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REVIEW
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Therapeutic Potential of Long Non-Coding RNAs of HIV-1, SARS-CoV-2, and Endogenous Retroviruses

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Long non-protein coding RNAs (lncRNAs, predicted to be up to 200,000 in the human genome) are nucleic acids of more than 200 nucleotides that not only play primordial roles in the regulation of chromatin states, but also are capable of decoying or scaffolding proteins (e.g., transcription factors, TFs; host and viral proteins), DNA (e.g., promoters and enhancers), and RNA (e.g., miRNAs and hnRNAs) in 3D conformations acting in a chaperonin-like fashion. Specifically, lncRNAs modulate gene expression during the regulatory layers of transcription, RNA processing (splicing and indirectly editing), translation, and post-translational modifications including phosphorylation, acetylation, and ubiquitination. Accumulated evidence indicates that lncRNAs regulate antiviral immune responses mainly by transcription of IFN regulatory factors 1 (IRF1) and 4 (IRF4), which contribute to type I interferon (IFNα and IFNβ) upregulation. Some of the most common TFs regulated by lncRNAs are TP53, CTCF, MYC, SOX2, EZH2 SFPQ, SUZ12, STAT1, STAT3, and NF-kappa B. In this review, the known functions of selected lncRNAs genes in HIV/AIDS (*MALAT1, HEAL, NRON, TAR-gag, TP53COR1/lincRNA-p21, NEAT1, NKILA, LINC01426* [formerly *Uc002yug.2*], *FAS-AS1, LINC00173* [formerly *FLJ42957/NCRNA00173*], *GAS5*, and *HIV-encoded antisense lncRNA*) and COVID-19 (*EGOT, MALAT1, NEAT1, DANCR, HOTAIR, FENDRR, LINC1505, FALCOR*, and *HISLA*) are discussed. Furthermore, *MALAT1* is also involved in subsequent complications such as deep vein thrombosis (DVT) in COVID-19. In addition, after the increased understanding of the role of lncRNAs from Human Endogenous Retroviruses (HERVs, predicted to be at least 582 different with 725,763 repeats of them in the human genome) in cancer (TROJAN) and heart development (BANCR), transcripts of HERVs as lnc-EPAV and lnc-ALVA1-AS1 have recently drawn attention as host protective agents against viral infections. A deeper knowledge of host and viral lncRNAs interactions and their regulation will pave the way for the design of novel drugs inspired by host- and viral-encoded

lncRNAs. These novel drugs have the potential to reduce the burden of HIV/AIDS and COVID-19 twofold: (1) by increasing their efficacy and (2) by minimizing the side effects of current drugs. We expect that lncRNA drugs will be able to modulate human and viral transcription in an unprecedented way but still effectively maintain homeostasis by deploying functionality below the pathogenic threshold.

Keywords: long noncoding RNA, acquired immunodeficiency syndrome (AIDS), SARS-CoV-2, COVID-19, endogenous retroviruses (ERVs), HIV-1, drug development, gene regulation and expression

INTRODUCTION

Non-coding RNAs (ncRNA) were initially classified as "evolutionary junk", but their important role in the regulation of transcription (1), cell differentiation (2), development (3), metabolic reprograming (4), and many others has been demonstrated [reviewed in (5–7)]. Because they act at the RNA level and most of them are not transcribed, they were originally called "riboregulators" (8). They can be divided into two large classes: the small non-coding RNAs are commonly from ∽20 to 200 nucleotides (nt), while those longer than 200 nt and up to ∽100 kb and lacking open reading frames are long non-coding RNAs (lncRNA) (9–11). The non-coding elements comprise 80% of the human genome (10). It has been suggested that between ~21,488 and ~200,000 lncRNAs (12, 13) and a subset of these, the lincRNAs, sum up >14,279 (14, 15) in humans. RNA polymerase II is responsible for lncRNA transcription (8, 16), and its biogenesis is similar to mRNAs in the sense that they are polyadenylated, capped, and spliced (5). However, it is worth mentioning that lincRNAs are less efficiently spliced. This can be partially explained because lincRNAs have weaker splicing-related motifs and lower binding to U2 small nuclear RNA auxiliary factor 2 (U2AF2, formerly U2AF65) (17). Depending on their functions, lncRNAs can be classified as *cis*-acting (within 10 k upstream or downstream of the coding genes they regulate) or *trans*-acting [identified by expression levels, according to Pearson's correlation coefficient $|r| > 0.95$ (18) reviewed in (5)]. LncRNA scaffolds, guide lncRNAs, lncRNA decoys, enhancer RNAs (eRNAs), promoter-associated lncRNAs (PALRs), precursor lncRNA [reviewed in (19)], and a heterogeneous subgroup are involved in X-chromosome inactivation, telomere regulation, and imprinting (reviewed in (6)). Depending on their position in the genes, lncRNAs can also be classified as exonic, intronic, or intergenic (20). An additional classification regarding evolution are the Transcribed Ultra-Conserved Regions lncRNAs (T-UCRs, ≥481) (21, 22). An alternative and comprehensive classification can be found at (23).

LncRNAs regulate innate immunity in host–virus interactions. During viral infection, cellular lncRNAs directly regulate viral genes and modify both viral replication and pathology through changes mediated by virus in transcriptome of the host (24–26). Also, several lncRNAs could upregulate IFN-I (IFNα and IFNβ) expression to induce an antiviral response (27–30), reviewed in (31). Although lncRNAs seem to not have protein-coding function, some of them actually encode functional small peptides (32–34) [reviewed in (35, 36)]. In this review, we will focus on lncRNAs. LncRNAs can regulate different gene modulation processes. They regulate gene expression during the regulatory layers of transcription (37), RNA processing as splicing and indirectly editing (38), and/or translation (39). LncRNAs can control post-translational modification of proteins such as phosphorylation (40), acetylation (41), and ubiquitination (42, 43). In brief, they can act as a decoy or scaffold of other molecules such as proteins (44–46), RNA,and DNA (47). Also, their subcellular location gives important clues about its function in different biological processes. In the nucleus, they guide transcription factors or complexes that modify chromatin. In the cytosol, they control stability of mRNA (48) or compete with endogenous mRNA for access to the protein expression machinery (23). In the cytoplasm, lncRNAs can bind directly to transcription factors (TFs) (49). Interestingly, several lncRNAs are located near genes that encode TFs as well (50). However, particularly long intergenic non-coding RNAs (lincRNAs) regulate both the expression of neighboring genes and distant genomic sequences (6). At the transcription level, lncRNAs regulate accessibility to chromatin in processes that involve RNA polymerase and histone modification enzymes. Furthermore, their ability to bypass chromatin-modifying complexes to impact the basal transcriptional machinery and gene promoters has been demonstrated (51). One classical example of lncRNA in a non-disease state is the X-inactivation specific transcript (*XIST*) in women that recruits the polycomb complex. *XIST* induces chromosome silencing of the sexual chromosome from which it was transcribed (52) [reviewed in (53)]. LncRNAs can also stabilize mRNAs and regulate their decay by diverse mechanisms such as (1) binding to target mRNAs, (2) sequestering miRNAs and/or ribosome-binding proteins [RBPs, these lncRNAs are also called competitive endogenous RNAs (ceRNAs), decoys, or sponges], and (3) acting as scaffolds to enhance interaction of RBP-mRNA or interacting with m^6A machinery to modulate m^6A levels of target mRNAs. This induces gene expression (54). In addition to the complexity of their regulation, lncRNAs have slicing variants that are expressed in a tissue- and/or cell-specific manner (54). In recent years, an increased number of academic groups and pharmaceutical companies became interested in the development of novel therapies based on lncRNA regulation. Currently, at least 61 lncRNA-related clinical trials are ongoing worldwide for cancer, cardiovascular disease, diabetes, and other conditions/diseases (https://www.clinicaltrials.gov/ and **Figure 1**).

