



The Role of microRNA-155 in Viral Diseases of Humans

Sushmita Biswas¹, Neelakshi Sarkar^{2*}, Saheli Sarkar³, Neena Sharma⁴

¹Department of Botany, Brahmananda Keshab Chandra College, Bon-Hooghly, Kolkata, West Bengal, India

²Department of Zoology, Brahmananda Keshab Chandra College, Bon-Hooghly, Kolkata, West Bengal, India

³Department of Biosciences and Bioengineering, IIT Bombay, Mumbai, Maharashtra, India

⁴Department of Physiology, All India Institute of Medical Science (AIIMS), Vijaypur, Jammu, India

*Corresponding Author's Email: neelakshisarkar@gmail.com

Abstract

MicroRNAs, as key regulators of gene expression, have garnered significant attention in recent antiviral research due to their potential to modulate viral pathogenesis and host immune responses. On account of their potential to regulate gene expression, microRNAs are currently the focus of modern antiviral research. miR-155 is a multifunctional microRNA that plays a significant role in the regulation of the host immune system. Predictably, it also has a profound role in the pathogenesis of numerous viruses. Increasing research has revealed the involvement of miR-155 in various aspects of the host-viral interface. Studies have also shown that miR-155 or its inhibitor could be used as a potential tool in viral therapeutics and diagnostics. The current review aims to highlight viral diseases that have been significantly modulated by miR-155. This was achieved by searching several globally recognised and distinguished scientific databases, followed by data extraction and analysis. This work is particularly important, as exogenous molecular control of miR-155 expression could open new avenues for limiting viral proliferation.

Keywords: Hepatitis; microRNA; microRNA-155; Viral Disease; Viruses

Introduction

MicroRNAs are small (19 to 24 nucleotides), single-stranded, non-coding RNAs that are primarily synthesised from the introns (Ying, Chang & Lin, 2018; Anglicheau, Muthukumar & Suthanthiran, 2010). Due to their ability to bind to and silence DNA post-transcriptionally, facilitated by complementarity in their sequences, they have been widely utilised in research and therapeutic applications (Ying, Chang & Lin, 2018; Segert, Gissel Brecht & Bulyk, 2021; Tiwari, Mukherjee & Dixit, 2018; Ganju *et al.*, 2017; Rupaimoole & Slack, 2017; Bernardo *et al.*, 2015). Almost all living organisms synthesise microRNAs, with a total of 10,000 human microRNAs identified (Friedländer *et al.*, 2014). These small entities have tremendous potential to modulate various gene expressions. Studies have predicted that they can potentially target and regulate the expression of at least 30% of the entire mammalian genome (Li *et al.*, 2009; Xiong & Zhang, 2023). However, they exhibit distinct expression profiles in response to specific conditions in human body. For example, immune-related microRNAs such as miR-1, miR-9, miR-21, miR-121, miR-144, miR-155, miR-145, miR-181, and miR-146 (Chandan, Gupta & Sarwat, 2020) are increased when a pathogen invades body (Shang *et al.*, 2023). On the other hand, miR-17–92 cluster levels, miR-21, miR-590, and others are elevated during cancer (Peng & Croce, 2016; Hill *et al.*, 2025). Among them, microRNA-155 has been extensively studied as a typical multifunctional microRNA. Existing studies indicate that miR-155 controls various pathological and physiological

processes, such as cardiovascular diseases, immunity, haematopoiesis, inflammation, and cancer (Faraoni *et al.*, 2009). Increasing research has also shown that miR-155 plays a role in several viral infections, such as neuroviruses, circulating viruses, respiratory viruses, etc. (Dickey *et al.*, 2017). However, its mode of functioning varies in different viruses (Jafarzadeh *et al.*, 2021). The current review aims to compile all the information regarding the functioning of miR-155 in different viral infections in humans.

Biogenesis of microRNAs

MicroRNAs are tiny, non-coding RNA fragments that were first identified in *C. elegans* (Ying, Chang and Lin, 2018; Friedländer *et al.*, 2014; Dickey *et al.*, 2017). It has now been established that they regulate gene-expression profiles in numerous animal species at the post-transcriptional level (Friedländer *et al.*, 2014; Dickey *et al.*, 2017).

RNA Polymerase II transcribes the miRNAs, primarily from the intron regions of the genome, into primary miRNAs (pri-miRNAs) (Kim & Kim, 2007). These are then cleaved by RNA Pol-III, the Drosha, and DGCR8 complex into shorter, 70-nucleotide long, precursor miRNAs (pre-miRNAs) (Ying, Chang & Lin, 2018; Kim & Kim, 2007; Sarkar & Chakravarty, 2015). The pre-miRNAs then leave the nucleus and are transported by Exportin-5 into the cytoplasm, where the enzyme Dicer undergoes further processing, resulting in the formation of even shorter double-stranded RNA fragments (Bofill-De Ros & Vang Ørom, 2023). These miRNAs (22 nucleotides long) then bind with Argonaute and other enzymes to generate the RNA-induced silencing complex (RISC) (Hou *et al.*, 2024). The RISC approaches the target mRNA, and one of the two strands in the miRNA binds with it at its 3' UTR (untranslated region), while the other strand is degraded (Hart *et al.*, 2024). The binding of miRNA to the target mRNA represses its expression either by blocking the initiation of translation or by degrading the target mRNA (Ying, Chang & Lin, 2018).

MicroRNA-155

The miR-155 is produced from an exon present in a non-coding RNA that is transcribed from BIC (B cell integration cluster) on chromosome 21 (Lagos-Quintana *et al.*, 2002). It was initially recognised in chicken lymphomas as an oncogene. However, subsequent work revealed that it is a multifunctional microRNA and is associated with several biological processes, including haematopoiesis, cancer, immunity, inflammation, cardiovascular diseases, contraction of vascular smooth muscle, mediating renal function, and viral infections (Faraoni *et al.*, 2009; Mahesh & Biswas, 2019).

The role of MicroRNA-155 in regulating immune responses is manifold. It works in association with diverse types of immune cells, such as definite T cell populations, B cells, macrophages, dendritic cells, NK cells, etc. (Haasch *et al.*, 2002; O'Connell *et al.*, 2007) and regulates the production of cytokines and chemokines by them. The expression of miR-155 can alter the production of IFN- γ and IL-2 by T cells (Banerjee *et al.*, 2010; Das *et al.*, 2012; Gracias *et al.*, 2013). It has been reported to facilitate the IFN- γ -dependent T cell (both CD4⁺ helper T cells and CD8⁺ cytotoxic T cells) responses to tumours (Huffaker *et al.*, 2012). It also enhances the maturation of T regulatory cells [21, 22], and alters the CD8⁺ memory T cell: effector T cell ratio (Kohlhaas *et al.*, 2009; Almanza *et al.*, 2010). miR-155 targets and represses a variety of immunoregulatory proteins, signalling molecules, and transcription factors such as SOCS1, Jarid2, Ets1, PU.1, Fosl2, CEBP β , etc. (Wang *et al.*, 2010; Jiang *et al.*, 2019; Escobar *et al.*, 2014; Xie *et al.*, 2018; Elton *et al.*, 2013).

As increasing studies have proven the indissoluble association between miR-155 and immune-related genes/proteins, it is not surprising that it plays an important role in microbial infection (Zhou, Li & Wu, 2018) (including viral infections), as host immunity is a major player in such infections (Chandan, Gupta & Sarwat, 2020). Strikingly, there are indeed several reports that have recognised the vital role of miR-155 in host responses to numerous viral diseases (Peng *et al.*, 2023). This review explores how miR-155 is associated with viruses belonging to diverse families and the infections they cause.

Material and Methods

Globally accepted and distinguished scientific databases comprising PubMed, Scopus, Google Scholar, Springer, ScienceDirect, and Wiley Online Library were used to search literature by focusing on specific terms such as “microRNA-155”, “virus”, “pathways”, “treatment”, and “biomarker”. Only those studies that showed sufficient evidence of the involvement of miR-155 in host responses to viruses were considered. West Nile Virus, Ebola, etc., were excluded from the study due to limited reports. Only literature written in the English language was considered due to language barriers. This has used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as illustrated in Figure 1 (Page *et al.*, 2021).

