Black Sea Journal of Engineering and Science
doi: 10.34248/bsengineering.1447604

Open Access Journal
e-ISSN: 2619 – 8991

Review
Volume 7 - Issue 4: 804-814 / July 2024

AN EVALUATION OF LONG NON-CODING RNAS IN CANCER

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Abstract: Long non-coding RNAs (lncRNAs) gradually play significant roles in many fundamental biological functions. These genetic elements are considered major components of transcripts and critical components of cancer cells. Most genetic alterations in cancer cells occur in comparatively long, non-protein-encoding areas typically translated into lncRNAs. LncRNAs have essential functions in the pathophysiology of human diseases, particularly in the genesis, advancement, and metastasis of tumors, acting as either tumor suppressor genes or oncogenes. As a correlation, understanding the function and dynamic activity of lncRNAs is thought of as de novo and a promising biomarker for cancer therapeutics. The existence of differentially expressed lncRNAs with functional diversity in diverse anaplastic changes makes them valid elements in monitoring cancer cells. The application of sophisticated genetic tools such as next-gene sequencing on cancer transcriptomes has discovered multiple lncRNA functions in the context of anaplastic changes. Various lncRNAs expressed in different phenotypic situations have been found using the following and third-generation sequencing methods; however, many still need to be appropriately identified. This review summarizes and discusses previous studies on the role of lncRNAs in cancer cells, and underscores the therapeutic strategies associated with cancer-related lncRNAs.

Keywords: Long non-coding RNAs, Gene expression, Prognosis, Cancer

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Received: March 7, 2024
Accepted: May 31, 2024
Published: July 15, 2024

Cite as: Valioğlu F. 2024. An evaluation of long non-coding RNAs in cancer. BSJ Eng Sci, 7(4): 804-814.

1. Introduction

Cancer is the most life-devastating disease, with high morbidity and mortality worldwide (Qian et al., 2020). Despite crucial advances in recent years, several matters, such as deferred diagnosis and inadequate prognosis, remained unknown (Bartonicek et al., 2016; Patra et al., 2021). In clinical settings, proteins comprise most cancer-related indicators and treatments, although only 2% of the human genome's overall content gets translated into proteins. Due to the higher mutation rates compared to coding areas, scientists and researchers must concentrate more on non-coding regions (Cuykendall et al., 2017). During the last decade, RNA-based modalities against cancers have gradually been modified from concept to reality (Zhao et al., 2016). Among these treatments, non-coding ribonucleotide sequences (ncRNAs) without translation, with the suppression of mRNA transcription and direct physical inhibition of proteins, exert their treatment effects on tumors (Wang and Chang, 2011). Long ncRNAs (lncRNAs) lack the functionality of open reading frames (ORFs) and the ability to code for proteins (Bartonicek et al., 2016). The presence of >100,000 lncRNAs in the human genome was evaluated with the sequencing data ordinarily scattered in both the cytosol and nucleus (Ponting et al., 2009). The dynamic role of lncRNAs in cellular processes is complex and depends on the interaction with biological molecules such as DNA, RNAs, proteins, and other molecules. Even though lncRNAs are not subjected to the translation process, they interface with RNA-binding proteins, and can concurrently activate transcription factors or suppress target genes' post-transcriptional or post-translational level promoters (Khalil et al., 2009; Ulitsky and Bartel, 2013). Also, lncRNAs can regulate target genes both during transcription and translation, and the majority of them continue to exist in the nucleus even after transcription.

LncRNAs participate in the control expression of genes, coding and non-coding RNAs' transcription and post-transcriptional processes, histone modification and epigenetics, and chromatin rearrangement. LncRNAs, like protein-coding genes, are ordinarily polyadenylated transcribed using the activity spliced and produced by RNA polymerase II (Pol II). Furthermore, lncRNAs can promote or curb the constitution of transcription loops, resulting in the enlistment and/or inhibition of regulators controlling gene transcription (Huarte, 2015; Jarroux et al., 2017).

Additionally, lncRNAs have been shown to act as tumor suppressors or oncogenes in human cancers, similar to protein-encoding genes through various signaling pathways and molecular machinery (Smolle et al., 2017). A growing body of studies advocates the role of lncRNA in many aspects of biology, including the differentiation of cells, organ development, genome-wide imprinting, development, tumorigenesis, and quantitative compensation. Additionally, lncRNAs control the splicing of mRNA and function as the beginnings of other lncRNAs, like microRNAs (Jarroux et al., 2017). The occurrence of mutations, amplifications, and deletions in

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diverse cancer types can modify the expression of mature and precursor lncRNAs (Jiang et al., 2019). The various expressions or malfunctions of lncRNAs are closely related to cancer development, several pathologies, and expansion. Prior information has indicated that lncRNA profiling can allow us to distinguish certain genetic signatures regarding diagnostics and therapeutic outcomes in cancer patients. Upon finding the close relationship between lncRNAs and anaplastic conditions, certain lncRNA types can be introduced as putative biomarkers or therapeutic targets with acceptable accuracy for cancer detection and diagnosis (Jendrzejewski et al., 2012).

Several abnormalities can affect lncRNA expression profiles in different tumor types and tissues. A significant genomic fragment of ultra-conserved regions (UCRs) encodes a particular group of lncRNAs whose expression is changed with high probability in cancers. UCRs are in fragile or cancer-susceptible sites and/or genomic regions related to various anaplastic changes, also known as cancer-associated genomic regions (CAGRs). Different genomic profiling research has demonstrated the particularity of UCRs in leukemias and other cancers (Ponting et al., 2009).