LncRNAs are also involved in pathological processes in viral infections and cancer. HIV is the causative agent of AIDS. There

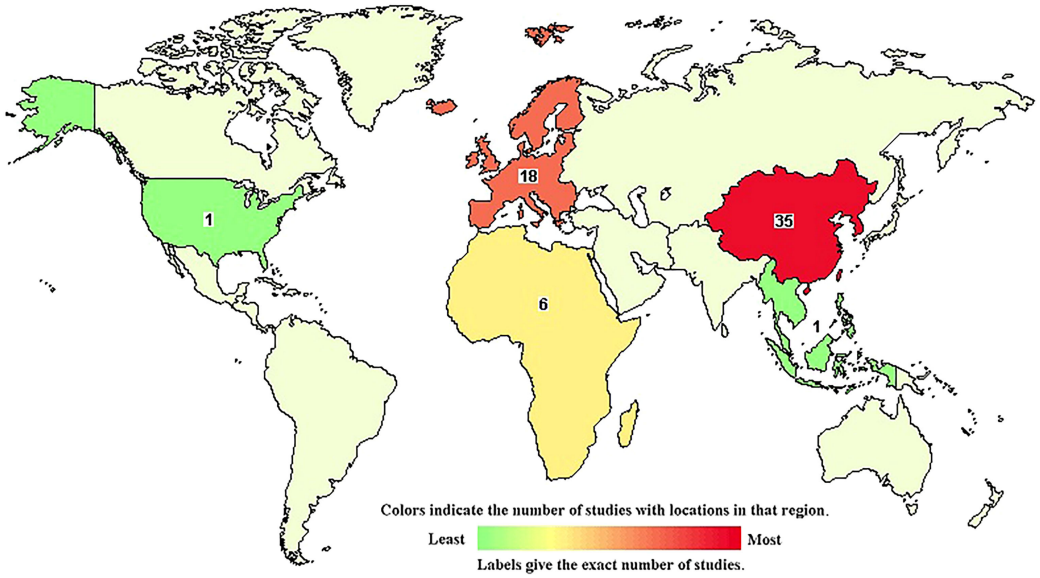

FIGURE 1 | World map of ongoing lncRNAs clinical trials according to (www.clinicaltrials.gov, accessed on March 15th, 2022). Numbers indicate the current clinical trials per country/region where the active substance of the treatment arm contains a lncRNA. Currently, there are 61 registered clinical trials, but none of them are for HIV-AIDS or COVID-19. The color of the country/region refers to the relative frequency of registered clinical trials in comparison with the other countries/regions (see the key of the figure).

are two strains of HIV, HIV-1 and HIV-2 (55). In this review, we will focus on lncRNAs encoded in HIV-1 and SARS-CoV-2 genomes as well in lncRNAs of human endogenous retroviruses (HERVs). For data of lncRNAs in other viruses, see (10). With the emergence of SARS-CoV-2 in 2019, the importance and the role that non-coding RNAs play in the infection process have been highlighted and recently investigated (56).

LncRNAs of HERVs and other host lncRNAs appear as a potential novel strategy to combat viral infections. It is important to know the mechanisms of action of lncRNAs in the development and outcome of infections for the development of more effective therapeutic strategies based on these complex gene regulation layer. In order to develop an adequate infectious process, viruses have the ability to decrease or increase the expression of lncRNAs; these changes can generate antiviral or proviral functions and completely modify the development of a disease. HIV alters the expression of important cellular lncRNAs (57), but the participation of other viruses has been just recently studied (10). Ma et al. (2021), reported 242 differentially expressed (DE) lncRNAs in early infection with HIV and might show cis-dependent regulation of B and T lymphocyte-associated protein gene (*BTLA*), zeta chain-associated protein kinase gene (*ZAP70*) and growth factor receptor-bound protein 2-related adaptor protein gene (*GRAP*). Some lncRNAs were predicted to act as ceRNAs to regulate expression of *fos* protooncogene, AP1 transcription factor subunit (*FOS*), fosb protooncogene, AP1 transcription factor subunit (*FOSB*), V-jun avian sarcoma virus 17 oncogene homolog (*JUN*), transcription factor 7-like 2 (*TCF7L2*), and hypoxia-inducible factor 1, α-subunit (*HIF1A*) (58). LncRNAs are crucial for viral reproduction (production of new infectious virus particles), either repressing or activating HIV-transcription. After HIV or SARS-CoV-2 infection, ncRNAs, including miRNAs, small interfering RNAs (siRNAs), and lncRNAs, are modulated by the virus, in order to achieve the successful replication (nucleic acid synthesis) cycle. Attempts have been made to compare the different datasets obtained by research groups on expression changes during infection, but it represents a great challenge because the expression levels are highly sensitive to external stimuli and it is difficult to define the basal levels that normally exist in cells, because interindividual variation exists (59). It has been identified as a deregulation response of many lncRNAs in response to either an infection process or changes in cytokines such as IFN, which end up impacting the viral replication that may occur (60). In addition, about 50% of HIV-1-positive patients receive combined antiretroviral therapy (cART), which includes a cocktail of inhibitors that target viral processes including entry, reverse transcription, integration, and/or protease-mediated cleavage (61). HIV-1 latency is a state in which viral RNA is hard to detect by conventional/clinic techniques. HIV-1 latency is one of the major barriers to eradicate HIV/AIDS because the virus remains largely undetected by the surveillance of the immune system.

In this review, we summarize the role of lncRNAs in some important viral infections such as COVID-19 and HIV-1/AIDS as well as briefly underline the importance of lncRNAs transcribed from HERVs, their functions, mechanisms, and some of their nucleic acid- and protein-binding partners. To avoid confusion in this review, lncRNA genes are written in italics and the transcripts of lncRNAs are not.

ROLE OF SELECTED LNCRNAS IN HIV/AIDS

Role of Metastasis-Associated Lung Adenocarcinoma Transcript 1

MALAT1 modulates epigenetic regulation of HIV-1 and alternative splicing of cellular precursor mRNAs (pre-mRNAs). Polycomb repressive complex 2 (PRC2) primarily trimethylates H3K27me3 to silence gene transcription. *MALAT1* prevents the binding of the catalytic subunit of PRC2 named enhancer of zeste 2 (EZH2) with HIV 5′-long terminal repeat (LTR, **Figure 2**). This reduces the LTR methylation mediated by PRC2 and activates HIV-1 replication (62). Experiments on overexpression of *MALAT1* in $CD4^+$ T cells increase HIV-1 replication, suggesting a potential application in reactivation of latent HIV-1 (**Table 1**).

Role of HIV-1-Enhanced lncRNA

HEAL is a lincRNA with a function in epigenetic regulation of HIV transcription. Active HIV infection upregulates *HEAL* in monocyte-derived macrophages (MDMs), T lymphocytes, and microglia. Its expression is dependent of viral replication and independent of viral entry. *HEAL* expression is downregulated in HIV-1-latent $CD4^+$T cells. HEAL targets the HIV promoter and upregulates viral transcription by histone acetylation and elongation by positive transcription elongation factor b (P-TEFb). Furthermore, HEAL binds to the transcription factor FUS (**Figure 2**), an RNA binding protein that together with HEAL recruits histone acetyltransferase p300 to the HIV-1 promoter. This also activates H3K27ac in the viral promoter and its progressive transcription. Blocking of HEAL could indirectly inhibit cyclin-dependent kinase 2 (CDK2) expression without altering its other relevant functions. Blocking HEAL also prevents viral recrudescence in both MDMs and T cells when azidothymidine (AZT) is discontinued (64). Downregulation of *HEAL* suggests a new epigenetic strategy to slow down HIV-1 infection (**Table 1**).

Role of the Non-Coding Repressor of Nuclear Factor of Activated T Cells

NRON serves as a scaffold and, together with ubiquitin ligase cullin A (CUL4A) and protease 26S, subunit 9 (S9p44.5) enzymes, sequesters the phosphorylated form of nuclear factor of activated T cell (NFAT) transcription factor in the cytoplasm. This inhibits HIV-1 transcription initiation (**Figure 2**). HIV-1 causes downregulation of *NRON* (74), so this mechanism increases gene expression and finally an increased efficacy of HIV-1 active replication in the cells (65). *NRON* expression in the HIV-1 cycle is complex. Firstly, early in the viral cycle, Nef inhibits NRON, thus activating viral transcription. Secondly, in the late stage of infection, the Vpu viral protein induces *NRON* expression to swap from viral transcription to viral assembly and budding (65). Thirdly, NRON can also regulate HIV latency in an NFAT-independent fashion by enhancing ubiquitin-proteasome-dependent degradation of the viral activator of transcription (Tat) (75) (**Table 1**). This suppresses viral transcription and facilitates HIV latency preventing transcriptional activation of proviruses. Knockdown of *NRON* could enhance viral production from primary $CD4^+$ T lymphocytes latently infected with HIV-1. In HIV-infected individuals receiving combination antiretroviral therapy (cART), expression of endogenous NRON in resting $CD4^+$T cells is inversely correlated with the expression level of intracellular viral RNA (75).

