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REVIEW

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P53 long noncoding RNA regulatory network in cancer development

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Abstract

The protein p53 as a transcription factor with strong tumor-suppressive activities is known to trigger apoptosis via multiple pathways and is directly involved in the recognition of DNA damage and DNA repair processes. P53 alteration is now recognized as a common event in the pathogenesis of many types of human malignancies. Deregulation of tumor suppressor p53 pathways plays an important role in the activation of cell proliferation or inactivation of apoptotic cell death during carcinogenesis and tumor progression. Mounting evidence indicates that the p53 status of tumors and also the regulatory functions of p53 may be relevant to the long noncoding RNAs (lncRNA)-dependent gene regulation programs. Besides coding genes, lncRNAs that do not encode for proteins are induced or suppressed by p53 transcriptional response and thus control cancer progression. LncRNAs also have emerged as key regulators that impinge on the p53 signaling network orchestrating global gene-expression profile. Studies have suggested that aberrant expression of lncRNAs as a molecular-genomic signature may play important roles in cancer biology. Accordingly, it is important to elucidate the mechanisms by which the crosstalk between lncRNAs and p53 occurs in the development of numerous cancers. Here, we review how several classes of lncRNAs and p53 pathways are

linked together in controlling the cell cycle and apoptosis in various cancer cells in both human and mouse model systems.

KEYWORDS
cancer, long noncoding RNA, noncoding RNA, P53, regulatory network, tumor genetic

1 | INTRODUCTION

Cancer continues to be associated with significant morbidity and mortality worldwide, accounting for an estimated 18.1 million new cases and 9.6 million deaths in 2018; therefore, planning to control cancer is a priority public health objective (Ferlay et al., 2019). It has been clear for many years that cancer is associated with mutated genes or alterations in gene expression levels, and exploring targets and trends in the genetics of human cancer is increasingly used for diagnostic and treatment purposes (Ahmadi, Gharibi, et al., 2017). Such genetic modifications are heterogeneous and may be related to activating mutations in oncogenes, which ultimately drive tumorigenesis or loss-of-function mutations in tumor-suppressor genes typically involved in cell growth regulation in physiological conditions (Esteller, 2011; Shali et al., 2016). Upon tumor establishment, developing hypoxia as well as inflammatory responses may confer survival advantages to the tumor cells and contribute to malignant progression leading to the acquisition of invasive properties and eventually to metastasis (Bartkowiak et al., 2012; Campbell et al., 2010; Yachida et al., 2010). It is notable that a vast majority of cancer-related mortalities are caused by such metastatic diseases (Gholamkhasi et al., 2020; Peitzsch et al., 2017). The p53 tumor suppressor protein is a critical guardian of genome integrity and mediator of apoptosis (Lavin & Gueven, 2006) whose disruption seems to be a general feature of malignant cells. Many studies have reported the aberrant expression of p53 in the malignant tumors of several organs and its correlation with various other oncogenes in the malignant transformation of cells (Chui et al., 2020). In response to DNAdamage induced by various stresses stimuli, which can facilitate mutations of the genome, the p53 is activated by increasing its stability and activity; however, under normal conditions, the p53 protein is maintained at low levels. In different types of tissues, depending on the extent of the damage, activated p53 protein can either arrest cell cycle to repair DNA or switch "on" the pathways of programmed cell death (often referred to as apoptosis), which force the injured cells to commit suicide (Green & Kroemer, 2009; Moll et al., 2005). Moreover, the induction of p53 function can inhibit DNA-damaged cells from cell cycle progression. Hence, p53 protein is considered the master regulator of cell fate and the guardian of the genome having a pivotal role in preventing cancer development (Efeyan & Serrano, 2007; Nabati et al., 2018).

Studies have shown that p53 directly activates a set of genes whose functions are to assist in the suppression of tumor growth through multiple pathways, including cell cycle arrest, apoptosis, and DNA repair (T. Riley et al., 2008). Besides the protein-coding genes, noncoding RNAs have been found to be the targets of p53. Noncoding RNAs (ncRNAs) are functional transcripts without protein-coding potential, which mainly consists of microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) (Eghbal-Fard et al., 2019). MiRNAs as the key mediators of messenger RNA (mRNA) downregulation have been characterized for inhibition of protein expression caused by p53, thereby disrupting the underlying processes that contribute to tumor initiation, progression, and invasion (Hermeking, 2012; Latha et al., 2019). LncRNAs are known to orchestrate transcriptional control of specialized cells in the human body (Ahmadi, Abdolmohammadi-Vahid, et al., 2017; Ahmadi, Gharibi, et al., 2017). Reportedly, lncRNAs are confirmed to control important aspects of the events underlying tumor development and progression, so that these cells are expected to die when the transcript is silenced. It is also possible to exploit the expression profile of lncRNAs to discern the status of cell biology. The number of lncRNAs has expanded to nearly 50,000 so far and is still growing. Furthermore, the lncRNAs display cell-type specific and time-dependent expression patterns, so that only a small subset is expressed in all cell types (Blokhin et al., 2018). Recently, the important role of lncRNAs has been established downstream of the p53 pathway in tumor suppression (Grossi et al., 2016; A. Zhang, Xu, et al., 2014), or they may function to regulate the p53 expression and/or activities. Thus, the focus of this review is to describe the functional correlations between the p53 pathway and some classes of lncRNAs in developing different cancers, although research is, by necessity, ongoing in this area.

2 | HUMAN TUMOR SUPPRESSORS

It is widely accepted that the deletion of tumor suppressor genes most frequently occurs at the pre-cancerous and/or early stages of the tumor either by genetic mutations or epigenetic posttranscriptional modifications (W. Sun & Yang, 2010). The resulting decrease in the function or expression of the affected tumor suppressor genes can cause the cells to acquire the ability to evade cell cycle arrest in different phases by various mechanisms (W. Sun & Yang, 2010). Many of these genes are regulated by a nearby antisense RNA transcript, adding to the complex regulatory network that controls tumor suppressor genes (Yu et al., 2008). Also, many cancer-associated genes tend to be expressed from bidirectional promoters that synthesize mRNA and divergent ncRNA (M. Q. Yang et al., 2007). There have been four major mechanisms describing the importance of tumor suppressors in preventing tumorigenesis,

including suppression of cellular proliferation, apoptosis induction, DNA damage repair, and prevention of metastasis. Many tumor suppressors seem to exert only one of these functions, while others may be involved in more than one mechanism (W. Sun & Yang, 2010). Of note, tumor-suppressive activities are not solely attributed to proteins, but also to lncRNAs (Y. Zhou et al., 2012).