Recent studies showed that many lncRNAs are present hotspots in various tumor conditions; it is estimated that nearly 102,000 lncRNAs can affect the dynamic growth of several cancer cells, holding promise for cancer treatment (Qian et al., 2020). Specifically, the role of lncRNAs in normal conditions and various pathologies emphasizes their critical role in cell bioactivity (Ghosal et al., 2013). For instance, BC-819 plasmid, including diphtheria toxin sequence and H19 promoter, has been utilized in clinical trials to treat ovarian, bladder, and pancreatic cancers (Smaldone and Davies, 2010). The transcription of the toxin from diphtheria with the activation of the H19 promoter occurs in the tumor sites. Therefore, BC-819 can effectively destroy tumor cells, diminish tumor expansion, and prolong the time to recurrence with local toxicity (Gofrit et al., 2014). The inhibition of lncRNA, namely LINC01212, as an effective anti-melanoma therapeutic strategy, increased the apoptotic changes of melanoma cells. Furthermore, although lncRNAs participate in cell proliferation/growth, several aspects of lncRNAs in the cancer niche are still unknown and require further investigation. Perception of the molecular mechanisms that patronage the pattern of lncRNAs in cancer advancement or their potential applications in cancer treatment seems critical.

2. Association between LncRNAS and Cancers

Cancers are multifaceted and complex conditions with several predisposing factors. In most types of malignancies, it is mandatory to enhance management tools and the number of available appraisements for better regenerative outcomes (Bartonicek et al., 2016). Irrespective of tumor niche, the function of lncRNAs is exceptionally complex and unpredictable. It has been shown that the bioactivity of lncRNAs is different inside cells under physiological conditions. For instance, the inhibition of gene expression, encoding polypeptides involved in the adjustment of the transcriptional process, and playing a role as suppressors of transcription factors in the nucleus (Schmitz et al., 2016). LncRNAs can regulate equilibrium, mRNA splicing, permanence of protein, and translation of protein to control cell bioactivities in the post-transcriptional step. Interestingly, the involvement of lncRNAs in DNA methylation, epigenetic changes, and adjustment of particular genes can make lncRNAs powerful genetic elements in tumorigenesis (Manolio et al., 2009). Numerous single-nucleotide polymorphisms (SNPs) with the potential to cause cancer hazards have been confirmed in non-coding portions of the human genome, according to genome-wide association studies (GWAS) (Figure 1) (Hindorff et al., 2009). Many SNPs in cancer cells were in proximity to the regions that encode lncRNAs and affect the expression of lncRNAs. More than 90% of SNPs are situated upstream in the exon of coding genes for protein (Pearson and Manolio, 2008).

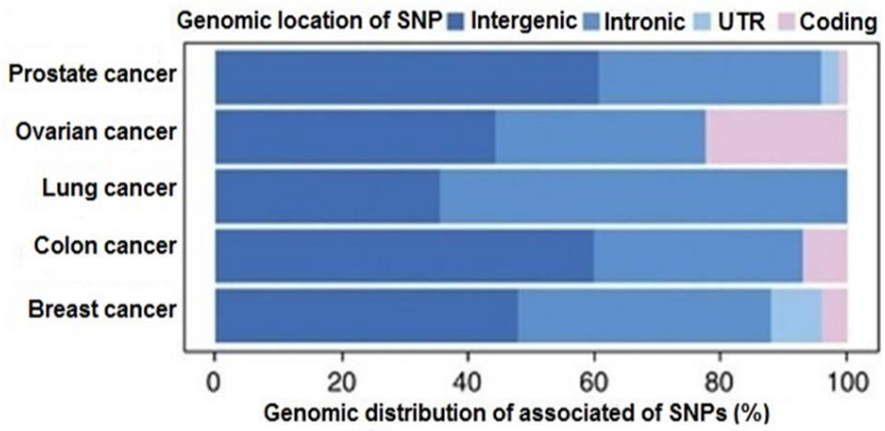

Figure 1. Genomics distributed single-nucleotide polymorphisms (SNPs) (%) in certain cancer types. Only few percentages of SNPs are discovered in coding parts of the genome; the majority of cancer-associated SNPs are intergenic or intronic non-coding areas (Cheetham et al., 2013).

The possible role of SNPs (rs7463708 into 8q24.21 gene) has been shown in the prostate cancer-sensitive lncRNA, PCAT-1 (ENSG00000253438). Therefore, it is imperative to investigate and register SNPs and introduce them as potential candidates for pathological conditions (Jendrzejewski et al., 2012). Additionally, the role of lncRNAs in particular tumors can be traced by employing GWAS and concentrating on the potential overlap of cancer risk regions (Pearson and Manolio, 2008). SNPs may be situated in a non-coding RNA sequence and, thus, participate in several different mechanisms. Presently, it is presumed that illness-related SNPs can occur in long non-coding RNAs. Also, functional SNPs can potentially be situated in open chromatin regions adjacent to lncRNAs and protein-coding genes. Since numerous lncRNAs are adjacent to non-coding SNPs, it provides a strong rationale for investigating the functional association between non-coding SNPs and lncRNAs (Cheetham et al., 2013). Notably, approximately 80% of SNPs linked to traits exist in non-coding introns or intergenic regions. Therefore, the development of more specific techniques for the exposure of RNA is fundamental. For instance, a preceding GWAS analysis identified an SNP (rs9442890) related to thyroid cancer sensibility. The suppression of the thyroid-specific lincRNA gene (PTCSC3) that indicates differentiated thyroid cancer prompted the appearance of decreased PTCSC3 in PTC cell lines and reduced tumor cell growth. As a result, compared to healthy thyroid tissue, PTCSC3 expression in tumors was considerably reduced, and the danger allele was associated with noticeably higher PTCSC325 suppression (Pasmant et al., 2011). This study indicates that many non-coding cancer-related danger regions identified by GWAS are translated into lncRNAs with critical control roles in cancer biology. LncRNAs are related with enhanced sensitivity to cancer and are engaged in tumor development and cell-cycle regulation. Thus, the concentrated rescreening of cancer-related areas for new, unique, and distinctive non-coding transcripts that might be essential regulators of carcinogenesis is therefore made possible by this method (Jendrzejewski et al., 2012).

