cells

MDPI

Review

Aid or Antagonize: Nuclear Long Noncoding RNAs Regulate Host Responses and Outcomes of Viral Infections

Viraj Kulkarni [1], Sahana Jayakumar [2], Mahesh Mohan [2] and Smita Kulkarni [2,*]

[1] Disease Intervention and Prevention Program, Texas Biomedical Research Institute, San Antonio, TX 78227, USA; vkulkarni@txbiomed.org
[2] Host-Pathogen Interaction Program, Texas Biomedical Research Institute, San Antonio, TX 78227, USA; sjayakumar@txbiomed.org (S.J.); mmohan@txbiomed.org (M.M.)
* Correspondence: skulkarni@txbiomed.org; Tel.: +1-2102589691

Abstract: Long noncoding RNAs (lncRNAs) are transcripts measuring >200 bp in length and devoid of protein-coding potential. LncRNAs exceed the number of protein-coding mRNAs and regulate cellular, developmental, and immune pathways through diverse molecular mechanisms. In recent years, lncRNAs have emerged as epigenetic regulators with prominent roles in health and disease. Many lncRNAs, either host or virus-encoded, have been implicated in critical cellular defense processes, such as cytokine and antiviral gene expression, the regulation of cell signaling pathways, and the activation of transcription factors. In addition, cellular and viral lncRNAs regulate virus gene expression. Viral infections and associated immune responses alter the expression of host lncRNAs regulating immune responses, host metabolism, and viral replication. The influence of lncRNAs on the pathogenesis and outcomes of viral infections is being widely explored because virus-induced lncRNAs can serve as diagnostic and therapeutic targets. Future studies should focus on thoroughly characterizing lncRNA expressions in virus-infected primary cells, investigating their role in disease prognosis, and developing biologically relevant animal or organoid models to determine their suitability for specific therapeutic targeting. Many cellular and viral lncRNAs localize in the nucleus and epigenetically modulate viral transcription, latency, and host responses to infection. In this review, we provide an overview of the role of nuclear lncRNAs in the pathogenesis and outcomes of viral infections, such as the Influenza A virus, Sendai Virus, Respiratory Syncytial Virus, Hepatitis C virus, Human Immunodeficiency Virus, and Herpes Simplex Virus. We also address significant advances and barriers in characterizing lncRNA function and explore the potential of lncRNAs as therapeutic targets.

Keywords: lncRNA; virus; epigenetics

Citation: Kulkarni, V.; Jayakumar, S.; Mohan, M.; Kulkarni, S. Aid or Antagonize: Nuclear Long Noncoding RNAs Regulate Host Responses and Outcomes of Viral Infections. *Cells* **2023**, *12*, 987. https://doi.org/10.3390/cells12070987

Academic Editors: Chava Kimchi-Sarfaty and Upendra Katneni

Received: 6 October 2022
Revised: 12 March 2023
Accepted: 15 March 2023
Published: 23 March 2023

1. Introduction

During the past decade, several genome-wide RNAi [1–14] and CRISPR [15–22] studies have identified host proteins critical for viral replication. Protein-coding open reading frames constitute less than 2% of the human genome [23], and the bulk of the transcriptome is noncoding RNA (ncRNA). Among the different ncRNA subclasses, long noncoding RNAs (lncRNAs) were reported to constitute nearly 68% of the transcriptome [24]. Many lncRNAs regulate various cellular processes [25,26] and are emerging as versatile regulators of gene expression with prominent roles in health and disease [27,28].

A variety of viral infections alter host lncRNA expressions. Dramatic changes in lncRNA expressions have been observed in the cells infected with Influenza A Virus (IAV) [29], Sendai Virus (Sev), Respiratory Syncytial Virus (RSV) [30], Hepatitis C Virus (HCV) [31], Adenovirus [32], Human Papilloma Virus (HPV) [33], pathogenic human enterovirus [34], Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV and SARS-CoV-2) [35–45], Human Immunodeficiency Virus (HIV) [46–51], Muscovy Duck ReoVirus

(MDRV), and Herpes Simplex Virus (HSV) [52]. These studies are only beginning to reveal the myriad changes in lncRNA expression upon viral infection and indicate the role of lncRNAs in viral pathogenesis.

The pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) released during infections, stress, and non-programmed cell death are detected by the pattern recognition receptors (PRRs), such as Toll-like receptors (TLR), retinoic acid-inducible gene (RIG)-like receptors (RLRs), nucleotide oligomerization domain (NOD)-like Receptors (NLRs), and C-type lectin receptors (CLRs). The activation of PRRs leads to the transcription of inflammatory genes induced by ATF2 and NF-κB, the transcription of specific antiviral genes induced by IRF3 and IRF7, and the synthesis of Type I interferons (IFN-I). PRR activation by virus infection [53–58] and various ligands, such as lipopolysaccharides (TLR4) or Poly I: C induces the expression of lncRNAs [59–64]. In addition, stimulating cells by cytokines, such as IFN-I [65] and TNF-α [66], induces differential expressions of lncRNAs. Viral infections, including specific viral proteins can upregulate the expression of stress-induced and other lncRNAs [67,68]. Thus, the transcriptome of virus-infected cells presents an opportunity to discover and characterize novel lncRNAs that may play a significant role in cellular defense, immune response, and viral propagation. For instance, IFN–alpha (IFNα) stimulation or infection with RNA viruses upregulates lncRNA *ISIR* [69]. *ISIR* activates the Interferon Regulatory Factor-3 (IRF3) and strengthens the interferon response to viral infections. Indeed, several transcriptomic studies have highlighted the marked dysregulation of lncRNAs in virally infected cells [70]. We have listed prominent nuclear RNAs with a significant impact on immune response, viral replication, and latency in Table 1. We also discuss the molecular mechanisms of their action wih more details in this review.

Table 1. Cellular and viral nuclear lncRNAs regulate viral replication and persistence.

LncRNA	Virus	Mechanism	Reference
		Proviral lncRNAs	
NRAV	IAV, SeV, MDRV, HSV	Histone modification and reduction in active transcription marks at ISG.	Ouyang et al., 2014 [57]
TSPOAP1-AS1	IAV	*TSPOAP1-AS1* inhibits FNβ1 transcription, ISRE activation, and ISG expression.	Wang et al., 2019 [62]
Lnc-MxA	IAV	Lnc-MxA inhibits IFNβ transcription by binding to its promoter and enhances viral replication.	Li et al., 2019 [61]
VIN	IAV, VSV	*VIN* increases virus replication and viral gene expression. Molecular mechanisms are unknown.	Winterling et al., 2014 [29]
EGOT	HCV, IAV, SFV	*EGOT* inhibits the expression of several ISGs and enhances viral replication. Molecular mechanisms are unknown.	Carnero et al., 2016 [31]
Lethe	HCV	*Lethe* inhibits RelA-mediated DNA-binding; inhibits expression of antiviral factors, protein kinase R (PKR), 2′,5′-oligoadenylate synthetase (OAS) proteins, and Interferon Regulatory Factor 1 (IRF1), and enhances HCV replication	Rapicavoli et al., 2013 [66]; Xiong et al., 2015 [71]
LncRNA RP11-288L9.4	HCV	*TSPOAP1-AS1* inhibits expression of IFNα-inducible protein 6 (IFI6) by histone modification and enhances HCV replication.	Liu et al., 2019 [72]
NRIR	HCV	*NRIR* inhibits transcription of several interferon-stimulated genes (ISG) and enhances HCV replication.	Kambara et al., 2014 [65]
Lnc_000641	pseudorabies virus (PRV)	*Lnc_000641* inhibits IFNα transcription, phosphorylation of transcription factors (Jak and STAT1), and increases PRV replication.	Fang et al., 2021 [73]
NEAT1	HSV-1	*NEAT1* recruits STAT3 to viral gene promoters to increase viral gene expression.	Wang et al., 2017 [74]
		Antiviral lncRNA	
IVRPIE	IAV	*IVRPIE* upregulates IFNβ and several ISGs, including IRF1, IFIT1, IFIT3, Mx1, ISG15, and IFI44L, by affecting histone modification of these genes.	Zhao et al., 2020 [63]

Table 1. *Cont.*

LncRNA	Virus	Mechanism	Reference
OASL-IT1	ZKIV	*OASL-IT1* enhances expression of IFN-β, Mx1, IFITM1 and inhibits ZKIV replication.	Wang et al., 2021 [75]
LUARIS	EMCV, HBV, HCV	*LUARIS* upregulated the level of IFN-stimulated genes through interactions with hnRNPU and ATF2 and suppressed EMCV, HBV, and HCV.	Nishitsuji et al., 2016 [76]
NEAT1	Hantaan virus	*NEAT1* relocates SFPQ to paraspeckles, increases RIG-I and DDX60 transcription, increases IFN- γ, and inhibits virus.	Ma et al., 2017 [56]
		LncRNAs influence the long-term persistence of the virus	
NRON	HIV	*NRON* mediates degradation of HIV Tat protein.	Li et al., 2016 [77]
MALAT1	HIV	*MALAT1* promotes HIV reactivation from latent provirus.	Qu et al., 2019 [78]
7SK	HIV	*7SK* promotes HIV latency by inactivating p-TEFb.	Nguyen et al., 2001 [79] Contreras et al., 2007 [80]; Budhiraja et al., 2013 [81]; Eilebrecht et al., 2017 [82]
uc002yug.2	HIV	*uc002yug.2* promotes viral reactivation by inhibition of Transcription Repressor RUNX1.	Huan et al., 2018 [83]
lincRNA-p21	HIV	*lincRNA-p21* inhibits DSB-induced cell death, promotes viral persistence.	Barichievy et al., 2018 [84]
HEAL	HIV	*HEAL* promotes viral reactivation by recruiting histone acetyltransferase p300 to HIV-1 promoter region.	Chao et al., 2019 [85]
NEAT1	HIV	*NEAT1* sequesters unspliced HIV transcripts in nuclear paraspeckle bodies promoting long-term persistence of HIV.	Zhang et al., 2013 [51]
HIV antisense lncRNA	HIV	*HIV antisense lncRNA* recruits chromatin remodeling proteins such as DNMT3a, the enhancer of Zeste 2 (EZH2), and histone deacetylase 1 (HDAC-1) to HIV 5′long terminal repeat. These proteins bring about H3K9 dimethylation, H3K27 trimethylation, and histone deacetylation, resulting in epigenetic silencing of viral transcription.	Saayman et al., 2014 [86]
KSHV-encoded *PAN RNA*	KSHV	*PAN* RNA binds lysine demethylases UTX and JMJD3, and the lysine methyltransferase MLL2 facilitates the recruitment of histone demethylases to the viral chromatin.	Rossetto et al., 2012 [87] Rossetto, 2013 [88] Rossetto, 2016 [89]
HCMV-encoded *RNA4.9*	HCMV	*RNA4.9* tethers the components of the polycomb repression complex (PRC) to the major immediate early promoter region (MIEP) and represses viral transcription.	Rosseto., 2013 [90]
EBV-encoded *BART lncRNA*	EBV-associated epithelial tumors	*BART* lncRNAs downregulate the expression of the tumor suppressor gene RASA1 and unfolded protein response (UPR) genes. BART lncRNAs regulate host gene expressions through chromatin modification.	Marquitz., 2015 [91]; Verhoeven, 2019 [92]
EBV-encoded lncRNA *BHLF1*	EBV-associated epithelial tumors	*BHLF1* localizes at the surface of the viral replication compartment and forms an RNA–DNA hybrid at the site of virus transcription.	Park & Miller, 2018 [93]; Rennekamp & Lieberman, 2011 [94]

Overlapping patterns in lncRNA expression, in response to virus infections, suggest the functional role of lncRNAs in the clinical manifestations of these infections. Similarly, intersecting changes in global lncRNA expression patterns in SARS-CoV and influenza virus infection indicate a lncRNA-based signature of respiratory virus infection and a functional role for the virus-induced lncRNAs in clinical outcomes [95]. After performing a whole-transcriptome analysis of the host response to severe acute respiratory syndrome coronavirus (SARS-CoV) infection across four founder mouse strains, Peng et al. found several noncoding RNAs to be similarly regulated in SARS-CoV and influenza virus-infected mice [95]. However, the functional mechanisms and impact of these overlapping patterns of lncRNAs in respiratory viral infections are yet to be determined. In addition, the virus-induced lncRNAs may have diagnostic potential, such as the antiviral lncRNA EDAL induced by multiple neurotropic viruses in mice [96]. Thus, careful analyses of lncRNA

expression and function in infected cells are critical to improving our understanding of viral pathogenesis.

Nevertheless, diversity in the form and function of lncRNAs makes them both intriguing and challenging to study. The human DNA is predicted to encode over 100,000 lncRNAs [97,98], but only a tiny fraction of these have been characterized. Several types of lncRNAs are described in the literature, including but not limited to lncRNAs transcribed from intergenic, enhancer, and promoter regions, as well as sense and antisense lncRNAs that overlap other protein-coding genes [23,99,100]. Most lncRNAs are expressed at lower levels than protein-coding mRNAs. Several factors, including repressive histone modifications at lncRNA gene promoters [101,102], transcription through phosphorylation-deficient Polymerase II (pol II), weak or aberrant splicing, and termination contribute to lower transcription levels of lncRNAs than the protein-coding mRNAs. Additionally, degradation by nuclear exosomes leads to overall diminished expression levels of most lncRNAs [103]. Nevertheless, the expression levels of several lncRNAs are either similar or even exceed those of protein-coding mRNAs. For example, *MALAT1* and *NEAT1* are expressed ubiquitously at high levels in most cells [104].

A significant fraction of lncRNA is preferentially localized in the nucleus. This nuclear retention is due to specific sequence motifs encoded within some lncRNAs, such as Alu repeats [105], AGCCC motif of *BORG* [106], E and M fragments of *MALAT1* [107], repeating RNA domain (RDD) of human *FIRRE* [108], and retained introns in the nuclear *TUG1* [109]. The nuclear retention of Kaposi Sarcoma-associated Herpes Virus (KSHV)-encoded lncRNA and *PAN RNA* (polyadenylated nuclear RNA) is dependent on the presence of an expression and nuclear retention element (ENE) [110]. The ENE contains a uracil (U)-rich internal loop that interacts with the 3′-poly(A) tail to form a triple helical loop to protect *PAN* RNA from a rapid nuclear deadenylation-dependent decay by exonucleases [111–113]. In addition, viral ORF57 stabilizes the expression of *PAN* RNA and increases its nuclear accumulation [88,114,115]. RNA-stabilizing ENE-like structures are also found in human lncRNAs, such as *MALAT1* and *MENβ* [116]. Protein-coding mRNAs and many lncRNAs share the mechanisms for posttranscriptional processing, nuclear export, and trafficking within the cells [117]. Like the protein-coding mRNAs, many lncRNAs are exported from the nucleus by the nuclear export complexes, TREX (transcription export complex), and NFX (nuclear RNA export factor) [117–119]. However, some lncRNAs are retained in the nucleus due to poor binding to the nuclear export complexes [119,120]. In addition, functional nuclear lncRNAs escape exosome degradation through specific, high-affinity interactions with DNA and proteins that tether them to the chromatin.

Functional nuclear lncRNA transcripts employ diverse mechanisms to regulate gene expression, including but not limited to the recruitment, depletion, or relocalization of chromatin-modifying proteins, transcription factors, and RNA; the direct interaction with DNA; and the regulation of chromatin organization, as well as intra/inter-chromosomal interactions, transcription, and splicing [108,121–127]. Nuclear lncRNAs have been shown to regulate the localization of splicing factors and impact the expression of antiviral genes [83,128]. LncRNAs are typically expressed at significantly lower levels than protein-coding mRNAs. Per-cell copies of lncRNAs (0.3–1000) are remarkably low compared to their protein binding partners. Recent data show that lncRNAs adopt distinct mechanisms to affect dramatic changes in target gene expression, even with a few copies. A few lncRNA molecules seed and organize functional territory wherein the lncRNAs recruit diffusible RNAs or proteins, thus enriching the functional effectors at a specific genomic site [129–131]. Quinodoz et al. showed that most lncRNAs included in their study remain at their target loci close to the lncRNA transcription site and do not diffuse elsewhere in the nucleus or cytoplasm [130]. Markaki et al. further elucidated how only a few lncRNA molecules can initiate the "crowding" of transcriptional regulators at several target loci [129]. *Xist* lncRNA silences over 1000 genes on the X-chromosome. Markaki et al. showed that just two *Xist* RNA molecules could recruit a multiprotein structure and increase the local concentration of regulators to silence the transcription of target genes. X-chromosome

compaction and densification of a silencer protein, SPEN, induces silencing across the entire X-chromosome. Thus, X-chromosome genes that do not directly interact with *Xist* RNA are also silenced [129]. Markaki et al. also showed that *Xist* remains restricted on the X-chromosome [129]. Other lncRNAs, such as *MALAT1,* interact with several genes far from their transcription site and across chromosomes. These observations raise further questions about how some lncRNAs stay localized to their transcription site, and if any specific features dictate lncRNA movement and localization. For some lncRNA loci, the transcript does not exhibit any regulatory function. However, the process of lncRNA transcription itself may contribute to the regulation of adjacent gene expression by remodeling chromatin or recruiting transcriptional regulatory factors [132]. Thus, nuclear lncRNAs are versatile tools for rapidly activating or suppressing specific genes or gene networks, and some viruses have been shown to hijack this machinery to establish infections successfully.

Here, we review the impact of nuclear lncRNAs on the regulation of gene expression and viral disease outcomes. Most nuclear lncRNAs described here utilize epigenetic mechanisms to regulate gene transcription. Nevertheless, we also have a few nuclear lncRNAs that play a significant role in viral infections by regulating mRNA splicing of the host response genes.

