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Long noncoding RNAs in the p53 network

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Abstract

The tumor-suppressor protein p53 is activated in response to numerous cellular stresses including DNA damage. p53 functions primarily as a sequence-specific transcription factor that controls the expression of hundreds of protein-coding genes and noncoding RNAs, including microRNAs (miRNAs) and long noncoding RNAs (lncRNAs). While the role of protein-coding genes and miRNAs in mediating the effects of p53 has been extensively studied, the physiological function and molecular mechanisms by which p53-regulated lncRNAs act is beginning to be understood. In this review, we discuss recent studies on lncRNAs that are directly or indirectly regulated by p53 and how they contribute to the biological outcomes of p53 activation. Published 2016. This article is a U.S. Government work and is in the public domain in the USA.

INTRODUCTION

The advent of RNA-sequencing (RNA-seq) has revealed the transcriptional complexity of the human genome. Thousands of long noncoding RNAs (lncRNAs), a heterogeneous class of noncoding RNAs >200 nucleotides (nt) long with low or no coding potential, have been identified by RNA-seq. According to the most recent version of Gencode (v24) 15,941 lncRNAs are transcribed from the human genome. Although the function of the vast majority of lncRNAs has not been investigated, increasing evidence suggests that some lncRNAs regulate critical cellular processes^{1,2} including cellular proliferation, differentiation and development, dos-age compensation, chromosomal imprinting, and genomic stability.^{3–12}

lncRNAs can mediate their effects by diverse mechanisms; they can act as molecular scaffolds to recruit chromatin modifiers at specific genomic loci and thereby activate or repress target gene expression.^{13,14} They can regulate gene expression in *cis*^{15–17} or in *trans*¹⁸ such as splicing,⁶ mRNA translation,¹⁹ and mRNA degradation.²⁰ In addition, lncRNAs can act as decoys for RNA-binding proteins or as sponge for microRNAs (miRNAs)^{21,22} or by directly interacting with RNA and DNA by base pairing.^{23,24} lncRNAs can be localized in the nucleus and/or cytoplasm^{25,26} and based on their genomic localization and proximity to protein-coding genes they have been classified as intergenic, intronic, bidirectional, sense, or antisense.²⁷

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A major challenge in the lncRNA field is figuring out the molecular mechanisms by which they act. Unlike miRNAs that act via the RNA interference (RNAi) pathway,²⁸ each lncRNA has the potential to mediate its effect via a unique molecular mechanism. Identifying the molecular interactors of an lncRNA may also provide insights on the function of the lncRNA. Another approach to identify the function of an lncRNA is by identifying the transcription factors that drive its expression. For example, if an lncRNA is transcriptionally regulated by p53, it can mediate the effects of p53 by regulating the expression of select genes in the p53 network.

The master regulatory transcription factor p53 is the most frequently mutated protein in human cancer.²⁹ p53 is the most extensively studied transcription factor that is activated during the stress response including replicative stress, oxidative stress, hypoxia, DNA damage, nutrient deprivation, and telomere shortening.^{30–32} The outcomes of p53 activation are diverse and include induction of cell cycle arrest, apoptosis, autophagy and senescence, and inhibition of invasion, migration, stemness, and metabolic reprogramming, all together leading to tumor suppression.^{33,34} Transcriptional regulation of protein-coding genes by p53 is very well documented in literature.^{31,33} In addition, others and we have shown that several miRNAs are direct targets of p53 and function as downstream effectors of p53.^{35–40} More recently, specific lncRNAs have been identified as p53 targets and some of these have been shown to function in p53 signaling. In this review, we provide an update on the role of lncRNAs in p53 signaling. In particular, we summarize the known roles of lncRNAs in the p53 network.

p53-REGULATED lncRNAs lncRNAs at the p21 Locus

p21 (also known as *CDKN1A*, cyclin-dependent kinase inhibitor 1) mediates p53-dependent G1 growth arrest.^{41,42} The lncRNAs, *lincRNA-p21* and *PANDA*, have been identified to be located and transcribed from the p21 locus. *LincRNA-p21* regulates gene expression both at the transcriptional level as well as post-transcriptionally by associating with the RNA-binding protein HuR. *PANDA* on the other hand regulates the expression of proapoptotic genes by interacting with the transcription factor NF-YA and regulates senescence by interacting with scaffold-attachment-factor A (SAFA).

LincRNA-p21—The *LincRNA-p21* was identified by microarrays performed from p53^{LSL/LSL} MEFs (mouse embryonic fibroblasts) and lung tumor cells derived from mice expressing KRAS (p53^{LSL/LSL}). In this study, the endogenous p53 locus was inactive by insertion of a STOP cassette flanked by loxP sites (LSL) in the first intron and the p53 expression could be restored by Cre recombination. p53^{LSL/LSL} MEFs (Cre+/-) were treated with the DNA-damaging agent Doxorubicin and KRAS (p53^{LSL/LSL}) tumor cells were treated with hydroxytamoxifen for p53 restoration. *LincRNA-p21* was identified as one of the 11 lncRNAs induced by p53 in both the systems.⁴³

LincRNA-p21 is located on chromosome 17, ~15 kb upstream of the *Cdkn1a* (p21) gene and hence named as *lincRNA-p21*. This lncRNA was the first identified p53-regulated intergenic lncRNA and was reported to have a proapoptotic function in the p53 network⁴³ (Figure 1(a)). Gene expression analysis following independent knockdown of *lincRNA-p21* and p53

in MEFs identified a large subset of commonly repressed genes, including regulators of apoptosis and cell cycle, suggesting that *lincRNA-p21* is a downstream effector of p53-dependent transcriptional response.⁴³ Knocking down *lincRNA-p21* in MEFs and treatment with Doxorubicin increased cell survival without significantly altering the cell cycle.⁴³ In this study, *lincRNA-p21* was shown to mediate its function in *trans* by associating with the RNA-binding protein hnRNP-K and this interaction is needed for proper localization of hnRNP-K at repressed genes loci and regulation of p53-mediated apoptosis⁴³ (Figure 1(a)).

