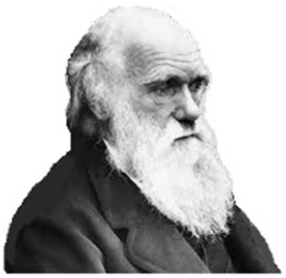
Available online at www.worldnewsnaturalsciences.com



World News of Natural Sciences

An International Scientific Journal

WNOFNS 44 (2022) 24-42 EISSN 2543-5426

MicroRNA and Immune Response to Viral, Bacterial and Fungal Infections

Oluwafemi Ojo Agosile[1], Utibe Benson[2], Ugochukwu Oduwe[3], Nyerovwo Charity Okei[4], Sunday Joseph Fajobi[5], Sunday Onyedikachukwu Akachukwu[6], Bolaji Oyenike Oyetayo[7], Akinwale John Faniyi[8], Prisca Chinonso Njoku[9], Abolaji Samson Olagunju[10,*]

[1]Department of Biochemistry, Adekunle Ajasin University, Akungba-Akoko, Ondo State, Nigeria
E-mail address: agosileoluwafemi@gmail.com

[2]Department of Medical Laboratory Science, Rivers State University, Port Harcourt, Rivers State, Nigeria
E-mail address: queen.isijola@gmail.com

[3]Department of Medical Laboratory Services, University of Benin Teaching Hospital, Benin-city, Edo State, Nigeria
E-mail address: oduweugo@gmail.com

[4]Department of Biological Sciences, University of Camerino, Camerino Macerata, Italy
E-mail address: okeicharity@gmail.com

[5]Department of Pharmacology, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria
E-mail address: sundayjoseph3030@gmail.com

[6]Department of Microbiology, University of Nigeria, Nsukka, Enugu State, Nigeria
E-mail address: akachuks05@gmail.com

[7]Department of Pharmacology and Therapeutics, University of Ibadan, Ibadan, Oyo State, Nigeria
E-mail address: bolajioyetayo709@gmail.com

[8]Department of Medical Laboratory Science, Ladoke Akintola University of Technology, Ogbomosho, Oyo State, Nigeria
E-mail address: faniyiakinwale2014@gmail.com

[9]Department of Biochemistry, University of Lagos, Lagos, Nigeria
E-mail address: priscanjoku0@gmail.com

[10]Department of Immunology, Institute of Biomedical Science, University of Sao Paulo, Brazil
*E-mail address: abolajisamson05@gmail.com

(Received 12 June 2022; Accepted 06 July 2022; Date of Publication 07 July 2022)

ABSTRACT

Several kinds of microRNA have been studied as prospective biomarkers in the pursuit of better diagnostics tests for infectious diseases. miRNA which is processed mostly from introns plays a significant role in gene expression involving cell differentiation, proliferation, apoptosis, metabolism, and immune response. Many miRNA mimics or inhibitors are in their clinical phases and advancement in RNA interference will make miRNA become effective tools in the treatment of human infectious diseases. miRNA has been discovered to be largely involved in viral gene regulation as well as the change of host cellular genes during viral infections. The role of miRNA in most bacterial infections has not been thoroughly explored compared to viral infections. Recent studies have highlighted the vital role of host immunity against bacterial infections. miRNA that is sequenced due to fungal infections bear a close similarity to those produced in response to allergy or inflammation. Host-derived miRNA plays a vital role in immune regulation; inflammatory responses may be enhanced or inhibited by its upregulation or downregulation. Here, we outlined the involvement of microRNA in viral, fungal, and bacterial infections and the immune response associated. Further studies on these, will provide advanced diagnostic and treatment protocols for infectious diseases.

***Keywords*:** microRNA, miRNA, infectious disease, introns, immune response

1. INTRODUCTION

MicroRNA (miRNA) is an RNA sequence with 22 nucleotides that regulates how genes involved in the synthesis of proteins are expressed. It was found in 1993 by Ambros and associates while seeking to understand the underlying mechanisms of gene regulation in nematodes, which they assumed were unique to nematodes [1]. Non-coding RNAs consisting of 22 nucleotides make up miRNAs. The majority of miRNAs are produced from DNA sequences into primary miRNAs (pri-miRNAs), which are then converted into precursor miRNAs (pre-miRNAs) and mature miRNAs by RNA polymerase II. In the majority of cases, miRNAs and the 3′ UTR of target messenger RNAs (mRNAs) interact to inhibit expression. Nevertheless, additional areas, such as the 5′ UTR, coding sequence, and gene promoters, have been found to interact with miRNAs. MicroRNAs (miRNAs, miRs) are small single-stranded RNA molecules that can trigger and control gene expression.

They have broadened our understanding of gene expression [2]. Similar to how the RNA interference pathway works, miRNAs stop translation by binding to complementary sequences in the 3′ untranslated regions of mRNA transcripts [3]. miRNAs modify protein production after the transcription of a gene. After a gene is transcribed, miRNAs alter protein synthesis. Despite the fact that the discovery of miRNAs is still in its early stages, it is obvious that miRNAs are significantly involved in gene regulation. Cell differentiation, proliferation, apoptosis as well as metabolism, and immune response are controlled by miRNAs [4][5]. Predictably, pathogens have developed mechanism that enables them to subvert the immune response by exploiting host miRNAs [6]. The discovery of the importance of miRNAs' physiological functions in immunity has facilitated the development of miRNA-based testing and treatments [7].

Infectious diseases are oftentimes referred to as transmissible/communicable diseases that are caused as a result of infection, presence, and pathogenic agents' growth or its toxic products existing in a host organism with the evidence of illness (disease symptoms) [8].

They are caused by disease-causing agents known as pathogens, which can be transmitted by various means such as through inhalation, physical contact, contamination of food, body fluids, or objects. Infectious pathogens include prions, living parasites (protozoa and helminths), bacteria, fungi, and nonliving viruses [9].

Many classes of miRNA have been investigated as possible biomarkers to improve diagnostic procedures for infectious disorders [10]. Their functions in protozoan, bacterial and viral infections are well understood than ever and how they regulate proteins that are associated with innate and adaptive immune when an infection occurs. Studies have shown dysregulation of miRNA levels during infections [11].

miRNAs are gaining substantial recognition in their clinical application in managing infectious diseases. This review summarizes the manner of alteration and the participation of the host immune cells during bacterial, viral, and fungal infections are summarized in this article. Finally, we look at how miRNAs might be used as diagnostic indicators and therapeutic targets, as well as the challenges that miRNA research faces.

Biogenesis of MicroRNA

In the synthesis of miRNA, RNA Polymerase II/III genes are processed post- or co-transcriptionally [12]. Most of the miRNAs identified originate from introns with a few having protein-coding regions of exon origin. These miRNAs are usually intragenic while a few remainders are transcribed independently; intergenic genes that do not have a host gene and are controlled by their promoters [2]. miRNAs are considered family if the transcription occurs as one long transcript referred to as a cluster. This cluster may have a similar seed region [13]. Canonical and non-canonical miRNA biogenesis are the two types of miRNA biogenesis.

The canonical pathway involves the use of a microprocessor complex composed of the RNA binding protein DiGeorge syndrome critical region 8 (DGCR8) and the ribonuclease (III) enzyme Drosha to generate pri-miRNA. The pri-mRNA produced from the gene is then processed into pre-miRNA [14]. DGCR8 recognizes N6 methylated GCAC and other patterns in pri-miRNA, while Drosha, a nuclear RNase III, cleaves the primary miRNA complex at the base of its hairpin structure, bringing about the formation of pre-miRNA [15]. The pre-miRNA is subsequently carried to the cytoplasm by an exportin 5(XPOR)/RanGTP complex, where it is converted by the RNase III endonuclease Dicer into a 22-nucleotide long miRNA duplex [16]. The various proteins actively involved in the canonical pathway, primarily Dicer, Drosha, Exportin 5, and AGO2, are integrated with the production of miRNA in the non-canonical pathway. The Drosha/DGCR8-independent pathway and the Dicer-independent pathway are two types of this pathway (Figure 1).

