MICRORNA

Another piece in the p53 puzzle

DOI:
10.1038/nrc2178

URLs

p53
http://www.ncbi.nlm.nih.gov/sites/entrez?Db=gene&Cmd=ShowDetailView&TermToSearch=7157

The p53 network controls many pathways important for tumour suppression by regulating transcription. Three papers, by Moshe Oren and colleagues, Joshua Mendell and colleagues, and Gregory Hannon, Michele Cleary and colleagues, have shown that some of p53's functions may be mediated through transcriptional activation of microRNAs (miRNAs).

All three groups compared the expression of miRNAs in cells with or without p53 expression. Hannon, Cleary and colleagues examined mouse embryonic fibroblasts (MEFs) and found that the expression of the miRNAs miR-34a, miR-34b and miR-34c were increased by p53 expression. Oren and colleagues, and Mendell and colleagues, examining H1299 lung cancer cells and HCT116 colon cancer cells, respectively, identified miR-34a as being regulated by p53.

Is miR-34a a direct transcriptional target of p53? All three groups identified a putative p53-binding site within *mir-34a*. Chromatin immunoprecipitation (ChIP) by Oren and colleagues, and Hannon, Cleary and colleagues showed that the activation of p53 resulted in binding to *mir-34a* promoters in HCT116 cells and wild-type MEFs, respectively, in agreement with previously published ChIP data. Furthermore, all three groups showed that luciferase reporter expression was induced by the *mir-34a* promoter in the presence of p53 expression, and expression was inhibited by mutation of the p53-binding site in the promoter. Hannon, Cleary and colleagues also showed that *mir-34b* and *mir-34c* are direct transcriptional targets of p53.

All three groups showed that genotoxic stress led to p53-dependent upregulation of miR-34a; overall this was shown in various mouse tissues and cancer cell lines. Oren and colleagues also confirmed this *in vivo*, demonstrating that whole body irradiation induced miR-34a expression in the lungs of wild-type, but not *Trp53*$^{-/-}$, mice. Oncogene activation can also induce p53. Using a mouse model of hepatocellular carcinoma in which mouse livers express oncogenic *Hras* and an inducible short hairpin RNA against *Trp53*, Hannon, Cleary and colleagues showed that reactivating p53 led to induction of miR-34s, indicating *in vivo* regulation by p53 and oncogenic stress.

Apoptosis and growth arrest are common consequences of p53 activation. Hannon, Cleary and colleagues showed that the ectopic expression of miR-34s induced cell-cycle arrest in primary human fibroblasts and four tumour cell lines. Genes involved in cell-cycle control were specifically downregulated in the *mir-34*-transfected tumour cells, indicating that p53 might repress these genes by inducing miR-34s. The other two groups found that p53-dependent expression of miR-34a led to increased apoptosis. In H1299 cells and MCF7 breast cancer cells ectopically expressing miR-34a, Oren and colleagues showed a small, but significant, increase in apoptosis. Furthermore, inhibition of endogenous miR-34a in U2OS (*TP53*$^{+/+}$) osteosarcoma cells abrogated p53-dependent etoposide-induced apoptosis. Mendell and colleagues found that ectopic expression of miR-34a in HCT116 (*TP53*$^{+/+}$) cells potently induced p53-dependent apoptosis. Moreover, in HCT116 cells, miR-34a-regulated genes are enriched for those involved in cell cycle and apoptosis.

Heiko Hermeking and colleagues have similar data. They showed that p53 upregulates miR-34a in response to DNA damage, leading to G1 cell-cycle arrest and apoptosis in various cancer cell lines.

These groups have unravelled another part of the p53 tumour-suppressor network. The human *mir-34a* gene lies on chromosome 1p36, which is frequently lost in cancer, and Mendell and colleagues found that *mir-34a* is frequently lost in pancreatic cancer cell lines. These data indicate that miR-34a, and possibly other miR-34 family members, might contribute to tumorigenesis.

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