Molecular Life

New insights into the role of non-coding RNAs as transcriptional targets of p53

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Abstract

P53 classifies as one of the main tumor suppressor gene and the identification of its direct transcriptional targets such as certain non-coding RNAs (ncRNAs) is important for understanding the development and progression of cancer. Multiple ncRNAs are targeting **p53** and are involved in many cellular processes such as cell cycle arrest, metabolism, apoptosis, autophagy and feedback mechanisms. Also, various ncRNAs were found to modulate p53-dependent gene regulation. These include microRNAs such as *miR-660*, *miR-486*, *miR-34* and lncRNAs such as nuclear enriched abundant transcript 1 (NEAT1), which contribute to the tumor-suppressor function of the p53 protein. Long intergenic non-coding RNA, *LincRNA-p21*, has been proclaimed to promote apoptosis while other p53-regulated lncRNAs including *PANDA* and *Pint* antagonize p53 activity by limiting the activation of proapoptotic genes. Taking into account the activity of the proapoptotic transcription factor p53, new conclusions point to a new concept of cellular quality control since ncRNAs-based deregulation in cancer functions in the absence of p53 coding sequence mutations.

Keywords: long non-coding RNAs; p53; apoptosis; *lincRNA-p21*

INTRODUCTION

Discovered by mistake, **p53** is nowadays the main tumor suppressor molecule with numerous mechanisms related to cancer inhibition. Known in the scientific literature as 'the guardian of the genome', the gene and the protein generate more than 80000 entries in PubMed in connection with various types of cancers (1-3). This strong relationship between p53 and malignant pathologies is mainly caused by the mutated forms of the gene, which are altered in more than half of all cancers (4, 5). The activation of the protein is stimulated by stress alarms of various origins such as the activation of oncogenes, the acquisition of DNA damage and hypoxia. The perception of these stress signals results in the arrest of the cell cycle in the associated checkpoints in order to permit DNA corrections, or, if the damage is too extensive, the cell undergoes programmed cell death (6). The main role of p53 as a carcinogenic inhibitor consists in the regulation at the transcriptional level of the target genes that control various cellular processes including programmed cell death, DNA repair mechanisms, autophagy, metabolism, cell cycle control and thus genetic integrity (7-10).

The elements targeted by p53, a cancer suppressor interacting with numerous target genes, were presented through meta-analysis statistics, which showed that the target genes characterized by high confidence are involved in numerous feedback loops at cellular level such as cell cycle arrest, metabolism, and mRNA translation. At the same time, a series of mechanisms were associated with the modulatory aspects of gene control in response to p53 (11-13). To our knowledge, research studies revealed that p53 can act as a catalyst of transcription. Moreover, gene down-regulation by p53 is indirect and

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depends on p21 expression. Considering the importance of p53 as an activator of transcription, new ideas point to a straightforward concept of cellular quality control (12, 13).

The stimulation of p53 is induced by oncogenic activation, stress at the ribosomal level or hypoxia and DNA damage, which initiate a series of p53 vibrations ultimately leading to the activation of target genes (6, 13). The p53 transcription factor needs two transactivation domains in order for the controlling action on gene expression to take place while the transactivation of target genes relies on the interconnected interaction between the p53 proteins at DNA response elements (REs) (12, 14-16).

The kinetics of P53-activating target genes changes through stimulus- and promoter-specific enrollment of transcription induction ingredients and polymerase II enzymes (17-20). However, evidence based on genome-wide profiling does not support the promoter-specific actions of the protein, thus suggesting an unsophisticated p53 binding (12).

Non-coding RNAs (ncRNAs) comprise a class of sequences that are able to regulate gene expression without undergoing translational processes (20).

p53-regulated lncRNAs

Pint long intergenic non-coding RNAs (*lincRNA*) links the p53 mechanism with epigenetic silencing through the Polycomb repressive complex 2. The activation of lncRNA *NEAT1* that is a direct target (transcription level) of p53 enforces the tumor-suppressor mechanisms of this protein (30, 31). Presenilin (PS)-2, an essential gene associated with familial Alzheimer's disease (AD) could induce apoptosis through the p53/*miR-34*a axis (32). *PANDA lincRNA* correlates with nuclear transcription factor Y subunit alpha (NF-YA) and blocks it's binding to promoters of apoptosis-related genes, thus suppressing apoptosis in normal human fibroblasts (33). However, results relying on different experimental models have limited applicability. For example, studies that modulated the expression of *lincRNA-p21* or *miR-34* (loss of function or overexpression strategies) hardly overlap with those that adopted knockout mice.