2. Chromatin–lncRNA Interactions Regulate Viral Infections

Chromatin structure plays a critical role in activating and repressing transcription. Many lncRNAs modulate gene expression within the spatial proximity of their transcription site and distant gene networks through either sequence-specific, direct DNA-binding, or indirectly through their chromatin-binding protein partners. Emerging data indicate that lncRNA-chromatin interactions regulate the antiviral interferon (IFN) response, viral transcription, and latency. We have listed several lncRNAs with known antiviral or proviral activity in Table 1. The precise mechanism of action of some lncRNAs remains to be further explored. This section discusses known nuclear lncRNAs regulating immune response and viral transcription through direct interaction with chromatin and histone modification.

Direct interaction: Many nuclear lncRNAs interact with the double-stranded DNA directly in a sequence-specific manner. These interactions form triple helices [133–140] and R-loops [141]. The triple helices recruit coactivator or corepressor proteins to activate [134,136,139] or repress [133,135] gene transcription, respectively. The lncRNA–DNA triple helices can form near the transcription start site (proximal) or at distant regulatory regions (distal). *Lnc-MxA* is an IFN-induced lncRNA upregulated during IAV infection. *Lnc-MxA* binds to the *IFNB1* promoter forming a triplex, which then interferes with the binding of IRF3 and p65 transcription factors to the *IFNB1* promoter, resulting in the abrogation of the *IFNβ* transcription [61] (Figure 1). Type I IFNs, such as IFNβ, promote the transcriptional activation of hundreds of interferon-stimulated genes (ISGs), many of which inhibit virus replication [142]. Thus, *Lnc-MXA* enhances viral replication by dampening the interferon response [61].

Elevated expression levels of lncRNA *MIR4435-2HG* have been reported in primary myeloid-derived dendritic cells (mDCs) isolated from patients who spontaneously controlled HIV replication (elite controllers, ECs) [134]. An elevated expression of *MIR4435-2HG* increased triple-helix formations at an intronic gene enhancer and enhanced *RPTOR1* (Regulatory Associated Protein Of MTOR Complex I) gene expression. Activating chromatin marker H3K27ac is enriched at the site of the triple helix, likely through the specific recruitment of histone acetyltransferases [134]. RPTOR1 increased glycolysis and metabolic activity of mDCs in response to TLR3 stimulation. Hartana et al. identified a role for *MIR4435-2HG* in enhancing the metabolic activity of mDCs, which is likely to increase the functional responsiveness of mDCs, thereby facilitating more effective immune activity in ECs [134].

Virally encoded lncRNAs also use this mechanism to modulate viral gene transcription. For example, the Epstein–Barr virus (EBV) forms virus-induced nodular structures (VINORCS). VINORCS are composed of viral and cellular proteins required for viral replication. EBV-encoded lncRNA *BHLF1* localizes in the viral replication compartment [93], forming an RNA–DNA hybrid at the virus transcription start site [94]. This hybrid structure

then recruits RNA-binding proteins to form VINORCs and facilitate selective processing and the export of viral mRNAs, thus enhancing viral replication.

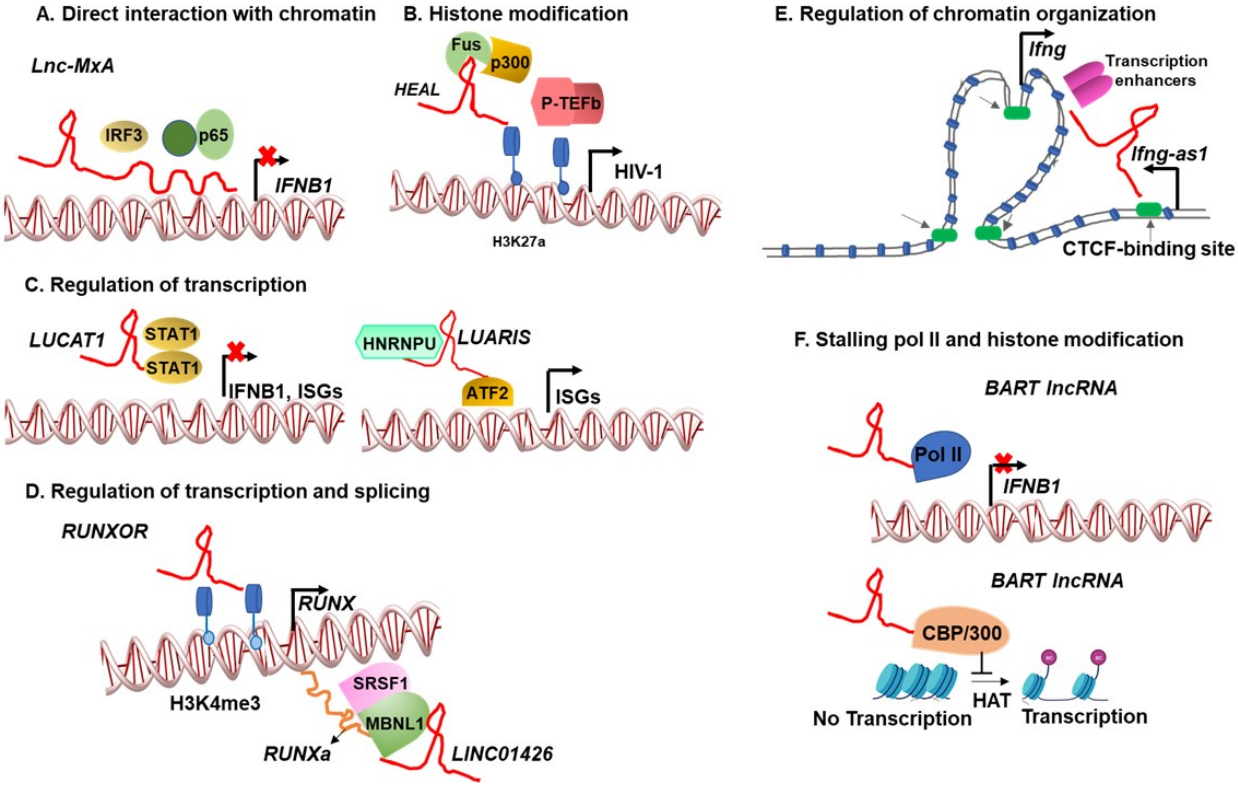

Figure 1. Virus-induced nuclear lncRNAs regulate gene expression using various mechanisms, such as (**A**) Direct interaction of *Lnc-MxA* with the promoter region of *IFNB1*, which inhibits recruitment of transcription factors and *IFNB1* transcription; (**B**) *HEAL* lncRNA recruits histone-modifying proteins and transcription elongation factors at HIV promoter and enhances HIV transcription; (**C**) *LUCAT1* sequesters STAT1 transcription factor and inhibits *IFNB1* transcription, whereas *LUARIS* localizes ATF2 to the promoter region of interferon-stimulated genes (ISGs) and enhances their expression; (**D**) *RUNX* mRNA transcription and isoform expression are regulated by neighboring lncRNAs *RUNXOR* and *LINC01426*; (**E**) *Ifng-as1* transcript is likely to enhance *Ifng* expression by recruiting and enriching transcriptional enhancers (transcription factor or chromatin modifiers). In addition, the *Ifng-as1* locus impacts the chromatin organization independent of the *Ifng-as1* transcription or lncRNA sequence through a CTCF-binding site encoded within the *Ifng-as1* gene region; (**F**) *BART* lncRNA stalls Pol II at the promoter region of *IFNB1* and inhibits its transcription. *BART lncRNA* also associates with CREB-binding protein (CBP/300) and inhibits its histone acetylation activity, thus inhibiting gene expression.

Histone modification: Post-translational histone modifications, such as phosphorylation, acetylation, methylation, ubiquitination, SUMOylation, and GlcNAcylation, are key regulators of the chromatin state and transcriptional activity. Nuclear lncRNAs interact with the proteins that add (writers) [143–145], remove (erasers) [144,146,147], or recognize (readers) [148,149] these histone modifications and modulate their functions. Several lncRNAs use this mechanism to regulate the expression of ISGs. The expression of some ISG-regulating lncRNAs is significantly modulated in virus-infected cells. For example, viruses such as IAV, SeV, MDRV, and HSV significantly downregulate lncRNA *NRAV*, which inhibits the expression of critical ISGs through histone modifications at the promoters of these genes. In this context, an *NRAV* overexpression leads to reduced H3K4 trimethylation (H3K4me3), activating transcription and enriched repressive H3K27 trimethylation (H3K27me3) at the transcription start sites of ISGs [57]. Although the exact

mechanism of how *NRAV* regulates histone trimethylation is unknown, *NRAV* is shown to bind a regulatory protein ZONAB, which may be involved in histone modifications. The *NRAV*-mediated regulation of ISG transcription was attributed, at least partially, to its interaction with ZONAB [57]. Likewise, a host cell-encoded lncRNA induced in response to IAV infection, termed, "Inhibiting IAV Replication by Promoting IFN and ISG Expression" (*IVRPIE*), enhances the expression of IFN-β and several critical ISGs, including IRF1, IFIT1, IFIT3, MxA, ISG15, and IFI44L, through histone modifications at these loci [63]. MxA and ISG15 can suppress the replication of highly pathogenic Influenza A viruses [150]. Likewise, IFITM1 and IFITM3 can inhibit an early step of Influenza A virus replication [2]. Thus, *IVRPI* inhibits IAV replication by enhancing the expression of IFN-β and antiviral ISG proteins. HCV-induced lncRNA *RP11-288L9.4* inhibits the expression of IFNα-inducible Protein 6 (IFI6) through histone modifications [72].

The host-encoded lncRNA *HEAL* is expressed at high levels in human macrophages upon HIV infection and binds directly to the HIV promoter, along with an RNA-binding protein fused in liposarcoma (FUS) [85]. The *HEAL*–FUS complex recruits the histone acetyltransferase p300 to enhance H3K27 acetylation and enriches Transcription Elongation Factor P-TEFb to the HIV promoter, thus increasing HIV transcription [85] (schematic presentation of *HEAL*–FUS-driven HIV transcription in Figure 1). LncRNA *MALAT1* interacts with Polycomb Repressive Complex 2 (PRC2) proteins, namely EZH2, Suz12, and EED, which then catalyze the methylation of Histone H3 at Lysine 27 to repress gene transcription. In tumor cells, *MALAT1* facilitates EZH2-binding to its target loci, driving H3K27 trimethylation-mediated repression of multiple tumor-suppressor genes, such as E-cadherin [151,152], NDRG1 [153], p21, and p27 [154]. *MALAT1* is expressed at high levels in HIV-infected cells, where it enhances HIV transcription from latent provirus [78]; it localizes EZH2 to its target sites in tumors; and in HIV infection, it sequesters EZH2 away from the HIV long terminal repeat (LTR), thus preventing PRC2-mediated H3K27 trimethylation and promoting HIV viral reactivation [78].

The KSHV-lytic protein (K-Rta) induces the expression of a cellular lncRNA *KIKAT/LINC01061* (KSHV-Induced KDM4A-Associated Transcript) [68]. Yang et al. showed that *KIKAT* interacts with a histone lysine demethylase (KDM4A) and re-localizes KDM4A from the transcription start site (TSS) of the Angiomotin (AMOT) gene. The *KIKAT*-mediated relocation of KDM4A increased the AMOT transcription and angiomotin-dependent cell migration, thus implicating its role in angiogenesis in Kaposi's sarcoma [68]. *KIKAT* was also shown to enhance KSHV reactivation. While KDM4A was shown to regulate KSHV replication [155,156], its binding on the KSHV genome was not impacted by *KIKAT* [68].

Virus-encoded lncRNAs also utilize histone modification strategies to establish and regulate their latent infection. This mechanism has been demonstrated in HIV infection, where a virus-encoded antisense lncRNA (antisense transcript; *Ast*) recruits chromatin remodeling proteins such as DNMT3a, EZH2, and HDAC-1 to HIV 5′ long terminal repeat (LTR). These proteins mediate H3K9 dimethylation, H3K27 trimethylation, and histone deacetylation, resulting in the epigenetic silencing of viral transcription [86,157,158].

KSHV remains persistent for a lifetime in patients. KSHV remains latent for a long duration, followed by a short lytic cycle. During latency, the KSHV episome is tethered to the host genome through KSHV latency-associated nuclear antigen (LANA) protein (KSHV life cycle is reviewed in [159]). LANA protein binds the viral episome and the host nucleosomal proteins to tether the viral episome to the cellular genome. The KSHV-encoded lncRNA, *PAN* RNA ([160], is the most abundant viral transcript [114]. The absence of *PAN* RNA results in reduced virus production [88,161,162]. The KSHV-lytic protein (K-Rta) induces *PAN* RNA expression at very high levels [163]. *PAN* RNA interacts with KSHV latency-associated nuclear antigen (LANA) and sequesters LANA from the viral DNA episomes, thus facilitating lytic reactivation [114,164]. A recent study showed that *PAN* RNA sequesters LANA-interacting nucleosomal protein CHD4 (chromodoain helicase binding protein 4) [165]. The CHD4 and LANA complex co-localize to the episome, where CHD4 prevents the aggregation of RNA polymerase II on the KSHV episome and inhibits

KSHV reactivation [165]. Thus, *PAN* RNA facilitates KSHV reactivation by the sequestration of the LANA/CHD4 complex from the KSHV episome [165]. *PAN* RNA encodes two main *cis*-acting elements, the Mta response element, (MRE) and the expression and nuclear retention element (ENE). Gutierrez et al. found that ENE is not required for viral replication but is essential for the nuclear retention of *PAN* RNA [110]. Viral protein ORF59 binds to *PAN* RNA during reactivation, recruiting chromatin-modifying factors to the viral genome [166]. *PAN* RNA physically interacts with the viral promoter, lysine demethylases UTX and JMJD3, and lysine methyltransferase MLL2 [87]. It recruits histone demethylases to the viral genome [88]. In addition, *PAN RNA* interaction sites have also been detected on the host genome, suggesting that it potentially interacts with transcriptional regulators and chromatin modifiers to modulate cellular gene expression, immune response, and cell cycle control [88,162].

3. Virus-Induced lncRNAs Regulate the Transcription and Splicing of Host and Viral Genes

Virus-induced lncRNAs modulate antiviral interferon responses by regulating the activation, availability, and localization of transcription factors. *Lnc-000641*, a pseudorabies virus (PRV)-induced lncRNA, inhibits the phosphorylation of upstream-activating kinases and transcription factors (Jak and STAT1), thereby reducing downstream IFNα transcription, thus facilitating increased PRV replication [73]. Along similar lines, HCV-induced lncRNA, *Lethe*, interacts with NF-κB subunit RelA and inhibits RelA-mediated DNA binding [66]. This prevents RelA-mediated transcriptions of the activating antiviral factors, 2′,5′-oligoadenylate synthetase (OAS), interferon regulatory factor 1 (IRF1), and protein kinase R (PKR), thus, enhancing HCV replication [71]. LPS-stimulated or virus-infected human dendritic cells (DCs) upregulate the expression of lncRNA *LUCAT1*, which functions as a potent regulator of the IFN-α/β response [167]. *LUCAT1* sequesters STAT1 in the nucleus preventing STAT1 from binding to the promoters of ISGs and blocking their expression [167] (Figure 1). The virus infection or activation through PAMPs can also downregulate the expression of lncRNAs that regulate the immune response. For example, Aznaourova et al. recently showed that SARS-CoV-2 infection or PAMP-mediated stimulation inhibits the expression of a nuclear lncRNA, *PIRAT*. *PIRAT* recruits transcription factor PU.1 to pseudogenes and suppresses PU.1 binding to promoters of alarmin genes (*S100A8* and *S100A*), thus inhibiting alarmin gene expression. Alarmins promote the production of inflammatory cytokines. The SARS-CoV-2 infection also enhances the expression of another lncRNA, *LUCAT1*, which augments alarmin gene transcription. Thus, the SARS-CoV-2 infection upregulates *LUCAT1* and downregulates *PIRAT*, increasing alarmin production and aggravating inflammatory mediators contributing to the severity of COVID-19 [168]. LncRNA *LUARIS* (a.k.a. *lncRNA#32*) upregulated the ISG expression through interactions with host proteins HNRNPU and ATF2, resulting in the inhibition of encephalomyocarditis virus (EMCV), Hepatitis B, and Hepatitis C virus replication [76]. While HNRNPU stabilized *LUARIS* transcript, the *LUARIS*–ATF2 interaction was found to be critical for activating ISG transcription, indicating that *LUARIS* enhanced recruitment of the transcription factor ATF2 to the promoters of ISGs, thus enhancing ATF2-mediated transcription (Figure 1). In addition, *7SK* snRNA sequesters P-TEFb, a general transcription elongation factor and human co-factor for HIV-1 transactivator (Tat) protein, into the catalytically inactive *7SK* snRNP and inhibits HIV transcription [79–82]. The human T-cell leukemia virus (HTLV)-encoded antisense lncRNA is recruited to the CC chemokine receptor (CCR4) and enhances its transcription to support the proliferation of HTLV-infected cells [169].

Many lncRNAs regulate neighboring genetic loci in a transcript-dependent manner by interfering with the recruitment of transcription factors or Poll II at the promoter, altering chromatin modification or reducing accessibility. LncRNAs can form RNA–DNA triplexes that enrich gene regulatory proteins at the neighboring loci. For example, *PTENpg1* localizes on the promoter of its adjacent locus, *PTEN*, and recruits histone methyl transferases (EZH2 and DNMT3a) to the *PTEN* promoter, dampening *PTEN* transcription [170]. LncRNAs also act as a scaffold for the locus-specific recruitment of chromatin-modifying enzymes. For example, lncRNA *APOAS1* provides a scaffold for the chromatin-modifying histone

demethylase protein, LSD1, to localize the *APOA1* gene and repress *APOA1* gene expression [171]. HCV infection induces one such lncRNA that regulates transcription of its neighboring protein-coding gene and alters the antiviral immune response. HCV-infected cells express a nuclear lncRNA *GCSIR* (GPR55 cis-regulatory suppressor of immune response RNA, a.k.a *Lnc-ITM2C-1*) that enhances the transcription of its neighboring gene, *GPR55*, through yet unknown molecular mechanisms. The GPR55 protein, in turn, inhibits the expression of several ISGs, thus, dampening antiviral responses [60].

