

Review Article

Long noncoding RNAs (lncRNAs) in HIV-mediated carcinogenesis: Role in cell homeostasis, cell survival processes and drug resistance

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ABSTRACT

There is accruing data implicating long non-coding RNAs (lncRNAs) in the development and progression of non-communicable diseases such as cancer. These lncRNAs have been implicated in many diverse HIV-host interactions, some of which are beneficial to HIV propagation. The virus-host interactions induce the expression of HIV-regulated long non-coding RNAs, which are implicated in the carcinogenesis process, therefore, it is critical to understand the molecular mechanisms that underpin these HIV-regulated lncRNAs, especially in cancer formation. Herein, we summarize the role of HIV-regulated lncRNAs targeting cancer development-related processes including apoptosis, cell cycle, cell survival signalling, angiogenesis and drug resistance. It is unclear how lncRNAs regulate cancer development, this review also discuss recent discoveries regarding the functions of lncRNAs in cancer biology. Innovative research in this field will be beneficial for the future development of therapeutic strategies targeting long non-coding RNAs that are regulated by HIV, especially in HIV associated cancers.

1. Introduction

Human immunodeficiency virus-1 (HIV-1) infection is a crucial etiological factor for various non-communicable diseases, which include HIV-associated nephropathies [1,2], cardiomyopathies [3] and cancer [4]. HIV-1 contributes to cancer development directly through oncogenic effects of HIV proteins, such as *Trans*-activator of transcription (Tat) and indirectly through immunosuppression and promoting coinfections by other oncogenic viruses [5–8]. HIV was discovered in 1983 as the aetiological cause of acquired immunodeficiency syndrome (AIDS), which is a global pandemic that continues to devastate many communities, worldwide [9]. As of 2017, there were 36.9 million people living with HIV, globally [10] with the majority of these infections occurring in the resource-limited countries, especially those in the sub-Saharan Africa [11]. HIV is classified under retroviruses, a subgroup of lentiviruses [12]. This subgroup of viruses targets white blood cells expressing the cluster of differentiation 4 (CD4⁺) [12]. White blood cells targeted by this virus include T cells, macrophages and dendritic cells [12]. HIV attaches and invades these cells using its glycoproteins, gp120 and gp41, which promote viral entry by fusing with the host co-receptors; namely the C–C chemokine receptor type 5 (CCR5) and

C–X–C chemokine receptor type 4 (CXCR4) [13]. Accumulation of this infectious virus decreases CD4⁺ T cells, resulting in a weakened immune system, which becomes unable to combat the effects of opportunistic pathogens, thus, ultimately leading to the development of full-blown AIDS [12].

The HIV is composed of two forms; type 1 and type 2, with both virus types targeting the same cells, exhibiting similar morphology, tropism, and modes of transmission; however, they differ genetically and antigenically, with HIV type 2 being less pathogenic than HIV type 1 [14]. HIV-1 virus is responsible for the ongoing HIV/AIDS pandemic as it accounts for over 95% of HIV infections, worldwide [15]. HIV-1 virus is categorised into four groups; namely, O (Outlier), M (Major), N (non-M, non-O), and lastly, P group, which was the last group to be discovered [16]. Group M viruses have dominated the global HIV pandemic since its outbreak in 1981 [16]; and the other 3 groups are relatively rare and occur only in certain geographical areas, including Cameroon and Europe [17–19]. HIV-2 virus is reported to be less infectious than HIV-1 and remains generally limited to the Western parts of Africa, but other cases have been reported in Europe [20], the United States of America, as well as in India [21]. HIV type 2 is comprised of nine groups (A–I), HIV-2 subtype data is inadequate and only few recombinants have been

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studied [22]. Although antiretroviral therapy has prolonged the survival of HIV-affected people, an increasing number of HIV-infected people are at a risk of developing cancer, especially Kaposi’s sarcoma, invasive cervical cancer and B-cell lymphomas [23].

Cancer, an umbrella term for malignancies with deregulated cell proliferation, resistance to apoptosis, and enhanced survival signals, has been reported as the second cause of death after cardiovascular diseases [24]. There is a steady increase in cancer-related mortalities and soaring incidence rates despite the current therapeutic advances, and thus, cancer continues to be a global menace [25]. There are over 200 different types of cancers, with unique characteristics and challenges for their treatment [24]. Dalton et al. [26] indicated that 70% of deaths from cancer in 2018 occurred in developing countries, including, but not limited to, South Africa, Zimbabwe and Nigeria. These high incidence

rates can be attributed to gaps in current diagnostic and therapeutic strategies, which include chemotherapy, radiation and surgery. The new challenge is the rise of HIV-related cancers, worldwide, especially in Sub-Saharan Africa (SSA). Oncoviral infections are credited as aetiological factors for the development of 12% of human cancers, worldwide, with 80% of cases occurring in developing countries, including SSA [27,28]. Infectious agents such as HIV-1 in certain SSA countries drive the rates of these cancers [29,30]. These oncoviruses can integrate their genomes directly into the host genome or first undergo reverse transcription to DNA (RNA virus) before integration into the host genome [31]. Oncoviruses have developed several strategies to drive virus-induced oncogenesis, and these strategies include inactivation of host tumour suppressors by viral proteins [32], and alteration of host gene expression due to the integration of viral genome into the host

Table 1
Long noncoding RNAs deregulated in AIDS-defining cancers.

