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EXTRA VIEWS

Neat-en-ing up our understanding of p53 pathways in tumor suppression

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ABSTRACT
Although the p53 transcription factor has a well-established role in tumor suppression, little is known about how the non-coding targets of p53 mediate its tumor suppression function. Analysis of ncRNAs regulated by p53 revealed *Neat1* as a direct p53 target gene. *Neat1* has physiological roles in the development and differentiation of the mammary gland and corpus luteum, but its roles in cancer have been conflicting. To unequivocally understand *Neat1* function in cancer, we used *Neat1* null mice. Interestingly, we found that *Neat1* deficiency promotes transformation both in oncogene-expressing fibroblasts and in a mouse model for pancreatic cancer. Specifically, *Neat1* loss in the pancreas results in the enhanced development of preneoplastic lesions associated with dampened expression of differentiation genes. While the exact mechanisms underlying tumor suppression are unknown, there are several described mechanisms that may be responsible for *Neat1*-mediated tumor suppression. Collectively, these findings suggest that *Neat1* enforces differentiation to suppress pancreatic cancer.

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Introduction

The p53 transcription factor plays a critical role in tumor suppression, as illustrated by the high incidence of *p53* mutations in a variety of human tumor types and the completely penetrant cancer phenotype of *p53* null mice [1,2]. p53 is a cellular stress sensor, activated by signals such as DNA damage and oncogene expression. Upon activation, p53 can induce cell cycle arrest, which allows damaged cells time to repair their DNA before re-entering the cell cycle, thus promoting genome integrity and cell survival. Alternatively, p53 can respond to stress signals by triggering apoptosis to eliminate damaged or hyperproliferative cells. In recent years, many additional processes potentially relevant to tumor suppression have been found to be regulated by p53, such as metabolic reprogramming, differentiation, and migration [3]. The ability of p53 to suppress cancer depends on its function as a transcriptional activator, as clearly demonstrated using mouse models, although the transcriptional targets through which it suppresses cancer remain elusive [4–6]. p53 binds specific DNA response elements throughout the genome and regulates a panoply of genes, including protein-coding genes and non-coding RNAs (ncRNAs). Although functional studies of p53-regulated genes have largely focused on protein-coding genes, a cadre of ncRNAs, including several microRNAs, have also been functionally analyzed and shown to contribute to the p53 pathway in different ways. These ncRNAs include large intergenic ncRNAs (lincRNAs), a class of ncRNAs that have received significant attention for their diverse mechanisms in regulating different biological processes, including cancer. These p53-regulated lincRNAs, which modulate p53 stability, activity and responses, include: *LincRNAp21* [7,8], *PANDA* [9], *Pint* [10], *PVT1* [11,12], *PR-lncRNA-1* and *10* [13], *PINCR* [14], *TUG1* [15,16], *LED* [17], *TRINGS* [18], *DINO* [19], and *PURPL* [20], (Table 1). Only *loc285194* and *LincRNAp21* have been reported to function in tumor suppression, as expression of either suppresses xenograft tumor growth in mice [21,22]. Since these initial discoveries, the next-generation sequencing revolution has continued to lead to the identification of novel lincRNAs that could be important for understanding p53 function in tumor suppression [23]. In fact, analysis of p53 ChIP-sequencing and

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Table 1. LincRNAs directly regulated by p53 with functions potentially relevant to p53-mediated tumor suppression.