In addition to regulating transcription, neighboring or intragenic lncRNAs can also modulate the splicing of their protein-coding neighbors. RUNX1 transcription and protein expression are tightly controlled by several lncRNAs transcribed from the neighboring loci. RUNX1 represses HIV-1 replication in T cells by binding to the HIV-1 LTR [172]. RUNX1 gene encodes three transcript variants that produce three different protein isoforms, RUNX1a, b, and c. Among the three, RUNX1b and c have been shown to bind the HIV–LTR and suppress HIV transcription [83]. *LINC01426* (a.k.a. *uc002yug.2*) is transcribed from a locus upstream of *RUNX1*. It enhances the recruitment of splicing factors (MBNL1 and SFRS1) to the regional RNA duplexes resulting in increased *RUNXa* isoform and the relative reduction of *RUNX1b* and c isoform expressions [83]. In addition, *LINC01426* increases the production of HIV protein Tat through unknown mechanisms. Thus, *LINC01426* promotes viral reactivation by inhibiting transcription repressive forms of RUNX1 and enhancing Tat expression [83]. Another lncRNA *RUNXOR* is transcribed from a promoter upstream of the *RUNX1* gene that overlaps with *RUNX1* mRNA. RUNXOR increases H3K4me3 marks at the promoter of *RUNX1* and activates *RUNX1* transcription. Interestingly, myeloid-derived suppressor cells (MDSCs) in people living with HIV (PLWH) showed increased *RUNXOR* expression (Figure 1). An increased expression of *RUNXOR* in MDSCs results in the expression of critical immunosuppressive molecules that cause T cell suppression in PLWH [173].

Although there is an increasing number of lncRNAs identified as novel regulators of host–virus interaction, the precise functional mechanisms of many remain unknown. HCV, IAV, and the Semliki Forest virus (SFV) induce a nuclear lncRNA transcript eosinophil granule ontogeny transcript (*EGOT*). The molecular mechanism of *EGOT*-mediated suppression of the IFN-signaling pathway and enhancement of viral production is yet to be determined [31]. *BISPR* is an IFN-stimulated lncRNA that significantly regulates the antiviral *BST2* gene expression through yet unknown mechanisms [174,175]. IAV-induced lncRNA *TSPOAP1-AS1* inhibits the expression of IFNβ and other ISGs through unknown mechanisms [62]. Interestingly, *TSPOAP1-AS1* is localized in the nucleus and cytoplasm, but IAV-infected cells showed increased nuclear levels of *TSPOAP1-AS1*, implicating a nuclear mechanism of ISG inhibition. ZIKA virus (ZKIV) infection induces lncRNA *OASL-IT1*. *OASL-IT1* enhances IFNβ and ISG (Mx1 and IFITM1) expression and inhibits ZKIV replication through unclear mechanisms [75]. IAV H1N1, H3N2, H7N7 strains, and VSV-infected cells upregulate a nuclear lncRNA *VIN*. The molecular mechanisms of *VIN*-mediated upregulation of viral gene expression remain to be determined [29].

4. Heterogeneity in lncRNA Form, Function, and Phenotype

Some lncRNA transcripts utilize diverse mechanisms that occasionally produce contrasting phenotypes highlighting the complexities of their gene regulatory functions. In addition, many lncRNAs are transcribed from genomic regions that encode sequences regulating chromatin structure, which makes investigating molecular mechanisms and interpreting lncRNA functions very challenging in these instances.

This is best exemplified by lncRNA *Ifng-as1*. In mice and humans, *Ifng-as1* [Nettoie Salmonella pas Theiler's (*NEST*), also named *TMEVPG1*] is transcribed from the opposite strand of the *IFNG* protein-coding region. *Ifng-as1* was initially identified as a susceptibility locus for Theiler's virus persistence in mice [176]. In follow-up studies, the RNAi-mediated knockdown of human *IFNG–AS1* expression in human T-helper (Th1) cells and significantly reduced *IFNG* transcriptions [177,178]. Similarly, the transgenic expression of mouse *Ifng-as1* enhanced the IFN-γ expression and established resistance to Salmonella enterica and

increased persistence of Theilers' virus in mice [179]. These contrasting phenotypes indicated the essential role of lncRNAs in modulating immune responses to distinct pathogens and disease outcomes. The ectopically expressed *Ifng-as1* transcript binds to a histone methyltransferase complex component (WDR5) and enhances H3K4 trimethylation at the *Ifng* locus in an in vitro cell line model [179]. These approaches indicated that *Ifng-as1* is a trans-acting lncRNA that recruits chromatin modifiers in a sequence-specific manner. A recent study employed CRISPR tools to compare *Ifng-as1* knockout (KO; DNA+RNA product deletion) and *Ifng-as1*-polyA knock-in (KI; truncated non-functional RNA) modification in mice [180]. Deleting DNA (KO) and truncating RNA (KI) inhibited *Ifng* gene expression, but KO mice showed more severe impairment in defense against infection. This study further determined that deleting the *Ifng-as1* locus (KO) eliminates one of the CTCF-binding sites, thus disrupting the chromatin looping required for optimal *Ifng* gene expression. The truncated *Ifng-as1* (KI) does not affect chromatin architecture but diminishes *Ifng* expression. The *Ifng-as1* transcript will likely enhance *Ifng* expression by recruiting and enriching transcription factors or chromatin modifiers. These critical experiments dissecting the effects of the lncRNA transcript and chromatin structure showed that *Ifng-as1* regulates *Ifng* expression in cis, and *Ifng-as1* locus impacts the chromatin organization independent of the Ifng-as1 transcription or lncRNA sequence (Figure 1).

Human *IFNG-AS1* expression was significantly higher in CD4+ Th1 cells, the antigen-specific memory precursor, and the central memory CD8+ T than in the effector memory T cells in LCMV-infected mice. Similarly, the *IFNG–AS1* expression is maintained long term (up to a decade) at high levels in human memory T cells [180] and abundantly expressed in activated Natural Killer (NK) cells [181]. These findings highlight the differences in *IFNG–AS1* expressions in various immune cell phenotypes and indicate its functional relevance in acute and memory responses to viral infections. From a clinical perspective, polymorphisms in the human *IFNG–AS1* gene have been associated with autoimmune and inflammatory disorders [182–184], further underscoring their role in immunity and chronic inflammatory diseases in humans.

An IFN-stimulated nuclear lncRNA, *NRIR* (a negative regulator of interferon response; a.k.a. *lncRNA-CMPK2*), produces stimulation-specific contrasting phenotypes. Specifically, *NRIR* inhibited the transcription of several ISGs and enhanced HCV replication in hepatocytes [65]. Moreover, *NRIR* inhibited the expression of IFITM3, a well-characterized ISG, in endothelial and epithelial cells during Hantaan virus infection [185]. However, in monocytes, *NRIR* silencing significantly reduced the LPS-induced expression of ISGs, including MX1, IFITM3, ISG15, and chemokines such as CXCL10. Although these contrasting findings strengthen the role of *NRIR* as a regulator of IFN responses, they highlight the cell-type and stimulus-specific functions of lncRNAs [186].

The lncRNA *NEAT1* sequesters both protein and RNA in the nuclear bodies. An infection with IAV and HSV induces the expression of lncRNA *NEAT1*, which sequesters splicing factor proline glutamine-rich (SFPQ/PSF) to the paraspeckles. SFPQ/PSF acts as a repressor of *IL-8* and HSV viral genes [187], but at the same time, it is essential for IAV mRNA polyadenylation [128]. *NEAT1* activates the antiviral gene *IL-8* transcription by sequestering SFPQ/PSF [187]. However, *NEAT1* also recruits STAT3 to viral gene promoters and upregulates the viral replication in HSV-1 infections [74]. Thus, *NEAT1* functions as an antiviral factor by inducing cytokine response but is simultaneously hijacked by HSV to facilitate viral gene expression. Similar to HSV-1 infection, *NEAT1* upregulation by Hantaan virus (HTNV) infection promotes RIG-I and DDX60 transcription by relocating SFPQ from the promoters of both genes to paraspeckles [56]. Since RIG-I and DDX-60 expression are essential for interferon γ (IFN- γ) production [188,189], it appears that the induction of *NEAT1* enhances antiviral responses against HTNV. During the HIV-1 replication cycle, *NEAT1* sequesters unspliced HIV transcripts in nuclear paraspeckle bodies, thus, preventing the nuclear export of HIV mRNA and promoting the long-term persistence of HIV [51].

Viral infections can also hijack lncRNA functions by manipulating their RBP partners, which are critical for lncRNA activity. For example, HIV integration induces double-stranded breaks (DSB) that initiate the apoptosis pathway in the infected CD4+ T cells. Unlike CD4+ T cells, HIV-infected macrophages have been reported to evade DSB-induced apoptosis by accelerating the decay of *lincRNA-p21*, a lncRNA that inhibits the transcription of pro-survival genes induced during the canonical DNA damage pathway. Two protein binding partners, namely HuR and hnRNP-K, are critical for the stability and function of *lincRNA-p21*. HIV infection of macrophages results in the sequestration of HuR and hnRNP-K in the cytoplasm, where it increases *lincRNA-p21* decay and reduces *lincRNA-p21* levels in the cells. Decreased availability of hnRNP-K in the nucleus reduces the functional nuclear *lncRNA-p21*/hnRNP-K complex required to suppress pro-survival genes. Thus, by sequestering the proteins essential for maintaining *lincRNA-p21* stability and function, HIV inhibits DSB-induced cell death and promotes its persistence in infected macrophages [84]. The expression of lncRNA *SAF* is significantly upregulated in HIV-1-infected human monocyte-derived macrophages (MDM) and HIV-1-infected airway macrophages obtained by the bronchoalveolar lavage of HIV-1-infected individuals. The downregulation of *SAF* increases caspase-3/7 activity levels in virus-infected MDMs, thus inducing apoptosis. Although the mechanisms of *SAF*-mediated regulation of caspase3/7 activity are not completely understood, it is proposed to be a potential target to cause cell death in HIV-infected macrophages and reduce overall HIV burden [190].

Viral lncRNAs have also been shown to manipulate large cellular gene networks through diverse mechanisms. The Epstein–Barr virus (EBV), a tumor-causing virus, is associated with various human cancers [191,192] and encodes noncoding RNAs termed BamHI A rightward transcripts (*BART*s) expressed at high levels in EBV-associated epithelial tumors [93]. *BART*s include microRNAs and lncRNAs [93,192,193]. An alternative splicing of *BART*s results in multiple spliced forms of *BART* lncRNA, with putative open reading frames in *BARF0*, *RK-BARF0*, *RPMS1*, and *A73*, none of which encode proteins [194,195]. *BART* lncRNAs regulate EBV lytic replication [196] and an extensive cellular gene network that influences adhesion, oxidoreductase activity, inflammation, and metastasis [91]. *BART* lncRNAs regulate the expression of tumor suppressor gene *RASA* unfolded protein response (UPR) genes and may contribute to host DNA methylation [91]. High levels of CpG island methylation leading to host gene silencing is associated with EBV-positive gastric carcinomas [197]. *BART* lncRNA significantly inhibits mitochondrial antiviral signaling (MAVS)-induced *IFNB1* promoter activity [92]. Verhoeven et al. [92] observed that *BART* lncRNA *RMS1* is associated with RNA Polymerase II (Pol II) and the CREB-binding protein (CBP/p300) complex in the nucleus. CBP activates transcription by recruiting the transcriptional machinery and also functions as a histone acetyltransferase (HAT) to alter chromatin structure. Thus, *BART* lncRNAs may mediate epigenetic regulation of gene expression through an interaction with the chromatin remodeling complex. They further showed that *BART* lncRNA *RMS1* stalled Pol II at the promoter region of *IFNB1* and inhibited its transcription [92]. Verhoeven et al. showed that *BART* lncRNA *RMS1* expression could inhibit MAVS-induced HAT activity, further indicating that *BART* lncRNA may regulate chromatin remodeling during the gene transcription process in viral infection [92]. An overexpression of *BART* lncRNA *RMS1* also upregulates the transcription of *IKZF3* mRNA, which encodes Aiolos protein normally expressed only in lymphoid cells. Aiolos is expressed in solid and liquid tumors at high levels, promoting tumor cell survival and metastasis [92]. Thus, *BART* lncRNA contributes to viral oncogenesis through multiple mechanisms. In addition, EBV-encoded miRNAs regulated host protein-coding as well as lncRNAs in the EBV-infected cells (reviewed in [198]).

Similarly, human cytomegalovirus (HCMV) encodes at least four known lncRNAs (*RNA1.2*, *RNA2.7*, *RNA4.9*, and *RNA 5.0*). *RNA4.9* localizes in the nuclear viral replication complex (VRC) [199], whereas *RNA1.2*, *RNA2.7*, and *RNA5.0* predominantly localize to the cytoplasm [199,200]. Repressive histone modifications around the major immediate early promoter (MIEP) region inhibit HCMV lytic cycle and latency in myeloid cells [201–204].

RNA4.9 is transcribed in latently infected CD14 (+) monocytes and CD34 (+) cells, tethers the components of the PRC complex to the MIEP, enriches the repressive H3K27me3 mark at MIEP, and inhibits viral transcription [90]. *RNA4.9* also mediates the formation of the RNA–DNA hybrid and the initiation of viral DNA replication in the lytic phase [199]. Though *RNA2.7* localizes primarily in the cytoplasm, it has been shown to function in the nucleus and mitochondria. *RNA2.7* binds Polymerase II (PolII) and blocks its interaction with phosphorylated cyclin-dependent kinase (pCDK), thus inhibiting the phosphorylation of Pol II. The inhibition of Pol II phosphorylation leads to host cell cycle arrests and facilitates viral replication [205]. *RNA2.7* interacts directly with the mitochondrial complex protein GRIM-19, prevents its relocalization, and maintains high ATP production levels during lytic infection [206]. In addition, *RNA2.7* is shown to have additional functions with yet unknown molecular mechanisms, such as the inhibition of apoptosis and maintenance of latency by the suppression of lytic gene expression in latent cells [207]. *RNA2.7* stabilizes cellular transcripts that promote cellular motility and viral spread in lytic infection [208]. *RNA1.2* is expressed at high levels during lytic infection, inhibits cellular NF-kB activation, and mediates the extracellular release of IL-6 [209].

Herpes simplex virus (HSV)-encoded Latency-associated transcript (*LAT*) is the only viral transcript expressed during the latent infection of neurons and plays an important role in HSV latency. *LAT* long non-coding transcript accumulates in the nucleus and contributes to the silencing of viral lytic genes by the heterochromatization of their promoters. *LAT* is suspected to be involved in the recruitment of chromatin remodeling complexes during heterochomatization, although the mechanisms are unclear [210–214]. In addition, the *LAT* transcript encodes microRNA (miRNA), small RNA (sRNA), short non-coding RNA (sncRNA), and open reading frame (ORF) encoding proteins that mediate numerous functions to maintain latency. The functions of *LAT*-encoded miRNAs, sRNAs, sncRNAs, and ORFs have been studied extensively and reviewed previously [215,216].

Numerous studies have revealed that while some lncRNAs affect multiple viral infections, several virus-induced lncRNAs act independently or in concert to regulate a single pathway. Although our understanding of lncRNA function in viral pathogenesis has significantly improved, future studies should focus on identifying and characterizing lncRNAs that have pronounced effects on virus replication, infection outcomes, and, more importantly, their molecular mechanisms. Investigating the mechanisms of lncRNA functions has immense therapeutic potential, as lncRNAs could serve as molecular targets for future antiviral therapy.

5. Therapeutic Potential of lncRNAs

Given their proven role in cellular defense and viral pathogenesis, careful functional studies are needed to define the diagnostic or therapeutic potential of lncRNAs. While most research focuses on understanding lncRNA functional biology, recent studies also explored their potential diagnostic and therapeutic targets [217]. Most studies described in this review have used lncRNA knockdown or overexpression to decipher the functional impact of lncRNAs on the expression of their protein-coding targets, viral replication, and immune response. A diverse array of modalities, such as RNA interference using si/shRNA [218], antisense oligonucleotides (ASO) [219], CRISPR-mediated knockout (CRISPR-KO), knock-in (CRISPR-KI) [180], transcriptional activation or inhibition (CRISPRi/a), and CRISPR-mediated RNA silencing [220–223] are available to manipulate lncRNA expression for functional studies (Table 2). In addition, various strategies have been employed to augment lncRNA expression in the local genomic context. Talen-mediated knock-in of strong promoters upstream of lncRNA transcription start site [224] and transcriptional activation using CRISPR/dCas9 (CRISPRa) [225] have been used to activate lncRNA expression from their endogenous loci. CRISPR-display is a compelling strategy that allows for the site-specific delivery of lncRNA transcripts using CRISPR/dCas9 and guide the RNA sequence fused with the lncRNA sequence [226]. Small-scale lncRNA knockdown screens have yielded significant insights into the role of virus-induced lncRNAs on viral pathogenesis [77,227].

Many experimental methods are used to probe lncRNA interactions with their protein-binding partner or chromatin and investigate lncRNA functions. However, most methods are technically challenging, need skilled researchers, specialized equipment, and reagents, and, thus, are prohibitively expensive for most laboratories. Several computational methods are being developed to predict lncRNA interactions and functions systematically. For example, lncRNA–DNA interactions that may regulate transcription could be predicted using computational methods such as Triplexator [228,229], Triplex Domain Finder [230], LongTarget [231], and Triple [232,233], which examine whether lncRNAs form triplexes with target promoters and enhancers. "Super-lncRNAs" [234] predict lncRNAs that bind super-enhancers through triplex formation. However, the functional impact of lncRNAs on virus infection must be rigorously investigated using genome-wide functional studies in cellular models and primary cells.

Table 2. Methods to modulate lncRNA expression for functional studies.