Infectious Diseases

Infectious diseases are oftentimes referred to as transmissible/communicable diseases that are caused as a result of infection, presence, and pathogenic agents' growth or its toxic products existing in a host organism with the evidence of illness (disease symptoms) [8]. They are caused by disease-causing agents known as pathogens, which can be transmitted by various means such as through inhalation, physical contact, contamination of food, body fluids, or objects. Infectious pathogens include prions, living parasites (protozoa and helminths), bacteria, fungi, and non-living viruses [9]. The understanding of factors that facilitates transmission helps to mitigate and control the spread of infectious diseases.

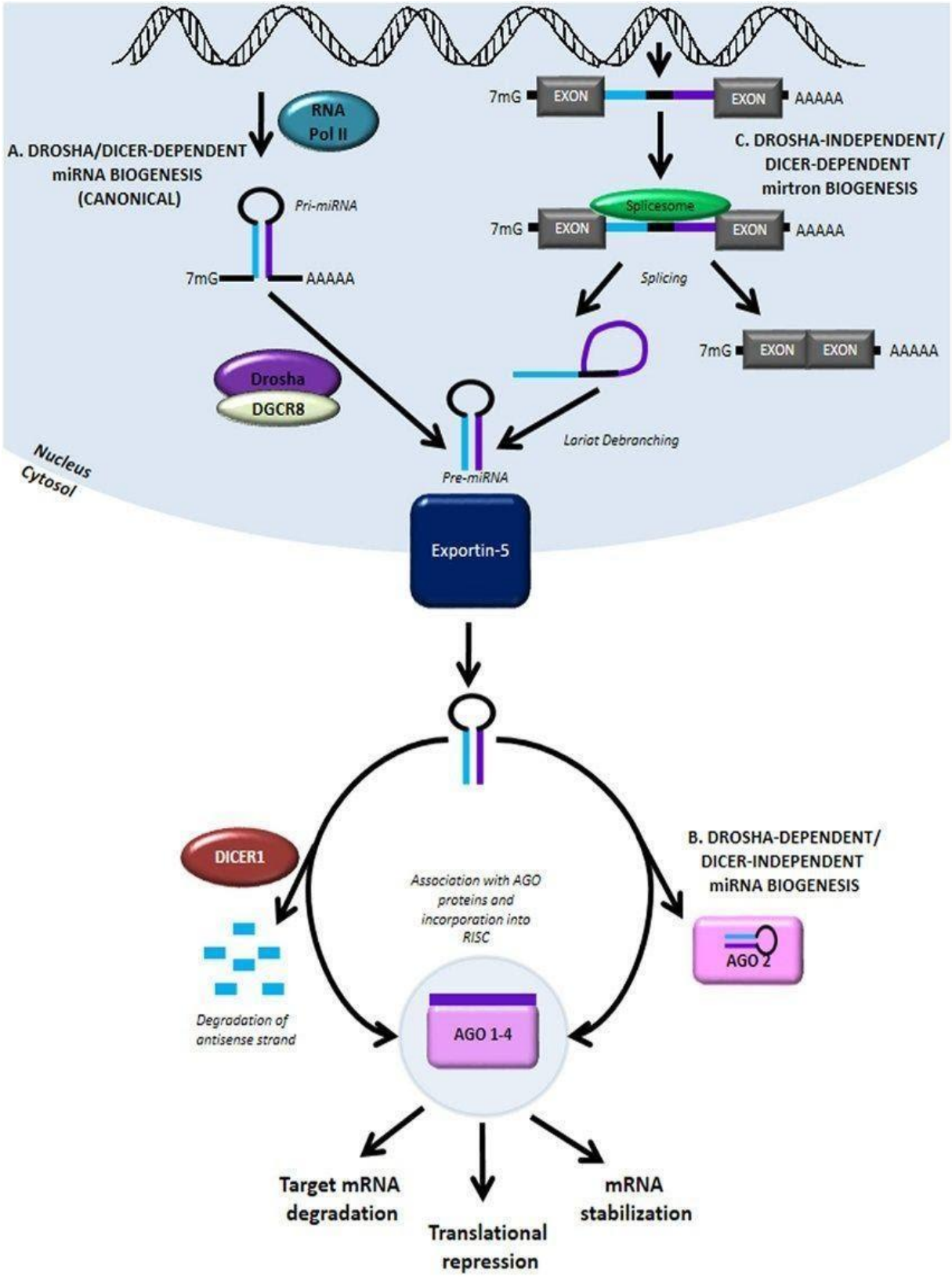


Figure 1. Canonical and Non-canonical pathway [17].

Infectious diseases are termed contagious when a non-infected person is more prone to infection when exposed to a carrier of the pathogen or its secretions (e.g., influenza). Contagiousness does not apply to other modes of infection, such as vector/sexual transmission (Figure 2).

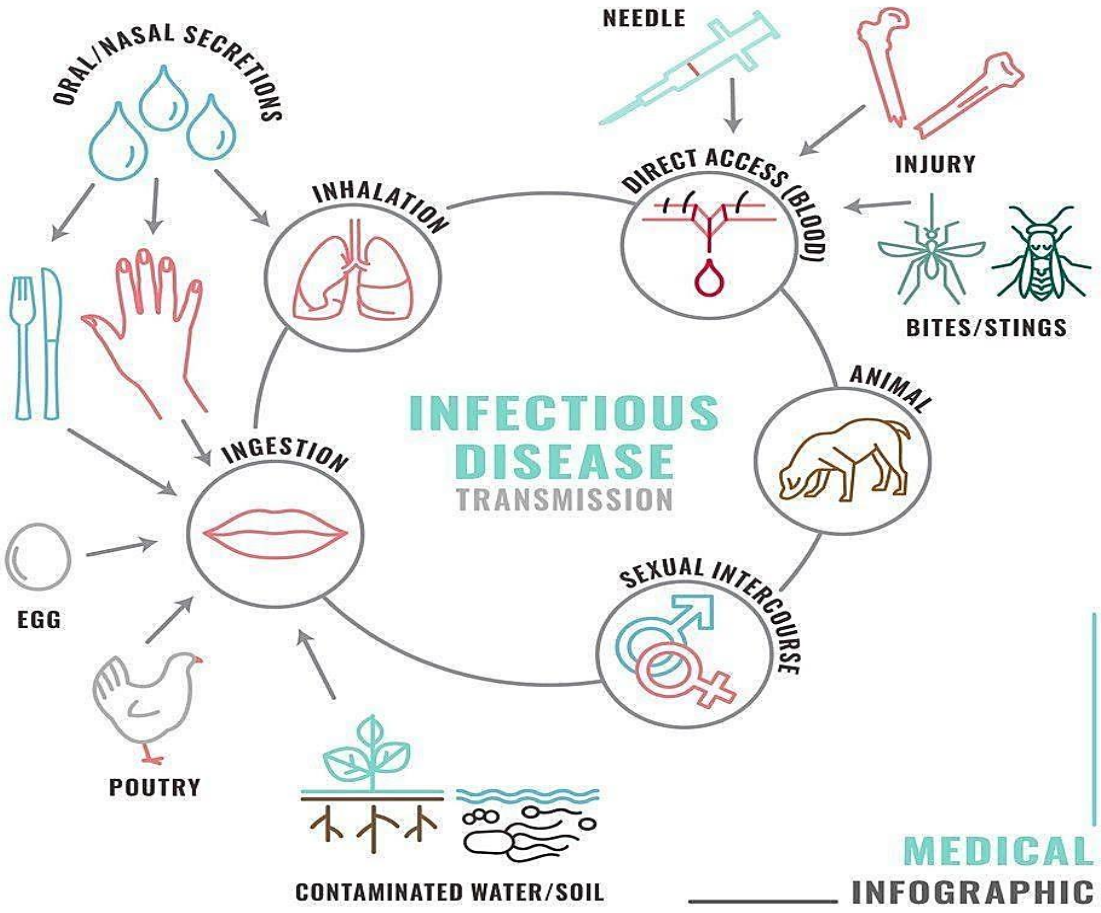


Figure 2. Mode of Transmission of Infectious Disease [18].

