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Review

Noncoding RNA activated by DNA damage (*NORAD*): Biologic function and mechanisms in human cancers

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ABSTRACT

Noncoding RNA activated by DNA damage (*NORAD*) is a newly identified long non-coding RNA (lncRNA) comprising one exon located on Chr20q11.23. *NORAD* is unique among lncRNAs because it is highly conserved, abundantly expressed, upregulated upon DNA damage, and maintains chromosomal stability in human cells. *NORAD* is dysregulated in different types of cancers and has been implicated in several processes correlated with carcinogenesis, such as cell proliferation, invasion, metastasis, and apoptosis. The mechanisms underlying the effects of *NORAD* are complex and involve multiple factors and signaling pathways. The biologic function and mechanisms of *NORAD* in human cancers are systematically reviewed here to provide new directions for future research.

1. Introduction

Long noncoding RNAs (lncRNAs) have recently attracted attention because of their emerging functions in disease and development [1,2]. LncRNAs are non-protein-coding RNA molecules longer than 200 nucleotides that lack any detectable open reading frame [3]. They are involved in a spectrum of biological processes including epigenetic regulation, alternative splicing, imprinting, RNA decay, and translation [4,5]. Therefore, aberrant lncRNA expression could underlie various human disorders and diseases. Furthermore, some lncRNAs exhibit developmental- and tissue-specific expression patterns [6–8]. These characteristics are critical for their functional analysis and highlight the potential of lncRNAs as diagnostic and prognostic markers. The exact number of lncRNAs encoded in the human genome is undetermined, although most estimates place the number in the tens of thousands [9,10]. The biological roles and mechanisms of lncRNA action are complex. In particular, how lncRNA sequences and structures form interfaces with other cellular factors remains largely unexplored or elusive.

Noncoding RNA activated by DNA damage (*NORAD*, also known as *LINC00657*) is a recently characterized lncRNA that is required for maintaining chromosomal stability and proper mitotic divisions in human cells [11,12]. It is 5.3 kilobases (kb) in length and comprises one exon, and is located on chromosome 20q11.23 (Fig. 1). *NORAD* is a highly conserved cytoplasmic lncRNA that is ubiquitously present in human cell lines and tissues, suggesting a relevant cellular function.

2. Discovery and characterization of *NORAD*

Because of their heterogeneity, modest evolutionary conservation, and generally low abundance relative to protein-coding genes [13,14], few lncRNAs are extensively characterized, and the functional relevance of the vast majority of lncRNAs remains unclear. Lee et al. identified lncRNAs involved in the DNA damage response by mining a previously published dataset of murine lncRNAs induced by doxorubicin in a p53-dependent manner [11]. A poorly-characterized 4.9 kb unspliced lncRNA, annotated as 2900097C17Rik caught their attention because of its unusual high conservation (65% nucleotide identity with its human ortholog, *LINC00657*) and abundance (> 300 copies per cell). The human ortholog was termed *NORAD* by Lee et al. [11].

3. *NORAD* regulates genome stability

To investigate the functions of *NORAD*, Lee et al. constructed a *NORAD*-deficient human cancer cell line using genome-editing methods [11]. They found that *NORAD*$^{-/-}$ cells had significant chromosomal instability characterized by a tendency to lose and gain chromosomes and an increased frequency of spontaneous tetraploidization. The chromosomal instability phenotype could be reverted by restoring endogenous *NORAD* expression. Researchers further analyzed NORAD-