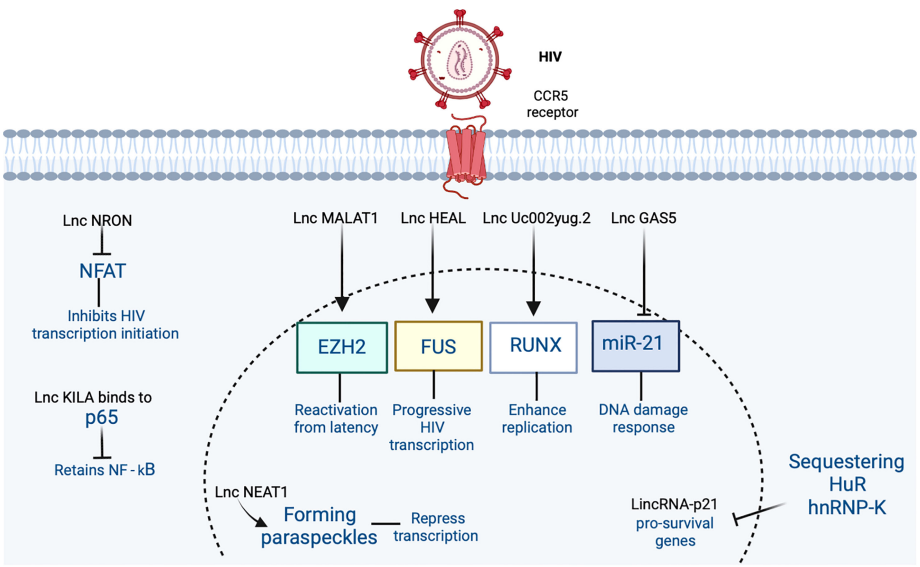

FIGURE 2 | The participation of lncRNA in HIV-1 infection is shown. HIV-1 binds to the CCR5 receptor in the cell. In the figure, the lncRNAs that induce an increase or inhibition are shown with different indicators (↑ and ⊥ respectively). Figure was designed in Biorender by AVRR (https://biorender.com/).

TABLE 1 | Selected lncRNAs of HIV-1 including their first report, known function, and nucleic acid/protein-binding partners.

Classification	Name	Gene symbol	First disease/assay reported	Function/stage in infection	Gene regulation layer	Nucleic acids/ Protein binding Partners
lncRNA	Metastasis-Associated Lung Adenocarcinoma Transcript 1	*MALAT1*	Non-small cell lung cancer (63)	Activates replication and reactivation from latency	Epigenetic, alternative splicing	miR-142-3p, miR-3p/PRC2, STAT1, STAT3, STAT5A, IRF1, IRF4
lincRNA	HIV-1-Enhanced LncRNA	*HEAL*	*In vitro* HIV-1 infection (64)	↓ in latency, acetylation of H3K27Ac, recruits p300, ↑CDK2, viral recrudescence	Epigenetic (histone acetylation), transcription by P-TEFb	HIV-1 promoter/ FUS
lncRNA	Non-coding Repressor Of NFAT	*NRON*	*In vitro* HIV-1 infection (65)	↓ in latency, NFAT sequestering, degradation of Tat, thus tunes the degree of T-cell activation and HIV-1 LTR-mediated transcription	Transcription	?/CUL4A, 26S, S944.5
lincRNA	Trans Activation Response RNA-gag	*Tar-gag*	Exosomes from uninfected cells increase HIV-1 transcription in infected cells under cART (66)	Tat sequestering and aid in Tar degradation leads to HIV-1 silencing	Transcription	?/hnRNPA2B1
lincRNA	Tumor protein 53 pathway corepressor 1 gene	*TP53COR1* (lincRNA-p21)	*In vitro* HIV-1 infection (67)	Apoptosis induced by DSBs in $CD4^+$ T cells, downregulation allow pro survival genes in macrophages	Transcription	?/ELAVL1, hnRNPK, PRC2
lncRNA	Nuclear paraspeckle assembly transcript 1	*NEAT1*	*In vitro* HIV-1 infection (67)	Paraspeckles assembly, viral defense association with regulators of inflammasome, enhances viral replication	Represses transcription, epigenetic (histone modification), apoptosis bypass, indirectly influences RNA editing	HIV-1 mRNA/ hnRNPU, STAT1, STAT3, STAT5A, IRF1, IRF4
lncRNA	Nuclear factor kappa-B interacting lncRNA	*NKILA*	*In vitro* HIV-1 infection (68)	By NF-κB sequestering, inhibits replication and infection	Prevents NF-κB-mediated transcription	?/p65
lincRNA	Long intergenic non-protein coding RNA 1426	*LINC01426* (formerly *Uc002yug.2)*	↑in esophageal squamous cell carcinoma (ESCC) (69)	By ↑Tat expression and ↓ regulation of RUNX1b and RUNX1c, enhance HIV replication and latent reactivation	Inhibits replication, alternative splicing of *RUNX1 (*69)	?/?
lncRNA	Fas cell surface death receptor-antisense transcript 1	*FAS-AS1*	B-cell lymphoma (70)	Production of sFas leads to resistance to fas-mediated apoptosis (70), survival of infected macrophages	Regulated by epigenetics (EZH2-mediated histone trimethylation), ↓Regulation of caspases 3 and 7	?/?
lincRNA	Long intergenic non-protein coding RNA 173	*LINC00173* (formerly NCRNA00173 or FLJ42957)	Involved in blood homeostasis (71)	↓Regulate levels of cytokines *IFNG*, *CCL3*, and *CXCL8* in T cells	Transcription ↓regulation of cytokine genes and/or ↓regulation of IFN-γ translation	?/?
lncRNA	Growth arrest-specific transcript 5	*GAS5*	↓regulation in HIV-1 infected cells (65)	Attenuation of HIV replication, TCR activation	Transcription sponging acting as ceRNA, ↓replication	miR21, miR-873/ NS3 (of hepatitis C virus) (72)
lncRNA	HIV-encoded antisense long non-protein coding RNA	*HIV-encoded antisense lncRNA*	*In vitro* HIV-1 infection (73)	Inhibits expression of viral genes	Epigenetic (recruits and guides a chromatin-remodeling complex)	?/DNMT3a, HDAC-1, EZH2, G9a?

Role of Trans-Activation Response RNA-gag

This lncRNA was named *TAR-gag* because it contains the complete trans-activation response RNA (TAR) and U5 sequence of the 5-LTR and part of the *gag* gene (for an interaction network of gag, nc, ma, and rev viral proteins with human proteins, see **Figure 3**). Heterogeneous nuclear ribonucleoprotein A2/B1 protein (hnRNPA2B1) may package TAR and TAR-gag into exosomes by binding to their 5′-GGAG-3′ motif. For this reason, the authors suggest that true HIV-1 latency *in vivo* is very unlikely due to the high number of exosomes (10^8–10^{11}) to which tissues and cells in fluids are constantly exposed (66) (**Table 1**). TAR-gag can also silence HIV-1 transcription and latency sequestering Tat and promote its degradation (for an interaction network of Tat, Vpr, and vif viral proteins with human proteins, see **Figure 4**). The TAR-gag mechanism acts as an "RNA machine" by binding to proteins that suppress transcription and forming an RNA–protein complex that regulates the gene expression of HIV-1 (61).

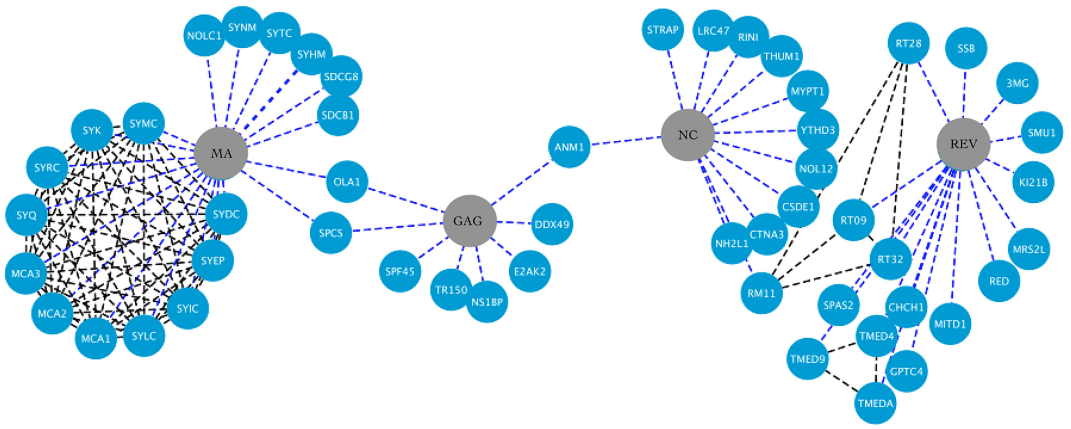

FIGURE 3 | HIV-1-host protein interaction network. HIV-1 proteins Ma, Gag, Nc and Rev are shown in the central nodes in gray color, contacting each of them with the human proteins, which are nodes in blue color. Interactions between viral and human proteins are shown in the blue dotted lines, while interactions between the same human proteins are shown in the black dotted lines. Figure created in Cytoscape (https://cytoscape.org/download.html).

Role of Long Intergenic Non-Protein Coding RNA p21

LincRNA-p21 is encoded by the tumor protein p53 pathway corepressor 1 gene (*TP53COR1*, www.genenames.org). Apoptosis is caused by double-strand breaks (DSBs) such as those induced by retrovirus integration as in the case of HIV-1. Apoptosis is coordinated by lincRNA-p21, which is p53-regulated. LincRNA-p21 mediated its function by binding in a complex with one of its three protein partners ELAV-like RNA-binding protein 1 (ELAVL1, formerly called Hu-antigen R or HuR), heterogeneous nuclear ribonucleoprotein K (hnRNPK), or PRC2 (67) (**Figure 2**). ELAVL1 contains three ribonucleoprotein-type consensus motifs and bind to cis-acting AU-rich elements (AREs). A core element of 27 nucleotides contains AUUUA, AUUUUA, and AUUUUUA motifs (76). HIV enables lincRNA-p21 degradation by sequestering ELAVL1 in the nucleus. Also, HIV sequesters hnRNPK in the cytoplasm through the pro-survival MAP2K1/ERK2 pathway, thus inducing transcription of pro-survival genes in macrophages. This is in contrast to T cells, where maturing cells switch off the MAP2K1/ERK2 cascade (67). In brief, HIV-1 induces apoptosis in $CD4^+$ T cells but mainly is non-cytopathic in macrophages leading to the long-term dissemination of the virus (**Table 1**).