Long noncoding RNAs	Classification based on genomic location	Classification based on mode of action	^a Differential expression	Cancer type	Neighboring coding genes	Subcellular localization	Mechanism/s	Reference
NRON	Antisense lincRNA	Scaffold	Down	T cell leukemia	MVB12B	Cytoplasm	Modulate HIV replication by blocking NFAT transcriptional regulator which regulate HIV gene expression	[45]
NEAT1	LincRNA	Guide	Up	T cell leukemia	FRMD8 and MIR612	Nucleus	Maintain the integrity of the nuclear paraspeckle to promote HIV replication; enhances cytokine production	[46]
ANRIL	Antisense lincRNA	Scaffold	Down	Kaposi sarcoma	CDKN2A and CDKN2B	Nucleus	Epigenetic silencing of INK4B tumor suppresser	[47,48]
MEG3	LincRNA	Signal, Scaffold, Guide and Decoy	Up	Kaposi sarcoma and Liver cancer	DLK1, RTL1, and DIO3	Cytoplasm	Increases the transcription of p53	[49–51]
HOTAIR	Antisense lincRNA	Scaffold	Up	Breast cancer, Lung cancer, Prostate cancer and Ovarian cancer	HOXD	Cytoplasm	Gene silencing by demethylation of H3K4 me3	[44,51, 52]
MALAT1	LincRNA	Signal	Up	Cervical carcinoma	LTBP3	Nucleus	Increase HIV-1 transcription; promote cell migration and proliferation.	[53,54]
H19	LincRNA	Decoy	Up	Cervical carcinoma	IGF2	Cytoplasm	Promote cell proliferation	[55,56]
GASS	LincRNA	Decoy	Down	Breast cancer, Gastric cancer, Lung cancer and Prostate cancer	E2F4 FGF1	Nucleus	Inhibits HIV-1 replication; regulate cell proliferation, apoptosis and invasion	[57,58]
uc002yug.2	LincRNA	Scaffold and Guide	Up	Oesophageal squamous cell carcinoma	RUNX1	Nucleus	Support carcinogenesis by promoting alternative splicing of RUNX1; Increase HIV-1 replication	[59]
Fas-AS1	antisense lincRNA	Decoy	Up	Acute T-cell leukemia, Uterine carcinoma and Histocytic Lymphoma	Fas	Nucleus	Inhibits Fas-mediated programmed cell death	[60]
NFAT	LincRNA	Signal	Up	B cell lymphoma, Glioblastoma, Pancreatic cancer, Colon cancer and Ovarian cancer	Interleukin (IL) 2 and Cyclin E	Cytoplasm	Promote HIV-1 infection	[61–63]
LincRNA-p21	LincRNA	Decoy	Down	Hepatocellular carcinoma, Prostate cancer and Breast cancer	p21	Cytoplasm	Regulate cell cycle and proliferation	[64,65]
lncARSR	LincRNA	Decoy	Up	Renal cancer, Hepatocellular carcinoma and Ovarian cancer	SOX4	Cytoplasm	Promote cell proliferation, migration and invasion	[66]
DLEU1	Antisense lincRNA	Decoy	UP	Cervical cancer, Colorectal cancer, Gastric cancer and Ovarian cancer	KPNA3	Nucleus	Inhibit apoptosis and promote cell proliferation, migration and invasion	[67,68]

^a The differential expression are compared to healthy individuals.

genome [33]. Some of these strategies function through a group of RNAs known as Long non-coding RNAs (lncRNAs), which are aberrantly expressed in cancer [34]. These non-coding RNAs (ncRNAs) also promote viral viability by resisting the cellular antiviral response in order to maintain viral latency, promoting viral replication and genome packaging [35]. ncRNAs promote HIV replication because the advanced stage of the HIV infection contributes to immune suppression which is associated with increased cancer risk such as coinfections by other oncogenic viruses which directly cause cancer. Therefore, it is accepted that the progression of HIV to advanced stages is a key factor for HIV-mediated carcinogenesis [5,6]. The effects of some ncRNAs in promoting HIV progression may differ at different stages of the virus lifecycle as summarised in Table 1 [36]. These ncRNAs include, NEAT1, which is identified as a transcriptional regulator that modulates HIV-1 expression by storing excess unspliced instability (INS) transcripts within paraspeckle bodies in the nucleus [46]. Overexpression of NEAT1 leads to increased storage of unspliced HIV-1 RNA transcripts, which serve as a counterbalance for HIV-1 transcription in the cell [46]. Other examples of ncRNAs that showed differential expression at different phases of the virus life cycle include MALAT1, which resulted in an increased HIV-1 transcription by modifying the epigenetic status of HIV-1 genome promoter. In addition to MALAT1, one also finds Epstein-Barr virus-encoded small RNAs (EBERs) [37] and uc002yug.2 long non coding RNA [38] that assist in maintaining viral latency and facilitating HIV-1 replication in host cells. For instance, in surgical lung biopsies of HIV subtype E-infected pediatric patients, Epstein-Barr virus-encoded small RNAs (EBERs) are coexpressed with p24, a HIV core protein that facilitates HIV adsorption, membrane fusion, and entry into the host cells [37]. Additionally, Huan et al. [38] found that uc002yug.2 long non coding RNA has the potential to increase HIV replication, HIV long terminal repeat activity, and the activation of latent HIV in oesophageal squamous cell carcinoma and CD4⁺ T cells derived from HIV-infected patients. It is also worth noting that HIV alters the transcription of various lncRNAs to regulate the expression of viral genes and inhibits host antiviral defenses [39]. Therefore, the altered transcription of these lncRNAs can result in tumour formation [40].

In the last few years, researchers have devoted their time and resources in an effort to understand the role played by long non-coding

RNAs during cancer development and progression [41]. Therefore, this review examines and analyses HIV-associated lncRNAs that are deregulated in cancer and how they mediate drug resistance, the effect of these lncRNAs in cancer-related processes, which include apoptosis, cell cycle and angiogenesis will also be explored. There have been no reports implicating the role of lncRNAs in carcinogenesis in HIV-2 infected individuals, but there is emerging evidence that implicates lncRNAs in HIV-1-mediated carcinogenesis where they play important roles in regulating gene expression to favour cancer development. Since HIV-1 is more virulent, infects more people than HIV-2 and has direct pro-oncogenic effects, therefore the focus of this review is centered on the impact of lncRNAs on HIV-mediated carcinogenesis, focussing on HIV-1. As shown in Fig. 1, HIV-1 alters the transcription of lncRNAs to promote tumour formation. The figure shows that since lncRNAs control transcriptional processes, they provide an opportunity for HIV to hijack cellular machinery and manipulate gene expression to promote cancer through modulation of lncRNAs.