3. LncRNAS in Cancer Diagnosis and Prognosis

LncRNAs play essential roles in cancer pathogenesis, and their dysfunction is closely related to progression and cancer development (Schmitz et al., 2016). The advancing of cancer coincides with the accumulation of epigenetic and genetic changes in the host cells. Many possible mechanisms whereby lncRNAs can impact chromatin structure, modifications, transcription, or other chromatin-associated functions orchestrated by epigenetic mechanisms have been evaluated. So, the capability to function in recruiting protein factors to regulate methylation and chromatin states the stability of proteins and complexes is vital in lncRNA biology (Campos and Reinberg, 2009). Regarding prognosis, lncRNAs are associated with tumor cell invasion, proliferation, metastasis, and patient survival. Although lncRNAs cannot code for proteins, several lncRNAs can be translated into neuropeptides. Indeed, several studies have utilized these polypeptides to create antibodies for detecting and treating cancer, for instance lncRNA-6585 and the antibodies in treating cervix cancer (CN109337903A). Lately, clinical trial complexes have advocated for the unique abilities of several lncRNAs. Expression of lncRNAs has been linked to tumor rate, metastases, stage, and overall survival (OS) in cancer, suggesting that they may be used as a prognostic indicator (Bartonicek et al., 2016).

Besides, some lncRNAs overlap with different cancers, and approximately 60% of improperly expressed lncRNAs are specific to cancer and may be isolated from the blood without interfering with normal functions. These characteristics make lncRNAs potential candidates for cancer identification. For example, one report has demonstrated that lncRNA UCA1 is sensitive to bladder cancer. UCA1 has been identified as a biomarker for bladder cancer, particularly in individuals with cursory G2-G3 (Campos and Reinberg, 2009). Also, lncRNAs cannot be only utilized as an autonomous biomarker but can also be composite with other lncRNAs or proteins to enhance the accuracy and sensitivity of detection. By assessing the expression of different lncRNAs in peripheral blood, tissue samples, or urine precipitates, many pertinent lncRNAs have been classified as ancillary or identified biomarkers in cancer detection and prediction (Liu et al., 2019). As well, some studies have reported that changes in circulating lncRNA levels correlate with cancer development. For instance, Weber et al., in their research with peripheral blood cells as a lncRNA source, demonstrated that MALAT-1 levels could reflect the presence of nonsmall cell lung cancer with a specificity of 96%25. Additionally, LncRNA MALAT-1 was also identified at considerably higher levels in the plasma of patients with prostate cancer as compared to healthy people, and these changes in circulating MALAT-1 levels were connected with prostate cancer with rather high specificity (84.8%) (Ren et al., 2012). Also, lncRNAs enhance distinctive or prognostic precision for independent or auxiliary biomarkers non-invasively extracted from tissues, biofluids, and tumor cells. Moreover, the fundamental mechanisms of lncRNAs as therapeutic targets were considered in various cancers. Because of the crucial functions of lncRNAs in cancer biology, lncRNA-based therapies could be promising for cancer patients (Mercer et al., 2009). Despite the potential of lncRNAs as diagnostic and treatment targets, there are several challenges to lncRNAs in the context of cancer. One of the challenges associated with lncRNA in cancer therapy is the lack of specificity in function and the lack of understanding of the mechanisms underlying lncRNA. Despite, many lncRNAs have been implicated in cancer development and progression, the precise

molecular mechanisms through which they exert their effects are often not well understood. Another challenge, due to the instability and susceptibility of lncRNA to degradation by nucleases in the bloodstream, is the delivery of lncRNAs to target tissues or cells. So, to address the challenges, there is a need for further research to better understand molecular mechanisms and the functions of lncRNAs in cancer.

4. Chromatin State and Methylation

A significant number of lncRNAs can interact with chromatin-remodeling complexes, driving them to certain genomic loci, while others have been implicated in the architectural conformation and activity of transcriptional enhancers (Mattick, 2001). Abnormal expression of genes drives modifications in chromatin architecture that cause instability in genomics. LncRNAs can arbitrate the chromatin-modifying apparatus to cooperate with chromatin and mediate the transcriptional silencing of numerous genes. These lncRNAs are situated in the nucleus and interact with CRCs to control the expression of genes located on a similar chromosome in *cis* or another chromosome in *trans* by fine-tuning chromatin architecture (Liu et al., 2019). So, epigenetic remodeling is attained with the interplay of a lncRNA through the polycomb repressive complex (PRC1 and PRC2), which is essential for histone methylation (Mattick, 2001; Mercer et al., 2008a). Extensive GWAS of RNA-protein linkages demonstrated that chromatin-modifying assemblies, such as PRC2, connect via many lncRNAs (Khalil et al., 2009). Additionally, proteins, including PRC1, PRC2, poly compressor complexes, and components of the Trithorax family members a significant function in the molecular pathogenesis of cancer types that regulate chromatin architecture (Kanhere et al., 2010). PRC2 offers a potential explanation that many lncRNAs could influence CRCs (Mercer et al., 2008b). A few lncRNAs identified in several human tissues can bind to Trithorax CRCs and/or activated chromatin, and at least 38% can integrate into PRC2 (Dinger et al., 2008). Thus, it is assumed that several lncRNAs (ANRIL, HOTAIR, XIST, and KCNQ1OT1) are engaged in the control of chromatin structure, and the method for operation of lncRNAs via interaction with CRCs may be more widespread (Kim and Sharpless, 2006). Antisense non-coding RNA in the INK4 locus (ANRIL) is one of the oncogenic long non-coding RNAs, that is needed to enlist the PRC1 and PRC2 polycomb complexes to the INK4B loci and mute the tumor suppressor gene p15INK4B, which is important for senescence, cell-cycle suppression, and stress-related apoptosis (Figure 2) (Kotake et al., 2011).

