allows not only the evaluation of this interaction directly in the program, but also other databases use this database to form more robust bases [151].

Diana-microT is a tool that uses an improved target prediction algorithm, it was created to incorporate data from miRBase and Ensembl predicting *in silico* interactions for miRNA-gene for *Homo sapiens, Mus musculus, Drosophila melanogaster* and *Caenorhabditis elegans*. This tool allows users without robust knowledge in bioinformatics to perform advanced multi-step functional miRNA analyzes in an online web interface [154].

miRDB is a predictive database of miRNA targets and functional annotations. It annotates 3.5 million predicted targets regulated by more than 7000 miRNAs, plus prediction of cell-specific miRNA targets. This database has been constantly updated and has been predictive of miRNA functions by integrative analysis of target prediction and genetic ontology data [155,163].

miRWalk was created to generate possible interactions of miRNA with all regions of a gene, gathering 13 datasets of prediction of pre-existing miRNA targets, it contains not only the predicted targets but also the validated ones, in addition it is a tool with multiple possibilities of analyzes such as integration of miRNAs evaluating genes, epigenomics, pathways, ontologies, protein classes, phenotype, genotype, nucleotide polymorphisms, functional networks, tandem mass spectra and relevant articles from PubMed [156].

DIANA-TarBase and miRTarBase are reference databases dedicated to predicting interactions between miRNAs and their targets with robust experimental support. They integrate information on gene regulation of miRNAs specific to cell types, while hundreds of thousands of miRNA binding sites are reported after literature survey considering functional studies of miRNAs experimentally validated by reporter assay, Western blot, microarray, sequencing generation, RNA expression, protein expression, and biological function for various validation experiments related to the role of miRNA [158,159].

KEGG (https://www.kegg.jp) is a database that integrates various biological processes classified into systems, genomic, chemical and health characteristics. In it, it is possible to find miRNAs in biological networks. More than 99 % of the human pathways evaluated by KEGG contain genes directed by miRNAs or harbor them (host genes). It is also possible to highlight the importance of integrating miRNAs (experimentally validated and predicted) in biological networks to reinforce new biologically important miRNA-mRNA interactions [161,164].

mirPath is a miRNA pathway analysis web server. This platform provides information on polymorphisms (SNPs) at miRNA target sites or to annotate all predicted and experimentally validated miRNA targets in a selected molecular pathway. is a highly specific tool for analyzing miRNA-targeted pathways through a web interface. Recently, a new target-specific enrichment analysis tool for miRNAs, enrichemiR, has emerged. This tool compares a set of genes of interest using the results of a differential expression analysis. In addition, it generates cumulative distribution (CD) plots of warp change comparing targets and non-targets. Similarly, these online tools allow for flexible and real-time analysis for users who do not have training in bioinformatics, since their use is intuitive, and their results are generated with interactive graphics that help in the interpretation of the results [160,162].

6. Obstacles and advances of miRNAs to clinical application

Despite the great advance in the understanding and application of miRNAs, few studies have progressed to clinical trials and none of them have progressed to phase III [165]. There are some obstacles regarding the delivery of miRNAs in therapies: (1) few therapeutic candidates; (2) large amount of endogenous miRNA targets; (3) low binding affinity with its target; (4) degradation of miRNA in delivery (5) control of unexpected and non-specific consequences to the patient and activation of the immune system [165–167].

Part of these limitations can be minimized or overcome by the targeted delivery system, through structural modifications in miRNAs and control of adverse effects through preclinical tests. All these measures will improve miRNA binding with the target and improve the efficiency

of selective delivery to the specific tissue more safely [167].

Currently, miRNA delivery systems have shown encouraging advances. Delivery methods based on lipid, polymeric, inorganic and exosome systems, in addition to viral vectors such as retroviral, lentiviral, adenovirus, adeno-associated and bacteriophage-based vectors, have helped to overcome challenges in this therapeutic approach [168, 169]. Therefore, it is believed that in the coming years assays associated with therapeutic miRNAs will tend to generate more robust and lasting results to the point of establishing themselves in clinical practice and effectively contributing to public health.

7. Conclusion

Considering the advances in the last 30 years of miRNAs, it is safe to predict that these small transcripts may soon assume new positions in human therapeutics. Its tissue stability, the possibility of non-invasive prognosis and diagnosis through the detection of biological liquids, the support of bioinformatics platforms, the wide variety of delivery systems and its endogenous identity are properties that reinforce its potential in clinical medicine. Current trials suggest that miRNAs may be the next-generation drugs through a personalized medicine and able to overcome biological challenges and traditional therapeutic limitations.

Despite recent advancements, no miRNA candidate has yet been established as a primary therapy or integrated with standard treatments. However, the potential of miRNAs in the diagnosis and treatment of diseases is increasingly recognized. Their diverse functions and the complex nature of the diseases they target present challenges and opportunities in their identification, which can serve as first-line treatments. Additional research is necessary to leverage the potential of miRNAs, which hold promise for accurate diagnosis and innovative treatment approaches for infectious diseases.

Funding

This research was funded by FAPESB (Fundação de Amparo à Pesquisa do Estado na Bahia), grant number PET0004/2015 (Edital PROINTER), CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior), financial code 001 and CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico).

CRediT authorship contribution statement

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Declaration of competing interest

All authors declare that they have no commercial or financial relationships that could be construed as a potential conflict of interest disclosure.

Acknowledgments

Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES – Finance Code 001) supported this study. We thank Layse Carvalho and Luana Chaves for secretariat assistance.

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