There is a lack of consensus regarding knock-out experimental models as far as the effects of *LincRNA-p21* deficiency are concerned. Some studied showed that *LincRNA-p21* removal declined p21 expression and promoted the proliferation of mouse embryonic fibroblasts (MEFs), while in other experiments there was no decline in p21 protein level following the loss of function of *LincRNA-p21*. A possible answer to this dichotomy is that a complete loss of linc-RNA-p21 (as achieved by genetic deletion) is mandatory in order to deregulate the expression of p21. Therefore, future studies on lncRNAs and p21 interaction need to resolve this issue (34-38) (Table 1).

Based on the description of mouse lncRNAs directly induced by p53, *LincRNA-p21* has been proposed to promote apoptosis, while other p53-regulated lncRNAs, including *PANDA* and *Pint*, antagonize p53 activity by limiting the activation of proapoptotic genes (33, 37) (Fig. 1). Originally discovered in mice (m*LincRNA-p21*), *LincRNA-p21* is also present in humans (hm*LincRNA-p21*). However, the homology between these two lncRNAs is limited to a short transcript region of 130nt at 5'end including the binding site for the hnRNPk protein and the p53-response element. Moreover, many m*LincRNA-p21* target genes validated in mice are not controlled by p53 in humans while in human diseases h*LincRNA-p21* is a specific target of *NEAT1*, which modulates p53-induced tumor-suppressor function and transactivation (28, 39, 40). Tests of functional screening and expression profiling revealed that *LincRNA-p21* also interacts with cellular reprogramming, conducting towards inhibition of the process. Exceptionally, *LincRNA-p21*, which is transcribed as a result of p53 stimulation, does not determine cell senescence and apoptosis in the reprogramming process. Alternately, *LincRNA-p21* acts simultaneously with the histone H3 lysine 9 (H3K9) methyltransferase SETDB1, which is recurrently overexpressed in melanoma. The conservation DNA methyltransferase DNMT1 determined by the RNA-binding heterogeneous nuclear ribonucleoprotein K (HNRNP-K) interacts directly and binds to the promoter regions that are silenced in tumor cells (28, 39-41).

Consequently, *LincRNA-p21* impairs reprogramming by promoting CpG methylation or H3K9me3 at the promoters of pluripotency genes. Thus, lncRNAs underline a hidden connection between heterochromatin regulation and p53 as a transcription factor (42) (Fig. 1).

p53-regulated miRNAs

Certain ncRNAs were found to regulate p53-dependent gene control (21, 22). These include microRNAs such as *miR-660* and *miR-486*, which are p53-dependent, and long non-coding RNAs (lncRNAs) such as TUG1 (taurine upregulated gene 1), the p53/TUG1/polycomb repressive complex-2 (PRC2)/homeodomain-containing protein (HOXB7) interaction as targets for the diagnosis and treatment of non-small cell lung carcinoma (NSCLC), *miR-34*, *LincRNA-p21*, p53 induced non-coding transcript (*Pint*) and p21-associated ncRNA DNA damage-activated (*PANDA*) (24-30) (Table 1).

THE DUAL NATURE OF p53 REGULATION IN CANCER

The crosstalk between the p53 network and miRNAs is important in cancers. Firstly, miRNAs can modulate the activity of p53 by various mechanisms. Moreover, the removal of mutated p53 (which represses certain