3 | P53 TUMOR SUPPRESSOR (TP53) GENE AND p53 PROTEIN

The protein p53 was first identified in 1979 and, years later, was characterized as a tumor suppressor. In human, the TP53 is located in chromosome 17p13.1 and contains 11 exons. The coded protein is approximately 53 kDa in molecular weight with 393 amino acids in length (Nikolova et al., 2000). P53 is a nuclear transcription factor with sequence-specific DNA-binding activity that forms a tetramer and binds target genes to affect their transcription (Kamada et al., 2016). It regulates these genes either through direct transcriptional regulation or by modulating the activities of other proteins. P53-induced gene expression may lead to the induction of growth arrest in the G1 phase or before mitosis in the G2 phase. This cell cycle arrest enables the repair of DNA lesions. By undergoing programmed cell death, cells that are arrested in the cell cycle are eliminated and thus protect against the fixation of DNA mutations. Frequent mutations of the p53 gene are thought to have an important role in a wide variety of human cancers. Tumor cells harboring p53 defects are deficient in repairing DNA damage and disrupt cell cycle checkpoints, resulting in genomic instability and cellular transformation (Benchimol, 2001).

4 | P53 AND CANCERS

Several of the mechanisms by which cancer cells inactivate p53 include p53 binding to viral proteins, alteration of genes whose products either regulate p53 activity (mouse double minute 2 homolog [*Mdm2*] or *p19*ARF genes), and abnormal cytoplasmic localization of p53. Genetic alteration in the p53 gene is, however, the most common aberration of p53 in human malignancies. The most frequent sites of mutations in the TP53 gene is in the exons 4–9, which encode for the conserved central DNA-binding region of the protein. Single-base substitutions constitute a large proportion of all mutations in the TP53 gene. Mutations beyond six codons called the hotspot codons account for approximately 30% of all p53 mutations and influence the protein-DNA interactions and also the conformation of the protein (Hermeking, 2012). Many p53 mutants are reported to disrupt p53 function and drive tumorigenesis by dominant-negative effects over normal TP53 allele; that is, when a mutant allele not only lose its tumor-suppressive activities but also interfere with the function of wild-type p53 in a manner advantageous for neoplastic transformation (Aubrey et al., 2018; Merkle et al., 2017). Because the p53 protein functions as a tetrameric transcription factor, mono-allelic mutation of the p53 gene is thought to inhibit the function of wild-type p53 protein within a heterotetrameric complex (Kamada et al., 2016). It has been demonstrated that dominant negative p53 mutants (e.g., R248Q) are closely associated with a poor outcome in patients with various cancers (Nakazawa et al., 2019). Also, abnormal expression or the aberrant regulation of the protein frequently occurs in cancer cells with normal TP53 alleles. In an alternative mechanism, factors (such as cadmium) that prevent normal folding of p53 protein, may possibly affect its DNA-binding ability and prevent normal p53-dependent responses. Taken together, it has, therefore, been suggested that all cancer cells represent some abnormalities of the p53 tumor suppressor gene (Nikolova et al., 2000).

5 | INACTIVATION OF TP53 BY THE SMALL DNA TUMOR VIRUSES

The first hints for the role of the oncogenic virus in human cancers were found at the beginning of the 20th century, when Ellerman and Bang (1909), and Rous (1911) isolated an RNA leukemia virus and an RNA containing sarcoma virus, respectively. Richard Shope described the first DNA tumor virus known as shope fibroma virus (SFV), a 160 kb double-stranded DNA virus of the Poxvirus family (Upton et al., 1987). During the period of 1930–1960s, small DNA tumor viruses like simian vacuolating virus 40 (SV40), polyoma virus, the papilloma viruses, and human adenoviruses were discovered (Upton et al., 1987). The transformation of cells by DNA tumor viruses is accompanied by biochemical and morphological modifications, including variation in growth control. Each of these virally transformed cells contains segments of the viral genome, only some sequences of which are expressed as mRNA and protein in these cancers. The viral genome encodes a T/tumor antigen oncoprotein locus that can express four different transcripts generated by alternative splicing (Shuda et al., 2008). Studies on the viral encoded tumor antigens point to the role of these oncogenic products in regulating cell cycle-specific proteins, such as p53 (Lane & Crawford, 1979; Linzer & Levine, 1979), retinoblastoma tumor suppressor protein (Rb) (DeCaprio et al., 1988), protein phosphatase 2A (Pallas et al., 1990), and Budding Uninhibited by Benzimidazoles 1 (Bub1) (Cotsiki et al., 2004). Many of the early efforts in the area have proven that T antigens functionally inactivate the tumor suppressor p53, leading to deregulated expression of many genes that are modulated by p53, such as those involved in cell proliferation, DNA damage/repair, and apoptosis (Tornesello et al., 2018). The T antigen gene of the SV40 virus comprises half of the DNA and is expressed early after infection (Pipas, 2009). Experiments clearly indicate that the expression of the T antigen of SV40 DNA provides functions that are necessary for transformation (Pipas, 2009). The mechanism that T antigen uses to elicit transformation was evidenced by a combination of immunoprecipitation experiments with mutational analysis that led to the validation of two targets, the tumor suppressors p53 and pRb (retinoblastoma protein) (Pipas, 2009). Several studies have already

appeared that report the presence of T antigen–p53 complexes both in SV40-transformed and infected cells (Lane & Crawford, 1979; Linzer & Levine, 1979). In addition, it has been demonstrated that SV40 T antigen mutants that are defective for p53 binding, are also defective in transformation (Kierstead & Tevethia, 1993; Peden et al., 1998; J. Y. Zhu et al., 1991), suggesting that association of T antigen with p53 is required for transformation. This interaction can repress p53-dependent transcription via blocking its DNA binding, thus making p53 unable to bind its target promoters (Lilyestrom et al., 2006). This function is contrary to those of T antigen from Merkel cell polyomavirus (MCV), in which MCV T antigen-induced DNA damage response (DDR) activates the p53 pathway causing cell growth inhibition (J. Li, Wang, et al., 2013). Alternatively, the growth arrest response induced by p53 can be blocked through mechanisms that are independent of direct association with T antigen in SV40-infected cells (Gjoerup et al., 2000).

6 | NcRNAs

It is currently estimated that only about 1.5% of the total DNA sequence comprises protein-coding fragments in the human genome (Lander et al., 2001). At the same time, it has been shown that ~75% of the genomic sequence is being transcribed into RNA and that the protein-coding region encompassing intronic sequences does not exceed 25% of all RNA transcribed from the human genomic DNA (Djebali et al., 2012). NcRNAs are the fraction of RNAs that do not encode proteins. Over the last years, a large number of various non-protein-coding RNA molecules (ncRNAs) involved in gene regulation have been identified. NcRNAs are classified into two main categories according to their sizes; long ncRNAs whose sizes are larger than 200 bps and small ncRNAs less than 200 bp. There also appears to be other classes of ncRNAs within these two groups (Gibb et al., 2011). As an example, it has been revealed that some miRNAs are produced from lncRNAs. MiRNAs are a well-known group of ncRNAs, which contribute to gene expression by multiple mechanisms. Another class of ncRNAs is lncRNAs whose functions in regulating molecular pathways are being gradually discovered (Garofalo & Croce, 2011).

