Bibliographic and bioinformatics analysis of infection-related microRNAs

Tiago Miranda[1], Sónia Silva[2], Bruna Gonçalves[2]

[1] Informatics Department, University of Minho

[2] Centre of Biological Engineering, University of Minho

Abstract. Infectious diseases continue to be a significant global health issue, affecting millions of people each year. The study of microRNAs (miRNAs) has shed light on their crucial role in the pathogenesis and response to infectious diseases. As diagnostic tools, miRNAs provide specific and stable markers that can improve the accuracy of disease detection and monitoring. Their therapeutic potential is also significant, with the possibility of altering miRNA expression to develop new treatments. The increasing investigations on this new field reflect the urgent need to clarify the current knowledge about infection-related miRNAs. In order to address this need, a systematic literature search will be conducted using databases such as Web of Science, PubMed, Embase, Scopus, OVID, Medline, and Cochrane Library. The literature will be managed using Zotero and Rayyan software, and a bibliographic database for infection-related miRNAs will be created following the PRISMA 2020 flowchart. Subsequently, miRNAs will be retrieved from the selected literature, and their bioinformatics analysis will be performed using web-based resources including miRBase, miRTarBase, Metascape, and DIANA-miRPath. The culmination of this research is the creation of a bibliographic database and the bioinformatics analysis of selected data aiming to clarify the current knowledge on infection-related microRNAs.

1. Introduction

1.1 Infections in humans

Throughout history, infectious diseases have ravaged humanity, causing widespread death through epidemics and everyday illnesses. Thankfully, since the groundbreaking discovery that microorganisms cause many diseases, significant progress has been made. It is now understood how pathogens behave and revolutionary strategies have been developed to combat them. These advancements include improved hygiene practices, vaccines for prevention, diagnostic tests for accurate identification, and powerful antimicrobials for treatment. As a result, the burden of infectious diseases has significantly decreased, and some have even been completely eradicated [1].

While advancements in medicine have led to significant progress in controlling some infectious diseases, others continue to pose a significant threat to global health. This challenge is multifaceted. It includes a wide range of illnesses caused by various pathogens, such as fungi (e.g. candidiasis), bacteria (e.g. pneumonia), viruses (e.g. influenza, HIV, HPV) and parasites (e.g. malaria). Infectious diseases claim millions of lives worldwide every year [2]. Over the past few decades, new hurdles have emerged: the rise of novel diseases, the wider spread of existing pathogens, the development of drug-resistant strains, and even the resurgence of previously controlled diseases due to gaps in public health coverage [1].

Therefore, combating infectious diseases remains a high priority in the 21st century. A multi-pronged approach that leverages new methods for tracking is urgently needed, preventing, diagnosing, and ultimately treating infections.

1.2 MicroRNAs

MicroRNAs (miRNAs) are a fascinating class of molecules found in most eucaryotes, including humans. Though they don't code for proteins (hence the term "non-coding RNA"), they act as master regulators, influencing how genes are expressed. They are produced from DNA and go through a maturation process, ending up as single-stranded RNA molecules of around 22 nucleotides long [3] (Figure 1).

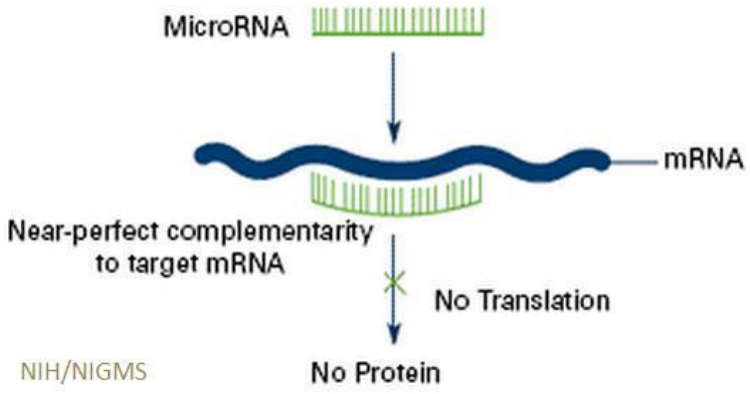

Figure 1 – MicroRNAs stick to mRNA molecules and prevent the mRNAs from being translated into proteins [4].

