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Journal of Cancer Biology & Research

Review Article

A Review: p53 Relationship with Long Non-Coding RNAs (lncRNAs)

Musadiq Ali*

University of the Punjab, Pakistan

***Corresponding author**

Musadiq Ali, School of biological sciences, University of the Punjab, Lahore 54590, Pakistan

Submitted: 20 June 2025

Accepted: 14 August 2026

Published: 15 August 2026

ISSN: 2373-9436

OPEN ACCESS

Keywords
- p53
- lncRNAs

Abstract

p53 is a tumor suppressor gene and it has been mapped to chromosome 17.Under stress, p53 levels rises in the cell and leads to cell cycle arrest in G1 phase. Long noncoding RNAs (lncRNAs) are relatively abundant component of mammalian transcriptome. There are many Long noncoding RNA which are regulated by p53. In this review we have discussed some of the lncRNAs which are related to p53 such as MALAT1, NEATl, LOC285194, LOC401317, PANDA, lincRNA-p21, LincRNA-ROR, lincRNA H19, MEG3 and PURPL. It is very difficult to discriminate between lncRNAs and mRNA. But there are some criteria which can be used to discriminate between protein coding genes and lncRNAs such as lncRNA genes are shorter and have fewer number of exons. Exon in lncRNAs are shorter than protein coding genes. Protein coding genes have protein coding domains as demonstrated by pfam.

INTRODUCTION

p53, a gene that codes for a protein which acts as transcriptional factor involves in cell cycle regulation. It is very important for cells in multicellular organisms to suppress cancer. p53 has been described as "the guardian of the genome", due to its role in preventing genome mutation [1]. The name is due to its molecular mass: it is in the 53 kDa fraction of cell proteins. In normal condition p53 is present at lower level in the cell. After stress, p53 level rises in the cell and leads to transcription of many other genes, leading to inhibition of G1/S-Cdk and S-Cdk complex arresting cell in G1 phase.

lncRNAs contain 200-100,000 nucleotides. lncRNAs exhibit an mRNA-like structure with a poly (A) tail in certain cases. lncRNA have been classified based on their location with respect to protein coding genes such as; i) Intergenic lncRNAs (lincRNA): Located between two protein-coding genes; ii) intronic lncRNAs: Transcribed from the introns of protein-coding genes; iii) overlapping lncRNAs: Contain a coding gene within an intron on the same strand; iv) antisense lncRNAs: Transcribed from the opposite of the protein-coding strand; v) processed lncRNAs: Do not contain an open reading frame (ORF) [2]. lncRNAs are a relatively abundant component of the mammalian transcriptome and have been implicated in several cellular functions, such as regulation of gene transcription by recruitment of chromatin-modifying enzymes.

It is very difficult to separate coding and non coding transcript. There are some criteria which can be used to differentiate between lncRNAs and protein coding genes such as lncRNA genes are shorter than protein coding genes and have fewer number of exons [3-5]. Exons in the lncRNAs are longer than protein coding genes [4-6]. Most of lincRNAs have many introns in their sequences but some lincRNAs are found with single exon e.g. Malat1 and Neat1 [7]. Splicing of lincRNAs occurs inefficiently as compared to protein coding genes [8]. Mostly lincRNAs are linear but some circular isoform has been observed [9]. Many lincRNA has been found to be stabilizied by triple helical structure at their 3'end [10,11] .lncRNAs can have snoRNAs at both ends [12]. It has been found that lincRNAs are more tolerable than other portion of the genome for retrotransposon insertion.

On the other hand, Protein coding genes have known protein domains as shown in the pfam database. Protein coding region has sequence similarity to protein sequences which are found in the protein sequence alignment data bases. Expression of lncRNA is more variable than mRNA in many tissues [3-5]. The median lncRNAs level is only about a tenth than median mRNA level [3-16].

It has been described previously in the literature that

many lncRNAs are under the control of p53. These p53 associated lncRNAs may act as better biomarkers for early diagnosis and prognosis of different type of tumors. p53 regulated lncRNA have been broadly classified in to 2 groups. Group 1 are those lncRNAs serving as p53 regulators such as MALAT1, maternally expressed gene 3 (MEG3), p53-eRNAs, and Wrap53.Group1 lincRNA regulate the mRNA stability of p53 and have impact on the transcription of p53 target genes. Group 2 lincRNAs act as p53 effector for e.g lncRNA-p21, PANDA, H19, and loc285184.lincROR is a unique that it not only suppress the DNA damage induced by p53 but also form auto regulatory loop with p53 [17]. In this review, some lncRNA are discussed which are under the control of p53 such as lincRNA-p21, LincRNA-ROR, lincRNA H19, MEG3 and PURPL, MALAT1, NEATI, LOC285194, LOC401317, PANDA.

MALAT1

MALAT1 metastasis-associated lung adenocarcinoma transcript-1 is intergenic long non coding RNA. MALAT1 size is 7kb in human having single exon. Because of depletion of MALAT1, cell cycle arrest occurs in human. Its depletion also leads to activation of p53 and its target genes [18]. It has been shown that MALATI lincRNA is not essential for life and development in mice [19-21]. Abundant MALATI isoform is non polyadenylated. It have triple helical structrure at its 3' end [10,11]. It is localizied to speckles, a suborganelle inside the nucleus.