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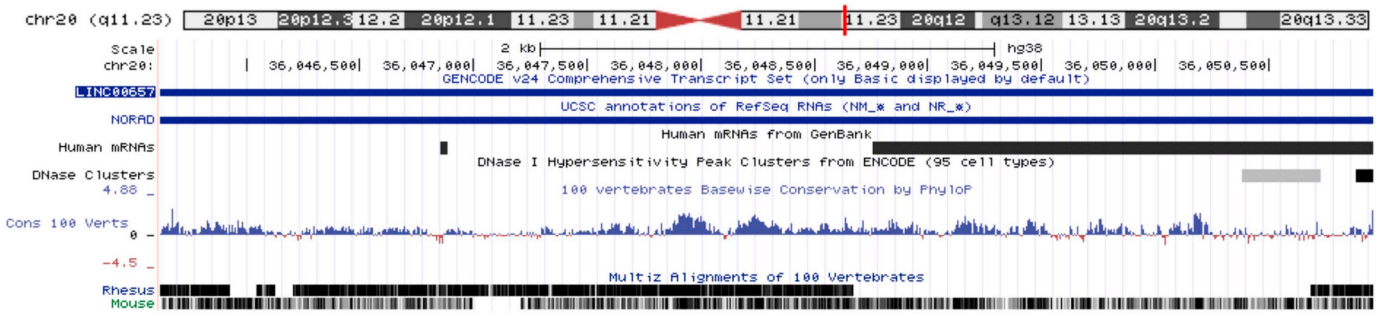

Fig. 1. UCSC Genome browser (http://genome.ucsc.edu/) view of the 20q11.23 region in humans, which contains the *NORAD* gene.

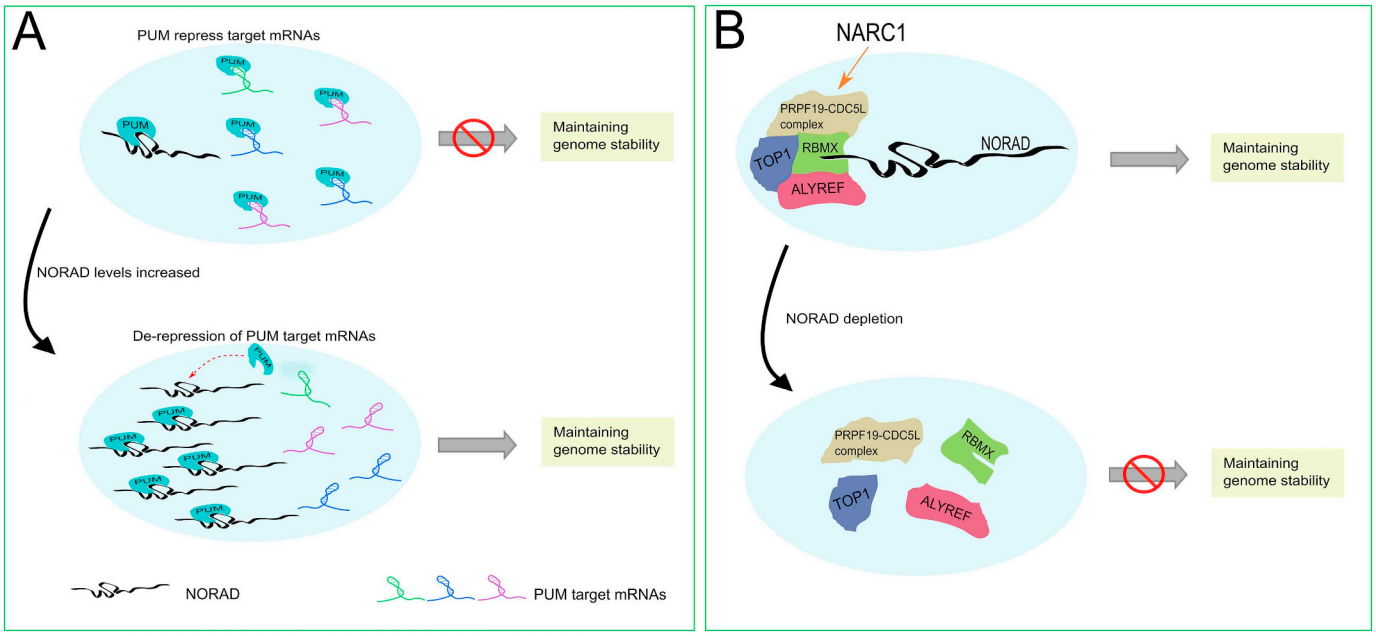

Fig. 2. Schematic model for the role of *NORAD* in maintaining genome stability. A. In response to DNA damage, *NORAD* levels increase and sequester most of PUM, leading to the stabilization of PUM targets and the maintenance of the genomic stability of cells. B. *NORAD* is required for the RBMX-mediated assembly of a ribonucleoprotein complex termed NARC1, which contains the known suppressors of genomic instability TOP1, ALYREF, and the PRPF19-CDC5L complex. Depleting *NORAD* results in genomic instability.