Method	Use	Advantages	Limitation
siRNA/shRNA	Knockdown	Inexpensive, cost-effective for large-scale screening	Nuclear lncRNAs cannot be targeted efficiently by siRNA; structural constraints limit accessibility, large-scale off-target cleavage, and knockdown may be short-lived.
Antisense Oligo (ASO)	Knockdown	Efficient degradation of nuclear lncRNA	Structural constraints limit accessibility, large-scale off-target cleavage, and knockdown may be short-lived.
CRISPR/Cas9	Gene knockout or knock-in	Easily programmable to target genes of interest, most definitive	CRISPR/Cas9-mediated frameshift mutations are not helpful for most lncRNAs as their functional sequence motifs are unknown. CRISPR/Cas9 excision of the entire lncRNA gene may disrupt overlapping coding or noncoding RNA region.
CRISPRi	Inhibition of transcription	Easily programmable to target genes of interest	CRISPRi may deregulate overlapping coding or noncoding RNA region, the functions of lncRNA transcript from those of promoter or enhancer element encoded within the lncRNA locus or small peptide encoded by the transcript.
CRISPR/Cas13d	Knockdown	Easily programmable, independent of PAM, superior RNA knockdown efficiency and dramatically higher specificity than currently available methods, stable long-term expression	Cannot decipher the function of enhancer element encoded within the lncRNA locus or small peptide encoded by the transcript
CRISPRa	Activation of transcription	Easily programmable, enhanced lncRNA expression from the endogenous loci	Dependence on protospacer-adjacent motif (PAM); may deregulate overlapping coding or noncoding RNA region; and the functions of lncRNA transcript cannot be distinguished from those of promoter or enhancer element encoded within the lncRNA locus or small peptide encoded by the transcript.
CRISPR-display		Easily programmable, allows site-specific delivery of lncRNA transcript to desired genomic loci; this method can be used to test both *cis* and *trans* effects of lncRNA transcripts and distinguish them from the act of lncRNA transcription.	Limited by the number of available functional RNA motifs and RNA-binding protein functions

The thorough investigation of lncRNA in tumor biology [235] using preclinical models led to the development of lncRNA-based diagnostic [236] and therapeutic modalities for cancer, with some showing promising results in human clinical trials [237]. LncRNAs that show the potential to enforce viral latency or reactivation could be good candidates for direct therapeutic targeting. The epigenetic modulation of viral latency using latency reversal agents such as HDAC inhibitors can affect a wide gene network and show off-target effects. Recruiting or deterring an lncRNA to or from a virus promoter could provide specificity in altering viral latency. An interaction with a specific RNA-binding protein partner is essential to lncRNA function; accordingly, small molecule therapeutics may be used directly to disrupt the critical interactions [84,238]. Computational tools are being

researched and developed to use nucleotide sequences and structural motifs of lncRNAs to predict their subcellular localization [239–242], interactions with RNA-binding proteins, and functions. However, successful therapeutic targeting of lncRNAs will depend on our ability to precisely identify relevant RNA motif/s and better understand the structural and functional features of lncRNAs.

6. Conclusions

In recent years, we have seen an avalanche of new information on lncRNA expression in virus-infected cells and the identification of several lncRNAs affecting viral replication and host immune responses, all of which have improved our understanding of the diverse functional potential of lncRNAs. This is a burgeoning area of research beyond mammalian species [243]. Some aspects of lncRNAs have not yet been studied in infectious disease research. For example, cellular stress, such as DNA damage [244,245], rapamycin treatment [246], and cellular differentiation [247], regulate the subcellular localization of lncRNAs. A recent study showed that an influenza virus-induced murine lncRNA, Lnc45, resides mainly in the nucleus in uninfected cells but translocates to the cytoplasm in H5N1-infected cells and dramatically impedes viral replication [248]. This observation highlights the need for a systematic study of the cellular redistribution of lncRNAs in viral infections. Some lncRNAs are highly conserved across species, but most show lower sequence conservation than protein-coding genes [249–251]. Therefore, it is necessary to examine the sequence and functions of relevant lncRNAs in higher animal models that are closer to humans like non-human primate (NHP) species and evaluate the use of NHP models in preclinical studies for the therapeutic targeting of lncRNAs. The systemic or specific delivery of lncRNAs or lncRNA-inhibiting RNA-based therapeutics is currently under investigation for the clinical management of several human diseases [252]. Optimal delivery modalities to target specific cells and tissues are being intensely studied. An in-depth analysis of lncRNAs in viral infections, particularly, those establishing latent reservoirs, such as HIV infection, has enormous potential for discovering novel regulatory mechanisms associated with immune response/inflammation, viral replication, and long-term viral persistence. These studies can potentially lead to identifying novel and highly selective therapeutic targets.

Author Contributions: V.K., M.M. and S.K. conceptualized the framework, and all authors (V.K., M.M., S.J., S.K.) contributed to the writing and editing of the review. All authors have read and agreed to the published version of the manuscript.

Funding: V.K., S.J., M.M. and S.K. are supported by the Texas Biomedical Research Institute, Texas Biomed Forum award (2019) to V.K., and San Antonio precision partnerships award to S.K. Research reported in this publication was supported in parts by the National Institute Of Allergy and Infectious Diseases of the National Institutes of Health under Award Number R56AI150371 (S.K.), R01AI157850 (S.K.), R21 AI140956 (S.K.) and R01DA042524 and R01DA052845 to MM. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Brass, A.L.; Dykxhoorn, D.M.; Benita, Y.; Yan, N.; Engelman, A.; Xavier, R.J.; Lieberman, J.; Elledge, S.J. Identification of host proteins required for HIV infection through a functional genomic screen. *Science* **2008**, *319*, 921–926. [CrossRef]
2. Brass, A.L.; Huang, I.C.; Benita, Y.; John, S.P.; Krishnan, M.N.; Feeley, E.M.; Ryan, B.J.; Weyer, J.L.; van der Weyden, L.; Fikrig, E.; et al. The IFITM proteins mediate cellular resistance to influenza A H1N1 virus, West Nile virus, and dengue virus. *Cell* **2009**, *139*, 1243–1254. [CrossRef]
3. Cherry, S.; Doukas, T.; Armknecht, S.; Whelan, S.; Wang, H.; Sarnow, P.; Perrimon, N. Genome-wide RNAi screen reveals a specific sensitivity of IRES-containing RNA viruses to host translation inhibition. *Genes. Dev.* **2005**, *19*, 445–452. [CrossRef] [PubMed]
4. Deffrasnes, C.; Marsh, G.A.; Foo, C.H.; Rootes, C.L.; Gould, C.M.; Grusovin, J.; Monaghan, P.; Lo, M.K.; Tompkins, S.M.; Adams, T.E.; et al. Genome-wide siRNA Screening at Biosafety Level 4 Reveals a Crucial Role for Fibrillarin in Henipavirus Infection. *PLoS Pathog.* **2016**, *12*, e1005478. [CrossRef]

5. Karlas, A.; Machuy, N.; Shin, Y.; Pleissner, K.P.; Artarini, A.; Heuer, D.; Becker, D.; Khalil, H.; Ogilvie, L.A.; Hess, S.; et al. Genome-wide RNAi screen identifies human host factors crucial for influenza virus replication. *Nature* **2010**, *463*, 818–822. [CrossRef]
6. Konig, R.; Zhou, Y.; Elleder, D.; Diamond, T.L.; Bonamy, G.M.; Irelan, J.T.; Chiang, C.Y.; Tu, B.P.; De Jesus, P.D.; Lilley, C.E.; et al. Global analysis of host-pathogen interactions that regulate early-stage HIV-1 replication. *Cell* **2008**, *135*, 49–60. [CrossRef] [PubMed]
7. Lipovsky, A.; Popa, A.; Pimienta, G.; Wyler, M.; Bhan, A.; Kuruvilla, L.; Guie, M.A.; Poffenberger, A.C.; Nelson, C.D.; Atwood, W.J.; et al. Genome-wide siRNA screen identifies the retromer as a cellular entry factor for human papillomavirus. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 7452–7457. [CrossRef]
8. Martin, S.; Chiramel, A.I.; Schmidt, M.L.; Chen, Y.C.; Whitt, N.; Watt, A.; Dunham, E.C.; Shifflett, K.; Traeger, S.; Leske, A.; et al. A genome-wide siRNA screen identifies a druggable host pathway essential for the Ebola virus life cycle. *Genome Med.* **2018**, *10*, 58. [CrossRef]
9. Ooi, Y.S.; Stiles, K.M.; Liu, C.Y.; Taylor, G.M.; Kielian, M. Genome-wide RNAi screen identifies novel host proteins required for alphavirus entry. *PLoS Pathog.* **2013**, *9*, e1003835. [CrossRef] [PubMed]
10. Sivan, G.; Martin, S.E.; Myers, T.G.; Buehler, E.; Szymczyk, K.H.; Ormanoglu, P.; Moss, B. Human genome-wide RNAi screen reveals a role for nuclear pore proteins in poxvirus morphogenesis. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 3519–3524. [CrossRef] [PubMed]
11. Wu, K.X.; Phuektes, P.; Kumar, P.; Goh, G.Y.; Moreau, D.; Chow, V.T.; Bard, F.; Chu, J.J. Human genome-wide RNAi screen reveals host factors required for enterovirus 71 replication. *Nat. Commun.* **2016**, *7*, 13150. [CrossRef] [PubMed]
12. Yasunaga, A.; Hanna, S.L.; Li, J.; Cho, H.; Rose, P.P.; Spiridigliozzi, A.; Gold, B.; Diamond, M.S.; Cherry, S. Genome-wide RNAi screen identifies broadly-acting host factors that inhibit arbovirus infection. *PLoS Pathog.* **2014**, *10*, e1003914. [CrossRef]
13. Yeung, M.L.; Houzet, L.; Yedavalli, V.S.; Jeang, K.T. A genome-wide short hairpin RNA screening of jurkat T-cells for human proteins contributing to productive HIV-1 replication. *J. Biol. Chem.* **2009**, *284*, 19463–19473. [CrossRef] [PubMed]
14. Zhou, H.; Xu, M.; Huang, Q.; Gates, A.T.; Zhang, X.D.; Castle, J.C.; Stec, E.; Ferrer, M.; Strulovici, B.; Hazuda, D.J.; et al. Genome-scale RNAi screen for host factors required for HIV replication. *Cell Host Microbe* **2008**, *4*, 495–504. [CrossRef]
15. Baggen, J.; Persoons, L.; Vanstreels, E.; Jansen, S.; Van Looveren, D.; Boeckx, B.; Geudens, V.; De Man, J.; Jochmans, D.; Wauters, J.; et al. Genome-wide CRISPR screening identifies TMEM106B as a proviral host factor for SARS-CoV-2. *Nat. Genet.* **2021**, *53*, 435–444. [CrossRef]
16. Krasnopolsky, S.; Kuzmina, A.; Taube, R. Genome-wide CRISPR knockout screen identifies ZNF304 as a silencer of HIV transcription that promotes viral latency. *PLoS Pathog.* **2020**, *16*, e1008834. [CrossRef]
17. Kulsuptrakul, J.; Wang, R.; Meyers, N.L.; Ott, M.; Puschnik, A.S. A genome-wide CRISPR screen identifies UFMylation and TRAMP-like complexes as host factors required for hepatitis A virus infection. *Cell Rep.* **2021**, *34*, 108859. [CrossRef]
18. Li, B.; Clohisey, S.M.; Chia, B.S.; Wang, B.; Cui, A.; Eisenhaure, T.; Schweitzer, L.D.; Hoover, P.; Parkinson, N.J.; Nachshon, A.; et al. Genome-wide CRISPR screen identifies host dependency factors for influenza A virus infection. *Nat. Commun.* **2020**, *11*, 164. [CrossRef]
19. Li, Y.; Muffat, J.; Omer Javed, A.; Keys, H.R.; Lungjangwa, T.; Bosch, I.; Khan, M.; Virgilio, M.C.; Gehrke, L.; Sabatini, D.M.; et al. Genome-wide CRISPR screen for Zika virus resistance in human neural cells. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 9527–9532. [CrossRef] [PubMed]
20. Park, R.J.; Wang, T.; Koundakjian, D.; Hultquist, J.F.; Lamothe-Molina, P.; Monel, B.; Schumann, K.; Yu, H.; Krupzcak, K.M.; Garcia-Beltran, W.; et al. A genome-wide CRISPR screen identifies a restricted set of HIV host dependency factors. *Nat. Genet.* **2017**, *49*, 193–203. [CrossRef]
21. Thamamongood, T.; Aebischer, A.; Wagner, V.; Chang, M.W.; Elling, R.; Benner, C.; Garcia-Sastre, A.; Kochs, G.; Beer, M.; Schwemmle, M. A Genome-Wide CRISPR-Cas9 Screen Reveals the Requirement of Host Cell Sulfation for Schmallenberg Virus Infection. *J. Virol.* **2020**, *94*, e00752-20. [CrossRef] [PubMed]
22. Zhu, Y.; Feng, F.; Hu, G.; Wang, Y.; Yu, Y.; Zhu, Y.; Xu, W.; Cai, X.; Sun, Z.; Han, W.; et al. A genome-wide CRISPR screen identifies host factors that regulate SARS-CoV-2 entry. *Nat. Commun.* **2021**, *12*, 961. [CrossRef] [PubMed]
23. Consortium, E.P.; Bernstein, B.E.; Birney, E.; Dunham, I.; Green, E.D.; Gunter, C.; Snyder, M. An integrated encyclopedia of DNA elements in the human genome. *Nature* **2012**, *489*, 57–74. [CrossRef]
24. Iyer, M.K.; Niknafs, Y.S.; Malik, R.; Singhal, U.; Sahu, A.; Hosono, Y.; Barrette, T.R.; Prensner, J.R.; Evans, J.R.; Zhao, S.; et al. The landscape of long noncoding RNAs in the human transcriptome. *Nat. Genet.* **2015**, *47*, 199–208. [CrossRef] [PubMed]
25. Nagano, T.; Fraser, P. No-nonsense functions for long noncoding RNAs. *Cell* **2011**, *145*, 178–181. [CrossRef]
26. Wilusz, J.E.; Sunwoo, H.; Spector, D.L. Long noncoding RNAs: Functional surprises from the RNA world. *Genes. Dev.* **2009**, *23*, 1494–1504. [CrossRef]
27. Chen, Y.G.; Satpathy, A.T.; Chang, H.Y. Gene regulation in the immune system by long noncoding RNAs. *Nat. Immunol.* **2017**, *18*, 962–972. [CrossRef]
28. Wapinski, O.; Chang, H.Y. Long noncoding RNAs and human disease. *Trends Cell Biol.* **2011**, *21*, 354–361. [CrossRef]
29. Winterling, C.; Koch, M.; Koeppel, M.; Garcia-Alcalde, F.; Karlas, A.; Meyer, T.F. Evidence for a crucial role of a host non-coding RNA in influenza A virus replication. *RNA Biol.* **2014**, *11*, 66–75. [CrossRef] [PubMed]

