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Review Article

The role of long non-coding RNA NORAD in digestive system tumors

Yussel Pérez-Navarro [a], Yarely M. Salinas-Vera [b], Cesar López-Camarillo [c], Elisa Elvira Figueroa-Angulo [d], María Elizbeth Alvarez-Sánchez [a,*]

[a] Posgrado en Ciencias Genómicas, Laboratorio de Patogénesis Celular y Molecular Humana y Veterinaria, Universidad Autónoma de la Ciudad de México, Ciudad de México, CDMX, Mexico
[b] Centro Nacional de Identificación Humana, Comisión Nacional de Búsqueda, Secretaría de Gobernación, Camino a Santa Teresa No 1679, Jardines del Pedregal, Ciudad de México, Mexico
[c] Posgrado en Ciencias Genómicas, Laboratorio de Oncogenómica y Proteómica del cáncer, Universidad Autónoma de la Ciudad de México, Ciudad de México, Mexico
[d] Licenciatura en Ciencias Genómicas, Laboratorio de Patogénesis Celular y Molecular Humana y Veterinaria, Universidad Autónoma de la Ciudad de México, Mexico

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ABSTRACT

In recent years, it has been discovered that the expression of long non-coding RNAs is highly deregulated in several types of cancer and contributes to its progression and development. Recently, it has been described that in tumors of the digestive system, such as colorectal cancer, pancreatic cancer, and gastric cancer, DNA damage-activated lncRNA (NORAD) was frequently up-regulated. The purpose of this review is to elucidate the functions of NORAD in tumors of the digestive system, emphasizing its involvement in important cellular processes such as invasion, metastasis, proliferation, and apoptosis. NORAD acts as a ceRNA (competitive endogenous RNA) that sponges microRNAs and regulates the expression of target genes involved in tumorigenesis. Thus, the mechanisms underlying the effects of NORAD are complex and involve multiple signaling pathways. This review consolidates current knowledge on the role of NORAD in digestive cancers and highlights the need for further research to explore its potential as a therapeutic target. Understanding the intricate functions of NORAD could elucidate the way for innovative approaches to cancer treatment.

1. Introduction

Tumors in the digestive system, particularly colorectal cancer (CRC), gastric cancer (GC), and liver cancer (LC), are responsible for over 4 million new cases globally. These types of cancer are among the top 10 leading causes of cancer-related deaths [1,2]. The choice of treatment for cancer often relies on the stage of the condition [3]. These treatments encompass surgical procedures, chemotherapy, radiation therapy, and targeted therapy [4]. Nonetheless, there are limitations to the effectiveness of these treatments. Thus, there is an immediate requirement to discover new therapeutic targets that can potentially enhance the clinical management of digestive system tumors [3].

Long non-coding RNAs (lncRNAs) are a group of molecules that play crucial roles in genetic regulation and have a wide range of biological functions [5,6]. Over the last decade, advances in sequencing and bioinformatics technologies have allowed the discovery of more than 16, 000 lncRNAs using human GENCODE statistics (https://www.gencodegenes.org/), revealing their abundance and heterogeneity in the human genome [7]. The transcripts referred to as lncRNAs are longer than 200 nucleotides and lack a significant open reading frame [8]. In contrast to protein-coding RNAs, lncRNAs show little evolutionary conservation across different species and demonstrate specific expression patterns in particular tissues or cells [9].

~~In the 1980s, H19 was discovered as the first eukaryotic lncRNA gene, notable for its sequence conservation in mammals, its absence of translation despite containing open reading frames, and its crucial role in embryonic development~~ [4]~~.~~

Based on their relative positioning to genes that code for proteins in the genome, lncRNAs are categorized. LncRNAs can be antisense sequences, which are transcribed in the opposite direction of a coding gene at the same locus [10]. Sense. they are located within the exons of a gene and are transcribed in the 5'to 3' direction, unlike antisense lncRNAs which are transcribed from the complementary strand of a gene. Bidirectional. transcribed from both strands [11]. Intergenic lncRNAs (LINC RNA) are transcribed from intergenic regions located between coding genes [12,13]. Intronic lncRNAs are transcribed within the introns of a coding gene and those that overlap with protein-coding genes (Fig. 1.

* Corresponding author.
E-mail addresses: yussel.perez@estudiante.uacm.edu.mx (Y. Pérez-Navarro), yarely.vera.ms@gmail.com (Y.M. Salinas-Vera), cesar.lopez@uacm.edu.mx (C. López-Camarillo), figueroaelisaelvira@gmail.com (E.E. Figueroa-Angulo), maria.alvarez@uacm.edu.mx (M.E. Alvarez-Sánchez).