Infectious agents are transmitted from a natural reservoir to a susceptible host through various means. They are classified under two major modes, the direct and indirect modes [19]. Direct transmission occurs when the pathogenic agent is transferred directly, mode of direct transmission include physical contacts, droplet transmissions or aerosols and vertical (trans-placental /congenital) or perinatal transmission while indirect transmission takes place when there is a medium of transfer between the reservoir and the susceptible host and can be categorized into three[20]: biological(when a pathogenic agent grows and multiplies in a biological vector (intermediate host), mechanical(when a pathogen is transferred physically by a living entity (mechanical vector) or vehicle (non-living) to a susceptible host and does not need the pathogen to grow or multiply within an organism) and airborne(through the release of

particles containing infectious agents or evaporated aerosol droplets in aerosols suspension a long distance and still retain the ability to infect).

MicroRNA in Infectious Diseases

Infectious diseases are responsible for 15 percent of death globally [21]. Many classes of miRNA have been investigated as possible biomarkers to improve diagnostic procedures for infectious disorders [10]. Their functions in protozoan, bacterial and viral infections are well understood than ever, and how they regulate proteins that are associated with innate and adaptive immune when an infection occurs. Studies have shown dysregulation of miRNA levels during infections [11]. For example, *Listeria monocytogenes* (*L. monocytogenes*) infection in epithelial cells altered the regulation of miR-145, miR-155, let-7a1, miR-16, miR-146b [22]. miRNA such as miR-448, miR-431, miR-351, miR-296, and miR-196 are frequently modified in hepatitis C virus (HCV) infection of the liver [23]. Let-7 targets NF-kB inhibitor A20 modify the immune response of macrophages to *Mycobacterium tuberculosis* (Mtb) infection [24]. In drug development, miRNAs are now been used as therapeutic agents because their small sequences are normally conserved in many species [25]. These therapeutic agents are either mimics or inhibitors of naturally occurring miRNAs [11]. For instance, miR-122 enhances the stability of the RNA genome of HCV thereby increasing the production of the HCV virus. Administration of 16-nt is complementary to the 5' -end of miR-122 lowered the population of the virus and damage to the liver of mice [26]. Mice inflammatory responses to endotoxin were enhanced by the administration of exosomes containing miR-155 and miR-146a *in vivo* [27]. Many miRNA mimics or inhibitors are currently in clinical trials, and advances in RNA interference will enable miRNA to be used as useful therapeutic tools in the management of human infectious diseases [11].

MicroRNA in Bacterial Infections

Bacteria have developed intricate strategies to exploit miRNAs of the host to produce an immune-tolerant condition and alter the immune mechanism of the host to their advantage thereby enhancing its survival rate and latency/persistence. miRNAs are an important aspect of an efficient immune response from the host's perspective, as they are involved in infection control and clearance [28]. Macrophages, lymphocytes, neutrophils, and innate lymphoid cells are host immune cells that use phagocytosis, secretion of cytokines, and generation of inflammatory responses to identify, process, and remove invading bacteria. Pathogen-associated molecular patterns (PAMPs) bind to NOD-like receptors (NLRs), Toll-like Receptors (TLRs), and other pattern-recognition receptors (PRRs) to trigger multiple inflammatory signals that finally result in the production of pro-inflammatory cytokine or apoptosis. As soon as the intruders have been removed, negative immunoregulatory cytokines and Th2 cells will take up the function of controlling the degree of immunologic reaction to elicit minimal allergies and reduced damage to the tissue [5]. Using disease-causing pathogens such as *Salmonella enterica, Salmonella Typhimurium, Helicobacter pylori (H. pylori), Mycobacterium tuberculosis, Listeria monocytogenes*, and others, the potential of bacterial pathogens to modify host miRNAs has now been well understood and experimentally proven [29].

H. pylori have a high ability to colonize the human stomach and is consequently responsible for a variety of gastrointestinal disorders around the world, including peptic ulcers,

gastritis, and gastric cancer [30]. Infection of epithelial cells of the stomach with *H. pylori* has been reported to alter in miRNA expression including miR-146a, miR-16, miR-155, miR-152/miR-200b, miR-1289, miR-210, miR-30b, and let-7 [5]. In patients infected with *H. pylori*, a histological investigation revealed upregulation of miR-155 in sections of mucosal tissue. In the BIC/miR-155 promoter, potential binding sites for activator protein-1 (AP-1) and nuclear factor-B (NF-B) have been found, and both AP-1 and NF-B are necessary for the induction of miR-155 in gastric epithelial cells during *H. pylori* infection [31]. Because Th17 responses and pathogen-specific T helper type 1 (Th1) were defective in miR-155 knockout mice, they were unable to manage infection of *H. pylori* and have minimal protection from infection following *H. pylori*-specific vaccination than wild-type mice [5]. CTB-UE, a multi-epitope vaccination, may alleviate stomach inflammatory responses during *H. pylori* infection by the upregulation of miR-155 and the inhibition of Th17 responses [32]. miR-146a is another miRNA that had been demonstrated to be overexpressed during infection caused by *H. pylori* in gastric mucosal tissues, gastric epithelial cells, and in an NF-κB-dependent manner.

According to other studies, *H. pylori* infection triggers the overexpression of miR-146a resulting in decreased production of prostaglandin-endoperoxide synthase 2 (PTGS2) [5]. Mechanistically, the virulence factor of *H. pylori* CagA was discovered to be a key factor in alterations of miRNA expression induced by *H. pylori*, 61 miRNAs were variably expressed in a CagA-dependent manner. miR-320 and miR-370, two tumor-suppressing miRNAs were also found to be down-regulated by CagA [33].

The Mycobacterium genus contains virulent pathogens that cause diseases that continue to be serious public health concerns [28]. Mycobacterium contains extremely pathogenic species such as *Mycobacterium leprae* (*M. leprae*) the organism that causes leprosy and *Mycobacterium tuberculosis* (*M. tuberculosis*) which causes tuberculosis, as well as opportunistic pathogens like *Mycobacterium avium* (*M. avium*), which can affect immunocompromised people [33]. Various cellular models, experimental settings, and Mycobacterium species have been used by several studies to investigate miR-155's role and regulation in mycobacterial infection [34]. miR-155 enhances the survival and function of specific T-cells and that of infected macrophages, allowing for an efficient adaptive immune response by the secretion of cytokines needed to fight infection [35]. The activation of miR-27b in murine macrophages because of M. tuberculosis infection is another example of a miRNA's dual participation in infection [36].

A relationship has been established between Mycobacterium species pathogenicity, tumor necrosis factor (TNF) production, and differential regulation of miR-125b and miR-155, according to a new study. miR-125b targets TNF-mRNA directly, but miR-155 may increase the production of TNF through its target SHIP1, a negative regulator of the PI3K/AKT pathway. Lipomannan, a component of the cell wall of bacteria, stimulates cells either from *M. tuberculosis* or *Mycobacterium smegmatis* (*M. smegmatis*) strain, causing negative effects on TNF-synthesis. Lipomannan from *M. tuberculosis* impedes TNF-synthesis, whereas lipomannan from *M. smegmatis* enhances it. *M. tuberculosis* produces a lot of miR-155 but very little miR-125b, while *M. smegmatis* produces a lot of miR-125b but very little miR-155 [37]. It has been established that the miRNA response to Mycobacterium spp. is dependent on the cell environment and bacterial type. For instance, miR-21, miR-142-3p, and miR-29a levels were reported to upregulate in serum of patients with tuberculosis and infected macrophages while they are decreased in the peripheral blood samples and $CD4^+$ T-cells of tuberculosis-infected patients [33].

