c-Myc inactivation of p53 through the pan-cancer lncRNA MILIP drives cancer pathogenesis

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Introduction

The proto-oncoprotein c-Myc and the tumour suppressor p53 interact in a negative feedback manner to maintain cellular homeostasis under physiological conditions: while c-Myc induces the expression of ARF tumour suppressor (p14ARF in human and p19ARF in mouse) that binds to and inhibits mouse double minute 2 homolog (MDM2) leading to p53 activation, p53 transcriptionally inactivates c-Myc and also represses c-Myc through microRNA-mediated mechanisms.

The frequently imbalanced expression of c-Myc over p53 signifies that this interaction is paralysed in cancer cells.

Although p53 suppression is often associated with the loss of ARF, we show here that c-Myc can alternatively inactivate p53 through a long noncoding RNA (lncRNA) that we name MILIP (c-Myc-inducible lncRNA inactivating p53).

MILIP promotes tumorigenicity

MILIP binds to and promotes p53 polyubiquitination and degradation through inhibiting TRIML2-mediated p53 SUMOylation

Summary

The expression of the pan-cancer-associated lncRNA MILIP driven by c-Myc is important for maintaining cancer cell viability and tumorigenicity.

c-Myc inactivates p53 through the lncRNA MILIP, providing an explanation as to how wild-type p53 can be repressed by c-Myc independently of the loss of ARF.

MILIP may represent a potential anti-cancer target for counteracting the c-Myc-axis.

c-Myc inactivation of p53 through MILIP in cancer cells A schematic model illustrates that c-Myc inactivates p53 through transcriptionally upregulating the lncRNA MILIP that competes with TRIML2 for binding to p53, thus leading to the decrease in p53 SUMOylation and the increase in p53 polyubiquitination and subsequent degradation.

C-Myc represses p53 through MILIP

A. In genomics Pathway Analysis (IPA) of RNA-seq data showed that p53 signaling was the mostly enriched pathway in A549 cells transfected with a MILIP siRNA (si-MILIP2) relative to those introduced with the control siRNA. Orange bars represent pathways that were activated, and blue bars, inactivated. DEGs differentially expressed genes. B. Induced knockdown of MILIP upregulated p53 protein expression. C. Inhibition of MILIP transcription by siRNA-mediated CRISPR interference increased the expression of p53. D. c-Myc knockdown upregulated p53 expression, which was diminished by MILIP overexpression.