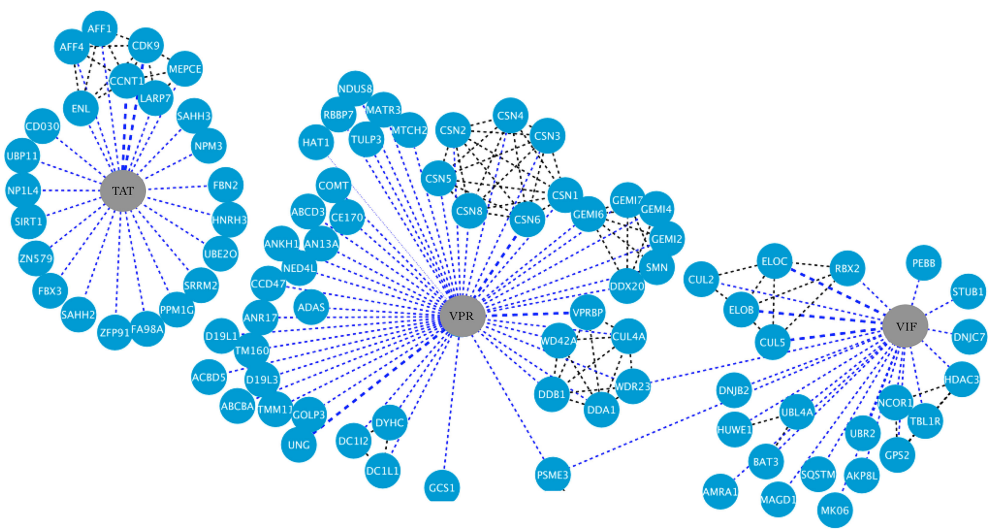

FIGURE 4 | HIV-1-host protein interaction network. HIV-1 proteins Tat, Vpr, and Vif are shown in the central nodes in gray color, contacting each of them with the human proteins, which are nodes in blue color. Interactions between viral and human proteins are shown in the blue dotted lines, while interactions between the same human proteins are shown in the black dotted lines. Figure created in Cytoscape (https://cytoscape.org/download.html).

Role of Nuclear Paraspeckle Assembly Transcript 1

Paraspeckles are non-membranous organelles located in the nucleus where many RNAs reside and RNA-binding proteins (RBPs) as well. Two of these RBPs are insulin-like growth factor-binding protein 7 (IGFBP7, formerly prostacyclin-stimulating factor or PSF) and non-Pou domain-containing octamer-binding protein (NONO, formerly p54 nuclear RNA-binding protein or p54NRB). The function of paraspeckle bodies is suggested to be gene regulation through nuclear retention of RNA for editing by the adenosine deaminase acting on RNA 1 (ADAR1) enzyme. NEAT1 controls RNA regulatory processes by forming a critical scaffold to assemble paraspeckles, substructures that are very important for HIV replication (77). *NEAT1* is involved in different pathways as viral defense, innate, and inflammatory responses. *NEAT1* has two isoforms, *NEAT1_1* or *MENε* (3.7 kb) and *NEAT1_2* or *MENβ* (23 kb). Upon HIV-1 infection in diverse cell lines such as Jurkat, MT4, THP1, and THP1 differentiated with phorbol-12-myristate-13-acetate (PMA), isoforms NEAT1_1 and NEAT1_2 were upregulated ~3- to 7-fold and ~6- to 11-fold, respectively (77). NEAT1 represses HIV transcription (58) (**Figure 2**) and this enhances HIV-1 replication in activated $CD4^+$T cells in a post-transcriptional stage. Jurkat $CD4^+$ T-cell lines with a knockout (KO) of the *NEAT1* gene were more prone to the induction of apoptosis when compared with parental Jurkat cells (78). Quantitative PCR (qPCR) showed that *NEAT1* is downregulated in the plasma of infected patients and this expression correlates with $CD4^+$ T-cell count. Furthermore, in PBMCs, *NEAT1* was upregulated in highly active antiretroviral therapy (HAART)-naïve patients ($n = 31$) and downregulated in patients receiving HAART ($n = 28$) (79). *NEAT1* is further associated with regulator proteins of inflammasome and by its assembly with the immune-controlled ribonuclear complex (15). NEAT1 inhibits virus production through nuclear-to-cytoplasm export of Rev-dependent instability element (INS)-containing HIV-1 mRNAs. Thus, this evidence suggests that paraspeckles are indeed the depot for storing HIV-1 Rev-dependent INS-containing RNAs that are diverted away from splicing (77). In HeLa cells, *NEAT1* KO can promote the export of HIV-1 mRNA from the nucleus towards the cytoplasm and enhance viral production (15). NEAT1 contributes to antiviral response in a similar way to MALAT1 when the former interacts with STAT1, STAT3, STAT5A, and interferon regulatory factors 1 and 4 (IRF1 and IRF4) TFs. NEAT1 also interacts with heterogeneous nuclear ribonucleoprotein U (hnRNPU) altering histone modification of target genes (10). HIV-1 takes advantage of *NEAT1* downregulation by promoting infection and enhancing viral replication (79) (**Table 1**).

Role of Nuclear Factor Kappa-B-Interacting lncRNA

NKILA potently inhibits the replication and infection production of clones of HIV-1 with different co-receptor tropisms including R5X4-tropic 89.6, brain-derived Yu2, and macrophage-tropic AD8 strains. KILA binds to p65 and retains NF-κB in the cytoplasm (**Figure 2**). HIV-1 counterattacks downregulating *NKILA* by decreasing H3K27 acetylation in the *NKILA* promoter (68) (**Table 1**).

Role of Long Intergenic Non-Protein Coding RNA 1426

LINC01426 (formerly Uc002yug.2) is encoded by gene *LINC01426* (www.genecards.org). LINC01426 enhances replication of HIV and latent HIV activation by increasing the expression of Tat protein and downregulating Runt-related transcription factor 1b and 1c (*RUNX1b* and *RUNX1c*). In primary $CD4^+$T cells derived from HIV-1 patients successfully treated with HAART, the expression of LINC01426 was lower than in those HAART-naïve patients. Overexpression of LINC01426 in resting $CD4^+$ T cells derived from individuals treated with HAART and after T-cell activation by phytohemagglutinin M (PHA-M) led to significant HIV reactivation (80) (**Table 1**).

Role of fas Cell Surface Death Receptor-Antisense Transcript 1

In macrophages, which are resistant to virus-induced apoptosis, *FAS-AS1* [formerly SAF; for correct guidelines of lncRNA nomenclature according to the Human Genome Organization Gene Nomenclature Committee (HGNC), see (81, 82)] regulates apoptotic effector caspases. Downregulation of *FAS-AS1* increases the caspase-3 and caspase-7 activities in HIV-infected MDMs and exclusively induces cell death in macrophages infected with HIV. In bronchoalveolar lavage (BAL), macrophages obtained from HAART-naïve individuals show increased *FAS-AS1* expression. *FAS-AS1* is useful in the survival of persistently HIV-1-infected macrophages. Also, *FAS-AS1* is increased in HIV-positive lung alveolar macrophages from chronically infected patients (83) (**Table 1**).

Role of Long Intergenic Non-Protein Coding RNA 173

Two independent RNA-seq studies revealed that expression of *LINC00173* (formerly NCRNA00173 or FLJ42957, https://www.genenames.org) is increased ≥2-fold during HIV-1 infection and the location of this lncRNA is mainly in the nucleus. There are two isoforms of this lncRNAs, lnc173 TSV1 and lnc173 TSV2, which are polyadenylated. These can be detected by qPCR (84). It is likely that LINC00173 has a role in the regulation of cytokine levels in T cells during immune responses associated with HIV-1 because Jurkat cells with KO for *LINC00173* and exposed to PMA and ionomycin express higher mRNA levels of cytokine genes *IFNG*, *CCL3*, and *CXCL8* than control cells, in contrast with *IL2* and *TNF* genes, whose mRNA levels do not differ. Furthermore, in the same report, *LINC00173* KO clones also produced increased protein levels of IFN-γ (84) (**Table 1**).