Name	Reported function	Ref.
PANDA	Interacts with NF-YA to inhibit the expression of pro-apoptotic genes upon DNA damage and promote cell survival.	[9]
NEAT1	Suppresses cellular transformation in oncogene-expressing fibroblasts and in the pancreas by enforcing the expression of differentiation genes. It can enhance cell proliferation, cell survival, cell invasion and EMT in some cancer cell lines. Finally, it can promote ATR signaling upon replication stress, preventing the accumulation of DNA damage.	[24,25,48,50–55]
PINCR	Interacts with Matrin 3, inducing cell cycle arrest and cell survival upon DNA damage in human colorectal cancer cells.	[14]
TUG1	Interacts with *PRC2* and represses *HOXB7*, decreasing cell proliferation in non-small cell lung cancer.	[15,16]
PVT1	The *PVT1* locus contains the lincRNA *PVT1* and different microRNAs, including miR-1204, which was shown to have antiproliferative effects and to trigger apoptosis through the increase of p53 levels. *PVT1* was also shown to promote cell survival.	[11,12]
lincRNA-p21	Interacts with hnRNP-K to act as a global mediator of p53-dependent repression and is required for cell cycle arrest and apoptosis induction in response to DNA damage.	[7,8]
DINO	Enhances p53 stabilization upon DNA damage.	[19]
PURPL	Destabilizes p53 under basal conditions.	[20]
PR-lncRNA-1,10	Act to facilitate p53 binding to target genes, promoting cell cycle arrest and inducing cell death upon DNA damage.	[13]
PINT	Interacts with PRC2 to inhibit proliferation in human cells. In mouse cells, promotes proliferation and survival.	[10]
Loc285194	Inhibits miR-211 to limit proliferation of colorectal and breast cancer cell lines *in vitro*. It also dampens subcutaneous tumor growth of colorectal cancer cells.	[21]
LED	Binds and activates strong enhancers, supporting the p53 transcriptional response and inducing cell cycle arrest upon p53 activation.	[17]
TRINGS	Interacts with STRAP and inhibits necrosis upon glucose starvation.	[18]

RNA-sequencing experiments in p53-proficient and deficient cells was essential for the recent identification of the *Neat1* lincRNA as a p53 target gene [24–28], the subject of this commentary.

Neat1 was initially described as a Virus-Inducible ncRNA (VINC) upregulated in the mouse brain upon infection with *Japanese encephalitis* or *Rabies* viruses [29]. Subsequent studies demonstrated that *Neat1* is also upregulated in response to infection of other viruses, such as HIV, Influenza virus and herpesvirus, and is involved in the induction of innate immune responses, thereby limiting viral replication [30–32]. Shortly thereafter, another study described two ubiquitously expressed nuclear-enriched ncRNAs, which were named *NEAT1* and *NEAT2* (Nuclear Enriched Autosomal noncoding Transcripts; *NEAT2* is also known as *MALAT1*) [33]. This study further demonstrated that *NEAT1* has two variant transcripts, one short (~3.7 KB, named *NEAT1*_1) and one much longer variant (~23 KB, named *NEAT1*_2). Moreover, *NEAT1* localizes to subnuclear structures called paraspeckles – RNA- and protein-containing structures proposed to control the expression of protein-coding genes by retaining their cognate A-to-I edited RNAs in the nucleus [34]. Interestingly, *Neat1* is essential for the formation of paraspeckles [35] and both *Neat1* and paraspeckles are specific to mammalian cells [36], suggesting that this type of nuclear compartmentalization might represent a strategy that is needed for the complex regulation of gene expression occurring in mammals.

Physiological roles for *Neat1*

Our understanding of *Neat1* has come in part from investigating its physiological functions in mice. Initial studies of *Neat1* null mice revealed no obvious phenotypes, suggesting that *Neat1* is dispensable for normal development [37]. However, subsequent studies showed that *Neat1* null females display compromised lactation, associated with reduced mammary epithelial cell proliferation and defective lobular-alveolar development [38]. In addition, *Neat1* null mice exhibit defects in ductal and branching morphogenesis, indicating a role for *Neat1* in the proper development of mammary ducts [38]. *Neat1* deficiency is also associated with a stochastic impaired ability of female mice to get pregnant [39]. This phenotype is attributable to defective formation of the corpus luteum – a temporary endocrine structure involved in the establishment of pregnancy – and diminished progesterone levels. This corpus luteum defect may be explained by the requirement for *Neat1* for the proper expression of genes necessary for corpus luteum differentiation,

such as *Star*. These findings are in keeping with previous observations suggesting a potential role for *Neat1* in differentiation in various contexts. For example, *NEAT1* is expressed in many cell types, with the exception of embryonic stem cells, where its expression is only detected upon differentiation [40]. *NEAT1* is also upregulated during differentiation of neurons, glia, myeloid cells, and muscle, further supporting a role for *NEAT1* in cellular differentiation [41–44].