HOTAIR (HOX transcript antisense RNA) is a metastasis-related gene situated in the mammals HOXC locus that is a poor prognostic biomarker of many cancer types, transcribed through the HOXC loci at 12q13.13 (Gupta et al., 2010).

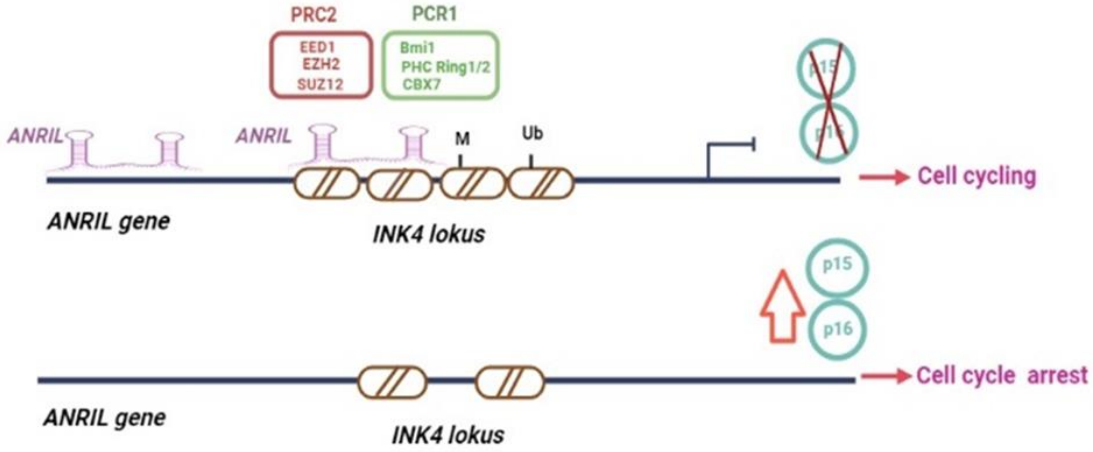

Figure 2. Schematic of antisense non-coding RNA in the INK4 locus's (ANRIL's) position and role in controlling the cell cycle.

HOTAIR lncRNA suppresses gene expression at the HoxD locus by interacting with PRC2 and deciding the location of PRC2 (Rinn et al., 2007). The interaction of HOTAIR with PRC1 and PRC2 promotes histone alterations at specific sites and may be potential regulators of epigenetic transcriptional suppression (Gupta et al., 2010). It was recently discovered that HOTAIR is a scaffold component for at least two different histone-distinct alteration assemblies. Thus, HOTAIR has been associated with the inactivation of metastasis repressor genes, reschedules the chromatin to encourage cancer metastasis, and enhances CRC proliferation and metastasis through the PCR2 combine. Also, HOTAIR lncRNAs with direct transcription factors to specific sites can direct MEG3 (maternally expressed gene 3) to interact with PRC2 and make a complex with DNA (Kotake et al., 2011). Currently, the relationship between HOTAIR overexpression in breast cancer tissues and patients' lower survival times has been established. Hence, HOTAIR can be utilized as a biological agent for the early identification of breast cancer and is nearly connected with the metastasis of breast cancer. Besides,

HOTAIR has been entangled in tumorigenesis in pancreatic cancer. Also, HOTAIR has demonstrated high efficacy in recognizing specimens from colorectal cancer patients with a specificity of 92.5%. (Figure 3) (Gupta et al., 2010).

Distinguished instances of histone-modifying complexes communicating with lncRNAs are interactions of a non-coding RNA with PRC2 derivation from X-chromosome inactivation studies in mammals. This mechanism epigenetically silences one of two X chromosomes in female embryos of mammals to ensure that females have the same number of genes linked to X as male embryos (Hung et al., 2011). The X-inactivating-specific transcript (Xist) is a lncRNA that is known to play a crucial role in the deactivation of X during female development and is a regulator of repressive complexes on the X chromosome inactivation (XCI) (Pontier and Gribnau, 2011). As for its structure, its function depends on six conserved Repeat regions (Rep A to F). Xist only is transcribed from the X chromosome's future inactive isoform (Xi) and is accountable for PRC1/2 binding.

PRC1 has been reported to interact with Xist B-repeats and PRC2 with Xist A-repeats. For example, a section encompassing the Xist B/C-repeat is required for PRC1 recruitment in the case of PRC1-Xist B repetitions (Da Rocha et al., 2014). Also, HNRNPK, which interacts physically with PRC1, was shown to play a role in RNA binding by mapping this relationship to the B repeat primarily (Pintacuda et al., 2017). For the PRC2 interaction with the RepA, Xi can institute the PRC2 binding and release to induce histone trimethylation and its across-Xi H3K27 trimethylase activity. Xist A-repeats have been demonstrated to engage EZH2 directly by interacting with its stem and loops (Zhao et al., 2008). Eventually, a natural heterochromatin arrangement and hushing of one of the two X chromosomes can result from transcriptional silencing of the whole Xi (Au et al., 2011). For example, studies with the X chromosome in mammalian species indicate that lncRNAs are expressed at various amounts in various cellular stages and may be essential for organizing chromatin structure, creating and preserving epigenetics throughout various biological processes, which can be transformed into signals that serve as markers to represent the status of development or sickness (Pontier and Gribnau, 2011). For instance, the inactivation of the X chromosome can be detected by Xist gene expression, that is normally transcribed by the passive X chromosome (Au et al., 2011).

