

Review

Non-Coding RNAs and Reactive Oxygen Species–Symmetric Players of the Pathogenesis Associated with Bacterial and Viral Infections

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Abstract: Infections can be triggered by a wide range of pathogens. However, there are few strains of bacteria that cause illness, but some are quite life-threatening. Likewise, viral infections are responsible for many human diseases, usually characterized by high contagiousness. Hence, as bacterial and viral infections can both cause similar symptoms, it can be difficult to determine the exact cause of a specific infection, and this limitation is critical. However, recent scientific advances have geared us up with the proper tools required for better diagnoses. Recent discoveries have confirmed the involvement of non-coding RNAs (ncRNAs) in regulating the pathogenesis of certain bacterial or viral infections. Moreover, the presence of reactive oxygen species (ROS) is also known as a common infection trait that can be used to achieve a more complete description of such pathogen-driven conditions. Thus, this opens further research opportunities, allowing scientists to explore infection-associated genetic patterns and develop better diagnosis and treatment methods. Therefore, the aim of this review is to summarize the current knowledge of the implication of ncRNAs and ROS in bacterial and viral infections, with great emphasis on their symmetry but, also, on their main differences.

Keywords: infections; bacterial; viral; ncRNAs; ROS; microbiology; infectious diseases; diagnosis

1. Introduction

Infectious diseases caused by bacterial and viral pathogens remain a major global health problem. Despite all of the recent advances in antibiotic and antiviral developments, unsolved antimicrobial resistances and the lack of broad-spectrum virus-targeting medications still impose many challenges upon both the medical and economical systems [1,2]. In the United States, about 2.8 million individuals get an antibiotic-resistant infection each year, while the annual estimation of healthcare-associated infections can reach beyond 720,000 cases [3–5]. Moreover, according to the World Health Organization, despite the efforts made toward developing better antibacterial drugs, none of the 43 antibiotics within the current clinical trials fully addresses the problem of antimicrobial resistance. Likewise, viral infections are also a frequent cause of illness in all age groups. However, children, elders, and those with a suppressed or deficient immune system usually have a much

higher risk of developing a viral infection [6]. Moreover, while the climate changes and the geographical movements increase, the number of viral infections has risen as well. Therefore, the incidences of bacterial and viral infections have now become a critical, worldwide issue.

Community or hospital-acquired pneumonia accounts among the main causes of morbidity, mortality, and healthcare-associated costs. Nowadays, there is a wider spectrum of recognized causes of such conditions: bacterial infections, viral infections, or viral and bacterial coinfections. However, the epidemiology of respiratory infections has changed over the past decades, as 40% of patients develop a viral infection as the primary cause of an illness. Still, bacterial coinfections are described as being commonly associated with the influenza virus. Such bacterial strains include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes*. Furthermore, beyond influenza, many other respiratory viruses are well-described as primary causes of pneumonia: respiratory syncytial virus, rhinoviruses, adenoviruses, human metapneumovirus, parainfluenza viruses, and finally, coronaviruses [7–10].

Starting in December 2019, another respiratory virus was added to the viral infection bookmarks as the novel SARS-CoV-2 virus infection, which reached pandemic proportions, causing a severe respiratory disease called COVID-19 that has affected beyond 162 million individuals, causing more than 3.3 million deaths (May 2021). Like other coronaviruses such as the Middle East Respiratory Syndrome (MERS) CoV and Severe Acute Respiratory Syndrome (SARS) CoV, the novel coronavirus was reported to spread via respiratory droplets and close contact from human to human, which made it highly infectious and dangerous [11].

The lack of specificity associated with the current methods for discriminating between bacterial and viral infections represents a global health threat, especially in diseases such as pneumonia, the leading cause of hospitalization, with approximately 120 million new cases and one million deaths worldwide each year [12]. Furthermore, both respiratory bacteria and viruses are usually collected from children with pneumonia, so rapidly and accurately identifying the infectious pathogens can guide the treatment management and facilitate the judicious use of antibiotics. Even if there is a growing availability of molecular techniques for pathogen detection, laboratory results are typically available long after the final treatment decisions are made. As a consequence, antibiotic resistance, due to excessive and oftentimes unnecessary use of antimicrobial drugs, is emerging at a disturbing rate, outpacing novel antibiotic developments and inevitably elevating healthcare-associated costs. Therefore, the need for specific and efficient methods to rapidly determine the exact type of an infection has become urgent. Therefore, the current repertoire of molecular biomarkers associated with bacterial and viral pathogenesis (Figure 1) is expected to be extended.