The role of *Neat1* in tumorigenesis

Beyond analysis of the physiological functions of *Neat1*, additional studies have focused on the role of *Neat1* during cancer development. Following initial observations that *NEAT1* is elevated in a variety of human cancers relative to normal tissue counterparts [45], suggesting a pro-tumorigenic function, analysis of human cancer data focused on correlating *NEAT1* expression with cancer outcome. Higher levels of *NEAT1* were connected to worse prognosis in a range of human cancers, such as colorectal, laryngeal and gastric cancers, as well as glioma, suggesting that *NEAT1* could be acting as an oncogene in these cancers [46–49]. Some functional studies *in vitro* using cancer cell lines from liver, breast, prostate and nasopharyngeal tumors also suggested that *NEAT1* expression could enhance cell proliferation, cell survival, cell invasion, epithelial-mesenchymal transition (EMT), and subcutaneous tumor growth [25,48,50–55]. Perhaps the most compelling evidence to support the oncogenic activity of *NEAT1* came from a study of *Neat1* knockout mice subjected to a DMBA-TPA skin carcinogenesis protocol [25]. In this study, *Neat1* deficiency was shown to confer resistance to chemically-induced skin cancer. This oncogenic function was attributed to a role for *Neat1* in promoting ATR signaling in the face of replication stress, preventing the accumulation of DNA double strand breaks and consequent death of incipient cancer cells.

Previous studies have also suggested that *NEAT1* may have tumor suppressor activity in some contexts. First, *NEAT1* expression was found to be downregulated in lung, liver, esophageal, nasopharyngeal, and retinal cancers, as well as acute promyelocytic leukemias, relative to normal tissue counterparts [27,44,56,57]. Second, *NEAT1* overexpression can reduce cell proliferation in lung cancer and osteosarcoma cell lines upon treatment with nutlin or Adriamycin [27]. Third, high-level *NEAT1* expression predicted better overall survival in nasopharyngeal cancer, and *NEAT1* overexpression radically decreased nasopharyngeal cancer cell growth in subcutaneous tumor studies, through a mechanism that involves the inhibition of miR-101-3p [57]. Finally, recent studies have shown that a high frequency of point mutations and deletions are detected in the *NEAT1* promoter in both liver and breast cancers [50,58], and that mutations found in the *NEAT1* promoter in breast cancers are typically associated with decreased expression of *NEAT1*. Although the point mutations described in breast cancer have not yet been shown to involve the p53 binding site, the deletions typically involve the p53 response element. In addition, *NEAT1* was suggested to promote therapeutic responses, as the successful treatment of acute promyelocytic leukemias with all-trans retinoic acid (ATRA), which induces differentiation and blocks tumor cell propagation, depends on the presence of *NEAT1* [44].

Taken together, some of these studies have supported a role for *NEAT1* in promoting cancer, while other studies have demonstrated a role for *NEAT1* in suppressing cancer. These apparently contradictory results can be reconciled by a couple of different explanations. First, it may be that the two *NEAT1* isoforms have different cellular functions and many of the aforementioned studies may not have studied the specific isoforms involved in the context examined. Indeed, increased *NEAT1_2* expression correlates with better survival in colorectal cancer patients, while the opposite is observed with the isoform *NEAT1_1* [59]. Moreover, the knockdown of *NEAT1_1* in colorectal cancer cell lines attenuated invasiveness and cell growth, while the knockdown of *NEAT1_2* enhanced cell growth in the same cell lines. Second, it may be that *NEAT1*'s mechanism of action differs according to the cell type or context, with it acting as a tumor suppressor in some settings and an oncogene in others. It is also possible that *NEAT1* might have different roles at different stages of tumorigenesis, initially suppressing tumorigenesis, and later promoting tumor development. This paradigm is not uncommon, as in the case of β-catenin which inhibits early pancreatic cancer lesions but promotes the development of later stage lesions [60], or the apoptosis-promoting

protein Perp which is necessary at early steps of skin papilloma development, but opposes carcinogenesis at later stages [61]. Finally, many of these studies were correlative rather than functional, highlighting the necessity for functional studies.