7 | LncRNAs

As mentioned before, long ncRNAs have been characterized as transcripts >200 nucleotides in size that lack coding regions for the amino acid sequences, as typically defined through an absence of open reading frames and codon conservation (Derrien et al., 2012; Morris & Mattick, 2014). Such ncRNAs have various biological functions and implicate in diverse molecular processes like X-chromosome in-activation or transcriptional gene activation (Leighton et al., 1995; Penny et al., 1996). It is known that functional RNA transcripts not encoding proteins cover most of the transcriptome, far more than coding transcripts (nearly 60,000 lncRNAs) in the human genome (Iyer et al., 2015). As different data sets show only a moderate overlap with each other (between 30% and 40%), it is clear that the whole lncRNA transcriptome is still incompletely represented and that their number might further increase (Derrien et al., 2012).

LncRNAs are a highly heterogeneous class of genes, distinguished from other ncRNAs mainly by their larger size (>200 nt). The genomic annotations provided by the GENCODE consortium have grouped lncRNAs into five categories with respect to their location and orientation relative to adjacent protein-coding genes (Derrien et al., 2012); the long intergenic ncRNAs (lincRNAs) that do not intersect any protein-coding gene locus, exonic antisense lncRNAs that overlap with the exonic region of a coding gene locus on the opposite DNA strand, intronic lncRNA transcripts positioned within an intron but not exons of a coding gene on the same or opposite strand, overlapping lncRNAs, which overlap with a protein-coding gene on the same or opposite strand, and the last category is the processed transcripts considered as an individual subclass, which do not harbor an open reading frame. Of note, current studies are indicative of no explicit functional differences between these ncRNA categories (Morris & Mattick, 2014).

8 | ALTERATION OF lncRNAs IN CANCER

Accumulating evidence demonstrates that lncRNAs may have a role in tumor biology (Prensner et al., 2011). The number of dysregulated lncRNAs identified in cancer cells highlights the relevance of these ncRNAs to malignancy and to the progression of the established disease and patients outcomes (Tsai et al., 2010). Mechanistically, most well-studied lncRNAs modulate gene expression through transcriptional (e.g., enhancer RNAs [eRNAs], Mousavi et al., 2013) rather than posttranscriptional regulation (e.g., metastasis-associated lung adenocarcinoma transcript 1 [MALAT1], Tripathi et al., 2010; lnc-Spry1, Rodríguez-Mateo et al., 2017; and BC200, J. Huang et al., 2014) of target genes. This function is mediated through cis- or transregulatory effects (D. Wang, Garcia-Bassets, et al., 2011). Table 1 summarizes the proposed mechanisms of the functions of lncRNAs in different cancers.

Although somatic mutation of lncRNAs in cancer has not been reported so far, numerous lncRNAs with altered expression have been identified in neoplastic cells. However, to what extent lncRNAs may undergo genomic amplification/deletion, somatic point mutations, or other targeted aberrations in cancers, remains an open question. As an instance, within prostate cancer cells, nearly half harbor gene fusions of the members of the E-twenty-six or erythroblast transformation specific (ETS) family of transcription factors, including ETS-related gene (*ERG*), ETS variant 1 (*ETV1*), *ETV4*, *ETV5*, which result in translocation of an androgen-regulated promoter to the ETS locus, leading to uncontrolled production of ETS family genes (Prensner & Chinnaiyan, 2009). According to previous research, a patient with prostate cancer has been found to have a gene fusion between an intergenic androgen-regulated region described as prostate-specific lncRNA (*PCAT-14*) and ETV1 gene (Poliseno et al., 2010; Prensner et al., 2011). Similarly,

TABLE 1 Mechanisms of lncRNA function in cancers

Cis-regulatory lncRNAs	Molecular mechanism(s) of lncRNA	Examples	Cancer type	Function	Reference
	Epigenetic transcriptional regulation	ANRIL	Prostate and gastric cancer	Coupling with histone modifying or chromatin remodeling protein complexes	Zhao et al. (2008), Kotake et al. (2011), Mercer et al. (2009)
		AIR	Breast cancer, hepatocellular		
		H19			
		KCNQ1OT1			
		XIST			
	Enhancer-associated long ncRNAs	HOTTIP	MLL-rearranged leukemias	Influencing the activity of gene enhancers	K. C. Wang, Yang, et al. (2011), Ørom et al. (2010)
Transregulatory lncRNAs	Epigenetic transcriptional regulation	HOTAIR	Breast cancer, liver, lung, and pancreatic tumors	Coupling with histone-modifying or chromatin-remodeling protein complexes	Yap et al. (2010), Y. Zhou et al. (2012), X. Zhang et al. (2010), Braconi et al. (2011), Huarte and Rinn (2010), Gibb et al. (2011)
	Modulating tumor suppressor activity	GAS5	Breast cancer	Suppression of tumor suppressor genes	
		MEG3	Pituitary tumors, leukemias.		
		Line-p21	Mouse Sarcoma, lymphoma tumors		
	Regulation of mRNA processing and translation	MALAT1	Lung cancer	Regulating mRNA splicing, editing, and export	Bond and Fox (2009), Prasanth et al. (2005), Bernard et al. (2010), Tripathi et al. (2010)
		NEAT1	Prostate, colon, breast		

Abbreviations: ANRIL, antisense noncoding RNA in the INK4 locus; GAS5, growth arrest-special transcript 5; HOTAIR, HOX transcript antisense RNA; HOTTIP, HOXA transcript at the distal tip; lncRNA, long noncoding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MEG3, maternally expressed gene 3; MLL, mixed-lineage leukemia; mRNA, messenger RNA; ncRNA, noncoding RNA; NEAT1, nuclear enriched abundant transcript 1; XIST, X-inactive-specific transcript.

in a patient with B-cell lymphoma, growth arrest-specific transcript 5 (GAS5), a tumor-suppressor lncRNA, have been shown to fuse with the B-cell lymphoma 6 (*BCL6*) gene to retain the full coding sequence of *BCL6* (Huret, 2013). Finally, other studies have reported the genomic loss of lncRNA PTENP1, a pseudogene of the phosphatase and tensin homolog (PTEN), leading to aberrant expression of PTENP1 in prostate and colon cancers (Poliseno et al., 2010). These data demonstrate the occurrence of lncRNAs somatic aberrations in cancers, though most studies have identified multiple changes in gene expression patterns as a frequent alteration of lncRNAs that has been associated with tumorigenesis. As in the case of several prominent oncogenes, such as Kirsten RNA-associated rat sarcoma (*KRAS*), which unlikely show functional aberrations due to changes in protein expression level, it is likely that some lncRNAs display structural aberrations (e.g. mutation, small insertions/deletions) rather than overt changes in expression level (Mestdagh et al., 2010). Thus, lncRNAs mutations continue to be an area of great importance in future cancer research.