The intracellular bacteria *Listeria monocytogenes* (*L. monocytogenes*) creates severe sickness in immunocompromised people and pregnant women. In certain cells, *L. monocytogenes* may hijack miRNA-mediated host defense. Following Listeria infection in epithelial cells, miR-155, miR-146b, miR-16, miR-145, and let-7a1 were highly dysregulated. *L. monocytogenes* caused considerable changes in macrophage's miRNA expression, according to [38]. The most changed miRNAs were miR-146a, miR-125a-3p/5p, miR-155, and miR-149. The TLR2 axis was discovered to be regulated by miR-125a-3p/5p, while NF-B p65 affected the transactivation of miR-155 upon infection [5]. Lind et al. also discovered that cytotoxic T cells lacking the miR-155 gene were insensitive to AKT signaling after TCR cross-linking responses to *L. monocytogenes* infection. This suggests that proper CD8+ T-cell response stimulation requires miR-155[39]. By targeting IFN-γ, miR-29 reduced immunological responses to *L. monocytogenes* infection in CD4+ T cells, CD8+ T cells, and natural killer cells. miR-21, on the other hand, inhibited the uptake of listeria monocytogenes in macrophages, allowing infection to be controlled [5].

Salmonella is a Gram-negative intracellular bacterium that belongs to the Enterobacteriaceae family that causes gastroenteritis and typhoid fever in people and animals [40]. The role of miRNA dysregulation in disease etiology has been discovered in studies. *Salmonella typhimurium (S. typhimurium)* infection enhanced the production of miR-29a, which then targeted Caveolin 2, a tight junction factor connected to bacterial pathogen absorption, to change the activation state of the small Rho GTPase CDC42 [5]. In *S. typhimurium*-infected zebrafish embryos, the introduction of some members of the apolipoprotein gene were inhibited by miR-146.

This suggests that during inflammation, miR-146 may be involved in the regulation of lipid metabolism [41]. When Salmonella was infected, TLR4 detection of bacterial LPS reduced the expression of let-7 miRNAs. The expression of important cytokines IL6 and IL-10 was boosted when these miRNAs were downregulated [5]. Maudet *et al.*, argued that miRNAs are possible modulators in infection caused by *S. typhimurium* and that different miRNAs impede different stages of infection using a mix of high screening with a collection of miRNA mimics and RNA-seq. They also discovered that when Salmonella infection was present, a decrease in the miR-15 increased the cyclin D1expression. Salmonella replication in hosts was greatly boosted when host cells were inhibited at the G2/M phase [42]. Furthermore, miR-155 inhibited both lymphocytes and dendritic cells' function resulting in a reduction in immunological responses overall. miR-155-deficient mice were not protected from virulent *S. Typhimurium* after being vaccinated with an engineered vaccine [5]. Macrophage colony-stimulating factor (M-CSF, CSF1) is a cytokine that attracts macrophages to the site of infection in other to help fight the disease. Intestinal epithelial miR-128 is modulated by virulent *Salmonella enteritidis*, which suppresses epithelia-secreted M-CSF and prevents macrophage mobilization [43].

To add to the infection models listed above, miRNAs had been implicated in immune responses of the host to other bacterial infections. Even though NF-B activation is necessary for miR-155 introduction, little is known about the fundamental processes of miR-155 introduction by diverse pathogens or stimuli [5]. The microRNAs miR-16 and miR-15a have been connected to sepsis caused by bacterial infections [44]. TLR4 rather than TLR3 is necessary for triggering macrophage miR-718 expression in *Neisseria gonorrhoeae* infection models [45]. *Vibrio harveyi* and LPS stimulation have also been shown to drastically upregulate miR-214. To prevent massive inflammation, increasing miR-214 suppressed the production of inflammatory cytokines by binding MyD88 [46].

Bacterial pathogens live in host cells in a variety of ways including manipulation of miRNA expression. This modification might be studied as a new research viewpoint because of the intricate bacterial and host cell interaction [33].

MicroRNA in Viral Infection

Viral infections are linked to changes in host miRNA levels. Host miRNAs can have both direct and indirect impacts on viral infection. miRNAs have a direct effect on virus control because they target specific sections of viral RNA. Modulation of a cellular transcript generating a host component required for various phases of the life cycle of the virus is the indirect effect. Virus infections, on the other hand, may decrease the production of miRNAs as part of the antiviral response. Viral pathogens exploit the host's cellular mechanisms to produce viral miRNAs (v-miRNAs) found in the Epstein-Barr virus for the first time (EBV) [47]. These v-miRNAs not only control virus replication by targeting their transcripts, but they also suppress host gene expression, create settings that are favorable to replication and latency, and evade detection by the immune system of the host. Virus infection can also trigger increased or decreased expression of host micro RNAs, which can either impede or promote viral replication [48].

The initial defense against all infections is the host's inborn immune responses. The immune response includes natural killer cells; granulocytes, epithelial cells, macrophages, monocytes, and dendritic cells [49]. Innate immune cells sense viral infection primarily through germline-encoded pattern recognition receptors (PRRs) on the cell or in specific intracellular compartments [50]. Recent research has discovered that miRNAs belonging to the host can attach to numerous RNA viruses, influencing their pathogenicity. (+)-strand RNA viral genome replication mimics mRNAs in the cell, allowing the miRNA to attach to viral RNA, which could be comparable to how host mRNAs are regulated. The impact of these miRNAs is by inhibiting viral genome translation in other to hinder viral replication [51]. Type I IFN-inducible miR-128, for example, specifically affects two locations in the transportin TNPO3 mRNA, significantly lowering protein levels and TNPO3 mRNA. Downregulation of the nuclear importer TNPO3, which is required for the reproduction of human immunodeficiency virus (HIV-1), limits viral replication [52].

Others also demonstrated that miR-128 inhibits HIV replication by specifically attacking the viral genome's 3′-UTR. miRNAs, such as miR-323, hsa-miR-324-5p, miR-485, miR-3145, miR-491, and miR-654 prevent infection caused by influenza virus by attacking polymerase basic protein 1 (PB1), which is the major factor of the viral polymerase complex [48]. miR-548g-3p has previously been found to attach to the stem-loop. The 5′-UTR promoter of dengue virus (DENV), prevents viral RNA-dependent RNA polymerase (NS5) from being recruited to the viral genome and so suppresses viral reproduction [53]. Other research utilizing in silico analytic methods revealed that several human miRNAs bind all SARS-CoV-2 genes except E and ORF6. hsa-miR-203b-3p, for instance, was assumed to attack ORF3a and ORF1ab and has already been proven to limit the reproduction of the influenza A virus [54]. Although hsa-miR-148a-3p was discovered to bind the ORF1a, S, E, and M genes in SARS-CoV to impede interspecies replication and transmission, it has also been identified to bind the ORF8 gene. In SARS-CoV-2, hsa-let-7c-5p is anticipated to bind ORF1ab, and was discovered to have been implicated in H1N1 influenza A virus reduction by binding its M1 gene. As a consequence, inhibiting COVID-19 with a miRNA mimic could likewise affect COVID-19.

Some miRNAs in humans that bind the genome of SARS-CoV-2 are also efficient against SARS-CoV, MERS-CoV, and coronavirus NL63 (HCoV-NL63) in humans [48].

The majority of viruses make their non-coding RNAs (ncRNAs). Viruses connect with proteins that will be important for their function and stability just like their host. Viral ncRNAs have been linked to several biological processes, such as cellular transformation, viral persistence, viral reproduction, and host immune evasion [55]. HSUR 1, short uracil (U)-rich ncRNA encoded by *Herpesvirus saimiri* (HVS), has a complementary sequence with miR-27. miR-27 is cleaved when it binds to HSUR 1, and this decreased T cells during HVS infection [56].