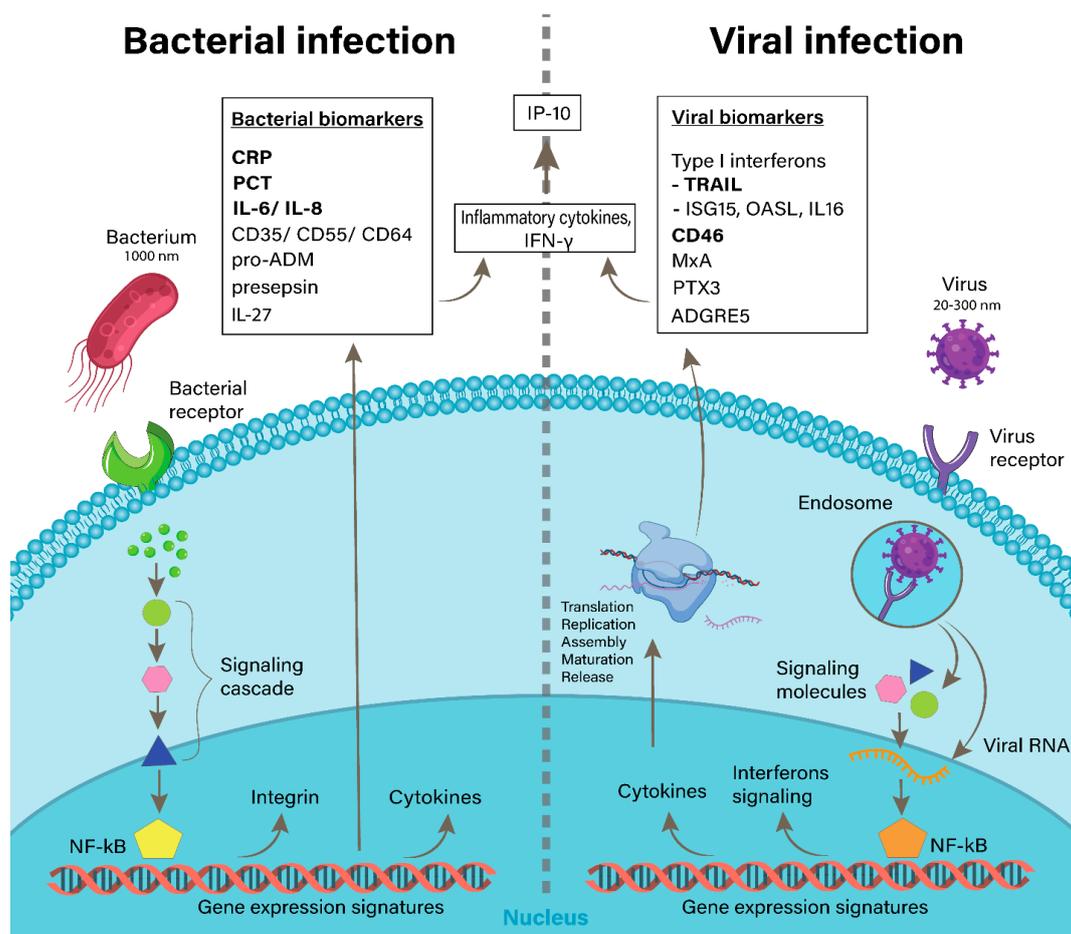


Figure 1. Comparative illustration between bacterial and viral infection pathogenesis. **(Left)** Bacterial infection pathways and their biomarkers that differentiate from viral ones. A differential diagnosis of bacterial infections is carried out using the relevant circulatory proteins, such as C-reactive proteins (CRP), interleukin-6 (IL6), and a biomarker-based biochemical-procalcitonin (PCT) for bacterial infections. Some functions for CRP are recruiting a complement system, stimulating phagocytosis, and inducing an inflammatory response. **(Right)** Viral infection pathways in a cell and their biomarkers. Regarding gene expression signatures, viruses are more likely to trigger interferon (IFN)-related signatures, whereas bacteria are more likely to induce integrin-related signatures. The most significant performance in the cytokine infection biomarker family was interferon (IFN) such as type I interferon that relates to ISG15, OASL, IL16, and TRAIL. The last one is a member of the tumor necrosis factor (TNF) family, and it plays an important role in programmed cell death, such as the apoptosis of infected cells. **(Middle)** A proinflammatory chemokine secreted by immune cells, IP-10 is a biomarker for both types of infections. Abbreviations: CRP: C-reactive protein, PCT: procalcitonin, TRAIL: TNF-related apoptosis-inducing ligand, IP-10: interferon-gamma-induced protein-10, pro-ADM: pro-adrenomedullin, ISG15: Interferon Stimulated Gene 15, OASL: 2',5'-Oligoadenylate Synthetase Like, MxA: myxovirus resistance protein A, PTX3: Pentraxin 3, and ADGRE5: Adhesion G Protein-Coupled Receptor E5 [13–16].

Consequently, as the molecular level seems to be deprecated when it comes to diagnosing infectious diseases, the latest approaches tend to zoom in on the problem and focus on the genetic signature associated with those bacterial and viral pathogens. In this field, even if accounting for only 1.5% of the human genetic signature, the protein-coding exons remain the most studied sequences [17,18]. However, in recent years, the non-protein-coding portions of the genome have gained lots of interest, and the non-coding RNAs (ncRNAs) that were previously considered “junk RNA” are now emerging as key regulators of gene expressions in many physiological and pathological processes [19]. Ranging in size from 20 nucleotides in microRNAs (miRNAs) up to >10,000 in long non-coding RNAs (lncRNAs), ncRNAs are proven to take part in many different human disorders, including bacterial and viral infections [20–22]. Still, those two categories are just the tip of the iceberg, while

there are many other types of ncRNAs identified so far: transcribed ultra-conserved regions (T-UCRs), small nucleolar RNAs (snoRNAs), PIWI-interacting RNAs (piRNAs), and large intergenic non-coding RNAs (lincRNAs) [17,23]. Nevertheless, ever since Warburg's 1908 observation of the increased oxygen consumption in fertilized sea urchin eggs that marked the first milestone in the ROS field, these oxygen species have been extensively studied within various scientific fields, including infectious diseases. Thus, while significantly contributing to regulating multiple physiological and pathological functions, ROS are also among the first signs of infectious diseases. Hence, their potential as valuable biomarkers for bacterial or viral infections started to be noticed [24]. Furthermore, ROS are known to play critical roles in immune defense mechanisms, including inflammation, against different pathogens, such as bacteria and viruses [25,26]. This trait could lead the way to innovative treatment strategies based on ROS and their immune implications in immune systems.

Most of the times, ncRNAs exist in clusters of 2–7 genes with small intervening sequences. Their biogenesis starts with post-or co-transcriptionally processing RNA II/III transcripts. About half of the currently identified miRNAs are intragenic and processed mostly from introns, while the remaining are intergenic, independently transcribed and regulated by self-promoters [23,27]. There are two distinct pathways when it comes to miRNA biogenesis. The canonical one that begins with the generation of pre-miRNA transcripts, which are further cleaved by the microprocessor complex Drosha and DiGeorge Syndrome Critical Region 8 (DGCR8) in order to obtain pre-miRNAs that will be further exported into the cytoplasm and mature into the mature miRNA duplexes. In the end, either its 5' or 3' strands will be loaded into the Argonaute (AGO) protein family to finally form miRNA-induced silencing complexes (miRISC). The noncanonical one starts with the cleavage of small hairpin RNAs (shRNA) that will be further exported via Exportin5/RanGTP (same as in the canonical pathway) into the cytoplasm to undergo AGO2-dependent and Dicer-independent cleavage. This noncanonical pathway will ultimately end with the formation of miRISC complexes [28].

Now, even if sometimes miRNAs and lincRNAs are more alike than they are different in term of biogenesis, there are also many differences within this process. Several DNA classes, such as enhancers or promoters, can be the starting point for lincRNA transcription, a process closely regulated by cell type-and stage type-specific stimuli. Most of the times, lincRNAs are transcribed by RNA polymerase II (Pol II), capped, polyadenylated, and further spliced during their transcription. However, sometimes, Pol II-transcribed lincRNAs are poorly processed and remain in the nucleus, but the remaining are usually spliced and ousted into the cytoplasm. If the lincRNAs contain one or only a few exons, their transfer into the cytoplasmic space is ensured by nuclear RNA export factor 1 (NXF1). In some cases, lincRNAs can be transcribed by a dysregulated Pol II, and as a consequence, they stick to the chromatin to be later degraded by the nuclear exosome. Other mechanisms involved in lincRNAs biogenesis are the development of mature ends by ribonuclease P cleavage, the establishment of small nucleolar RNA and protein complex caps, and the formation of circular structures. However, the processes associated with lincRNAs biogenesis and regulation are not yet fully understood, but one thing is for sure. miRNAs and lincRNAs do share a symmetry regarding their involvement in certain infectious diseases [29–31].