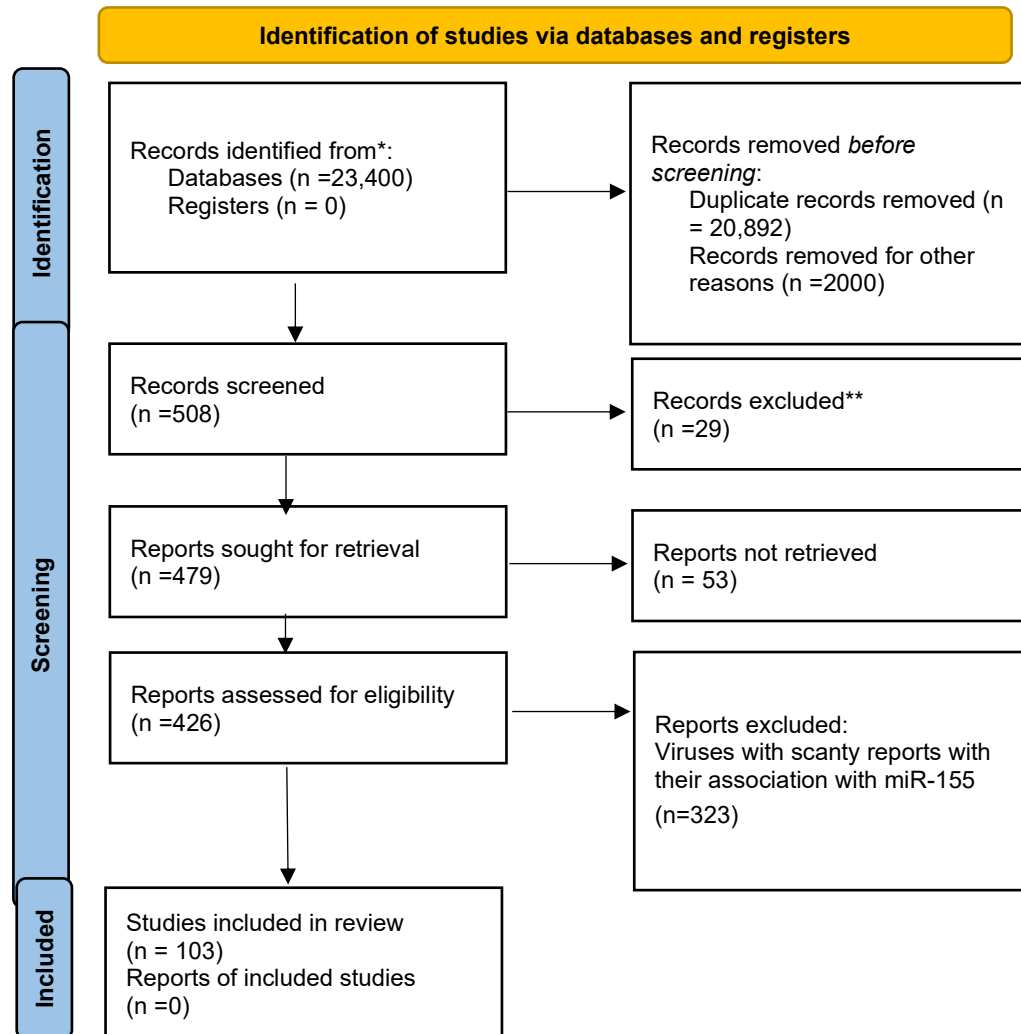


Figure 1: PRISMA Flow Diagram Depicting the Systematic Selection Process of Databases for Viral Diseases Associated with microRNA 155

DNA Viruses:

- **Herpesviridae**
 - **Herpes Simplex Virus:**

Herpes Simplex Virus (HSV) causes lesions in the skin, mucosa, eyes, etc., during its primary infection. It also invades the nervous system and establishes a lifelong latent infection there (Zhu & Viejo-Borbolla, 2021). Intermittently, such latent infections might be reactivated (probably due to fever, stress, exposure to UV light, etc.) and can even invade the brain, causing Herpes Simplex Encephalitis (HSE) (Roizman & Whitley, 2013; Whitley *et al.*, 1952). Infection in the brain in adults is generally caused by

HSV-1, which affects the temporal lobe of the brain, causing focal haemorrhagic necrosis with fatal consequences (Whitley *et al.*, 2006). These lesions in the brain are a result of both the infection by the virus and the immune responses of the host (Wang *et al.*, 2007). MicroRNA-155 (miR-155) plays a major role in this regard. Studies show that miR-155 knock-out mice were more susceptible to HSV infection than wild-type mice. This includes both zosteriform infection (affecting the brain) and ocular infection (affecting the eyes) (Zingale, Gugliandolo & Mazzon, 2021). The host responses (such as astrogliosis and CD8+ T cell responses) were also found to be more pronounced in the wild-type mice than in those where miR-155 was knocked out (Bhela *et al.*, 2014). Reduction of CD8+ T cell responses in the miR-155 knockout host consequently also reduced cytokines such as TNF- α and/or IFN- γ (Bhela *et al.*, 2014).

A recent study proposed that during ocular infection caused by HSV-1, accumulation of CD4+ helper T cells (mainly in corneas) was diminished in microRNA-155 KO hosts than wild type6 (Bhela *et al.*, 2015). Low frequency of Th1 and Th17 cells were also noted in HSV-infected microRNA-155 KO lesions and lymphoid organs. When treated with Local antagomir-155, host cells also exhibited a reduction in neutrophil infiltration to corneas and decreased the expression of IL-16, IL-1 β , IFN- γ , and IL-6 (Bhela *et al.*, 2015). The wild types are more autoimmune than the miR-155 KO host (Thompson *et al.*, 2023). Overexpression of microRNA-155 targeted and reduced SOCS1 in the microglial cell, which elevated the levels of NO and cytokines. HSV reactivation has been highly associated with stress. Interestingly, the levels of glucocorticoids increase in stress which triggers the decrease of miR-155. Hence miR155 might play an inhibitory role against HSV (Zheng *et al.*, 2012; Mulik *et al.*, 2012).

A contrasting study by Wang *et al.* stated that HSV-1 infection elevated the levels of miR-155-5p, and this consequentially facilitated HSV-1 replication (Wang *et al.*, 2019). They proposed that miR-155-5p elevated the synthesis of the SRSF2 gene, which aids in the duplication of viruses. In the brain, HSV infection has been shown to increase the expression of miR155 and different inflammatory cells (Zingale, Gugliandolo & Mazzon, 2021). All these studies together indicate that miR155 has a profound role in regulating the HSV infection-related immune responses (Table 1).

Epstein Bar Virus

Epstein-Barr Virus (EBV) is transmitted primarily through body fluids like saliva, blood, etc. It infects epithelial cells of the oropharynx and parotid gland, then infects B cells and becomes latent in the body (Damania, Kenney & Raab-Traub, 2022). However, it might cause Burkitt's Lymphoma, Nasopharyngeal carcinoma, and other lymphoproliferative diseases in immune-compromised individuals (Shannon-Lowe, Rickinson & Bell, 2017).

Several studies indicated that EBV-positive B cell malignancies cause up-regulation of miR-155 (Wood *et al.*, 2018; Lu *et al.*, 2008; Wang *et al.*, 1991). EBV carries two genes, LMP1 (Latency membrane protein 1) and EBNA2 (EBV nuclear antigen 2), which enhance the expression of miR-155 (Wood *et al.*, 2018; Lu *et al.*, 2008). Studies show that viral EBNA2 and a B cell transcription factor called Interferon Regulatory Factor 4 (IRF4) activate host genes that encode miR-155. EBNA2 also promotes the transcription of IRF-4 (L. Wang *et al.*, 2011a). Thus, EBNA2 stimulates the synthesis of miR-155 both directly and indirectly via IRF-4 (Wang *et al.*, 2011b). Studies have established that this up-regulation is mediated by specific enhancers dependent on the Notch signalling transcription factor RBPJ (Wood *et al.*, 2018). The viral LMP-1 protein is a potential activator of NF- κ B, which is essential for EBV-mediated immortalisation of the B cells (Awasthi *et al.*, 2022). Interestingly, miR-155 enhances NF- κ B by targeting IKKB. Lu *et al.* showed that inhibition of miR-155 could resist EBV-mediated carcinogenesis in B cells by deactivation of NF- κ B (Lu *et al.*, 2008). The multiple roles of miR-155 in EBV infection have been summarised in Table 1.