According to Mishra et al., miR-30e-5p and miR-30e are introduced by infection caused by hepatitis B virus (HBV) which regulates the innate immune responses [57]. miR-372 and miR-302b regulate the mitochondrial-mediated antiviral immune system by modulating metabolic demand and mitochondrial activity, according to research into the involvement of miRNAs in mitochondrial-mediated innate immunity. Increased expression of these miRNAs stops the generation of type I IFN (IFN/) and cytokines that cause inflammation in dsRNA virus infection [58]. Inhibiting the activities of miR-372 and miR-302b may thus have an antiviral property on RNA viral disease [48]. Zhao et al. looked into the differential expression of miRNAs and discovered that miR-136 was upregulated fivefold in A549 of human lung epithelial cells and had potent antiviral activities in vitro against H5N1 influenza A virus and vesicular stomatitis virus (VSV) [59].

MicroRNA in Fungal Infection

Fungi are classified under eukaryotic microorganisms. They can be found in a variety of places ranging from indoor to outdoor settings. Most species of fungi are saprophytic in nature, obtaining their nutrient from organic materials. A very small percentage of the over 1.5 million species have been identified to be primary or opportunistic disease-causing agents. Personal contact with fungal species has been linked to some negative health impacts, these includes; lung, sinus, and subcutaneous infections, as well as respiratory morbidities such as hypersensitivity pneumonitis, allergies, and asthma. The immunological response of the host and the fungus species exposed determine each of these health impacts. Recent studies show that the miRNA profile that is seen after exposure to fungi is similar to those that are found in other allergy-induced or inflammatory-mediated studies [60].

Several studies carried out to ascertain miRNA profiles after acute and chronic exposure to fungi have identified the following 5 clinically significant fungi: *Paracoccidioides brasiliensis (P. brasiliensis)* [61], *Cryptococcus neoformans (C. neoformans)* [62], *Aspergillus fumigatus (A. fumigatus)* [63], *Candida albicans (C. albicans)* [64], and *Stachybotrys charternum* (*S. charternum*) [60].

P. brasiliensis which is a dimorphic fungus causes paracoccidioidomycosis, a major public health concern in Latin America [65]. The disease starts when spores are inhaled into an individual's lungs, germinating into yeast. This leads to a primary lung infection or further spread throughout the body, causing oral and cutaneous sores. Differentially expressed miRNAs in human and mice models after *P. brasiliensis* exposure were investigated in two investigations [60]. Marioto *et al.*, examined the profiles of miRNA of mice given *P. brasiliensis*in the veins and found that the let-7 family, miR-126a-5p, miR-301a-3p, miR-340-5p, miR-369-3p, miR-30b-5p, miR-20a-5p, miR-19b-3p, miR-130a-3p, and miR-26b-5p, and miR-221-3pwere up-regulated after 28 days [61].

Another study looked at the serum miRNA profile of *P. brasiliensis*-infected humans and discovered that 8 out of 752 miRNAs were differentially expressed. miR-125b-5p, miR-132-3p, miR-186-5p, miR-604, miR-29b-3p, miR-376c-3p, and miR-30b-5p were among the elevated miRNAs, while miR-423-3p was the only downregulated miRNA. These miRNAs have been established to play a major function in macrophage polarization or TLR2 signaling, both of which are signs of a Th1 immune response [66]. These investigations found an increase in miR-30b-5p, which suggest that it might be used as a biomarker for *P. brasiliensis* infection [60].

Aspergillus fumigatus is a common pathogenic fungus species found in the soil, occupational settings [67], and indoor settings [68]. Depending on the host's preexisting circumstances, inhaling *Aspergillus fumigatus* unicellular spores can cause different grades of an illness, known as aspergillosis. When monocytes and dendritic cells of humans are stimulated with *A. fumigatus*, in comparison to a control, LPS, miR-132 is activated [69]. These data point to a Th2-elicited response that is backed up by the study *A. fumigatus* inhalation exposure on animals [70].

Candidiasis is a fungal infection caused by numerous Candida species that are mainly endogenous in origin. This manifests with a variety of symptoms depending on the infection site. Candidiasis is a type of opportunistic fungal infection that can affect the gastrointestinal tract popularly known as thrush, some parts of the groin, foot, and hands, or it can progress to invasive candidiasis and spread throughout the body, including the blood, eyes, heart, brain, and bones [71]. miR-155, miR-146a, miR-455, and miR-125a, were elevated in mice macrophages activated by 10^6 cells/mL heat-inactivated *Candida albicans*, indicating that these miRNAs are involved in macrophage polarization. In human monocytic THP-1 cells infection caused by *C. neoformans*, miR-146a was also found to be increased, blocking the production of inflammatory cytokines and nuclear factor-B activation [62].

Host Derived MicroRNA in Immune Responses

Host-derived miRNA has a major role in immune expression and can modulate and influence the cells of the adaptive and innate immune systems. Its upregulation or downregulation may enhance or inhibit inflammatory responses. Significant changes were observed in miRNA-155 of the primary murine macrophage during their exposure to cytokines IFN-β. Toll-Like Receptor (TLR) ligands can activate, and regulate miRNA-155, and miRNA-155, and also act on SH-2 containing inositol 5’ polyphosphates 1 (SHIP 1) in macrophages and granulocytes expansion during inflammation [72]. miRNA-147 inhibits excessive inflammation in macrophages by activating TLR 2, TLR3, and TLR 4 in MyD88 and TRIF manner [73]. miRNA-92a inhibits inflammation by TLR4, by targeting MAKK4 [74].

Differentiation of granulocyte is regulated positively by miRNA 223, miRNA-223 controls the function of cells in human neutrophils introduced by bacterial lipopolysaccharide LPS by regulating NF-kB/MYD88 [75]. Expression of miRNA-146a was also found to be markedly increased during dendritic cell differentiation, this causes the modulation of inflammatory cytokines and increases dendritic cell apoptosis [76].

Decrease in effector CD8+ of miRNAs in T-cells were found to cause upregulation in CD8+ T-cells level and more expression of miRNA with shorter 3’UTRs was found in the CD4+ T-cells activation. Studies also show that reduced T-cell count occurs if the biogenesis of miRNA is disrupted [77]. Some T-cell clones are deleted due to the expression of miRNA-188, overexpression of miRNA-155 causes the CD4+ T-cell differentiation to Th1 cells [78].

miRNA such as miRNA-10, miRNA-146a, and miRNA-155 also regulate the role of regulatory T-cells which are necessary for immune cells homeostasis and prevention of auto-immune conditions [79].

[80] stated that defective Ago2 hemopoiesis affects early differentiation of B-cell and causes impairment in the production of peripheral B-cell. It prevents the transition of pro-B to pre-B-cell development and a subsequent decrease in the population of B-cell occurs by dicer or Ago2 deletion during the biogenesis of miRNA. The absence of miRNA-155 causes the production of defective antibodies leading to the impairment of immune response to antigenic stimulation [81].

2. CONCLUSION

miRNAs are small non-coding RNA transcript derived from RNA, it consists of about 18-22 nucleotides and has been important regulators of biological processes including gene expression and immune regulation. They were first discovered by Ambros and Ruvkun groups in 1993and are abundant in the body occurring in several parts of the body such as the lungs, liver, and kidney and modifying the functions of these organs.

Increase or decrease of miRNA is responsible for the occurrence and progress of certain disease conditions as well as the host's resistance to certain diseases. miRNA may enhance or inhibit the survival and multiplication of certain pathogens and miRNA derived from pathogens has been found to be an important tool used by pathogens to manipulate the host mechanism to its advantage. miRNAs are important in the regulation of the body defense system of the host. Their expression controls the functions of the cells involved in the defense of the host against conditions like inflammation or diseases. miRNA is crucial in the diagnosis of numerous diseases and may act as an important biomarker for infectious diseases.