Role of Growth Arrest-Specific Transcript 5

Gas5 is downregulated in HIV-1-infected cells (65). GAS5 could act as ceRNA, because it suppresses miR-873 expression, which can promote replication of HIV. Thus GAS5 downregulates HIV replication (85). Furthermore, GAS5 regulates functions of $CD4^+$

T cells through mir21-mediated signaling in people living with HIV (PLHIV, **Figure 2**). This regulates signaling molecules involved in the damage of DNA and cellular responses after T-cell receptor (TCR) activation (86) (**Table 1**).

Role of HIV-Encoded Antisense lncRNA

This antisense lncRNA is localized in the 5′LTR and replaces the components of endogenous cellular pathways. This lncRNA recruits and guides a chromatin-remodeling complex by binding to methyltransferase 3a (DNMT3a), histone deacetylase 1 (HDAC-1), and the polycomb protein enhancer of zeste homolog 2 (EZH2). The presence of these proteins at 5′LTR leads to epigenetic changes in histones associated with the viral promoter. This results in a downregulation of HIV-1 gene expression. Suppression of this lncRNA with small single-stranded antisense RNAs leads to the activation of viral gene expression DNA (73) (**Table 1**).

Other lncRNAs in HIV Infection

In monocyte-derived macrophages, lncRNA differentiation antagonizing non-protein coding RNA (*DANCR*) is downregulated by IFN-ε stimulation, and 21 interactions with mRNAs were predicted. This was in contrast to classic lncRNAs such as *NEAT1, GAS5*, and *MALAT1*, which showed no differential expression in HIV-infected MDMs (87). Another lncRNA is AK130181, which represses HIV transcription and induces latency through NF-κB signaling. Interestingly, lncRNA LOC102549805 (lncRNA-U1) modulates neurotoxicity of HIV Tat protein (88). Additional lncRNAs in HIV-1 infection were recently reviewed in (89).

POTENTIAL OF LNCRNAS IN HIV/AIDS DIAGNOSTICS

Plasma levels of lincRNA chr12:57761837-57762303 and lincRNA: chr2:165509129-165519404 were better markers for HIV-1 infection whereas LincRNA chr5:87580664-87583451, XLOC_001148, and lincRNA chr10:128586385-128592960 were better markers for HIV-2 infection (90). The presence of NEAT1 in plasma has been suggested as a biomarker of HIV-1 infection (79).

POTENTIAL OF LNCRNAS IN PROGNOSIS OF HIV/AIDS

Schynkel et al. (2020) analyzed the transcriptomic change of macrophages treated with three types of IFNs (IFN-α, IFN-γ, and IFN-ε) and 6 h post-infection with HIV-1. They found differential expression of 474 genes. From these, 112 (24%) were classified as non-coding; within these seven DE genes, they coincided between the four conditions of IFN finding five lncRNAs, namely, AC053503.1, NRIR, C8orf3, AL359551.1, and MIR3945HG, as well as two pseudogenes, namely, neutrophil cytosolic factor 1C pseudogene (*NCF1C*) and guanylate binding protein 1 pseudogene 1 (*GBP1P1*) (87).

In elite controllers of HIV, it has been suggested that in myeloid dendritic cells, the *lnc MIR4435-2* host gene (MIR4435-2HG) enhances metabolic function through epigenetic mechanisms including H3K27 enrichment at an intronic enhancer of the regulatory associated protein of mammalian target of rapamycin [mTOR] (*RPTOR)* locus, which is the main component of the mTOR complex 1 (mTORC1) by means of a predicted triple helix of RNA–DNA. These changes shows features of trained innate immunity (91).

RUNX1 overlapping RNA (RUNXOR) is an lncRNA and an important regulator of myeloid-derived suppressor gene. RUNXOR and RUNX are upregulated in MDSCs that expand and accumulate in human PBMCs in people living with HIV (PLHIV). RUNXOR and RUNX are associated with expression of immunosuppressive molecules such as reactive oxygen species, arginase 1, signal transducer and activator of transcription 3 (STAT3), IL-6, and inducible nitric oxide (NO) synthase (92).

A total of 242 lncRNAs were DE in HAART-naïve people living with HIV (PLHIV) patients. Seventeen of those lncRNAs were predicted to regulate *TCF7L2* and *HIF1A* genes, which are involved in HIV transcription. Twenty DE lncRNAs probably share miRNA response elements with JUN and FOS, which are associated with both HIV-1 replication and immune activation (58).

Chemokine, CC motif, receptor 5-antisense (CCR5-AS) is an lncRNA that regulates differential expression of CCR5, the major co-receptor of HIV. High expression of *CCR5-AS* sequesters the RALY heterogeneous nuclear ribonuclear protein (RALY) preventing its binding to CCR5 3′-UTR. This prevents the decay of *CCR5* mRNA (93).

LNCRNAS AS POTENTIAL THERAPY IN HIV/AIDS

For the complete transcription of HIV-1, two stimuli are necessary. Firstly, the activation of T cells, and secondly, the translation of the viral protein Tat. With this rationale, one therapeutic approach is that peptides capable of competing for Tat binding and stimulating a viral ncRNA response have been applied. Peptide F07 #13 can induce the silencing of transcriptional genes by inducing viral ncRNA (e.g., TAR-gag and TAR) that act with transcriptional suppressor proteins cullin 4B (CUL4B), PRC2, and SIN3 transcription regulator family member A (SIN3A), ultimately leading to ubiquitination of Tat (61). Inhibition of lncRNAs that induce latency can be achieved by post-transcriptional degradation of the lncRNA with short hairpin RNA (shRNA), antisense oligonucleotide (ASO), or siRNA. Improved design of modified siRNA and ASOs has led to a higher efficacy and stability, while off-target effects are reduced. This can be attained by lncRNA transcription inhibition of by gene editing by CRISPR-Cas or promoter blockade (94, 95). As the function of lncRNAs is through formation of secondary structures with both proteins and

nucleic acids, a diverse collection of RNA decoys, nanobodies, small molecules, and aptamers to induce steric hindrance are being evaluated in ongoing efforts (96). Most of the current approaches for therapy are focused on pathogenic lncRNA inhibition by delivery of lncRNA made of synthetic RNA. For lncRNA delivery, a feasible approach is to use adeno-associated virus, herpes virus, ncRNA sponges, chemical modified ncRNAs, non-viral vectors, computed tomography-guided injections, and endoscopic ultrasound (97).

The lack of sequence conservation across species is one of the main challenges of lncRNA research. One solution could be humanized mouse models. In addition, specific markers of HIV-1 latently infected cells remain to be identified. Induction of apoptosis in virus-infected cell only, is caused by downregulation of the lncRNA heterogeneous nuclear ribonucleoprotein U gene (HNRNPU, formerly SAF) with siRNA. This leaves unaffected the bystander cells (83). The effectiveness and safety of lncRNA-mediated therapy should be demonstrated in non-human primates as well as in clinical trials. Importantly, the elimination of reservoirs of latent HIV-1 remains the major hurdle to find a complete cure for HIV-1 infection. The approaches to trying to tackle this are killing infected cells, gene therapy, "shocking and kill" HIV-1 out of latency [reviewed in (97)], and/or HIV-1 silencing, e.g., through the histone chaperones, namely, chromatin assembly factor I, subunits A and B (CHAF1A and CHAF1B) (98). Nevertheless, none of these potential solutions are likely to eradicate HIV in the short term; a combination of them could lead to a feasible functional cure in the mid or long term.