Abbreviations:*NORAD*, Noncoding RNA activated by DNA damage; PUM, Pumilio; RBMX, RNA binding motif protein X-linked; NARC1, *NORAD*-activated ribonucleoprotein complex 1; TOP1, DNA topoisomerase I; ALYREF, Aly/REF export factor; PRPF19, pre-mRNA processing factor 19; CDC5L, cell division cycle 5 like.

interacting proteins using mass spectrometry and identified the Pumilio (PUM) proteins, PUM1/PUM2, two RNA-binding proteins belonging to the Pumilio–Fem3-binding factor family [15]. PUM1 and PUM2 bind with high specificity to sequences in the 3′-UTR of target mRNAs through their PUM homology domains [16], thereby accelerating turnover and decreasing translation [17,18]. Among PUM targets are a large set of genes that play a critical role in maintaining chromosomal stability and a euploid state, including key factors required for mitosis, DNA repair, and DNA replication. Because of its abundance and multitude of PUM binding sites, *NORAD* can sequester a significant fraction of the total cellular pool of PUM proteins and act as a negative regulator of PUM activity. Lee et al. suggested that *NORAD* functions as a PUM1/PUM2 decoy, preventing RNA-binding proteins from interacting with and destabilizing their targets (Fig. 2A). As a result, the expression of these important genes and the genomic stability of cells are maintained.

Consistent with these results, Ulitsky's group reported that *NORAD* contains at least 17 binding sites for PUM proteins, most of which are located in conserved positions within the repeated units [12]. These authors showed that *NORAD* is bound by both PUM1 and PUM2 through these binding sites. Inhibition of *NORAD* expression in osteosarcoma cells demonstrated that *NORAD* modulates the mRNA abundance of PUM targets, in particular those implicated in mitotic progression, and this modulation depends on canonical PUM binding sites. In addition, their results suggested that the main effects of *NORAD* on PUM targets are mediated by affecting mRNA stability rather than to translation [12]. Further study demonstrated that KH RNA binding domain containing, signal transduction associated 1 (KHDRBS1, also known as SAM68, which is an abundant, multifunctional, and cell cycle-regulated RNA-binding protein) is required for efficient recruitment of PUM2 to *NORAD*, regulation of PUM activity by *NORAD*, and proper chromosome segregation in mammalian cells [19].

The results of the above two studies were obtained from *in vitro* mixing of exogenous *NORAD* fragments with cytoplasmic extracts, which may not accurately represent the protein contacts of *NORAD* in living cells. To examine the direct interactions of *NORAD* with proteins in live cells, Munschauer et al. performed RNA antisense purification combined with quantitative liquid chromatography/mass spectrometry using mass tag quantification [20]. They found that *NORAD* interacts with proteins involved in DNA replication and repair in steady-state cells and localizes to the nucleus upon stimulation with replication stress or DNA damage. In particular, *NORAD* interacts with RNA binding motif protein X-linked (RBMX), a component of the DNA-damage response, and contains the strongest RBMX-binding site in the transcriptome. *NORAD* is required for the RBMX-mediated assembly of

Table 1
Functional characterization of *NORAD* in various cancers.

Cancer type	Expression	Role	Biological function	Related gene and protein	References
Breast cancer	Upregulated	Oncogene	Proliferation, cell growth	–	[31]
Esophageal squamous cell carcinoma	Upregulated	–	–	–	[32]
Pancreatic cancer	Upregulated	Oncogene	Migration, invasion, metastasis, EMT	RhoA, miR-125a-3p, *E*-cadherin, N-cadherin, vimentin, ZEB1, Rock1	[33]
Lung cancer	–	Oncogene	Migration, EMT	Smad2, Smad3, SERPINE1, SNAI1, FN1, CDH1	[34]
Colorectal cancer	Upregulated	Oncogene	Proliferation, migration, invasion, apoptosis	miR-202-5p	[35]
Bladder cancer	Upregulated	Oncogene	Proliferation	PUM2, E2F3	[36]
Cervical cancer	Upregulated	Oncogene	Proliferation, invasion, EMT	SIP1, miR-590-3p, E-cadherin, Snail, vimentin	[37]
Hepatocellular carcinoma	Downregulated	Tumor suppressor	Proliferation, migration, invasion	PTEN, miR-106a-5p	[38]