9 | P53 AND lncRNAs

Studies suggest that p53 controls the expression of many genes and at the same time, a far more sophisticated regulatory network, such as translational and posttranslational modifications, have emerged to affect p53 itself (Halaby & Yang, 2007; Kruse & Gu, 2009). Upon activation, p53 is localized at promoters of target genes at specific binding sites or response elements and thereby drives the transcription of downstream genes such as p21 (Cip1) (Harper et al., 1993). Two binding domains have been identified in the tumor suppressor p53 protein: a sequence-specific DNA-binding domain and a sequence-independent domain at the carboxyl/C terminus that enhances the non-DNA-binding form of p53 (Harms & Chen, 2005). It has been shown that the C terminus of p53 regulates DNA binding by sequence-nonspecific interaction with RNA (K. J.-L. Riley & Maher, 2007; Yoshida et al., 2004). The interaction between p53 and RNA disrupts oligomerization of p53, leading to p53 latency (Yoshida et al., 2004). These studies propose a potentially important role of RNA in p53 activation.

LncRNAs have emerged as one of the key components of the p53 regulatory network in the human cell. In this regard, several lncRNAs have been reported to modify p53 function, described as critical p53 regulators. On the other hand, numerous studies indicate that p53 is able to regulate lncRNAs expression. For simplicity, a variety of lncRNAs were categorized into two groups (Table 2): Group 1 included the lncRNAs acting as p53 regulators, such as MALAT1, maternally expressed gene 3 (MEG3), p53-eRNAs, and WD40-encoding RNA antisense to p53 (Wrap53) and the Group 2 lncRNAs can serve as the effectors of p53 signaling pathway, such as lincRNA-p21, P21-associated ncRNA DNA damage activated (PANDA), and H19. Regulator of reprogramming (ROR) is found to be a unique lncRNA serving as p53 repressor as well as to be a p53 effector in response to DNA damage (Hung et al., 2011; Kaneko et al., 2010). Figure 1 depicts an overview of the regulatory network involving lncRNAs and p53 pathways.

10 | LncRNAs SERVING AS p53 REGULATORS

10.1 | MEG3

Reports have revealed that the MEG3 lncRNA acts as a tumor suppressor gene in many cancers. It is now evident that MEG3 is widely downregulated in the vast majority of human cancer tissues,

TABLE 2 Summary of some upstream and downstream lncRNAs of the p53 pathway

	Function	Example
p53 regulators	MALAT1/Neat2	Serves as a p53 repressor and is expressed in a cell cycle-dependent manner, with low levels during G1 and G2 and high levels during G1/S and M phases
	MEG3	As a tumor suppressor, MEG3 inhibits tumor cell proliferation possibly through induction of apoptosis, MEG3 interact with MDM2 or p53 to disrupt p53-MDM2 interaction or simply facilitate degradation of MDM2
	Wrap53	Plays a critical role in the regulation of p53 at the RNA level
	eRNAs	Have enhancer activity and interact intrachromosomally with multiple neighboring genes in a p53-dependent manner
p53 effectors	PANDA	PANDA is a p53 effector in response to DNA damage to suppress apoptosis while CDKN1A induces cell cycle arrest
	Loc285194	Loc285194 is found to be induced by p53 through interaction with the putative p53RE in the upstream region of loc285194 as a putative tumor suppressor
	H19	H19 interacts with p53, leading to the inactivation of p53
	Line RNA-p21	LincRNA-p21 serves as a p53 target and plays a role in triggering apoptosis

Abbreviations: CDKN1A, cyclin-dependent inhibitor kinase 1A; eRNA, enhancer-derived RNA; lincRNA, long intergenic ncRNA; lncRNA, long noncoding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MDM2, mouse double minute 2 homolog; MEG3, maternally expressed gene 3; NEAT2, nuclear enriched abundant transcript 2; p53RE, p53 response element; PANDA, P21-associated ncRNA DNA damage activated; Wrap53, WD40-encoding RNA antisense to p53.

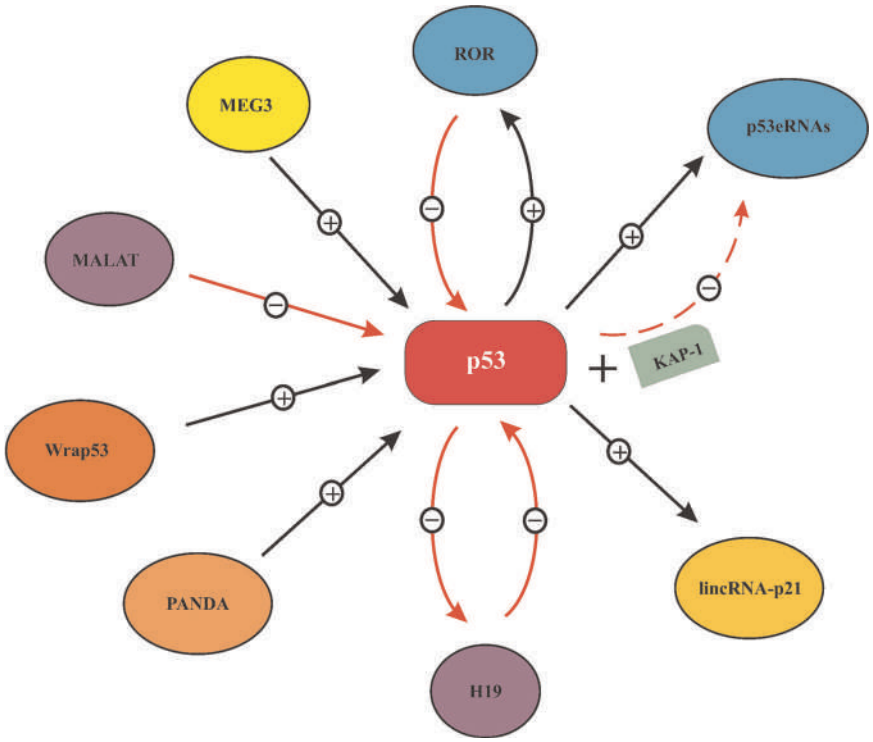

FIGURE 1 Crosstalk between mutant p53 and lincRNA-p21 in cancer cells. The nuclear factor NF-YA functions as a cofactor of p53 for lincRNA-p21 induction. The induction of lincRNA-p21 downstream of the p53 pathway upregulates p21 transcription and therefore promote p53-dependent apoptosis. LincRNA-p21 also mediates crosstalk between the p53 and JAK/STAT signaling pathways via blocking STAT3 phosphorylation, leading to the repression of its target genes and tumor suppression. JAK/STAT, Janus kinase/signal transducer and activator of transcription; KAP1, KRAB-associated protein-1; lincRNA-p21, long intergenic noncoding RNA p21; MALAT, metastasis-associated lung adenocarcinoma transcript; MEG3, maternally expressed gene 3; F-YA, nuclear transcription factor Y subunit α; PANDA, P21-associated ncRNA DNA damage activated; ROR, lncRNA-regulator of reprogramming