2. Long non coding RNAs

lncRNAs are 200 nucleotides long, non-protein-coding RNA transcripts that may either possess or lack a poly(A) tail, and have no potential of encoding a polypeptide chain. According to the presence or absence of a poly(A) tail at their 3' ends, they may also possess both exons and introns; however, they lack the potential to code for protein products [41,42]. Based on genomic location, lncRNAs are classified into five types; namely, (a) antisense lncRNAs generated from the antisense strand of protein-coding genes, (b) intergenic lncRNAs transcribed from intergenic regions of both strands, (c) intronic long non-coding RNAs synthesized from introns of protein-coding genes, (d) sense lncRNAs synthesized from the sense strand of protein-coding genes, and (e) lastly, bidirectional lncRNAs synthesized from the opposite strand of the protein-coding genes within 1000 bp of the promoter of the protein coding genes [43,44]. Long noncoding RNAs are also classified based on biogenesis and mode of action as summarised in Table 1. Based on genomic location, nuclear paraspeckle assembly transcript 1 (NEAT1) lncRNA is the most studied, and is classified as Long intergenic non-coding RNA (lincRNA) [46]. HIV promotes NEAT1 expression [46], which functions as an oncogene towards the development and

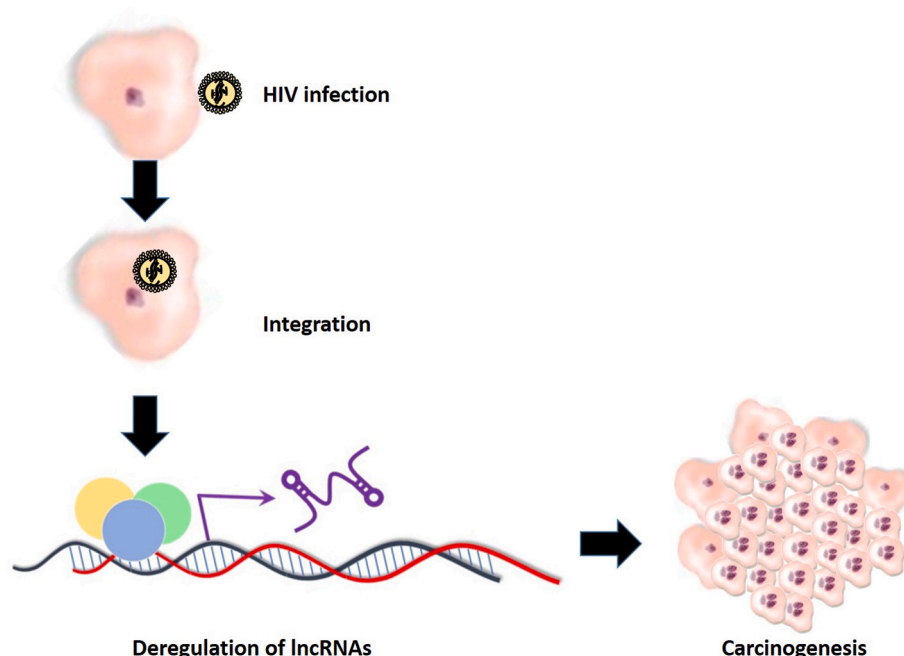


Fig. 1. HIV infection deregulate the expression of long noncoding RNAs resulting in the development of cancer. Adapted from Butova et al. [218].

progression of different malignancies, such as colorectal cancer [69], hepatocellular carcinoma [63], lung cancer [70], oesophageal squamous cell carcinoma [71] and glioma [72]. lncRNAs also classified based on their mode of action, thus, there are (i) decoy lncRNAs that titrates away DNA-binding proteins, such as transcription factors, for example, Growth Arrest Specific 5 (GAS5), which is able to bind to the DNA-binding domain of glucocorticoid receptor (GR) and titrates down the amount of GR available to bind to genomic glucocorticoid response elements [73,74]. Secondly, one finds (ii) scaffolding lncRNAs that enable two or more proteins to interact, and this is exemplified by non-coding repressor of nuclear factor of activated T cells (NRON), which interacts with human nuclear factor of activated T cells (NFAT) and inhibit its transcriptional activity, NRON also brings the phosphorylated NFAT into a cytoplasmic RNA-protein complex through scaffolding [45]. Moreover, there are (iii) guide lncRNAs, which directs regulatory factors such as chromatin modification enzymes, and this can occur through RNA-DNA interactions or through RNA in synergy with a DNA-binding protein, e.g NEAT1 which recruits epigenetic regulators to their target genes through its role as a guide [45]. Lastly, there are (iv) signalling lncRNAs, which regulate gene expression in response to diverse stimuli, and these are cell type-specific. These are exemplified by Maternally Expressed 3 (MEG3), which binds to cognate genomic regions through RNA-DNA hybrids and modulates the expression of target genes [43,75].

2.1. Cellular roles of lncRNAs

Studies showed that lncRNAs are involved in several major biological processes including dosage compensation (e.g Xist), nuclear organization (e.g MALAT1), alternative splicing of pre-mRNA (e.g DGCR5) and regulation of protein expression (e.g GAS5) [74]. A number of proteins are regulated by lncRNAs, including transcription factors which are crucial players in transcriptional regulation. lncRNA GAS5 is known to interact with active glucocorticoid receptors (GRs) through the DNA-binding domain of a transcription factor in order to inhibit their binding to glucocorticoid response element (GRE); consequently, blocking glucocorticoid-GR-GRE interaction induced targeted gene transcription [73,76]. This effect suggests that lncRNAs can act as a binding competitor for DNA Binding Proteins (DBPs) to regulate gene expression [73,76].

Additionally, some lncRNAs are implicated in regulating the expression of many protein-coding genes. For instance, some lncRNAs can directly modulate the expression of genes by binding to chromatin, modifying chromatin complexes or by epigenetically modulating histone proteins to change the expression of homeostasis-related genes, as demonstrated by HOX transcript antisense intergenic RNA (HOTAIR) [77,78]. HOTAIR dysregulation may alter the epigenome, consequently, contributing to the disease initiation and progression through changing cellular homeostasis [77,78]. The expression of HOTAIR in cancer is positively correlated with growth, angiogenesis, progression and drug resistance, largely because it regulates several downstream targets via various signalling pathways, including mTOR signalling pathway [79] and Wnt/ β -catenin pathway [80]. HOTAIR mediates these signalling pathways by upregulating the phosphorylation of phosphoinositide 3-kinase (PI3K), serine/threonine kinase (AKT) and mammalian target of rapamycin (mTOR) proteins [79,81].

lncRNAs are also implicated in dosage compensation, X-chromosome inactivation (XCI), which refers to the random selection and transcriptional silence of one of two X-chromosomes in females at the early stages of embryonic development, which is a unique dosage compensation mechanism found in mammals [82]. This process is modulated by X-inactive specific transcript (Xist) lncRNA in association with chromatin modifying complex [83]. Additionally, lncRNAs also play an important role in nuclear organization, and this is exemplified by Wang et al. [84] who showed that Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1) executes its oncogenic

activities by shaping the activities of nuclear speckles. Although MALAT1 is non-essential for speckle formation and integrity, the knockdown of this lncRNA has been linked to phenotypic changes including impaired cell cycle progression [85], apoptosis [86] and reduced cell motility [87].