Hence, for their various implications in many different biological processes, ncRNAs have gathered more interest and started to be largely studied, up to the point where now we can confirm their involvement in mediating host–pathogen interactions and their associated immune responses [32]. There are numerous miRNAs that act alongside bacterial or viral pathogenesis or the host immune reaction, including miR-30, miR-146, miR-128, miR-155, miR-15, miR-1289, miR-29, miR-K12-1, miR-K12-3, and others [33–35]. Although lincRNAs are not as conserved as miRNAs, they have an important contribution in regulating the gene expression, including the antiviral response [32]. Among the most important infection-associated lincRNAs to be found were: lincRNA-CD244, lincRHOXF1, lincRNA-CMPK2, IFNG-AS, and linc-SGK1 [32,36–38].

Physiologically, cellular metabolism produces ROS as byproducts that are further involved in many biological processes, including cell signaling, hormone regulation, transcription, apoptosis, ion transport, and immunomodulation. Hence, they lend fundamental aid to the normal functioning of the immune system, especially regarding adaptive immune responses [39]. However, ROS are used by phagocytes and other cell types against different pathogens, and it seems that such defense mechanisms can occur directly through oxidative damage or indirectly by various nonoxidative mechanisms such as autophagy, pattern recognition receptors signaling, T-lymphocyte responses, and neutrophil extracellular trap formation. Still, there are certain pathogens in which ROS can also appear as infection promoters, including *Mycobacterium tuberculosis*, *S. pneumoniae*, *Pseudomonas aeruginosa*, Kaposi's sarcoma-associated herpesvirus (KSHV), human immunodeficiency virus (HIV), porcine circovirus type 2 (pcV2), etc. [40]. Therefore, ROS has proven to be an important involvement regarding many infectious diseases as well.

2. Non-Coding RNAs in Bacterial and Viral Infections

ncRNAs are known as a class of RNA molecules that do not code for proteins and which represent 98% of the human genome composition [41]. ncRNAs, including miRNAs, lncRNAs, and circular RNAs (circRNAs), are involved in the regulation of both physiological and pathological cellular processes. Hence, they play a key role in different human diseases through a variety of gene-regulation mechanisms [42] and in the modulation of the host defense system [43].

During infections, both the host and bacteria have two options: to either adapt to the changes of the environmental or physiological factors or react. The vast majority of bacteria can trigger the expression of so-called "virulence genes", which play a major part in disease pathogenesis, allowing the bacteria to benefit from the host resources. Likewise, infected organisms sense the intrusion and react by activating innate or adaptive immune responses. This complex interplay is referred to as host–pathogen crosstalk [44].

RNA is itself a key regulator molecule, as its physicochemical characteristics make ncRNAs versatile tools for interfering with gene expressions. Thus, a single ncRNA can regulate several pathways simultaneously, and one single gene can be modulated by various ncRNAs for efficient control in a broad range of conditions [44,45].

miRNAs are key regulators of the innate immune defense in response to lipopolysaccharides (bacteria membrane-associated components) [46]. This work has led to the characterization of miR-146 as an anti-inflammatory miRNA. Furthermore, miR-155, miR-146, let-7, and miR-29 also play important roles in the host cells' response to bacteria [47–49]. The contribution of lncRNAs in defense against viruses, especially in inflammatory responses to LPS and live bacteria, has shed more light upon the involvement of ncRNAs in the antiviral responses. Recently, lncRNA profiles in response to infections were analyzed in several mammalian cell lines, and their defense mechanisms were elucidated. Hence, ncRNAs have proven their involvement in the pathogenesis of bacterial and viral infections (Figure 2) [44].

Since ncRNAs have steadily emerged as key regulators of bacterial and viral infections, and novel genomic-based approaches have been developed, providing a more in-depth perspective of the interplay between certain pathogens and ncRNAs [50]. Finally, as one of the most powerful traits of ncRNA structures is to aim for multiple targets by precise base pairing, this allows cells to regulate gene expressions. The vast majority of miRNAs and lncRNAs are differentially regulated in response to bacterial or viral infections within various types of cell and tissues. Therefore, ncRNAs are considered a reservoir of gene expressions that can fine-tune an impressive repertoire of genetic targets (Table 1).

