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Review Paper

Noncoding RNAs: modulators and modulatable players during infection-induced stress response

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Abstract

The human genome has an almost equal distribution of unique and transposable genetic elements. Although at the transcriptome level, a relatively higher contribution from transposable elements derived RNA has been reported. This is further highlighted with evidence from pervasive transcription. Of the total RNA, noncoding RNAs (ncRNAs) are significant contributors to the transcriptome pool with sizeable fraction from repetitive elements of the human genome, inclusive of Long Interspersed Nuclear Elements (LINEs) and Short Interspersed Nuclear Elements (SINEs). ncRNAs are increasingly being implicated in diverse functional roles especially during conditions of stress. These stress responses are driven through diverse mediators, inclusive of long and short ncRNAs. ncRNAs such as MALAT1, GAS5, miR-204 and miR-199a-5p have been functionally involved during oxidative stress, endoplasmic reticulum (ER) stress and unfolded protein response (UPR). Also, within SINEs, Alu RNAs derived from primate-specific Alu repeats with ∼11% human genome contribution, playing a significant role. Pathogenic diseases, including the recent COVID-19, leads to differential regulation of ncRNAs. Although, limited evidence suggests the need for an inquest into the role of ncRNAs in determining the host response towards pathogen challenge.

Key words: ncRNAs; infections; stress response; unfolded protein response (UPR); ER stress; SARS-CoV-2

Introduction

Until recently, a great proportion of RNA not coding for any protein (∼98%) was referred to as 'junk'. This ncRNA is a new 'treasure trove' for their involvement in various gene regulations and disease pathogenesis. ncRNAs are classified into two broad categories with a base number cut-off of 200 nucleotides (nts) [1]. ncRNAs below 200 nts are termed as small noncoding RNAs (e.g. miRNA, piRNA, snRNA, rRNA, tRNA, snoRNA), while ncRNAs with more than 200 nts are termed as long ncRNAs (lncRNAs). lncRNAs are further classified as long intergenic ncRNA (lincRNA), natural antisense transcript, bidirectional lncRNA and intronic lncRNA [2, 3].

After RNA polymerase II mediated transcription, lncRNAs undergo specific post-transcriptional modifications similar to mRNA like 5′-capping, 3′-polyadenylation and intracellular transport [4]. Emerging experimental pieces of evidence highlight the gene regulatory activity of ncRNAs at both transcriptional and translational levels like splicing, epigenetic modulations, transcription and translation [2]. A few ncRNAs contain a short open reading frame and are associated with ribosomes, indicating their possible additional role in mRNA regulation [5, 6]. The cellular interactions of ncRNAs are mainly mediated by base pairing, secondary structures and transcriptional regulations [7]. The transcriptome wide distribution and functional classification of ncRNAs are depicted in Figure 1.

Next-generation sequencing (NGS) enabled evidence highlighted the functional role of ncRNAs in several disease pathologies, infections, inflammation and stress [8–14]. ncRNAs are dysregulated in many disease pathologies, either as a secondary

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Janani Srinivasa Vasudevan: I am interested to understand the host–pathogen interaction from the Genomics perspective. This includes knowing the genome features of the pathogen as well as the host response.
Rajesh Pandey: Lab is working towards INtegrative GENomics of HOst-PathogEn (INGEN-HOPE). Elucidation of the role of ncRNA during host stress response leading to physiological homeostasis is one of the central themes.

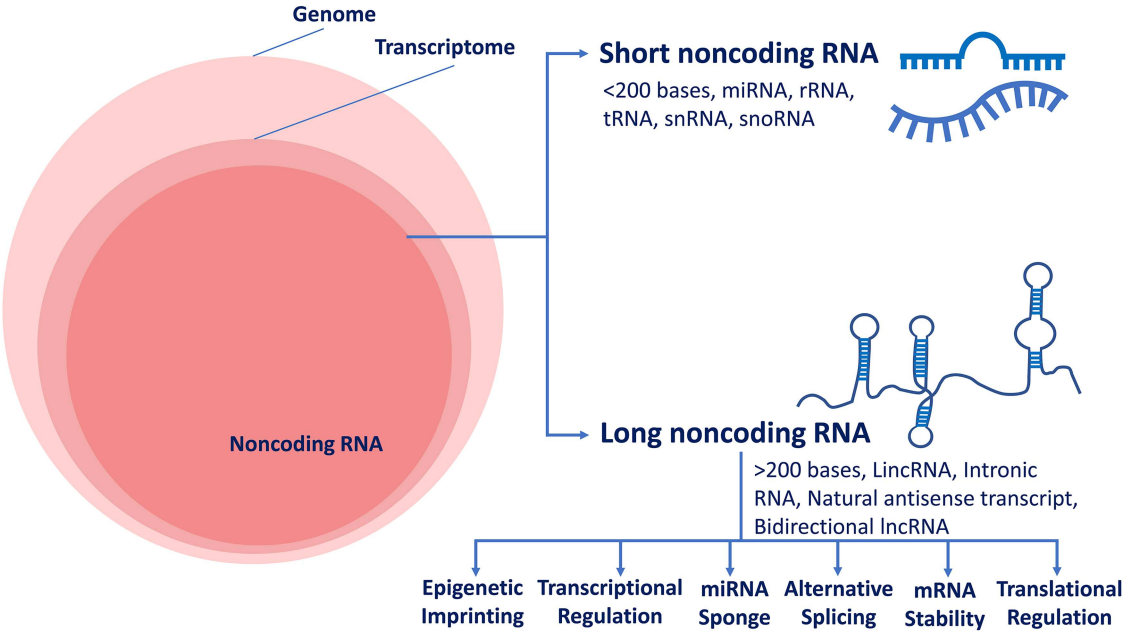

Figure 1. Transcriptome wide distribution and functional classification of ncRNAs. The left panel shows Venn diagram with components that constitute the human genome. The right panel shows different classes of ncRNAs.

effect of disrupted mRNA expression or they may act as an active driver of the pathogenesis [7]. Augmented understanding of the ncRNA functions might facilitate molecular insight into the inflammation, stress and immune regulation, especially host–pathogen interaction. This may help identify putative therapeutic interventions towards infectious diseases. Oxidative stress, endoplasmic reticulum (ER) stress, unfolded protein response (UPR), immune action and inflammation are the major hallmarks of infection. This review aims to bring together the facets of above-mentioned signs of infection and highlights the role of ncRNAs during pathogen-induced stress response.