In addition to nuclear organization, lncRNAs are also involved in splicing process, lncRNAs regulate alternative splicing (AS) through different mechanisms, which include, interaction with splicing factors and initiating RNA-RNA duplexes with pre-mRNA molecules to affect splicing events. DiGeorge Syndrome Critical Region Gene 5 (DGCR5) lncRNA is implicated in alternative splicing events and upregulated in oesophageal squamous cell carcinoma (ESCC) [88,89]. Duan et al. [88] showed that DGCR5 interacts with Serine and Arginine Rich Splicing Factor 1 (SRSF1) and regulates the alternative splicing event of *Myeloid leukemia 1 (MCL-1)*, an anti-apoptotic gene of the B-cell lymphoma 2 (Bcl-2) family, which leads to increased ratio of MCL-1L isoform, an oncogene that promotes tumour growth in myeloid cell leukemia. To promote cancer, MCL-1L keeps mitochondrial membranes stable, suppressing the release of cytochrome c, thus, stimulating cell survival and inhibiting apoptosis [90].

There is an increasing evidence that lncRNAs are deregulated by HIV, which is implicated in a number of diseases, including Tuberculosis [91] and HIV-mediated cancers [92]. HIV infection is accompanied by the integration of its genome randomly into the host genome [92]. This action induces structural alterations that promote replication, trigger innate immunity and ultimately weakens the immune system by destroying the white blood cells, thus, allowing the development of AIDS-defining cancers [92–94]. In each of these processes, HIV manipulates host lncRNAs that are involved in innate immunity or cellular response to DNA damage [93]. NRON serves as an example of host lncRNAs that are manipulated by HIV because it negatively regulates HIV replication, knockdown of the NRON by HIV has been shown to increase HIV replication through increasing the activity of nuclear paraspeckle assembly transcript 1 (NFAT1) which is augmented in cervical cancer and Kaposi's sarcoma [95,96].

As the HIV-infected population ages with occurrence among young adults of 15–24 years [97], research on HIV-associated cancers has become an area of focus; however, despite the use of Highly active antiretroviral therapy (HAART), HIV patients are still vulnerable to life threatening diseases such as virus induced cancers [98]. In HIV infected patients, co-infection with oncogenic viruses induces cell transformation, in addition, HIV also encode few proteins with pro-oncogenic effects, thus potentiating tumorigenesis [99]. To potentiate tumorigenesis, Tat protein transactivates the Human papillomavirus (HPV) long control region and enhances the expression of HPV-18 oncoprotein, E7, in cervical cancer cells [7]. Additionally, HIV oncoprotein, Negative factor (Nef), also promote cancer by increasing the expression of cellular myelocytomatosis (c-MYC) expression, which led to genomic instability in Burkitt lymphoma [100].

3. HIV-regulated lncRNAs promote carcinogenesis

It is known that HIV infection is a risk factor for the development of various types of cancers, including non-Hodgkin lymphoma [101], Kaposi's sarcoma [102] and cervical cancer [29,103]. Despite ongoing research, few factors are known to cause cancer among HIV-positive individuals. Immunodeficiency and the prevalence of traditional cancer risk factors (e.g., smoking, infection with oncogenic virus) [104,105] appear to be key risk factors, but evidence is emerging that HIV may also have direct pro-oncogenic effects as well. However, it remains elusive as to whether these factors work independently or in a synergistic manner. It is believed that HIV-associated immunodeficiency exerts its cancer-predisposing effects via two primary mechanisms [1]: reduced body's ability to clear and control oncogenic virus infections and [2] reduced immune surveillance of malignant cells [92,106]. As evidence accumulates, it has been found that HIV itself may exert direct

oncogenic effects via its Tat protein [107] involving multifaceted mechanisms including synergism with other oncogenic viruses [107], blockage of tumour suppressor gene function [108] and disruption of cell cycle regulation [109].

Additionally, the development of HIV-associated cancers is partly attributed to deregulation of lncRNAs that modulate viral and host gene expressions. The role of lncRNAs in HIV-mediated carcinogenesis can be virus-dependent, because, although regulatory lncRNAs have been shown to originate from both the virus and the host cells [95], during infection, HIV modulate the expression profiles of both the host and viral lncRNA. The tightly regulated expression of these lncRNA may enable HIV to achieve synchronized gene expression required for replication success [95] thus leading to a weakened immune system that causes persistence of oncoviruses.

Deregulation of oncogenic lncRNAs such as MALAT-1 are linked to most cancers investigated to date and affect major cancer hallmarks [110,111]. To promote cancer, MALAT1 modulates several molecular signalling pathways, including MAPK/ERK [112], PI3K/AKT [113] and Wnt/ β -catenin [114], positively influencing tumour cell proliferation, migration and invasion. In addition, HIV-1 also dysregulates lncRNAs to enhance replication and regulate the expression of host genes, bypassing apoptosis and the immune response, resulting in tumour formation [35, 39]. lncRNAs deregulated by HIV-1 have crucial roles in several aspects of cancer, and these include regulation of cell survival; for example, NRON has been shown to inhibit cancer proliferation [45,115]. Additionally, lncRNAs deregulated by HIV-1 are also implicated in the regulation of apoptosis e.g p53-dependent lincRNA p-21 which plays a central role in global p53 responses to genomic instability [40].

Several lncRNAs such as GAS5, which is downregulated by HIV-1 viral infection, play a crucial role during carcinogenesis [73,116]. GAS5 expression levels are downregulated in numerous malignant tumours, including breast [117], gastric cancer [118], prostate cancer [119], lung cancer [120], and steosarcoma [121]. The low expression of this transcript increased proliferation and attenuated apoptosis because GAS5 overexpression leads to apoptosis and decrease in S-stage cells in normal cells, while GAS5 silencing has the opposite effect suggesting that GAS5 regulates normal growth stagnation [73,76,122]. Although the precise molecular mechanism of GAS5 in carcinogenesis remains unclear, it is possible that the downregulation of GAS5 in cancer is due to its tumour repressor effects, which include regulating transcription through acting as a decoy by binding to miR-196a-5p, which is associated with increased tumour growth [123,124] and by regulating transcription through histone methylation/demethylation.