However, in another study, via conditional knockout of *lincRNA-p21* in MEFs, the authors found that *lincRNA-p21* functions predominantly in *cis* and regulates the expression of its neighboring gene p21¹⁵ (Figure 1(a)) unlike the previous study which reported that *lincRNA-p21* regulates gene expression in *trans* by binding to hnRNP-K.⁴³ It is unclear if this discrepancy in the two studies could be because of different approaches used to deplete *lincRNA-p21*. Huarte et al. used RNAi to knock-down *lincRNA-p21* whereas Dimitrova et al. used *lincRNA-p21* conditional knockout MEFs.

The confusion on the mechanism of action of *lincRNA-p21* was resolved in a recent study on the *in vivo* characterization of this lncRNA.⁴⁴ Using a knockout mouse model and a massively parallel enhancer assay, the authors delineated the functional elements at the *lincRNA-p21* (designated as *Linc-p21* in this study) locus. They showed that even in tissues with no detectable *linc-p21* expression, deletion of this locus significantly affects local gene expression, including that of p21. The authors systematically interrogated the underlying DNA sequence for enhancer activity and identified multiple enhancer elements. In sum, the findings from this elegant *in vivo* study suggests that the *cis*-regulatory effects mediated by *linc-p21* may also be due to DNA enhancer elements.

LincRNA-p21 also regulates genes at the post-transcriptional level.¹⁹ For instance, the RNA-binding protein HuR associates with *lincRNA-p21* and recruits let-7/Ago2 to *lincRNA-p21* leading to its degradation (Figure 1(b)). Knocking down HuR leads to an increase in the *lincRNA-p21* levels both in nucleus as well as in cytoplasm. In the absence of HuR, *lincRNA-p21* can associate with select mRNAs including *JUNB* and *CTNNB1* and inhibit their translation. However, an increase in cytoplasmic HuR levels decreases *lincRNA-p21* expression, resulting in upregulation of *JUNB* and *CTNNB1* mRNA translation.¹⁹ Thus, HuR regulates translation of select mRNAs by influencing *lincRNA-p21* levels (Figure 1(b)).

LincRNA-p21 is also reported as a key regulator of cell proliferation and apoptosis during atherosclerosis.⁴⁵ The expression of *lincRNA-p21* was significantly lower in atherosclerotic plaques of ApoE (−/−) mice, an animal model for atherosclerosis, as compared to wild-type mice. *LincRNA-p21* represses cell proliferation and induces apoptosis in human smooth muscle cells and mouse mononuclear macro-phage cells. In addition, the authors of this study showed that this lncRNA interacts with MDM2 in both human and mouse and knocking down *lincRNA-p21* decreased p300/p53 interaction and increased MDM2/p53 interaction, thus affecting p53-transcriptional activity.⁴⁵ Furthermore, *lincRNA-p21* is a mediator of both UVB-induced and p53-mediated apoptosis in mouse and human keratinocytes and also ING1b-induced apoptosis.^{46,47} *LincRNA-p21* is also induced during

hypoxia and there is positive feedback loop between HIF-1 α and *lincRNA-p21* that promotes glycolysis under hypoxia⁴⁸ (Figure 1(c)). Finally, *lincRNA-p21* also plays a role in regulating somatic reprogramming by forming a complex with hnRNPK and either H3K9 methyltransferase SETDB1 or DNA methyltransferase DNMT1, at the pluripotency gene promoters.⁴⁹

PANDA—The p53-regulated lncRNA *PANDA* refers to ‘P21 Associated NcRNA DNA damage Activated.’ *PANDA* was identified in a study where the authors created an ultra-high density tiling arrays comprising the promoters of 56 cell cycle genes including *CDKN2A* (p16), *p14ARF*, and *CDKN2B* (p15) to examine 54 pairs of polyade-nylated RNA samples. These RNA samples were obtained after diverse perturbations including cell cycle synchronization, DNA damage, differentiation stimuli, oncogenic stimuli, or carcinogenesis.²² They identified five lncRNAs including *PANDA* at the *p21* promoter that are induced by DNA damage.

PANDA is a monoexonic lncRNA located ~5 kb upstream of the *p21* transcriptional start site and ~2.5 kb upstream of the major p53 response element of p21. *PANDA* plays a role in maintaining cell cycle arrest and survival following DNA damage.²² Knocking down *PANDA* in human fibroblasts sensitized the cells to DNA damaged-induced apoptosis and increased the expression of several genes encoding canonical activators of apoptosis.²² *PANDA* interacts with the nuclear transcription factor NF-YA and thereby restricts binding of NF-YA to the chromatin, limiting the activation of apoptotic genes²² (Figure 2). *PANDA* also interacts with SAFA and this interaction has a crucial role in senescence.⁵⁰ The authors found that *PANDA* is present at ~130 copies per nucleus in proliferating fibro-blasts and ~1200 copies per nucleus in senescent fibroblasts. In proliferating cells, *PANDA* interacts with SAFA and this interaction represses senescence-promoting genes by recruiting polycomb repressive complex (PRC) proteins BMI1–PRC1 and EZH2– PRC2 to promoters of these genes e.g., *p21* and *PANDA* itself.⁵⁰ Also, in proliferating cells, the binding affinity of NF-YA to *PANDA* is low and therefore it can activate E2Fs (Figure 2). However, in senescent cells, the SAFA-*PANDA*-PRC complex is disrupted and the expression of prosenescence genes including p21 is upregulated. *PANDA* can now interact with NF-YA and block proliferation by sequestering NF-YA away from occupying E2F/NF-YA target gene promoters.⁵⁰

In summary, *p21*, which is a well-studied target of p53 and a major cell cycle regulator, houses two lncRNAs upstream of its promoter and these two lncRNAs regulate contrasting phenotypes. While *lincRNA-p21* is proapoptotic and functions in *cis*, *PANDA* is antiapoptotic and functions in *trans*, in the context of DNA damage.