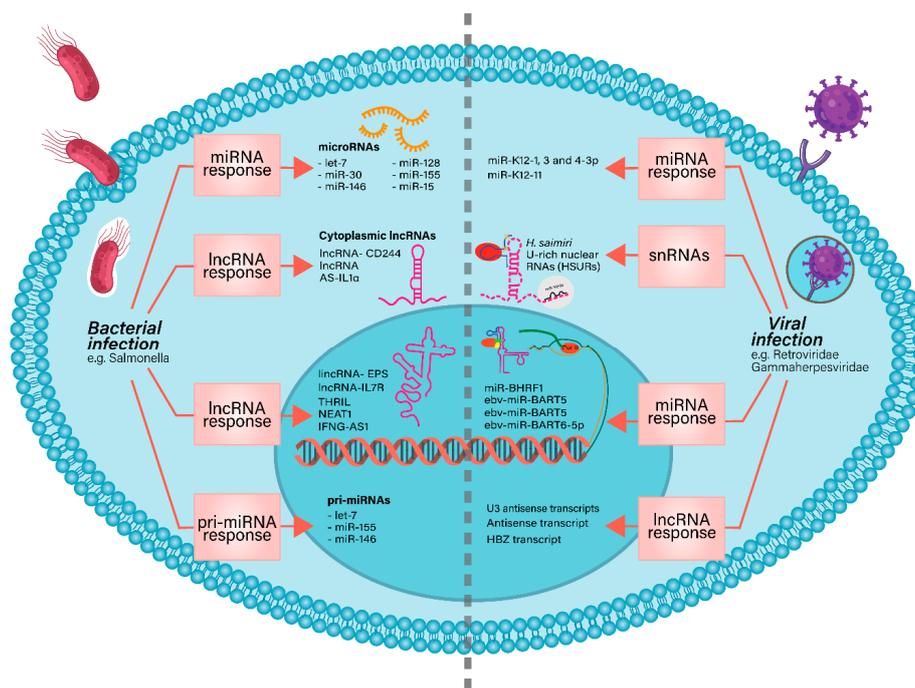


Figure 2. ncRNAs that modulate the response of a cell to bacterial or viral infections. **(Left)** The human ncRNA response to infections by the pathogenic bacterium *Salmonella*. When infections appear, a complex interplay of miRNA and lncRNA occurs, and that is utilized to respond to the *Salmonella* infection. For example, miRNAs miR-155 and miR-146 regulate different sets of transcripts, thus promoting or reducing inflammation. Some examples of miRNA and lncRNAs are shown in the image. **(Right)** The ncRNA types are involved in the host immune response against viral infections via the regulation of gene expressions. lncRNAs from the Retroviridae–antisense transcript, epigenetically regulates gene transcription, and miR-BHRF1 from Gammaherpesviridae promote cell cycle progression and proliferation and inhibit apoptosis. See more in Table 1 [32,44,50–52].

Table 1. ncRNAs associated with bacterial or viral infections.

ncRNA	Regulation	Target/Function	Pathogen	References
miR-1289	↑	Gastric acidity	<i>Helicobacter pylori</i>	[33]
miR-30c	↑	SUMOylation	<i>Salmonella</i>	[53]
miR-30e	↑	Macrophage response to IFN- γ	<i>Mycobacterium tuberculosis</i>	[54]
miR-132	↑	Macrophage response to IFN- γ	<i>Mycobacterium tuberculosis</i>	[54]
miR-26a	↑	Macrophage response to IFN- γ	<i>Mycobacterium tuberculosis</i>	[54]
miR-125b	↑	Production of TNF- α	<i>Mycobacterium tuberculosis</i>	[55,56]
miR-99b	↑	Production of TNF- α	<i>Mycobacterium tuberculosis</i>	[55,56]
miR-155	↓	Production of TNF- α	<i>Mycobacterium tuberculosis</i>	[55,56]
Let-7f	↓	NF- κ B pathway inhibition	<i>Mycobacterium tuberculosis</i>	[57]
miR-29	↓	IFN- γ production	BCG	[35]
	↑	Activation of the pro-survival Akt pathway	<i>Listeria monocytogenes</i>	[34]
	↓	Reduction of humoral immune responses	<i>Citrobacter rodentium</i>	[58]
miR-155	↑	RIP1/3-related necroptosis and PARP-1-mediated necrosis	<i>Salmonella</i>	[59]
	↑	Down-regulation of SHIP	<i>Francisella tularensis</i>	[60]
	↑	Decreased the production of IL-8 and GRO- α	<i>Helicobacter pylori</i>	[33]

Table 1. Cont.

ncRNA	Regulation	Target/Function	Pathogen	References
miR-146a	↑	Suppression of nitric oxide production	<i>Mycobacterium tuberculosis</i>	[61]
miR-128	↑	p53 knockdown	<i>Salmonella</i>	[62]
lncRNA-CD244	↑	Inhibition of TNF- α and INF- γ expression	<i>Mycobacterium tuberculosis</i>	[36]
NeST	↑	IFN- γ transcription	<i>Salmonella enterica</i>	[63]
NEAT1	↑	Decrease the expression of IL-6	<i>Mycobacterium tuberculosis</i>	[37]
	↑	Export of Rev-dependent instability element (INS)	Human immunodeficiency virus	[64]
	↑	IL-8 secretion	Influenza virus	[65]
	↑	Regulation by IRF1, IRF4, STAT1 and STAT3	SARS-CoV-2 virus	[66]
miR-618	↑	Dysregulation of immune function	SARS-CoV-2 virus	[67]
lncRHOF1	↑	siRNA-mediated disruption	Sendai virus	[38]
miR-24-1-5p miR-512-5p miR-4640-3p miR-383	↑	Biomarkers for mild dengue forms		[68]
hsa-miR-21-5p hsa-miR-146a-5p hsa-miR-590-5p hsa-miR-188-5p hsa-miR-152-3p	↑	Biomarker for mild dengue form	Dengue virus	
	↑	non-invasive molecular markers for detecting DENV infection		
miR-548g-3p	↑	Suppress DENV multiplication		[69]
miR-133a miR-484 miR-744 miR-122	↑	Downregulate DENV replication		[70]
	↑	Stabilizes the HCV genome		[68]
lncRNA-CMPK2	↑	Interferon response modulation	Hepatitis C virus	[71]
GAS5 miR-25	↑	Decoy of HCV NS3 protein		[72]
miR-130a/b let-7a BART BHLF1 miR-141	↓	HCV reduces their levels offsetting their antiviral capacity		[73,74]
	↑	Tumorigenesis	Epstein–Barr virus	[75]
	↑	Pro-viral effect	Enterovirus 71	[76]
miR-485-5p	↑	Suppression of the antiviral response and enhanced viral replication	Newcastle disease virus	[77]
miR-148	↑	Valuable biomarkers for severe influenza virus infections		[78]
miR-31 miR-29a	↓		Influenza virus	
miR-34c-3p miR-29a-3p miR-30c-5p miR-181a-5p miR-323 miR-491 miR-654 miR-146a	↑	Biomarker		[79,80]
	↓	Biomarkers		[79,80]
	↑	Inhibition of influenza virus replication		[81]

Table 1. Cont.

ncRNA	Regulation	Target/Function	Pathogen	References
MALA1 LINC01426 (uc002yug. 2)	↑	Activate HIV-1 replication and reactivates HIV-1 from latency	Human immunodeficiency virus	[82,83]
7SKRNA NEAT1 NRON	↑	Repress HIV-1 infection		[83–85]
GAS5	↓	Inhibits HIV-1 replication		[83,86]
HEAL	↑	Regulates HIV-1 transcription		[83,87]
LINC00173	↓	Dysregulates the immune response		[88]
MALAT-1	↑	Cervical cancer cell growth	Human papilloma virus	[89]
	↑	Induction of unfolded protein response	Flaviviruses	[90,91]
miR-155	↑	Biomarker for poor prognosis		[90,91]
miR-218	↓	Inhibition of cancer cell migration and invasion	Human papilloma virus	[91–93]
miR-195	↓	Biomarker for advanced clinical stages		[91,94]
miR-375	↓	Biomarker for poor prognosis		[91,94]
miR-34a miR-23b	↓	Increased migration of cervical cancer cell lines		[91,95]

Both bacterial and viral infections can alter the expression of miRNAs and lncRNAs [96], which are supposed to regulate the inflammatory response of immune cells toward infections. For example, miR-99b plays a crucial role in the pathogenesis of *M. tuberculosis* infection, and the downregulation of miR-99b in dendritic cells upregulates different proinflammatory cytokines, such as IL-6, IL-12, and IL-1 β [55]. TNF- α is an important target with a key role in the host defense response to *M. tuberculosis* infection. Thus, *M. tuberculosis* can inhibit TNF- α production via modulation of the miRNA host response and accelerate infection by facilitating replication in the host cell [55,97]. *M. tuberculosis* also decreases the production of TNF- α by regulating miR-125b, miR-155, and miR-99b [58]. Finally, miRNA let-7 regulates the immune response to *M. tuberculosis* infection via A20, an inhibitor of the NF- κ B pathway [54].