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Abbreviations

ANP32E	Acidic Leucine-rich Nuclear Phosphoprotein 32 Family Member E
AP	Adenomatous Polyposis
CAF	Cancer-Associated Fibroblasts
CDDP	Cis-Diamino Dichloro Platinum
ceRNA	competitive endogenous RNA
CRC	Colorectal cancer
EC	Esophageal cancer
EMT	epithelial-mesenchymal transition
EBV	Epstein-Barr Virus
5-FU	5-fluorouracil
FOXO6	Forkhead Box O6
GC	Gastric Cancer
HCC	Hepatocellular carcinoma
HIF1A	Hipoxia-inducible factor 1A
Kb	Kilobases
KMT2D	Lysine Methyltransferase 2D
LncRNAs	long non-coding RNA
LINC RNA	Intergenic lncRNAs
MIEN1	Migration and Invasion Enhancer 1
MTDH	Methaderin
miRNAs	microsRNAs
mTOR	Mechanistic Target Of Rapamycin Kinase
Nectin-4	Nectin Cell Adhesion Molecule 4
NORAD	Non-coding RNA activated by DNA damage
NRU	NORAD repeat units
PC	Pancreatic cancer
PD-L1	Programmed Cell Death 1 Ligand 1
PUM	Pumilio homologs
RhoA	Ras Homolog family member A
ROCK1	Rho-associated coiled-coil containing protein kinase 1
TGFβ	Transforming Growth Factor A
UC	ulcerative colitis
VEGF-A	Vascular Endothelial Growth Factor A
VM	vasculogenic mimicry
WNT	Wingless-related integration site

Panel A) [14]. This diversity of lncRNAs interacts with DNA, RNA, and proteins to carry out diverse functions, which include the regulation of gene expression both at the transcriptional and post-transcriptional level, as well as the modulation of chromatin architecture and interference in cell signaling pathways [15]. For instance, lncRNAs act as i) molecular guides, recruiting chromatin-modifying enzymes to their binding sites to modulate gene expression and chromatin dynamics; ii) molecular decoys, blocking and sequestering transcriptional factors; iii) scaffolds, they function by forming ribonucleoprotein complexes with different associated proteins to regulate transcription of their target genes, iv) miRNA sponges [13]. The ability of lncRNAs to "sponge" complementary miRNAs, acting as competitive endogenous RNAs (ceRNAs), and promoting the inhibition of target genes of these miRNAs is another well-characterized mechanism. This impact affects the progression of cancer (Fig. 1. Panel B) [11,16].

These findings have facilitated the way for the identification and characterization of numerous non-coding transcripts, highlighting the complexity and versatility of lncRNAs in biological processes [17,18].

This review will center on exploring the role and fundamental mechanisms of lncRNA NORAD-associated ceRNA networks in controlling the advancement of digestive system tumors. It is our hope that this review will stimulate further research aimed at creating innovative and improved therapeutic strategies for treating digestive system tumors.

2. Characterization of lncRNA NORAD

The Non-coding RNA Activated by DNA Damage (NORAD), also referred to as LINC00657 modulates the chromosomal stability in human cells [19]. Compared to other lncRNAs, NORAD is highly conserved and shows high expression levels in response to DNA damage [20]. NORAD is encoded on the 20q11.23 chromosome and consists of a single exon with a length of 5.3 kilobases (kb) [19]. It comprises 10 repetitions with various structural motifs, which enable NORAD to function as a scaffold that sequesters a range of ribonucleoprotein complexes.

Previous research has indicated that NORAD is mainly situated in the cytoplasm of human cells, and its structure consists of repeated elements called "NORAD repeat units" (NRU). The majority of NRUs display one or two binding sites for the mammalian Pumilio homologs (PUM): PUM1 and PUM2 [19–21]. Surprisingly, NORAD silencing induces chromosomal instability in previously stable, diploid human cell lines, due to the interaction between NORAD with PUM proteins. Interestingly, Genomic instability is caused by the excessive suppression of target transcripts, which, in the absence of NORAD, is crucial for preserving the integrity of chromosomal transmission and is regulated by PUM proteins [20].