30. Sun, S.; Yao, M.; Yuan, L.; Qiao, J. Long-chain non-coding RNA n337374 relieves symptoms of respiratory syncytial virus-induced asthma by inhibiting dendritic cell maturation via the CD86 and the ERK pathway. *Allergol. Immunopathol. (Madr)* **2021**, *49*, 100–107. [CrossRef] [PubMed]
31. Carnero, E.; Barriocanal, M.; Prior, C.; Pablo Unfried, J.; Segura, V.; Guruceaga, E.; Enguita, M.; Smerdou, C.; Gastaminza, P.; Fortes, P. Long noncoding RNA EGOT negatively affects the antiviral response and favors HCV replication. *EMBO Rep.* **2016**, *17*, 1013–1028. [CrossRef]
32. Zhao, H.; Chen, M.; Lind, S.B.; Pettersson, U. Distinct temporal changes in host cell lncRNA expression during the course of an adenovirus infection. *Virology* **2016**, *492*, 242–250. [CrossRef]
33. Liu, H.; Xu, J.; Yang, Y.; Wang, X.; Wu, E.; Majerciak, V.; Zhang, T.; Steenbergen, R.D.M.; Wang, H.K.; Banerjee, N.S.; et al. Oncogenic HPV promotes the expression of the long noncoding RNA lnc-FANCI-2 through E7 and YY1. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2014195118. [CrossRef]
34. Kuo, R.L.; Chen, Y.T.; Li, H.A.; Wu, C.C.; Chiang, H.C.; Lin, J.Y.; Huang, H.I.; Shih, S.R.; Chin-Ming Tan, B. Molecular determinants and heterogeneity underlying host response to EV-A71 infection at single-cell resolution. *RNA Biol.* **2021**, *18*, 796–808. [CrossRef]
35. Devadoss, D.; Acharya, A.; Manevski, M.; Pandey, K.; Borchert, G.M.; Nair, M.; Mirsaeidi, M.; Byrareddy, S.N.; Chand, H.S. Distinct Mucoinflammatory Phenotype and the Immunomodulatory Long Noncoding Transcripts Associated with SARS-CoV-2 Airway Infection. *medRxiv* **2021**. [CrossRef]
36. Laha, S.; Saha, C.; Dutta, S.; Basu, M.; Chatterjee, R.; Ghosh, S.; Bhattacharyya, N.P. In silico analysis of altered expression of long non-coding RNA in SARS-CoV-2 infected cells and their possible regulation by STAT1, STAT3 and interferon regulatory factors. *Heliyon* **2021**, *7*, e06395. [CrossRef] [PubMed]
37. Morenikeji, O.B.; Bernard, K.; Strutton, E.; Wallace, M.; Thomas, B.N. Evolutionarily Conserved Long Non-coding RNA Regulates Gene Expression in Cytokine Storm During COVID-19. *Front. Bioeng. Biotechnol.* **2020**, *8*, 582953. [CrossRef]
38. Mukherjee, S.; Banerjee, B.; Karasik, D.; Frenkel-Morgenstern, M. mRNA-lncRNA Co-Expression Network Analysis Reveals the Role of lncRNAs in Immune Dysfunction during Severe SARS-CoV-2 Infection. *Viruses* **2021**, *13*, 402. [CrossRef]
39. Natarelli, L.; Parca, L.; Mazza, T.; Weber, C.; Virgili, F.; Fratantonio, D. MicroRNAs and Long Non-Coding RNAs as Potential Candidates to Target Specific Motifs of SARS-CoV-2. *Noncoding RNA* **2021**, *7*, 14. [CrossRef] [PubMed]
40. Shaath, H.; Alajez, N.M. Identification of PBMC-based molecular signature associational with COVID-19 disease severity. *Heliyon* **2021**, *7*, e06866. [CrossRef]
41. Tang, H.; Gao, Y.; Li, Z.; Miao, Y.; Huang, Z.; Liu, X.; Xie, L.; Li, H.; Wen, W.; Zheng, Y.; et al. The noncoding and coding transcriptional landscape of the peripheral immune response in patients with COVID-19. *Clin. Transl. Med.* **2020**, *10*, e200. [CrossRef]
42. Turjya, R.R.; Khan, M.A.; Mir Md Khademul Islam, A.B. Perversely expressed long noncoding RNAs can alter host response and viral proliferation in SARS-CoV-2 infection. *Future Virol.* **2020**, *15*, 577–593. [CrossRef]
43. Vishnubalaji, R.; Shaath, H.; Alajez, N.M. Protein Coding and Long Noncoding RNA (lncRNA) Transcriptional Landscape in SARS-CoV-2 Infected Bronchial Epithelial Cells Highlight a Role for Interferon and Inflammatory Response. *Genes.* **2020**, *11*, 760. [CrossRef]
44. Wu, Y.; Zhao, T.; Deng, R.; Xia, X.; Li, B.; Wang, X. A study of differential circRNA and lncRNA expressions in COVID-19-infected peripheral blood. *Sci. Rep.* **2021**, *11*, 7991. [CrossRef]
45. Xiong, Y.; Liu, Y.; Cao, L.; Wang, D.; Guo, M.; Jiang, A.; Guo, D.; Hu, W.; Yang, J.; Tang, Z.; et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. *Emerg. Microbes Infect.* **2020**, *9*, 761–770. [CrossRef] [PubMed]
46. Chang, S.T.; Sova, P.; Peng, X.; Weiss, J.; Law, G.L.; Palermo, R.E.; Katze, M.G. Next-generation sequencing reveals HIV-1-mediated suppression of T cell activation and RNA processing and regulation of noncoding RNA expression in a CD4+ T cell line. *MBio* **2011**, *2*, e00134-11. [CrossRef]
47. Peng, X.; Sova, P.; Green, R.R.; Thomas, M.J.; Korth, M.J.; Proll, S.; Xu, J.; Cheng, Y.; Yi, K.; Chen, L.; et al. Deep sequencing of HIV-infected cells: Insights into nascent transcription and host-directed therapy. *J. Virol.* **2014**, *88*, 8768–8782. [CrossRef] [PubMed]
48. Schynkel, T.; Szaniawski, M.A.; Spivak, A.M.; Bosque, A.; Planelles, V.; Vandekerckhove, L.; Trypsteen, W. Interferon-Mediated Long Non-Coding RNA Response in Macrophages in the Context of HIV. *Int. J. Mol. Sci.* **2020**, *21*, 7741. [CrossRef] [PubMed]
49. Trypsteen, W.; Mohammadi, P.; Van Hecke, C.; Mestdagh, P.; Lefever, S.; Saeys, Y.; De Bleser, P.; Vandesompele, J.; Ciuffi, A.; Vandekerckhove, L.; et al. Differential expression of lncRNAs during the HIV replication cycle: An underestimated layer in the HIV-host interplay. *Sci. Rep.* **2016**, *6*, 36111. [CrossRef] [PubMed]
50. Trypsteen, W.; White, C.H.; Mukim, A.; Spina, C.A.; De Spiegelaere, W.; Lefever, S.; Planelles, V.; Bosque, A.; Woelk, C.H.; Vandekerckhove, L.; et al. Long non-coding RNAs and latent HIV—A search for novel targets for latency reversal. *PLoS ONE* **2019**, *14*, e0224879. [CrossRef] [PubMed]
51. Zhang, Q.; Chen, C.Y.; Yedavalli, V.S.; Jeang, K.T. NEAT1 long noncoding RNA and paraspeckle bodies modulate HIV-1 posttranscriptional expression. *MBio* **2013**, *4*, e00596-12. [CrossRef] [PubMed]
52. Ouyang, J.; Hu, J.; Chen, J.L. lncRNAs regulate the innate immune response to viral infection. *Wiley Interdiscip. Rev. RNA* **2016**, *7*, 129–143. [CrossRef]

53. Fan, J.; Cheng, M.; Chi, X.; Liu, X.; Yang, W. A Human Long Non-coding RNA LncATV Promotes Virus Replication Through Restricting RIG-I-Mediated Innate Immunity. *Front. Immunol.* **2019**, *10*, 1711. [CrossRef]
54. Jiang, M.; Zhang, S.; Yang, Z.; Lin, H.; Zhu, J.; Liu, L.; Wang, W.; Liu, S.; Liu, W.; Ma, Y.; et al. Self-Recognition of an Inducible Host lncRNA by RIG-I Feedback Restricts Innate Immune Response. *Cell* **2018**, *173*, 906–919.e913. [CrossRef] [PubMed]
55. Lin, H.; Jiang, M.; Liu, L.; Yang, Z.; Ma, Z.; Liu, S.; Ma, Y.; Zhang, L.; Cao, X. The long noncoding RNA Lnczc3h7a promotes a TRIM25-mediated RIG-I antiviral innate immune response. *Nat. Immunol.* **2019**, *20*, 812–823. [CrossRef] [PubMed]
56. Ma, H.; Han, P.; Ye, W.; Chen, H.; Zheng, X.; Cheng, L.; Zhang, L.; Yu, L.; Wu, X.; Xu, Z.; et al. The Long Noncoding RNA NEAT1 Exerts Antihantaviral Effects by Acting as Positive Feedback for RIG-I Signaling. *J. Virol.* **2017**, *91*, e02250-16. [CrossRef] [PubMed]
57. Ouyang, J.; Zhu, X.; Chen, Y.; Wei, H.; Chen, Q.; Chi, X.; Qi, B.; Zhang, L.; Zhao, Y.; Gao, G.F.; et al. NRAV, a long noncoding RNA, modulates antiviral responses through suppression of interferon-stimulated gene transcription. *Cell Host Microbe* **2014**, *16*, 616–626. [CrossRef]
58. Xie, Q.; Chen, S.; Tian, R.; Huang, X.; Deng, R.; Xue, B.; Qin, Y.; Xu, Y.; Wang, J.; Guo, M.; et al. Long Noncoding RNA ITPRIP-1 Positively Regulates the Innate Immune Response through Promotion of Oligomerization and Activation of MDA5. *J. Virol.* **2018**, *92*, e00507-18. [CrossRef]
59. Gonzalez-Moro, I.; Olazagoitia-Garmendia, A.; Colli, M.L.; Cobo-Vuilleumier, N.; Postler, T.S.; Marselli, L.; Marchetti, P.; Ghosh, S.; Gauthier, B.R.; Eizirik, D.L.; et al. The T1D-associated lncRNA Lnc13 modulates human pancreatic beta cell inflammation by allele-specific stabilization of STAT1 mRNA. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 9022–9031. [CrossRef]
60. Hu, P.; Wilhelm, J.; Gerresheim, G.K.; Shalamova, L.A.; Niepmann, M. Lnc-ITM2C-1 and GPR55 Are Proviral Host Factors for Hepatitis C Virus. *Viruses* **2019**, *11*, 549. [CrossRef]
61. Li, X.; Guo, G.; Lu, M.; Chai, W.; Li, Y.; Tong, X.; Li, J.; Jia, X.; Liu, W.; Qi, D.; et al. Long Noncoding RNA Lnc-MxA Inhibits Beta Interferon Transcription by Forming RNA-DNA Triplexes at Its Promoter. *J. Virol.* **2019**, *93*. [CrossRef] [PubMed]
62. Wang, Q.; Zhang, D.; Feng, W.; Guo, Y.; Sun, X.; Zhang, M.; Guan, Z.; Duan, M. Long noncoding RNA TSPOAP1 antisense RNA 1 negatively modulates type I IFN signaling to facilitate influenza A virus replication. *J. Med. Virol.* **2019**, *94*, 557–566. [CrossRef] [PubMed]
63. Zhao, L.; Xia, M.; Wang, K.; Lai, C.; Fan, H.; Gu, H.; Yang, P.; Wang, X. A Long Non-coding RNA IVRPIE Promotes Host Antiviral Immune Responses Through Regulating Interferon beta1 and ISG Expression. *Front. Microbiol.* **2020**, *11*, 260. [CrossRef] [PubMed]
64. Zhang, Q.; Chao, T.C.; Patil, V.S.; Qin, Y.; Tiwari, S.K.; Chiou, J.; Dobin, A.; Tsai, C.M.; Li, Z.; Dang, J.; et al. The long noncoding RNA ROCKI regulates inflammatory gene expression. *EMBO J.* **2019**, *38*, e100041. [CrossRef]
65. Kambara, H.; Niazi, F.; Kostadinova, L.; Moonka, D.K.; Siegel, C.T.; Post, A.B.; Carnero, E.; Barriocanal, M.; Fortes, P.; Anthony, D.D.; et al. Negative regulation of the interferon response by an interferon-induced long non-coding RNA. *Nucleic Acids Res.* **2014**, *42*, 10668–10680. [CrossRef] [PubMed]
66. Rapicavoli, N.A.; Qu, K.; Zhang, J.; Mikhail, M.; Laberge, R.M.; Chang, H.Y. A mammalian pseudogene lncRNA at the interface of inflammation and anti-inflammatory therapeutics. *Elife* **2013**, *2*, e00762. [CrossRef]
67. Sonkoly, E.; Bata-Csorgo, Z.; Pivarcsi, A.; Polyanka, H.; Kenderessy-Szabo, A.; Molnar, G.; Szentpali, K.; Bari, L.; Megyeri, K.; Mandi, Y.; et al. Identification and characterization of a novel, psoriasis susceptibility-related noncoding RNA gene, PRINS. *J. Biol. Chem.* **2005**, *280*, 24159–24167. [CrossRef]
68. Yang, W.S.; Yeh, W.W.; Campbell, M.; Chang, L.; Chang, P.C. Long non-coding RNA KIKAT/LINC01061 as a novel epigenetic regulator that relocates KDM4A on chromatin and modulates viral reactivation. *PLoS Pathog.* **2021**, *17*, e1009670. [CrossRef] [PubMed]
69. Xu, J.; Wang, P.; Li, Z.; Li, Z.; Han, D.; Wen, M.; Zhao, Q.; Zhang, L.; Ma, Y.; Liu, W.; et al. IRF3-binding lncRNA-ISIR strengthens interferon production in viral infection and autoinflammation. *Cell Rep.* **2021**, *37*, 109926. [CrossRef]
70. Qiu, L.; Wang, T.; Tang, Q.; Li, G.; Wu, P.; Chen, K. Long Non-coding RNAs: Regulators of Viral Infection and the Interferon Antiviral Response. *Front. Microbiol.* **2018**, *9*, 1621. [CrossRef]
71. Xiong, Y.; Yuan, J.; Zhang, C.; Zhu, Y.; Kuang, X.; Lan, L.; Wang, X. The STAT3-regulated long non-coding RNA Lethe promote the HCV replication. *Biomed. Pharmacother.* **2015**, *72*, 165–171. [CrossRef] [PubMed]
72. Liu, X.; Duan, X.; Holmes, J.A.; Li, W.; Lee, S.H.; Tu, Z.; Zhu, C.; Salloum, S.; Lidofsky, A.; Schaefer, E.A.; et al. A Long Noncoding RNA Regulates Hepatitis C Virus Infection Through Interferon Alpha-Inducible Protein 6. *Hepatology* **2019**, *69*, 1004–1019. [CrossRef] [PubMed]
73. Fang, L.; Gao, Y.; Liu, X.; Bai, J.; Jiang, P.; Wang, X. Long non-coding RNA LNC_000641 regulates pseudorabies virus replication. *Vet. Res.* **2021**, *52*, 52. [CrossRef] [PubMed]
74. Wang, Z.; Fan, P.; Zhao, Y.; Zhang, S.; Lu, J.; Xie, W.; Jiang, Y.; Lei, F.; Xu, N.; Zhang, Y. NEAT1 modulates herpes simplex virus-1 replication by regulating viral gene transcription. *Cell Mol. Life Sci.* **2017**, *74*, 1117–1131. [CrossRef]
75. Wang, Y.; Huo, Z.; Lin, Q.; Lin, Y.; Chen, C.; Huang, Y.; Huang, C.; Zhang, J.; He, J.; Liu, C.; et al. Positive Feedback Loop of Long Noncoding RNA OASL-IT1 and Innate Immune Response Restricts the Replication of Zika Virus in Epithelial A549 Cells. *J. Innate Immun.* **2021**, *13*, 179–193. [CrossRef]
76. Nishitsuji, H.; Ujino, S.; Yoshio, S.; Sugiyama, M.; Mizokami, M.; Kanto, T.; Shimotohno, K. Long noncoding RNA #32 contributes to antiviral responses by controlling interferon-stimulated gene expression. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 10388–10393. [CrossRef] [PubMed]

77. Li, J.; Chen, C.; Ma, X.; Geng, G.; Liu, B.; Zhang, Y.; Zhang, S.; Zhong, F.; Liu, C.; Yin, Y.; et al. Long noncoding RNA NRON contributes to HIV-1 latency by specifically inducing tat protein degradation. *Nat. Commun.* **2016**, *7*, 11730. [CrossRef]
78. Qu, D.; Sun, W.W.; Li, L.; Ma, L.; Sun, L.; Jin, X.; Li, T.; Hou, W.; Wang, J.H. Long noncoding RNA MALAT1 releases epigenetic silencing of HIV-1 replication by displacing the polycomb repressive complex 2 from binding to the LTR promoter. *Nucleic Acids Res.* **2019**, *47*, 3013–3027. [CrossRef]
79. Nguyen, V.T.; Kiss, T.; Michels, A.A.; Bensaude, O. 7SK small nuclear RNA binds to and inhibits the activity of CDK9/cyclin T complexes. *Nature* **2001**, *414*, 322–325. [CrossRef] [PubMed]
80. Contreras, X.; Barboric, M.; Lenasi, T.; Peterlin, B.M. HMBA releases P-TEFb from HEXIM1 and 7SK snRNA via PI3K/Akt and activates HIV transcription. *PLoS Pathog.* **2007**, *3*, 1459–1469. [CrossRef]
81. Budhiraja, S.; Famiglietti, M.; Bosque, A.; Planelles, V.; Rice, A.P. Cyclin T1 and CDK9 T-loop phosphorylation are downregulated during establishment of HIV-1 latency in primary resting memory CD4+ T cells. *J. Virol.* **2013**, *87*, 1211–1220. [CrossRef] [PubMed]
82. Eilebrecht, S.; Benecke, B.J.; Benecke, A.G. Latent HIV-1 TAR Regulates 7SK-responsive P-TEFb Target Genes and Targets Cellular Immune Responses in the Absence of Tat. *Genomics Proteomics Bioinformatics* **2017**, *15*, 313–323. [CrossRef] [PubMed]
83. Huan, C.; Li, Z.; Ning, S.; Wang, H.; Yu, X.F.; Zhang, W. Long Noncoding RNA uc002yug.2 Activates HIV-1 Latency through Regulation of mRNA Levels of Various RUNX1 Isoforms and Increased Tat Expression. *J. Virol.* **2018**, *92*, e01844-17. [CrossRef] [PubMed]
84. Barichievy, S.; Naidoo, J.; Boulle, M.; Scholefield, J.; Parihar, S.P.; Coussens, A.K.; Brombacher, F.; Sigal, A.; Mhlanga, M.M. Viral Apoptosis Evasion via the MAPK Pathway by Use of a Host Long Noncoding RNA. *Front. Cell Infect. Microbiol.* **2018**, *8*, 263. [CrossRef]
85. Chao, T.C.; Zhang, Q.; Li, Z.; Tiwari, S.K.; Qin, Y.; Yau, E.; Sanchez, A.; Singh, G.; Chang, K.; Kaul, M.; et al. The Long Noncoding RNA HEAL Regulates HIV-1 Replication through Epigenetic Regulation of the HIV-1 Promoter. *mBio* **2019**, *10*, e02016-19. [CrossRef]
86. Saayman, S.; Ackley, A.; Turner, A.W.; Famiglietti, M.; Bosque, A.; Clemson, M.; Planelles, V.; Morris, K.V. An HIV-encoded antisense long noncoding RNA epigenetically regulates viral transcription. *Mol. Ther.* **2014**, *22*, 1164–1175. [CrossRef] [PubMed]
87. Rossetto, C.C.; Pari, G. KSHV PAN RNA associates with demethylases UTX and JMJD3 to activate lytic replication through a physical interaction with the virus genome. *PLoS Pathog.* **2012**, *8*, e1002680. [CrossRef]
88. Rossetto, C.C.; Tarrant-Elorza, M.; Verma, S.; Purushothaman, P.; Pari, G.S. Regulation of viral and cellular gene expression by Kaposi's sarcoma-associated herpesvirus polyadenylated nuclear RNA. *J. Virol.* **2013**, *87*, 5540–5553. [CrossRef]
89. Rossetto, C.C.; Tarrant-Elorza, M.; Verma, S.; Purushothaman, P.; Pari, G.S. Correction for Rossetto et al., Regulation of Viral and Cellular Gene Expression by Kaposi's Sarcoma-Associated Herpesvirus Polyadenylated Nuclear RNA. *J. Virol.* **2016**, *90*, 4255. [CrossRef] [PubMed]
90. Rossetto, C.C.; Tarrant-Elorza, M.; Pari, G.S. Cis and trans acting factors involved in human cytomegalovirus experimental and natural latent infection of CD14 (+) monocytes and CD34 (+) cells. *PLoS Pathog.* **2013**, *9*, e1003366. [CrossRef]
91. Marquitz, A.R.; Mathur, A.; Edwards, R.H.; Raab-Traub, N. Host Gene Expression Is Regulated by Two Types of Noncoding RNAs Transcribed from the Epstein-Barr Virus BamHI A Rightward Transcript Region. *J. Virol.* **2015**, *89*, 11256–11268. [CrossRef]
92. Verhoeven, R.J.A.; Tong, S.; Mok, B.W.; Liu, J.; He, S.; Zong, J.; Chen, Y.; Tsao, S.W.; Lung, M.L.; Chen, H. Epstein-Barr Virus BART Long Non-coding RNAs Function as Epigenetic Modulators in Nasopharyngeal Carcinoma. *Front. Oncol.* **2019**, *9*, 1120. [CrossRef]
93. Park, R.; Miller, G. Epstein-Barr Virus-Induced Nodules on Viral Replication Compartments Contain RNA Processing Proteins and a Viral Long Noncoding RNA. *J. Virol.* **2018**, *92*, e01254-18. [CrossRef] [PubMed]
94. Rennekamp, A.J.; Lieberman, P.M. Initiation of Epstein-Barr virus lytic replication requires transcription and the formation of a stable RNA-DNA hybrid molecule at OriLyt. *J. Virol.* **2011**, *85*, 2837–2850. [CrossRef]
95. Peng, X.; Gralinski, L.; Armour, C.D.; Ferris, M.T.; Thomas, M.J.; Proll, S.; Bradel-Tretheway, B.G.; Korth, M.J.; Castle, J.C.; Biery, M.C.; et al. Unique signatures of long noncoding RNA expression in response to virus infection and altered innate immune signaling. *mBio* **2010**, *1*, e00206-10. [CrossRef] [PubMed]
96. Sui, B.; Chen, D.; Liu, W.; Wu, Q.; Tian, B.; Li, Y.; Hou, J.; Liu, S.; Xie, J.; Jiang, H.; et al. A novel antiviral lncRNA, EDAL, shields a T309 O-GlcNAcylation site to promote EZH2 lysosomal degradation. *Genome Biol.* **2020**, *21*, 228. [CrossRef]
97. Fang, S.; Zhang, L.; Guo, J.; Niu, Y.; Wu, Y.; Li, H.; Zhao, L.; Li, X.; Teng, X.; Sun, X.; et al. NONCODEV5: A comprehensive annotation database for long non-coding RNAs. *Nucleic Acids Res.* **2018**, *46*, D308–D314. [CrossRef] [PubMed]
98. Uszczynska-Ratajczak, B.; Lagarde, J.; Frankish, A.; Guigo, R.; Johnson, R. Towards a complete map of the human long non-coding RNA transcriptome. *Nat. Rev. Genet.* **2018**, *19*, 535–548. [CrossRef]
99. Derrien, T.; Johnson, R.; Bussotti, G.; Tanzer, A.; Djebali, S.; Tilgner, H.; Guernec, G.; Martin, D.; Merkel, A.; Knowles, D.G.; et al. The GENCODE v7 catalog of human long noncoding RNAs: Analysis of their gene structure, evolution, and expression. *Genome Res.* **2012**, *22*, 1775–1789. [CrossRef]
100. Griffiths-Jones, S. Annotating noncoding RNA genes. *Annu. Rev. Genomics Hum. Genet.* **2007**, *8*, 279–298. [CrossRef]
101. Lagarde, J.; Uszczynska-Ratajczak, B.; Carbonell, S.; Perez-Lluch, S.; Abad, A.; Davis, C.; Gingeras, T.R.; Frankish, A.; Harrow, J.; Guigo, R.; et al. High-throughput annotation of full-length long noncoding RNAs with capture long-read sequencing. *Nat. Genet.* **2017**, *49*, 1731–1740. [CrossRef]
102. Mele, M.; Mattioli, K.; Mallard, W.; Shechner, D.M.; Gerhardinger, C.; Rinn, J.L. Chromatin environment, transcriptional regulation, and splicing distinguish lincRNAs and mRNAs. *Genome Res.* **2017**, *27*, 27–37. [CrossRef]