2.1. NcRNAs Involved in Bacterial Infections

In another case, miR-29 expression was found downregulated in mice infected with *Listeria monocytogenes* or *Mycobacterium bovis* bacillus Calmette-Guérin (BCG), the downregulation being observed in IFN- γ -producing natural killer cells, CD4(+) T cells, and CD8(+) T cells [35].

miR-155 is another important ncRNA that can trigger a powerful immune response against bacterial pathogens. miR-155 was required for optimal CD8+ T-cell responses to *Listeria monocytogenes* [34] but had a slower clearance upon *Citrobacter rodentium* infection [58]. In macrophages, miR-155 upregulation by Salmonella infection was mediated by RIP1/3-related necroptosis and PARP-1-mediated necrosis, leading to macrophage death [59]. The release of proinflammatory cytokines in human monocytes infected with *Francisella tularensis* was found positively regulated by miR-155 [60]. Moreover, miR-155-containing exosomes were found to be important adjuvants for improving vaccine efficacies and, also, to combat infections like the one produced by *Helicobacter pylori* [98]. Furthermore, miR-155 decreased the production of IL-8 and GRO- α in gastric epithelial cells after *H. pylori* infection [99]. Toll-like receptors (TLRs) are germline-encoded pattern recognition receptors (PRRs) known as key players in host cell identification and responses to bacterial and viral agents [100]. Studies regarding the biological function of miR-146a during mycobacterial

infection proved that it promotes mycobacterial survival in macrophages through the suppression of nitric oxide production [61]. Recent evidence has revealed mir-133a-1-3p and mir-133a-2-3p as potential circulating miRNAs associated with Gram-positive bacterial infections [101].

In vivo studies found that the intragastric delivery of anti-miR-128 enhances M-CSF-mediated macrophage recruitment and suppresses *Salmonella* infection, with miR-128 expression being induced via the p53 signaling pathway [62].

There is growing evidence that lncRNAs can act as positive or negative effectors on antibacterial immunity. Thus, the host uses lncRNAs to protect itself from microbial invasion by regulating the immune-related genes at the epigenetic, transcriptional, and post-transcriptional levels. However, bacteria can also control the host signaling pathways by guiding the host lncRNAs to evade immune clearance [32]. In *M. tuberculosis* infection, lncRNA-CD244 is upregulated by the T-cell inhibitory molecule CD244 and functions as an epigenetic inhibitor of TNF- α and INF- γ expression [36]. *Salmonella enterica* pathogenesis was decreased by lncRNA Nettoie Salmonella pas Theiler's (NeST), which induces IFN- γ transcription, especially in activated CD8+ T cells [63]. In peripheral blood mononuclear cells (PBMCs) from patients infected with *M. tuberculosis*, NEAT1 was found upregulated, decreasing the expression of IL-6 and increasing the replication of *M. tuberculosis*, indicating an antituberculosis role of NEAT1 [37]. Intracellular bacteria, such as Salmonellae, Mycobacteria, Helicobacter, and Listeria, were observed to interfere with the expression of lncRNAs in order to alter host cell immune defense systems [32].

2.2. ncRNAs in Viral Infections

Some viruses can also produce miRNAs necessary for their survival and for evading host immune responses. The mechanisms involved in these processes consist of viral replication [102], host immune system evasion [103], viral latency, and the regulation of host and viral genes [104]. The interaction between viral RNAs and host miRNAs is proven to be necessary for viral RNA stability, replication, or other pathogenesis-associated processes [105]. Furthermore, viruses can counteract miRNA antiviral defenses by releasing specific virulence factors that are known as viral suppressors of RNA silencing (VSRs) [106]. The degradation of miRNAs after a viral infection requires the 3'-end addition of non-templated nucleotides by tailing enzymes, then degradation by exonucleases [107].

Interestingly, miRNAs can inhibit SARS-CoV-2 infection by blocking viral replication, cellular receptors, and the function of viral proteins [108]. In terms of COVID-19 treatment options, miR-618 can be an important target, as it regulates the immune responses and viral replication [67]. Likewise, inflammation-associated miR-31-5p was found to be one of the most upregulated miRNAs in the early stages of COVID-19 [109]. lncRNAs have been also identified to be involved in virus replication, promoting viral infection. Viral genes can regulate the levels of cellular lncRNAs by modulating the protein-encoding gene expression. Additionally, cellular lncRNAs are used by viruses to regulate the expression and function of both host and viral genes [110]. Herpesviruses produce persistent infections. In this case, macrovesicles transfer viral and cellular factors, allowing the virus to regulate the cellular microenvironment, with advantages for both the virus and the host [75]. Most induced lncRNAs have been observed as direct targets of IFN signaling or IFN stimulated genes (ISGs) in viral infections, as is the case of mouse macrophages infected with vesicular stomatitis virus (VSV) [111]. The viral infections identified in some organs, such as the placenta in mammals, are also linked to some lncRNAs [112].

In a recent study, it was observed that lncRHOXF1, which triggers the host response to viral infections, increases in human trophoblast progenitor cells. However, lncRHOXF1 can be disrupted by siRNA during infection, decreasing the expression of viral response genes and, finally, enhancing virus replication [38]. The upregulation of NEAT1 was observed in T cells infected by HIV-1, the downregulated NEAT1 being responsible for the increase of HIV-1 replication and, also, for the delivery of HIV-1 mRNA

from the nucleus to cytoplasm [64]. Influenza virus and HSV infection also induced NEAT1 expression, and cytokines such as IL-8 promoted the action of NEAT [65]. The expression of NEAT1 was also increased in the lung tissues of patients infected with SARS-CoV-2 virus [66]. lncRNA-CMPK2 increased Hepatitis C virus replication while being strongly upregulated in a group of HCV-infected human livers, enhancing its role in the modulation of the interferon response [71]. Hepatitis C virus replication was inhibited via GAS5 by targeting the viral NS3 protein, the innate immune response being poor [72]. Zhang et al. observed that the Epstein–Barr virus (EBV) is able to encode its own viral lncRNAs (BART lncRNAs and BHLF1 lncRNA), which are involved in tumorigenesis-associated processes [75].