Using *Neat1* knockout mice to study tumorigenesis

To unequivocally understand the role of *Neat1* in cancer development, we recently used *Neat1* null mice as a clean genetic model to study the consequences of complete *Neat1* deficiency for tumorigenesis. We first derived primary mouse embryonic fibroblasts (MEFs) from these mice to assess the contribution of *Neat1* to transformation suppression in a classic oncogene-expressing fibroblast model, in which p53 plays a central role. In this model, E1A; Hras^{G12V} oncogene-expressing mouse embryonic fibroblasts (MEFs) with intact p53 form colonies inefficiently in transformation assays, whereas E1A; Hras^{G12V};*p53-/-* MEFs efficiently form colonies. Interestingly, we found that E1A;Hras^{G12V} MEFs null for *Neat1* exhibit greatly increased colony formation, to levels that rival the enhanced colony formation seen upon p53 loss [24]. We further established the role of *Neat1* in transformation suppression *in vivo*, in a subcutaneous xenograft model where we found the E1A;Hras^{G12V}-expressing fibroblasts formed tumors much faster when null for *Neat1*. Next we sought to examine the role of *Neat1* in transformation suppression in epithelial cancers, which constitute the vast majority of human cancers. RNA-sequencing analysis of premalignant pancreatic cancer lesions showed that *Neat1* expression is p53-dependent in these cells, and we therefore focused on pancreatic cancer development. Consistent with a transformation suppression role in these cells, we found that *Neat1_1* overexpression sufficed to inhibit transformation of *p53* null pancreatic cancer cells. To establish the significance of this role *in vivo*, we analyzed the consequences of *Neat1* deficiency in an autochthonous mouse model for pancreatic cancer driven by Cre-activated Kras^{G12D} expression in the pancreas [62]. In this model, either the acinar cells (epithelial cells responsible for producing digestive enzymes) or the ductal cells (epithelial-cells lining the ducts that deliver digestive enzymes into the duodenum) of the exocrine pancreas can undergo dedifferentiation and cellular transformation upon constitutive Kras activation, giving rise to premalignant lesions known as pancreatic intraepithelial neoplasias (PanINs) and cystic and intraductal papillary mucinous neoplasms (IPMNs), respectively [63,64]. Strikingly, Kras^{G12D}-expressing *Neat1* deficient mice succumbed to enhanced development of pancreatic neoplasias, including PanINs and IPMN-like precursor lesions, relative to *Neat1*-expressing mice (Figure 1) [24]. While we did not observe cancer in the time frame examined, these premalignant lesions may ultimately evolve into metastatic pancreatic cancer. Together, these studies revealed that *Neat1* has an essential role in suppressing the transformation of normal pancreatic acinar and ductal cells into premalignant lesions. Our study was thus the first to demonstrate a transformation suppression role for *Neat1 in vivo*, in a well-established genetically engineered mouse model for cancer.

To reveal the underlying mechanisms for *Neat1* transformation suppression, we analyzed genome-wide expression in E1A;Hras^{G12V}-expressing wild-type or *Neat1* null fibroblasts by RNA-sequencing. We then compared the gene expression profiles of these *Neat1*-proficient and deficient cells, which led to the conclusion that *Neat1* controls the transcriptional output of 1305 genes (q-value: 0.005, FDR: 0.5%). Interestingly, we observed that many of these genes are also regulated by *Neat1* in the pancreas of mice harboring Kras^{G12D} mutations,

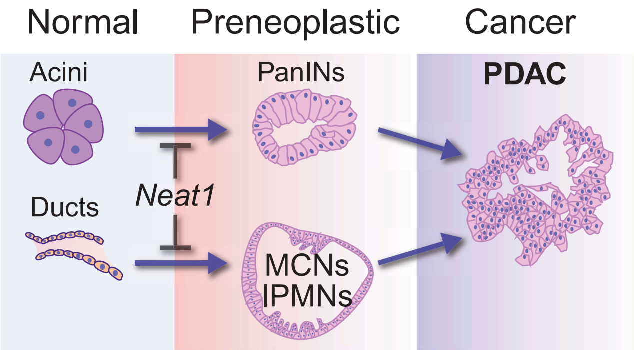

Figure 1. The role of *Neat1* in suppressing transformation in pancreatic cancer.

