Nature Reviews Molecular Cell Biology | Published online 2 Aug 2017; doi:10.1038/nrm.2017.80

Getty Images

CANCER BIOLOGY

A Neat target of p53

The tumour suppressor p53 is activated by various types of cellular stress, including DNA damage and oncogenic signalling. Activated p53 induces the transcription of a plethora of genes, leading to cell cycle arrest or apoptosis, and to tumour suppression. Whereas the p53 target genes involved in cell cycle arrest and apoptosis are well characterized, the mechanisms of p53-mediated tumour suppression are less clear. Mello *et al.* now show that the long intergenic non-coding RNA *Neat1* (nuclear-enriched abundant transcript 1) is a p53 target gene that can suppress the initiation of pancreatic cancer.

Using previously generated chromatin immunoprecipitation followed by sequencing (ChIP–seq) and RNA sequencing data sets obtained from mouse embryonic fibroblasts (MEFs), the authors identified *Neat1* as a direct target gene of p53. Subsequent analyses in various mouse and human cells showed that its expression is induced by p53 in response to different genotoxic and non-genotoxic agents.

Interestingly, in MEFs *Neat1* was not required for p53-mediated cell cycle arrest or apoptosis in response to acute DNA damage, but for the suppression of oncogenic transformation. Homozygous loss of *Neat1* (*Neat1*$^{-/-}$) facilitated the transformation of MEFs by E1A and oncogenic Ras; conversely, *Neat1* overexpression decreased the transformation of p53$^{-/-}$ pancreatic cancer cells.

Pancreatic cancer can arise from cystic lesions, as well as through the dedifferentiation of pancreatic acinar cells into ductal-like cells, which leads to the formation of pre-malignant lesions; both types of lesion can ultimately progress to pancreatic cancer.

> “p53-induced expression of *Neat1* suppresses the development of pancreatic pre-malignant lesions”

Neat1 expression was p53-dependent also in the pre-malignant pancreatic epithelium of an oncogenic-Ras-expressing mouse model of pancreatic ductal adenocarcinoma. Homozygous and even heterozygous loss of *Neat1* in these mice substantially increased cystic lesion formation, acinar cell dedifferentiation and pre-malignant lesion formation.

Genome-wide analysis revealed significant changes in the expression of many genes following *Neat1* loss. Of note, the expression of various genes that regulate pancreas development decreased in MEFs and pancreata of oncogenic Ras–*Neat1*$^{-/-}$ mice.

Thus, p53-induced expression of *Neat1* suppresses the development of pancreatic pre-malignant lesions, probably by preventing dedifferentiation of pancreatic cells following oncogene activation. The mechanisms by which *Neat1* controls gene expression are still poorly understood.

Eytan Zlotorynski

ORIGINAL ARTICLE Mello, S.S. *et al. Neat1 is* a p53-inducible lincRNA essential for transformation suppression. *Genes Dev.* **31**, 1095–1108 (2017)