Oxidative stress response during infection

Normal cellular aerobic metabolism produces reactive oxygen species (ROS) as a by-product in multiple organelles such as mitochondria, ER and peroxisome. ROS are oxygen-containing reactive chemicals like hydrogenperoxide (H_2O_2), superoxide ($O_2^{\bullet-}$) and hydroxyl radical ($^{\bullet}OH$). These are subsequently scavenged by antioxidant enzymes to maintain the redox homeostasis [15]. Generally, ROS are involved in cellular signal transduction, cytokine regulation, immunomodulation, regulation of transcription and apoptosis. An imbalance between ROS generation and scavenging disrupts the redox homeostasis, leading to the accumulation of ROS in cells, and oxidative stress. This damages tissue, protein, lipid and DNA, followed by activation of inflammatory signalling pathway and eventually, cell death [16, 17].

Role of ncRNAs during infection-induced oxidative stress

Since the first report in 1979 [18], several studies have reported viral infection induced oxidative stress, and cellular damage, including members of Flaviviridae genus such as Zika virus [19, 20], Dengue virus (DENV) [21, 22], Hepacivirus [23, 24] and West Nile virus [25, 26]. DENV induces NOX-mediated oxidative stress, activates interferon regulatory factor 3 (IRF3), interferon regulatory factor 7 (IRF7), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), signal transducer and activator of transcription 1 (STAT1) causing cell damage, particularly in dendritic cells [21]. DENV also induces CCL5 and CCAAT/enhancer-binding protein β (C/EBPβ) leading to hepatocellular oxidative stress [27]. Highly pathogenic strains of Influenza A virus (IAV) are also reported to induce oxidative stress. The H3N2 and HKx31 strains of IAV induce both cellular and mitochondrial ROS, causing cellular damage and lung injury [28–30], whereas PR8 strain induces NOX2 NADPH oxidase-mediated ROS in the endosome which modulate IAV pathogenesis [31]. Reduction of oxidative stress was found to decrease inflammation and facilitate disease recovery in both the cases [30, 31].

In human immunodeficiency virus (HIV) infected individuals, increase in oxidative stress, with an elevated level of ROS production, oxidized nucleotide (8-oxo-G), lipid peroxidation and associated formation of malondialdehyde (MDA) in plasma were detected [32–35]. Other studies also highlighted reduced total antioxidant activity [36], decreased reduced glutathione/oxidized glutathione (GSH/GSSG) ratio [37] in lung epithelial fluid and decreased GSH content in blood during HIV infection [33–35]. The majority of the Hepatitis C virus (HCV) proteins (E1, E2, NS3, NS4B, NS5A) induce oxidative stress in hepatocytes, hepatic stellate cells and peripheral blood mononuclear cells (PBMC) [38–42]. Localization of HCV core proteinsin ER and mitochondria affects Ca_2^+ efflux from ER to mitochondria. This causes oxidation of GSH and increased mitochondrial ROS [43]. The association of oxidative stress during infection seems to be important as several studies highlight that antioxidant treatment leads to better infection management [31, 44, 45].

Two independent research groups reported the involvement of miR-155 in oxidative stress during infection. Wang *et al.* [46] reported the role of miR-155 during *Mycobacterium* infection, while Yang *et al.* [47] highlighted the same in acute kidney

Table 1. ncRNAs involved in stress and immune response

ncRNAs	Cellular stress response	Immune response	References
MALAT1	MALAT1 regulates generation of ROS	MALAT1 induce IL-6, IL-1β, TNF-α, CXCL8 and acts as sponge of miR-146a	[62–64]
NEAT1	Modulates superoxide in LPS-treated rat mesangial cells	Promotes activation of NLRP3, NLRC4 & AIM2 inflammasome to activate IL-1β and pyroptosis	[65, 66]
HULC	Upregulated by oxidative stress; regulate CCA cell migration and invasion by targeting IL-6 and CXCR4 via sponging miR-372/miR-373	Regulates expression of proinflammatory VCAM1, ICAM1, Il-6 TNF-α & IL-8 during LPS-induced sepsis	[67–69]
XIST	Upregulated by oxidative stress; induces endothelial to mesenchymal transition (EMT) & promotes oxidative stress-induced Osteosarcoma cell invasion & migration	IL-6 is increased with XIST expression in CFA/LPS induced female mice	[70, 71]
H19	Upregulated in oxidative stress; regulate CCA cell migration & invasion by targeting IL-6 & CXCR4 via sponging let-7a/let-7b	H19 elevate levels of TNF-α, IL-6, IL-8 & IL-1β mediated by NF-κB induced signalling cascade in *H. pylori* infected cells. H19 overexpression negatively regulates miR-874 and decreases proinflammatory cytokines in sepsis	[67, 72, 73]
GAS5	Decreases the level of ROS & MDA; increases the level of SOD	GAS5 is associated with KLF2 regulation & NF-κB inhibition in sepsis	[74, 75]
UCA1	Downregulate UCA1 reduces oxidative stress; inflammation in Parkinson's through the inhibition of the PI3K/Akt signalling pathway	Regulates expression of proinflammatory VCAM1, ICAM1, Il-6 TNF-α & IL-8 during LPS-induced sepsis. UCA1 increase expression of MEF2C to inhibit NF-κB and proinflammatory cytokines	[68, 76, 77]
HOTAIR	HOTAIR overexpression prevented ischemia–reperfusion-induced oxidative stress by activating AMP-activated protein kinase alpha (AMPKα)	Regulates activation of NF-κB & its target IL-6, iNOS by degrading IκBα. HOTAIR upregulation negatively regulates miR-211 and upregulates IL-1β, IL-6R, IL16 & TNF-α in monocytes	[78–80]
FOXD3-AS1	Regulates oxidative stress-induced lung epithelial cell death through negative regulation of miR-150	FOXD3-AS1 negatively regulates IL-3 & IL-13 in CD4+ T cells in allergic rhinitis	[81, 82]

injury during sepsis. In the latter case, the study also showed that antagonizing the miR-155 ameliorated the liver injury by decreasing the oxidative stress [47]. Another study highlighted the involvement of miR-4321 and miR-4270 in NADPH oxidase 5 (NOX5)-mediated oxidative stress in sepsis-induced acute kidney injury [48].

