

Microrna Control of P53 Proteasomal Degradation

June 16, 2014

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The tumor suppressor p53 regulates key events in the cellular lifecycle, including cell cycling, cell death, and senescence. Disruption of p53 in model systems leads to increased frequency and earlier development of cancer. Similarly, p53 function is altered in the majority of human cancers. Restoring normal p53 activity in these tumors could therefore slow or reverse cancer progression. MicroRNAs (miRNAs), small non-coding RNAs that regulate gene expression, represent one potential strategy to restore p53 activity in the tumor environment. In a recent study published in *Cancer Research*, Drs. Yemin Wang and Toshiyasu Taniguchi (Human Biology and Public Health Sciences Divisions), along with their collaborators, demonstrate that overexpression of one miRNA, miR-542-3p, upregulated p53 expression and activity in a tumor cell model, suggesting that this strategy may be a viable approach for future cancer therapeutics.

miRNAs are derived from nuclear transcripts that are processed through a cascade of enzymatic cleavage steps, culminating in a 22 nucleotide long mature molecule. This mature miRNA in complex with the RNA-induced silencing complex (RISC) recognizes and silences mRNA transcripts through both enzymatic and non-enzymatic mechanisms. Several miRNAs regulate p53 expression; for example miR-29 indirectly increases p53 expression by downregulating the expression of two negative regulators of p53 (Park, et al., 2009). However, miRNAs had not yet been systematically investigated for their ability to regulate p53 expression.

To identify miRNAs that regulate p53 expression, the researchers screened a library of 810 miRNA mimics for their effect on p53 protein expression in an osteosarcoma cell line. This screen identified 17 negative regulators of p53 and 13 potential positive regulators of p53. The strongest potential positive regulator, miR-542-3p, is downregulated in many cancers, so the authors selected this molecule for further analysis.

Overexpression of either miR-542-3p or a plasmid encoding the unprocessed precursor sequence (pri-miR542) both increased steady state levels of p53; however, this effect was not due to an increase in p53 transcription. Instead, this increase in p53 expression was due to inhibition of proteasome-mediated degradation of p53, extending the half-life of the protein from 50 minutes to

130 minutes. Microarray-based expression profiling confirmed that miR-542-3p primarily alters the p53 pathway; however, several ribosomal subunits were also downregulated. Specifically, the ribosomal protein RPS23 is a direct target of miR-542-3p, and depletion of RPS23 led to the sequestration of MDM2, the primary E3 ubiquitin ligase targeting p53. Taken together, these data suggest that miR-542-3p stabilizes p53 indirectly by inhibiting MDM2-mediated proteasomal degradation of the tumor suppressor.

Disruption of the tumor suppressor p53 is a major driver of most human cancers. Several small molecules have been developed with activities that range from correcting the folding of mutant p53 to inhibiting proteasomal degradation of p53. Previous studies have demonstrated that several miRNAs regulate p53, and the current study by Wang, et al. confirms that miRNAs may be potent therapeutic agents to target the p53 pathway. "We focused on one microRNA (miR-542-3p) in this study, but we identified many other microRNAs that affect p53 expression in our microRNA library screen. Following up these microRNAs is an important future direction in order to comprehensively understand the interaction between microRNAs and p53," said Dr. Taniguchi.

[Wang Y, Huang JW, Castella M, Huntsman DG, Taniguchi T](#). 2014. p53 Is Positively Regulated by miR-542-3p. *Cancer Res*. Epub ahead of print, doi: 10.1158/0008-5472.CAN-13-1706.

See also: [Park SY, Lee JH, Ha M, Nam JW, Kim VN](#). 2009. miR-29 miRNAs activate p53 by targeting p85 alpha and CDC42. *Nat Struct Mol Biol*. 23-9.

p53 Is Positively Regulated by miR-542-3p

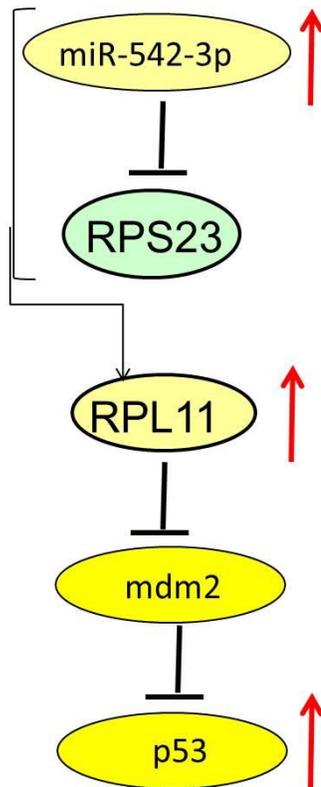


Image courtesy Dr. Toshiyasu Taniguchi

Pathway of miR-542-3p regulation of p53. miR-542-3p directly targets the ribosomal protein RPS23. In consequence, the ribosomal protein RPL11 is upregulated, inhibiting the E3 ubiquitin ligase MDM2, ultimately reducing proteasomal degradation of p53.