including bladder, gastric, colorectal, glioma, breast, and oesophagal squamous cell carcinomas (Y. Zhou et al., 2012). It was not until recently, however, that the biological role of MEG3 in gastric cancer was described. In one in vitro study, ectopic expression of MEG3 was found to modulate the proliferation ability and metastasis of gastric cancer cells by controlling p53 protein expression (G. Wei & Wang, 2017). Other studies suggest that the inducible over-expression of MEG3 may work via transcriptional decrease of *MDM2* gene expression, thus causing the accumulation of p53 protein in the context of breast tumor tissues (L. Sun et al., 2016). Moreover, MEG3 provides a further level of p53 regulation via promoting p53 binding to its target promoters (J. Zhu et al., 2015). Indeed, MEG3 was initially shown to bind to p53 in vitro. The in vivo proof for the interaction of MEG3 and p53 was recently discovered and the study supported the notion that MEG3 has no effects on MDM2–p53 binding, which was distinct from the proposed mechanism for MEG3 function (Bauer et al., 2019). Additional studies have provided further mechanistic insight into the structural and functional properties of MEG3 interacting with p53, which contributes to the enhanced upregulation of p53 target genes (Uroda et al., 2019). Selective 2′-hydroxyl acylation analyzed by primer extension (SHAPE) RNA structure analysis dissected the specific highly conserved MEG3 core domains, and further systematic cell-based assays showed that these motifs are strictly essential for stimulation of the p53, mutation of which markedly perturbs MEG3-binding characteristics and impairs p53 pathway activation (Uroda et al., 2019). Since p53 activation is also related to endoplasmic reticulum (ER) stress, the regulatory relationship between MEG3 and ER stress has also been studied to unveil the mechanism. It was confirmed that MEG3 forms part of an ER stress-related apoptotic effectors and that the ER stress-related proteins expression was regulated by MEG3 under ER stress, leading to increased p53 expression via the nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) pathway (R. P. Chen et al., 2016). Overall, a wide variety of mechanisms, therefore, participate in the MEG3-induced p53-dependent apoptosis. Alternatively, as evidenced in a non-small cell lung cancer cell line, the MEG3-P53 pathway may also participate in chemotherapy-induced apoptosis so that the inhibition of MEG3 was shown to attenuate cell apoptosis induced by paclitaxel (Xu et al., 2018). In addition, an association of MEG3 expression and p53 level has been described to be involved in antiproliferative properties of a variety of antitumor agents in other cell systems, such as pancreatic (Hu et al., 2016), ovarian (Xiong et al., 2017), and human lung adenocarcinoma cells (J. Liu et al., 2015). In breast cancer progression, ubiquitously expressed transcript (UXT), which is markedly elevated in some human tumors, has been shown to modulate the expression of MEG3,

leading to the inhibition of p53-induced apoptosis, promoting invasion and accelerating tumor growth (Z.-F. Huang et al., 2020). Figure 2 illustrates the mechanisms by which MEG3 affects p53-dependent and p53-independent apoptotic pathways.

10.2 | MALAT1

MALAT1, also known as nuclear-enriched transcript 2 (NEAT2), was initially identified as a prognosis marker associated with non-small cell lung cancer invasion and metastasis (Ji et al., 2003). It was further found to be highly upregulated in various cancer cell types and is believed to promote cell proliferation, invasion, and migration (Gutschner et al., 2013; Yoshimoto et al., 2016). Remarkably, MALAT1 is almost invariably overexpressed in epithelial carcinomas with p53 malfunction (Jeffers et al., 2013) and has been proposed as a potential genetic marker for epithelial tumors (Yamada et al., 2006). Moreover, high MALAT1 levels have been shown to have a negative impact on treatment outcomes in patients with osteosarcoma (Fellenberg et al., 2007). At the molecular level, MALAT1 is found to play critical roles in regulating cellular processes of RNA processing and gene transcription (L. Yang et al., 2011). More detailed cellular functions of MALAT1 have recently been discovered and may be important in cell cycle arrest, cellular senescence, and apoptosis. Evidence suggests that MALAT1 stimulates sirtuin1 (SIRT1) deacetylase activity and thereby, inhibits p53 activity by promoting SIRT1-mediated p53 deacetylation (R. Chen et al., 2017). It is well known that decreased acetylation of p53 is associated with reduced transcription levels of its target genes (Vousden & Prives, 2009). In this context, MALAT1 activity seems to interfere with the physical interaction between SIRT1 and depleted in breast cancer 1 (DBC1), which is a nuclear protein involved in gene expression regulation (R. Chen et al., 2017). DBC1 has been reported to suppress the activity of multiple epigenetic modifiers like SIRT1 (Kim et al., 2008). MALAT1 also bind DBC1 and compete with SIRT1 for DBC1-binding sites. In another mechanism, MALAT1 can function in repressing the promoter activity of the p53 gene, leading to the regulation of p53 expression in human lung adenocarcinoma cells