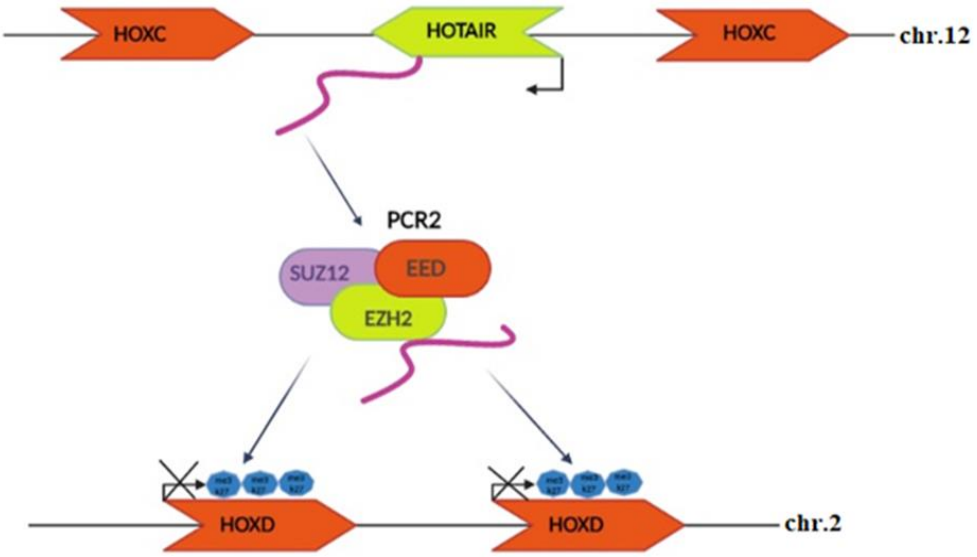

Figure 3. Illustration of the HOX transcript antisense RNA (HOTAIR), a long noncoding RNA that controls the expression of HOX genes in trans. LncRNA HOTAIR, which is translated from the HOXC group of genes (chr. 2) attaches polycomb repressive complex (PRC2) combination of the polycomb-group of proteins and directs it to the HOXD group (chr.257 12) cause to methylation of H3K27 and silence nearby HOXD genes.

5. LncRNAS in the Stability of Protein Complexes

Elucidating the expression patterns of lncRNAs is essential for a comprehensive understanding of their roles in many model systems (Bartonicek et al., 2016). Many lncRNAs apply their oncogenic roles by interacting directly with proteins or protein complexes. As a scaffold, they can collect whole protein complexes and affect the epigenetic programs of the transcriptome. Dyscontrol of lncRNA expression is related to various developmental flaws and diseases. In this manner, HOTAIR interfaces with PRC2 to bring in EZH2 to increase H3K27 trimethylation or LSD1 to demethylate H3K4me2 (Gupta et al., 2010). Other lncRNAs function as essential controllers of protein signaling networks, which contribute to carcinogenesis. The promoter region of LincRNA-p21 has binding locations for the tumor inhibitor p53, which is triggered by p53 in reactions to harm to DNA. Thus, lincRNA-p21 acting as a transcriptional repressor, like the p53 activator, could have a significant function in tumor suppression (Fatima

et al., 2015). So, research has revealed that lncRNAs can affect cancer mechanisms via various statuses because large parts of the human genome are transcribed into lncRNAs. For example, lncRNAs disrupt transcriptional mechanisms or possibly maintain the shape of nuclear speckles (Liz et al., 2014). LncRNAs influence mRNA stability and miRNA-mediated gene regulation by assisting as natural sponges for miRNA or competitive endogenous RNA (Hanahan and Weinberg, 2000). In other cases, lncRNAs function post-transcriptionally as splicing, mRNA decay, protein translation, protein stability regulators, or as molecular tools for microRNAs (Hanahan and Weinberg, 2011).

6. Regulatory Roles of LncRNAs in Cancers

6.1. Identification of LncRNAs in Tumor Pathogenesis Oncogenes or Suppressors

Finding the regulatory role of lncRNAs has led to exciting applications in diagnosis and treatment. It is crucial to postulate that lincRNAs could have essential functions in multiple oncogenic pathways and tumor suppressors. LincRNAs may impede cell cycle progression because of damage to DNA caused by stress and the environment (Huarte et al., 2010). Future studies are critical in determining whether LincRNAs can act as a tumor suppressor or oncogenic factor.

For the evaluation of lncRNAs, many molecular approaches like expression with microarrays, tiling arrays, next-generation sequencing, and methylation analysis have been described. LncRNAs were initially recognized in phenomena associated with carcinogenesis owing to their varied expression compared to normal tissues. Other research has argued the implications of multiple lncRNAs in carcinogenesis or cancer development or involved in p53 regulation. The promoters of the p53-induced LincRNAs had dramatically increased levels of retained p53 domains contrasted with the promoters of all LincRNAs (Khalil et al., 2009; Papait et al., 2013). These lncRNAs appear as vital controllers of gene expression via synergistically interacting with other fundamental mechanisms. The role of lincRNAs in various biological processes, as well as the expression patterns of specific lincRNAs (lncRNA-p21, PANDA, H19, MEG3 lncRNA, and lincRNA-EPS) and genes in the p53-dependent transcriptional pathway are summarized in Figure 4. Several lncRNAs are implicated in oncogenic and tumor suppressor functions (Huarte et al., 2010).

Similarly, A-p21 (named for its locality to the CDKN1A/p21 locus) in its promoter includes binding regions for the tumor suppressor p53, which is straight upregulated by p53 upon DNA damage in the classical p53 pathway, lncRNA-p21 is localized in the promoters of genes and is downregulated, especially in maintaining gene repression and genes regulating apoptosis (Baldassarre and Masotti, 2012). LincRNA-p21, a downstream repressor in the p53 transcriptional response and transcriptional repressor, may be crucial in tumor suppression by working similarly to the p53 activator (Figure 5).