Table 1: A Summary of the Modulation of Host Mir-155 By Different Viruses and the Associated Changes in the Host Immune Pathways

Sl. No.	Virus	Cells affected by the virus	Effect of Virus on miR-155 and corresponding effect on body	Potential use of miR155	Ref
1.	Herpes Simplex Virus (DNA Virus)	Cells of skin, mucosa, eyes. Cells of nervous system.	- miR155 KO renders cell more susceptible to HSV. - Invasion of HSV elevates miR155. Activation of host cell immune Responses (CD8+ Tcells, CD4+ T cells, TNF-α, IFN-γ, IL-1β, IL-6, IFN-γ, 1L-16 and neutrophil infiltration as an aftermath of miR155 induction. - Suppression of miR155 reduces inflammation in corneas.	Studies propose that use of antagomiRs against miR-155 reduces lesions in eyes. However targeting miR155 for HSV therapy has not yet been acknowledged.	Kim and Kim (2007) Kohlhaas et al. (2009) Mulik et al. (2012) Bhela et al. (2015) Wang et al. (2011a) Whitley et al. (1982) Whitley (2006)
2.	Epstein Bar Virus (DNA Virus)	Epithelial cells of the oropharynx and parotid gland and B cells	- Up regulation of miR-155 (promoted by viral EBNA2 protein) - NF-κB activated by viral LMP-1 protein and miR155 - Promotion of carcinogenesis.	miR-155 silencing resists EBV mediated carcinogenesis.	Shannon-Lowe, Rickinson & Bell (2017) Lu et al. (2008) Momen-Heravi et al. (2014) Wang et al. (2011b) Wang et al. (1991) Wood et al. (2018) Xu et al. (2008)
3.	Hepatitis C Virus (RNA virus)	Hepatocytes	- Virus Up-regulates miR-155 via the NF-κB and p300 pathway (in HCV genotypes, 1,2 and 3) - Inhibition of Apoptosis and promotion of cell proliferation by Wnt signaling pathway. - Up-regulation of Inflammatory cytokines like TNF-α, IL-10, IFN-γ, IL-12.	MiR155 knock out diminishes HCV viral load and HCV associated acute lymphoid Leukemia <i>in vitro</i>	Cheng et al. (2015) Zeisel et al. (2009) Zhang et al. (2021) Zhou et al. (2021)
4.	Japanese Encephalitis Virus (RNA Virus)	Neuronal cells	- Activation of miR-155 - Activation of inflammation in neuronal cells by targeting SHIP-1. - Upregulation of TNF-α, IL-6, IL-10, MCP-1, IFN-γ	Overexpression of miR155 can reduce JEV in microglial cells.	Bhela et al. (2014) Campbell et al. (2011) Filgueira & Lannes (2019) Pareek et al. (2014) Rastogi and Singh (2020) Thounaojam et al. (2014) Yun and Lee (2013)

5.	SARS-CoV-2 (RNA Virus)	Alveolar cells	• Activation of miR-155 in acute and post-acute phases. • Activation of IL-1 signaling pathway. • MiR-155 has a role in the synthesis of ACE2 (Receptor of SARS-CoV-2) • Repression of miR-155 could inhibit cytokine storm in the lungs.	Can serve as a potential Biomarker to detect disease severity of and death. AntagomiR-155 can serve as a treatment strategy.	Arghiani <i>et al.</i> (2021) Donyavi <i>et al.</i> (2021) Ganju <i>et al.</i> (2017) Hu <i>et al.</i> (2021) Kassif-Lerner <i>et al.</i> (2022) Kooshkaki <i>et al.</i> (2020) Widiasta <i>et al.</i> (2020) Soni <i>et al.</i> (2020) Singhal <i>et al.</i> (2020) Hosseini <i>et al.</i> (2020)
6.	Influenza A Virus (RNA)	Epithelial cells of respiratory tract	• Activates miR-155 • Enhancement of CD8+ T cell responses and antibody responses. • Overexpression of miR-155 increases the amount of IL-6, IFN-β by targeted inhibition of SOCS-1.	miR-155 gene incorporated in the IAV vaccine exhibits enhanced immunogenicity against the Virus.	Izzard <i>et al.</i> (2014) Shen <i>et al.</i> (2020)
7.	Hepatitis B Virus (Reverse Transcribing Viruses)	Hepatocytes	• Inhibition of miR-155 mediated through down-regulation of TLR7 • miR-155 silencing impairs NK cell responses in chronic HBV patients. • Over-expression of miR-155 can decrease viral load by targeted inhibition of CEBP-β and activating immune responses through JAK-STAT pathway.	Ectopic expression of miR-155 could decrease the HBV viral load <i>in vitro</i> .	Chen <i>et al.</i> (2020) Nguyen <i>et al.</i> (2020) Sarkar and Chakravarty (2015) Sarkar <i>et al.</i> (2015) Tang <i>et al.</i> (2018) Yu <i>et al.</i> (2016)
8.	Human Immunodeficiency Virus (Reverse Transcribing Viruses)	CD4 T cells	• Activation of miR-155 • Activation of T cells and host immunity • miR-155 can diminish HIV infection by targeting HIV-1 dependency factors	MiR155 can be used as a biomarker to detect immune Responses against HIV infection	Jin <i>et al.</i> (2016) Campbell-Yesufu and Gandhi (2011) (German Advisory Committee Blood, 2016) Cheng, Lin & Cheng, (2021) Dey <i>et al.</i> (2016) Ruelas <i>et al.</i> (2015) Swaminathan <i>et al.</i> (2012) Zhang <i>et al.</i> (2021)

RNA VIRUSES

- **Flaviviridae**
- **Hepatitis C Virus**

The Hepatitis C virus (HCV) infects hepatocytes causing chronic liver inflammation, and is transmitted either vertically from pregnant mother to child or horizontally through contaminated blood and semen (Cacoub & Comarmond, 2017; Ganta *et al.*, 2018).

Numerous studies have found that miR-155 levels are upregulated during HCV infection, primarily mediated by NF- κ B (Bala *et al.*, 2012; Zhang *et al.*, 2012). Zhang *et al.*, 2021 reported that this NF- κ B mediated up-regulation of miR-155 was increased by p300 (Zhang *et al.*, 2012). A rise in miR-155

levels resulted in the accumulation of β -catenin and an increase in the levels of c-myc and survivin, and this consequently inhibited apoptosis and promoted proliferation of the cells via the Wnt signalling pathway (Zhang *et al.*, 2012). On the other hand, inhibition of miR-155 triggered G0/G1 arrest (Zhang *et al.*, 2012). In another study from Egypt, Hassan *et al.*, 2020 showed that knock out of miR-155 *in vitro* diminishes HCV viral load in HCV associated acute lymphoid leukemia (Hassan *et al.*, 2020). In addition, Bala *et al.* (2012) demonstrated that increased miR-155 levels in HCV-infected cells augmented inflammation by up-regulation of the cytokine TNF- α and resulted in Inflammation mediated hepatocyte damage Zhou *et al.* (2021) also reported a similar rise in TNF- α corresponding to higher levels of miR-155 in CD14+ monocytes from HCV-infected patients They reported increased expression of the JNK, IL-10 and IL-12, and Tim 3 genes Cheng *et al.* (2015) after a few years, found that Tim-3 is overexpressed in HCV infected natural killer (NK) cells where miR-155 was down-regulated, but reconstitution of miR-155 enhanced IFN- γ production via phosphorylation of signal transducer and activator of transcription 5 (STAT-5). All these together indicate that miR155 facilitates the progression of disease during HCV infection (Table 1). Interestingly, El-Ekiaby *et al.* (2012) reported a HCV genotype dependent differential modulation of miR-155. Precisely, they found that miR-155 levels were down-regulated in peripheral blood mononuclear cells (PBMCs) infected with particularly HCV genotype 4 (GT4) (in contrast to infection with HCV genotypes 1, 2, and 3 where miR155b was up-regulated).

Japanese encephalitis virus (JEV)

Japanese encephalitis (JE) is a kind of viral disease in which the flavivirus is transmitted by mosquitoes and infects neuronal cells (Yun & Lee, 2013) It invades the central nervous system resulting in the inflammation of the brain and might lead to serious conditions like encephalitis (Filgueira & Lannes, 2019). Campbell *et al.* (2011) reported that fatality in JEV-infected individuals can soar up to 30% (Campbell *et al.*, 2011).

Thounaojam *et al.* (2014) found that miR155 levels were increased during JE infection They also proved that this increase in miR-155 levels triggers Inflammation in neuronal cells by blocking its target SHIP (Src Homology 2 containing inositol Phosphatase-1) and enhancing the synthesis of inflammatory cytokines (IL-6, TNF- α , MCP-1) and interferon- β through activation of TBK-1 (Tank Binding Kinase-1). They proposed that modulation of miR-155 could be used as a therapeutic option in managing JE (Campbell & Gandhi, 2011). Additionally, Pareek *et al.* (2014) affirmed that over-expression of mir155 in microglia is associated with the reduction of JEV reproduction and elevation of IFN- β , TNF- α , IL-10, and other interferon-stimulated genes. They proposed that induction of miR-155 may be beneficial in limiting the virus). Another independent report by Rastogi reveals that JEV-mediated up-regulation of miR-155 inhibits the non-canonical NF- κ B pathway via TRAF-3 and PELI-1 in human microglial cells (Rastogi & Singh, 2020).

➤ **Coronaviridae:**

• **SARS-CoV 2:**

The novel SARS CoV-2 infection caused a severe pandemic and almost crippled the world since 2019 when it was first detected. It is a type of Corona Virus that has been found to affect the respiratory systems in humans and bears a history of zoonotic transfer from bats. The manifestations in the host are largely dependent on the host's immune responses post-infection. This ranges from low or moderate infection causing fever, cough, loss of smell and taste, etc., but may even lead to pneumonia-like symptoms and death (Hu *et al.*, 2021). The severity of this infection is generally caused by a cytokine storm that takes place as an aftermath (Singhal, 2020; Kooshkaki *et al.*, 2020).