The role of NORAD in ceRNA mechanisms has not been analyzed in depth using *in-silico* methods [16,20]. It is crucial to understand the impact of the lncRNA-miRNA-mRNA coregulation network on processes such as cell proliferation, apoptosis, invasion and metastasis *In silico* analysis reveals that NORAD plays a key role as a regulator in the lncRNA-miRNA-mRNA network, significantly influencing cell proliferation, apoptosis, invasion and metastasis. By sequestering 5 miRNAs (miR-6894-3p, miR-1303, miR-6511a-5p, miR-6865-3p and miR-140-3p) and regulating the expression of mRNAs, such as CASP7, BRCA1, CDK6, HGF, RHOB, among others (Fig. 2, supplementary data). This approach provides a comprehensive view of NORAD's interactions and competence within the cellular network, as well as its potential as a therapeutic target.

Furthermore, this lncRNA NORAD is overexpressed in several cancers of the digestive system, including gastric, esophageal, and colorectal cancer, and is associated with a poor prognosis [22]. Table 1 presents a comprehensive compilation of recent research exploring the NORAD role, in various types of digestive system cancers. Each entry in the table describes how NORAD acts as an oncogene through different axes of regulation, and how these interactions affect key biological functions such as cell proliferation, migration, invasion, autophagy, and resistance to therapies in different types of cancer, including cancer gastric, esophageal, hepatic, pancreatic and colorectal. The referenced studies provide a detailed insight into the intricate molecular processes underlying the development of cancer and propose potential avenues for therapeutic intervention in future clinical practice.

3. LncRNA NORAD in digestive system cancers

3.1. Molecular mechanisms of lncRNA-NORAD in gastric cancer

Gastric cancer (GC) constitutes the most frequent neoplasm of the gastrointestinal tract, as well as the five leading cause of cancer mortality. According to GLOBOCAN data in 2022, 968,784 cases were reported worldwide [2]. GC is a multifactorial disease, whereby a multitude of factors can exert an influence on its development. These include environmental factors, such as dietary habits, alcohol consumption, smoking, infections with the bacterium *Helicobacter pylori* and *Epstein-Barr virus* (EBV), and genetic factors, such as family history [42]. A recent study demonstrated that NORAD is overexpressed in gastric

cancer cell lines, AGS and BGC-823, in comparison to non-tumor cells. Interestingly, they found that silencing NORAD downregulated the expression of Ras Homolog family member A (*RhoA*) and Rho-associated coiled-coil containing protein kinase 1 (*ROCK1*), resulting in a cell proliferation, migration, and invasion inhibition, and promoting cell apoptosis [23]. Also, NORAD suppression has been shown to promote cell apoptosis by downregulating the expression of pro-apoptotic proteins such as *Bax*, *PTEN*, and *E-cadherin*, but downregulating the expression of *Bcl-2* [43].

NORAD plays a pivotal role in GC development and progression, functioning as a competitive endogenous RNA (ceRNA) to sponge its target miRNAs. This has been previously demonstrated [24], NORAD lncRNA is overexpressed in GC tissues and cell lines, and its expression was negatively correlated with miR-214 expression. Furthermore, NORAD overexpression is associated with proliferation induction and apoptosis inhibition through miR-214/Akt/*mTOR* regulatory axis in GC cells both *in vivo* and *in vitro* [24].

Similarly, researchers showed that downregulation of NORAD suppressed GC cell growth by sponge miR-608, resulting in the upregulation of *FOXO6* expression [25]. Another research group confirmed that lncRNA NORAD is involved in cancer progression [26], silencing NORAD repressed cell proliferation and G2/M cell cycle transition through the NORAD/miR-204-5p/*KMT2D* regulatory axis, mediating PTEN/PI3K/AKT signaling in GC [26]. Recent advances in major GC treatments, such as chemotherapy with oxaliplatin and capecitabine, have significantly prolonged the survival rate in GC patients [44]. It has been proven that lncRNA NORAD is a key regulator of oxaliplatin resistance, promoting autophagy activation through the miR-433-3-p/*ATG5* and *ATG12* regulatory axis [27]. On the other hand, despite advances in treatments, the rate of metastasis remains high [45]. It is therefore essential to study the influence of the tumor microenvironment on metastasis regulation. The cross-regulation mechanism