Neat1 blocks the transformation of normal pancreatic acinar and ductal cells into premalignant lesions, namely Pancreatic Intraepithelial Neoplasias (PanINs) and Intraductal Papillary Mucinous Neoplasm (IPMN)-like lesions, respectively. Both premalignant lesions may ultimately develop into malignant pancreatic ductal adenocarcinoma (PDAC).

suggesting that *Neat1*'s global control of transcription is a general effect observed in different cell types. Among the genes downregulated in *Neat1* null cells, there was an enrichment of genes associated with different developmental programs, including nervous system development, axon guidance, and pancreas development. The genes involved in pancreas development included *Bhlha15* (also known as *Mist1*) and *Sox9*. While the former has been shown to be essential for late-stage differentiation of acinar cells, the latter has a general role in pancreas development and is known as a transcription factor that maintains ductal cell identity. The downregulation of *Bhlha15* or *Sox9* in the pancreas of *Neat1*-deficient mice could cause dedifferentiation and increased formation of PanINs or IPMN-like lesions, respectively. Our data suggest that *Neat1* acts as a tumor suppressor by safeguarding the expression of genes involved in cellular differentiation, thus opposing de-differentiation events driven by oncogenic drivers such as mutant Kras.

Potential mechanisms for *NEAT1* action in tumor suppression

The exact mechanisms by which *NEAT1* might regulate gene expression to suppress transformation are unclear, but could relate to any of several different molecular functions ascribed to *NEAT1*, all ultimately impinging upon gene expression (Figure 2). As mentioned briefly above, one of the first functions associated with paraspeckles, and by association with *NEAT1*, was the ability to post-transcriptionally modulate the expression of genes that undergo RNA editing (A-to-I), through the nuclear retention of edited RNAs in paraspeckles [34,36,40]. Interestingly, this mechanism of action is reversible, and upon stress, the edited sequence can be cleaved from the RNAs, allowing release from the nucleus, delivery to the cytoplasm, and expression of the regulated gene. *NEAT1* was also found to interact with the splicing machinery and the Drosha-DGCR8 Microprocessor, regulating the maturation of pre-mRNAs and pri-miRNAs [65–68], respectively, thereby controlling processes that rely on alternative splicing or on miRNA-regulated gene expression programs. Yet another way that *NEAT1* has been shown to change the transcriptional output of the cell is through the retention of proteins such as transcription factors in paraspeckles [69]. Interestingly, the retention of one single protein, the transcriptional and splicing regulator SFPQ, in paraspeckles via interaction with *NEAT1* impedes the ability of SFPQ to bind the chromatin of target genes, leading to changes in the transcriptional output, such as the repression of *ADAR2B* and the induction of *IL8* [31,69]. There is also evidence that *NEAT1* can globally directly interact with the