Role of ncRNAs during disease-induced oxidative stress

Several ncRNAs are associated with oxidative stress during different diseases. In some cases, ncRNAs were reported to regulate oxidative stress response, while their expression is also modulated by oxidative stress. Expression of miRNAs during oxidative stress has been observed in Parkinson's disease [49], Alzheimer's disease [50], Ageing [51], Cancer [52], Diabetes [53] and Osteoarthritis [54]. Tsai *et al.* [55] reviewed the role of ncRNAs in systemic lupus erythematosus (SLE)-mediated oxidative stress with functional role of miR-21, miR-29b, miR-126b and miR-146a. In other diseases, miR-500a-5p and miR-144 have been shown to regulate oxidative stress during breast cancer and anaemia, respectively [56, 57]. The role of ncRNAs during oxidative stress in different disease conditions is collated in Table 1.

Alu RNA, a member of SINE repeat family, is also involved in the stress response during infection. Although a small number of Alu RNAs (10^3–10^4 molecules/cell) are present in normal cells, the number increases drastically to nearly 20-fold during stress response in cancer and viral infections [58–60]. Accumulation of Alu RNA in endothelial cells promotes the production of ROS and IL-1β. This is mediated by the NF-κB signalling pathway with lower expression of endothelial nitric oxide synthase (eNOS) and superoxide dismutase 2 (SOD2) [61]. A focussed elucidation of the functional role of ncRNAs in regulating the oxidative stress response holds potential.

ER stress and UPR during infection

To establish a favourable environment for viral replication, some of the positive-strand RNA viruses (HCV, SARS-CoV and DENV) modulate viral protein driven rearrangement of host intracellular organelle membranes like ER [83, 84]. This modified organelle is called Double Membrane Vesicle (DMV), where structural and non-structural viral proteins accumulate and alter the protein and lipid content of the ER [85–87]. After processing at ER, the nascent replicated viral genome is trafficked through the Golgi complex and secretory pathway and thereafter leaves the infected cell after maturation [88]. This membrane remodelling induces ER stress by triggering a cellular signalling pathway, UPR. This pathway aims to maintain cellular homeostasis and ER protein levels. If homeostasis is not achieved, the cell progresses towards apoptosis.

Mechanism of UPR

The UPR is mediated by three transmembrane proteins which sense the viral and misfolded proteins. These sensors are PKR-like ER Protein Kinase (PERK), Inositol-Requiring Protein 1 (IRE1) and Activating Transcription Factor 6 (ATF6) [89]. Viral proteins distract the regulatory element Binding immunoglobulin Protein (BiP) from binding to UPR sensors. IRE1 activation by dimerization and phosphorylation aids in splicing of the X-box binding protein 1 (XBP1) mRNA followed by the subsequent translation of spliced XBP1 transcription factor, XBP1s [90]. This splicing enables the expression of chaperones and proteins

essential for the ER-Associated Degradation (ERAD) pathway. ERAD leads to the production of proinflammatory cytokines [91], lipid synthesis [92], autophagy response [93] and regulatory protein P58IPK [94] (Figure 2). Activated IRE1 also initiates mRNA degradation to decrease the protein load on the ER by Regulated IRE1-Dependent Degradation (RIDD) pathway [95]. Moreover, IRE1 also recruits Tumor Necrosis Factor (TNF) receptor associated factor 2 (TRAF2) to the ER membrane to phosphorylate IκB and promote NF-κB activation [96]. Phosphorylated IRE1 activates c-Jun N terminal kinase (JNK) signalling pathway to maintain the balance between apoptosis and survival.

PERK is activated similarly to IRE1. Activated PERK attenuates the global protein production by phosphorylating the α-subunit of translation factor, eIF2α. Simultaneously, activated PERK induces the expression of ATF4 [97] through an alternative translation cascade. This, in turn, induces expression of transcription factor CCATT/Enhancer-Binding Protein-Homologous Protein (CHOP) and Growth Arrest and DNA Damage Inducible Protein 34 (GADD34). CHOP is a pro-apoptotic protein, which inhibits anti-apoptotic protein B cell lymphoma 2 (BCL2) [98]. GADD34 is a phosphatase that inhibits the phosphorylation of eIF2α [99]. Additionally, PERK phosphorylates NF-E2 related factor 2 (NRF2) and induces the genes involved in antioxidant response (Figure 2) [100].

Following ER stress, ATF6 translocates to the Golgi apparatus and undergoes a two-step proteolytic cleavage, with the release of transcriptionally active N-terminal domain. The truncated ATF6 then translocates to the nucleus, where it transactivates the ER stress response element (ERSE) harbouring the UPR genes such as *BiP*, *GRP94* and *P58IPK* (Figure 2) [101].

UPR during infections

Several studies have reported as to how the DNA and RNA viruses modulate the UPR pathway selectively for their replication and to suppress apoptosis until viral replication is complete [102, 103]. Some pathogens directly interact with the ER functioning, causing ER stress and UPR activation [104]. Duodenal biopsy of HIV patients and liver cells of HCV patients show activated ER stress response [105, 106]. Along with overexpression of the GRP94 in severe acute respiratory syndrome coronavirus (SARS-CoV) infected cells, significant phosphorylation of PKR and PERK has also been reported [107]. Zika virus and Rhinovirus, a major cause of cystic fibrosis, were also found to induce the ER stress response and impaired UPR [108, 109]. The UPR activation by IAV [110–112] and respiratory syncytial virus (RSV) infection [113] in A549 and primary HTBE cell lines have also been reported.

UPR can also be activated by bacteria, such as facultative intracellular bacteria, *Brucella melitensis* and *Listeria monocytogenes* [114, 115], as well as bacterial toxins such as pore forming toxin, cholera toxin and shiga toxins.