Donyavi *et al.* (2021) established that the levels of miR-155-5p were significantly high in the Peripheral Blood Mononuclear cells (PBMCs) from COVID-19 patients in acute and post-acute phases than in healthy controls. He proposed that it could be used as a potential circulating biomarker to detect the severity of the disease Several other independent studies also had similar findings. They proposed that the up-regulation of miR-155 is in coordination with the heightened Inflammation among acute and post-acute patients (Xiao *et al.*, 2019; Han, Li & Jiang, 2016). The increased levels of miR-155 in infected patients could indicate body inflammation and cardiac myocyte-specific damage. Kassif-Lerner *et al.*

(2022) showed that miR-155 could be used as a prospective biomarker for predicting death in SARS-CoV-2 infected patients. Arghiani, Nissan and Matin (2021); demonstrated that the upregulated miR155 levels trigger the IL-1 signaling pathway, and therefore, its appropriate management could limit the Inflammation caused by the virus. Interestingly, Soni *et al.* (2020) validated that the repression of miR-155 could decrease the lung cytokine storm induced by covid-19. Strikingly, in addition to this, Widiasta *et al* (2020).; proved that miR-155 had a role in the synthesis of ACE2 (angiotensin-converting enzyme 2) which happens to be a receptor for SARS-Cov 2 and facilitates its entry into host cells. Thus, antagomiRs against miR-155 could be used as a treatment strategy to combat Sars-CoV2 infection.

➤ **Orthomyxoviridae:**

• **Influenza A Virus:**

The Influenza A Virus (IAV) is one of the four influenza viruses that affects the epithelial cells of the respiratory tract (Shen *et al.*, 2020). Though rarely may also lead to acute respiratory distress syndrome (ARDS) and death. miR155 has been extensively studied in the context of IAV. Infection with IAV elevates mir155 (Shen *et al.*, 2020). It enhances CD8+ T cell responses and specific antibody responses in patients infected with IAV (Izzard *et al.* 2014). Izzard *et al.* (2014) proposed that overexpression of miR-155 in IAV infected cells consequentially facilitated the amount of IL-6 and IFN- β in the human body system by targeted inhibition of SOCS1. Shen *et al.* (2020) showed that miR155 enhances inflammatory responses against IAV by targeting S1PR1 (sphingosine-1-phosphate receptor 1). In two independent studies, Rodriguez and Thai *et al.* revealed that the miR-155 KO host could not create a proper humoral defence against IAV infection. On the other hand, Gracias *et al.* (2013) found that miR155 enhances influenza-specific CD8+T responses cells in transgenic mice. Izzard *et al.* (2014) designed a vaccine where he integrated the miR-155 gene with the IAV genome and showed enhanced immunogenicity against the virus.

Reverse Transcribing Viruses

➤ **Hepadnaviridae:**

• **Hepatitis B virus:**

The hepatitis B virus (HBV) is a DNA virus with a genome that is partially double-stranded. It infects the liver cells (hepatocytes) that may lead to fatal liver diseases like Liver Cirrhosis and Hepatocellular carcinoma (Nguyen *et al.*, 2020). The outcome of this infection is highly dependent on the host's immune responses, so miR155 plays a major role in it (Nguyen *et al.*, 2020; Tang *et al.*, 2018).

Several studies independently showed that HBV suppresses miR155 in Peripheral Blood mononuclear cells (PBMCs) and liver cells (Yu *et al.* 2016; Ge *et al.*, 2017). They have proposed that the virus paralyzes the host immune system and inflammatory responses to establish itself since various cytokines and Interferons were also found to be down-regulated during infection (Yu *et al.* 2016; Ge *et al.*, 2017; Su *et al.*, 2011). Sarkar *et al* (2015) proposed that this down-regulation of miR155 resulted as an aftermath of TLR7 inhibition by HBV (2015). Ge *et al.* showed that reduced expression of miR155 impairs Natural Killer cell responses in chronic HBV patients (2017), whereas Chen *et al.* 2020 showed that microRNA-155 regulates HBV replication by contributing to autophagy induced by SOCS1 signalling (Chen *et al.*, 2020).

Su *et al.* overexpressed miR155 ectopically in hepatoblastoma cell lines and found that it mildly inhibits HBV by activating innate immune responses mediated through the JAK-STAT pathway. Likewise, Sarkar *et al.* also found that overexpression of miR155 suppresses HBV replication through targeted inhibition of the transcription factor- CEBP- β (Sarkar *et al.*, 2015).

➤ **Reoviridae:**

• **Human Immunodeficiency Virus:**

Human Immunodeficiency Virus (HIV) is communicated through body fluids like blood, semen etc. and infects the CD4+ T cells in the blood, thereby reducing their count. This results in severe immune deficiency leaving the body susceptible to secondary infection (German Advisory Committee Blood,

2016). When the CD4+ T cell count drops below 200 per mm³ of blood, the condition is termed Acquired Immunodeficiency Syndrome (AIDS) (Battistini *et al.*, 2022).

Jin *et al.* (2016) suggested that the levels of miR-155 are up-regulated in the PBMCs of HIV-1 positive patients and that this could be associated with the activation of T cells. Zhang *et al.* (2021) also re-confirmed this finding, stating that higher miR-155 levels could be an indicator of immune activation (Zhang *et al.*, 2021). Jin *et al.* (2016) further proposed that miR-155 could be used as a biomarker to detect immune responses against HIV-1 infection. Another independent study established that miR-155 has the potential to reinforce latency in HIV patients who had a sudden reactivation of infection following latency (Ruelas *et al.*, 2015). Swaminathan *et al.* (2012) showed that miR-155 could diminish HIV-1 infection by targeting numerous HIV-1 dependency factors. In another study from the Indian Subcontinent, Dey *et al.* (2016) established that the levels of miR-155, along with miR-382-5p, were significantly higher in HIV patients with regular disease progression compared to long-term non-progressors, and these miRNAs could be used as an indicator to distinguish the two groups.

Discussion

The outcome of viral infections is largely dependent on the host. Evidently, host factors, if managed properly, can be effectively used to curb viral pathogenesis. Because of their potential to regulate gene expression, microRNAs are currently the focus of modern antiviral research. These small RNAs and their inhibitors can be efficiently delivered to the host via exosomes and liposomes (Momen-Heravi *et al.*, 2014). In this respect, miR-155 has been profoundly studied in several viral infections (Table 1). Its capacity to trigger numerous inflammatory cytokines and antiviral interferons is manifold. It can effectively stimulate the humoral (specific antibodies) and cell-mediated (CD4+ and CD8+ T cells) arms of adaptive immunity (Haasch *et al.*, 2002; O'Connell *et al.*, 2007). Though it is highly likely that miR-155 could favour the host in the process of viral elimination, there are a number of viruses (HSV, EBV, HCV, SARS) where it increases the chances of amplified inflammation and carcinogenesis. Antagonists against miR-155 have proven to have promising results in limiting EBV and HCV-mediated carcinogenesis and also cytokine storms during SARS-CoV-2 infection (Lu *et al.*, 2008; Widiasta *et al.*, 2020). Appropriate testing through human clinical trials could open up new treatment options.

After reviewing several literatures available online, this could not find any correlation between the mechanisms of miR-155 mediated viral clearance and the type of cells that harbour the virus. Of the studied viruses, some affect the neuronal cells, some affect the immune cells, some paralyse the cells of the respiratory tract, and others affect hepatocytes. Interestingly, the level of miR-155 is elevated in all of these cells upon viral invasion, with the exception of HBV in hepatocytes, where miR-155 is down-regulated. Obviously, the viral nucleic acids trigger the expression of Toll-like receptors (TLR3, 4, 7, 8), which eventually activate miR-155 through the downstream TRIF-MyD88 signalling pathway (Jafarzadeh *et al.*, 2021). However, HBV suppresses TLR7 and thus represses miR-155 (Sarkar *et al.*, 2015).

miR-155 has potential in viral clearance in the case of both HBV and HIV. Interestingly, both of these viruses have shared means of transmission, and about 10-20% of HIV-positive patients across the globe are co-infected with HBV (Cheng, Lin & Cheng, 2021). Activation of miR-155 could be a novel treatment option in such cases, as miR-155 imparts both anti-HBV and anti-HIV effects by targeting key HIV and HBV dependency factors (Swaminathan *et al.*, 2012; Sarkar *et al.*, 2015).

A very significant finding in this regard is that the incorporation of miR-155 in the IAV vaccine enhances its immunogenicity. Thus, the use of miR-155 as an adjuvant while designing vaccines or immune therapy could also be tested in other viral infections.

Owing to its vital role in the mediation of inflammation, miR-155 could also serve as a biomarker to trace disease progression. Excess miR-155 levels are suggestive of severe damage to the host, as has been proved in the case of HIV (Jin *et al.*, 2016). In SARS-CoV-2 infection, it could even predict death (Donyavi *et al.*, 2021; Soni *et al.*, 2020).