Nevertheless, some miRNAs could be found present in both bacterial and viral infections while also being highly involved in multiple biological processes (Table 2).

Table 2. Common miRNAs for both bacterial and viral infections.

ncRNA	Target/Function		Pathogen Regulation		References
	Viral	Bacterial	Viral	Bacterial	
miR-146a	-Inhibition of influenza virus replication; -Unknown	Suppression of nitric oxide production -Production of TNF- α -Activation of the pro-survival Akt pathway	\uparrow Influenza virus $\uparrow\downarrow$ Hepatitis C virus	\uparrow <i>Mycobacterium tuberculosis</i>	[61,81]
miR-155	Biomarker for poor prognosis, IFN-related molecule	-Reduction of humoral immune responses -RIP1/3-related necroptosis and PARP-1-mediated necrosis	\uparrow Hepatitis C virus	\downarrow <i>Mycobacterium tuberculosis</i> \uparrow <i>Listeria monocytogenes</i> \downarrow <i>Citrobacter rodentium</i> ; \uparrow <i>Salmonella</i>	[55,61,90]
miR-16 miR-30c	Increased production of ROS Biomarker	Unknown SUMOylation	\downarrow SARS-CoV-2 \downarrow Influenza virus	\downarrow <i>C. trachomatis</i> \uparrow <i>Salmonella</i>	[113,114] [53,79]
NEAT1	Repress HIV-1 infection, export of Rev-dependent instability element (INS)	Decrease the expression of IL-6	\uparrow Human immunodeficiency virus	\uparrow <i>Mycobacterium tuberculosis</i>	[37,64]
miR-133a	Downregulate DENV replication	Biomarker-circulating miRNA	\uparrow Dengue virus	<i>Gram-positive bacterial (mir-133a-1-3p, mir-133a-2-3p)</i>	[70,101]
let-7	-HCV reduces their levels offsetting their antiviral capacity; -TLR4 and STAT3 signaling	-Induced acute inflammation characterized by neutrophil infiltration	\downarrow Hepatitis C virus (let-7a) \downarrow Hepatitis B virus (let-7)	\downarrow <i>Helicobacter pylori</i>	[73,74,114,115]
miR-125b	TLR2/MyD88 signaling	Production of TNF- α	\downarrow Hepatitis C Virus	\uparrow <i>Mycobacterium tuberculosis</i>	[55,56,114]
miR-29	Biomarker for severe influenza virus infections	-IFN- γ -production; -Unknown	\downarrow Influenza virus (miR-29a)	\downarrow BCG <i>Listeria monocytogenes</i> \downarrow <i>C. trachomatis</i>	[35,78,114]
miR-372, miR-373	NFIB-dependent signaling	Cell cycle and apoptosis	\uparrow Hepatitis B Virus	\downarrow <i>Helicobacter</i>	[49,114]
mir-122	Stabilizes the HCV genome	Unknown	\uparrow Hepatitis C Virus	\downarrow <i>Enterobacteriaceae</i> spp.	[68,114]
miR-223	Antiviral–target Indirect: STMN1 mRNA	Unknown	DENV-2 (strain TR1751)	\uparrow <i>Enterobacteriaceae</i> spp.	[68,114]
miR-125b	TLR2/MyD88 signaling/ Immune response	Directly targets mRNA of TNF	\downarrow Hepatitis C Virus	\uparrow <i>Mycobacteria</i>	[49,114]
miR-21	-STAT3 signaling; -Non-invasive molecular markers for detecting DENV infection.	Immune response	\uparrow Hepatitis B virus \uparrow Dengue virus hsa-miR-21-5p	\uparrow <i>Salmonella</i>	[49,68,114]

2.3. Other ncRNAs Involved in Bacterial or Viral Infections

Among the wide class of ncRNAs, we can also find piRNAs, which are an animal-specific group of small silencing RNAs that bear the 2'-O-methyl-modified 3' termini and regulate the synthesis of PIWI proteins. While other types of ncRNAs such as miRNAs and siRNAs are derived from double-stranded precursors, piRNA biogenesis starts from long single-stranded transcripts. With respect to their biologic activity, piRNAs are primarily involved in regulating genome stability, but they were recently found to be associated with different bacterial and viral infections [116]. Hence, piRNA expression patterns were found to be correlated with a metastatic stage of HPV-positive head and neck squamous cell carcinoma (HNSCC), which affects over 550,000 individuals each year [117]. Recent studies have confirmed the status of piRNAs as new players in pulmonary tuberculosis pathogenesis, which is caused by *M. tuberculosis* bacteria, due to their involvement in transcription, protein binding, and immunity [118,119].

While initially thought of as byproducts of aberrant splicing, circRNAs have recently regained their status as a special type of evolutionarily conserved, covalently closed single-stranded RNA and are now highly investigated for their biological roles: the regulation of gene expression, protein encoding, protein activity inhibition, etc. [120]. Furthermore, as confirmed by a recent study, circRNAs are also found to be associated with both viral infections (virus-derived circRNAs: HPV16 circE7, HBV circRNA, MHV68 circM11_ORF69, KSHV circvIRF4, EBV circ_RPMS1, circBARTs, circvIRF4, circEBNA_U, etc.) and with the host immune response against viral infections (host circRNAs: hsa_circ_0000479, hsa_circ_0004812, hsa_circ_0005389, hsa_circ_0003863, hsa_circ-GATAD2A, hsa_circRNA3046, etc.), where they regulate both viral replication and the host antiviral immune responses [121]. Likewise, when it comes to bacterial infections, circRNAs do participate in associated pathogenesis, such as in pulmonary tuberculosis, where hsa_circRNA_001937 is upregulated and hsa_circRNA_102101 downregulated, highlighting their potential as valuable clinical biomarkers [122].

It is already well-known that most viruses rely on their host cell translation machinery in order to efficiently synthesize their own viral proteins. In fact, recent evidence has highlighted diverse implications of host transfer RNAs (tRNAs) in the process of virus replication and associated pathogenesis. For instance, different RNA viruses (IAV, HIV-1, NiV, and HAV) manipulate host tRNA pools to favor viral protein translation. Furthermore, the formation of tRNA-derived fragments upon infection was also found to promote viral replication. It seems that viruses can pursue these processes by either adjusting host cell tRNAs to specifically match the viral codon usage or by shifting their viral codon usage towards the host codon [123].