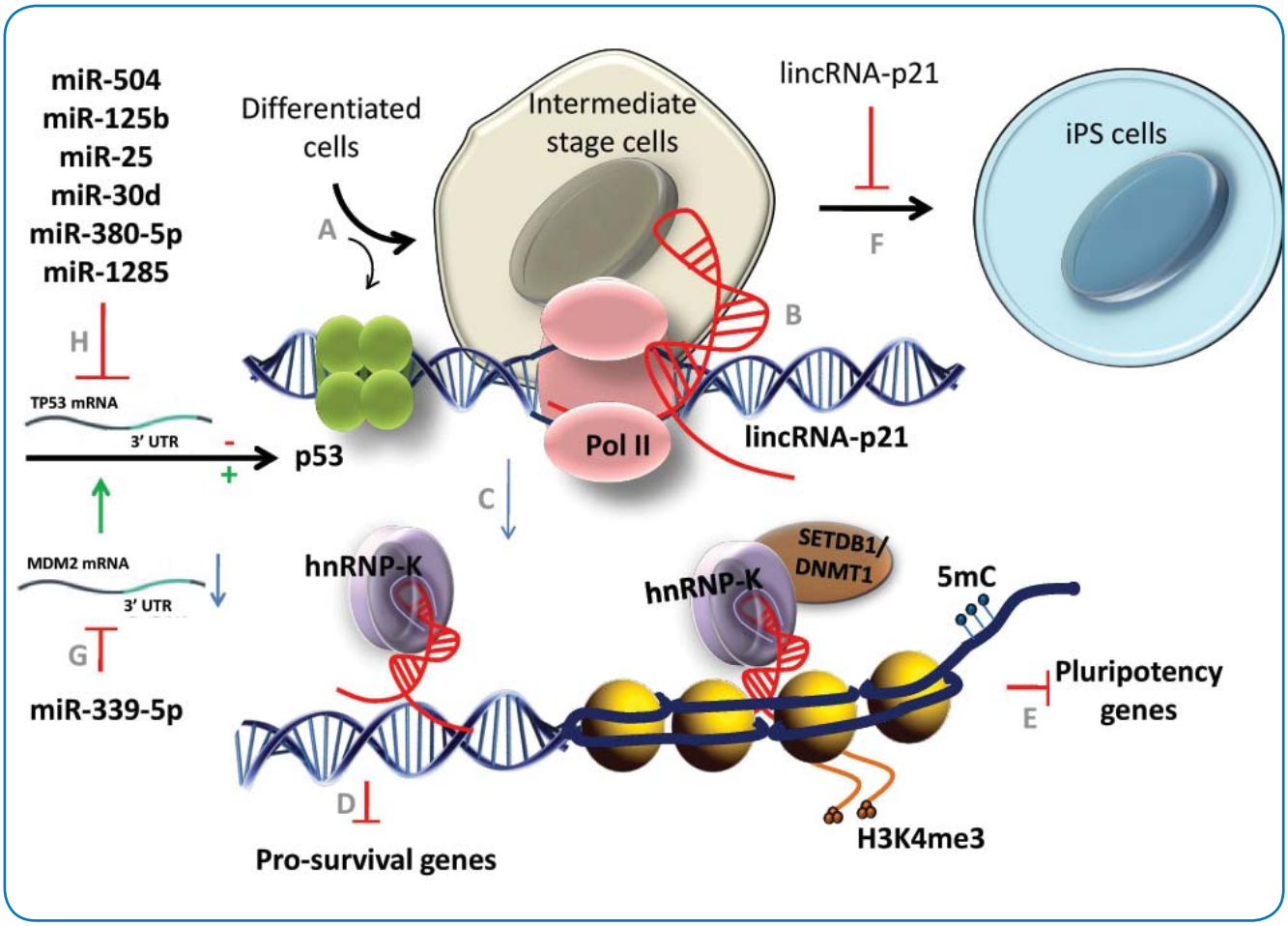

Fig. 1. – *LincRNA-p21* and miRNAs impair cellular reprogramming. p53 is maintaining the intermediate stage of cells in terms of cells reprogramming through lincRNA-p21. (A) The transformation of differentiated cells into intermediate stage cells promotes the expression of TP53 and results in an increased amount of p53. (B) The protein is able to stimulate the transcription of lincRNA-p21, which further (C) combines with hnRNP-K, directing together the inhibition of pro-survival gene expression (D). The intermediate stage may also be maintained through epigenetic modification mediated by lincRNA-p21 instead of through the apoptosis mechanism. (E). This sequence indirectly combines with SETDB1/DNMT1 and binds the promoter of pluripotency genes, thus highlighting histone modification *via* H4K4me3 and DNA methylation. In this way, the translation of the target genes is impaired and the transition towards iPSC is inhibited (F). On the one hand, miR-339-5p activates p53, thus acting as a tumor suppressor through the direct binding of 3'-UTR of MDM2 mRNA, where MDM2 inhibits the level of p53 (G). On the other hand, microRNAs interfere with p53 expression by interacting with the 3'UTR of p53 mRNA in a sequence-specific manner (H).
Abbreviations: iPSC – induced pluripotent stem cells; H3K9 – histone H3 lysine 9;
SETDB1 – Histone-lysine N- methyltransferase; HNRNP-K – heterogeneous nuclear ribonucleoprotein K;
DNMT1 – DNA methyltransferase; H3K9me3 – histone demethylase.

miRNAs activated by wild-type p53) interferes with cell senescence and apoptosis, thus having a key role in tumor progression and invasion. Therefore, multiple myeloma is an incurable blood cancer characterized by an overproduction of immunoglobulin. Since p53 is hardly mutated in this type of cancer, multiple myeloma is a reliable model for the study of microRNA overexpression as a complementary mechanism of p53 suppression (20, 43).

Over the past seven years, research has identified 11 microRNAs (miRNAs) that negatively control p53 expression by directly targeting the 3' untranslated region (3' UTR) (Fig. 1). These miRNAs are able to suppress the expression of the tumor suppressor genes and implicitly promote pro-carcinogenic mechanisms. Examples include miR-25 and miR-30d, which are both capable to exert regulatory actions in terms of apoptosis, senescence and cell cycle arrest by inhibiting p53 stress-response pathways (44).

Following a similar direct binding mechanism, miR-125b is also able to influence the fate of the p53 transcript, as it exerts inhibitory action on protein levels in different human cells like neuroblastoma and lung fibroblast cells, thus generating a resistant phenotype that does not respond to cell death signals. Moreover, this inhibitory action is further translated in terms of

Table 1. Example of non-coding RNAs modulating the p53-dependent mechanism