EXPRESSION OF LNCRNAS IN COVID-19 AND MURINE MODELS

The role of lncRNAs in both the initiation and progression of viral infection has been reported. In a mouse model, RNA sequencing of influenza A virus and SARS-CoV-2-infected lung tissues also demonstrated the key roles of lncRNAs in pathogenesis of respiratory virus by inducing interferon (IFN). In this model, the pathogenesis regulation is mediated by signal transducer and activation of transcription (STAT1). In COVID-19 patients, an increasing chemokine expression has been observed in reduced or absence of type I (IFNα and IFNβ) and III (IFNλ1, IFNλ2, IFNλ3, and IFNλ4) interferons (99). Thus, the lncRNA network of COVID-19 patients showed a significant downregulation of IFN-I response (15). Furthermore, in SARS-CoV-2 infection, 527 bronchoalveolar lavage fluid (BALF) and 239 protein-coding genes (PCGs in peripheral blood mononuclear cell-PBMC) could be influenced by 162 and 106 cis-acting lncRNAs, respectively. Main pathways involved are myeloid local site activation, immune system, iron homeostasis regulation, and degranulation of neutrophils in the tissue-specific regulation of host pyrin domain (PYD) and C-terminal caspase-recruitment domain (CARD)-containing protein (*PYCARD*) and *IFNG* gene (PBMC) as well as calpain 1 (*CAPN1*) gene mediated by *MALAT1* and *NEAT1* lncRNAs (99). Another report suggests that 195 and 155 lncRNAs are down- and upregulated, respectively (100). Furthermore, another group reported that, in the GEO database (GSE147507) in more than one cell line, the DE lncRNAs were *LINC00312, LINC00473*, *LINC00605*, HLA complex group 11 (*HCG11*), HIF1A-antisense 2 (*HIF1A-AS2*), eosinophil granule ontogeny (*EGOT*), erythrocyte membrane protein band 4.1-like 4A-antisense 1 (*EPB41L4A-AS1*), *LINC00115, LINC00174, LINC00265, LINC00662, LINC00842*, myocardial infarction-associated transcript (*MIAT*), *NEAT1, MALAT1*, maternally expressed 3 and 9 (*MEG3* and *MEG9*), RNA component mitochondrial RNA processing endoribonuclease (*RMRP*), telomerase RNA component (*TERC*), and zinc finger protein 674–antisense 1 (*ZNF674-AS1*) and decreased expressions of TP3 target 1 (*TP53TG1*), *LINC00488*, prostate androgen-regulated transcript 1 (*PART1*), and *LINC00857* (101). Also in a murine model, a report suggests that there are 5,329 different lncRNAs (15). In the binding of lncRNA and transcription factors, those more relevant were IRF1, STAT1, and MYC1. Notably, in lungs of COVID-19 patients, expression of *NEAT1* was also increased significantly (101). Interestingly, expression of *MALAT, NEAT1*, and *MIAT* was common between SARS-CoV-2-infected cells and those infected with HIV. An increased expression of *MALAT1* and abnormal expression of other lncRNAs was reported in BAL fluid of COVID-19 patients (15, 99, 101). Hox antisense intergenic RNA (HOTAIR), NEAT1, MALAT1, LINC00589 (formerly tumor-suppressor lncRNA on chromosome 8p12 or TSLNC8), and cardiac autophagy inhibitory factor (CAIF) lncRNAs may regulate IL-6 expression. In contrast, *XIST*, cyclin-dependent kinase inhibitor 2B-antisense RNA gene (*CDKN2B-AS1*, formerly antisense RNA in the *INK4* locus or *ANRIL*), repulsive guidance molecule domain family, member B-antisense 1 (*RGMB-AS1*), *NEAT1*, MAS-related G-protein coupled receptor, member D (*MRGPRD*, formerly *Gm499*), and cytochrome C oxidase subunit II (*MT-CO2*, formerly *Cox2*) lncRNAs encoded in the mitochondria genome have been implicated in the formation of inflammasome (100). Another group reported 410 differentiated lncRNA among COVID-19 patients and controls (20). Different results, particularly the role of IFN-I in COVID-19 patients, must be due to the application of different methodologies, different tested time points, and non-comparable cell lines analyzed (101). The majority of these lncRNAs have been predicted by *in silico* approaches except *NEAT1* (upregulation) and *DANCR* (downregulation). LncRNAs in cytokine storm are RAS gene associated with diabetes 51-antisense 1 (*RAD51-AS1*, formerly *TODRA*), non-coding RNA activated by DNA damage (*NORAD*, formerly *LINC00657*), and *GAS5* (15).

Role of MALAT1

Regarding the possible complications of COVID-19 infection, MALAT1 ameliorates deep vein thrombosis (DVT). The mechanism is through inhibition of proliferation and migration of endothelial progenitor cells and finally thrombosis dissolution *via* the Wnt/β-catenin signaling pathway (102). In addition, MALAT1 reduces the epigenetic silencing of viral transcription by regulating interactions of promoter-enhancer upregulating viral transcription and infection. MALAT1

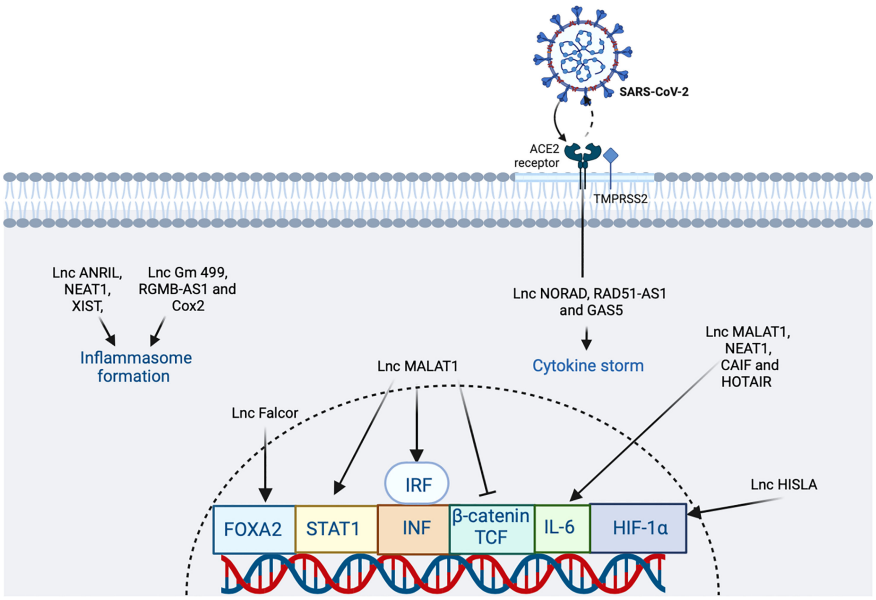

FIGURE 5 | The participation of lncRNA in SARS-CoV2 infection. The virus binds the ACE2 receptor in the host cell. In the figure, the lncRNAs that induce an increase or inhibition are shown with different indicators (↑ and ⊥ respectively). The figure was designed in Biorender by AVRR (https://biorender.com/).

TABLE 2 | Selected lncRNAs of SARS-CoV-2 including their first report, known function, and nucleic acid/protein-binding partners.

Classification	Name	Gene symbol	First disease/assay reported	Function	Gene regulation layer	Nucleic acids/ Protein binding Partners
lncRNA	Eosinophil granule ontogeny	*EGOT*	Early eosinophil development marker (103)	Antiviral response	Promotes colon cancer cells autophagy, prevents cell growth and metastasis (104)	mirNA-33a-5p, mirNA-33b-5p (*in silico*) (104)/ ELAVL1
lncRNA	Metastasis-Associated Lung Adenocarcinoma Transcript 1	*MALAT1*	Non-small cell lung cancer (63)	Counteract deep vein thrombosis (DVT), ↓p53 activation, ↓type I IFN by *IFNG* gene, regulates *CAPN1*, *PYCARD* and *IL6* genes	Epigenetics through sequestering of miRNAs, transcription	miR-142-3p, miR-3p/PRC2, STAT1, STAT3, STAT5A, IRF1, IRF4
lncRNA	Nuclear paraspeckle assembly transcript 1	*NEAT1*	*In vitro* HIV-1 infection (67)	Inflammasome formation, differentiate mild from severe damage in COVID-19, regulates *CAPN1*, *PYCARD*, *IFNG* and *IL6* genes	Transcription	HIV-1 mRNA/ hnRNPU, STAT1, STAT3, STAT5A, IRF1, IRF4
lncRNA	Differentiation Antagonizing Non-protein Coding RNA	*DANCR*	Monocytes associated with osteoporosis (105)	Regulates inflammation by cholinergic inhibition, ↑transcription and ↑translation of IL6 and TNF-α (105)	Transcription and translation	?/?
lincRNA	Hox antisense intergenic RNA	*HOTAIR*	Cancer invasiveness (106)	Interacts with Spike at both DNA and mRNA, regulates *IL6* gene	Transcription and translation	*IL6* gene, S mRNA/?
lncRNA	FOXF1 adjacent non-coding developmental regulatory RNA	*FENDRR*	Heart development (*Fendrr* in mice) (107)	Interacts with Spike at both DNA and mRNA	Transcription and translation	*S* mRNA?/?
lincRNA	Long intergenic non-protein coding RNA 1505	*LINC1505*	Act in the circuitry controlling pluripotency and differentiation (www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSM749287)	Interacts with Spike at both DNA and mRNA	Transcription and translation	*S* mRNA?/?
lncRNA	FOXA2-adjacent long non protein-coding RNA	*FALCOR*	Chronic peribronchial airway inflammation and goblet cell metaplasia (108)	Regulate *FOXA2* expression	Transcription	*FOXA2* gene/?
lncRNA	HIF-1α-stabilizing lncRNA	*HISLA*	Glycolysis and chemoresistance of breast cancer (109)	Stabilizes HIF-1 α by binding to EGL1	Transcription	?/EGL1

interacts with STAT1, STAT3, STAT5A, IRF1, and IRF4. MALAT1 is a negative regulator of type I IFN production (10) (**Figure 5**) and sequesters miR-142-3p and miR-146a-5p to repress their anti-inflammatory activities and its overexpression, thus promoting inflammation (10). Deletion of *MALAT1* led to the activation of p53 and its target genes, which affect the normal progression of the cell cycle (15) (**Table 2**). In addition, in a mouse model of SARS-CoV-2 infection, *Malat1* was downregulated by tubulin α1 (TubA1A), the 60S ribosomal protein (Rlp6), and the endoplasmic reticulum protein retention receptor 3 (Kdelr3) (15).