Role of ncRNAs during UPR

Several examples of ncRNA interactions in the UPR pathway are known; however, they are mostly reported in diseases like diabetes, cancer and cardiovascular disease with little evidence during infectious diseases. In diabetic pancreatic β-cells, miR-204 controls the PERK activity [116]. PERK is also known to induce the expression of miR-483, which disrupts cellular ATP homeostasis during UPR [117]. In diabetic progenitor cells, miR-200 and miR-466 are degraded by RIDD activity of IRE1, resulting in abnormal angiogenesis [118]. Few miRNAs have also been reported to be involved in the IRE1-XBP1 axis, which in turn also regulate miRNAs through XBP1 and IRE1 [119]. In ATF6 axis, calreticulin, a Ca^{+} binding protein, is regulated by miR-455. Besides, ncRNA-RB1, which shares a bidirectional promoter region with *RB1* gene, is involved in the regulation of calreticulin. CHOP and IRE1 were reported to regulate miR-216b level [120]. lncRNA-GADD7 is induced in palmitate-induced ER stress and is a general regulator of oxidative stress [121]. In hepatocellular carcinoma, lincRNA-p21 acts as a tumour suppressor. The lncRNA TUG1 was reported to reduce apoptosis through ER stress reduction in cold-induced liver injury [122]. Expression of lncRNA MALAT1 was increased in flavivirus infection through PERK-dependent transcriptional activity [123].

McMahon *et al.* [119] summarized the involvement of different miRNAs during UPR. Quan *et al.* [124] explored transcriptome-wide changes in ncRNA expression during UPR to identify potential regulators of UPR genes. Although several studies highlight the role of ncRNAs during the UPR in different diseases, there is scope for mechanistic elucidation.

Immune response to infection

In the event of pathogen invasion, the host cell quickly recognizes the pathogen-associated molecular pattern (PAMP). This happens through pattern-recognizing receptor (PRR) located on the host cell membrane (TLR-1,2, 4, 5 and 6), endosomal membrane (TLR 3, TLR7/8 and TLR 9) or cytoplasm (retinoic acid inducible gene 1-like receptor- RLR and NOD like receptor- NLR). TLR-1, 2, 4, 5 and 6 detect bacterial pathogenic components of lipopolysaccharide (LPS) and flagellin. Cytoplasmic and endosomal TLR 3, TLR 7/8 and TLR 9 detect viral nucleic acid components of dsRNA, ssRNA and viral DNA, respectively. Upon detection of the PAMP, PRR activates NF-κB, activator protein 1 (AP1) and IRF. This induces inflammatory and immune response via the expression of several proinflammatory cytokines, chemokines and interferons. These interferons bind with respective receptors and activate JAK/STAT signalling. The phosphorylated STAT translocates to the nucleus and is involved in the ISGF3 transcription complex (STAT1, STAT2, IRF9) formation. This initiates the expression of IFN-Stimulated Genes (ISG) to mediate antiviral responses [125].

Natural killer cells kill the infected cells by perforin and granzymes. Dendritic cell and macrophage phagocytize and neutralize the pathogens through lysosomal degradation by enzymes and ROS and RNS production [126]. The degraded pathogen-derived particles are presented by macrophages and dendritic cells (antigen presentation) and, in turn, initiate the immune response. Excessive production of the ROS triggers ER stress and impairs cellular function such as antigen presentation and successive T-cell activation [127]. A detailed representation of the immune responses upon pathogen infection is depicted in the Figure 3.

Differential expression of ncRNAs during infection

Differential expression of ncRNAs has been reported to modulate the PRR-mediated signalling cascade, cytokine-mediated inflammatory pathway and interferon-mediated antiviral pathways [128]. For example, in HCV-infected patient's liver, lncRNA-CMPK2 is upregulated. The knockdown of lncRNA-CMPK2 leads to the reduction of HCV replication and upregulation of IFN response in human primary hepatocytes [129]. Another study reported increased levels of lncRNA-EGOT, mediated by NF-κB, in HCV and influenza infection, although