Conclusion

MicroRNA-155 exhibits a multifaceted role during viral infections, whereby in the case of certain viruses, it supports viral pathogenesis, while in others it prevents it. Nevertheless, it can also be used as a biomarker. Appropriate studies in animal models and clinical trials could offer promising insights. This is particularly important as the exogenous control of miR-155 expression might provide a new alternative to confine viral proliferation.

Acknowledgement

The authors are thankful to the Principal, Brahmananda Keshab Chandra College, Kolkata, India for allowing us access to the library and e-library facilities of the institution.

Abbreviations: HSV-Herpes Simplex Virus, EBV-Epstein Bar Virus, JEV-Japanese Encephalitis Virus, HBV-Hepatitis B Virus, HCV-Hepatitis C Virus, HIV- Human Immunodeficiency Virus, SARS-CoV 2-Severe Acute Respiratory syndrome corona virus 2.

References

- Almanza, G., Fernandez, A., Volinia, S., Cortez-Gonzalez, X., Croce, C. M., & Zanetti, M. (2010). Selected microRNAs define cell fate determination of murine central memory CD8 T cells. *PLoS One*, 5(6), e11243. <https://doi.org/10.1371/journal.pone.0011243>
- Anglicheau, D., Muthukumar, T., & Suthanthiran, M. (2010). MicroRNAs: small RNAs with big effects. *Transplantation*, 90(2), 105-112. <https://doi.org/10.1097/tp.0b013e3181e913c2>
- Arghiani, N., Nissan, T., & Matin, M. M. (2021). Role of microRNAs in COVID-19 with implications for therapeutics. *Biomedicine & Pharmacotherapy*, 144, 112247. <https://doi.org/10.1016/j.biopha.2021.112247>
- Awasthi, P., Dwivedi, M., Kumar, D., & Hasan, S. (2022). Insights into intricacies of the latent membrane protein-1 (LMP-1) in EBV-associated cancers. *Life Sciences*, 313, 121261. <https://doi.org/10.1016/j.lfs.2022.121261>
- Bala, S., Tilahun, Y., Taha, O., Alao, H., Kodys, K., Catalano, D., & Szabo, G. (2012). Increased microRNA-155 expression in the serum and peripheral monocytes in chronic HCV infection. *Journal of Translational Medicine*, 10(1), 151. <https://doi.org/10.1186/1479-5876-10-151>
- Banerjee, A., Schambach, F., DeJong, C. S., Hammond, S. M., & Reiner, S. L. (2010). MicroRNA-155 inhibits IFN- γ signaling in CD4+ T cells. *European Journal of Immunology*, 40(1), 225–231. <https://doi.org/10.1002/eji.200939592>
- Bernardo, B. C., Ooi, J. Y. Y. S., Lin, R. C. Y., & McMullen, J. R. (2015). *miRNA therapeutics: A new class of drugs with potential therapeutic applications in the heart*. *Future Medicinal Chemistry*, 7(13), 1771–1792. <https://doi.org/10.4155/fmc.15.107>
- Bhela, S., Mulik, S., Gimenez, F., Reddy, P. B., Richardson, R. L., Varanasi, S. K., Jaggi, U., Xu, J., Lu, P. Y., & Rouse, B. T. (2015). Role of MIR-155 in the pathogenesis of herpetic stromal keratitis. *American Journal of Pathology*, 185(4), 1073–1084. <https://doi.org/10.1016/j.ajpath.2014.12.021>
- Bhela, S., Mulik, S., Reddy, P. B. J., Richardson, R. L., Gimenez, F., Rajasagi, N. K., Veiga-Parga, T., Osmand, A. P., & Rouse, B. T. (2014). Critical role of MicroRNA-155 in herpes simplex encephalitis. *The Journal of Immunology*, 192(6), 2734–2743. <https://doi.org/10.4049/jimmunol.1302326>
- Bofill-De Ros, X., & Vang Ørom, U. A. (2024). Recent progress in miRNA biogenesis and decay. *RNA biology*, 21(1), 36-43. <https://doi.org/10.1080/15476286.2023.2288741>
- Cacoub, P., & Comarmond, C. (2016). New insights into HCV-related rheumatologic disorders: A review. *Journal of Advanced Research*, 8(2), 89–97. <https://doi.org/10.1016/j.jare.2016.07.005>
- Campbell, G., Hills, S., Fischer, M., Jacobson, J., Hoke, C., Hombach, J., Marfin, A., Solomon, T., Tsai, T., Tsui, V., & Ginsburg, A. (2011). Estimated global incidence of Japanese encephalitis: *Bulletin of the World Health Organization*, 89(10), 766–774. <https://doi.org/10.2471/blt.10.085233>
- Campbell-Yesufu, O. T., & Gandhi, R. T. (2011). Update on Human Immunodeficiency Virus (HIV)-2 infection. *Clinical Infectious Diseases*, 52(6), 780–787. <https://doi.org/10.1093/cid/ciq248>
- Chandan, K., Gupta, M., & Sarwat, M. (2020). Role of host and Pathogen-Derived MicroRNAs in immune regulation during infectious and inflammatory diseases. *Frontiers in Immunology*, 10, 3081. <https://doi.org/10.3389/fimmu.2019.03081>

- Chen, L., Ming, X., Li, W., Bi, M., Yan, B., Wang, X., Yang, P., & Yang, B. (2020). The microRNA-155 mediates hepatitis B virus replication by reinforcing SOCS1 signalling–induced autophagy. *Cell Biochemistry and Function*, 38(4), 436–442. <https://doi.org/10.1002/cbf.3488>
- Cheng, Y. Q., Ren, J. P., Zhao, J., Wang, J. M., Zhou, Y., Li, G. Y., Moorman, J. P., & Yao, Z. Q. (2015). MicroRNA-155 regulates interferon- γ production in natural killer cells via Tim-3 signalling in chronic hepatitis C virus infection. *Immunology*, 145(4), 485–497. <https://doi.org/10.1111/imm.12463>
- Cheng, Z., Lin, P., & Cheng, N. (2021). HBV/HIV coinfection: Impact on the development and clinical treatment of liver diseases. *Frontiers in Medicine*, 8, 713981. <https://doi.org/10.3389/fmed.2021.713981>
- Damania, B., Kenney, S. C., & Raab-Traub, N. (2022). Epstein-Barr virus: Biology and clinical disease. *Cell*, 185(20), 3652–3670. <https://doi.org/10.1016/j.cell.2022.08.026>
- Das, L. M., Torres-Castillo, M. D. L. A., Gill, T., & Levine, A. D. (2012). TGF- β conditions intestinal T cells to express increased levels of miR-155, associated with down-regulation of IL-2 and itk mRNA. *Mucosal Immunology*, 6(1), 167–176. <https://doi.org/10.1038/mi.2012.60>
- Dey, R., Soni, K., Saravanan, S., Balakrishnan, P., Kumar, V., Boobalan, J., Solomon, S. S., Scaria, V., Solomon, S., Brahmachari, S. K., & Pillai, B. (2016). Anti-HIV microRNA expression in a novel Indian cohort. *Scientific Reports*, 6(1), 28279. <https://doi.org/10.1038/srep28279>
- Dickey, L. L., Hanley, T. M., Huffaker, T. B., Ramstead, A. G., O'Connell, R. M., & Lane, T. E. (2017). MicroRNA 155 and viral-induced neuroinflammation. *Journal of Neuroimmunology*, 308, 17–24. <https://doi.org/10.1016/j.jneuroim.2017.01.016>
- Donyavi, T., Bokharaei-Salim, F., Baghi, H. B., Khanaliha, K., Janat-Makan, M. A., Karimi, B., Nahand, J. S., Mirzaei, H., Khatami, A., Garshasbi, S., Khoshmirsafa, M., & Kiani, S. J. (2021). Acute and post-acute phase of COVID-19: Analyzing expression patterns of miRNA-29a-3p, 146a-3p, 155-5p, and let-7b-3p in PBMC. *International Immunopharmacology*, 97, 107641. <https://doi.org/10.1016/j.intimp.2021.107641>
- El-Ekiaby, N., Hamdi, N., Negm, M., Ahmed, R., Zekri, A. R., Esmat, G., & Abdelaziz, A. I. (2012). Repressed induction of interferon-related microRNAs miR-146a and miR-155 in peripheral blood mononuclear cells infected with HCV genotype 4. *FEBS Open Bio*, 2(1), 179–186. <https://doi.org/10.1016/j.fob.2012.07.005>
- Elton, T. S., Selemon, H., Elton, S. M., & Parinandi, N. L. (2012). Regulation of the MIR155 host gene in physiological and pathological processes. *Gene*, 532(1), 1–12. <https://doi.org/10.1016/j.gene.2012.12.009>
- Escobar, T. M., Kanellopoulou, C., Kugler, D. G., Kilaru, G., Nguyen, C. K., Nagarajan, V., Bhairavabhotla, R. K., Northrup, D., Zahr, R., Burr, P., Liu, X., Zhao, K., Sher, A., Jankovic, D., Zhu, J., & Muljo, S. A. (2014). MIR-155 activates cytokine gene expression in TH17 cells by regulating the DNA-Binding protein JARID2 to relieve Polycomb-Mediated repression. *Immunity*, 40(6), 865–879. <https://doi.org/10.1016/j.immuni.2014.03.014>
- Faraoni, I., Antonetti, F. R., Cardone, J., & Bonmassar, E. (2009). miR-155 gene: A typical multifunctional microRNA. *Biochimica Et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1792(6), 497–505. <https://doi.org/10.1016/j.bbadis.2009.02.013>
- Filgueira, L., & Lannes, N. (2019). Review of Emerging Japanese Encephalitis Virus: New Aspects and Concepts about Entry into the Brain and Inter-Cellular Spreading. *Pathogens*, 8(3), 111. <https://doi.org/10.3390/pathogens8030111>
- Friedländer, M. R., Lizano, E., Houben, A. J., Bezdan, D., Báñez-Coronel, M., Kudla, G., ... & Estivill, X. (2014). Evidence for the biogenesis of more than 1,000 novel human microRNAs. *Genome Biology*, 15, 1-17. <https://doi.org/10.1186/gb-2014-15-4-r57>
- Ganju, A., Khan, S., Hafeez, B. B., Behrman, S. W., Yallapu, M. M., Chauhan, S. C., & Jaggi, M. (2017). miRNA nanotherapeutics for cancer. *Drug Discovery Today*, 22(2), 424-432. <https://doi.org/10.1016/j.drudis.2016.10.014>
- Ganta, N. M., Gedda, G., Rathnakar, B., Satyanarayana, M., Yamajala, B., Ahsan, M. J., Jadav, S. S., & Balaraju, T. (2018). A review on HCV inhibitors: Significance of non-structural polypeptides. *European Journal of Medicinal Chemistry*, 164, 576–601. <https://doi.org/10.1016/j.ejmech.2018.12.045>
- Ge, J., Huang, Z., Liu, H., Chen, J., Xie, Z., Chen, Z., Peng, J., Sun, J., Hou, J., & Zhang, X. (2017). Lower Expression of MicroRNA-155 Contributes to Dysfunction of Natural Killer Cells in Patients with Chronic Hepatitis B. *Frontiers in Immunology*, 8, 1173. <https://doi.org/10.3389/fimmu.2017.01173>
- German Advisory Committee Blood (Arbeitskreis Blut), Subgroup 'Assessment of Pathogens Transmissible by Blood'. (2016). Human immunodeficiency virus (HIV). *Transfusion Medicine and Hemotherapy*, 43(3), 203-222. <https://doi.org/10.1159/000445852>
- Gracias, D. T., Stelekati, E., Hope, J. L., Boesteanu, A. C., Doering, T. A., Norton, J., Mueller, Y. M., Fraietta, J. A., Wherry, E. J., Turner, M., & Katsikis, P. D. (2013). The microRNA miR-155 controls CD8+ T cell responses by regulating interferon signaling. *Nature Immunology*, 14(6), 593–602. <https://doi.org/10.1038/ni.2576>