LNCRNAS IN POTENTIAL PROGNOSIS IN COVID-19

Also, in the case of autoimmunity in SARS-CoV-2-infected patients, some lncRNAs act through inflammatory pathways including TLR and NF-κB signaling (10). Approximately 15%–20% of COVID-19 patients develop severe pneumonia and acute respiratory distress syndrome (ARDS). LncRNA GATA5 is elevated and positively correlated with severe COVID-19 (11). In another study, vitamin D receptor gene (*VDR*) expression was lower in COVID-19 patients compared with non-infected controls. Differences were not found with *Linc00511* or *Linc00346* (110). Also, DANCR (in lungs) and NEAT1 lncRNAs targeting microRNAs were associated with genes that differentiate mild from severe damage in SARS-CoV-2 (111).

LNCRNAS IN COVID-19 DIAGNOSIS

Genotyping of SARS-CoV-2 has been very useful in monitoring both viral evolution and transmission during the COVID-19 pandemic (112). However, in a more practical and affordable way, alternative strategies have been developed to demonstrate the presence of the virus in the samples of suspected individuals. The most common methods to identify the presence/absence of SARS-CoV-2 is reverse transcription (RT)-PCR (sensitivity = 82.2%; specificity = 100%) (113). Additional strategies include RT loop-mediated isothermal amplification (without the need for RNA extraction) (sensitivity = 87.5%; specificity = 100%) (114) and deep learning computer-aided diagnosis (CAD) based on digital chest x-ray images (overall detection accuracy = 96.31%; classification accuracy = 97.40%) (115). Transcript level combination of cytochrome p450, subfamily XXVIIB, polypeptide 1 (*CYP27B1*), *VDR*, small nucleolar RNA host gene 16 (*SNHG16*), structural maintenance of chromosomes 3 (SMC3, formerly chondroitin sulfate proteoglycan 6 or *CSHG6*), *Linc00511*, and *Linc00346* could be a potential alternative method to COVID-19 diagnostics (sensitivity = 0.62; specificity = 0.81) (110).

LNCRNAS AS POTENTIAL DRUG TARGETS IN COVID-19

LncRNAs interactions with IFN in SARS-CoV-2 is an interesting research topic (15). The clotting alteration in COVID-19 may be related to inflammatory cytokines; thus, a better understanding of the cytokine regulation by lncRNAs will be helpful to understand this clinical phenotype and develop therapeutic targets to lncRNAs or molecules mimicking their function. Forty percent of known lncRNAs were found regulating different processes in the central nervous system (CNS) (15).

It has been suggested that lncRNAs can target and bind cytokine nucleotide sequences leading to downregulation of these cytokines. IFN-α is a common antiviral therapy in critically ill COVID-19 patients. Induction of *MALAT1* expression by viral infection promotes activation of interferon regulatory factor 3 (IRF3) and production of type I IFN (**Figure 5**). Inhibition of the excessive inflammation may be a useful complement to COVID-19 therapy. Potential approaches in the clinic include oligonucleotide knockdown, RNAi knockdown, and viral gene therapy interfering with gene transcription, protein translation, and extranuclear messengers (15). Furthermore, lncRNAs are spatially correlated with TFs across the genome as, e.g., the case of FOXA2-adjacent long non protein-coding RNA (lncRNA Falcor) that can regulate forkhead box A2 (*FOXA2*) expression. Alteration of the regulatory feedback loop of Falcor-FoxA2 leads to altered cell migration and adhesion, thus causing goblet cell metaplasia and chronic peribronchial airway inflammation (15). Also, IL-6, transforming growth factor, beta 1 (TGF-β1, formerly TGF-β), nucleotide oligomerization domain-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome, and cholinergic signaling have been proposed as potential targets in COVID-19 (15). In the cholinergic inhibition, *DANCR* was found to potentially regulate inflammation. The identification of dysregulated or altered lncRNAs during SARS-CoV-2 infection could be a strategy for mitigating symptoms in patients and to limit viral genome amplification enhancing the immune response (15). The most relevant lncRNAs during COVID-19 seem to be HOTAIR, FOXF1 adjacent non-coding developmental regulatory RNA (FENDRR, formerly FOXF1-AS1), LINC01505 (**Table 2**), and imprinted maternally expressed non-coding transcript (H19). Furthermore, FENDRR, HOTAIR, and LINC1505 potentially interact with the mRNA of spike protein (116). In macrophages, HIF-1α-stabilizing lncRNA (HISLA) regulates HIF-1α transcription factor by inhibition of its binding to EGL9 family hypoxia-inducible factor 1 protein (EGL1, formerly prolyl hydrolase domain-containing protein 2 or PHD2) (**Table 2**) (for an interaction network of SARS-CoV-2 proteins with human proteins, see **Figure 6**). This keeps continuous activation of an aerobic state in tumor cells. In the case of the treatment of COVID-19 using the strategy of an aptamer-siRNA chimera-mediated *HISLA* knockdown, this approach is promising but requires further investigation (15) (**Figure 5**).

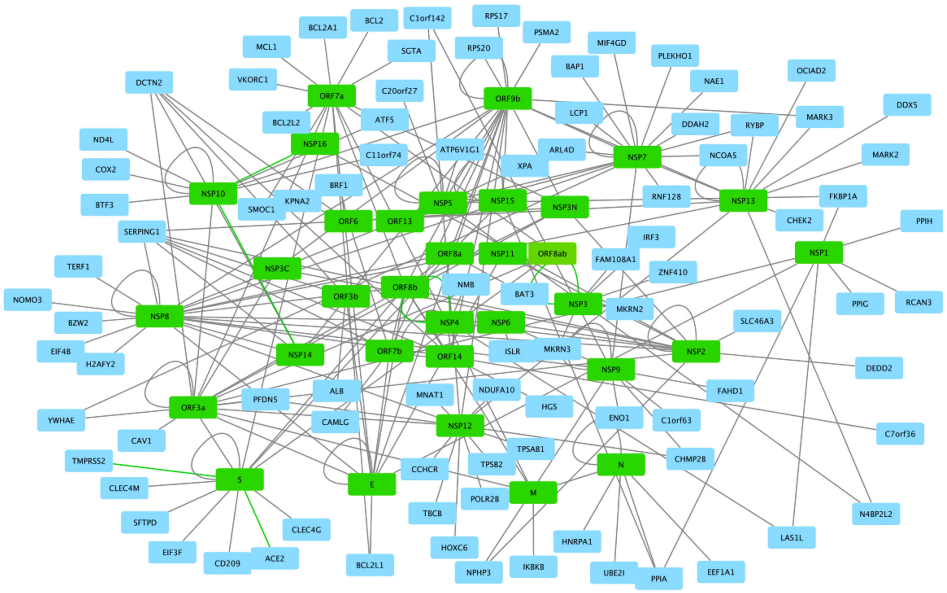

FIGURE 6 | SARS-CoV2 -host protein interaction network. Viral proteins are shown in green boxes and human proteins are shown in blue boxes. Interactions between viral and human proteins are shown in the black lines. The figure was created in Cytoscape (https://cytoscape.org/download.html).

HOST LNCRNAS FROM ENDOGENOUS RETROVIRUSES

Human endogenous retroviruses [HERVs, reviewed in (117)] are transposable elements comprising ∽10% of our genome and ranging from full-length proviruses to short gene fragments. HERVs are remnants of infectious exogenous retroviruses that became part of our DNA and now are inherited in a Mendelian manner. The HERV database [HERVd, http://herv.img.cas.cz (118)] contains 519,060 entities and 725,763 repeats of 582 different ERVs (accessed on March 3, 2022) that belong to 150 families. HERVs, working as Pathogen Associated Molecular Patterns (PAMPs), have become important parts of immune mechanisms to fight invading pathogens at least for dengue virus, herpes simplex viruses, influenza viruses, and HIV-1. Mechanisms used by ERVs are regulation of viral expression, enhancement of cellular sensing pathways, direct restriction of virion assembly, and blocking of entry receptors (117). Also, some ERVs are responsible for inserting proviruses in host genome facilitating infection and/or viral latency.

Host cells are armed with a variety of pattern recognition receptors (PRRs) that recognize nucleic acids from virus such as phospholipase A and acyltransferase 4 (PLAAT4, formerly retinoid acid-inducible gene 1or RIG-1) that recognizes 5′-triphosphate RNA, interferon induced with helicase C domain 1 (formerly melanoma differentiation-associated protein 5 or MDA5) that recognizes double-stranded RNAs (dsRNA), toll-like receptors 7 and 8 (TLR7 and TLR8) that recognize single-stranded RNA (ssRNA), toll-like receptor 3 (TLR3) that recognizes both dsRNA and poly I:C, toll-like receptor 9 that recognizes CpG DNA and DNA-immunoglobulin (Ig) complexes, and DNA-dependent activator of IRFs (DAI) that recognizes double-stranded DNA (dsDNA) [reviewed in (119)].