NRON, which is involved in the regulation of HIV is also downregulated in triple-negative breast cancer (TNBC) in comparison to healthy tissues, thus indicating the possibility of being a tumour repressor [115]. Niu et al. [115] also showed that NRON overexpression downregulated small NF90-associated RNA (snaR) lncRNA to inhibit cancer cell proliferation. Generally, lncRNA NRON inhibits NFAT, a transcription factor that enhances HIV replication and transcription [45]. NRON also forms a complex with ubiquitin ligase cullin 4B (CUL4B) and Proteasome 26S Subunit, Non-ATPase 11 (PSMD11) to recruit HIV protein Tat which is associated with the occurrence of several tumours, for degradation through ubiquitination, suggesting tumour inhibitory effects of NRON [125].

4. HIV proteins modulate cancer-related lncRNAs

The viral proteins expressed and released by HIV-1-infected cells include Tat, viral envelope glycoprotein (gp120), Nef, reverse transcriptase (RT) and matrix protein p17 [8]. These proteins cause oxidative stress by deregulating oxidative stress pathways, leading to a surge in reactive oxygen species (ROS) production and inducing mitochondrial dysfunction, which gives rise to direct carcinogenic effects [8, 126–129]. The HIV proteins are also capable of enhancing tumorigenic potential in already transformed cells, where they can operate alone or

together with other oncoproteins, including those from HPV, one of the most common oncoviruses [8]. As a stand alone carcinogenesis inducer, Tat promoted carcinogenesis by reducing the expression of a member of the Rb family, pRb2 and cyclin-dependent kinase inhibitors, p21 and p17, at the mRNA level [130].

Immunodeficiency associated with enhanced susceptibility to viral infections is considered the most important pathway of increased cancer risk in HIV patients [131]. There is substantial evidence which demonstrates that HIV is an oncogenic virus because it causes immunosuppression by permitting the coinfection of other oncogenic viruses [29, 132]. To promote cancer, HIV also encode few proteins with pro-oncogenic effects [8,133]. These HIV proteins are implicated in HIV-mediated carcinogenesis and they modulate different cellular players, including lncRNAs (Table 2). As shown in Table 2, some HIV-1 proteins appear to be directly involved in cell transformation and propagation of malignant cells. These HIV-1 oncotranscripts favours neoplastic progression through modulation of different lncRNAs, including LINC00313, uc002yug.2, lincRNA-p21, HEAL and NRON, which are involved in HIV replication, apoptosis, angiogenesis and cell migration. Literature on the interaction of HIV matrix protein p17 with lncRNAs is scarce, but according to Lncrna2target V3.0 prediction tool (<http://bio-annotation.cn/lncrna2target/browse.jsp>), the first two lncRNAs targeted by p17 are lncRNA152 and NBAT1 which are both involved in carcinogenesis.

5. HIV-associated cancers and deregulated lncRNAs

HIV attacks the human body in three stages, the first stage is acute infection, which develops few weeks after exposure to the virus through bodily fluids of infected patient. During this stage, the body produces antibodies to fight off the HIV virus that is multiplying at a rapid rate. Once acute infection is over most patients do not experience any symptoms while the virus continues to replicate, this stage is called asymptomatic stage and it lasts for years [140]. Without HAART treatment, asymptomatic stage typically progresses to AIDS in 10 years or longer.

The progression from asymptomatic stage results in immunosuppression due to several factors, which include malfunctioning of innate signalling pathways, an increased viral replication rate and viral load, gradual damage of peripheral CD4+T cells, and reduction of T lymphocytes at mucosal sites, all of which contribute to AIDS development [140]. Based on these hallmarks of HIV infection, it is reasonable to conclude that the progression of HIV to its advanced stages is a key factor for HIV-mediated carcinogenesis because after infection, the host expresses HIV oncoproteins and becomes vulnerable to opportunistic infections resulting with immunodeficiency, which directly and indirectly cause HIV-related cancer such as Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer with remarkable level of immunosuppression [101–103].

Early in its pandemic, HIV was linked to the development of cancer, some of the first reported cases included non-Hodgkin lymphoma (NHL) [141] and Kaposi sarcoma (KS) [142], which are now common cancers in AIDS patients [23]. Malignancies that are linked to HIV are classified as AIDS-defining cancers (ADCs) or non-AIDS-defining cancers (NADCs) [143]. ADCs are more common in people living with HIV and they signal progression to the development of AIDS. On the other hand, although NADCs are also associated with HIV, their manifestation does not mean that HIV has progressed to AIDS [143,144]. Kaposi sarcoma, non-Hodgkin lymphoma (NHL) and cervical cancer are regarded as AIDS-defining cancers [23]. Anal cancer, pulmonary cancer, head and neck cancer, liver cancer, Hodgkin lymphoma and lung cancer are regarded as non-AIDS-defining cancers [143,144]. HIV does not contribute directly to the development of NADCs but since HAART does not fully restore health, the suppressed immune system of HIV-infected people with reduced ability to control oncogenic viral processes explains the increased risk of developing NADCs [145].

Table 2
HIV proteins that promote carcinogenesis and modulate the expression of lncRNAs.

HIV protein	Mode of action	lncRNAs	Cancer type	Reference
Tat	Induce angiogenesis and tumorigenesis by targeting LINC00313 lncRNAs. Facilitate the uc002yug.2-mediated regulation of HIV-1 reactivation.	LINC00313	Kaposi's sarcoma	[38,133,134]
Gp120	Invade apoptosis by dysregulating lincRNA-p21.	uc002yug.2-lincRNA-p21	Cervical cancer	[135,136]
Reverse transcriptase	Enhance lncRNA HEAL through its ability to phosphorylate cyclin-dependent kinase 2 gene (CDK2) required for efficient HIV-1 replication.	HEAL	Glioblastomas	[128,137]
Nef	Regulate NRON to enhance HIV replication and promote breast cancer growth and progression.	NRON	Murine mammary gland adenocarcinoma	[45,138]
p17	Promote cell migration and invasion.	lncRNA152 NBAT1	Breast cancer B-cell lymphomas	[121,139]

HIV-infected people have 2800-fold increased risk of developing Kaposi sarcoma, 10-fold elevated risk for NHL and three times elevated risk for cervical cancer in comparison with the overall population [145, 146]. Several factors increase the risk of cancer development amongst HIV-infected patients including the expression of HIV oncoproteins, viral coinfection, immunosuppression and high-risk lifestyle choices such as smoking [145–148]. HIV-induced immune suppression increases replication of oncogenic viruses such as hepatitis viruses, HPV and Epstein-Barr virus, which directly cause cancer [145–148]. Many etiological mechanisms contribute to HIV-associated cancers resulting in the imbalance between cellular proliferation and apoptosis. HIV influences cell proliferation by expressing Tat protein, which promotes cell survival by inducing an increase in the levels of proliferation markers such as cyclin A together with a decline in the expression of cell cycle inhibitors such p21, thus dodging apoptosis and favouring cancer development [124,149]. Previously, the carcinogenesis process has been linked to deregulated genes, especially the protein-coding genes, such as *Retinoblastoma binding protein 6 (RBBP6)* [150,151], *Survivin* [152] and *Death-Associated Protein Kinase 1 (DAPK-1)* [153], suggesting that these gene products play pivotal role in cell homeostasis.