Pint—The lncRNA *Pint* (p53-induced noncoding transcript), also known as *lincRNA-Mkln1*, was identified in the same study that discovered *lincRNA-p21*.⁴³ *Pint* is predominantly nuclear and a direct p53 target induced after p53 activation. Knocking down *Pint* followed by Doxorubicin treatment decreases the number of cells in S phase, and simultaneously increases the population of cells in G1 and apoptotic cells.⁵¹ Overexpressing *Pint* increased cell proliferation and decreased cellular apoptosis, suggesting that *Pint* is a positive regulator of proliferation during DNA damage.⁵¹ Gene expression analysis in MEFs

transfected with antisense oligos to deplete *Pint* or control antisense oligos, and subsequent treatment with Doxorubicin revealed that *Pint* regulates the expression of genes involved in cellular growth and proliferation and cell survival, and several genes in the mitogen-activated protein kinase (MAPK), transforming growth factor (TGF)- β , and p53 signaling pathways⁵¹ (Figure 3). By performing RNA immunoprecipitation (RIP) experiments from Doxorubicin-treated MEFs followed by IP with Suz12 subunit of PRC2, the authors found enrichment of *Pint* RNA in PRC2 immunoprecipitates. In addition, the authors confirmed the interaction between *Pint* and PRC2 by performing RNA pull-down experiments using *in vitro* synthesized biotinlabeled *Pint* RNA. They showed that the interaction between *Pint* and PRC2 is required for the targeting of PRC2 to repress the expression of subset of genes, thus regulating cell proliferation.⁵¹

Furthermore, the authors explored the possibility of existence of *Pint* ortholog in humans. They found an lncRNA at a syntenic location in the human genome that shared high 5' end sequence homology to the mouse *Pint* RNA. The human ortholog of *Pint* is also transcriptionally regulated by p53 and significantly downregulated in colorectal tumors compared with normal tissue suggesting a potential tumor-suppressor lncRNA (Figure 3).⁵¹

Interestingly, human *Pint* has the opposite phenotype of the mouse ortholog. Contrary to what was observed in MEFs, HCT116 (colorectal cancer) cells overexpressing *Pint* showed a significant decrease in proliferation, both in the presence or absence of Doxorubicin-induced DNA damage, as well as in the number of cells in S phase and increase in the percentage of cells in both G1 and G2/M phases.⁵¹ In conclusion, lncRNA *Pint* represents an interesting example of p53-regulated lncRNA with high sequence homology in both human and mouse species. Although both the orthologs are predominantly nuclear, interact with PRC2, and regulate similar pathways, knocking down *Pint* expression in MEFs has a phenotype similar to HCT116 cells overexpressing human *Pint*; this unexpected result may represent species-specific molecular interactors of this lncRNA.

PR-lncRNA-1* and *PR-lncRNA-10—Sanchez et al., 2014 performed RNA-seq and p53-ChIP-seq from HCT116 cells treated with the chemotherapeutic drug 5-FU (5-Fluorouracil) and identified 18 lncRNAs directly regulated by p53, of which 3 showed conserved regulation in mouse cells. Among these 18 lncRNAs, *RP11-467J12.4 (PR-lncRNA-1)* was identified as a nuclear, multiexonic, intergenic lncRNA regulated in a p53-dependent manner in both human and mouse cells. Another lncRNA, *PR-lncRNA-10* was identified as a nonannotated intergenic nuclear lncRNA with no mouse orthologs.⁵²

Both *PR-lncRNA-1* and *PR-lncRNA-10* are negative regulators of cell survival and proliferation as knocking down these lncRNAs increased proliferation and decreased apoptosis in the presence or absence of Doxorubicin or 5-FU.⁵² Gene expression profiling after depletion of *PR-lncRNA-1* or *PR-lncRNA-10*, following DNA damage suggested that *PR-lncRNA-1* regulates the expression of genes involved in apoptosis and proliferation such as *BCL2L* and *BIRC3*, the DNA polymerase subunit *POLA1* and the cytokine *TGFB2*. *PR-lncRNA-10* was found to regulate the expression of p21, the transcription factor *JUNB* and the apoptosis regulators *BIRC6*, *TP53I3*, and *FAS*.⁵² Furthermore, p53-ChIP experiments in the presence and absence of *PR-lncRNA-1* or *PR-lncRNA-10* followed by 5-FU treatment

revealed that these lncRNAs are also required for the efficient binding of p53 to some of its target genes. However, the molecular mechanism by which these two lncRNAs regulate binding of p53 to its targets remains unclear.

NORAD—*NORAD* (noncoding RNA activated by DNA damage) has recently been identified as a lncRNA with high degree of evolutionary conservation in mammals. The mouse ortholog of *NORAD* was identified among several lncRNAs induced after Doxorubicin treatment in p53^{+/+} and p53^{-/-} MEF.⁵³ The function and mechanism of this lncRNA has recently been identified.³

Interestingly, although *NORAD* is induced after Doxorubicin treatment in a p53-dependent manner, it is not a direct p53 target. *NORAD* is a very abundant, cytoplasmic lncRNA expressed at ~300–1400 copies per cell. Genetic deletion of *NORAD* in HCT116 cells suggested that this lncRNA regulates chromosomal stability.³ *NORAD*^{-/-} cells can have tetraploid DNA content, variable chromosome numbers with 4N DNA content and both diploid and tetraploid *NORAD*^{-/-} clones undergo chromosomal rearrangements.³ To search for functional domains in *NORAD*, the authors used an elegant approach by aligning the sequence of *NORAD* to itself using the BLAST algorithm. This approach uncovered a ~400 nt domain that is repeated five times in the *NORAD* transcript. Using *in vitro* RNA pull-downs followed by mass spectrometry, the authors found that *NORAD* binds to PUMILIO protein PUM2 and this interaction occurs in each of the five domains. Moreover, the authors confirmed the *NORAD*-PUM2 interaction by PARCLIP on endogenous PUM2 in HCT116 cells and this analysis identified 15 binding sites for PUM1/PUM2 protein per molecule of *NORAD*. To determine the functional significance of this interaction, the authors performed RNA-seq in *NORAD*^{+/+} and *NORAD*^{-/-} HCT116 cells and found that PUM2 CLIP targets were significantly downregulated in *NORAD*^{-/-} cells, representing genes that are regulators of the cell cycle, mitosis, DNA repair, and DNA replication. These results were further supported by the RNA-seq with PUM1/2 overexpressing HCT116 cells that depicted expression profiles with similar patterns as *NORAD*^{-/-} cells and PUM1/2 overexpression also increased level of aneuploidy.³ More importantly, depleting PUM1/2 in *NORAD*^{-/-} cells using CRISPR/Cas9 or TALENs, partially suppressed chromosomal instability and surprisingly, the double knockout led to considerable aneuploidy, highlighting that tight control of PUM1/2 levels is necessary to maintain genomic stability. Altogether, this study demonstrates that PUM1/2 proteins are downstream of *NORAD* and play an important role in the maintenance of genomic stability (Figure 3). In sum, *NORAD* is a very abundant lncRNA indirectly regulated by p53. *NORAD* has multiple binding sites for cellular protein *PUMILIO*. *NORAD* sequesters a significant fraction of *PUMILIO* proteins and making them unavailable to repress the target genes. These targets represent genes that are critical for mitosis, DNA repair, and DNA replication. In the absence of *NORAD*, there is increased genomic instability leading to aneuploidy.