These tiny regulators interact with messenger RNA (mRNA), the molecule that carries the instructions for protein building. Primarily, miRNAs bind to the 3' untranslated region (UTR) of target mRNAs. This interaction can either lead to the degradation of the mRNA or prevent it from being translated into protein (Figure 1). But miRNAs can be more versatile than that. Under certain conditions, they can also activate translation or even regulate transcription, the initial step of gene expression. The effectiveness of this interaction depends on various factors, including where miRNAs are located within the cell, how abundant they are, and how strongly they bind to their target mRNA. Interestingly, miRNAs can even be released from cell vesicles, acting as chemical messengers for cell communication [5].

The importance of miRNAs extends far beyond the basic cellular machinery. They play a crucial role in shaping cell differentiation and development. When their expression goes awry, it can be linked to various diseases, including cancers, immune disorders, and infections. They are even involved in how our bodies adapt to environmental stresses like exposure to harmful microbes. Studies have shown that miRNAs are part of the defense system against bacteria, with some bacteria even influencing miRNA activity to manipulate host cells [3].

1.3 Applications of miRNAs

MicroRNAs, are small yet highly conserved molecules that wield significant influence in regulating gene expression. They operate post-transcriptionally, affecting messenger RNA (mRNA) by either degradation or inhibition of translation into proteins. With the capacity to impact at least 30% of human genes, miRNAs present a potential target for therapeutic intervention. Their regulatory functions extend across diverse cellular processes, spanning from immune system modulation to cell death regulation and even tumor formation. Remarkably, certain miRNAs exhibit dual roles, acting as either oncogenes or tumor suppressors depending on the cellular context [6]. This inherent regulatory capacity of miRNAs in the immune system has spurred interest in exploring their potential for combatting infections. Given their ability to modulate the immune response, scientists are investigating whether manipulating miRNAs could offer a novel strategy for infection control and minimizing tissue damage, particularly in immunocompromised individuals. Delving deeper into the specific roles of miRNAs within the immune system holds promise for the development of miRNA-based targeted therapies at combating life-threatening infections. Such advancements could significantly enhance our arsenal against pathogens and improve outcomes for affected individuals [7].

1.3.1 Therapeutic

The discovery of miRNAs just two decades ago has opened exciting possibilities in medical research. They hold immense promise as potential cures or treatments for various diseases, with the success of Miravirsen, the first miRNA-based drug for hepatitis C, serving as a prime example [8]. However, developing miRNA-based therapeutics faces challenges due to their unique structure, requiring innovative approaches for effective delivery within the body [8].

While miRNA research is still evolving, their role in regulating gene expression opens doors for therapeutic applications. Disruptions in miRNA function are linked to a wide range of diseases [7, 9]. By manipulating miRNA expression or function, we can potentially develop new treatment strategies. For example, delivering synthetic miRNAs (mimicking tumor suppressor miRNAs) or miRNA inhibitors (silencing oncogenic miRNAs) could regulate cellular processes gone awry in diseases [5, 9].

1.3.2 Diagnostic and prognostic

Early disease detection is crucial for improving treatment outcomes. Altered levels of circulating miRNAs can serve as promising diagnostic and prognostic markers, helping predict treatment efficacy and the risk of disease recurrence [10]. This allows doctors to tailor treatment plans based on individual patient needs and monitor their response to therapy more effectively.

Beyond their cellular functions, miRNAs are emerging as powerful tools for diagnosing and monitoring human diseases like cancers, diabetes, infections, heart problems, and neurodegenerative diseases [7, 9]. Their unique properties make them ideal candidates for biomarkers. Unlike traditional methods, miRNAs offer high specificity and can be easily accessed from various bodily fluids like blood through non-invasive biopsies. Additionally, they are remarkably stable within these fluids, ensuring their integrity during analysis [11].