Recently, there is an increasing number of lncRNAs that have cellular function and some are linked to tumorigenesis, including HIV-associated cancers [45,94,95,132,135]. HIV has been shown to influence proliferation, inhibiting apoptosis and promoting cell survival by inducing the expression of lncRNAs, which uses their oncogenic nature to promote the expression of anti apoptotic proteins (e.g Bcl-2), maneuvering DNA damage responses and cell cycle check points, thus promoting the development of ADCs [94].

5.1. Deregulated lncRNAs in Kaposi sarcoma

Kaposi sarcoma associated herpes virus (KSHV) infection is aggravated by HIV-1, which is among the most important co-pathogens [30]. KSHV causes Kaposi sarcoma (KS), a cancer of endothelial cells that is a hallmark of the worldwide AIDS crisis [103]. HIV promotes KS pathogenesis by two mechanisms: (i) inducing the production of inflammatory cytokines which causes a profound impairment of the immune system, allowing the development of KS [154], and (ii) the release of HIV proteins, particularly HIV Tat protein which promote human herpesvirus (HHV)-8 replication [155,156]. Furthermore, lncRNAs are also associated with Kaposi sarcoma (Table 3), the dysregulation of these lncRNAs in Kaposi sarcoma is correlated with the degree of cancer prognosis and has been shown to influence cell proliferation, invasiveness, metastasis and regulation of tumor suppressor proteins [155,156]. The association between lncRNAs and HIV infection has been demonstrated to orchestrate and manipulate transcriptional and post-transcriptional effects both *in vitro* and *in vivo*, making them a target for clinical use. *in vivo* studies on molecular mechanisms of lncRNAs in KS are limited, hence, clinical trials to explore and verify the safety and efficacy of lncRNA drugs are far from over. Despite the comparatively small number of *in vivo* studies currently available, lncRNAs have a pivotal role in cancer, as well as in HIV infection.

Table 3
lncRNAs associated with the development and progression of ADCs.

ADCs	Tumour suppressor inhibitor	Cell cycle dysregulation	Apoptosis inhibition
Kaposi sarcoma	PTENP1 [157]	LINC00313 [133] UCA1 [48]	DLEU2 [157]
Non-Hodgkin lymphoma	TUG1 [158,159]	ZFAS1 [159] PANDA [158] MALAT1 [161]	ZFAS1 [159] FAS-AS1 [160] MIAT [162]
Cervical cancer	OIP5-AS1 [163]	DLEU2 [164]	GAS5 [58,165] HOTAIR [166] CRNDE [167,168]

Note: () Reference.

5.2. Deregulated lncRNAs in non-Hodgkin lymphoma

In HIV-infected individuals, non-hodgkin lymphoma (NHL) accounts for a large proportion of human malignancies. HIV induces immunosuppression and chronic antigenic stimulation, these conditions, coupled with infections such as Epstein-Barr virus which increases the expression of proteins involved in escaping antitumor immunity such as programmed death-ligand 1 (PD-L1), may provide a conducive environment for HIV-induced NHL [6]. Additionally, lncRNAs are implicated but the roles and mechanisms of abnormally expressed lncRNAs in NHL are still unclear. Several lncRNAs whose expression is aberrant in NHL have been examined functionally in an attempt to shed light on their role in various tumor cell biology aspects (Table 3). Huang et al. [169] also added that lncRNAs are also capable of regulating multiple signalling pathways such as Wnt/ β -catenin and oncogenic genes through epigenetic mechanisms. Regarding epigenetic mechanisms, it was found that HOTAIR's function is positively correlated with epigenetic regulation through recruitment of Polycomb Repressive Complex 2 (PRC2) proteins (EZH2, SUZ12, and EED), which promote H3K27me3, that is strongly tied to aggressive Diffuse large B-cell lymphoma [169,170]. According to Oh et al. [170], it is possible that lncRNA deregulation can contribute to tumorigenesis by interacting with epigenetic regulators.

5.3. Deregulated lncRNAs in cervical cancer

HIV positive women have a higher prevalence of cervical precancerous lesions. Despite the successful use of HAART in reducing HIV related deaths, HAART prolongs life, increasing the risk of exposure to HPV and allowing for the onset of invasive cervical cancer [171]. Moreover, it has been suggested that lncRNAs play significant roles in cervical cancer progression by sponging miRNAs thus enhancing the oncogenic effect of viral oncoproteins [172]. This effect was shown by Thymopoietin pseudogene 2 (*TMPOP2*) lncRNA, which upregulated *E6/E7* genes by scavenging tumor repressor microRNAs like miR-375 and miR-139 that target HPV E6/E7 mRNA [172]. Other mechanisms deregulated by lncRNAs in cervical cancer are summarised in Table 3. According to Table 3, lncRNAs play a critical role in enhancing the processes involved in viral-mediated cervical cancer.

Additionally, another lncRNA implicated in cervical cancer is HOTAIR, Sharma et al. [173] showed that HPV16 E7 modulate HOTAIR expression and function, this is possible because in order to promote cancer, HOTAIR recruits the chromatin remodelling complex PRC2, creating H3K27me3 marks which induce gene silencing. RNA immunoprecipitation confirmed the interaction between HPV16 E7 and HOTAIR, illustrating one of the mechanisms of HPV16 E7 carcinogenesis [173]. In summary, recent discoveries in this field have revealed the close connection between HIV, HPV and lncRNAs, proving that lncRNAs play a significant role in HPV-induced carcinogenesis.