TUG1—The lncRNA *TUG1* (Taurine Upregulated Gene 1) was identified in a screen for genes upregulated by taurine (a cysteine derivative important for neural development), and siRNA-based depletion of *TUG1* in the developing mouse eye blocked retinal development.⁵⁴ Later, *TUG1* was identified among the 39 lncRNAs induced after DNA damage in both

human and mouse fibroblasts in a p53 dependent manner and its promoter contains several conserved binding sites for p53.^{13,53} By performing a RIP-ChIP assay in the HeLa cells as well as human fibroblast cells, this lncRNA was found to be associated with PRC2.¹³ SiRNA-mediated knock down of *TUG1* in human fibroblasts leads to upregulation of genes involved in cell cycle control. Knockdown of *TUG1* significantly increased cell proliferation, *in vitro* clonogenicity, and cell cycle progression in the nonsmall cell lung cancer cell lines SPC-A1 and NCI-H1650.⁵⁵ *TUG1* regulates tumorigenicity *in vivo*, as nude mice injected with scramble/sh*TUG1*-transfected SPC-A1 cells develop bigger tumors and displayed higher Ki-67 staining.⁵⁵ Knockdown of *TUG1* upregulates homeobox B7 (HOXB7) expression and ChIP assays showed that knockdown of *TUG1* resulted in the loss of H3K27 trimethylation and PRC2 binding to the genomic loci of HOXB7, confirming that HOXB7 was a bona target of TUG1/PRC2-regulated genes.⁵⁵ The exact mechanism how *TUG1* limits cell proliferation is not known, however, one possible mechanism is via epigenetically regulating HOXB7 expression.

Interestingly, some other studies in different cancer types reported a contrasting phenotype. They showed that *TUG1* promotes cell proliferation of esophageal squamous cell carcinoma,⁵⁶ urothelial carcinoma of bladder,⁵⁷ osteosarcoma,⁵⁸ and hepatocellular carcinoma.⁵⁹ In hepatocellular carcinoma cells, *TUG1* silencing resulted in decreased proliferation, colony formation, tumorigenicity, and induced apoptosis. *TUG1* epigenetically repressed Krüppel-like factor 2 (KLF2) transcription by binding to PRC2 and recruiting it to KLF2 promoter region.⁵⁹ In conclusion, as mentioned previously that lncRNAs can function in a cell type specific manner, *TUG1* is an example of p53-regulated lncRNA that has opposite effects in different cancer types.

PVT1—Plasmacytoma Variant Translocation 1 (*PVT1*) locus encodes several noncoding RNAs including *PVT1* and a cluster of six miRNAs, miR-1204, miR-1205, miR-1206, miR-1207–5p, miR-1207–3p, and miR-1208.⁶⁰ The *PVT1* locus was first discovered in mouse, frequently associated with translocations in plasmacytomas.⁶¹ In humans, the *PVT1* locus maps to chromosome 8 (8q24), which is a site of genetic alterations, including translocations, amplifications, and viral integration in a wide variety of malignancies and lies ~60 kb downstream of the *MYC* oncogene.⁶² p53 induces transcription on the *PVT1* locus and there is a conserved p53-binding site ~1200 bp downstream of the *PVT1* transcriptional start site and 172 bp upstream of the miR-1204 stem-loop sequence.⁶³ *PVT1* functions as a competitive endogenous RNA in miRNA-mediated sponge interactions in normal breast tissues, but not in the cancerous cells.⁶⁴ It has a strong binding preference to the miR-200 family.⁶⁴ *PVT1* also interacts with MYC protein and prevents its degradation by reducing phosphorylation of its T-58 residue.⁶⁵

LINP1—Similar to *NORAD*, the lncRNA *LINP1* (lncRNA in nonhomologous end joining pathway 1) is not directly regulated by p53. *LINP1* is overexpressed in human triple-negative breast cancer and associates with two proteins of the NHEJ DNA repair pathway, Ku80 and DNA-PKcs.⁶⁶ Knocking down *LINP1* delays ionizing radiation (IR)-induced DNA damage and increases γ -H2AX levels. Wild-type p53 negatively regulates *LINP1* expression as its expression is higher in the breast cancer tumors with mutant p53.

Activation of p53 by Nutlin-3a treatment in MCF10A (breast cancer) and HCT116 cells that express wild-type p53 significantly decreased the expression of *LINPI*. However, Nutlin-3a treatment of MDA-MB-231 cells that express mutant p53 or HCT116 cells with homozygous *TP53* deletion, does not alter *LINPI* levels.⁶⁶ No p53-binding site was found on the *LINPI* promoter suggesting that it is not a direct transcriptional target of p53. Interestingly, exon 2 of *LINPI* has binding sites for miR-29, which is positively and directly regulated by p53 and therefore, miR-29 may be the mediator of p53-regulated *LINPI* expression.⁶⁶

DDSR1—LncRNA-*DDSR1* (DNA damage sensitive RNA1) is a ~1.6-kb long transcript that is induced in response to different DNA-damaging agents including camptothecin, etoposide, and Neocarzinostatin (NCS).⁶⁷ *DDSR1* has NF-κB-binding site ~1.1 kb upstream of the transcription start site and its induction after DNA damage is regulated by the ATM-NF-κB signaling pathway. Although p53 can promote *DDSR1* induction upon DNA damage, it is not necessary for *DDSR1* induction. Additionally, depletion of *DDSR1* followed by camptothecin treatment leads to upregulation of several p53 target genes including *p21*, *PUMA*, and *GADD45* suggesting that *DDSR1* negatively regulates p53-mediated gene expression. Knocking down *DDSR1* reduced cell proliferation in several cell lines including U2OS, PC3, and A549. Furthermore, depletion of *DDSR1* followed by camptothecin treatment significantly reduces the levels of γ-H2AX, phosphor-RPA (Ser4/8), phospho-CHK1 (Ser345), and phosphor-p53 (Ser15). However, there was no increase in phosphor-ATM suggesting that *DDSR1* acts downstream of ATM and regulates DNA damage response signaling. By using MS2-TRAP-tagged RNA affinity purification followed by mass spectrometry, the authors identified several DNA-damage related proteins to be associated with *DDSR1* including heterogeneous nuclear ribonucleoprotein U-like 1 (hnRNPUL1) and BRCA1 which are involved in homologous recombination (HR). The authors further showed that *DDSR1* regulates the recruitment of HR repair factors BRCA1 and RAP80 to the double-strand breaks and thus modulating DNA repair by HR. In summary, *DDSR1* is a p53-regulated lncRNA that is not directly regulated by p53 and plays an important role in maintaining genome stability.