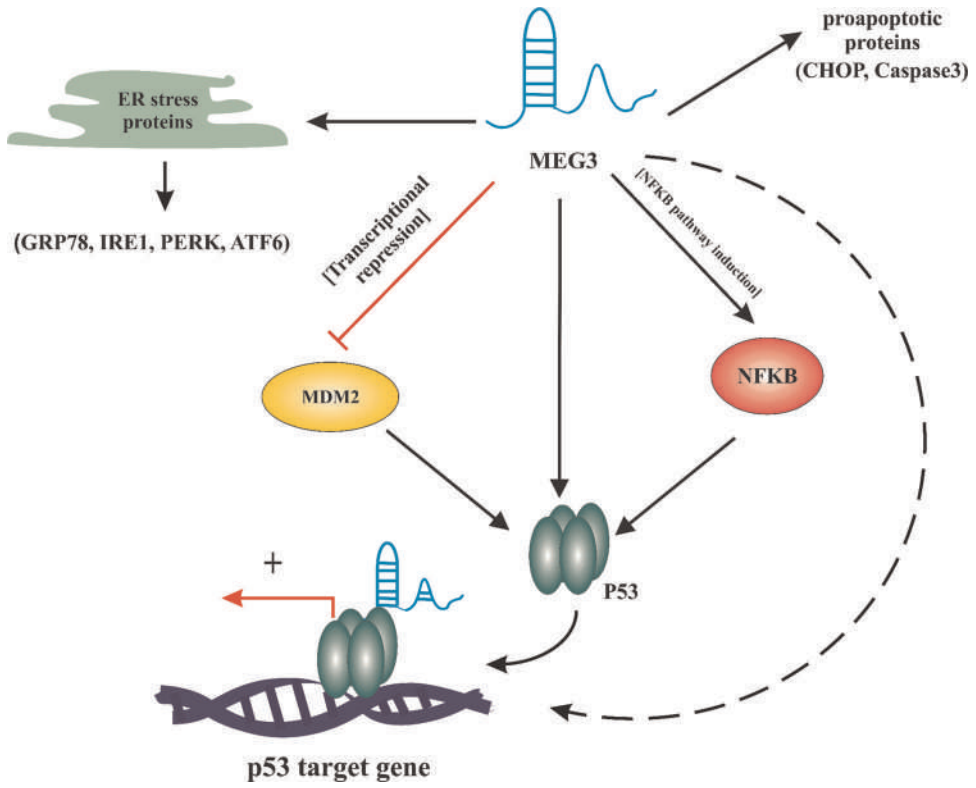

FIGURE 2 Positive and negative regulations of p53 signaling by lncRNAs. Various lncRNAs are involved in controlling epigenetic regulation of target gene expression by functioning either upstream or downstream of the p53 signaling pathway. These lncRNAs act as tumor suppressors, such as MEG3, Wrap53, PANDA, or as oncogenes like MALAT, and H19. LncRNAs may also play critical roles in the p53 signaling pathway as effector molecules, including lincRNA-p21 and p53eRNAs. ROR has been identified as an autoregulatory element for p53 response. ATF6, activating transcription factor 6; CHOP, CCAAT-enhancer-binding protein homologous protein; ER, endoplasmic reticulum; eRNA, enhancer RNA; GRP78, glucose-regulated protein 78; IRE1, inositol-requiring enzyme 1; LincRNA-p21, long intergenic noncoding RNA p21; lncRNA, long noncoding RNA; MALAT, metastasis-associated lung adenocarcinoma transcript; MDM2, mouse double minute 2 homolog; MEG3, maternally expressed gene 3; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; PANDA, P21-associated ncRNA DNA damage activated; ROR, lncRNA-regulator of reprogramming; Wrap53, WD40-encoding RNA antisense to p53

(Tano et al., 2018). Luciferase reporter gene assays have identified specific MALAT1-responsive regions in the p53 promoter by which MALAT1 negatively regulate transcription factors designed to target these elements and hence modulates p53 promoter activity (Tano et al., 2018). Furthermore, constitutive overexpression of MALAT1 in the presence of polyoma and papilloma oncoproteins has also been reported to disturb or even prevent the expression/function of p53. This finding has raised the potential value of MALAT1 to serve as a biomarker for p53 deregulation in cancerous tissues (Jeffers et al., 2013).

10.3 | Wrap53

In eukaryotic genomes, natural antisense transcripts (NAT) are lncRNA molecules that represent reverse complementary sequences to other transcripts and exert trans and cis effects on other genes to regulate gene expression (Lehner et al., 2002). Numerous NATs with potential regulatory functions are encoded by mammalian genomes. Epigenetic events altering gene expression by NATs can occur by either transcriptional (gene promoter) or posttranscriptional mechanisms (Kong et al., 2018). Wrap53 is a natural p53 antisense transcript originated from the p53 locus acting as a posttranscriptional regulator of the p53 gene. Studies indicate that Wrap53 has a positive impact on endogenous basal p53 mRNA levels (Farnebo, 2009). The 5′-untranslated region (UTR) of p53 mRNA is shown to overlap a complementary sequence on Wrap53 and this Wrap53/p53 RNA matching has the capacity to protect p53 mRNA from degradation, thereby sustaining p53 protein expression in response to DNA damage (Mahmoudi et al., 2009). The induction of Wrap53 antisense transcript is found essential to target cells for p53-dependent death, indicating the functional importance of Wrap53 in p53 regulation (Mahmoudi et al., 2009). A number of regulatory RNA molecules and proteins, such as transcription factors, miRNAs, the ZF protein CTCF (an acronym for a "CCCTC-binding factor"), and antisense transcripts interplay to regulate p53 gene expression (Saldaña-Meyer & Recillas-Targa, 2011). Among the various involved parties, the zinc finger CTCF is distinct and able to operate in parallel with Wrap53 RNA in regulating human p53 gene expression. Apart from its DNA-binding characteristics, CTCF is capable of binding a variety of RNAs, including Wrap53. Consistently, both CTCF and the Wrap53 transcripts acting upstream of p53, participate in the transcriptional response of p53 to DNA damage by CTCF binding to Wrap53 (Saldaña-Meyer et al., 2014).

10.4 | P53-eRNAs

Enhancer RNAs (eRNAs) represent a different class of ncRNAs functional in transcriptional activation (Shiekhattar, 2013). Enhancer regions in the genome interact intrachromosomally with and do control neighboring genes. P53 binding to specific enhancer regions is capable of regulating a variety of enhancer elements whose expression conveys long-distance regulation of p53-dependent gene expression (Melo et al., 2013). These regulatory regions termed p53-bound enhancer regions are required for the transcriptional enhancement of multiple target genes and efficient p53-dependent cell death (Melo et al., 2016). In fact, direct transcriptional regulation by p53 occurs for a small group of nearby coding genes, and many p53-binding sites lie in the distant transcripts, predominantly within enhancer regions throughout the genome (Uzunbas et al., 2019). Integrative genome-wide analysis indicates that enhancer recognition is a hallmark of p53 function in response to DNA damage (Younger et al., 2015). The results point to the role of enhancer RNAs in epigenetic regulation of gene expression in a cell-type-specific manner (Ong & Corces, 2012). Notably, an enhancer does not necessarily have a specific target and can influence a set of genes. Contrary to the aforementioned findings, there are other studies uncovering unexpected roles and diverse functional outcomes as a result of interaction between enhancer-containing regions and p53 (M. Li et al., 2012). In mouse embryonic stem (ES) cells, a distinct mode for the p53-mediated transcriptional network by inhibiting enhancer activity has been proposed. Under stress, p53 activity promotes ES cell differentiation and this is associated with repression of p53-bound enhancers but not with their activation (M. Li et al., 2012). It has been reported that interfering with enhancer activity is partial because of interactions between p53 and KRAB-associated protein-1 (KAP1). KAP1 is a mediator of transcription repression that promotes heterochromatin formation (Y. Zhu et al., 2012).

11 | P53-REGULATED lncRNAs

11.1 | LincRNA-p21

LincRNA-p21 is a p53-related gene associated with cell proliferation, apoptosis, and cell cycle (Yoon et al., 2012). Several lines of evidence have implicated lincRNA-p21 in the development of human diseases, such as tumorigenesis of colorectal cancer, non-small cell lung cancer (NSCLC), chronic lymphocytic leukemia (CLL), skin tumors, and prostate cancer (Castellano et al., 2016; Hall et al., 2015; Isin et al., 2014; Işın et al., 2015; G. Wang et al., 2014; Zhai et al., 2013). In many studies, lincRNA-p21 appears to be a potential tumor suppressor. For example, lincRNA-p21 is reported to be evidently downregulated in colorectal cancer tissues (X. Li, Pu, et al., 2013), and human hepatocellular carcinoma (Ning et al., 2015). The role of lincRNA-p21 is closely related to the classical cancer signaling pathway controlling cellular responses to DNA damage or apoptosis. It has been noted that lincRNA-p21 functions as a tumor suppressor during the progression of esophageal squamous cell carcinoma and has been known to induce cell cycle arrest at the G1 phase mediated by the p53 pathway (Y. Zhang et al., 2019). Indeed, lincRNA-p21 is identified as a target of wild-type p53 in this signaling pathway and as recently reported by another group is also transcriptionally regulated by the mutant p53 (Jin et al., 2019). Notably, the wild-type