6. HIV influence the functions of cellular lncRNAs

HIV is implicated in the regulation of decoy lncRNAs, which bind proteins or RNAs, resulting in the negative regulation of protein expression. GAS5, a tumour suppressor decoy lncRNA, is downregulated during HIV-1 infection, GAS5 interacts with microRNA-873 to repress its HIV-1 replication promoting activity [73]. Additionally, HIV has been shown to modulate the expression of lncRNAs involved in direct protein localization; in cancer cells, HIV modulated the expression of NEAT1, which binds to RNA-binding proteins to orchestrate the formation of paraspeckles [46]. The formation of paraspeckles are suggested to be involved in regulating gene expression by nuclear RNA retention [174]. Moreover, HIV can also influence signal lncRNAs, which have binding sites for transcription factors or chromatin-modifying enzymes in order to activate or repress gene expression. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) lncRNA has been shown to promote HIV through binding to PRC2. Consequently, MALAT1 blocks the binding of Enhancer of zeste homolog 2 (EZH2), a core component of PRC2, to the HIV-1 promoter, making EZH2 unable to mediate the epigenetic silencing of HIV transcription because the progression of HIV is a key factor for HIV-mediated carcinogenesis [54]. Lastly, HIV also influences scaffold lncRNAs that act as organising structure where molecules can bind and interact in order to regulate gene expression. Imam et al. [45] exemplified this effect by showing that NRON, a non-coding repressor of the NFAT, is downregulated due to subsequent HIV-1 infection. NRON has been demonstrated to regulate HIV-1 replication by binding to NFAT as scaffold, thus blocking NFAT to promote HIV-1 infection [45].

7. Cell homeostasis and cell survival processes

In simple terms, cell homeostasis refers to the balance between cellular proliferation and apoptosis. When this balance is disturbed, the system moves from a physiological to a pathological state. Cellular homeostasis ensures organ integrity through the control of cell survival, proliferation, and death, in order to make sure that healthy cells as opposed to cancerous cells, generally stop dividing when they come into contact with neighboring cells [175]. A loss of this conserved genetic program favors neoplastic progression, a key step in malignant transformation. During cellular homeostasis, cell survival is controlled to ensure that cells only grow and divide when required because deregulation of this process is an important hallmark of carcinogenesis. Cell survival is regulated by cell survival pathways, which affect transformation-relevant biological processes, including proliferation, migration and angiogenesis [175].

To understand the role of HIV-regulated lncRNAs in cell homeostasis and cell survival, we have analysed data from various aspects of cancer development pathways/cellular processes including apoptosis, cell cycle, cell survival pathways and angiogenesis. Analysis of data from these processes and cancer drug resistance revealed an overlap between lncRNAs deregulated in HIV-associated cancer and lncRNA impacted by HIV. Examples of these lncRNAs include NEAT1, which regulate proliferation and invasion of cervical cancer cells by targeting AKT/PI3K [176]. Moreover, HIV also affects NEAT1 expression because it plays a role in maintaining the integrity of the nuclear paraspeckle required to

promote HIV replication [46]. MALAT1 also serves as an example of those lncRNAs deregulated in HIV associated cancer and impacted by HIV. MALAT1 is an oncogenic lncRNA involved in proliferation, invasion and metastasis in KSHV tumorigenesis [177]. Additionally, highly upregulated MALAT1 promotes HIV transcription in HIV-infected CD4⁺ T lymphocytes [54].

HIV manipulate host lncRNAs by inducing strong modifications in the cell transcriptome [35]. This strategy enhances HIV's resistance to antiviral immune response, thus promoting the expression of lncRNAs which stimulate a variety of viral-host interactions, which contribute to the growth and spread of the virus [35]. Since the progression of HIV is a key factor for HIV-mediated carcinogenesis, it is possible that during the late stages of HIV infection, HIV alter the expression of tumour suppressor lncRNAs to promote the development and progression of cancer.

7.1. HIV regulated lncRNAs foster apoptosis resistance

Apoptosis is a programmed cell death essential for maintaining cell balance in the human body. One of the hallmarks of cancer cells is their resistance to apoptosis, which plays a key role in the prevention of cancer progression by targeting damaged pro-cancerous cells. Apoptosis initiates a cascade of caspase-related signalling complexes either in response to the intracellular signal or in response to the receptors on the cell surface (extrinsic pathways).

It is now emerging that the overexpression or knockdown of different HIV-regulated lncRNAs in specific types of tumours inhibit or activate the apoptosis process [178]. Fas-antisense 1 (Fas-AS1) is a type of lncRNA that is regulated by HIV, but the molecular mechanism remains to be experimentally validated, to support this notion, Boliar et al. [178] showed that the expression of Fas-AS1 is upregulated in HIV infected cells versus uninfected cells indicating that this variation is HIV infection specific. Fas-AS1 has been shown to inhibit apoptosis in macrophages by targeting effector caspases, interestingly, the down-regulation of Fas-AS1 expression with siRNA treatment activated effector caspase-3/7 only in HIV-infected macrophages without affecting the uninfected cells [178]. Therefore, it is possible that Fas-AS1 can use similar mechanism in cancer cells to either promote or inhibit apoptosis.

Another example is NEAT1 whose expression is altered by HIV-1 infection; this lncRNA is also implicated in imatinib-induced apoptosis inhibition of chronic myeloid leukemia cells [179]. To reverse apoptosis, other HIV-associated lncRNAs induce cell proliferation, which is exemplified by NFAT lncRNA. NFAT promotes cell proliferation through induction of glypican 6 (GPC6), a cell-surface glycoprotein [180]. NFAT directly binds to the GPC6 promoter and stimulates its transcription, to promote cell proliferation, GPC6 triggers cell proliferation by inhibiting canonical β -catenin and increasing non-canonical Wnt5A signalling, which induces p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK) to mediate resistance to apoptosis [180].

7.2. HIV-regulated lncRNAs modulate the cell cycle

The cell cycle in eukaryotes is controlled by regulatory networks, which ensure that specific events occur in an orderly manner through tightly regulated transitions. Contrary to the abundant knowledge of proteins that control the cell cycle [181], very little is known about the role of long non-coding RNAs, especially those that are regulated by HIV in cell-cycle progression. Since a large number of HIV-regulated lncRNAs display deregulated expression in human cancers, it is possible that these lncRNAs regulate the cell cycle. On that note, MALAT1, a lncRNA which promotes HIV transcription [54] has been shown to regulate the expression of cell cycle genes in bone cancer and is required for G1/S and mitotic progression. Additionally, GAS5, a lncRNA that inhibits HIV-1 replication through interaction with miR-873 [73], is also implicated in the cell cycle arrest in normal T-cell lines and human peripheral blood T-cells, GAS5 increased the proportion of cells in G1 while decreasing the proportion of cells in S phase

[73].