The potential of miRNAs as biomarkers was first realized in cancer research in 2008, where they were used to detect diffuse large B-cell lymphoma in patient serum [12, 13]. Since then, their potential has been explored in numerous other diseases, including diabetes, heart disease, and viral infections [14, 15, 16]. However, identifying a single, unique miRNA signature for each disease might be challenging. Researchers suggest analysing a panel of circulating miRNAs for a more practical approach. Large-scale studies using diverse patient populations and well-defined miRNA panels are necessary to validate this approach [16].

This stability and accessibility are crucial factors that pave the way for their application in medicine. Specifically, miRNAs have shown promise in pinpointing the onset and progression of various diseases. Studies have revealed that levels of specific miRNAs fluctuate in response to disease development and treatment, making them accurate diagnostic tools [17, 18, 19].

For example, miRNA expression profiles can effectively differentiate between healthy and tumor tissues, with the ability to identify the stage of diseases like melanoma (a type of skin cancer) [5]. This sensitivity enables the prediction of disease progression, informs treatment decisions such as selecting the most effective drugs, and facilitates the monitoring of patient response to therapy [17, 18, 19].

In conclusion, miRNAs are revolutionizing medicine in two significant ways: as potential therapeutic targets and powerful diagnostic tools. Their unique properties make them highly attractive for both applications. With ongoing research and development, miRNA-based therapies and diagnostic panels hold the potential to greatly enhance disease management and improve patient outcomes [20].

1.4. MiRNAs bioinformatics databases

Various bioinformatics databases support the analysis of molecular data, particularly miRNAs. Among them, MiRBase stands out as a comprehensive repository for miRNA sequences and annotation. It offers a plethora of information on microRNAs, including sequences, biogenesis details, genomic coordinates, literature references, and community annotations. Moreover, MiRBase serves as a gateway to external resources, providing access to predicted and experimentally validated miRNA targets. Researchers rely on MiRBase for post hoc analyses and quality assessment of miRNA data, making it a fundamental tool in miRNA research [21]. In parallel, miRTarBase focuses on experimentally validated miRNA-target interactions (MTIs), offering researchers a reliable database of MTIs curated from the scientific literature. Employing natural language processing (NLP) techniques,

miRTarBase systematically filters research articles related to miRNA function studies. With over three hundred and sixty thousand validated MTIs, miRTarBase ensures the integrity and accuracy of its data through rigorous experimental validation methods such as reporter assays and next-generation sequencing. Continuously updated, miRTarBase remains at the forefront of miRNA research, providing the most current and comprehensive collection of validated MTIs [22].

Additionally, DIANA-miRPath provides advanced miRNA pathway analysis capabilities. It enables researchers to analyze predicted or experimentally validated miRNA interactions and perform sophisticated merging and meta-analysis algorithms. With features like hierarchical clustering of miRNAs and pathways, heat map visualization, and SNP identification in miRNA binding sites, DIANA-miRPath facilitates in-depth exploration of miRNA-mediated pathways and their biological implications [23].

Metascape is a bioinformatics tool for gene list analysis, offering features like Batch Analysis and comprehensive gene annotation services. MSBio platform provides tools like Docker & Singularity. Over 5600 studies have been facilitated by its publication [24].

Overall, these bioinformatic databases and tools play integral roles in advancing our understanding of miRNA biology and its significance in various biological processes and diseases.

1.5. Systematic literature search

Systematic literature reviews are essential in all areas of Investigation, particularly in fields like medical science. They aim to identify, evaluate and summarize the findings of all studies over a health-related issue, thereby making the available evidence more accessible to researchers and decision makers. A systematic literature search is a crucial step in conducting a systematic literature review. This process involves utilizing various databases such as Web of Science, PubMed, Embase, Scopus, OVID, Medline, and the Cochrane Library. These databases allow researchers to retrieve literature indexed within them, applying filters such as keywords and publication dates to narrow down relevant studies [25]. Following the search, retrieved literature can be managed using bibliographic management software like Zotero and Rayyan.