and mutant p53 differentially regulate lincRNA-p21 expression in cells. Mutant p53 is found to potentiate lincRNA-p21 induction of head and neck squamous cell carcinoma (HNSCC) cells in an nuclear transcription factor Y subunit α (NF-YA)-dependent manner. NF-YA as an essential cofactor in cancer is required to enhance the expression of lincRNA-p21 by mutated but not wild-type p53 (Jin et al., 2019). It is now recognized that the lincRNA-p21 mediate crosstalk between the p53 and Janus kinase (JAK)–signal transducers and activators of transcription (STAT) signaling pathways, which contributes to the development of HNSCC. Signaling via JAK2/STAT3 pathway is an important event in malignant transformation (Johnson et al., 2018). According to recent research, the induction of lincRNA-p21 downstream of the p53 pathway can inhibit STAT3 phosphorylation through direct binding and therefore decreases the respective target genes of STAT3 in HNSCC-HN6 cells (Johnson et al., 2018). Furthermore, lincRNA-p21 may have additional functions in p53-dependent p21 transcription. Using a genetic approach, lincRNA-p21 has been described to act as a transcriptional coactivator of p53, influencing p21 expression in a cis-regulatory model (Dimitrova et al., 2014). In this way, lincRNA-p21 might also implicate in regulating a subset of polycomb-repressive complex 2 (PRC2) target genes through p21 (Campbell et al., 2010; Dimitrova et al., 2014). Some data also show that lincRNA-p21 plays a role in tumor-associated macrophages (TAMs) that contribute to cancer progression. More recently, it has been demonstrated that lincRNA-p21 is an important regulator of TAMs functional phenotype in the tumor microenvironment by interrupting p53 interaction with MDM2 (L. Zhou et al., 2020). Figure 3 represents the crosstalks between p53 and lincRNA-p21 in cell cycle arrest and tumor suppression.

11.2 | PANDA

PANDA is another evolutionarily conserved p53-regulated ncRNA located between lincRNA-p21 and the cyclin-dependent kinase inhibitor 1A (CDKN1A)/p21 transcription start site; however, its expression is not dependent on p21. Whereas p21 promotes cell cycle arrest, PANDA, whose expression is also induced in response to DNA damage, may have growth-promoting activity (Baldassarre & Masotti, 2012). In the human genome, the p21 and PANDA coding region are shown to be regulated by the p53 tumor suppressor, whereby p53 binds to upstream of the p21 transcription start site and activates the transcription of both target promoters (C.-L. Wei et al., 2006). PANDA, in turn, negatively affects the transcription of apoptosis activators, such as apoptotic peptidase activating factor 1 (APAF1), B-cell lymphoma-2-interacting killer (BIK), FAS, and leucine-rich and death domain (LRDD; Hung et al., 2011). PANDA mediates antiapoptotic functions by specifically associating with and repressing the NF-YA binding to promoters of canonical activators of apoptosis in normal human fibroblasts (Kotake & Kitagawa, 2015). On the other hand, the involvement of PANDA in the p53 pathway through other effects has been established. The RNA interference-mediated depletion of PANDA has been shown to substantially decrease the p53 protein but not the p53 mRNA level, showing a new role for PANDA in the stabilization of p53 protein, which is independent of NF-YA (Kotake et al., 2016). The molecular mechanism(s) involved in this process remain(s) unknown.

11.3 | H19

In contrast to the previous reports, which indicate that lncRNA H19 has tumor-suppressive effects (Yoshimizu et al., 2008), other studies show that H19 may function as an oncogene in various cancers. H19 RNA has been characterized as an oncogene in breast, bladder, gastric cancer, and hepatocellular carcinomas (Lottin et al., 2002; Yoshimura et al., 2018; E.-B. Zhang, Han, et al., 2014). Several studies have reported the increased expression of H19 after hypoxic exposure (Matouk et al., 2007). Experiments in vitro and in vivo have shown a tight link between p53 status and H19 RNA induction upon hypoxia (Matouk et al., 2010). Several reports demonstrate a critical role for hypoxia-inducible factor-α (HIF1-α) in H19 upregulation when p53 is impaired (Matouk et al., 2010; Raveh et al., 2015), indicating an inhibitory effect of p53 on H19 induction. A further detailed experiment confirmed functional links between miR-675, the mature product of H19 (Cai & Cullen, 2007), and p53 activation in bladder cancer cells. MiR-675 is an miRNA processed from H19 and is known to play substantial roles in tumorigenesis driven by H19 RNA. Quantitative analysis of gene expression shows that bladder cancer tissues and cell lines express a markedly increased level of miR-675 compared with normal control. Moreover, the enhanced expression of miR-675 may promote bladder cancer growth and inhibit cell apoptosis in vitro, partly through a negative regulatory role on p53 (C. Liu et al., 2016). Also, hypoxia-induced H19 might be one of the mechanisms involved in the pathogenesis of NSCLC via dysregulation of p53 as a direct target gene of miR-675 (Zheng et al., 2019). A recently published study found that the interaction of lncRNA H19, p53, and tumor necrosis factor-α-induced protein 8, which is an oncogenic molecule produced by TNF-α, play crucial roles in breast cancer metastasis (Zeng et al.,). LncRNA H19 has been found to cause induction of epithelial-to-mesenchymal transition in breast cancer, especially triple-negative breast cancer by antagonizing p53 and increasing the expression of its target gene TNFAIP8.

12 | ROR AS A p53 EFFECTOR AND REGULATOR

12.1 | LncRNA-ROR

The newly discovered lncRNA ROR was initially identified in induced pluripotent stem cells (iPSCs) as a critical factor that enables differentiated cells to reprogram into iPSCs. ROR was further demonstrated to have important regulatory roles in cancer biology,