LncRNAs THAT REGULATE p53

MALAT1—*MALAT1* (Metastasis Associated Lung Adenocarcinoma Transcript 1) also known as nuclear-enriched abundant transcript 2 (*NEAT2*) is an abundant nuclear lncRNA overexpressed in many cancers, and its high expression is associated with hyperproliferation and metastasis.⁶⁸ *MALAT1* regulates gene expression and pre-mRNA splicing by interacting with pre-mRNA splicing factors including serine arginine dipeptide-containing SR family splicing factors and recruitment of SR splicing factors from nuclear speckles to sites of transcription.^{6,69} Overexpression of *MALAT1* promotes cell proliferation and migration *in vitro*, and promotes tumor growth and metastasis *in vivo*⁷⁰ whereas silencing *MALAT1* expression results in reduced migration, metastasis, and tumorigenicity.⁷¹

In human fibroblasts, *MALAT1* levels are differentially regulated during cell cycle with low levels during G1 and G2 and high levels during G1/S and mitosis.⁵ Depletion of *MALAT1* using antisense oli-gos severely affects G1 to S transition and mitotic progression, and

results in increased accumulation γ H2AX.⁵ Gene expression profiling from control or *MALAT1*-depleted cells results in downregulation of several genes involved in G1/S transition and S-phase progression. Furthermore, *MALAT1*-depleted cells showed enhanced β -galactosidase (β -gal) staining indicative of cellular senescence.⁵

Depletion of *MALAT1* also results in the activation of p53 and its targets such as *p21*.⁵ These results indicated that p53 could be a downstream mediator of *MALAT1*. To test this, the authors depleted *MALAT1* in the tumorigenic cell lines including HeLa, U2OS, and WI-38-VA13, having weak p53, p16, and Rb activity. These cells did not show G1 or G1/S arrest and showed a normal S-phase progression. However, these cells displayed nuclear breakdown phenotype due to defective chro-mosomal segregation and mitotic abnormalities. Their data suggest that in normal diploid human lung fibroblasts, the cell cycle arrest observed upon *MALAT1* depletion is primarily due to p53 activation, because it can be rescued by knocking down p53 expression in these cells. However, the molecular mechanism by which *MALAT1* influences p53 signaling is not clear yet.

MEG3—A lncRNA that functions in both p53-dependent and independent manner is human maternally expressed gene 3 (*MEG3*).⁷² Overexpression of *MEG3* in HCT116 cells induces p53 protein levels, stimulates transcription from p53-dependent promoter and selectively regulates p53 target gene expression.^{73,74} *MEG3* overexpression stimulates the expression of the p53 target *GDF15* by enhancing p53 binding to the p53 response element in its promoter region; however, *MEG3* does not influence p21 levels in HCT116 cells. The mechanism of p53 regulation by *MEG3* is not clear, but *MEG3* overexpression also downregulates *MDM2* expression and this could be one of the mechanisms whereby *MEG3* activates p53.⁷³ Whether *MEG3* directly interacts with MDM2 and p53 and regulate their levels or there are specific RNA-binding proteins that mediate these interactions need to be tested.

MEG3 also inhibits cell proliferation in a p53-independent manner.⁷³ In breast cancer cells, ectopic expression of *MEG3* induces cell cycle arrest, decrease cell proliferation and colony formation potential of breast cancer cells, and promotes cell migration and invasion.⁷⁵ Furthermore, ectopic expression of *MEG3* in MCF7 and MB231 cells decreases the RNA as well as protein levels of MDM2 and increases those of p53, p21, Maspin, and KAI1, and also increases p53 transcriptional activity on the promoters of p21, Maspin, and KAI1.⁷⁵ The discrepancy in the p21 upregulation after *MEG3* overexpression in the above two reports could be due to cell type-specific function of *MEG3*; however, this needs further investigation.

H19—*H19* is a maternally expressed lncRNA ~2.7 kb long that is reciprocally imprinted and regulated with its neighboring gene *IGF2*.⁷⁶ *H19* has oncogenic properties and during hypoxic stress, and it regulates the expression of genes involved in angiogenesis, survival, and tumorigenesis.⁷⁷ *H19* and p53 mutually counter regulate each other. p53 negatively regulates the expression of *H19 in vivo* by inducing DNA demethylation of the imprinting control region upstream to the *H19* gene,⁷⁸ and also suppress its promoter activity.⁷⁹ Presence of wild-type p53 inhibits the elevation of *H19* RNA under hypoxic stress in the nucleus⁸⁰ (Figure 4).

RNA-IP using an antibody against p53 from nuclear extracts of gastric cancer cell line AGS showed significant enrichment of *H19*, suggesting an association between *H19* and p53.⁸¹ This association causes partial inactivation of p53 and suppressed the protein level of the p53 target Bax.⁸¹ A highly conserved miRNA, miR-675, resides within exon-1 of the *H19* gene.⁸² In bladder cancer cells, *H19* derived miR-675 has a major role in inhibiting p53 activation and also decreases the ratio of Bax/Bcl-2 and cyclin D1 expression.⁸³ These findings indicate the counter-regulatory relationship between p53 and *H19*.