ncRNAs	Genetic role in cancer	Effects on p53	Ref
miR-34	Anti-tumor effect p53/*miR-34a*/SIRT1 causes Quercetin-Induced Apoptosis through positive feedback loop	Exhibits wild-type p53 in HepG2 cells	55
miR-660-p53-*miR-486* network	Synergistic effect in lung cancer treatment Cell-cycle arrest or cell death Escape of immune surveillance in malignant scenarios Expression of other miRNAs in NSCLC including *mir-181*, *mir-184*, and *mir-148*	Exhibits wild-type p53 in NSCLC Regulates PDL1 for NSCLC	56
miR-339-5p	Tumor suppression through MDM2 (inhibitor of p53 transcriptional activation)/p53 negative feedback loop	Activates p53 functions in cellular senescence and apoptosis in CRC, lung and breast cancers	54
miR-25	The regulation process mediated by *miR-25* impairs cell cycle arrest, apoptosis and senescence in multiple myeloma	Inhibits the effect of p53 on cellular senescence in HCT116 cells	44
miR-30d	The regulation process mediated by miR-30d impairs cell cycle arrest, apoptosis and senescence in multiple myeloma	Blocks the p53 stress-response pathway	44, 57
miR-125b	Involved in the promotion of neuroblastoma cells and lung fibroblasts in vitro by impairing programmed cell death; Increases the sensitivity of osteosarcoma cells to cisplatin; Reduced levels in HCC cells	Suppresses p53 actions in human lung fibroblast cells, neuroblastoma and osteosarcoma cells; Upregulates p53-cancer-associated pathways involved in cell cycle control, protein degradation, adhesion and expression related mechanisms (transcription and translation)	45, 46, 58
miR- 504	Negative regulator of p53-mediated apoptosis, p53 transcriptional activity and cell-cycle arrest in response to stress	Suppresses the p53 target Inhibits p53 protein amounts directly correlated with apoptotic levels and cell cycle arrest	47, 59
miR-380-5p	Apoptosis impairment Increased tumor related physical parameters (*e.g.*, size)	Down-regulates the p53 target	48, 57, 59
miR-92	Promotes proliferation	Inhibits p53 protein amounts directly correlated with apoptotic levels and cell cycle arrest	49
miR-141	Mediates cell survival under stress ondition in ovarian cancer cells -Inducing cancer metastasis	Down-regulates the p53 target	49, 60
miR-1285	Promotes tumor progression and etastasis, cell differentiation	Mutual inhibition of p53-miRNA	50, 51, 61
miR-200a	Promotes malignant cell transformation and metastasis	Mutual inhibition of p53-miRNA	52, 61
miR-16	Promotes tumor progression and metastasis, cell differentiation	Mutual inhibition of p53-miRNA	20, 53, 61
miR-15	Promotes tumor progression and metastasis, cell differentiation	Mutual inhibition of p53-miRNA	20, 53, 61
lncRNA-NEAT1	Stimulates cancer cell growth	Knockdown of p53-induced apoptosis	31
lincRNA-p21	Blocks cell senescence and apoptosis	not controlled by p53	12, 42
lncRNA-PANDA	Blocks cell senescence and apoptosis	not controlled by p53	12
lncRNA-PINT	Blocks cell senescence and apoptosis	not controlled by p53	12