7.3. HIV regulated lncRNAs are implicated in cell survival pathways

Survival pathways are known to prevent apoptosis, promote cell proliferation and cell survival [182]. HIV-regulated lncRNAs are deregulated in cell survival pathways indicating a need to explore them for biomarker discovery purposes. MALAT1, a lncRNA upregulated during HIV-1 infection, has been shown to promote the transcription of HIV-1 genes, especially those that are involved in cell survival pathways, such as Mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3'-kinase (PI3K)-Akt pathways [183,184]. This survival-promoting effect of MALAT1 has been demonstrated in osteosarcoma [185]; bladder cancer [183] and breast cancer [186]. NEAT1 lncRNA showed a related mechanism in multiple myeloma by promoting cell proliferation through activation of PI3K/AKT pathway [187]. Interestingly, HIV infection alone also promoted cell proliferation, cell survival and angiogenesis by up-regulating *ret proto-oncogene* (RET) via sponging miR-129-5p, thus activating the PI3K-Akt survival pathway [55,185].

HIV also maneuver host antiviral response by activating survival pathways by negatively regulating lincRNA-p21, which indirectly deactivates cell survival pathways [188]. lincRNA-p21 is induced by p53 and binds to heterogeneous nuclear ribonucleoprotein K (hnRNP K), allowing it to be localized at the promoter of pro-apoptotic genes. As a means of preventing this pro-apoptotic pathway, HIV initiates MAP2K1/ERK2 pathway, which causes hnRNP-K to be sequestered in the cytoplasm. Activated MAP2K1/ERK2 pathway protects HIV-infected cells from p53-induced apoptosis by degrading lincRNA-p21 and sequestering hnRNP-K in the cytoplasm [188]. lincRNA-p21 have been shown to inhibit the growth and progression of non-small-cell lung cancer [189], head and neck squamous cell carcinoma [190], prostate cancer [191], liver cancer [192], gastric cancer [193], oesophageal squamous cell carcinoma [194] and colorectal cancer [195].

Since HIV-regulated lncRNAs are deregulated in cell survival pathways, it can be a promising strategy to target inhibitors of cell survival pathways to alter lncRNAs that are involved in cancer drug resistance. Example of lncRNAs that should be targeted is Activated in Renal cell carcinoma with sunitinib resistance (ARSR). ARSR enhanced drug resistance in numerous tumours such as hepatocellular carcinoma [196, 197], osteosarcoma [198] and renal cancer [199] via activation of AKT signalling pathway. Interestingly, the PI3K inhibitor Buparlisib (BKM120) overcame this chemotherapy resistance by inhibiting the AKT, thus resulting in downregulated expression of ARSR long non-coding RNA [198,200]. Although the information on ARSR as a HIV-regulated lncRNA is limited, its downregulation by BKM120 suggests that inhibitors of cell survival pathways can be targeted to alter lncRNAs that are involved in cancer drug resistance.

7.4. HIV-regulated lncRNAs support angiogenesis

The development of new blood vessels (angiogenesis) is required in the pathogenesis of many disorders such as cancer, chronic inflammatory disorders (rheumatoid) and some eye diseases (age-related macular degeneration) [201–202]. Angiogenesis helps tumours to establish a blood supply to satisfy their need for oxygen and nutrients and to accomplish other metabolic functions [201,202]. Angiogenesis takes place during development, regeneration, and wound repair in physiological conditions [203]. The ability of tumours to induce the formation of new blood vessels has been a focus of cancer research for the past years and long noncoding RNAs are grabbing attention as rising stars in this process.

Studies on HIV-1 regulated lncRNAs implicated in promoting angiogenesis are limited but MALAT1, which is involved in HIV-1 viral infection has been shown to promote angiogenesis in breast cancer [204]. Interestingly, knockdown of MALAT1 inhibited breast cancer cell

proliferation [204]. Similar effects of MALAT1 in angiogenesis have been demonstrated in hepatocellular carcinoma, gastric cancer and colorectal cancer [205–207].

8. LncRNAs in cancer drug resistance

The problem of drug resistance remains a major challenge as it often leads to therapeutic failure [208]. To date, chemotherapeutic drug resistance mechanisms are still poorly understood. Since lncRNAs regulate gene expression through mechanisms such as chromatin modification, transcriptional, and post-transcriptional regulation [209], which simultaneously occur during the development of drug resistance, therefore, the role of lncRNAs in drug resistance must be critically evaluated, especially in AIDS defining cancers. lncRNAs have been shown to mediate chemoresistance in renal cell carcinoma [210], bladder cancer [211], prostate cancer [212], testicular cancer [210,213] and cervical cancer [214]. lncRNAs contribute to chemoresistance in various ways, including altering drug efflux, preventing DNA damage repair, causing mutations in drug targets and sponging miRNAs [210, 215,216].

Targeting other group of non coding RNAs called microRNAs is an interesting mechanism that lncRNAs are using to develop drug resistance across various cancer entities. ARSR lncRNA has been shown to induce drug resistance in Renal cell carcinoma (RCC), as a competing endogenous RNA (ceRNA), ARSR sequestered miR-34 and miR-449 to increase the levels of Anexelektto (AXL) receptor tyrosine kinase and mesenchymal-epithelial transition factor (c-MET), resulting in sunitinib resistance in RCC [199]. Another microRNA related mechanism, which enabled lncRNAs to regulate chemoresistance in cancer cells were described by Li et al. [217], where it was shown that deleted in lymphocytic leukemia 1 lncRNA (DLEU1) lncRNA induced cisplatin resistance in bladder cancer cells by sponging the tumor suppressive miR-99b. Although the information on the implication of HIV associated lncRNAs in drug resistance is limited, according to literature, microRNA could play an important role in regulating lncRNA-mediated drug resistance.

9. Conclusion

Investigation into the effect of HIV on the role and function of lncRNAs is still largely in its infancy. Future studies are required to have a deepened understanding of the role of HIV-regulated lncRNAs in promoting carcinogenesis targeting apoptosis, survival and angiogenesis processes. Since differentially expressed HIV-regulated lncRNAs act as negative or positive regulators in various critical steps of tumorigenesis, understanding of lncRNA-mediated carcinogenesis and drug resistance is of paramount importance. Deciphering the HIV-mediated processes, especially those linked to lncRNA deregulation may assist in the identification of novel diagnostic and prognostic biomarkers, as well as identification of new drug targets for therapeutic purposes.

Author contributions

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