Abbreviations:*NORAD*, Noncoding RNA activated by DNA damage; EMT, epithelial-mesenchymal transition; RhoA, ras homolog family member A; ZEB1, zinc finger E-box binding homeobox 1; Rock1, Rho associated coiled-coil containing protein kinase 1; Smad2/3, SMAD family member 2/3; SERPINE1, serpin family E member 1; SNAI1, snail family transcriptional repressor 1; FN1, fibronectin 1; CDH1, cadherin 1; PUM2, pumilio RNA binding family member 2; E2F3, E2F transcription factor 3; SIP1, SMAD-interacting protein 1; PTEN, phosphatase and tensin homolog.

a ribonucleoprotein complex termed *NORAD*-activated ribonucleoprotein complex 1 (NARC1), which contains the known suppressors of genomic instability DNA topoisomerase I, Aly/REF export factor (ALYREF), and the pre-mRNA processing factor 19 (PRPF19)–cell division cycle 5 like (CDC5L) complex (Fig. 2B). Depletion of *NORAD* or RBMX causes chromosome segregation defects (a known cause of genomic instability and aneuploidy), reduced replication-fork velocity, and altered cell-cycle progression, and these effects are rescued by wild-type *NORAD* expression [20]. However, *NORAD* could not restore genome stability when the RBMX-binding site was deleted. These findings indicate that DNA damage–mediated induction of *NORAD* can promote the assembly of the NARC1 complex in the nucleus to promote genome stability.

4. *NORAD* and cancer

NORAD has been called the “defender of the genome” because of its role in the preservation of chromosomal stability [21]. Therefore, its dysregulation may be implicated in tumorigenesis. Recent evidence indicates that *NORAD* is deregulated in numerous human cancers and acts as an important regulator of tumor progression (Table 1). The expression of *NORAD* is related to clinicopathological features and prognosis in cancer patients (Table 2).

4.1. NORAD in breast cancer

A study in breast cancer showed that *NORAD* is upregulated in the breast cancer cell lines MCF-7 and MDA-MB-231 compared with non-malignant HMLE cells [22]. MTT assays indicated that *NORAD* knockout significantly inhibits cell growth. Consistent with this result, clonogenic assays showed that the number of colonies is smaller in *NORAD* knockout than in vector control cells [22]. These findings suggest that *NORAD* affects tumor cell growth and proliferation and is a potential oncogene [22]. In addition, upregulation of *NORAD* is associated with poor overall survival in breast cancer patients [22].

4.2. NORAD in esophageal squamous cell carcinoma

The expression of *NORAD* is significantly upregulated in esophageal squamous cell carcinoma tissues compared with that in adjacent normal tissues [23]. In addition, high expression of *NORAD* is correlated with large tumor size and high UICC stage. Kaplan-Meier analysis indicates that patients with high *NORAD* expression have poor overall and disease-free survival, and multivariate analyses identify *NORAD* as an independent predictor of overall survival.

4.3. NORAD in pancreatic cancer

NORAD is highly expressed in pancreatic cancer tissues and upregulated under hypoxic conditions [24]. Pancreatic cancer patients with high *NORAD* expression have an increased risk of poor survival. Furthermore, *NORAD* overexpression promotes the migration and invasion of pancreatic cancer cells, whereas *NORAD* depletion inhibits hypoxia-induced epithelial-mesenchymal transition (EMT) and metastasis *in vitro* and *in vivo* [24]. *NORAD* may acts as a competitive endogenous RNA (ceRNA) to regulate the expression of the small GTP binding protein RhoA through competition with miR-125a-3p, thereby promoting EMT [24].

4.4. NORAD in lung cancer

Kawasaki et al. suggested a potential mechanism by which *NORAD* regulates EMT [25]. Their results demonstrated that *NORAD* positively regulates transforming growth factor-β (TGF-β) signaling and the TGF-

Table 2
Clinical significance of *NORAD* in various cancers.