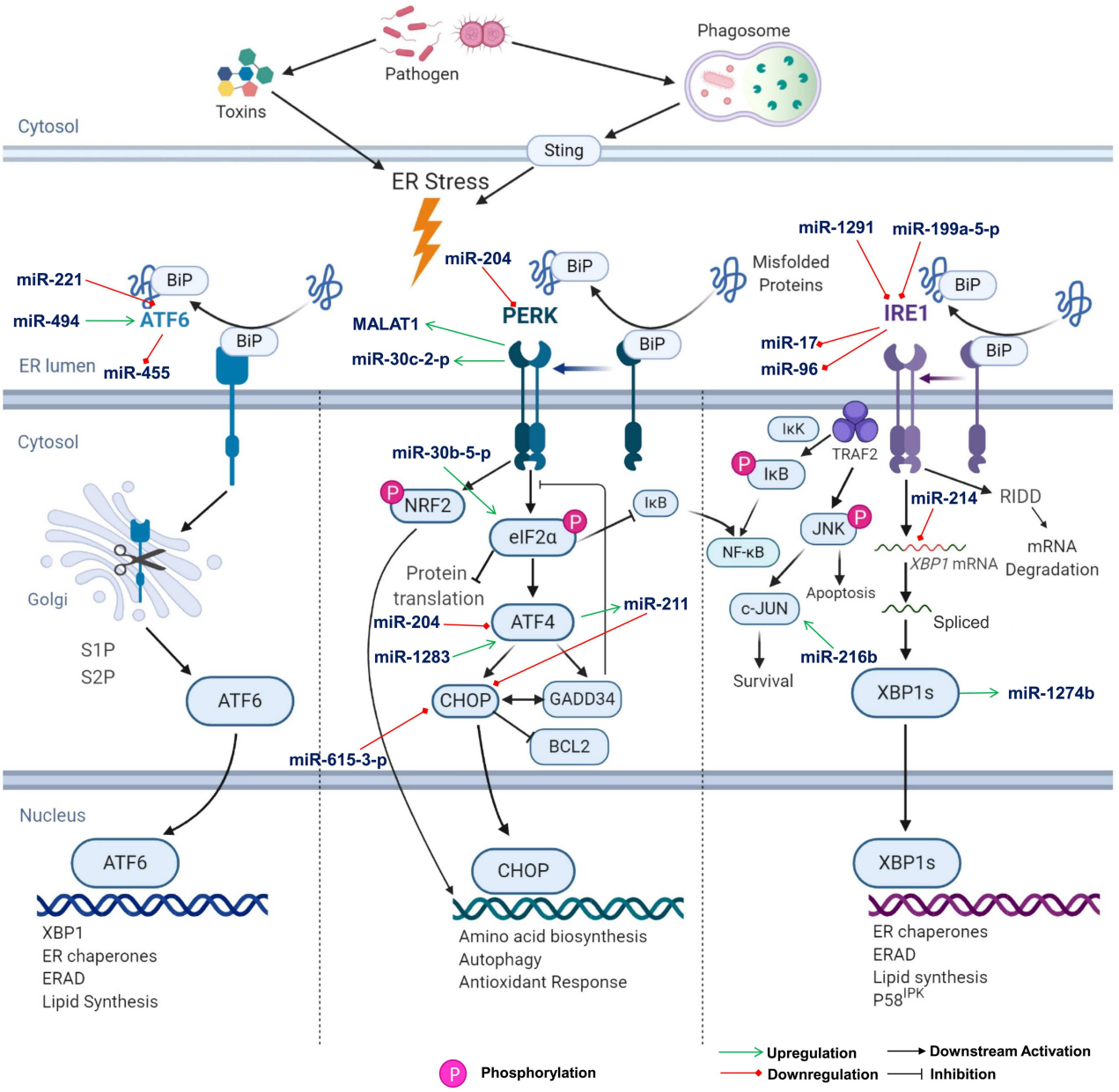

Figure 2. Unfolded protein response pathway. The signalling flow in a UPR pathway is shown schematically. From left to right, the panels represent ATF6, PERK and IRE1 axis of the UPR, respectively. Role of ncRNA at different stages are highlighted with arrows. (**eIF2α**- Eukaryotic transcription Initiation Factor 2 α, **S1P**- Site 1 protease, **S2P**- Site 2 protease, **BCL2**- B Cell Lymphoma 2). The acronyms for rest of the genes are included in the manuscript.

the mechanism and antiviral response is not elucidated [130]. lncRNA-GAS5 overexpression is also reported in HCV infection and GAS5 alleviates HCV replication by binding to its NS3 protein [131].

lncRNA-Negative Regulator of AntiViral response (NRAV) is reported to be associated with viral infections like IAV, RSV and Herpes Simplex virus. Downregulation of NRAV in infected cells enhances the ISG expression as a response to viral infection [132]. This might be mediated by lncRNA-NRAV associated protein ZONAB [133]. Nuclear Factor of Activated T cell (NFAT), an important modulator of T cell mediated immune response, plays a major role in HIV infection by increasing viral transcription and replication. lncRNA-Noncoding Repressor Of NFAT (NRON) acts as a protein-RNA scaffold and binds to NFAT and regulates its nuclear trafficking. Moreover, lncRNA-NRON downregulation by HIV protein, Nef increases the NFAT activity to facilitate viral protein synthesis and replication [134]. lncRNA Lethe functions as a decoy and interacts with the RelA subunit of NF-κB to negatively regulate NF-κB signalling. Additionally, lncRNA-Lethe overexpression suppresses the NF-κB mediated interleukin transcription [135]. NF-κB interacting lncRNA (lncRNA-NKILA), a post-translational regulator of NF-κB activity, negatively regulates NF-κB by blocking the IκB phosphorylation and subsequent degradation [136]. lncRNA NKILA and lncRNA-Lethe both act as negative regulators of NF-κB modulating