3. Reactive Oxygen Species in Bacterial and Viral Infections

Whenever a potentially harmful pathogen is spotted, one of the early responses of host innate immunity is the production of ROS. Free oxygen radicals are highly toxic to both bacterial and viral pathogens, usually being produced to prevent the colonization of certain pathogens. As a part of the intracellular redox profile, ROS are also involved in the orchestration of a wide variety of signaling networks. "Oxidative stress" describes a physiological state where oxygen radicals exceed those of antioxidants, hence potentiating apoptosis, tumorigenesis, and immune responses [124–127]. Here, we describe the implications of ROS in different bacterial and viral infections accordingly to multiple studies found in the scientific literature.

One research study reports that kinases Mst1 and Mst2 play an important role in the production of ROS by controlling mitochondrial trafficking and mitochondrion–phagosome juxtaposition. Mitochondria need to be juxtaposed to phagosomes in order to synergistically generate sufficient ROS in phagocytes to further ensure a proper microbial counteraction. It appears that Mst1 and Mst2 activate Rac GTPase in order to assemble the TRAF6–ECSIT complex required for mitochondrial recruitment to phagosomes. Sometimes, the Rac form is inactive (e.g., mutant Rac2D57N) and the ROS production levels are low, which elevates the susceptibility to bacterial infection [128].

In another study, ROS were reported to possess a highly antimicrobial effect against bacterial, viral, and fungal infections, as it can prevent and break down biofilms. These findings promote ROS as a highly suitable player in different chronic inflammatory diseases: chronic wounds, ulcers, burns, and, especially, in bacterial infection cases when antibiotics become ineffective. Furthermore, ROS-positive effects are also supported by early clinical data, as they could be used to reduce bacterial infection risks in the treatment of skin and soft tissue lesions [129].

Some opportunistic pathogens, such as *Acinetobacter baumannii*, are associated with different nosocomial infections, like bacteremia, pneumonia, meningitis, urinary tract, or wound infections. The production of ROS within the phagolysosome has effective antimicrobial properties. Hence, in *A. baumannii* infections, ROS contributes to the bactericidal functions of neutrophils and macrophages, playing a key role in the host defense, with toxic effects against the pathogens. However, the uncontrolled regulation of mitochondria-derived ROS could lead to chronic inflammation and pathologies during infections [130,131].

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase also produces important amounts of ROS that are engaged in the antimicrobial host defense and inflammation system. When absent or insufficient in humans, recurrent or severe bacterial infections are usually around the corner. Hence, the discharge of high concentrations of ROS helps with the clearance of invading bacteria. Host immune cells, such as neutrophils, will also release considerable amounts of ROS at the site of infection [132]. Furthermore, in the case of chronic granulomatous disease (CGD), an inherited condition characterized by recurrent bacterial and fungal infections, the impaired host defense is due to the defective production of ROS by phagocytes. This is caused by mutations in genes encoding the NADPH oxidase complex, but the pathogen, however, depends on the geographical area. In North America and Europe, the main bacteria responsible for such diseases are *S. aureus*, *Burkholderia cepacia*, *Serratia marcescens* [133–136].

Still, some studies indicate the negative effects of excessive ROS levels for host organisms. For example, in *H. pylori* infections, activated neutrophils ensure high amounts of ROS, but it seems that the bacteria itself produces ROS. Hence, researchers have reported that such *H. pylori*-induced ROS biogenesis could affect gastric epithelial cell signal transduction, resulting in gastric carcinogenesis [137].

Therefore, as byproducts of cellular metabolism, ROS can be either beneficial or detrimental to the host cells, depending on their concentration. Besides the already-renowned antimicrobial properties of ROS, they seem to also have an opposite effect when it comes to viral pathogenesis. Several viral infections cause elevated oxidative stress levels, and some viruses can use this ROS excess to enhance their pathogenesis. Some examples of such viral pathogens are: SARS coronavirus and rabies virus, rhinovirus, West Nile virus and vesicular stomatitis virus, hepatitis C virus, human immunodeficiency virus, and influenza virus [138].

Despite all the modern therapies available, viral infections still inflict an unacceptable grade of morbidity and mortality, as they are the primary cause of pneumonia. However, recent findings highlighted the fact that lung cells can protect themselves against viral pathogens, even in the absence of leukocytes. It seems that this protection is due to an induction of ROS, apparently without reliance on type I interferon signaling [139].

Virus-induced oxidative stress is essential for both the viral life cycle and its pathogenesis. To counteract the elevated levels of ROS induced by viral infections, host cells activate an antioxidative defense system pathway called erythroid 2p45-related factor 2 (Nrf2) that facilitates cytoprotection. Recently, a series of studies reported the capacity to positively or negatively regulate the Nrf2 pathway and the ROS levels via certain viruses. Furthermore, it seems that such a modulation of the host antioxidative response turned out to be essential for the progression of several viral diseases (Table 3) [140].

Table 3. Regulations of the Nrf2 pathway by pathogenic viruses.

Virus	Disease	ROS	Nfr2	Reference
MoMuLV ts1	Neurodegenerative disease	H ₂ O ₂ ↓	↑	[140,141]
	Neurodegenerative disease	↑	↑	[140,142,143]
HIV	Neurocognitive disorder	H ₂ O ₂ ↑	↑	[140,144]
	AIDS	↑	↑	[140,144–146]
HCV	Respiratory disorder	↑	↓	[140,147]
	HCC	ND	↑	[140,148]
Influenza	Respiratory disease	↑	Nuclear localization ↑	[140,149]
RSV	Respiratory disease	↑	↓	[140,150]
HBV	Viral hepatitis	↓	↑	[140]
HSV	Encephalitis neurotoxicity	↑	↑	[140,151,152]
HCMV	Congenital abnormalities	↑	↑	[140,153]
KSHV	Sarcoma	↑	Nuclear localization ↑	[140,154]
DENV	Fever	↑	↑	[140,155]

However, the presence of certain bacteria and viruses can cause the activation of host ROS generation systems that further exert antibacterial and antiviral effects (Table 4).

Table 4. Common host ROS generation systems for both viral and bacterial infections.