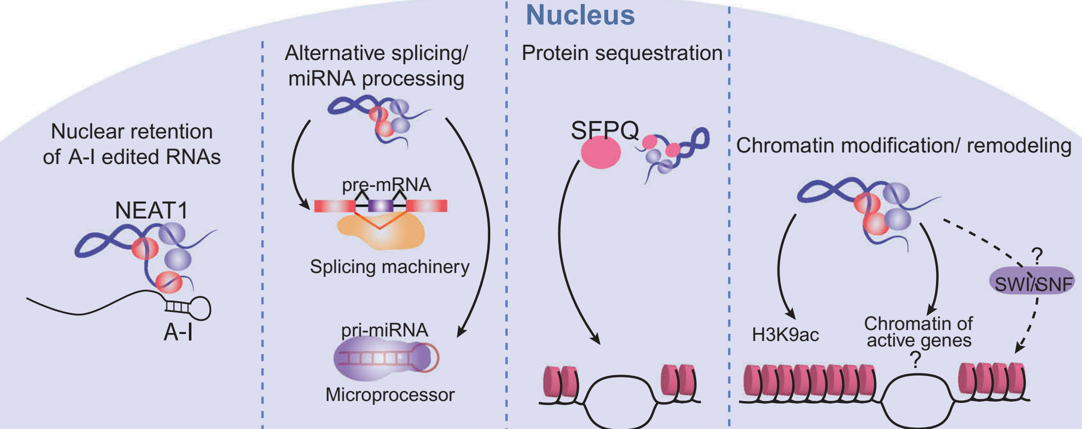

Figure 2. Mechanisms of *Neat1* action.

Different molecular mechanisms of action have been proposed for *NEAT1*. These include: retaining A-to-I edited pre-mRNAs in the nucleus, promoting processing of pre-mRNAs and pri-miRNAs, sequestering proteins into paraspeckles and away from chromatin, and modulating gene expression through direct interactions with chromatin. Interactions with chromatin can result in histone modification and potentially chromatin remodeling events through interactions with proteins from the SWI/SNF complex. In the figure, *NEAT1* is represented by a twisted blue line and paraspeckle proteins are represented by red and purple ovals.

chromatin of hundreds of active genes, though little is still known about the impact of these interactions [65]. One hypothesis is that *NEAT1* could bring together proteins from the paraspeckles and other subnuclear structures to the chromatin of active genes to regulate the expression of these genes [65]. *NEAT1* interactions with the chromatin might direct changes in the epigenetic landscape of the cells, as *NEAT1* has been shown to alter chromatin marks such as histone H3K4 trimethylation and histone H3K9 acetylation in specific genes [54]. *NEAT1* could also play a role in the control of chromatin remodeling. Proteins from the SWI/SNF chromatin remodeling complex were shown to be major components of the paraspeckles [70], where they participate in the assembly of the paraspeckles, in a nucleosome-remodeling activity-independent fashion. This unexpected interaction begs the question of whether or not *NEAT1* could alter chromatin organization by bringing these proteins to the chromatin of active genes or by retaining them at the paraspeckles. Interestingly, in our studies we observed that *Neat1* deficiency in fibroblasts decreases the expression of chromatin remodeling genes such as *Smarca1, Smarcc2* and *Arid1a*, which encode proteins from the SWI/SNF complex, reinforcing the connection between *NEAT1* and the SWI/SNF complex [24].

Collectively, these observations suggest a variety of potential mechanisms by which *NEAT1* might impact tumor development. It is possible that *NEAT1* suppresses tumors by impinging on gene expression through multiple different mechanisms at the same time or that only a subset of these mechanisms is essential for its function as a tumor suppressor. Furthermore, there may be tissue-specific differences in mechanisms of *NEAT1* action. Dissecting the molecular mechanisms that *NEAT1* employs in tumor suppression will ultimately expand our understanding of how lincRNAs contribute to tumorigenesis.

Summary and future perspectives

Our studies here using genetic mouse models have revealed a clear role for *Neat1* as a tumor suppressor, and suggest that *Neat1* loss may facilitate cellular transformation by promoting dedifferentiation. These observations suggest in turn that one aspect of p53 function is through activation of *Neat1* expression and stimulation of a differentiation program. Many questions remain, however. For example, is *Neat1*'s role as a tumor suppressor tissue-specific? The continued use of a clean genetic mouse model for *Neat1* deficiency in *in vivo* studies will be essential for determining *Neat1*'s role in tumorigenesis in different tissues. How does *Neat1* act at the molecular level to suppress cancer? The use of cutting-edge genomic techniques such as ChiRP-seq – a technique to detect RNA-chromatin interactions – and CLIP-seq – a genome-wide technique to map protein/RNA interactions – combined with RNA-seq, in a tumor suppression context, will help address this question by describing how interactions between *Neat1*, chromatin and RNA binding proteins form key regulatory networks that impact gene expression. Such future investigations will unravel the exact mechanisms of action of *Neat1* in tumor suppression, as well as the key proteins and chromatin interactions involved in this process.

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