103. Schlackow, M.; Nojima, T.; Gomes, T.; Dhir, A.; Carmo-Fonseca, M.; Proudfoot, N.J. Distinctive Patterns of Transcription and RNA Processing for Human lincRNAs. *Mol. Cell* **2017**, *65*, 25–38. [CrossRef]
104. West, J.A.; Davis, C.P.; Sunwoo, H.; Simon, M.D.; Sadreyev, R.I.; Wang, P.I.; Tolstorukov, M.Y.; Kingston, R.E. The long noncoding RNAs NEAT1 and MALAT1 bind active chromatin sites. *Mol. Cell* **2014**, *55*, 791–802. [CrossRef] [PubMed]
105. Lubelsky, Y.; Ulitsky, I. Sequences enriched in Alu repeats drive nuclear localization of long RNAs in human cells. *Nature* **2018**, *555*, 107–111. [CrossRef]
106. Zhang, B.; Gunawardane, L.; Niazi, F.; Jahanbani, F.; Chen, X.; Valadkhan, S. A novel RNA motif mediates the strict nuclear localization of a long noncoding RNA. *Mol. Cell Biol.* **2014**, *34*, 2318–2329. [CrossRef] [PubMed]
107. Miyagawa, R.; Tano, K.; Mizuno, R.; Nakamura, Y.; Ijiri, K.; Rakwal, R.; Shibato, J.; Masuo, Y.; Mayeda, A.; Hirose, T.; et al. Identification of cis- and trans-acting factors involved in the localization of MALAT-1 noncoding RNA to nuclear speckles. *RNA* **2012**, *18*, 738–751. [CrossRef]
108. Hacisuleyman, E.; Goff, L.A.; Trapnell, C.; Williams, A.; Henao-Mejia, J.; Sun, L.; McClanahan, P.; Hendrickson, D.G.; Sauvageau, M.; Kelley, D.R.; et al. Topological organization of multichromosomal regions by the long intergenic noncoding RNA Firre. *Nat. Struct. Mol. Biol.* **2014**, *21*, 198–206. [CrossRef]
109. Dumbovic, G.; Braunschweig, U.; Langner, H.K.; Smallegan, M.; Biayna, J.; Hass, E.P.; Jastrzebska, K.; Blencowe, B.; Cech, T.R.; Caruthers, M.H.; et al. Nuclear compartmentalization of TERT mRNA and TUG1 lncRNA is driven by intron retention. *Nat. Commun.* **2021**, *12*, 3308. [CrossRef] [PubMed]
110. Gutierrez, I.V.; Dayton, J.; Harger, S.; Rossetto, C.C. The Expression and Nuclear Retention Element of Polyadenylated Nuclear RNA Is Not Required for Productive Lytic Replication of Kaposi's Sarcoma-Associated Herpesvirus. *J. Virol.* **2021**, *95*, e0009621. [CrossRef] [PubMed]
111. Conrad, N.K.; Mili, S.; Marshall, E.L.; Shu, M.D.; Steitz, J.A. Identification of a rapid mammalian deadenylation-dependent decay pathway and its inhibition by a viral RNA element. *Mol. Cell* **2006**, *24*, 943–953. [CrossRef] [PubMed]
112. Conrad, N.K.; Shu, M.D.; Uyhazi, K.E.; Steitz, J.A. Mutational analysis of a viral RNA element that counteracts rapid RNA decay by interaction with the polyadenylate tail. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 10412–10417. [CrossRef]
113. Conrad, N.K.; Steitz, J.A. A Kaposi's sarcoma virus RNA element that increases the nuclear abundance of intronless transcripts. *EMBO J.* **2005**, *24*, 1831–1841. [CrossRef]
114. Rossetto, C.C.; Pari, G.S. PAN's Labyrinth: Molecular biology of Kaposi's sarcoma-associated herpesvirus (KSHV) PAN RNA, a multifunctional long noncoding RNA. *Viruses* **2014**, *6*, 4212–4226. [CrossRef]
115. Sahin, B.B.; Patel, D.; Conrad, N.K. Kaposi's sarcoma-associated herpesvirus ORF57 protein binds and protects a nuclear noncoding RNA from cellular RNA decay pathways. *PLoS Pathog.* **2010**, *6*, e1000799. [CrossRef] [PubMed]
116. Brown, J.A.; Valenstein, M.L.; Yario, T.A.; Tycowski, K.T.; Steitz, J.A. Formation of triple-helical structures by the 3'-end sequences of MALAT1 and MENbeta noncoding RNAs. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 19202–19207. [CrossRef]
117. Hautbergue, G.M. RNA Nuclear Export: From Neurological Disorders to Cancer. *Adv. Exp. Med. Biol.* **2017**, *1007*, 89–109. [CrossRef]
118. Guttman, M.; Amit, I.; Garber, M.; French, C.; Lin, M.F.; Feldser, D.; Huarte, M.; Zuk, O.; Carey, B.W.; Cassady, J.P.; et al. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. *Nature* **2009**, *458*, 223–227. [CrossRef]
119. Viphakone, N.; Sudbery, I.; Griffith, L.; Heath, C.G.; Sims, D.; Wilson, S.A. Co-transcriptional Loading of RNA Export Factors Shapes the Human Transcriptome. *Mol. Cell* **2019**, *75*, 310–323 e318. [CrossRef] [PubMed]
120. Cohen, H.R.; Panning, B. XIST RNA exhibits nuclear retention and exhibits reduced association with the export factor TAP/NXF1. *Chromosoma* **2007**, *116*, 373–383. [CrossRef]
121. Bergmann, J.H.; Spector, D.L. Long non-coding RNAs: Modulators of nuclear structure and function. *Curr. Opin. Cell Biol.* **2014**, *26*, 10–18. [CrossRef]
122. Clemson, C.M.; Hutchinson, J.N.; Sara, S.A.; Ensminger, A.W.; Fox, A.H.; Chess, A.; Lawrence, J.B. An architectural role for a nuclear noncoding RNA: NEAT1 RNA is essential for the structure of paraspeckles. *Mol. Cell* **2009**, *33*, 717–726. [CrossRef] [PubMed]
123. Engreitz, J.M.; Pandya-Jones, A.; McDonel, P.; Shishkin, A.; Sirokman, K.; Surka, C.; Kadri, S.; Xing, J.; Goren, A.; Lander, E.S.; et al. The Xist lncRNA exploits three-dimensional genome architecture to spread across the X chromosome. *Science* **2013**, *341*, 1237973. [CrossRef]
124. Guttman, M.; Rinn, J.L. Modular regulatory principles of large non-coding RNAs. *Nature* **2012**, *482*, 339–346. [CrossRef]
125. Mao, Y.S.; Sunwoo, H.; Zhang, B.; Spector, D.L. Direct visualization of the co-transcriptional assembly of a nuclear body by noncoding RNAs. *Nat. Cell Biol.* **2011**, *13*, 95–101. [CrossRef] [PubMed]
126. Rinn, J.L.; Chang, H.Y. Genome regulation by long noncoding RNAs. *Annu. Rev. Biochem.* **2012**, *81*, 145–166. [CrossRef] [PubMed]
127. Wang, K.C.; Chang, H.Y. Molecular mechanisms of long noncoding RNAs. *Mol. Cell* **2011**, *43*, 904–914. [CrossRef]
128. Landeras-Bueno, S.; Jorba, N.; Perez-Cidoncha, M.; Ortin, J. The splicing factor proline-glutamine rich (SFPQ/PSF) is involved in influenza virus transcription. *PLoS Pathog.* **2011**, *7*, e1002397. [CrossRef]
129. Markaki, Y.; Gan Chong, J.; Wang, Y.; Jacobson, E.C.; Luong, C.; Tan, S.Y.X.; Jachowicz, J.W.; Strehle, M.; Maestrini, D.; Banerjee, A.K.; et al. Xist nucleates local protein gradients to propagate silencing across the X chromosome. *Cell* **2021**, *184*, 6174–6192 e6132. [CrossRef]

130. Quinodoz, S.A.; Jachowicz, J.W.; Bhat, P.; Ollikainen, N.; Banerjee, A.K.; Goronzy, I.N.; Blanco, M.R.; Chovanec, P.; Chow, A.; Markaki, Y.; et al. RNA promotes the formation of spatial compartments in the nucleus. *Cell* **2021**, *184*, 5775–5790 e5730. [CrossRef]
131. Quinodoz, S.A.; Ollikainen, N.; Tabak, B.; Palla, A.; Schmidt, J.M.; Detmar, E.; Lai, M.M.; Shishkin, A.A.; Bhat, P.; Takei, Y.; et al. Higher-Order Inter-chromosomal Hubs Shape 3D Genome Organization in the Nucleus. *Cell* **2018**, *174*, 744–757 e724. [CrossRef]
132. Engreitz, J.M.; Haines, J.E.; Perez, E.M.; Munson, G.; Chen, J.; Kane, M.; McDonel, P.E.; Guttman, M.; Lander, E.S. Local regulation of gene expression by lncRNA promoters, transcription and splicing. *Nature* **2016**, *539*, 452–455. [CrossRef]
133. Grote, P.; Wittler, L.; Hendrix, D.; Koch, F.; Wahrisch, S.; Beisaw, A.; Macura, K.; Blass, G.; Kellis, M.; Werber, M.; et al. The tissue-specific lncRNA Fendrr is an essential regulator of heart and body wall development in the mouse. *Dev. Cell* **2013**, *24*, 206–214. [CrossRef] [PubMed]
134. Hartana, C.A.; Rassadkina, Y.; Gao, C.; Martin-Gayo, E.; Walker, B.D.; Lichterfeld, M.; Yu, X.G. Long noncoding RNA MIR4435-2HG enhances metabolic function of myeloid dendritic cells from HIV-1 elite controllers. *J. Clin. Invest.* **2021**, *131*, e146136. [CrossRef] [PubMed]
135. Kalwa, M.; Hanzelmann, S.; Otto, S.; Kuo, C.C.; Franzen, J.; Joussen, S.; Fernandez-Rebollo, E.; Rath, B.; Koch, C.; Hofmann, A.; et al. The lncRNA HOTAIR impacts on mesenchymal stem cells via triple helix formation. *Nucleic Acids Res.* **2016**, *44*, 10631–10643. [CrossRef] [PubMed]
136. Mondal, T.; Subhash, S.; Vaid, R.; Enroth, S.; Uday, S.; Reinius, B.; Mitra, S.; Mohammed, A.; James, A.R.; Hoberg, E.; et al. MEG3 long noncoding RNA regulates the TGF-beta pathway genes through formation of RNA-DNA triplex structures. *Nat. Commun.* **2015**, *6*, 7743. [CrossRef]
137. O'Leary, V.B.; Ovsepian, S.V.; Carrascosa, L.G.; Buske, F.A.; Radulovic, V.; Niyazi, M.; Moertl, S.; Trau, M.; Atkinson, M.J.; Anastasov, N. PARTICLE, a Triplex-Forming Long ncRNA, Regulates Locus-Specific Methylation in Response to Low-Dose Irradiation. *Cell Rep.* **2015**, *11*, 474–485. [CrossRef]
138. O'Leary, V.B.; Smida, J.; Buske, F.A.; Carrascosa, L.G.; Azimzadeh, O.; Maugg, D.; Hain, S.; Tapio, S.; Heidenreich, W.; Kerr, J.; et al. PARTICLE triplexes cluster in the tumor suppressor WWOX and may extend throughout the human genome. *Sci. Rep.* **2017**, *7*, 7163. [CrossRef]
139. Postepska-Igielska, A.; Giwojna, A.; Gasri-Plotnitsky, L.; Schmitt, N.; Dold, A.; Ginsberg, D.; Grummt, I. LncRNA Khps1 Regulates Expression of the Proto-oncogene SPHK1 via Triplex-Mediated Changes in Chromatin Structure. *Mol. Cell* **2015**, *60*, 626–636. [CrossRef]
140. Zhao, Z.; Senturk, N.; Song, C.; Grummt, I. lncRNA PAPAS tethered to the rDNA enhancer recruits hypophosphorylated CHD4/NuRD to repress rRNA synthesis at elevated temperatures. *Genes. Dev.* **2018**, *32*, 836–848. [CrossRef] [PubMed]
141. Arab, K.; Karaulanov, E.; Musheev, M.; Trnka, P.; Schafer, A.; Grummt, I.; Niehrs, C. GADD45A binds R-loops and recruits TET1 to CpG island promoters. *Nat. Genet.* **2019**, *51*, 217–223. [CrossRef]
142. Schoggins, J.W.; Wilson, S.J.; Panis, M.; Murphy, M.Y.; Jones, C.T.; Bieniasz, P.; Rice, C.M. A diverse range of gene products are effectors of the type I interferon antiviral response. *Nature* **2011**, *472*, 481–485. [CrossRef] [PubMed]
143. Kaneko, S.; Bonasio, R.; Saldana-Meyer, R.; Yoshida, T.; Son, J.; Nishino, K.; Umezawa, A.; Reinberg, D. Interactions between JARID2 and noncoding RNAs regulate PRC2 recruitment to chromatin. *Mol. Cell* **2014**, *53*, 290–300. [CrossRef]
144. Yang, L.; Lin, C.; Jin, C.; Yang, J.C.; Tanasa, B.; Li, W.; Merkurjev, D.; Ohgi, K.A.; Meng, D.; Zhang, J.; et al. lncRNA-dependent mechanisms of androgen-receptor-regulated gene activation programs. *Nature* **2013**, *500*, 598–602. [CrossRef] [PubMed]
145. Yang, Y.W.; Flynn, R.A.; Chen, Y.; Qu, K.; Wan, B.; Wang, K.C.; Lei, M.; Chang, H.Y. Essential role of lncRNA binding for WDR5 maintenance of active chromatin and embryonic stem cell pluripotency. *Elife* **2014**, *3*, e02046. [CrossRef] [PubMed]
146. Nagano, T.; Mitchell, J.A.; Sanz, L.A.; Pauler, F.M.; Ferguson-Smith, A.C.; Feil, R.; Fraser, P. The Air noncoding RNA epigenetically silences transcription by targeting G9a to chromatin. *Science* **2008**, *322*, 1717–1720. [CrossRef]
147. Yang, L.; Lin, C.; Liu, W.; Zhang, J.; Ohgi, K.A.; Grinstein, J.D.; Dorrestein, P.C.; Rosenfeld, M.G. ncRNA- and Pc2 methylation-dependent gene relocation between nuclear structures mediates gene activation programs. *Cell* **2011**, *147*, 773–788. [CrossRef] [PubMed]
148. Guttman, M.; Donaghey, J.; Carey, B.W.; Garber, M.; Grenier, J.K.; Munson, G.; Young, G.; Lucas, A.B.; Ach, R.; Bruhn, L.; et al. lincRNAs act in the circuitry controlling pluripotency and differentiation. *Nature* **2011**, *477*, 295–300. [CrossRef]
149. Tsai, M.C.; Manor, O.; Wan, Y.; Mosammaparast, N.; Wang, J.K.; Lan, F.; Shi, Y.; Segal, E.; Chang, H.Y. Long noncoding RNA as modular scaffold of histone modification complexes. *Science* **2010**, *329*, 689–693. [CrossRef]
150. Haller, O.; Staeheli, P.; Kochs, G. Protective role of interferon-induced Mx GTPases against influenza viruses. *Rev. Sci. Tech.* **2009**, *28*, 219–231. [CrossRef]
151. Fan, Y.; Shen, B.; Tan, M.; Mu, X.; Qin, Y.; Zhang, F.; Liu, Y. TGF-beta-induced upregulation of malat1 promotes bladder cancer metastasis by associating with suz12. *Clin. Cancer Res.* **2014**, *20*, 1531–1541. [CrossRef] [PubMed]
152. Hirata, H.; Hinoda, Y.; Shahryari, V.; Deng, G.; Nakajima, K.; Tabatabai, Z.L.; Ishii, N.; Dahiya, R. Long Noncoding RNA MALAT1 Promotes Aggressive Renal Cell Carcinoma through Ezh2 and Interacts with miR-205. *Cancer Res.* **2015**, *75*, 1322–1331. [CrossRef]
153. Cheng, Y.; Imanirad, P.; Jutooru, I.; Hedrick, E.; Jin, U.H.; Rodrigues Hoffman, A.; Leal de Araujo, J.; Morpurgo, B.; Golovko, A.; Safe, S. Role of metastasis-associated lung adenocarcinoma transcript-1 (MALAT-1) in pancreatic cancer. *PLoS ONE* **2018**, *13*, e0192264. [CrossRef] [PubMed]
154. Wang, X.; Sehgal, L.; Jain, N.; Khashab, T.; Mathur, R.; Samaniego, F. LncRNA MALAT1 promotes development of mantle cell lymphoma by associating with EZH2. *J. Transl. Med.* **2016**, *14*, 346. [CrossRef]