References

[1] Almeida MI, Reis RM, Calin GA. MicroRNA history: Discovery, recent applications, and next frontiers. *Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis.* 2011; 717(1-2): 1–8. https://doi.org/10.1016/j.mrfmmm.2011.03.009

[2] O'Brien J, Hayder H, Zayed Y, Peng C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. *Frontiers in endocrinology* 2018; 9: 402. https://doi.org/10.3389/fendo.2018.00402

[3] Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell.* 2004; 116(2): 281-297. https://doi.org/10.1016/s0092-8674(04)00045-5

[4] Trifari S, Pipkin ME, Bandukwala HS, Äijö T, Bassein J, Chen R, Martinez GJ, Rao A. MicroRNA-directed program of cytotoxic CD8+ T-cell differentiation. *Proceedings of the National Academy of Sciences* 2013; 110(46): 18608-18613. https://doi.org/10.1073/pnas.1317191110

[5] Zhou X, Li X,Wu M. miRNAs reshape immunity and inflammatory responses in bacterial infection. *Signal transduction and targeted therapy.* 2018; 3(1): 1-13, https://doi.org/10.1038/s41392-018-0006-9

[6] Kane M, Golovkina T. Common threads in persistent viral infections. *Journal of Virology* 2010; 84(9): 4116-4123. https://doi.org/10.1128/jvi.01905-09

[7] Tokarz P, Blasiak J. The role of microRNA in metastatic colorectal cancer and its significance in cancer prognosis and treatment. *Acta Biochimica Polonica.* 2012; 59: 4. https://doi.org/10.18388/abp.2012_2079

[8] Kumar S, Varela MF. Biochemistry of bacterial multidrug efflux pumps. *International journal of molecular sciences*. 2012; 13(4): 4484-4495. https://doi.org/10.3390/ijms13044484

[9] Ryan KJ, Ray CG. Sherris Medical Microbiology. 4th ed. McGraw Hill; 2004.

[10] Tribolet L, Kerr E, Cowled C, Bean AGD, Stewart CR, Dearnley M, Farr RJ. MicroRNA Biomarkers for Infectious Diseases: From Basic Research to Biosensing. *Front. Microbiol.* 2020; 11: 1197. https://doi.org/10.3389/fmicb.2020.01197

[11] Haidar M, Langsley G. Clinical Potential of miRNAs in Human and Infectious Diseases. *Molecular and Cellular Therapies.* 2020; 8(1): 1–18. https://doi.org/10.13052/mct2052-8426.811

[12] Ha M, Kim VN. Regulation of microRNA biogenesis. *Nature Reviews Molecular Cell Biology* 2014; 15: 509–524. https://doi.org/10.1038/nrm3838

[13] Tanzer A, Stadler PF. Molecular evolution of a microRNA cluster. *Journal of Molecular Biology* 2004; 339: 327–35. https://doi.org/10.1016/j.jmb.2004.03.065

[14] Alarcón C, Lee H, Goodarzi H, Halberg N, TavazoieSF. N^6-methyladenosine marks primary microRNAs for processing. *Nature.* 2015; 519: 482–485. https://doi.org/10.1038/nature14281

[15] Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH, Kim VN. MicroRNA genes are transcribed by RNA polymerase II. *The EMBO journal.* 2004; 23(20): 4051-4060. https://doi.org/10.1038/sj.emboj.7600385

[16] Okada C, Yamashita E, Lee SJ, Shibata S, Katahira J, Nakagawa A, Tsukihara T. A high-resolution structure of the pre-microRNA nuclear export machinery. *Science.* 2009; 326(5957): 1275-1279. https://doi.org/10.1126/science.1178705

[17] Heman-Ackah SM, Hallegger M, Rao M, Wood M. RISC in PD: the impact of microRNAs in Parkinson's disease cellular and molecular pathogenesis. *Frontiers in molecular neuroscience.* 2013; 6: 40. https://doi.org/10.3389/fnmol.2013.00040

[18] Shutterstock. Prevent infectious disease images [Internet]; 2021 [cited 2021 Oct 17]; Avalible from: https://www.shutterstock.com/search/prevent+infectious+disease

[19] Ellwanger JH, de Lima KV, Chies JA. Emerging infectious disease prevention: Where should we invest our resources and efforts? *Journal of infection and public health.* 2019; 12(3): 313-316. https://doi.org/10.1016/j.jiph.2019.03.010

[20] Krauss H, Weber A, Appel M, Enders B, Isenberg HD, SchieferHG,Slenczka W, von Graevenitz A, Zahner H. Zoonoses: Infectious Diseases Transmissible from Animals to Humans. D.C.3rd Edition. American Society for Microbiology Press. Washington; 2003. 456 p.

[21] WHO. Global Health Estimates 2016: Disease Burden by Cause, Age, Sex, by Country and by Religion, 2000-2016. Geneva: World Health Organization. 2018a.

[22] Izar B, Mannala GK, Mraheil MA, Chakraborty T, Torsten Hain. MicroRNA Response to *Listeria monocytogenes* Infection in Epithelial Cells. *Int. J. Mol. Sci.* 2012; 13: 1173-1185. https://doi.org/10.3390/ijms13011173

[23] Pedersen IM, Cheng G, Wieland S, Volinia S, Croce CM, Chisari FV, David M. Interferon modulation of cellular microRNAs as an antiviral mechanism. *Nature.* 2007; 449(7164): 919-922. https://doi.org/10.1038/nature06205

[24] Kumar M, Sahu SK, Kumar R, Subuddhi A, Maji RK, Jana K, Basu J. MicroRNA let-7 modulates the immune response to *Mycobacterium tuberculosis* infection via control of A20, an inhibitor of the NF-κB pathway. *Cell host & microbe* 2015; 17(3): 345-356. https://doi.org/10.1016/j.chom.2015.01.007

[25] Bader AG, Brown D, Winkler M. The promise of microRNA replacement therapy. *Cancer Res.* 2010; 70(18): 7027–7030. https://doi.org/10.1158/0008-5472.can-10-2010

[26] Elmén J, Lindow M, Silahtaroglu A, Bak M, Christensen M, Lind-Thomsen A, Hedtjärn M, Hansen JB, Hansen HF, Straarup EM, McCullagh K, Kearney P, Kauppinen S. Antagonism of microRNA-122 in mice by systemically administered LNA-antimiR leads to up-regulation of a large set of predicted target mRNAs in the liver. *Nucleic Acids Research.* 2008; 36(4): 1153-1162. https://doi.org/10.1093/nar/gkm1113

[27] Alexander M, Hu R, Runtsch MC, Kagele DA, Mosbruger TL, Tolmachova T, O'Connell RM. Exosome-delivered microRNAs modulate the inflammatory response to endotoxin. *Nature communications.* 2015; 6: 7321. https://doi.org/10.1038/ncomms8321

[28] Aguilar C, Mano M, Eulalio A. Multifaceted roles of microRNAs in host-bacterial pathogen interaction. *Microbiology spectrum.* 2019; 7(3): 7-3. https://doi.org/10.1128/9781683670261.ch17

[29] Das K, Garnica O, Dhandayuthapani S. Modulation of host miRNAs by intracellular bacterial pathogens. *Frontiers in cellular and infection microbiology*. 2016; 6: 79. https://doi.org/10.3389/fcimb.2016.00079

[30] Polk D, Peek R. Helicobacter pylori: gastric cancer and beyond. *Nat Rev Cancer* 2010; 10: 403–414. https://doi.org/10.1038/nrc2857

[31] Xiao B, Liu Z, Li BS, Tang B, Li W, Guo G, Shi Y, Wang F, Wu Y, Tong W, Guo H, Mao X, Zou, Q. M. Induction of microRNA-155 during Helicobacter pylori infection and its negative regulatory role in the inflammatory response. *The Journal of infectious diseases*. 2009; 200(6): 916-925. https://doi.org/10.1086/605443

[32] Lv X, Song H, Yang J, Li T, Xi T, Xing Y. A multi-epitope vaccine CTB-UE relieves Helicobacter pylori-induced gastric inflammatory reaction via up-regulating microRNA-155 to inhibit Th17 response in C57/BL6 mice model. *Human vaccines & immunotherapeutics* 2014; 10(12): 3561-3569. https://doi.org/10.4161/hv.36096

[33] Rad ZR, Rad ZR, Goudarzi H, Goudarzi M, Mahmoudi M, Sharahi JY, Hashemi A. MicroRNAs in the interaction between host–bacterial pathogens: A new perspective. *J Cell Physiol.* 2021; 236: 6249–6270. https://doi.org/10.1002/jcp.30333