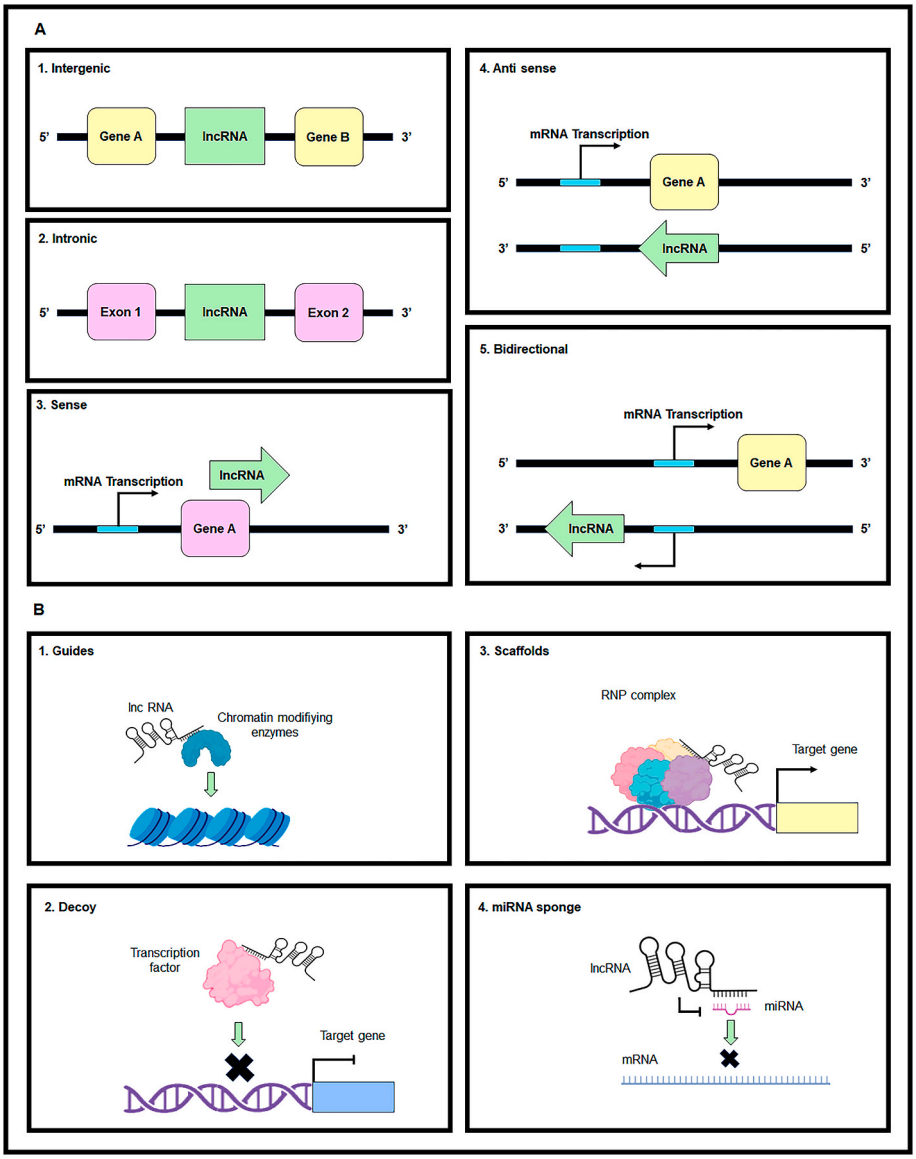

Fig. 1. The classification and role of lncRNAs. A) Classification of lncRNAs is based on their genomic position, such as intergenic, intronic, sense, antisense, and bidirectional. Intergenic lncRNAs are found between two genes and transcribed from intergenic regions. Intronic lncRNAs are processed from adjacent introns to exons. Sense lncRNAs are located within exons and transcribed in the 5′ to 3′ direction, while antisense lncRNAs are transcribed from the complementary strand of a gene. Bidirectional lncRNAs are transcribed from both DNA strands. B) Functions of lncRNAs include acting as molecular guides, decoys, scaffolds, and sponges for miRNAs. They recruit chromatin-modifying enzymes to their binding sites to regulate gene expression and chromatin dynamics. Molecular decoys block and sequester transcriptional factors. Scaffolds regulate the transcription of target genes by forming ribonucleoprotein complexes with associated proteins. miRNA sponges regulate gene expression by blocking miRNA binding to target genes.