155. Chang, P.C.; Fitzgerald, L.D.; Hsia, D.A.; Izumiya, Y.; Wu, C.Y.; Hsieh, W.P.; Lin, S.F.; Campbell, M.; Lam, K.S.; Luciw, P.A.; et al. Histone demethylase JMJD2A regulates Kaposi's sarcoma-associated herpesvirus replication and is targeted by a viral transcriptional factor. *J. Virol.* **2011**, *85*, 3283–3293. [CrossRef]
156. Yang, W.S.; Campbell, M.; Chang, P.C. SUMO modification of a heterochromatin histone demethylase JMJD2A enables viral gene transactivation and viral replication. *PLoS Pathog.* **2017**, *13*, e1006216. [CrossRef]
157. Kobayashi-Ishihara, M.; Yamagishi, M.; Hara, T.; Matsuda, Y.; Takahashi, R.; Miyake, A.; Nakano, K.; Yamochi, T.; Ishida, T.; Watanabe, T. HIV-1-encoded antisense RNA suppresses viral replication for a prolonged period. *Retrovirology* **2012**, *9*, 38. [CrossRef] [PubMed]
158. Zapata, J.C.; Campilongo, F.; Barclay, R.A.; DeMarino, C.; Iglesias-Ussel, M.D.; Kashanchi, F.; Romerio, F. The Human Immunodeficiency Virus 1 ASP RNA promotes viral latency by recruiting the Polycomb Repressor Complex 2 and promoting nucleosome assembly. *Virology* **2017**, *506*, 34–44. [CrossRef] [PubMed]
159. Purushothaman, P.; Dabral, P.; Gupta, N.; Sarkar, R.; Verma, S.C. KSHV Genome Replication and Maintenance. *Front. Microbiol.* **2016**, *7*, 54. [CrossRef]
160. Sun, R.; Lin, S.F.; Gradoville, L.; Miller, G. Polyadenylylated nuclear RNA encoded by Kaposi sarcoma-associated herpesvirus. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 11883–11888. [CrossRef]
161. Borah, S.; Darricarrere, N.; Darnell, A.; Myoung, J.; Steitz, J.A. A viral nuclear noncoding RNA binds re-localized poly(A) binding protein and is required for late KSHV gene expression. *PLoS Pathog.* **2011**, *7*, e1002300. [CrossRef]
162. Rossetto, C.C.; Pari, G.S. Kaposi's sarcoma-associated herpesvirus noncoding polyadenylated nuclear RNA interacts with virus- and host cell-encoded proteins and suppresses expression of genes involved in immune modulation. *J. Virol.* **2011**, *85*, 13290–13297. [CrossRef]
163. Song, M.J.; Brown, H.J.; Wu, T.T.; Sun, R. Transcription activation of polyadenylated nuclear rna by rta in human herpesvirus 8/Kaposi's sarcoma-associated herpesvirus. *J. Virol.* **2001**, *75*, 3129–3140. [CrossRef] [PubMed]
164. Campbell, M.; Kim, K.Y.; Chang, P.C.; Huerta, S.; Shevchenko, B.; Wang, D.H.; Izumiya, C.; Kung, H.J.; Izumiya, Y. A lytic viral long noncoding RNA modulates the function of a latent protein. *J. Virol.* **2014**, *88*, 1843–1848. [CrossRef]
165. Kumar, A.; Lyu, Y.; Yanagihashi, Y.; Chantarasrivong, C.; Majerciak, V.; Salemi, M.; Wang, K.H.; Inagaki, T.; Chuang, F.; Davis, R.R.; et al. KSHV episome tethering sites on host chromosomes and regulation of latency-lytic switch by CHD4. *Cell Rep.* **2022**, *39*, 110788. [CrossRef]
166. Hiura, K.; Strahan, R.; Uppal, T.; Prince, B.; Rossetto, C.C.; Verma, S.C. KSHV ORF59 and PAN RNA Recruit Histone Demethylases to the Viral Chromatin during Lytic Reactivation. *Viruses* **2020**, *12*, 420. [CrossRef]
167. Agarwal, S.; Vierbuchen, T.; Ghosh, S.; Chan, J.; Jiang, Z.; Kandasamy, R.K.; Ricci, E.; Fitzgerald, K.A. The long non-coding RNA LUCAT1 is a negative feedback regulator of interferon responses in humans. *Nat. Commun.* **2020**, *11*, 6348. [CrossRef]
168. Aznaourova, M.; Schmerer, N.; Janga, H.; Zhang, Z.; Pauck, K.; Bushe, J.; Volkers, S.M.; Wendisch, D.; Georg, P.; Ntini, E.; et al. Single-cell RNA sequencing uncovers the nuclear decoy lincRNA PIRAT as a regulator of systemic monocyte immunity during COVID-19. *Proc. Natl. Acad. Sci. USA* **2022**, *119*, e2120680119. [CrossRef]
169. Ma, G.; Yasunaga, J.I.; Shimura, K.; Takemoto, K.; Watanabe, M.; Amano, M.; Nakata, H.; Liu, B.; Zuo, X.; Matsuoka, M. Human retroviral antisense mRNAs are retained in the nuclei of infected cells for viral persistence. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2014783118. [CrossRef] [PubMed]
170. Johnsson, P.; Ackley, A.; Vidarsdottir, L.; Lui, W.O.; Corcoran, M.; Grander, D.; Morris, K.V. A pseudogene long-noncoding-RNA network regulates PTEN transcription and translation in human cells. *Nat. Struct. Mol. Biol.* **2013**, *20*, 440–446. [CrossRef] [PubMed]
171. Halley, P.; Kadakkuzha, B.M.; Faghihi, M.A.; Magistri, M.; Zeier, Z.; Khorkova, O.; Coito, C.; Hsiao, J.; Lawrence, M.; Wahlestedt, C. Regulation of the apolipoprotein gene cluster by a long noncoding RNA. *Cell Rep.* **2014**, *6*, 222–230. [CrossRef]
172. Klase, Z.; Yedavalli, V.S.; Houzet, L.; Perkins, M.; Maldarelli, F.; Brenchley, J.; Strebel, K.; Liu, P.; Jeang, K.T. Activation of HIV-1 from latent infection via synergy of RUNX1 inhibitor Ro5-3335 and SAHA. *PLoS Pathog.* **2014**, *10*, e1003997. [CrossRef] [PubMed]
173. Zhang, J.; Thakuri, B.K.C.; Zhao, J.; Nguyen, L.N.; Nguyen, L.N.T.; Khanal, S.; Cao, D.; Dang, X.; Schank, M.; Lu, Z.; et al. Long Noncoding RNA RUNXOR Promotes Myeloid-Derived Suppressor Cell Expansion and Functions via Enhancing Immunosuppressive Molecule Expressions during Latent HIV Infection. *J. Immunol.* **2021**, *206*, 2052–2060. [CrossRef] [PubMed]
174. Barriocanal, M.; Carnero, E.; Segura, V.; Fortes, P. Long Non-Coding RNA BST2/BISPR is Induced by IFN and Regulates the Expression of the Antiviral Factor Tetherin. *Front. Immunol.* **2014**, *5*, 655. [CrossRef]
175. Kambara, H.; Gunawardane, L.; Zebrowski, E.; Kostadinova, L.; Jobava, R.; Krokowski, D.; Hatzoglou, M.; Anthony, D.D.; Valadkhan, S. Regulation of Interferon-Stimulated Gene BST2 by a lncRNA Transcribed from a Shared Bidirectional Promoter. *Front. Immunol.* **2014**, *5*, 676. [CrossRef] [PubMed]
176. Vigneau, S.; Rohrlich, P.S.; Brahic, M.; Bureau, J.F. Tmevpg1, a candidate gene for the control of Theiler's virus persistence, could be implicated in the regulation of gamma interferon. *J. Virol.* **2003**, *77*, 5632–5638. [CrossRef]
177. Collier, S.P.; Collins, P.L.; Williams, C.L.; Boothby, M.R.; Aune, T.M. Cutting edge: Influence of Tmevpg1, a long intergenic noncoding RNA, on the expression of Ifng by Th1 cells. *J. Immunol.* **2012**, *189*, 2084–2088. [CrossRef]
178. Collier, S.P.; Henderson, M.A.; Tossberg, J.T.; Aune, T.M. Regulation of the Th1 genomic locus from Ifng through Tmevpg1 by T-bet. *J. Immunol.* **2014**, *193*, 3959–3965. [CrossRef]

179. Gomez, J.A.; Wapinski, O.L.; Yang, Y.W.; Bureau, J.F.; Gopinath, S.; Monack, D.M.; Chang, H.Y.; Brahic, M.; Kirkegaard, K. The NeST long ncRNA controls microbial susceptibility and epigenetic activation of the interferon-gamma locus. *Cell* **2013**, *152*, 743–754. [CrossRef]
180. Petermann, F.; Pekowska, A.; Johnson, C.A.; Jankovic, D.; Shih, H.Y.; Jiang, K.; Hudson, W.H.; Brooks, S.R.; Sun, H.W.; Villarino, A.V.; et al. The Magnitude of IFN-gamma Responses Is Fine-Tuned by DNA Architecture and the Non-coding Transcript of Ifng-as1. *Mol. Cell* **2019**, *75*, 1229–1242 e1225. [CrossRef]
181. Stein, N.; Berhani, O.; Schmiedel, D.; Duev-Cohen, A.; Seidel, E.; Kol, I.; Tsukerman, P.; Hecht, M.; Reches, A.; Gamliel, M.; et al. IFNG-AS1 Enhances Interferon Gamma Production in Human Natural Killer Cells. *iScience* **2019**, *11*, 466–473. [CrossRef]
182. Goris, A.; Heggarty, S.; Marrosu, M.G.; Graham, C.; Billiau, A.; Vandenbroeck, K. Linkage disequilibrium analysis of chromosome 12q14-15 in multiple sclerosis: Delineation of a 118-kb interval around interferon-gamma (IFNG) that is involved in male versus female differential susceptibility. *Genes. Immun.* **2002**, *3*, 470–476. [CrossRef]
183. Latiano, A.; Palmieri, O.; Latiano, T.; Corritore, G.; Bossa, F.; Martino, G.; Biscaglia, G.; Scimeca, D.; Valvano, M.R.; Pastore, M.; et al. Investigation of multiple susceptibility loci for inflammatory bowel disease in an Italian cohort of patients. *PLoS ONE* **2011**, *6*, e22688. [CrossRef]
184. Silverberg, M.S.; Cho, J.H.; Rioux, J.D.; McGovern, D.P.; Wu, J.; Annese, V.; Achkar, J.P.; Goyette, P.; Scott, R.; Xu, W.; et al. Ulcerative colitis-risk loci on chromosomes 1p36 and 12q15 found by genome-wide association study. *Nat. Genet.* **2009**, *41*, 216–220. [CrossRef]
185. Xu-Yang, Z.; Pei-Yu, B.; Chuan-Tao, Y.; Wei, Y.; Hong-Wei, M.; Kang, T.; Chun-Mei, Z.; Ying-Feng, L.; Xin, W.; Ping-Zhong, W.; et al. Interferon-Induced Transmembrane Protein 3 Inhibits Hantaan Virus Infection, and Its Single Nucleotide Polymorphism rs12252 Influences the Severity of Hemorrhagic Fever with Renal Syndrome. *Front. Immunol.* **2016**, *7*, 535. [CrossRef] [PubMed]
186. Mariotti, B.; Servaas, N.H.; Rossato, M.; Tamassia, N.; Cassatella, M.A.; Cossu, M.; Beretta, L.; van der Kroef, M.; Radstake, T.; Bazzoni, F. The Long Non-coding RNA NRIR Drives IFN-Response in Monocytes: Implication for Systemic Sclerosis. *Front. Immunol.* **2019**, *10*, 100. [CrossRef] [PubMed]
187. Imamura, K.; Imamachi, N.; Akizuki, G.; Kumakura, M.; Kawaguchi, A.; Nagata, K.; Kato, A.; Kawaguchi, Y.; Sato, H.; Yoneda, M.; et al. Long noncoding RNA NEAT1-dependent SFPQ relocation from promoter region to paraspeckle mediates IL8 expression upon immune stimuli. *Mol. Cell* **2014**, *53*, 393–406. [CrossRef] [PubMed]
188. Matthys, V.S.; Cimica, V.; Dalrymple, N.A.; Glennon, N.B.; Bianco, C.; Mackow, E.R. Hantavirus GnT elements mediate TRAF3 binding and inhibit RIG-I/TBK1-directed beta interferon transcription by blocking IRF3 phosphorylation. *J. Virol.* **2014**, *88*, 2246–2259. [CrossRef] [PubMed]
189. Oshiumi, H.; Miyashita, M.; Okamoto, M.; Morioka, Y.; Okabe, M.; Matsumoto, M.; Seya, T. DDX60 Is Involved in RIG-I-Dependent and Independent Antiviral Responses, and Its Function Is Attenuated by Virus-Induced EGFR Activation. *Cell Rep.* **2015**, *11*, 1193–1207. [CrossRef] [PubMed]
190. Boliar, S.; Gludish, D.W.; Jambo, K.C.; Kamng'ona, R.; Mvaya, L.; Mwandumba, H.C.; Russell, D.G. Inhibition of the lncRNA SAF drives activation of apoptotic effector caspases in HIV-1-infected human macrophages. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 7431–7438. [CrossRef]
191. Young, L.S.; Rickinson, A.B. Epstein-Barr virus: 40 years on. *Nat. Rev. Cancer* **2004**, *4*, 757–768. [CrossRef] [PubMed]
192. Zuo, L.; Yue, W.; Du, S.; Xin, S.; Zhang, J.; Liu, L.; Li, G.; Lu, J. An update: Epstein-Barr virus and immune evasion via microRNA regulation. *Virol. Sin.* **2017**, *32*, 175–187. [CrossRef]
193. Qiu, J.; Smith, P.; Leahy, L.; Thorley-Lawson, D.A. The Epstein-Barr virus encoded BART miRNAs potentiate tumor growth in vivo. *PLoS Pathog.* **2015**, *11*, e1004561. [CrossRef]
194. Chen, H.L.; Lung, M.M.; Sham, J.S.; Choy, D.T.; Griffin, B.E.; Ng, M.H. Transcription of BamHI-A region of the EBV genome in NPC tissues and B cells. *Virology* **1992**, *191*, 193–201. [CrossRef] [PubMed]
195. Smith, P.R.; de Jesus, O.; Turner, D.; Hollyoake, M.; Karstegl, C.E.; Griffin, B.E.; Karran, L.; Wang, Y.; Hayward, S.D.; Farrell, P.J. Structure and coding content of CST (BART) family RNAs of Epstein-Barr virus. *J. Virol.* **2000**, *74*, 3082–3092. [CrossRef] [PubMed]
196. Verhoeven, R.J.; Tong, S.; Zhang, G.; Zong, J.; Chen, Y.; Jin, D.Y.; Chen, M.R.; Pan, J.; Chen, H. NF-kappaB Signaling Regulates Expression of Epstein-Barr Virus BART MicroRNAs and Long Noncoding RNAs in Nasopharyngeal Carcinoma. *J. Virol.* **2016**, *90*, 6475–6488. [CrossRef]
197. Kang, G.H.; Lee, S.; Kim, W.H.; Lee, H.W.; Kim, J.C.; Rhyu, M.G.; Ro, J.Y. Epstein-barr virus-positive gastric carcinoma demonstrates frequent aberrant methylation of multiple genes and constitutes CpG island methylator phenotype-positive gastric carcinoma. *Am. J. Pathol.* **2002**, *160*, 787–794. [CrossRef]
198. Zhang, J.; Li, X.; Hu, J.; Cao, P.; Yan, Q.; Zhang, S.; Dang, W.; Lu, J. Long noncoding RNAs involvement in Epstein-Barr virus infection and tumorigenesis. *Virol. J.* **2020**, *17*, 51. [CrossRef]
199. Tai-Schmiedel, J.; Karniely, S.; Lau, B.; Ezra, A.; Eliyahu, E.; Nachshon, A.; Kerr, K.; Suarez, N.; Schwartz, M.; Davison, A.J.; et al. Human cytomegalovirus long noncoding RNA4.9 regulates viral DNA replication. *PLoS Pathog.* **2020**, *16*, e1008390. [CrossRef]
200. Lee, S.; Kim, H.; Hong, A.; Song, J.; Lee, S.; Kim, M.; Hwang, S.Y.; Jeong, D.; Kim, J.; Son, A.; et al. Functional and molecular dissection of HCMV long non-coding RNAs. *Sci. Rep.* **2022**, *12*, 19303. [CrossRef]
201. Murphy, J.C.; Fischle, W.; Verdin, E.; Sinclair, J.H. Control of cytomegalovirus lytic gene expression by histone acetylation. *EMBO J.* **2002**, *21*, 1112–1120. [CrossRef] [PubMed]

