

The Big Player Governs Small World Too

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Since its discovery, p53 has been a focus in cancer biology. Cancer genomic studies have revealed that p53 is mutated or deleted in over half of human cancers. Even in those tumors containing wildtype p53 gene, the p53 expression and activity are often deregulated.¹ Reduced or loss of p53 activity leads to cell hyperproliferation and genomic instability, common phenotypic features observed in precancerous lesions. In response to DNA damage stress, p53 is activated to provoke essential changes in global gene expression programs in the cell. First, p53 functions as a sequence-specific transcriptional activator. Hundreds of effector genes are transactivated in a p53-dependent manner, most of which share consensus p53 target sequences in their promoter regions.² These target genes are involved in cell cycle checkpoints, apoptosis, DNA repair, cell metabolism and differentiation. In addition to the protein-coding genes, recent findings have demonstrated that p53 is involved in the post-transcriptional regulation of gene expression via miRNAs, a type of small noncoding RNAs.

Hattori et al. in this issue reported that p53 is a central player that determines genome-wide and cell-specific changes in miRNA expression following ionizing radiation (IR).³ DNA damaging agents alter miRNA expression profiles in cells, which was previously analyzed in cells treated with cisplatin, doxorubicin, neocarzinostatin, UV and IR.⁴ Global miRNA expression analyses have revealed that a cohort of miRNAs is upregulated in p53-dependent manner following DNA damage, among which the miR-34 family was the first identified transcriptional target of p53.⁵ The p53 protein also functions as a transcriptional repressor. As an example, p53 suppresses the transcription of the miR-17-92 cluster gene by preventing recruitment of the TATA-binding

protein to the TAATA site in the promoter.⁶ Thus, fine-tuning between the p53 signaling and miRNA transcription enables cells to amplify the p53 signal, which enhances cell sensitivity to external signals. In their studies, Hattori et al. performed next-generation sequencing (NGS) and comprehensive computational analyses to identify differentially expressed miRNAs following IR. Whereas oligo DNA array and qPCR array have been widely used to determine miRNA expression profiles, the NGS method may have greater sensitivity. One major advantage of this method is the ability to measure changes in miRNA expression without prior knowledge, and thus to distinguish miRNAs with sequence similarity. It is also important to note that isolation of small RNA population in the current study significantly reduces "noises" from primary or precursor miRNAs that share the same stem-loop sequence with mature miRNAs.

The p53-dependent regulation of miRNA expression may be dependent on the nature and intensity of DNA damage stress. The current study described genome-wide changes during the DNA damage response (DDR) that involve the expression of 150 miRNAs.³ Not surprisingly, the DDR-induced changes exhibit cell-type dependent patterns even under certain DNA damaging treatment (5-Gy of IR). Only a small fraction of the miRNAs was altered in both of MCF10A and HCT116 cells after DNA damage, suggesting the complexity of regulatory mechanisms for miRNA expression. Analysis of promoter sequences of miRNA genes identified potential miRNA genes that are transcriptionally activated or repressed by p53. The authors suggested that p53 plays an important role in transcriptional regulation of miRNA expression. However, the results of the bioinformatic analysis deserve further validation. Post-transcriptional

regulation has been shown to be an important part of the effects of p53 on miRNA expression. A previous study by Suzuki et al. demonstrated that p53 facilitates the processing of primary miRNAs by interacting with DDX5 in the Drosha microprocessor.⁷ Most probably, p53 not only regulates the transcription of miRNA genes, but also modulates the post-transcriptional maturation of miRNAs. Transcriptional changes may be greater under certain circumstances.

What are biological and clinical relevance of the p53-mediated miRNA changes in the DDR? This study shows that half of the DDR-responsive miRNAs exhibits a significant association between their expression levels and cancer patient survival.³ Genomic instability is one of the most pervasive characteristics of tumor cells, which is caused by the combined effect of DNA damage, tumor-specific DNA repair defects, and a failure in cell cycle checkpoints. Although DNA damage drives genomic instability and ultimately the disease process, it also provides therapeutic opportunities. The current study suggests that tissue-specific miRNA alterations during the DDR may provide prognostic markers in patients with cancer.

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