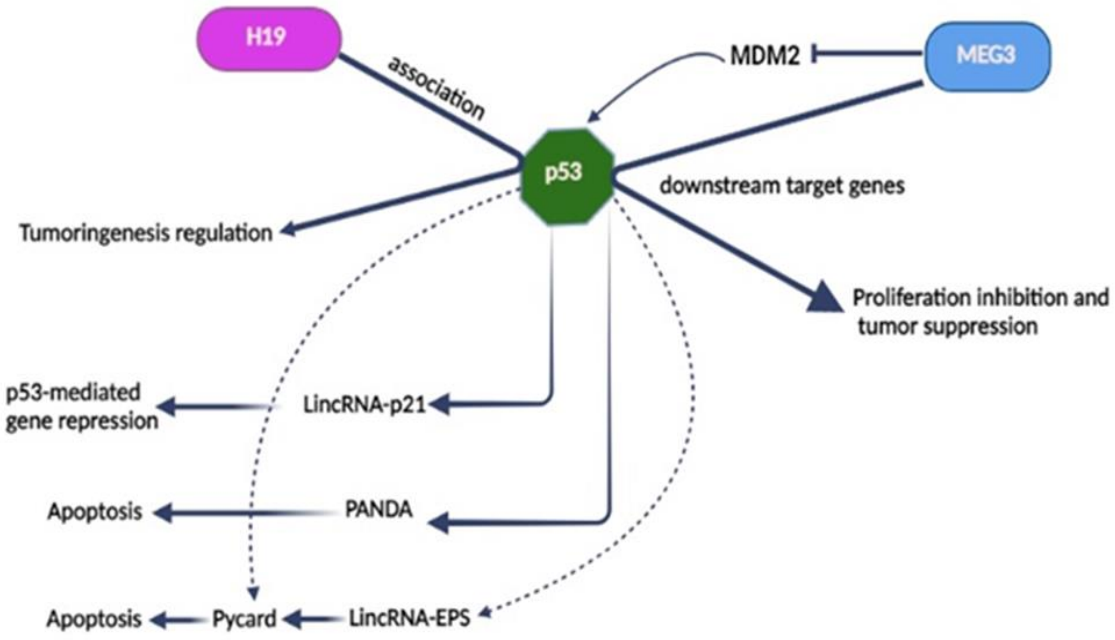

Figure 4. In the p53 path, maternally expressed 3 (MEG3) can either straight activate p53 through RNA-protein association or indirectly by inhibiting MDM2, the control of tumorigenesis is determined by the interaction of H19 with p53.The text has explored the functions of the long intergenic noncoding RNAs (lncRNAs); Long intergenic noncoding RNA p21(LincRNA-p21), P21-associated ncRNA DNA damage -activated (PANDA), and LincRNA-EPS.

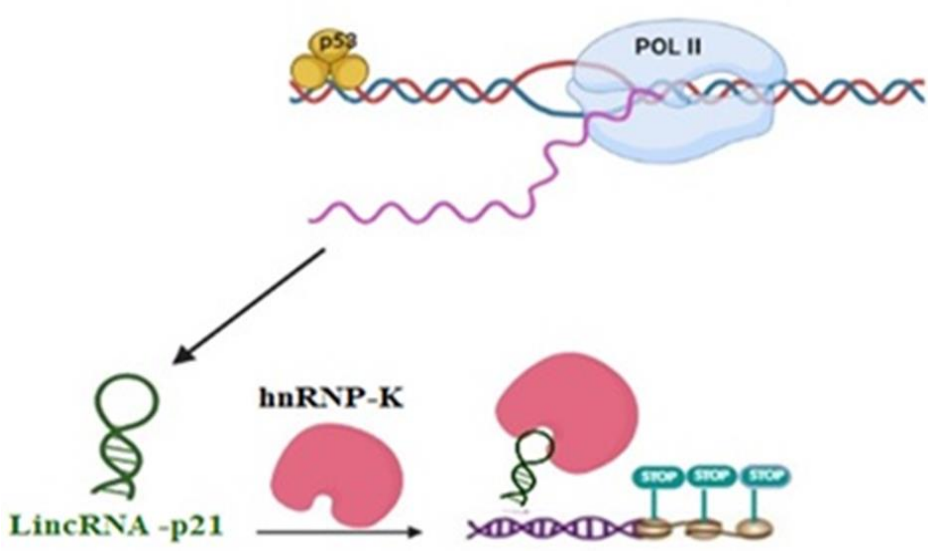

Figure 5. Mechanism of the roles of LincRNA-p21 in the transcriptional response to p53. LincRNA-p21 is triggered by the stimulation of p53 by attaching to its promoter (top left). LincRNA-p21 interacts with heterogeneous nuclear ribonucleoprotein K (hnRNP-K) to suppress genes which are downregulated as a result of the standard p53 transcriptional response.

Curiously, LincRNAs act as a suppressor in transcriptional reactions dependent on p53, and LincRNA-p21-determined transcriptional suppression is accomplished through the interaction of its genomic targets via hnRNP-K (heterogeneous nuclear ribonucleoprotein K). LincRNA-p21 is required for the induction of apoptosis and hnRNP-K binding. LincRNA-p21 has been shown to inhibit a vast range of genes associated with the p53 transcriptional response. Because hnRNP-K deficiency induces repression of similar genes that p53 and lincRNA-p21 suppress, lincRNA-p21-mediated gene suppression requires a physical link among LincRNA-p21 and hnRNP-K (Mitra et al., 2012). Indeed, two main phenotypic implications of p53 pathway activation are induction of apoptosis and growth stop which demonstrate the dysregulation of numerous genes controlling cell cycle and apoptosis by LincRNA-p21 and p53. Nevertheless, the accurate techniques in that LincRNA-p21 induced oppression at certain locations is just unknown (Baldassarre and Masotti, 2012).