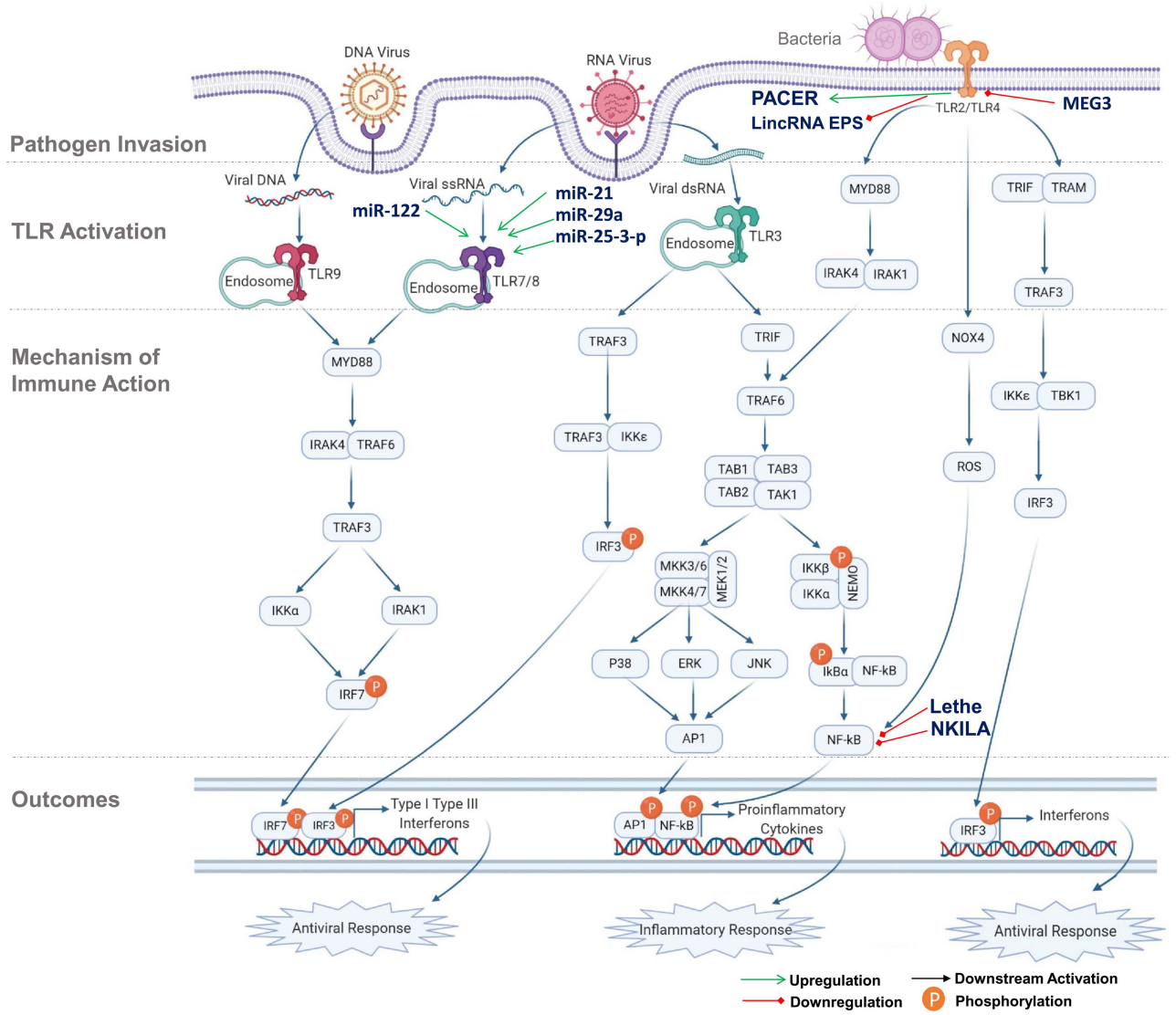

Figure 3. Immune response activation pathway. From top to bottom order, the panels show the pathogen invasion, TLR activation, mechanism of immune action and the outcomes, respectively. ncRNA regulations at different stages are highlighted. (**MYD88**- Myeloid Differentiation Primary Response 88, **TRIF**- Toll/Interleukin-1 Receptor) Domain-Containing Adaptor Protein, **TRAM**- Translocating Chain-Associated Membrane, **IRAK**- Interleukin-1 Receptor (IL-1R) Associated Kinase, **TAB**- TGF-β-Activated Kinase 1 and MAP3K7-Binding Protein, **TAK** (also known as MAP3K7, Mitogen-Activated Protein Kinase Kinase Kinase 7), **MEK** (also known as MAP2K, Mitogen-Activated Protein Kinase Kinase), **NEMO**- NF-κB Essential Modulator, **ERK**- Extracellular-signal-Regulated Kinase). The acronyms for rest of the genes are included in the manuscript.

the immune response. lncDC exclusively expressed in human dendritic cells is crucial for antigen uptake and T cell activation. lncDA binds to STAT3 and prevents its dephosphorylation and mediates transcription of genes essential for dendritic cell differentiation [137].

miRNAs can also modulate the expression of lncRNAs. miR-140 specifically binds with lncRNA NEAT1 and modulates expression of lncRNA NEAT1in adipocytes [138]. Multiple studies reported NEAT1 and miRNA-140 upregulation during both bacterial and viral infections [66, 139–141]. However, the mechanism towards miR-140 mediated regulation of NEAT1 is yet to be explored. Some of the lncRNAs act as competitive endogenous RNA (ceRNA) to sponge miRNA activity. lncRNA NRAV was reported to sponge miR-509-3p and promote the Rab5c-mediated respiratory syncytial virus replication [132]. RSV infection causes overexpression of NRAV, thereby facilitating viral replication. However, the same group reported the host antiviral response downregulated the NRAV expression to curb the viral replication. lncRNA PVT1 acts as ceRNA and adsorbs miR-203 to promote upregulation of E2F3 in RSV infection [142]. Several studies have also reported Alu RNA mediated induction of NF-κB in a TLR-independent manner activated NLRP3 inflammasome in retinal pigmented epithelial cells [143, 144]. ncRNA thus seems to be an important regulator of immune responses during infection.

Cytokines involved in inflammation

As discussed in the earlier section, upon pathogen recognition by PRRs and Toll-like receptor (TLRs), proinflammatory cytokines like IL-6, IL-1β and TNF-α are induced. This facilitates inflammatory response to clear infection by TNF-α, and

ROS-mediated phagocytosis in macrophages [145]. TNF-α and IL-6 promote the acute phase response and upregulate the C reactive protein (CRP) in the liver. This, in turn, activates the complement system leading to opsonization of the pathogen. IL-1β exhibits prostaglandin-mediated immune response and activates ROS, NO and iNOS [146, 147]. In the case of *Mycobacterium tuberculosis* (MTB) infection, the regulation of IL-1 and type 1 interferon leads to a distinct inflammatory response [148]. Increased expression of IL-10, a signature of RSV-infected lower respiratory tract cells, attenuates acute inflammatory response and late inflammatory changes [149]. Similarly, in RSV-infected children, IFN-γ, IL-8, TNF-α and other eosinophil activated chemokines (GM-CSF and Eotaxin) were increased in nasal lavage fluid [150]. In IAV H1N1 infections with acute respiratory distress syndrome (ARDS), higher level of IL-1RA, IL-6, IL-8, TNF-α, Interferon gamma induced Protein 10 (IP-10) and monocyte chemoattractant protein 1 (MCP-1) were reported [151, 152].

Like other cytopathic viruses, SARS-CoV-2 induces pyroptosis, a severe inflammatory cell death cascade [153, 154]. This includes IL-1β, IFN-γ, IL-6, IP-10, MCP-1, CXCL3, CXCL9 and CXCL10 [155–157]. In HIV-infected patients, the levels of CRP and proinflammatory cytokines like TNF-α, IL-6, B cell Activating Factor (BAFF) are increased irrespective of antiretroviral therapy [158]. HCV core and NS3-mediated increase in TNF-α and IL-10 have been reported in dendritic cells isolated from the blood of infected patients [159]. In HCV-infected liver cells, Nod-Like Receptor P3 inflammasome (NLRP3) stimulates IL-1β production and promotesthe production of other proinflammatory cytokines [160]. The degree of inflammation and tissue damage in HIV and HCV co-infected patients was found to be greater than the two individual infections [161]. In some cases, the robust local and systemic cytokine production, inflammatory infiltration and virus-induced tissue destruction lead to a condition called 'cytokine storm', observed in cases of IAV, SARS-CoV-2, RSV and dengue [162–165].