ROS Generator	Effect of ↑ ROS		Pathogen Trigger		Reference
	Virus	Bacteria	Virus	Bacteria	
Mitochondrial ROS	Damage the mtDNA, membrane lipid permeability, release of cytochrome C and apoptosis	-Bactericidal; -Stimulation of TLR9 by CpG-containing DNA and subsequent ROS production	Hepatitis C virus	<i>Salmonella typhimurium</i> <i>Staphylococcus aureus</i>	[156]
ER stress	Boosts proinflammatory cytokine production via MAPK-killing	Promote oxidative and nonoxidative mechanisms of microbe elimination	both	both	[156]
NADPH oxidase (NOX)	Induce activation of Caspase-3 and apoptosis	Promote oxidative and nonoxidative mechanisms of microbe elimination	both	both	[39]
NOX2-derived ROS in macrophages	Produce ROS in the phagosomal membrane, resulting in elimination of the pathogen	Induction of superoxide and H ₂ O ₂ in lung cell and nuclear ROS generation => histone acetylation and chromatin remodeling	Influenza A virus	<i>Escherichia coli</i> <i>L. monocytogenes</i>	[156,157]
NOX4	Induction of superoxide and H ₂ O ₂ in hepatocytes	Adjust inflammation through neutrophils that modulating inflammation	HCV infection	<i>P. aeruginosa</i>	[156,158]
NF-κB pathway	Inducing ROS-upregulation of antiviral genes in lymphocytes	Adjust inflammation through neutrophils that modulating inflammation	Japanese encephalitis virus (JEV)	<i>C. albicans</i>	[156,159]
Activation of NLRP3 inflammasome	Antiviral/antibacterial activity		RNA viruses DNA viruses	bacterial RNA	[156,160]

4. The Interplay between ncRNAs and ROS in Bacterial and Viral Infections

The regulatory role of cellular miR-17 in ROS generation has been observed in microglial cells exposed to the HIV-1 Tat C protein, the increasing levels of ROS production leading to the activation of microglial cells and intensification of cytokine production [161]. The suppression of miR-16 is a major contribution to lung destruction in patients with severe SARS-CoV-2 infections due to the increased production of ROS; the upregulation of miR-16 can be taken into account to inhibit the detrimental symptoms of COVID-19 [113].

lncRNA HOTAIRM1 induces increased levels of ROS during latent HIV infection and promotes myeloid-derived suppressor cell expansion, contributing to HIV progression

by impairing antiviral immunity [162]. The expressions of HOTAIRM1 are significantly upregulated in CD33+ myeloid cells derived from hepatitis C virus (HCV)-infected patients, and this promotes the activation of ROS [162]. Regarding miR-155, its increased expression was found linked to enhanced ROS production by targeting SHIP1 in macrophages after BCG infection [163]. Additionally, miR-155 negatively regulates ROS-triggered apoptosis during MTB infection, as well as the suppression of cytokine signaling 1 (SOCS1) and inhibits tumor necrosis factor alpha (TNF- α) [164]. Bacterial pulmonary infections are common in lung cancer patients and high levels of ROS due to TLR4 activation promoting primary lung cancer development through miR-21 [165]. In infected macrophages, the elimination of *M. tuberculosis* requires the presence of miR-27b that induces cell apoptosis through the p53-ROS-signaling pathway [166]. An enhanced expression of the miR-302/367 cluster increases the clearance of *P. aeruginosa* by the control of ROS production via regulation of the mitophagy response against infection. The production of ROS can be decreased by the inhibition of NF- κ B in macrophages, which may also reduce the cell damages produced by *P. aeruginosa* infection and maintain cellular homeostasis [167]. *E. faecalis* infection causes the downregulation of miR-17-92 cluster expression, a consequence of ROS stimulation that induces DNA damage [168]. Apoptotic-regulating miRNAs, such as miR-200a, are downregulated by the influenza virus but, due to the ROS conditions, are observed to enhance the antioxidant pathway in infected mice [169]. Epstein-Barr virus (EBV) nuclear antigen 1 (EBNA1) is a viral protein that induces malignant transformation through a modulated increase of ROS and the associated production of cell viability by the regulation of miRNA34a [170]. The level of ROS is regulated through the HOTAIR-Sirt1 signaling pathway in liver cells infected by Hepatitis C virus [171] BCG infection, which induces macrophage cell apoptosis and an increase of lincRNA-Cox2 expression, respectively, of ROS secretion [172]. Finally, in hepatitis B virus-related hepatocellular carcinoma, the lincRNA AX800134 was identified, an oncogenic factor whose upregulation could be reversed by ROS scavenger pyrrolidine dithiocarbamate (PDTC) [173].

5. Conclusions

Despite all of the collaborative, scientific efforts, bacterial and viral infectious diseases are still emerging as one of the leading causes of morbidity and mortality worldwide. None of the current diagnosis methods can rapidly and accurately discriminate between those two types of infections, and this is one of the reasons why clinicians tend to misguide proper diagnoses. These hard-to-avoid medical errors further increase the antimicrobial resistance and even cause more harm, or death, in some instances.

However, as recent advances in the field of genomics have allowed the discovery of ncRNAs, which have proven to be valuable players in both the host immune response and bacterial and viral pathogenesis, we are steadily stepping in the right direction. The implication of such ncRNAs (miRNAs and lincRNAs) is gaining more and more interest from the scientific community, especially since they have quite the potential to become the building blocks for better diagnosis and treatment options in infectious diseases.

As future directions regarding the use of ncRNAs in the management of bacterial or viral infections, using miRNAs and lincRNAs for the development of novel mRNA therapeutics, such as mRNA-based vaccines, shifts perspectives towards using ncRNAs for establishing novel and innovative therapeutic solutions [174–176]. Regarding the ROS associated with different bacterial or viral infections, extensive research must be conducted in order to uncover their potential in the development of novel and efficient diagnostic and treatment methods. One future lead might be their usage as therapeutic measures against viral infections, since they can impair RNA integrity faster than other molecules [177]. Therefore, encouragement to further pursuit research on the roles of ncRNAs and ROS in bacterial and viral infections represents an important message, as they can reshape the way we currently manage such cases in clinical setups.

Finally, gearing up healthcare providers with the proper tools for the early and efficient diagnosis of infectious diseases has become an urgent, global need. Therefore, the deeper

we decipher the molecular aspects of bacterial and viral pathogenesis, we find improved ways of eliminating them. ncRNAs could be candidates and become largely used in developing novel molecular diagnosis tools but, also, for crafting superior therapeutic options. ROS might actually be helpful with this process as well, due to their prooxidant properties that could be useful against different pathogenic infections.

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