NEATI

NEAT1 is a intergenic long noncoding RNA, which is responsible for inactivation of p53 [22]. NEATI is found at the upstream of MALATI lincRNA. It is expressed in mouse and human tissues [7]. NEAT1 has 2 isoforms. 3.7 kb Menε which ends with a proposed polyadenylation site, and 22.7 kb Menβ (beta).NEATI is localizied to paraspeckles inside the nucleus (Sunwoo et al, 2009). NEAT1 isoform, Menβ is essential for the formation of para speckles [23]. Depletion of NEAT1 by RNAi leads to disintegration of paraspeckles [24]. Both type of NEAT1 isoform have triple helical structure at their 3' end.

LOC285194

LncRNA Loc 285194 is transcriptionaly regulated by p53.Loc285194 is a lincRNA which is down regulated in many cancer types especially, osteo sarcoma in humans. Increased expression of loc285194 *in vivo* and *in vitro* leads to suppression of tumor. Loc285194 acts as tumor supressor by inhibiting the normal function of mir-211. It has been shown previously that loc285194 act as transcription target of p53 [25].

lincRNA-p21

lincRNA-p21 is intergenic long noncoding RNA. Its size is unknown. It is directly regulated by p53.lincRNA -p21 promoter has p53 binding domain. It was further observed that lincRNA-p21 function overlap with that of p53. It was observed that lincRNA-P21involves in p53 dependent apoptosis but not in the cell cycle arrest [26].

LOC401317

lncRNA LOC401317 is induced by p53. Over expression of lincRNA LOC401317 leads to inhibition of Nasopharyngeal carcinoma cell line HNE2 cells in humans, in vivo and in vitro. It inhibits cell cycle progress by increasing p21 expression. LOC401317 leads to decreases cyclin D1 and cyclin E1 expression. It promotes apoptosis through the induction of poly(ADP-ribose) polymerase and caspase-3 cleavage. Collectively, these results suggest that LOC401317 is directly regulated by p53 and exerts antitumor effects in HNE2 nasopharyngeal carcinoma cells [27].

PANDA

PANDA (P21 associated ncRNA DNA damage activated) is 1.5kb long and contains single exon. PANDA surrounds the transcription start site of CDKN1A.It is located ~5 kb upstream of the CDKN1A (p21) transcription start site. In humans fibroblast, it is induced by doxorubicin treatment along with CDKN1A gene.CDKN1A gene cannot directly activates the PANDA.P53 binds to CDKN1A and leads to activation of PANDA. It has been shown that PANDA cannot be activated in DNA damage without p53 [28].

LincRNA-ROR

LincRNA-ROR (lincRNA-Regulator of Reprogramming) gene is 2.6 kb. It is located on chromosome 18 (hg19 chr18:54,721,802-54,739,350), consisting of four exons. It has been shown that knockdown of lincRNA-ROR leads to increase in apoptosis and activation of p53 pathway [29]. However, lincRNA-ROR has little effect on the p53 in the unstressed cells. The lincRNA-ROR form a autoregulatory loop with p53. The expression of p53 is positively regulate the expression of lincRNA- ROR. P53 interacts with p53 response element in the promoter of lincRNA-ROR. High expression of lincRNA-ROR has been observed in embryonic stem cell and iPSCs. The expression of LincRNA-ROR has been found to be regulated by transcriptional factors such as Oct4, Sox2 and Nanog [30].

lncRNA H19

lncRNA H19 size is 2.3 kb. (The imprinted oncofetal

long non-coding RNA) is specifically expressed in the embryos. At birth it is repressed inside the human body. But it is highly expressed in the tumors. It is expressed at all stages of human cancers. In all type of human tumors its expression is up regulated. In tumors upregulation of lncRNA H19 leads to genomic instability and hypoxia. lncRNA H19 response in tumors correlate with the functioning of tumor suppressor gene p53.p53 suppress the promoter activity of lncRNA H19 gene [31,32].

MEG3

The size of MEG3 is 1.6kb. MEG3 is located on chromosome 14q32.MEG3 activates p53.Normally, in the cell, the level of p53 is very low due to its degradation by ubiquitin-proteasome pathway. The ubiquitin of p53 is mediated by MDM2 and E3 ubiquitin ligase. MEG3 downregulates MDM2 leading to activation of p53 [33].

PURPL

PURPL is long noncoding RNA which controls the level of p53 in the cell. Targeted depletion of PURPL in colorectal cancer cells leads to increase in the level of p53. MYBBP1A is a protein which interact and stabilize p53. PURPL interact with MYBBP1A and prevents its binding with p53 [34].

CONCLUSION AND FUTURE PROSPECT

There are many lncRNAs which are regulated by p53. It is need of hour to look for lncRNAs which are regulated by p53 directly. Those lncRNAs which are regulated by mutant p53 can act as biomarkers for early diagnosis and prognosis of tumors.

ACKNOWLEDGEMENTS

I pay tribute to Mr Wajid Ali (lecturer, Computer science, Government Islamia college civil lines, Lahore,) for providing his expertise on endnote, software.

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