ncRNAs in regulation of cytokine production

Expressions of many ncRNAs are altered during inflammatory response with a functional role. lincRNA-COX2 and PACER are upregulated in macrophages as a result of TLR4 stimulation by LPS [128, 135, 166], while, lincRNA-EPS is downregulated in LPS-stimulated TLR4 signalling [8]. lncRNA THRIL acts as a scaffold to hnRNPL and binds to TNF-α promoter inducing its transcription upon TLR2 stimulation [167]. lncRNA PACER, a decoy for binding and sequestering NF-κB p50 homodimer, regulates a key anti-inflammatory gene PTGS2 [166]. It is also reported that TLR7 signalling mediation by miR-122 activates acute pulmonary inflammation in mice [168]. Secretion of proinflammatory cytokines by macrophages is activated by miRNAs, miR-21, miR-29a and miR-25-3p through TLR8 signalling cascade [169, 170].

lncRNA ANRIL is positively associated with the expression of proinflammatory cytokines like IL-4, IL-6, IL-17, IL-13 and TNF-α in the nasal mucosa during allergic rhinitis [82]. MALAT1 has also been shown to increase the expression of IL-1β, IL-6, ICAM1, TNF-α and E-selectin in pulmonary microvascular endothelial cells [171]. lncRNA-Mirt2 acts as a checkpoint for rogue inflammatory response and prevents ubiquitinoylation of TRAF6. This inhibits the NF-κB mediated production of proinflammatory cytokines and acts as a feedback regulator of the inflammatory response [172]. lncRNA PMS2L2 was also shown to act as a negative regulator of inflammation associated miR-203 with possible involvement in LPS-induced inflammatory injury [173]. lncRNA SNHG16, by binding with miR-15a/16, modulates the TLR4-mediated signalling cascade [174]. Another lncRNA MEG3 protects the respiratory epithelial cell in RSV infection by suppressing TLR4-dependent NF-κB signalling axis [175]. Several studies reported the involvement of many other ncRNAs during inflammatory response (Table 1).

Cross-talk between ER stress, oxidative stress and immune response

All the three branches of UPR were shown to induce proinflammatory transcriptional programs, mainly governed by NF-κB and AP1 [176]. Keestra-Gounder *et al.* [177] reported Nucleotide-binding Oligomerization Domain (NOD) mediated (NOD1 and NOD2) increase in IL6 production, upon activation of IRE1 axis of UPR. RIDD has been associated with translational activation of RIG-1, thereby inducing NF-κB associated immune response against RNA viruses [178]. The cross-talk between ER stress, oxidative stress and immune response in the event of pathogen infection has been summarized in the Figure 4.

ncRNA and COVID-19

The SARS-CoV-2 virus is a positive-sense single-stranded RNA virus of the β-coronavirus family which caused the Coronavirus disease-2019 (COVID-19). SARS-CoV-2, in a similar fashion to SARS-CoV, infects the host cells by binding of angiotensin-converting enzyme 2 (ACE2) receptor and viral S protein fusion primed by transmembrane serine protease 2 (TMPRSS2) [179]. ACE2 converts angiotensin 2 to angiotensin 1 leading to ATP production and NADPH Oxidase 4 (NOX4) mediated ROS production [180, 181]. The other members of the Coronavirus family are reported to form an ER-derived DMV. SARS-CoV's ORF-7a, ORF-8a and ORF-9b are localized in host mitochondria. Of this, ORF-7a and ORF-8a facilitate the viral replication [182, 183], while ORF-9b suppresses the innate immunity by modulating the TRAF3/TRAF6 axis [184]. These ORFs share high sequence homology with the corresponding ORFs of SARS-CoV-2. It is plausible that SARS-CoV-2 also forms an ER-derived DMV to facilitate viral replication. Besides, a machine learning model of the SARS-CoV-2 genome revealed the possibility of host-mitochondrial localization of the virus, which may lead to the formation of mitochondria-derived DMVs for the replication of the virus [185]. Although this mitochondrial localization of viral RNA/protein is proposed to be mediated by direct interaction of viral Nsp with a mitochondrial import receptor Tomm70, there is no experimental evidence. Codo *et al.* [186] reported elevated levels of mitochondrial ROS in SARS-CoV-2 infected cells. This was shown to stabilize the HIF-1α, which in turn promotes glycolysis and excessive production of proinflammatory cytokines. The combined effect of the two events leads to decreasedviral load in cells.

The analysis of SARS-CoV infection associated mRNA expression revealed a quintuple ceRNA network involving miR-124-3p, lncRNA-Gm16917, circRNA-Ppp1r10, circRNA-C330019G07Rik, Ddx58 mRNA and transcription factor STAT2 [157]. Viral infection triggers IFN-mediated overexpression of Ddx58 containing the helicase domain which is crucial for viral replication. The Ddx58 is also a regulator of splicing during miRNA biogenesis. Thus, the viral helicase association with Ddx58 raises the possibility of altering miRNA biogenesis with viral replication advantage. 3'UTR of the Ddx58 mRNA has a binding site for the