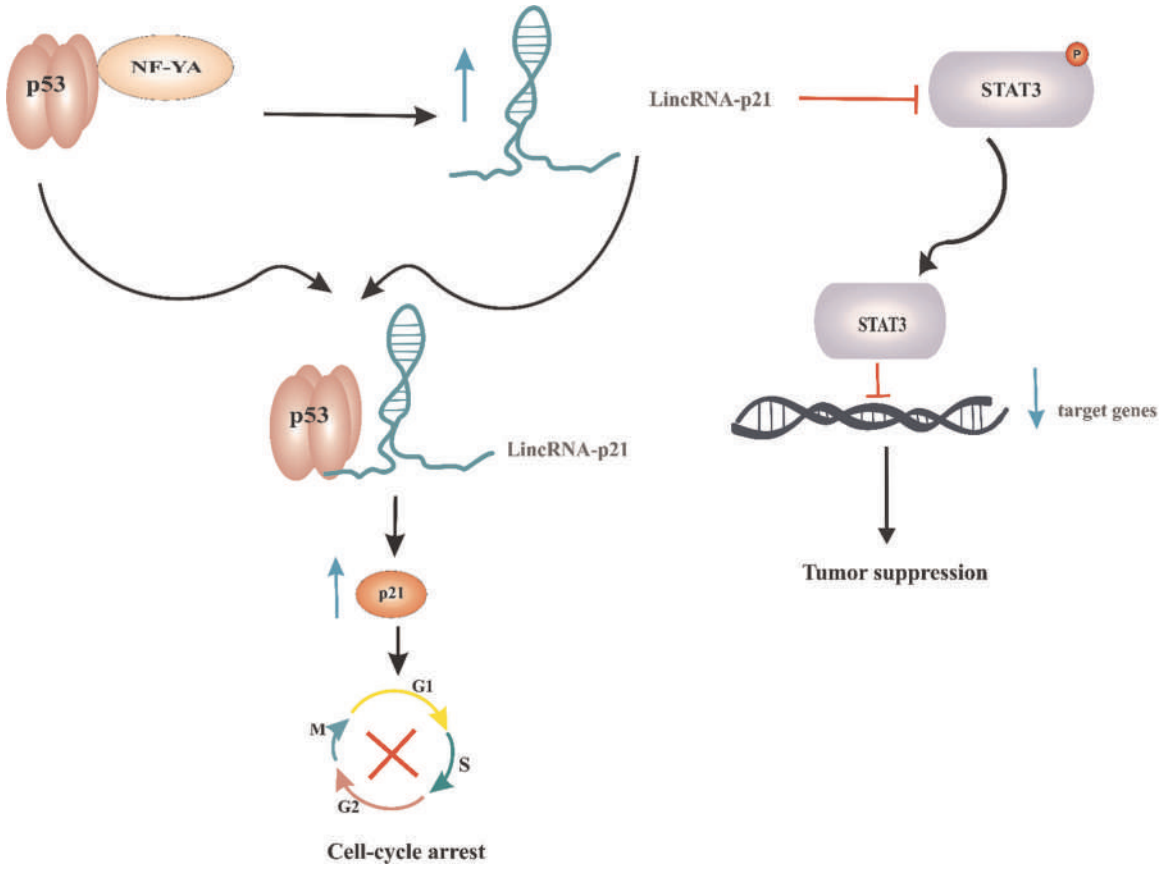

FIGURE 3 MEG3-dependent mechanisms of p53 upregulation. Under normal conditions, lncRNA MEG3 functions in different cellular compartments to protect p53 from degradation and enhance its gene expression, leading to p53 accumulation in the cell. In some cancer types, MEG3 also participate in NF-kB pathway induction thereby, which can activate the p53 pathway. Moreover, target gene binding of p53 is enhanced by interacting with MEG3 lncRNA. Alternatively, MEG3 can induce apoptosis via activation of ER stress-related (GRP78, IRE1, PERK, ATF6) and proapoptotic proteins (CHOP, caspase3) expression. ATF6, activating transcription factor 6; CHOP, CCAAT-enhancer-binding protein homologous protein; GRP78, glucose-regulated protein 78; IRE1, inositol-requiring enzyme 1; lincRNA-p21, long intergenic noncoding RNA p21; MEG3, maternally expressed gene 3; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NF-YA, nuclear transcription factor Y subunit α; PERK, protein endoplasmic reticulum kinase; STAT3, signal transducer and activator of transcription 3

particularly tumor-promoting activities in breast cancer, pancreatic cancer, nasopharyngeal carcinoma, and gallbladder cancer (Ahmadi, Abdolmohammadi-Vahid, et al., 2017; Hou et al., 2014; L. Li et al., 2016; S.-H. Wang et al., 2016; Zhan et al., 2016). lncRNA-ROR is considered to behave as a repressor of p53 and is also under the control of p53 (A. Zhang et al., 2013). Zhan et al. (2016) showed that lncRNA-ROR promotes tumor growth and invasion in vitro and confers metastatic capacities to pancreatic cancer cells in vivo. Their observations suggested that these effects may be mediated by lncRNA-ROR-induced activation of zinc finger E-box binding homeobox 1 (ZEB1), caused by inhibition of p53. H. Li et al. (2017) documented that knockdown of lncRNA-ROR could result in a remarkable increase in p53 protein level in colorectal cancer cells showing that lncRNA-ROR possesses a tumor-promoting function and is negatively correlated with p53 protein. Finally, a molecular mechanism integrating lncRNA-ROR and p53 pathway in resistance to radiotherapy for colorectal cancer has been uncovered by demonstrating that knockdown of lincRNA-ROR enhanced radiation sensitivity and growth inhibition by inducing the p53/miR-145 axis (P. Yang et al., 2017). In contrast, high p53 and ROR levels, as well as low miR-145 expression have been correlated with poor prognosis in NSCLC. In NSCLC tissues and lung cancer stem cells, silencing ROR and/or p53 upregulated miR-145 level and led to the suppression of cell proliferation and migration in vitro and in vivo (Li & Zheng, 2017). In addition, the authors unveil that p53 also acts to promote lncRNA-ROR transcription (Li & Zheng, 2017). Altogether, these results establish an autoregulatory feedback loop involving ROR and p53 that provides a mechanism ensuring cancer cell growth.

13 | CONCLUSION

Genomic analyses for cancer mutations have allowed the detection of functional mutations in the noncoding regions of the genome, particularly on the expression level of lncRNAs. There is ample

evidence that lncRNAs participate in the malignant transformation of human cells through their interactions with diverse macromolecules, such as DNA, RNA, and proteins (Halaby & Yang, 2007). P53, as a frequently mutated tumor suppressor gene in cancer, has been discovered to be closely associated with lncRNAs. As mentioned above, p53-related lncRNAs can be categorized into two groups as p53 regulators, such as MEG3, MALAT1, Wrap53, p53-eRNAs, and p53 effectors lncRNAs like lincRNA-p21, PANDA, H19, and ROR. We now understand that participation of lncRNAs in cancer biology can provide several benefits as novel diagnostic biomarkers and therapeutic targets in the clinic. LncRNAs have been reported to have tissue-specific and cancer-specific expression patterns (Ahmadi, Abdolmohammadi-Vahid, 2017; K. C. Wang, Yang, et al., 2011). In conclusion, compelling evidence claims for the advantages of lncRNAs over many current protein-coding biomarkers in tissue-of-origin tests and cancer diagnostics (D. Wang, Garcia-Bassets, et al., 2011). The history of ncRNA-based research suggests their utility for diagnostic monitoring and potential ncRNA-based therapies in human cancers. Currently, several ongoing clinical trials are addressing the safety and efficacy of RNA interference (RNAi)-based therapeutics in a variety of illnesses, including cancer. Such an approach can be adopted to target lncRNA transcripts.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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