One classic example of ERV is a murine lncRNA called lncRNA ERV-derived positively regulating antiviral responses (lnc-Epav). This lncRNA boosts antiviral gene expression by increasing levels of RelA, a subunit of NF-κB transcription factor. The way that lnc-EPAV works in *RELA* promoter is competitively binding and displacing the splicing factor, proline- and glutamine-rich (SFPQ, an inhibitor of *RELA* gene) (47) (**Table 3**). Also, mice deficient in lnc-EPAV shows a reduced expression of type I interferons. In humans, the role of EPAV seems to be performed by interacting to MER9a2, LTR5A, and MLT2A1 HERVs. Results were concordant with a mouse model increasing levels of RELA in SFPQ knockdown human cells (47) (**Figure 7**).

Another example of interaction with the immune response is the long non-coding endogenous avian leukosis virus on chromosome 1-antisense 1 (lnc-ALVE1-AS1), transcribed from *ALVE1* gene, that can activate or bind to the Toll-like receptor 3 (TLR3) inducing an antiviral innate immune response (123) (**Table 3** and **Figure 7**).

The lncRNAs related to HERVs have also been associated with functions in tissue growth, as in the case of V-raf murine sarcoma viral oncogene homolog B1 (BRAF)-regulated long non-coding RNA (BANCR), related to pro-migratory functions necessary in the development of the heart in humans and primates (121) (**Table 3**). This relationship with different tissues has also been analyzed with different types of cancer. In addition, lncRNA TROJAN is known to be involved in the proliferative state of breast cancer (BrCa) cells (**Table 3**). By reducing TROJAN expression, the proliferative potential *in vitro* is prevented, so this could reduce tumor volume

TABLE 3 | Selected lncRNAs of HERVs including their first report, known function, and nucleic acid/protein-binding partners.

Classification	Name	Symbol	First disease/assay reported	Function	Gene regulation layer	Nucleic acid/Protein binding Partners
lncRNA	Long non-coding ERV-derived positively regulated antiviral responses	*Lnc-EPAV*	Murine model of genome-wide profiling of ERV-derived lncRNA expression (47)	↑ levels of RELA, ↑expression of type I IFN	↑transcription	MER9a2, LTR5A and MLT2A1 HERVs/?
lncRNA	Long non-coding endogenous avian leukosis virus on chromosome 1-antisense 1	lnc-ALVE1-AS1	Primary chicken embryo fibroblast cells (CEFs) infected with avian tumor virus ALVJ	Induces a TLR3-dependent antiviral response	↑transcription	?/TLR3
lncRNA	V-raf murine sarcoma viral oncogene homolog B1 (BRAF)-regulated long non-coding RNA	Lnc-BANCR	Melanoma cell migration (120)	Pro-migratory for cells in the development of the heart in non-human primates (121), lung carcinoma, melanoma, gastric and bladder cancer (122)	Transcription	?/extracellular signal-regulated kinases ½ (ERK1/2)c-Jun N-terminal kinase (JNK) (122)
lncRNA	Long non-coding RNA TROJAN	Lnc-TROJAn	Breast cancer (BrCa) study	Proliferate state of BrCa	DNA replication/ mitosis	?/?

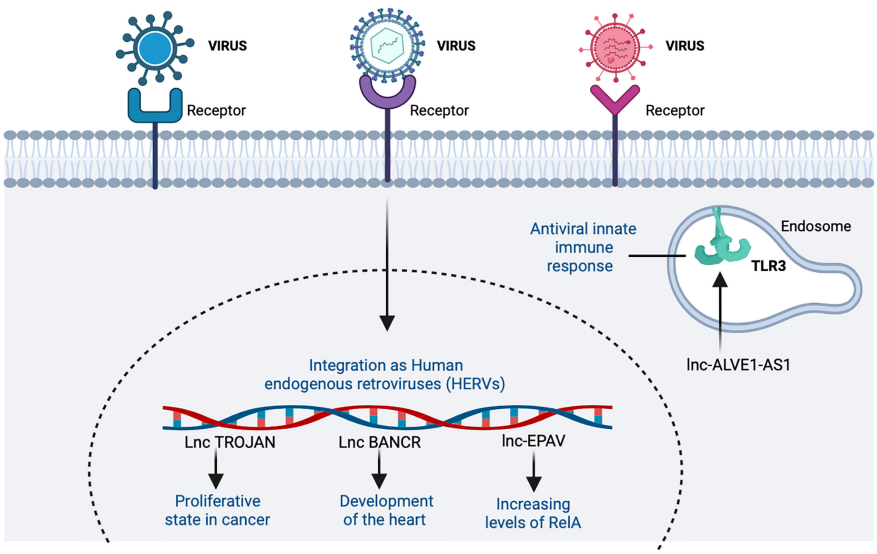

FIGURE 7 | The participation of host lncRNAs from endogenous retroviruses (ERVs). ERVs are remnants of infectious exogenous retroviruses that became fixed in the DNA. In the figure, the lncRNAs that induce an increase are shown with the indicator (↑). Figure was designed in Biorender by AVRR (https://biorender.com/).

and be a therapeutic target in the future (124). Even when these examples are in cancer, the similar cell cycle alterations with viral infection lead to hypothesize about a potential role of these HERVs in HIV/AIDS and/or COVID-19. Nevertheless, the importance of ERVs to antiviral immune response is becoming clear (47, 117); further basic and applied research is needed in this area.

CONCLUDING REMARKS

LncRNAs modulate both growth and viral replication as well as type I IFN expression mainly by stability regulation and interaction with mRNAs and proteins. The most relevant transcription factors that are regulated by lncRNAs are TP53, CTCF, MYC, SOX2, EZH2, SFPQ, and SUZ12 (125). In addition, lncRNAs seem to control the effector function of genes and peptides such as STAT1, STAT3, NF-κB, and IRFs and of many TFs, whose interactions remain to be discovered. The modulation of lncRNAs might regulate these transcription factors at both protein levels and at nucleotide motifs/structures. The key targeted potential therapies for SARS-Cov2 involve interfering gene transcription messengers and protein translation (15). Even when there are several questions to be solved, e.g., whether the cytokine storm activates ERVs in

response to SARS-CoV-2 infection in COVID-19 (as is true for viral lncRNAs), a better understanding of how lncRNAs regulate gene expression in a cell/tissue specific manner by interactions with mRNAs, these new therapeutic targets and biomarkers hold promise for the treatment and risk stratification of patients with HIV/AIDS and COVID-19.

In addition, a promising area of research is to catalog and interpret the polymorphisms, mutations, and indels in lncRNAs (126, 127), as well as their epitranscriptomic modifications (128–130) with ethnic and cell/tissue specificity. As an example of this, our group reported that the regulatory SNP (rSNP) rs5743417, which is common in African and Afro-Americans, causes a 33% transcription downregulation in the constitutively expressed gene human β-defensin 1 (*DEFB1*) in the A549 pulmonary epithelial cell line (131). *DEFB1* is a primordial gene of innate immunity involved in the defense against viruses [reviewed in (132)] including HIV-1 (133). In addition, hBD-1 peptide has other functions as well [reviewed in (134, 135)]. Interestingly, SNP rs5743417 overlaps with *GS1-24F4.2*, a lincRNA gene complementary to the X Kell blood-related 5 (*XKR5*) mRNA. *GS1-24F4.2* has a testis-specific expression that could shed light on male infertility associated with COVID-19 (136). Results like these increase the difficulty of interpretation of genetic variants at different regulation layers but at the same time open new opportunities to dissect both molecular and clinical impact of polymorphisms, whose interpretation in the light of functional genomics remained elusive in the past decades. In general, the integral impact of rSNPs could be explained (a) by the fact that SNPs could alter transcription factor binding sites (TFBS) mainly in promoters or enhancers (137), thus causing an up- or downregulation (131); (b) by the fact that SNPs can create novel TFBS (138) and thus modify homeostatic gene expression pathways; (c) by altering the normal structural and/or sponging function of lncRNAs (54); and (d) probably by indirectly introducing variations in the epitranscriptome.

With no doubt, lncRNAs research is coming of age. These novel drugs inspired by host- and viral-encoded lncRNA have the potential to reduce the burden of HIV/AIDS and COVID-19 twofold: (1) by increasing their efficacy and (2) by minimizing the side effects by modulating gene transcription instead of the more traditional approaches such as complete silencing, knockout/editing of genes, non-selective DNA methylation, or blockade/neutralization of host peptides and proteins. We expect that a new generation of lncRNAs could modulate human and viral transcription in a more specific and unprecedented way but still maintaining homeostasis below the pathogenic threshold.

AUTHOR CONTRIBUTIONS

AVRR: writing—original draft preparation and figures. EMP: writing and editing manuscript and tables. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: EP has a granted patent that protects a small molecule (and its synthesis and purification) that induces *DEFB1* transcription. This synthetic molecule could be applied as therapy for viral diseases including but not limited to HIV/AIDS and COVID-19. This patent is property of CIATEJ.

The remaining author declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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