[34] Yang S, Li F, Jia S, Zhang K, Jiang W, Shang Y, Chang K, Deng S, Chen, M. Early secreted antigen ESAT-6 of *Mycobacterium tuberculosis* promotes apoptosis of macrophages via targeting the microRNA155-SOCS1 interaction. *Cellular Physiology and Biochemistry*. 2015; 35(4): 1276-1288. https://doi.org/10.1159/000373950

[35] Rothchild AC, Sissons JR, Shafiani S, Plaisier C, Min D, Mai D, Gilchrist M, Peschon J, Larson RP, Bergthaler A, Baliga NS, Urdahl KB, Aderem A. MiR-155–regulated molecular network orchestrates cell fate in the innate and adaptive immune response to Mycobacterium tuberculosis. *Proceedings of the National Academy of Sciences.* 2016; 113(41): E6172-E6181. https://doi.org/10.1073/pnas.1608255113

[36] Liang S, Song Z, Wu Y, Gao Y, Gao M, Liu F, Wang F, Zhang Y. MicroRNA-27b modulates inflammatory response and apoptosis during Mycobacterium tuberculosis infection. *The Journal of Immunology.* 2018; 200(10): 3506-3518. https://doi.org/10.4049/jimmunol.1701448

[37] Rajaram MV, Ni B, Morris JD, Brooks MN, Carlson TK, Bakthavachalu B, Schoenberg DR, Torrelles JB, Schlesinger LS. Mycobacterium tuberculosis lipomannan blocks TNF biosynthesis by regulating macrophage MAPK-activated protein kinase 2 (MK2) and microRNA miR-125b. *Proceedings of the national academy of sciences.* 2011; 108(42): 17408-17413. https://doi.org/10.1073/pnas.1112660108

[38] Schnitger AKD, Machova A, Mueller RU, Androulidaki A, Schermer B, Pasparakis M, Krönke M, Papadopoulou N. Listeria monocytogenes Infectionin Macrophages Induces Vacuolar-Dependent Host miRNA Response. *PLoS ONE.* 2011; 6(11): e27435. https://doi.org/10.1371/journal.pone.0027435

[39] Lind EF, Elford AR, Ohashi PS. Micro-RNA 155 is required for optimal CD8+ T cell responses to acute viral and intracellular bacterial challenges. *The Journal of Immunology.* 2013; 190(3): 1210-1216. https://doi.org/10.4049/jimmunol.1202700

[40] Gunn JS. Salmonella host–pathogen interactions: A special topic. *Frontiers in microbiology*. 2011; 2: 191. https://doi.org/10.3389/fmicb.2011.00191

[41] Ordas A, Kanwal Z, Lindenberg V, Rougeot J, Mink M, Spaink HP, Meijer AH. MicroRNA-146 function in the innate immune transcriptome response of zebrafish embryos to Salmonella typhimurium infection. *BMC genomics.* 2013; 14(1): 1-15. https://doi.org/10.1186/1471-2164-14-696

[42] Maudet C, Mano M, Sunkavalli U, Sharan M, Giacca M, Förstner KU, Eulalio A. Functional high-throughput screening identifies the miR-15 microRNA family as cellular restriction factors for Salmonella infection. *Nature communications.* 2014; 5(1): 1-13. https://doi.org/10.1038/ncomms5718

[43] Zhang T, Yu J, Zhang Y, Li L, Chen Y, Li D, Liu F, Zhang C, Gu H, Zen K. Salmonella enterica serovar enteritidis modulates intestinal epithelial miR-128 levels to decrease macrophage recruitment via macrophage colony-stimulating factor. *The Journal of infectious diseases.* 2014; 209(12): 2000-2011. https://doi.org/10.1093/infdis/jiu006

[44] Verschoor CP, Dorrington MG, Novakowski KE, Kaiser J, Radford K, Nair P, Anipindi V, Kaushic C, Surette MG, Bowdish DM. MicroRNA-155 is required for clearance of *Streptococcus pneumoniae* from the nasopharynx. *Infection and immunity.* 2014; 82(11): 4824-4833. https://doi.org/10.1128/iai.02251-14

[45] Kalantari P, Harandi OF, Agarwal S, Rus F, Kurt-Jones EA, Fitzgerald KA, Golenbock DT. miR-718 represses proinflammatory cytokine production through targeting phosphatase and tensin homolog (PTEN). *Journal of Biological Chemistry.* 2017; 292(14): 5634-5644. https://doi.org/10.1074/jbc.m116.749325

[46] Chu Q, Sun Y, Cui J, Xu T. Inducible microRNA-214 contributes to the suppression of NF-κB-mediated inflammatory response via targeting myd88 gene in fish. *Journal of Biological Chemistry.* 2017; 292(13): 5282-5290. https://doi.org/10.1074/jbc.m117.777078

[47] Chen L, Zhou Y, Li H. LncRNA, miRNA and lncRNA-miRNA interaction in viral infection. *Virus research.* 2018; 257: 25-32. https://doi.org/10.1016/j.virusres.2018.08.018

[48] Hu J, Stojanović J, Yasamineh S, Yasamineh P, Karuppannan SK, Dowlath MJH, Serati-Nouri H. The potential use of microRNAs as a therapeutic strategy for SARS-CoV-2 infection. *Archives of Virology.* 2021; 1-24. https://doi.org/10.1007/s00705-021-05152-5

[49] Kitazawa H, Villena J. Modulation of respiratory TLR3-anti-viral response by probiotic microorganisms: lessons learned from Lactobacillus rhamnosus CRL1505. *Frontiers in immunology.* 2014; 5: 201. https://doi.org/10.3389/fimmu.2014.00201

[50] Li Y, Shi X. MicroRNAs in the regulation of TLR and RIG-I pathways. *Cellular & molecular immunology.* 2013; 10(1): 65-71. https://doi.org/10.1038/cmi.2012.55

[51] Trobaugh DW, Gardner CL, Sun C, Haddow AD, Wang E, Chapnik E, Mildner A, Weaver SC, Ryman KD, Klimstra WB. (2014). RNA viruses can hijack vertebrate microRNAs to suppress innate immunity. *Nature.* 2014; 506(7487): 245-248. https://doi.org/10.1038/nature12869

[52] Bochnakian A, Zisoulis DG, Idica A, Zhen A, Kewal Ramani VN, Daugaard I, Hamdorf M, Kitchen S, Lee K, Pedersen IM. Interferon-inducible microRNA miR-128 modulates HIV-1 replication by targeting TNPO3 mRNA. *Journal of virology.* 2019; 93(20): e00364-19. https://doi.org/10.1101/195511

[53] Wen W, He Z, Jing Q, Hu Y, Lin C, Zhou R, Wang X, Su Y, Yuan J, Chen Z, Yuan J, Wu J, Li J, Zhu X, Li M. Cellular microRNA-miR-548g-3p modulates the replication of dengue virus. *Journal of Infection.* 2015; 70(6): 631-640. https://doi.org/10.1016/j.jinf.2014.12.001

[54] Zhang S, Li J, Li J, Yang Y, Kang X, Li Y, Wu X, Zhu Q, Zhou Y, Hu Y. Up-regulation of microRNA-203 in influenza A virus infection inhibits viral replication by targeting DR1. *Scientific reports.* 2018; 8(1): 1-15. https://doi.org/10.1038/s41598-018-25073-9

[55] Tycowski KT, Guo YE, Lee N, Moss WN, Vallery TK, Xie M, Steitz JA. Viral noncoding RNAs: more surprises. *Genes & development.* 2015; 29(6): 567-584. https://doi.org/10.1101/gad.259077.115

[56] Abedini M, Zhang C. Performance Assessment of Concrete and Steel Material Models in LS-DYNA for Enhanced Numerical Simulation, A State of the Art Review. *Arch Computat Methods Eng.* 2021; 28: 2921–2942. https://doi.org/10.1007/s11831-020-09483-5