6.2. LncRNA-Panda (P21 Associated ncRNA DNA Damage Activated)

The Long Non-coding RNA-PANDA is another DNA hurt respondent that is located upstream and is caused by p53 of p21. PANDA is a 1.5 kb transcript that intercede anti-apoptotic effects and is created by damaged DNA in a p53-dependent mode. It is positioned 5 kb upstream of the CDKN1A (p21) transcription begin spot (Hung et al., 2011). PANDA regulates gene expression by precluding the binding of transcriptional regulators.

PANDA is involved in the regulation of pro-apoptotic genes like BIK and FAS by functioning for the transcription element nuclear transcription factor Y subunit alpha (NF-YA). For instance, p53-reliant PANDA by directly sequestering NF-YA restrains apoptosis (Krappinger et al., 2021). PANDA decrease increases the levels of NF-YA at pro-apoptotic target genes such as CCNB1, FAS, BBC3 (PUMA), and PMAIP1 (NOXA). PANDA increases the survival of cells by interacting through the apoptotic gene expression pathway, whilst CDKN1A (p21) induces cell cycle arrest (Barsyte-Lovejoy et al., 2006).

P53 mutations have been determined in an array of cancers, retaining the gene's capacity to activate the Panda cascade and exert anti-apoptotic effects, whilst enhanced survival of tumor cells results from the removal of its capacity to induce p21 and cause an arrest in the cell cycle. The attendance of a binding location for the transcription factor NF-YA, which engages via PANDA in a very unique way, differentiates the promoter zones of p53-dependent death of cell genes (Figure 6) (Krappinger et al., 2021).

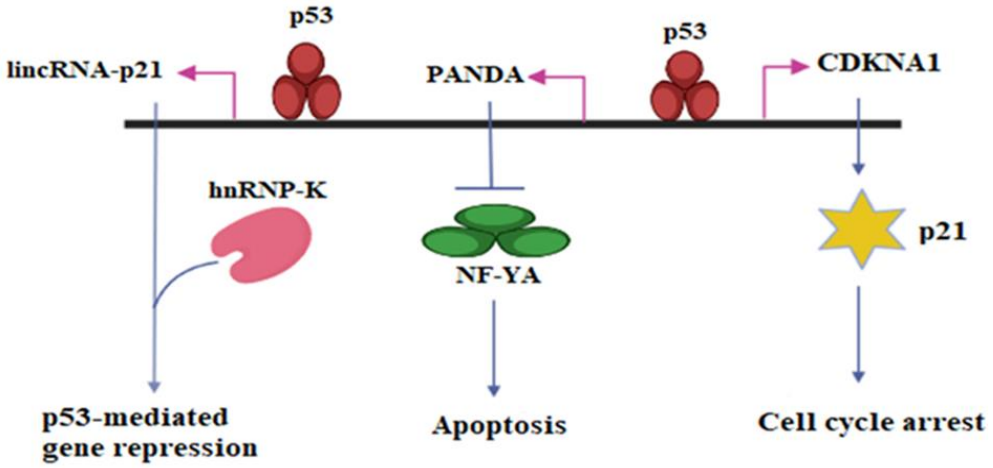

Figure 6. Schematic of orchestrating of the DNA harm response by coding and non-coding transcripts at the CDKN1A loci. Upon DNA harm, CDKN1A, non-coding transcripts PANDA, and LincRNA-p21 coordinately be activated by p53 binding at the CDKN1A loci. Cell cycle arrest is caused by CDKN1A, apoptosis is prevented by PANDA through NF-YA, and gene silencing is caused by LincRNA-p21 by recruiting hnRNP-K

6.3. LncRNA H19

Another lncRNA with extreme specificity and sensitivity for identification is H19. H19 is a paternally imprinted gene that is situated upon chromosome 11p15.5. LncRNA H19 is expressed throughout vertebrate embryogenesis but excludes bones and skeletal muscle and declines in post-natal development in the majority of tissues. Recently, LncRNA H19 was found upregulated in various tumors. The demise of overexpression and imprinting of H19 in various cancers causes H19 to act as an oncogene in the development and progression of tumors (Matouk et al., 2007). Genetic silencing of H19 promotes apoptosis in cancer cells of the stomach while abnormal expression of H19 has been found to increase cell proliferation. A recent study demonstrated that the overregulation of lncRNA H19 causes tumor development with the regulation of p53 function in stomach cancers. P53 efficiently inhibits the H19 promoter, and the connection of H19 with p53 identifies tumor development regulation (Hibi et al., 1996). In recent years, reported that lncRNA H19 has been significantly related to and upregulated in severe cancers, such as non-small cell lung, bladder, breast, thyroid, and liver carcinoma and gastric cancers (Barsyte-Lovejoy et al., 2006). Thus, several studies were conducted to scrutinize the indicative significance of lncRNA H19 in diagnosing cancer. However, there are still conflicting findings in terms of the identification reliability and accuracy of the diagnostic marker (Zhang et al., 2003).

6.4. LncRNA MEG3

Another lncRNA, the MEG3 (maternally expressed gene 3) is expressed in numerous natural tissues but lacking from a list of basic human tumors and tumor cell lines (although not from human cancer cells). It has been announced that various isoforms originate which contain 10 exons from the human MEG3 gene. The most likely reason for lncRNA MEG3 includes gene deletion, hypermethylation in various intergenic areas, and promoter hypermethylation. MEG3 is expressed in the growing nervous system, the paraxial mesoderm, and the epithelium of the kidney, pancreas, and salivary glands during higher levels of development (Kalyana-Sundaram et al., 2012).