Abbreviations: ncRNA – non-coding RNA; miR – microRNA; lncRNA-long non-coding RNA; lincRNA – long intergenic non-protein Coding RNA; NEAT1/VINC – Nuclear Enriched Abundant Transcript 1/Virus Inducible NonCoding RNA; lincRNA – long intergenic non-coding RNAs; PINT – P53 Induced Transcript; PANDA – p21-associated ncRNA DNA damage activated; SIRT1 – sirtuin 1; PDL1 – Programmed Death 1 Ligand; NSCLC – non-small cell lung carcinoma; MDM2- E3 ubiquitin ligase or mouse double minute 2 homolog (inhibitor of p53 transcriptional activation)

apoptosis levels under conditions of stress or development (45). MiR-125b overexpression promotes the cisplatin chemosensitivity of osteosarcoma cell lines through the modulation of Bcl-2 (46).

MiR-504 negatively regulates the p53 protein by decreasing its expression and functional roles in cells, including p53 as a transcription activator, apoptosis and also cell-cycle arrest. Consequently, miR-504 positively regulates cell tumorigenicity in vivo (47).

Decreased levels of miR-380-5p in neuroblastoma or embryonic stem cells cause the activation of p53 and apoptosis. Moreover, in in vivo preclinical models of neuroblastoma, the delivery of a miR-380-5p antagonist inhibited tumor size by impairing cell survival under stress (20, 48).

MiR-92 and miR-141 are important determinants of pluripotency and reprogramming by inferring with embryonic states, thus inducing pluripotent stem cells (49). P53 can also silence miR-1285, which increases p53 expression (50, 51).

MiR-200a has an oncogenic role by promoting malignant cell transformation and metastasis mediated by the mutual inhibition of p53 (52). Recent research showed the existence of a molecular circuitry in which miR-16, miR-15 and p53 specific targets cooperate in order to promote tumor invasiveness through stromal and cancer cells in two way communication (20, 53).

In addition, recent research revealed that miR-339-5p plays an important role in activating the p53 function in tumor suppression through directly binding to the 3'-UTR of MDM2 (E3 ubiquitin ligase or mouse double minute 2 homolog, an inhibitor of p53 transcriptional activation) mRNA. This miR diminishes MDM2 protein levels, thus increasing cellular p53 protein load, which induces the expansion of p53 actions such as the inhibition of cell migration, the stimulation of senescence and apoptosis processes (54).

CONCLUSION

In this review we established links between ncRNAs and the p53 network – a well known guardian of the genome, which is especially important during the stress response activated in all types of cancers. The endogenous *LincRNA-p21* functions as a key regulatory checkpoint under stress conditions and could serve as a valuable therapeutic target for tumors.

miRNAs switching from repression to activation act as cellular micro-hormones if the level of the target mRNA is below a stress threshold. They can also act as fine-tuners if the target mRNA level is over expressed.

In conclusion, the interaction between non-coding RNA-based regulatory mechanisms and the p53 system is obvious and has a crucial role in maintaining the quality control of cells.

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