Cancer type	Overexpression of *NORAD* and clinical features	References
Breast cancer	Poor overall survival	[31]
Esophageal squamous cell carcinoma	Larger tumor size, higher UICC stage, poor overall and disease-free survival	[32]
Pancreatic cancer	Poor overall survival	[33]
Lung cancer	–	[34]
Colorectal cancer	Positive metastasis, poor overall survival	[35]
Bladder cancer	Advanced histological stage, higher tumor stage, lymph node metastasis, poor overall survival	[36]
Cervical cancer	Positive lymph nodes metastasis, positive vascular invasion, advanced FIGO stage, poor overall survival	[37]
Hepatocellular carcinoma	Smaller tumor size, negative vascular invasion, earlier TNM stage, longer overall survival	[38]

Abbreviations:*NORAD*, Noncoding RNA activated by DNA damage.

β-induced EMT-like phenotype in lung adenocarcinoma cells in a PUM-independent manner. These authors revealed that *NORAD* regulates TGF-β signaling by mediating the signal-induced nuclear translocation of Smad complexes. In addition, they found that *NORAD* affects TGF-β signaling in human osteosarcoma U2OS cells, suggesting that it may widely function as a regulator of TGF-β signaling [25].

4.5. NORAD in colorectal cancer

The relative expression levels of *NORAD* are significantly upregulated in colorectal cancer tissues compared with adjacent normal tissues [26]. Furthermore, the expression of *NORAD* is positively correlated with metastasis and poor prognosis in colorectal cancer patients. *NORAD* overexpression promotes cell proliferation, migration, and invasion and inhibits cell apoptosis by downregulating miR-202-5p [26].

4.6. NORAD in bladder cancer

Expression analysis of *NORAD* in bladder cancer shows its significant upregulation [27], and high expression of *NORAD* is associated with more advanced histological stage, higher tumor stage, lymph node metastasis, and worse survival in patients with bladder transitional carcinoma. *NORAD* knockdown significantly reduces tumor proliferation concomitant with PUM2 upregulation and E2F transcription factor 3 (E2F3) downregulation [27].

4.7. NORAD in cervical cancer

A recent study showed that *NORAD* expression is significantly upregulated in cervical cancer tissues and cell lines [28]. High *NORAD* expression is correlated with lymph node metastasis, vascular invasion, advanced FIGO stage, and poor overall survival in cervical cancer patients. *NORAD* inhibition suppresses cervical cancer cell proliferation, invasion, and EMT. Investigation of the underlying mechanism suggested that *NORAD* acts as a ceRNA to regulate SMAD-interacting protein 1 (SIP1, also known as zinc finger *E*-box binding homeobox 2) and to promote proliferation and invasion through competitive binding to miR-590-3p in cervical cancer [28].

4.8. NORAD in hepatocellular carcinoma (HCC)

NORAD acts as a tumor suppressor in HCC [29], which contradicts the above results. *NORAD* is downregulated in HCC tissues and malignant HCC cell lines [29]. *NORAD* downregulation is correlated with poor overall survival in HCC patients. Moreover, *NORAD* expression is associated with tumor size, vascular invasion, and TNM stage. *NORAD* overexpression inhibits the proliferation, migration, and invasion of HCC cells *in vitro* and inhibits tumor growth *in vivo*. Further experiments demonstrated that *NORAD* functions as a ceRNA for miR-106a-5p to regulate phosphatase and tensin homolog (PTEN) epigenetically [29].

5. Conclusions and future perspectives

NORAD is the first example of an lncRNA that contains multiple highly conserved consensus binding sites for an RNA-binding protein. *NORAD* thus emerges as a paradigm for a lncRNA that acts in the cytoplasm by binding to a substantial number of particular RNA-binding proteins and affecting their ability to regulate their targets. Of note, *NORAD* knockdown not only affects the genes encoding 193 PUM protein targets, but also the expression of > 1000 other genes [11], suggesting that *NORAD* has additional modes of action aside from PUM protein sequestration. Considering this, Spiniello et al. used HyPR-MS (hybridization purification of RNA-protein complexes followed by mass spectrometry) to identify 415 *NORAD* interacting proteins including PUM1 [30], which expands the breadth of knowledge regarding its biological function.