MEG3 may directly activate p53 through RNA-protein interaction or indirectly by suppressing MDM2, both of which result in the choosy activation of p53 downstream targets including GDF-15 with tumor suppressor and anti-proliferative properties. Also, lncRNA MEG3 induces p53 protein accumulation and activates transcription through a promoter that is reliant on p53, selectively regulating the expression of p53 target genes (Ohtsuka et al., 2008). LncRNA MEG3 is related to increased susceptibility to cancer and is concerned with cell cycle regulation and tumor development. Finally, lncRNA MEG3 might be investigated as a new tumor suppressor lncRNA.

6.5. LincRNA-EPS

LincRNA-EPS (long intergenic ncRNA-erythroid pro-survival) is a 2531 nt transcript with three introns and four exons that has a 3' poly [A] tail and a 5' end cap structure that is activated during mice erythroid cell terminal differentiation (Atianand et al., 2016). LincRNA-EPS modulates erythroid cell proliferation. In comparison with the control cells, LincRNA-EPS knockdown cells in the G1 phase are enhanced and, significantly, a major fragment of these cells are in the sub-G1 population, demonstrating that they are undergoing apoptosis and/or necrosis. Thus, the cell cycle analysis demonstrates that LincRNA-EPS is directly regulated by p53 and can suppress the expression of many apoptotic genes and PYCARD, a pro-apoptotic gene, and inhibit programmed cell death. In addition, overexpression of the PYCARD gene can prevent erythroid cells from proliferating to promote apoptosis and interfere with their ability to differentiate and enucleate. There are different binding sites of regulatory

transcription factor p53 in the promoter of the PYCARD gene (Liu et al., 2016). Collectively, these results partially demonstrated the inhibition of programmed cell death (apoptosis) and regulation of erythroid differentiation of cells by LincRNA-EPS (Hu et al., 2011).

7. Pseudogene and LncRNA

Pseudogenes are roughly defined at the transcriptional or post-transcriptional stage as ancestral replicas of protein-coding genes. Pseudogenes can control original genes by changing the continuity of ancestral mRNA or generating endogenous siRNAs and they can additionally influence the expression of ancestral protein-coding genes through bimolecular processes that use RNA sequence homology (Tay et al., 2011). According to recent research, Pseudogenes are essential suppressors and promoters of human cancer, and a few of them are expressed as lncRNAs and play a role in gene silence. The finest example of a pseudogene acting as a lncRNA is found in Xist. Xist evolved from the protein-coding genes of pseudo-degeneration, in the placental mammal's descent (Poliseno et al., 2010). Other lncRNAs can perform as sequester biomolecules, a decoy, and restrict them from essential cellular processes. The instance of this approach is demonstrated with the tumor suppressor gene PTEN (phosphatase tumor suppressor gene and tensin homolog) and its pseudogene PTENP1. PTEN is a tumor suppressor gene that is post-transcriptionally regulated non-coding RNA expressed by PTEN, PTENpg1. PTENP1 performs a crucial function in cancer biology and as a microRNA sham for the PTEN tumor suppressor, limiting cell proliferation (Tay et al., 2011). PTENpg1 is a lncRNA that acts as a miRNA sponge to sequester many PTEN target miRNAs (Poliseno et al., 2010). Besides, PTEN is a negative control of the PI3K-Akt pathway and is epigenetically muted in several different cancers. The dose of PTEN expression is related to the intensity of epithelial cancers. It demonstrated that the exact regulation of the PTEN gene is vital to preserving cellular homeostasis (Tay et al., 2011).

8. Conclusions

LncRNAs are actively expressed in normal tissues and have been linked to several intracellular molecular cooperation systems as the activity of pathways or a part in cellular signaling through development and differentiation in response to various stimuli. LncRNAs play important roles in gene regulation and, more specifically, operate as scaffolds by recruiting proteins to control gene expression. This has an impact on a few cellular homeostasis factors, such as the proliferation of cells, their existence, migration, or stability of the genome. Besides, lncRNAs could form higher-ordered biologically appropriate functioning structures through RNA: RNA as well as RNA: protein interactions. Also, lncRNAs act as guides to attract transcription controllers to certain places by binding to microRNA to prevent destruction caused by miRNA. Owing to their diverse functions and highly specific expression lncRNAs, lncRNAs could serve to hold strong promise for cancer detection, predictive biomarkers, and treatments. Since lncRNAs may easily be extracted from bodily fluids like urine and plasma. So, having a thorough understanding of the expression, structures, and processes of lncRNAs can assist in detecting new, responsive biomarkers and treatment targets, opening new avenues for therapy. Additionally, lncRNAs are less toxic than protein-based anti-tumor medications, and because lncRNAs are seldom expressed, only a very low concentration of inhibitors is required to have an impact. Furthermore, bioinformatics and technology offer novel prospects for the discovery of lncRNA biomarkers. However, there are several obstacles to overcome, significant challenges remain in the advancement of efficacious lncRNA-based diagnostics and treatments, such as the deficit in specificity, limited understanding of mechanisms, and delivery challenges. yet in the long run, it is impossible to dismiss lncRNAs' potential and therapeutic importance. In conclusion, the extensive research of lncRNAs has given rise to a new desire for the identification and therapy of cancer. LncRNA investigation in cancer is expected to progress quickly in the upcoming years, with an emphasis on developing targeted therapies, investigating liquid biopsy diagnostics, and using bioinformatic tools for analysis.

Author Contributions

The percentage of the author(s) contributions is presented below. The author reviewed and approved the final version of the manuscript.

	F.V.
C	100
D	100
S	100
DCP	100
L	100
W	100
CR	100
SR	100

C= concept, D= design, S= supervision, DCP= data collection and/or processing, L= literature search, W= writing, CR= critical review, SR= submission and revision.

Conflict of Interest

The author declare that there is no conflict of interest.

Acknowledgments

The author sincerely acknowledges Prof. Sabzali JAVDOVI for his critical reading of the manuscript.

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