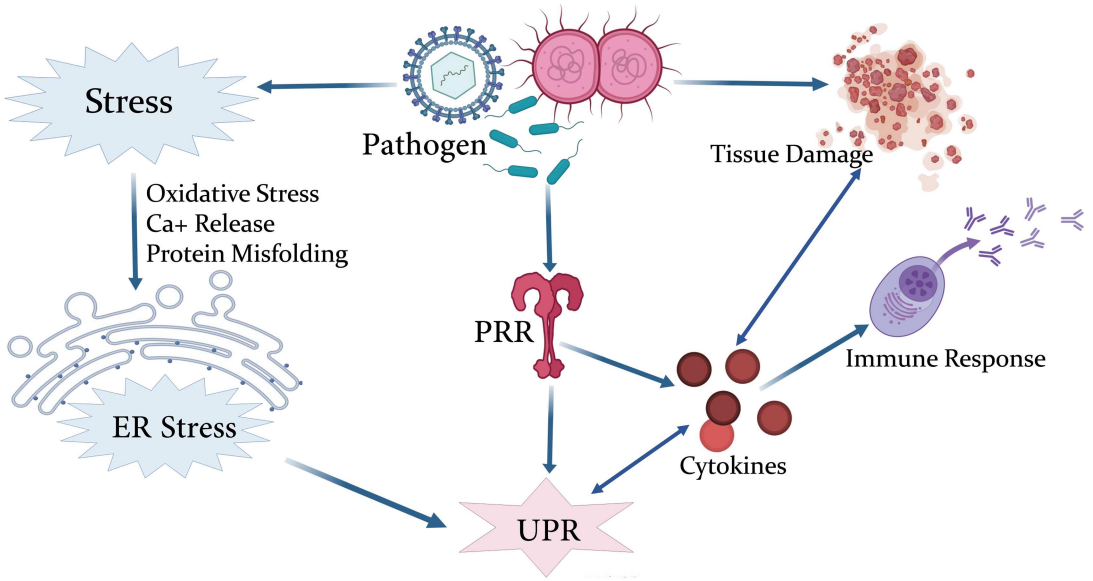

Figure 4. Crosstalk between ER stress, UPR and immune response. Graphical representation of the host response during pathogen challenge.

miR-124-3p which has an impact on mRNA stability. lncRNA-G16917 acts as a sponge to miR-124-3p with possible role in viral replication. A similar ceRNA network is plausible in response to SARS-CoV-2 infection. Using RNA-seq data of mock and SARS-CoV-2 infected normal human bronchial epithelial (NBHE) cells as well as lung biopsies of healthy and SARS-CoV-2 infected patients, Vishnubalaji *et al.* [187] analysed differentially expressed genes and ncRNAs. They reported 155 upregulated and 195 downregulated ncRNAs in SARS-CoV-2 infected NBHE cells. Comparing the data with differentially expressed ncRNAs in COVID-19 patients' lung biopsies, they identified five common upregulated and 57 common downregulated ncRNAs. RCC2-AS1, AC011603.3, AC145207.2, SNHG25 and AC008760.2 are the five common upregulated ncRNAs. MALAT1 and NEAT1 were slightly upregulated in SARS-CoV-2 infected NBHE cells as compared to mock. However, they were not found to be overexpressed in the lung tissues from COVID-19 patients.

HIF-1α is a key player involved in the regulation of glucose metabolism and translation of glycolysis associated genes. A possible mechanism for ncRNAs to influence the SARS-CoV-2 infection is through regulation of HIF-1α. Experimental pieces of evidence suggest the involvement of ncRNAs in the regulation of HIF-1α. The miR-130a-3p overexpression represses glycolysis by targeting the HIF-1α. HOTAIR acts as a decoy for miR-130a-3p and regulates the HIF-1αin hepatocellular carcinoma [188]. LincRNA-p21 regulates HIF-1α degradation in a hypoxic condition. Overexpression of lncRNA-Let suppresses HIF-1α expression in hepatocellular and breast cancer [189]. It would be interesting to explore the role of the differentially expressed ncRNAs in the host response to infections like SARS-CoV-2.

Discussion

There are multiple pieces of evidence that link expression of miRNAs and ncRNAs in oxidative and ER stress in a wide range of diseases. However, the involvement of ncRNAs and miRNAs in regulating the UPR during viral infection has limited evidence. Upon entering the cell, many positive-strand RNA viruses form DMV for the viral replication. The formation of DMV is dependent on various viral proteins as well as host protein. However, the involvement of ncRNAs in regulation of the host proteins involved in DMV formation during viral infection needs further investigation. Moreover, the exact mechanism of regulation of antiviral response by ncRNA is yet to be explored. ncRNAs may also be potentially targeted to alleviate stress and possibly aid in disease recovery.

In addition to the involvement in different stress responses, immune and inflammatory responses, ncRNAs are also being investigated as biomarkers and therapeutic targets in different diseases. The association of ncRNAs is well characterized in cancer. Multiple studies have also established the potential of ncRNAs as biomarkers and therapeutic targets [190, 191]. Both lncRNAs and miRNAs are detectable in body fluids, including saliva, blood, serum, urine, and thus offer a comparatively easier detection of diseases. For example urine-based detection of lncRNA-PCA3, a prostate cancer specific lncRNA, offers easier and more sensitive diagnosis than the conventional antigen-based test [192]. Similarly, MALAT1 is also detectable in urine for prostate cancer [193]. Urinary detection of UCA1 in transitional cell carcinoma, and salivary detection of HOTAIR in oral squamous cell carcinoma offers potential diagnosis methods [194, 195]. lncRNA UC001NCR and AX800134, of viral origin, are promising biomarkers in HBV-induced hepatocellular carcinoma [196]. ncRNAs are also explored as potential therapeutic targets. miRNAs can be targeted for therapeutic use by small molecules, and oligonucleotide-based approaches [191]. miR-122, which facilitates the HCV infection, is being targeted by specific inhibitor Miravirsen and is undergoing clinical trial [168]. Small molecules such as Enoxacin have been shown to regulate the miRNA expression levels in tumours [197]. miRNA expression level can also be altered by miRNA-mimics (miR-28-5p, miR-125-3p) and antagomirs (antagomir-122) [191, 198].

Although similar to other RNA-based diagnosis, the spatiotemporal expression of ncRNAs in diseases poses a challenge for identification as a biomarker. The same is true for its usage as prognostic marker. However, a deeper insight into the intricacies of ncRNA-based regulation of infection and its outcomes

may provide potential diagnostic and therapeutic options in infectious diseases.

Key Points

- Noncoding RNA (ncRNA) regulates the oxidative stress, induced during infections as well as diseases like Diabetes, Parkinson's, Alzheimer's and Cancer.
- Bacterial toxins, viral proteins, infection-induced ER stress and subsequent unfolded protein response.
- Differential expression of ncRNAs regulate pattern recognition receptors (PRR) mediated activation of immune response, cytokine signalling and antiviral response.
- *In vitro* and *in silico* studies indicate the involvement of ncRNAs in modulating cytokine storm and viral replication during the SARS-CoV-2 infection.

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Conflict of Interest

Authors wish to declare no conflict of interest. Funding body did not have any role in planning of the study.

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