Once the literature is gathered, the selection process typically follows PRISMA flow chart guidelines. The flow diagram depicts the flow of information through the different phases of a systematic review (Figure 2). It maps out the number of records identified, included and excluded, and the reasons for exclusions. The steps of PRISMA diagram (Figure 2) ensure a meticulous selection of literature relevant to the research question [27].

The PRISMA analysis follows a structured process divided into three key steps. Firstly, in the identification phase, database searches are conducted meticulously, with each database searched individually and comprehensive inclusion of search terms and limits. Secondly, in the screening phase, duplicates are removed to maintain data integrity. This is followed by title and abstract screening to identify relevant articles. Full texts are then retrieved, and eligibility is assessed, with excluded articles documented for transparency. Lastly, in the inclusion phase, the number of included studies is determined, ensuring transparency and reliability through thorough documentation [28].

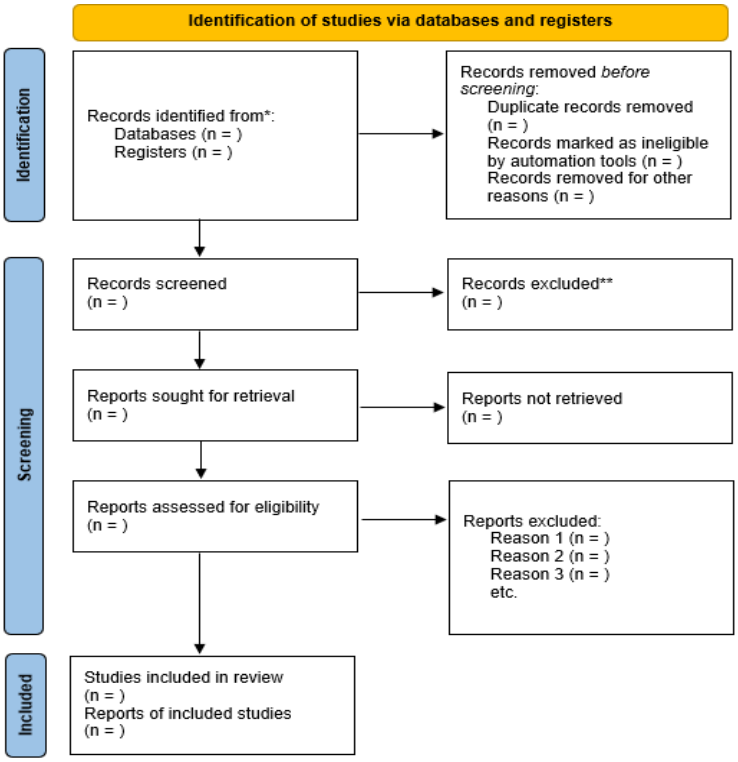

Figure 2 – The PRISMA 2020 flow chart for systematic reviews [26].

1.6. Objectives

Human cells respond to diseases like cancer, diabetes, and infections by producing various molecules, including microRNAs (miRNAs). Among these, miRNAs related to infectious diseases caused by fungi and bacteria are of particular interest due to the significant treatment challenges they present and their association with high mortality rates. The increasing investigations on this new field reflect the urgent need to clarify the current knowledge about infection-related miRNAs.

In order to clarify this knowledge, several bioinformatics databases and tools will be explored. Bioinformatics experts have developed biological databases and bioinformatics tools that allow extracting and analysing information from a large amount of data of interest.

The project aims to create a comprehensive bibliographic database and conduct bioinformatics analyses on selected data, by synthesizing information from diverse sources and employing advanced computational techniques, the project seeks to elucidate the current state of knowledge regarding infection-related miRNAs.

The project will have 2 main tasks:

- Systematic literature search using databases such as: Web of Science, PubMed, Embase, Scopus, OVID, Medline and Cochrane Library. Management of literature in Zotero and Rayyan software and creation of a bibliographic database for infection-related miRNAs, through the selection of literature following PRISMA 2020 flowchart.
- Retrieval of miRNAs from the selected literature and their bioinformatics analysis using web-based resources such as: miRBase miRTarBase, Metascape and DIANA-miRPath.

5. References

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