Also striking is the fact that *NORAD* interactomes are enriched for extracellular vesicle (EV) proteins [30]. This finding suggests that it could be a significant component of such vesicles. EVs are involved in cell-to-cell communication in tumor microenvironments [31]. As nanoscale biological vesicles, EV cargos are well protected and are not degraded [32]. LncRNAs are selectively sorted into EVs and can regulate cancer onset and progression in a variety of ways [33]. LncRNAs in EVs have strong potential as body fluid-based biomarkers and mediators of intercellular communication in tumor biology. A deeper understanding of the role of *NORAD* in EVs may help provide a new diagnostic, prognostic, and surveillance biomarker in cancer.

Genome instability is one of the hallmarks of cancer [34], and it is associated with metastasis, poor prognosis, and therapeutic resistance [35,36]. Approximately 60%–80% of human tumors exhibit chromosomal abnormalities suggesting chromosomal instability [37,38]. The accumulation of genome instabilities results in metabolic abnormalities, accelerated aging, and cancer development [39–42]. Therefore, maintaining genome stability is critical. Aberrant regulation of lncRNAs usually occurs in cancer cells, but the consequences and molecular mechanisms of this dysregulation remain obscure. The seminal discovery of the NORAD genome maintenance pathway enables future studies on the underlying causes of cancer caused by aberrant regulation of lncRNAs.

Given the role of genomic instability in tumorigenesis, *NORAD* should be a good tumor suppressor. However, the data described in this review suggests that although *NORAD* acts as a tumor suppressor in HCC, *NORAD* is upregulated in a variety of human cancers and acts as an oncogene. It will be both challenging and rewarding to clarify the contradictory role of *NORAD* in different cancers. *NORAD* is implicated in many aspects of carcinogenesis, including proliferation, invasion, metastasis, and apoptosis. As shown in Fig. 3, the mechanism underlying the effects of *NORAD* is complex and involves multiple factors and signaling pathways, including inducing EMT and sponging of tumor-associated miRNAs. Our understanding of the roles of *NORAD* in cancer remains at a preliminary stage. Few studies have examined the mechanisms of *NORAD* deregulation, and the precise molecular

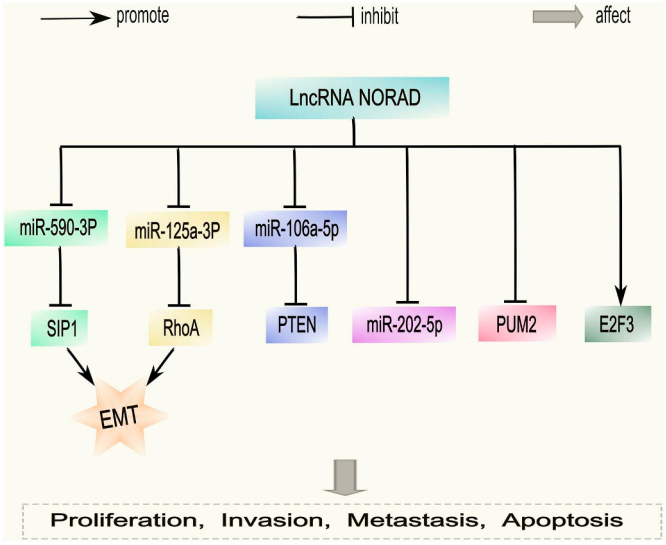

Fig. 3. Overview of the regulatory mechanisms of *NORAD* in cancer progression.
NORAD affects multiple biological processes including cell proliferation, invasion, metastasis, and apoptosis by interacting with different types of molecules. **Abbreviations:***NORAD*, Noncoding RNA activated by DNA damage; SIP1, SMAD-interacting protein 1; EMT, epithelial-mesenchymal transition; RhoA, ras homolog family member A; PUM2, pumilio RNA binding family member 2;E2F3, E2F transcription factor 3; PTEN, phosphatase and tensin homolog.

mechanisms upstream and downstream of *NORAD* are not thoroughly understood and require further systematic investigation. Further research is needed to gain a comprehensive understanding of the potential and limits of *NORAD* for cancer diagnosis and treatment.

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Conflict of interest

The authors declare that there is no conflict of interest.

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