202. Reeves, M.B.; Lehner, P.J.; Sissons, J.G.P.; Sinclair, J.H. An in vitro model for the regulation of human cytomegalovirus latency and reactivation in dendritic cells by chromatin remodelling. *J. Gen. Virol.* **2005**, *86*, 2949–2954. [CrossRef] [PubMed]
203. Reeves, M.B.; MacAry, P.A.; Lehner, P.J.; Sissons, J.G.; Sinclair, J.H. Latency, chromatin remodeling, and reactivation of human cytomegalovirus in the dendritic cells of healthy carriers. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 4140–4145. [CrossRef]
204. Sinclair, J.; Sissons, P. Latency and reactivation of human cytomegalovirus. *J. Gen. Virol.* **2006**, *87*, 1763–1779. [CrossRef] [PubMed]
205. Huang, Y.; Guo, X.; Zhang, J.; Li, J.; Xu, M.; Wang, Q.; Liu, Z.; Ma, Y.; Qi, Y.; Ruan, Q. Human cytomegalovirus RNA2.7 inhibits RNA polymerase II (Pol II) Serine-2 phosphorylation by reducing the interaction between Pol II and phosphorylated cyclin-dependent kinase 9 (pCDK9). *Virol. Sin.* **2022**, *37*, 358–369. [CrossRef] [PubMed]
206. Reeves, M.B.; Davies, A.A.; McSharry, B.P.; Wilkinson, G.W.; Sinclair, J.H. Complex I binding by a virally encoded RNA regulates mitochondria-induced cell death. *Science* **2007**, *316*, 1345–1348. [CrossRef] [PubMed]
207. Perera, M.R.; Sinclair, J.H. The Human Cytomegalovirus beta2.7 Long Non-Coding RNA Prevents Induction of Reactive Oxygen Species to Maintain Viral Gene Silencing during Latency. *Int. J. Mol. Sci.* **2022**, *23*, 11017. [CrossRef]
208. Lau, B.; Kerr, K.; Camiolo, S.; Nightingale, K.; Gu, Q.; Antrobus, R.; Suarez, N.M.; Loney, C.; Stanton, R.J.; Weekes, M.P.; et al. Human Cytomegalovirus RNA2.7 Is Required for Upregulating Multiple Cellular Genes To Promote Cell Motility and Viral Spread Late in Lytic Infection. *J. Virol.* **2021**, *95*, e0069821. [CrossRef]
209. Lau, B.; Kerr, K.; Gu, Q.; Nightingale, K.; Antrobus, R.; Suarez, N.M.; Stanton, R.J.; Wang, E.C.Y.; Weekes, M.P.; Davison, A.J. Human Cytomegalovirus Long Non-coding RNA1.2 Suppresses Extracellular Release of the Pro-inflammatory Cytokine IL-6 by Blocking NF-kappaB Activation. *Front. Cell Infect. Microbiol.* **2020**, *10*, 361. [CrossRef]
210. Amelio, A.L.; Giordani, N.V.; Kubat, N.J.; O'Neil J, E.; Bloom, D.C. Deacetylation of the herpes simplex virus type 1 latency-associated transcript (LAT) enhancer and a decrease in LAT abundance precede an increase in ICP0 transcriptional permissiveness at early times postexplant. *J. Virol.* **2006**, *80*, 2063–2068. [CrossRef] [PubMed]
211. Cliffe, A.R.; Coen, D.M.; Knipe, D.M. Kinetics of facultative heterochromatin and polycomb group protein association with the herpes simplex viral genome during establishment of latent infection. *mBio* **2013**, *4*, e00590-12. [CrossRef]
212. Cliffe, A.R.; Garber, D.A.; Knipe, D.M. Transcription of the herpes simplex virus latency-associated transcript promotes the formation of facultative heterochromatin on lytic promoters. *J. Virol.* **2009**, *83*, 8182–8190. [CrossRef]
213. Kwiatkowski, D.L.; Thompson, H.W.; Bloom, D.C. The polycomb group protein Bmi1 binds to the herpes simplex virus 1 latent genome and maintains repressive histone marks during latency. *J. Virol.* **2009**, *83*, 8173–8181. [CrossRef] [PubMed]
214. Wang, Q.Y.; Zhou, C.; Johnson, K.E.; Colgrove, R.C.; Coen, D.M.; Knipe, D.M. Herpesviral latency-associated transcript gene promotes assembly of heterochromatin on viral lytic-gene promoters in latent infection. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 16055–16059. [CrossRef]
215. Hancock, M.H.; Skalsky, R.L. Roles of Non-coding RNAs During Herpesvirus Infection. *Curr. Top. Microbiol. Immunol.* **2018**, *419*, 243–280. [CrossRef] [PubMed]
216. Zhang, Y.; Zeng, L.S.; Wang, J.; Cai, W.Q.; Cui, W.; Song, T.J.; Peng, X.C.; Ma, Z.; Xiang, Y.; Cui, S.Z.; et al. Multifunctional Non-Coding RNAs Mediate Latent Infection and Recurrence of Herpes Simplex Viruses. *Infect. Drug. Resist.* **2021**, *14*, 5335–5349. [CrossRef] [PubMed]
217. Arun, G.; Diermeier, S.D.; Spector, D.L. Therapeutic Targeting of Long Non-Coding RNAs in Cancer. *Trends Mol. Med.* **2018**, *24*, 257–277. [CrossRef]
218. Lennox, K.A.; Behlke, M.A. Cellular localization of long non-coding RNAs affects silencing by RNAi more than by antisense oligonucleotides. *Nucleic Acids Res.* **2016**, *44*, 863–877. [CrossRef] [PubMed]
219. Gagnon, K.T.; Corey, D.R. Guidelines for Experiments Using Antisense Oligonucleotides and Double-Stranded RNAs. *Nucleic Acid. Ther.* **2019**, *29*, 116–122. [CrossRef] [PubMed]
220. Abudayyeh, O.O.; Gootenberg, J.S.; Essletzbichler, P.; Han, S.; Joung, J.; Belanto, J.J.; Verdine, V.; Cox, D.B.T.; Kellner, M.J.; Regev, A.; et al. RNA targeting with CRISPR-Cas13. *Nature* **2017**, *550*, 280–284. [CrossRef] [PubMed]
221. Cox, D.B.T.; Gootenberg, J.S.; Abudayyeh, O.O.; Franklin, B.; Kellner, M.J.; Joung, J.; Zhang, F. RNA editing with CRISPR-Cas13. *Science* **2017**, *358*, 1019–1027. [CrossRef] [PubMed]
222. Konermann, S.; Lotfy, P.; Brideau, N.J.; Oki, J.; Shokhirev, M.N.; Hsu, P.D. Transcriptome Engineering with RNA-Targeting Type VI-D CRISPR Effectors. *Cell* **2018**, *173*, 665–676 e614. [CrossRef]
223. Smargon, A.A.; Cox, D.B.T.; Pyzocha, N.K.; Zheng, K.; Slaymaker, I.M.; Gootenberg, J.S.; Abudayyeh, O.A.; Essletzbichler, P.; Shmakov, S.; Makarova, K.S.; et al. Cas13b Is a Type VI-B CRISPR-Associated RNA-Guided RNase Differentially Regulated by Accessory Proteins Csx27 and Csx28. *Mol. Cell* **2017**, *65*, 618–630 e617. [CrossRef]
224. Xiang, J.F.; Yin, Q.F.; Chen, T.; Zhang, Y.; Zhang, X.O.; Wu, Z.; Zhang, S.; Wang, H.B.; Ge, J.; Lu, X.; et al. Human colorectal cancer-specific CCAT1-L lncRNA regulates long-range chromatin interactions at the MYC locus. *Cell Res.* **2014**, *24*, 513–531. [CrossRef] [PubMed]
225. Bester, A.C.; Lee, J.D.; Chavez, A.; Lee, Y.R.; Nachmani, D.; Vora, S.; Victor, J.; Sauvageau, M.; Monteleone, E.; Rinn, J.L.; et al. An Integrated Genome-wide CRISPRa Approach to Functionalize lncRNAs in Drug Resistance. *Cell* **2018**, *173*, 649–664 e620. [CrossRef]
226. Shechner, D.M.; Hacisuleyman, E.; Younger, S.T.; Rinn, J.L. Multiplexable, locus-specific targeting of long RNAs with CRISPR-Display. *Nat. Methods* **2015**, *12*, 664–670. [CrossRef] [PubMed]

227. Wang, J.; Zhang, Y.; Li, Q.; Zhao, J.; Yi, D.; Ding, J.; Zhao, F.; Hu, S.; Zhou, J.; Deng, T.; et al. Influenza Virus Exploits an Interferon-Independent lncRNA to Preserve Viral RNA Synthesis through Stabilizing Viral RNA Polymerase PB1. *Cell Rep.* **2019**, *27*, 3295–3304 e3294. [CrossRef] [PubMed]
228. Buske, F.A.; Bauer, D.C.; Mattick, J.S.; Bailey, T.L. Triplexator: Detecting nucleic acid triple helices in genomic and transcriptomic data. *Genome Res.* **2012**, *22*, 1372–1381. [CrossRef]
229. Buske, F.A.; Bauer, D.C.; Mattick, J.S.; Bailey, T.L. Triplex-Inspector: An analysis tool for triplex-mediated targeting of genomic loci. *Bioinformatics* **2013**, *29*, 1895–1897. [CrossRef]
230. Kuo, C.C.; Hanzelmann, S.; Senturk Cetin, N.; Frank, S.; Zajzon, B.; Derks, J.P.; Akhade, V.S.; Ahuja, G.; Kanduri, C.; Grummt, I.; et al. Detection of RNA-DNA binding sites in long noncoding RNAs. *Nucleic Acids Res.* **2019**, *47*, e32. [CrossRef] [PubMed]
231. He, S.; Zhang, H.; Liu, H.; Zhu, H. LongTarget: A tool to predict lncRNA DNA-binding motifs and binding sites via Hoogsteen base-pairing analysis. *Bioinformatics* **2015**, *31*, 178–186. [CrossRef]
232. Hon, J.; Martinek, T.; Rajdl, K.; Lexa, M. Triplex: An R/Bioconductor package for identification and visualization of potential intramolecular triplex patterns in DNA sequences. *Bioinformatics* **2013**, *29*, 1900–1901. [CrossRef] [PubMed]
233. Lexa, M.; Martinek, T.; Burgetova, I.; Kopecek, D.; Brazdova, M. A dynamic programming algorithm for identification of triplex-forming sequences. *Bioinformatics* **2011**, *27*, 2510–2517. [CrossRef]
234. Soibam, B. Super-lncRNAs: Identification of lncRNAs that target super-enhancers via RNA:DNA:DNA triplex formation. *RNA* **2017**, *23*, 1729–1742. [CrossRef]
235. Schmitt, A.M.; Chang, H.Y. Long Noncoding RNAs in Cancer Pathways. *Cancer Cell* **2016**, *29*, 452–463. [CrossRef] [PubMed]
236. Lee, G.L.; Dobi, A.; Srivastava, S. Prostate cancer: Diagnostic performance of the PCA3 urine test. *Nature reviews. Urology* **2011**, *8*, 123–124. [CrossRef]
237. Hanna, N.; Ohana, P.; Konikoff, F.M.; Leichtmann, G.; Hubert, A.; Appelbaum, L.; Kopelman, Y.; Czerniak, A.; Hochberg, A. Phase 1/2a, dose-escalation, safety, pharmacokinetic and preliminary efficacy study of intratumoral administration of BC-819 in patients with unresectable pancreatic cancer. *Cancer gene therapy* **2012**, *19*, 374–381. [CrossRef]
238. Connelly, C.M.; Moon, M.H.; Schneekloth, J.S., Jr. The Emerging Role of RNA as a Therapeutic Target for Small Molecules. *Cell Chem. Biol.* **2016**, *23*, 1077–1090. [CrossRef] [PubMed]
239. Ahmad, A.; Lin, H.; Shatabda, S. Locate-R: Subcellular localization of long non-coding RNAs using nucleotide compositions. *Genomics* **2020**, *112*, 2583–2589. [CrossRef]
240. Gudenas, B.L.; Wang, L. Prediction of LncRNA Subcellular Localization with Deep Learning from Sequence Features. *Sci. Rep.* **2018**, *8*, 16385. [CrossRef] [PubMed]
241. Li, M.; Zhao, B.; Yin, R.; Lu, C.; Guo, F.; Zeng, M. GraphLncLoc: Long non-coding RNA subcellular localization prediction using graph convolutional networks based on sequence to graph transformation. *Brief. Bioinform.* **2022**, *24*, bbac565. [CrossRef]
242. Zeng, M.; Wu, Y.; Lu, C.; Zhang, F.; Wu, F.X.; Li, M. DeepLncLoc: A deep learning framework for long non-coding RNA subcellular localization prediction based on subsequence embedding. *Brief. Bioinform.* **2022**, *23*, bbab360. [CrossRef] [PubMed]
243. He, Y.; Han, B.; Ding, Y.; Zhang, H.; Chang, S.; Zhang, L.; Zhao, C.; Yang, N.; Song, J. Linc-GALMD1 Regulates Viral Gene Expression in the Chicken. *Front. Genet.* **2019**, *10*, 1122. [CrossRef] [PubMed]
244. Munschauer, M.; Nguyen, C.T.; Sirokman, K.; Hartigan, C.R.; Hogstrom, L.; Engreitz, J.M.; Ulirsch, J.C.; Fulco, C.P.; Subramanian, V.; Chen, J.; et al. The NORAD lncRNA assembles a topoisomerase complex critical for genome stability. *Nature* **2018**, *561*, 132–136. [CrossRef] [PubMed]
245. Shen, Y.; Liu, S.; Fan, J.; Jin, Y.; Tian, B.; Zheng, X.; Fu, H. Nuclear retention of the lncRNA SNHG1 by doxorubicin attenuates hnRNPC-p53 protein interactions. *EMBO Rep.* **2017**, *18*, 536–548. [CrossRef]
246. Carrieri, C.; Cimatti, L.; Biagioli, M.; Beugnet, A.; Zucchelli, S.; Fedele, S.; Pesce, E.; Ferrer, I.; Collavin, L.; Santoro, C.; et al. Long non-coding antisense RNA controls Uchl1 translation through an embedded SINEB2 repeat. *Nature* **2012**, *491*, 454–457. [CrossRef]
247. Cai, R.; Sun, Y.; Qimuge, N.; Wang, G.; Wang, Y.; Chu, G.; Yu, T.; Yang, G.; Pang, W. Adiponectin AS lncRNA inhibits adipogenesis by transferring from nucleus to cytoplasm and attenuating Adiponectin mRNA translation. *Biochim. Biophys. Acta Mol. Cell Biol. Lipids* **2018**, *1863*, 420–432. [CrossRef]
248. Zhang, L.; Zheng, X.; Li, J.; Wang, G.; Hu, Z.; Chen, Y.; Wang, X.; Gu, M.; Gao, R.; Hu, S.; et al. Long noncoding RNA#45 exerts broad inhibitory effect on influenza a virus replication via its stem ring arms. *Virulence* **2021**, *12*, 2443–2460. [CrossRef]
249. Guo, C.J.; Ma, X.K.; Xing, Y.H.; Zheng, C.C.; Xu, Y.F.; Shan, L.; Zhang, J.; Wang, S.; Wang, Y.; Carmichael, G.G.; et al. Distinct Processing of lncRNAs Contributes to Non-conserved Functions in Stem Cells. *Cell* **2020**, *181*, 621–636.e622. [CrossRef]
250. Hezroni, H.; Koppstein, D.; Schwartz, M.G.; Avrutin, A.; Bartel, D.P.; Ulitsky, I. Principles of long noncoding RNA evolution derived from direct comparison of transcriptomes in 17 species. *Cell Rep.* **2015**, *11*, 1110–1122. [CrossRef]
251. Quinn, J.J.; Zhang, Q.C.; Georgiev, P.; Ilik, I.A.; Akhtar, A.; Chang, H.Y. Rapid evolutionary turnover underlies conserved lncRNA-genome interactions. *Genes. Dev.* **2016**, *30*, 191–207. [CrossRef] [PubMed]
252. Burnett, J.C.; Rossi, J.J. RNA-based therapeutics: Current progress and future prospects. *Chem. Biol.* **2012**, *19*, 60–71. [CrossRef]