- Haasch, D., Chen, Y., Reilly, R. M., Chiou, X. G., Koterski, S., Smith, M. L., Kroeger, P., McWeeny, K., Halbert, D. N., Mollison, K. W., Djuric, S. W., & Trevillyan, J. M. (2002). T cell activation induces a noncoding RNA transcript sensitive to inhibition by immunosuppressant drugs and encoded by the proto-oncogene, BIC. *Cellular Immunology*, 217(1–2), 78–86. [https://doi.org/10.1016/s0008-8749\(02\)00506-3](https://doi.org/10.1016/s0008-8749(02)00506-3)
- Han, Y., Li, Y., & Jiang, Y. (2016). The Prognostic Value of Plasma MicroRNA-155 and MicroRNA-146a Level in Severe Sepsis and Sepsis-Induced Acute Lung Injury Patients. *Clinical Laboratory*, 62(12), 2355–2360. <https://doi.org/10.7754/clin.lab.2016.160511>
- Hart, M., Kern, F., Fecher-Trost, C., Krammes, L., Aparicio, E., Engel, A., ... & Meese, E. (2024). Experimental capture of miRNA targetomes: disease-specific 3' UTR library-based miRNA targetomics for Parkinson's disease. *Experimental & Molecular Medicine*, 56(4), 935–945. <https://doi.org/10.1038/s12276-024-01202-5>
- Hassan, S. S., El-Khazragy, N., Elshimy, A. A., Aboelhussein, M. M., Saleh, S. A., Fadel, S., ... & Tamer, N. (2020). In vitro knock-out of miR-155 suppresses leukemic and HCV virus loads in pediatric HCV-4-associated acute lymphoid leukemia: A promising target therapy. *Journal of Cellular Biochemistry*, 121(4), 2811–2817. <https://doi.org/10.1002/jcb.29512>
- Hill, M., Stapleton, S., Nguyen, P. T., Sais, D., Deutsch, F., Gay, V. C., ... & Tran, N. (2025). The potential regulation of the miR-17–92a cluster by miR-21. *The International Journal of Biochemistry & Cell Biology*, 178, 106705. <https://doi.org/10.1016/j.biocel.2024.106705>
- Hosseini, E. S., Kashani, N. R., Nikzad, H., Azadbakht, J., Bafrani, H. H., & Kashani, H. H. (2020). The novel coronavirus Disease-2019 (COVID-19): Mechanism of action, detection and recent therapeutic strategies. *Virology*, 551, 1–9. <https://doi.org/10.1016/j.virol.2020.08.011>
- Hou, L., Liu, W., Zhang, H., Li, R., Liu, M., Shi, H., & Wu, L. (2024). Divergent composition and transposon-silencing activity of small RNAs in mammalian oocytes. *Genome Biology*, 25(1), 80. <https://doi.org/10.1186/s13059-024-03214-w>
- Hu, B., Guo, H., Zhou, P., & Shi, Z. L. (2021). Characteristics of SARS-CoV-2 and COVID-19. *Nature Reviews Microbiology*, 19(3), 141–154. <https://doi.org/10.1038/s41579-020-00459-7>
- Huffaker, T. B., Hu, R., Runtsch, M. C., Bake, E., Chen, X., Zhao, J., Round, J. L., Baltimore, D., & O'Connell, R. M. (2012). Epistasis between MicroRNAs 155 and 146a during T Cell-Mediated Antitumor Immunity. *Cell Reports*, 2(6), 1697–1709. <https://doi.org/10.1016/j.celrep.2012.10.025>
- Izzard, L., Ye, S., Jenkins, K., Xia, Y., Tizard, M., & Stambas, J. (2014). miRNA modulation of SOCS1 using an influenza A virus delivery system. *Journal of General Virology*, 95(9), 1880–1885. <https://doi.org/10.1099/vir.0.063834-0>
- Jafarzadeh, A., Naseri, A., Shojai, L., Nemati, M., Jafarzadeh, S., Baghi, H. B., Hamblin, M. R., Akhlagh, S. A., & Mirzaei, H. (2021). MicroRNA-155 and antiviral immune responses. *International Immunopharmacology*, 101, 108188. <https://doi.org/10.1016/j.intimp.2021.108188>
- Jiang, K., Yang, J., Guo, S., Zhao, G., Wu, H., & Deng, G. (2019). Peripheral circulating Exosome-Mediated delivery of MIR-155 as a novel mechanism for acute lung inflammation. *Molecular Therapy*, 27(10), 1758–1771. <https://doi.org/10.1016/j.ymthe.2019.07.003>
- Jin, C., Cheng, L., Höxtermann, S., Xie, T., Lu, X., Wu, H., Skaletz-Rorowski, A., Brockmeyer, N., & Wu, N. (2016). MicroRNA-155 is a biomarker of T-cell activation and immune dysfunction in HIV-1-infected patients. *HIV Medicine*, 18(5), 354–362. <https://doi.org/10.1111/hiv.12470>
- Kassif-Lerner, R., Zloto, K., Rubin, N., Asraf, K., Doolman, R., Paret, G., & Nevo-Caspi, Y. (2022). MIR-155: A potential biomarker for predicting mortality in COVID-19 patients. *Journal of Personalized Medicine*, 12(2), 324. <https://doi.org/10.3390/jpm12020324>
- Kim, Y., & Kim, V. N. (2007). Processing of intronic microRNAs. *The EMBO Journal*, 26(3), 775–783. <https://doi.org/10.1038/sj.emboj.7601512>
- Kohlhaas, S., Garden, O. A., Scudamore, C., Turner, M., Okkenhaug, K., & Vigorito, E. (2009). Cutting edge: the FOXP3 Target MIR-155 contributes to the development of regulatory T cells. *The Journal of Immunology*, 182(5), 2578–2582. <https://doi.org/10.4049/jimmunol.0803162>
- Kooshkaki, O., Derakhshani, A., Conradie, A. M., Hemmat, N., Barreto, S. G., Baghbanzadeh, A., Singh, P. K., Safarpour, H., Asadzadeh, Z., Najafi, S., Brunetti, O., Racanelli, V., Silvestris, N., & Baradaran, B. (2020). Coronavirus Disease 2019: A Brief review of the clinical manifestations and pathogenesis to the novel management Approaches and Treatments. *Frontiers in Oncology*, 10, 572329. <https://doi.org/10.3389/fonc.2020.572329>
- Lagos-Quintana, M., Rauhut, R., Yalcin, A., Meyer, J., Lendeckel, W., & Tuschl, T. (2002). Identification of Tissue-Specific MicroRNAs from Mouse. *Current Biology*, 12(9), 735–739. [https://doi.org/10.1016/s0960-9822\(02\)00809-6](https://doi.org/10.1016/s0960-9822(02)00809-6)