LincRNA-RoR

LincRNA-*ST8SIA3* or LincRNA-*RoR* (Regulator of Reprogramming) is another example of lncRNA that influences p53 proteins levels and is itself under p53 transcriptional control (Figure 4). *RoR* is upregulated during somatic cell reprogramming to induced pluripotent stem cells (iPSCs). Knockdown of LincRNA-*RoR* leads to upregulation of genes involved in the p53 response, oxidative stress response, and DNA damage-inducing agents.⁸⁴ In addition, knockdown of LincRNA-*RoR* leads to apoptosis and simultaneous knockdown of p53 partially rescued the apoptotic phenotype indicating that LincRNA-*RoR* plays a role in promoting survival in iPSCs and ESCs, likely by preventing the activation of stress pathways including the p53.⁸⁴

RoR does not regulate p53 protein levels in the unstressed cells, however, following DNA damage, it represses the induction of p53 protein and similarly siRNA-mediated knockdown of lincRNA-*RoR* increases p53 protein levels.⁸⁵ However, *RoR* does not influence p53 mRNA levels in the presence or absence of Doxorubicin, suggesting post-transcriptional regulation. *RoR* also represses the expression of p53 targets p21 and miR-145. Furthermore, *RoR* reduced p53-mediated G2/M arrest and apoptosis, following Doxorubicin treatment. RNA pulldown using biotin-labeled lincRNA-*RoR* identified its interaction with hnRNP I that occurred mainly in the cytoplasm.⁸⁵ Knocking down hnRNP I expression caused a decrease in p53 protein levels in the Doxorubicin-treated cells. A 28-base *RoR* sequence carries hnRNP I-binding motifs to directly interact with hnRNP I and repress p53.⁸⁵ More interesting finding in this study is the autoregulatory feedback loop between p53 and *RoR*. There is a p53-binding site within the 1-kb region upstream of *RoR* promoter and thus p53 transcriptionally controls *RoR* expression.⁸⁵ In summary, p53 activation can induce *RoR* expression and the increased *RoR* expression suppress p53 by a novel negative feedback loop and thus maintaining the cellular homeostasis as unwanted induction of p53 could be deleterious to the cells.

7SL—*7SL* is a 300-bp lncRNA that forms a ribonucleoprotein complex with six signal-recognition proteins. *7SL* is highly expressed in several cancer cell types including liver, lung, breast, and stomach, and siRNA-mediated knockdown of *7SL* reduces cell growth.⁸⁶ Silencing *7SL* increases the population of cells in the G1 and G2 phases of cell cycle, decreases the proportion of cells in S phase, and promotes cellular senescence and autophagy. Overexpressing *7SL* increased proliferation as measured by [³H]-thymidine incorporation, indicating increased DNA replication.⁸⁶ RNA pulldown experiments that utilized biotinylated antisense oligomers complementary to *p53* mRNA revealed that *7SL* interacts with *p53* mRNA and lowers p53 protein levels.⁸⁶ *7SL* competes with HuR for

binding with p53 and silencing *7SL* leads to increased HuR binding to *p53* mRNA, thus promoting p53 mRNA translation and accumulation.⁸⁶ These data suggest that the mechanism by which *7SL* promotes cell cycle progression and suppresses cellular senescence and autophagy in the cancer cells is by lowering p53 expression. However, in order to conclude that this competitive interaction could actually exist in a cell, it will be necessary to evaluate the stoichiometry ratios of *7SL* and HuR in the cancer cells.

It has been reported previously that p53 induces the expression of the transcription factor FOXP3 following DNA damage.⁸⁷ The FOXP3 is also expressed in tumor cells and is identified as a suppressor in several tumors.⁸⁸ Interestingly, it also binds to the promoter region of *7SL* and represses its transcription suggesting that *7SL* is a downstream target of FOXP3.⁸⁹ Overexpression of FOXP3 in MCF7 cells significantly increased p53 protein levels and this increase was mitigated by overexpression of *7SL* RNA suggesting that there exist a feedback loop between p53 and FOXP3, and *7SL* is involved in this regulatory mechanism of p53 by FOXP3.⁸⁹ Therefore, targeting *7SL* could reconstruct the p53/FOXP3 feedback loop and may inhibit tumor growth in certain cancer types such as breast cancer.

LOC572558—The lncRNA *LOC572558* was initially identified as one of the highly downregulated lncRNAs in an expression analysis of aberrantly expressed lncRNAs in bladder cancer and its levels are also low in bladder cancer cell lines.^{90,91} It is a negative regulator of bladder cancer cell growth. Overexpression of *LOC572558* inhibits bladder cancer cell proliferation, induces apoptosis, and decreases cell migration and invasion.⁹¹ To determine the mode of action for *LOC572558*, the authors performed a phosphoprotein antibody array in bladder cancer cells after overexpressing *LOC572558*. They found several proteins, which are important for cell proliferation, migration, invasion, and apoptosis as differentially phosphorylated after *LOC572558* overexpression. Among these, overexpression of *LOC572558* resulted in reduced phosphorylation of Akt, MDM2, and increased phosphorylation of p53.⁹¹ This increase in p53 activity could possibly account for decreased proliferation after *LOC572558* overexpression. However, the detailed mechanism of how *LOC572558* influences p53 phosphorylation levels is not known.

MT1JP—*MT1JP* is another lncRNA, which is downregulated in several types of cancer compared to adjacent normal tissues, including gastric, liver, colon, and lung.⁹² RNAi-mediated knockdown of *MT1JP* in normal human hepatic cell line, L02, led to an increase in the proportion of cells in S phase and a decrease in G1 phase, whereas, overexpression of *MT1JP* in the liver hepatocellular carcinoma cell line, HepG2, gave opposite phenotype indicating that *MT1JP* has a significant effect on the G1/S check point.⁹² Furthermore, knockdown of *MT1JP* promotes cell proliferation, decreases the percentage of apoptotic cells, and increases L02 cell migration and invasion. Gene expression analysis in L02 cells after knocking down *MT1JP* revealed that it regulates p53 target genes, for example, GADD45a and p21. Interestingly, *MT1JP* knockdown resulted in a decrease in the p53 protein level by affecting the polysome distribution of p53 mRNA, thereby influencing p53 translational efficiency.⁹² Thus, suggesting that *MT1JP* is an upstream regulator of p53. The *MT1JP* is a cytoplasmic lncRNA and RNA-pulldown experiments using biotin-labeled *MT1JP* followed by mass spectrometry identified interaction between *MT1JP* and RNA-

binding protein TIAR. RNA-IP experiments using IgG antibody and TIAR antibody revealed that TIAR interacts with p53 mRNA and knockdown of TIAR decreased p53 protein levels without affecting the RNA levels.⁹² Simultaneous knockdown of *MTIJP* and TIAR reduced p53 protein levels suggesting that *MTIJP* may regulate p53 protein by associating with TIAR.⁹² Additional experiments showed that altering the *MTIJP* levels affect the polysome distribution of p53 mRNA. Interestingly, knockdown of *MTIJP* does not influence TIAR mRNA or protein levels, but knockdown of TIAR increased the expression of *MTIJP*.⁹² Altogether, this data suggests that the translational regulation of p53 occur by a complex of *MTIJP* and TIAR, however, whether the regulatory effect of *MTIJP* on p53 translation depends on the presence of TIAR is yet to be determined.