[57] Mishra R, Bhattacharya S, Rawat BS, Kumar A, Kumar A, Niraj, K, Chande A, Gandhi P, Khetan D, Aggarwal A, Sato S, Tailor P, Takaoka A, Kumar H. MicroRNA-30e-5p has an integrated role in the regulation of the innate immune response during virus infection and systemic lupus erythematosus. *Iscience.* 2020; 23(7): 101322. https://doi.org/10.1016/j.isci.2020.101322

[58] Yasukawa K, Kinoshita D, Yaku K, Nakagawa T, Koshiba T. The microRNAs miR-302b and miR-372 regulate mitochondrial metabolism via the SLC25A12 transporter, which controls MAVS-mediated antiviral innate immunity. *Journal of Biological Chemistry*. 2020; 295(2): 444-457. https://doi.org/10.1074/jbc.ra119.010511

[59] Zhao L, Zhu J, Zhou H, Zhao Z, Zou Z, Liu X, Lin X, Zhang X, Deng X, Wang R, Chen H, Jin M. Identification of cellular microRNA-136 as a dual regulator of RIG-I-mediated innate immunity that antagonizes H5N1 IAV replication in A549 cells. *Scientific reports.* 2015; 5(1): 1-13. https://doi.org/10.1038/srep14991

[60] Croston TL, Lemons AR, Beezhold DH, Green BJ. MicroRNA regulation of host immune responses following fungal exposure. *Frontiers in immunology*. 2018; 9: 170. https://doi.org/10.3389/fimmu.2018.00170

[61] Marioto DTG, D., dos Santos Ferraro ACN, de Andrade FG, Oliveira MB, Itano EN, Petrofeza S, Venancio EJ. Study of differential expression of miRNAs in lung tissue of mice submitted to experimental infection by Paracoccidioides brasiliensis. *Medical mycology*. 2017; 55(7): 774-784. https://doi.org/10.1093/mmy/myw135

[62] Chen H, Jin Y, Chen H, Liao N, Wang Y, Chen J. MicroRNA-mediated inflammatory responses induced by Cryptococcus neoformans are dependent on the NF-κB pathway in human monocytes. *International journal of molecular medicine.* 2017; 39(6): 1525-1532. https://doi.org/10.3892/ijmm.2017.2951

[63] Gupta MD, Fliesse, M, Springer J, Breitschopf T, Schlossnage, H, Schmitt AL, Löffler J. Aspergillus fumigatus induces microRNA-132 in human monocytes and dendritic cells. *International Journal of Medical Microbiology.* 2014; 304(5-6): 592-596. https://doi.org/10.1016/j.ijmm.2014.04.005

[64] Dix A, Czakai K, Leonhardt I, Schäferhoff K, Bonin M, Guthke R, Einsele H, Kurzai O, Löffler J and Linde J. Specific and novel microRNAs are regulated as response to fungal infection in human dendritic cells. *Front Microbiol.* 2017; 8: 270. https://doi.org/10.3389/fmicb.2017.00270

[65] Goldani LZ, Wirth F. Animal models and antifungal agents in paracoccidioidomycosis: an overview. *Mycopathologia.* 2017; 182(7): 633-643. https://doi.org/10.1007/s11046-017-0130-z

[66] De Lacorte SJ, De Fátima DJ, Gullo FP, Costa MC, Fusco-Almeida AM, Enguita FJ, Mendes-Giannini MJS. Preliminary evaluation of circulating microRNAs as potential biomarkers in paracoccidioidomycosis. *Biomed Rep.* 2017; 6(3): 353–7. https://doi.org/10.3892/br.2017.849

[67] Pearson C, Littlewood E, Douglas P, Robertson S, Gant TW, Hansell AL. Exposures and health outcomes in relation to bioaerosol emissions from composting facilities: a systematic review of occupational and community studies. *Journal of Toxicology and Environmental Health*. 2015;18(1):43-69. https://doi.org/10.1080/10937404.2015.1009961

[68] Kauffman CA, Nicolasora NP. Epidemiology of Invasive Pulmonary Aspergillosis. In: ComarúPasqualotto A. (eds) Aspergillosis: From Diagnosis to Prevention. Springer, Dordrecht. 2009. https://doi.org/10.1007/978-90-481-2408-4_20

[69] Das Gupta M, Fliesser M, Springer J, Breitschopf T, Schlossnagel H, Schmitt AL,Kurzai O, Hunniger K, Einsele K, Loffler J. Aspergillus fumigatus induces microRNA-132 in human monocytes and dendritic cells. *Int J Med Microbiol.* 2014; 304(5–6): 592–6. https://doi.org/10.1016/j.ijmm.2014.04.005

[70] Croston, TL, Ajay PN, Angela RL, Goldsmith WT, Ja KG, Dori RG, Donald HB, Brett JG. Influence of Aspergillus fumigatus conidia viability on murine pulmonary micro RNA and m RNA expression following subchronic inhalation exposure. *Clinical & Experimental Allergy.* 2016; 46(10): 1315-1327. https://doi.org/10.1016/j.ijmm.2014.04.005

[71] CDC. Fungal Diseases: Candidiasis [Internet]; 2017 [cited 2021 Oct 17]; Available from: https://www.cdc.gov/fungal/diseases/candidiasis/index.html

[72] Johnnidis JB, Harris MH, Wheeler RT, Stehling-Sun S, Lam MH, Kirak O, Brummelkamp TR, Fleming MD, Camargo FD. Regulation of progenitor cell proliferation and granulocyte function by microRNA-223. *Nature.* 2008; 451: 1125. https://doi.org/10.1038/nature06607

[73] Curtale G, Rubino M, Locati M. MicroRNAs as molecular switches in macrophage activation. *Front Immunol.* 2019; 10: 799. https://doi.org/10.3389/fimmu.2019.00799

[74] Lai L, Song Y, Liu Y, Chen Q, Han Q, Chen W, Pan T, Zhang Y, Cao X, Wang Q. MicroRNA-92a negatively regulates Toll-like receptor (TLR)-triggered inflammatory response in macrophages by targeting MKK4 kinase. *J Biol Chem.* 2013; 288: 7956–67. https://doi.org/10.1074/jbc.M112.445429

[75] Ha TY. The role of microRNAs in regulatory T cells and in the immune response. *Immunenetwork.* 2011; 11(1): 11-41. https://doi.org/10.4110/in.2011.11.1.11

[76] Testa U, Pelosi E, Castelli G, Labbaye C. miR-146 and miR-155: two key modulators of immune response and tumor development. *Non-coding RNA.* 2017; 3: 22. https://doi.org/10.3390/ncrna3030022

[77] Rodríguez-Galán A, Fernández-Messina L, Sánchez-Madrid F. Control of immunoregulatory molecules by miRNAs in T cell activation. *Frontiers in immunology.* 2018; 9: 2148. https://doi.org/10.3389/fimmu.2018.02148

[78] Baumjohann D, Ansel KM. MicroRNA-mediated regulation of T helper cell differentiation and plasticity. *Nat Rev Immunol.* 2013; 13(9): 666-678. https://doi.org/10.1038/nri3494

[79] Hippen KL, Loschi M, Nicholls J, MacDonald K, Blazar BR. Effects of microRNA on regulatory T cells and implications for adoptive cellular therapy to ameliorate graft-versus-host disease. *Frontiers in immunology.* 2018; 9: 57. https://doi.org/10.3389/fimmu.2018.00057

[80] Xu S, Guo K, Zeng Q, Huo J, Lam KP. The RNase III enzyme dicer is essential for germinal center B-cell formation. *Blood.* 2021; 119: 767–76. https://doi.org/10.1182/blood-2011-05-355412

[81] Danger R, Braza F, Giral M, Soulillou JP, Brouard S. MicroRNAs, major players in B cells homeostasis and function. *Front Immunol.* 2014; 5: 98. https://doi.org/10.3389/fimmu.2014.00098