- Li, M., Marin-Muller, C., Bharadwaj, U., Chow, K. H., Yao, Q., & Chen, C. (2009). MicroRNAs: control and loss of control in human physiology and disease. *World Journal of Surgery*, 33, 667-684. <https://doi.org/10.1007/s00268-008-9836-x>
- Lu, F., Weidner, A., Liu, C., Volinia, S., Croce, C. M., & Lieberman, P. M. (2008). Epstein-Barr Virus-Induced MIR-155 attenuates NF- κ B signaling and stabilizes latent virus persistence. *Journal of Virology*, 82(21), 10436–10443. <https://doi.org/10.1128/jvi.00752-08>
- Mahesh, G., & Biswas, R. (2019). MicroRNA-155: a master regulator of inflammation. *Journal of Interferon & Cytokine Research*, 39(6), 321–330. <https://doi.org/10.1089/jir.2018.0155>
- Momen-Heravi, F., Bala, S., Bukong, T., & Szabo, G. (2014). Exosome-mediated delivery of functionally active miRNA-155 inhibitor to macrophages. *Nanomedicine Nanotechnology Biology and Medicine*, 10(7), 1517–1527. <https://doi.org/10.1016/j.nano.2014.03.014>
- Mulik, S., Xu, J., Reddy, P. B., Rajasagi, N. K., Gimenez, F., Sharma, S., Lu, P. Y., & Rouse, B. T. (2012). Role of miR-132 in Angiogenesis after Ocular Infection with Herpes Simplex Virus. *American Journal of Pathology*, 181(2), 525–534. <https://doi.org/10.1016/j.ajpath.2012.04.014>
- Nguyen, M. H., Wong, G., Gane, E., Kao, J., & Dusheiko, G. (2020). Hepatitis B Virus: Advances in Prevention, diagnosis, and therapy. *Clinical Microbiology Reviews*, 33(2), 10-1128. <https://doi.org/10.1128/cmr.00046-19>
- O'Connell, R. M., Taganov, K. D., Boldin, M. P., Cheng, G., & Baltimore, D. (2007). MicroRNA-155 is induced during the macrophage inflammatory response. *Proceedings of the National Academy of Sciences*, 104(5), 1604–1609. <https://doi.org/10.1073/pnas.0610731104>
- Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., McGuinness, L. A., ... Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical research ed.)*, 372. <https://doi.org/10.1136/bmj.n71>
- Pareek, S., Roy, S., Kumari, B., Jain, P., Banerjee, A., & Vratil, S. (2014). MiR-155 induction in microglial cells suppresses Japanese encephalitis virus replication and negatively modulates innate immune responses. *Journal of Neuroinflammation*, 11, 1-13. <https://doi.org/10.1186/1742-2094-11-97>
- Peng, X., Wang, Q., Li, W., Ge, G., Peng, J., Xu, Y., Yang, H., Bai, J., & Geng, D. (2023). Comprehensive overview of microRNA function in rheumatoid arthritis. *Bone Research*, 11(1), 8. <https://doi.org/10.1038/s41413-023-00244-1>
- Peng, Y., & Croce, C. M. (2016). The role of MicroRNAs in human cancer. *Signal Transduction and Targeted Therapy*, 1(1), 1-9. <https://doi.org/10.1038/sigtrans.2015.4>
- Rastogi, M., & Singh, S. K. (2020). Japanese Encephalitis Virus exploits microRNA-155 to suppress the non-canonical NF- κ B pathway in human microglial cells. *Biochimica et Biophysica Acta (BBA)-Gene Regulatory Mechanisms*, 1863(11). <https://doi.org/10.1016/j.bbagr.2020.194639>
- Roizman, B., & Whitley, R. J. (2013). An Inquiry into the Molecular Basis of HSV Latency and Reactivation. *Annual Review of Microbiology*, 67(1), 355–374. <https://doi.org/10.1146/annurev-micro-092412-155654>
- Ruelas, D. S., Chan, J. K., Oh, E., Heidersbach, A. J., Hebbeler, A. M., Chavez, L., Verdin, E., Rape, M., & Greene, W. C. (2015). MicroRNA-155 reinforces HIV latency. *Journal of Biological Chemistry*, 290(22), 13736-13748. <https://doi.org/10.1074/jbc.m115.641837>
- Rupaimoole, R., & Slack, F. J. (2017). MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. *Nature Reviews Drug Discovery*, 16(3), 203-222. <https://doi.org/10.1038/nrd.2016.246>
- Sarkar, N., & Chakravarty, R. (2015). Hepatitis B virus infection, microRNAs and liver disease. *International Journal of Molecular Sciences*, 16(8), 17746-17762. <https://doi.org/10.3390/ijms160817746>
- Sarkar, N., Panigrahi, R., Pal, A., Biswas, A., Singh, S. P., Kar, S. K., Bandopadhyay, M., Das, D., Saha, D., Kanda, T., Sugiyama, M., Chakrabarti, S., Banerjee, A., & Chakravarty, R. (2015). Expression of microRNA-155 correlates positively with the expression of Toll-like receptor 7 and modulates hepatitis B virus via C/EBP- β in hepatocytes. *Journal of Viral Hepatitis*, 22(10), 817–827. <https://doi.org/10.1111/jvh.12390>
- Segert, J. A., Gisselbrecht, S. S., & Bulky, M. L. (2021). Transcriptional silencers: driving gene expression with the brakes on. *Trends in Genetics*, 37(6), 514-527. <https://doi.org/10.1016/j.tig.2021.02.002>
- Shang, R., Lee, S., Senavirathne, G., & Lai, E. C. (2023). microRNAs in action: biogenesis, function and regulation. *Nature Reviews Genetics*, 24(12), 816–833. <https://doi.org/10.1038/s41576-023-00611-y>
- Shannon-Lowe, C., Rickinson, A. B., & Bell, A. I. (2017). Epstein–Barr virus-associated lymphomas. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 372(1732). <https://doi.org/10.1098/rstb.2016.027>