ZFAS1—The lncRNA *ZFAS1* is upregulated in colorectal cancer tissues. Silencing *ZFAS1* expression in HCT116 and DLD-1 inhibits proliferation, cell cycle, and colony formation on soft agar, and increases PARP cleavage.⁹³ *ZFAS1* interacts with CDK1 and is predicted to sponge miR-590-3p, which targets the 3' UTR of CDK1. Furthermore, *ZFAS1* silencing leads to decrease in the protein levels of p53 and cyclin B1. However, the molecular mechanism behind these interactions is elusive.⁹³

p53 and ENHANCER RNAs (eRNAs)

eRNAs are noncoding, nonpolyadenylated RNAs with sizes of up to 2 kb. They are produced from enhancer domains that are characterized by high levels of H3K4me1 and H3K27Ac, low levels of H3K4me3 and RNAPII and p300/CBP binding.⁹⁴ p53 can regulate transcription of multiple distantly located genes through binding to enhancers, although there is no p53 response element in the promoter of these genes. eRNAs are produced from these p53-bound enhancers regions in a p53-dependent manner and are involved in transcription enhancement of the neighboring genes.⁹⁵ Some eRNAs are also required for p53-mediated cell cycle arrest.⁹⁵ Global run-on and sequencing (GRO-seq) of MCF-7 cells after treatment with Nutlin-3a identified genome-wide p53-regulated eRNAs.⁹⁶ In addition to eRNAs, the authors also identified 194 Nutlin-3a-responsive lncRNA genes. One of these lncRNAs *LED* suppressed cell proliferation and significantly influenced the G1 arrest, following Nutlin-3a treatment and knocking down *LED* increases the percentage of mitotic cells after Nutlin-3a treatment.⁹⁶ Furthermore, *LED* knockdown significantly reduced the levels of p21. By using oligos antisense to *LED* and performing chromatin isolation by RNA purification technique (ChIRP), the authors found that *LED* associates with enhancer domains in chromatin and regulates the production of eRNAs from these enhancer regions possibly by influencing the accumulation of H3K9 acetylation at specific enhancer loci.⁹⁶ Knockdown of *LED* in MCF7 cells also decreased the p53-binding affinity at distal and proximal enhancers located upstream of p21 transcription start site. However, if *LED* influences the epi-genetic features of regulatory elements before dysregulating the p53 occupancy remains to be elucidated. In cancer cell lines and in tumor samples, especially in leukemia, *LED* promoter was methylated, particularly in cell lines with wild-type p53, suggesting a potential tumor suppression function of *LED*.⁹⁶

Another example of p53-bound enhancers (p53BER)-regulated lncRNA is *linc-475*, which has a p53-binding peak in its first intron and there is production of stress-dependent

antisense eRNAs from its intronic p53BER.⁹⁷ As *linc-475* is produced from a p53BER, there is a possibility that it might regulate the transcription of neighboring genes. To test, this the authors treated MCF7 cells with or without Nutlin-3a and performed circularized chromosome conformation capture (4C) assay followed by deep sequencing. Using the p53BER as a viewpoint, they found high frequency of interactions within the pro-moter region of the *linc-475* and the upstream (SPTLC and LOC100128076) and downstream (IARS) neighboring genes. Furthermore, *linc-475* is required for p53-mediated G1 arrest following nutlin-3a treatment, and knocking down *linc-475* increases the number of cells entering mitosis after nutlin-3a treatment.⁹⁷ Silencing as well as knocking out *linc-475* leads to a significant reduction in the mRNA and protein levels of p21, without affecting localization and protein levels of p53 and *linc-475* is required for proper binding of p53 and RNAPII to the p21 promoter.⁹⁷ Altogether, these results high-light the significance of lncRNAs originating from p53BER and their role in regulating p53 transcriptional activity (Table 1).

CONCLUSIONS AND PERSPECTIVES

In normal proliferating cells, p53 levels are low. However, when cells encounter stress, p53 signal-ing is activated to regulate DNA repair, metabolic reprogramming, cell cycle arrest, apoptosis, or senescence.³⁰ p53 regulates the expression of a repertoire of lncRNAs, and some of these lncRNAs are critical regulators of cell cycle arrest, DNA damage repair, chromosomal stability and apoptosis, altogether contributing to tumor-suppressor function of p53. LncRNAs are dysregulated in a variety of cancers and therefore can be utilized as biomarkers for disease progression and as thera-peutic targets.⁹⁸ Most lncRNAs are expressed at low levels, even after induction during the stress response. This low expression indicates that most lncRNAs may not function as global regulators of gene expression but they may regulate the expres-sion of a subset of genes expressed in a cell. If these genes happen to be important regulators of specific pathway, even low abundant lncRNAs can have critical functions.

In more than 50% of the cancers, p53 is mutated and a significant proportion of the remaining 50% inactivate p53 by a variety if mechanisms including overexpression of MDM2²⁹. However, more than 10 million patients across the world have intact p53 protein. In the tumors with intact p53 signaling, it would be important to understand the biology and molecular function of p53-regulated lncRNAs. Similar to the p53-regulated protein-coding genes, lncRNAs may have prosurvival or proapoptotic functions in tumor cells that can be utilized for future translational research. However, figuring out the function and mode of action of an lncRNA is not straightforward due to low abundance of most lncRNAs and the diverse mechanisms by which they function. Conservation and regulation by p53 in multiple cell lines can be used to select lncRNAs that may have important functions in the p53 pathway. If a given p53-regulated lncRNA shows partial conserva-tion between human and mice, the partially conserved regions may represent functional domains that are common to the human and mouse homologs. Such functional domains may act as binding sites for RNA-binding proteins that mediate the effect of the lncRNA. The identification of such domains may act as a critical step in selecting candidate biologically rel-evant p53-regulated lncRNAs. Analyses of candidate lncRNA expression in patient samples and determin-ing the

association with prognosis and tumor progression may indicate the role of the lncRNA in a given cancer type. Last but not the least, experiments in mouse models and patient-derived xenografts would establish the function of the lncRNA *in vivo*. Future genetic and molecular analyses of p53-regulated lncRNAs will be critical in elucidating the role of lncRNAs in the p53 network.