- Shen, S., Jiang, H., Zhao, J., & Shi, Y. (2020). Down-regulation of miR-155 inhibits inflammatory response in human pulmonary microvascular endothelial cells infected with influenza A virus by targeting sphingosine-1-phosphate receptor 1. *Chinese Medical Journal*, 133(20), 2429-2436. <https://doi.org/10.1097/cm9.0000000000001036>
- Singhal, T. (2020). A Review of Coronavirus Disease-2019 (COVID-19). *The Indian Journal of Pediatrics*, 87(4), 281–286. <https://doi.org/10.1007/s12098-020-03263-6>
- Soni, D. K., Cabrera-Luque, J., Kar, S., Sen, C., Devaney, J., & Biswas, R. (2020). Suppression of miR-155 attenuates lung cytokine storm induced by SARS-CoV-2 infection in human ACE2-transgenic mice. *BioRxiv*, 2020-12. <https://doi.org/10.1101/2020.12.17.423130>
- Su, C., Hou, Z., Zhang, C., Tian, Z., & Zhang, J. (2011). Ectopic expression of microRNA-155 enhances innate antiviral immunity against HBV infection in human hepatoma cells. *Virology Journal*, 8(1), 354. <https://doi.org/10.1186/1743-422x-8-354>
- Swaminathan, G., Rossi, F., Sierra, L., Gupta, A., Navas-Martín, S., & Martín-García, J. (2012). A role for microRNA-155 modulation in the Anti-HIV-1 effects of Toll-Like receptor 3 stimulation in macrophages. *PLoS Pathogens*, 8(9), e1002937. <https://doi.org/10.1371/journal.ppat.1002937>
- Tang, L. S. Y., Covert, E., Wilson, E., & Kottlilil, S. (2018). Chronic hepatitis B infection. *JAMA*, 319(17), 1802-1813. <https://doi.org/10.1001/jama.2018.3795>
- Thompson, J. W., Hu, R., Huffaker, T. B., Ramstead, A. G., Ekiz, H. A., Bauer, K. M., ... & O'Connell, R. M. (2023). MicroRNA-155 plays selective cell-intrinsic roles in brain-infiltrating immune cell populations during neuroinflammation. *The Journal of Immunology*, 210(7), 926-934. <https://doi.org/10.4049/jimmunol.2200478>
- Thounaojam, M. C., Kundu, K., Kaushik, D. K., Swaroop, S., Mahadevan, A., Shankar, S. K., & Basu, A. (2014). MicroRNA 155 regulates Japanese encephalitis Virus-Induced inflammatory response by targeting SRC homology 2-Containing inositol phosphatase 1. *Journal of Virology*, 88(9), 4798–4810. <https://doi.org/10.1128/jvi.02979-13>
- Tiwari, A., Mukherjee, B., & Dixit, M. (2018). MicroRNA key to angiogenesis regulation: MiRNA biology and therapy. *Current cancer drug targets*, 18(3), 266-277. <https://doi.org/10.2174/1568009617666170630142725>
- Wang, F., Kikutani, H., Tsang, S. F., Kishimoto, T., & Kieff, E. (1991). Epstein-Barr virus nuclear protein 2 transactivates a cis-acting CD23 DNA element. *Journal of Virology*, 65(8), 4101–4106. <https://doi.org/10.1128/jvi.65.8.4101-4106.1991>
- Wang, J. P., Bowen, G. N., Zhou, S., Cerny, A., Zacharia, A., Knipe, D. M., Finberg, R. W., & Kurt-Jones, E. A. (2011). Role of specific innate immune responses in herpes simplex virus infection of the central nervous system. *Journal of Virology*, 86(4), 2273–2281. <https://doi.org/10.1128/jvi.06010-11>
- Wang, L., Toomey, N. L., Diaz, L. A., Walker, G., Ramos, J. C., Barber, G. N., & Ning, S. (2011). Oncogenic IRFs Provide a Survival Advantage for Epstein-Barr Virus- or Human T-Cell Leukemia Virus Type 1-Transformed Cells through Induction of BIC Expression. *Journal of Virology*, 85(16), 8328–8337. <https://doi.org/10.1128/jvi.00570-11>
- Wang, P., Hou, J., Lin, L., Wang, C., Liu, X., Li, D., Ma, F., Wang, Z., & Cao, X. (2010). Inducible microRNA-155 feedback promotes type I IFN signaling in antiviral innate immunity by targeting suppressor of cytokine signaling 1. *The Journal of Immunology*, 185(10), 6226–6233. <https://doi.org/10.4049/jimmunol.1000491>
- Wang, Z., Li, K., Wang, X., & Huang, W. (2019). MiR-155-5p modulates HSV-1 replication via the epigenetic regulation of SRSF2 gene expression. *Epigenetics*, 14(5), 494–503. <https://doi.org/10.1080/15592294.2019.1600388>
- Whitley, R. J. (2006). Herpes simplex encephalitis: adolescents and adults. *Antiviral Research*, 71(2-3), 141-148. <https://doi.org/10.1016/j.antiviral.2006.04.002>
- Whitley, R. J., Soong, S. J., Linneman, C., Liu, C., Pazin, G., & Alford, C. A. (1982). Herpes simplex encephalitis: clinical assessment. *JAMA*, 247(3), 317-320. <https://doi.org/10.1001/jama.1982.03320280037026>
- Widiasta, A., Sribudiani, Y., Nugrahapraja, H., Hilmento, D., Sekarwana, N., & Rachmadi, D. (2020). Potential role of ACE2-related microRNAs in COVID-19-associated nephropathy. *Non-coding RNA Research*, 5(4), 153–166. <https://doi.org/10.1016/j.ncrna.2020.09.001>
- Wood, C. D., Carvell, T., Gunnell, A., Ojeniyi, O. O., Osborne, C., & West, M. J. (2018). Enhancer control of MicroRNA MIR-155 expression in Epstein-Barr Virus-Infected B cells. *Journal of Virology*, 92(19), 10-1128. <https://doi.org/10.1128/jvi.00716-18>
- Xiao, T., Ling, M., Xu, H., Luo, F., Xue, J., Chen, C., Bai, J., Zhang, Q., Wang, Y., Bian, Q., & Liu, Q. (2019). NF- κ B-regulation of miR-155, via SOCS1/STAT3, is involved in the PM2.5-accelerated cell cycle and proliferation of human bronchial epithelial cells. *Toxicology and Applied Pharmacology*, 377, 114616. <https://doi.org/10.1016/j.taap.2019.114616>
- Xie, Z., Qu, Y., Shen, P., Wang, B., Wei, K., & Du, B. (2018). PU. 1 attenuates TNF- α -induced proliferation and cytokine release of rheumatoid arthritis fibroblast-like synoviocytes by regulating miR-155 activity. *Molecular Medicine Reports*, 17(6), 8349-8356. <https://doi.org/10.3892/mmr.2018.8862>

- Xiong, Q., & Zhang, Y. (2023). Small RNA modifications: Regulatory molecules and potential applications. *Journal of Hematology & Oncology*, 16(1), 64. <https://doi.org/10.1186/s13045-023-01466-w>
- Xu, D., Zhao, L., Del Valle, L., Miklosy, J., & Zhang, L. (2008). Interferon regulatory factor 4 is involved in Epstein-Barr virus-mediated transformation of human B lymphocytes. *Journal of Virology*, 82(13), 6251–6258. <https://doi.org/10.1128/JVI.00163-08>
- Ying, S. Y., Chang, D. C., & Lin, S. L. (2018). The MicroRNA. *MicroRNA Protocols*, 1-25. https://doi.org/10.1007/978-1-4939-7601-0_1
- Yu, S., Deng, H., Li, X., Huang, Y., Xie, D., & Gao, Z. (2016). Expression of microRNA-155 is downregulated in peripheral blood mononuclear cells of chronic hepatitis B patients. *Hepatitis Monthly*, 16(1), e34483. <https://doi.org/10.5812/hepatmon.34483>
- Yun, S., & Lee, Y. (2013). Japanese encephalitis. *Human Vaccines & Immunotherapeutics*, 10(2), 263–279. <https://doi.org/10.4161/hv.26902>
- Zeisel, M. B., Barth, H., Schuster, C., & Baumert, T. F. (2009). Hepatitis C virus entry: molecular mechanisms and targets for antiviral therapy. *Frontiers in Bioscience (Landmark edition)*, 14, 3274. <https://doi.org/10.2741/3450>
- Zhang, Y., Wei, W., Cheng, N., Wang, K., Li, B., Jiang, X., & Sun, S. (2012). Hepatitis C virus-induced up-regulation of microRNA-155 promotes hepatocarcinogenesis by activating Wnt signaling. *Hepatology*, 56(5), 1631–1640. <https://doi.org/10.1002/hep.25849>
- Zhang, Z., Wu, Y., Chen, J., Hu, F., Chen, X., & Xu, W. (2021). Expression of microRNA-155 in circulating T cells is an indicator of immune activation levels in HIV-1 infected patients. *HIV Research & Clinical Practice*, 22(3), 71–77. <https://doi.org/10.1080/25787489.2021.1955196>
- Zheng, Y., Xiong, S., Jiang, P., Liu, R., Liu, X., Qian, J., Zheng, X., & Chu, Y. (2012). Glucocorticoids inhibit lipopolysaccharide-mediated inflammatory response by downregulating microRNA-155: A novel anti-inflammation mechanism. *Free Radical Biology and Medicine*, 52(8), 1307–1317. <https://doi.org/10.1016/j.freeradbiomed.2012.01.031>
- Zhou, X., Li, X., & Wu, M. (2018). miRNAs reshape immunity and inflammatory responses in bacterial infection. *Signal Transduction and Targeted Therapy*, 3(1), 14. <https://doi.org/10.1038/s41392-018-0006-9>
- Zhou, Y., Zhang, P., Zheng, X., Ye, C., Li, M., Bian, P., Fan, C., & Zhang, Y. (2021). miR-155 regulates pro- and anti-inflammatory cytokine expression in human monocytes during chronic hepatitis C virus infection. *Annals of Translational Medicine*, 9(21), 1618. <https://doi.org/10.21037/atm-21-2620>
- Zhu, S., & Viejo-Borbolla, A. (2021). Pathogenesis and virulence of herpes simplex virus. *Virulence*, 12(1), 2670–2702. <https://doi.org/10.1080/21505594.2021.1982373>
- Zingale, V. D., Gugliandolo, A., & Mazzon, E. (2021). MIR-155: An important regulator of neuroinflammation. *International Journal of Molecular Sciences*, 23(1), 90. <https://doi.org/10.3390/ijms23010090>