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FIGURE 1.

Diverse functions of lincRNA-p21 in nucleus and cytoplasm. (a) In response to DNA damage, p53 is upregulated and activates the transcription of coding as well as noncoding transcripts including lincRNA-p21. LincRNA-p21 functions in *cis* as well as in *trans*. In *cis* it regulates the expression of its neighboring gene p21. It has proapoptotic function and can regulate gene expression in *trans* by interacting with RNA-binding protein hnRNP-K. (b) LincRNA-p21 expression is induced during hypoxia. Under normal oxygen levels HIF-1α binds to VHL and is polyubiquitinated by VHL, leading to its degradation via proteasome. During hypoxic conditions, HIF-1α levels increase, which in turn increases the levels of lincRNA-p21. LincRNA-p21 can now bind to VHL and HIF-1α, therefore disrupting VHL-HIF-1α interaction. Once this interaction is disrupted the levels of HIF-1α accumulate, suggesting the existence of feedback loop between HIF-1α and lincRNA-p21. (c) LincRNA-p21 regulates translation in the cytoplasm. When cytoplasmic HuR levels are high, it associates with lincRNA-p21 and recruits let-7/Ago2 to lincRNA-p21 leading to its degradation and thus activates translation of select mRNAs. However, when the levels of HuR are low, lincRNA-p21 levels accumulate and it can now inhibit translation.

FIGURE 2.

Regulation of proliferation and survival by the p53-regulated lncRNA PANDA. *PANDA* is a direct target of p53 and its expression is induced following p53 activation after DNA damage. In response DNA damage *PANDA* has a prosurvival function as it promotes cell survival and inhibits apoptosis. *PANDA* interacts with the NF-YA and thus restricts the binding of NF-YA to chromatin, limiting the activation of apoptotic genes. In proliferating cells, *PANDA* interacts with SAFA and recruit PRC2-EZH2 and BMI1-PRC1 complexes that inhibit transcription of *PANDA* and prosenescence genes including p21. When the levels of *PANDA* decrease, its affinity to bind with NF-YA is low and NF-YA can now activate E2F and promote cell proliferation. *PANDA* acts in an autoregulatory loop with SAFA-BMI1-PRC1. In senescent cells, SAFA-PRC2-EZH2 and SAFA-BMI1-PRC1 complexes disintegrate and expression of *PANDA* and p21 is upregulated. *PANDA* now blocks proliferation by decoying NF-YA, which is also required for survival of senescent cells.

FIGURE 3.

LncRNAs in the p53 network. DNA damage activates p53 and its downstream transcriptional targets including lncRNAs. The human and mouse orthologs of lncRNA PINT have contrasting functions. Human PINT has a tumor-suppressor function, whereas mouse ortholog increases cell survival and proliferation. *PR-IncRNA1* and *PR-IncRNA10* have proapoptotic function and they inhibit cell survival and proliferation. The lncRNA TUG1 has diverse role in different cancer types. TUG1 can promote or inhibit cell proliferation and cell cycle progression depending on the tumor type. The lncRNA NORAD is not a direct transcriptional target of p53 and it interacts with PUMILIO proteins to maintain genomic stability.

FIGURE 4.

LncRNA-mediated regulation of p53. MEG3 induces p53 protein levels resulting in cell cycle arrest and inhibition of cell proliferation and thus inhibit tumorigenesis. MEG3 downregulates MDM2 expression that can possibly activate p53. LncRNAs H19, RoR, and 7SL act in an autoregulatory loop with p53. MT1JP regulates p53 protein by associating with RNA-binding protein TIAR.

TABLE 1

LncRNAs That Regulate p53 or Are Regulated by p53

	Annotation	Species	Accession Number	Reference
p53-regulated lncRNAs				
<i>LincRNA-p21</i>	Trp53cor1	Mouse	NR_036469, HM210889.1	43
<i>PANDA</i>	PANDAR	Human	NR_109836.1, JF803844	22
<i>PINT A, B, C</i>	Lncpint	Mouse	KC860257, KC860259, KC860258, NR_110470.1	51
<i>LncRNA</i>	LINC-PINT	Human	NR_109854.1, FLJ43663	51
<i>PR-lncRNA-1</i>	RP11-467J12.4	Human	NR_136518.1	52
<i>NORAD</i>	LINC00657	Human	NR_027451.1	3
<i>TUG1</i>	TUG1	Human	NR_110492.1	13,53,55
<i>PVT1</i>	PVT1	Human	NR_003367.3	60,63–65
<i>LINP1</i>	RP11-554I8.2	Human	HG502647.1	66
<i>DDSR1</i>	DDSR1	Human	KT318134	67
LncRNAs that regulate p53				
<i>MALAT1 (NEAT2)</i>	MALAT1	Human	NR_002819.3	5,6
<i>MEG3</i>	MEG3	Human	NR_003531.3	72–75
<i>H19</i>	H19	Human	NR_002196.2	78–81,83
<i>LincRNA-ST8SIA3 or LincRNA-RoR</i>	LINC-ROR	Human	NR_048536.1	84,85
<i>7SL</i>	RN7SL1	Human	NR_002715.1	86,89
<i>LOC572558</i>	PGM5-AS1	Human	NR_121192.1	90,91
<i>MT1JP</i>	MT1JP	Human	NR_036677.1	93
<i>ZFAS1</i>	ZFAS2	Human	NR_003606.2	93
p53 and enhancer RNAs				
<i>LED</i>	Linc00086, SMIM10L2A	Human	NR_024359.2	96
<i>Linc-475</i>	Linc00475	Human	NR_027341.1	97