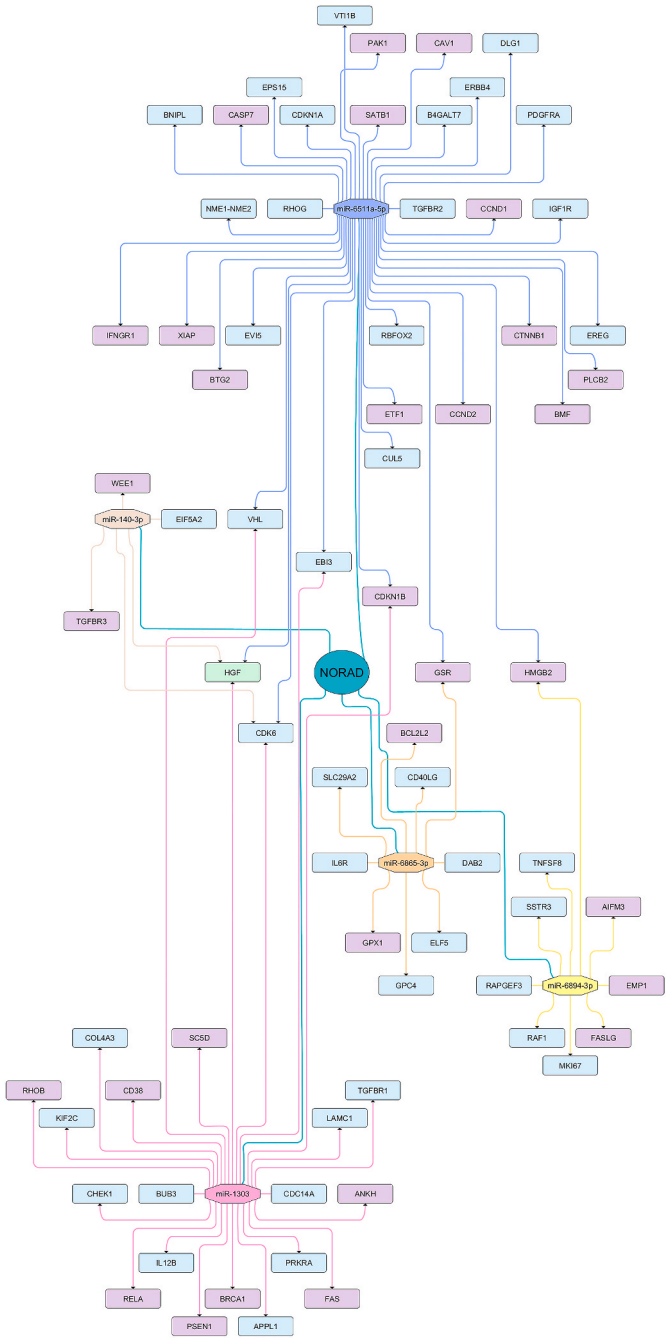

Fig. 2. Coregulatory network of lncRNA NORAD-miRNAs-mRNAs involved in apoptosis, proliferation, invasion, and metastasis processes. The lncRNA NORAD is represented by a circle, miRNAs by an octagon, and mRNAs by a rectangle. Apoptosis is represented in purple, cell proliferation in blue, and invasion and metastasis in green. lncRNA, long non-coding RNA; miRNA, microRNA; mRNA, messenger RNA.

between GC cells and cancer-associated fibroblasts (CAF) demonstrated that NORAD promotes IL-33 expression through miR-496 and CAFs could regulate GC cell proliferation and invasion (Fig. 3. Purple panel) [46]. These results imply that lncRNA NORAD may serve as a promising prognostic and therapeutic biomarker for patients with GC.

3.2. Molecular mechanisms of lncRNA NORAD in esophageal cancer

Esophageal cancer (EC) represents the sixth most common cause of cancer-related mortality and is amongst the most prevalent malignant conditions globally [47]. The median survival of patients in the last stage is less than 12 months [20].

Understanding the molecular mechanisms underlying EC has seen significant advances due to the study of lncRNAs. Among these, NORAD has emerged as a critical regulator in esophageal cancer progression, acting through several pathways that affect cell proliferation, invasion, and epithelial-mesenchymal transition (EMT) [26,37].

The overexpression of NORAD in esophageal cancer cells is associated with a poor prognosis, which suggests that it has the potential to act as a biomarker and a therapeutic target [28]. A study by Wu and collaborators demonstrated [29], that NORAD is overexpressed in EC tumor tissues compared to adjacent non-tumor tissues. This expression pattern was significantly associated with tumor size and a more advanced stage [48]. A Kaplan-Meier analysis indicated that patients with higher NORAD expression had shorter overall survival [29].

Recent studies have revealed that NORAD, has the capacity to act as an RNA sponge, sequestering specific miRNAs and, as a result, modulating the expression of crucial genes that are essential for tumor progression. A recently study found that lncRNA NORAD positively

Table 1
Molecular mechanisms of lncRNA NORAD in tumors of the digestive system.

Role	Regulation Axis	Biological function	References
Gastric Cancer			
Oncogene	*RhoA, ROCK1*	Promote proliferation, migration, and invasion.	[23]
Oncogene	miR-214/Akt/*mTOR*	Promotes cell proliferation and inhibits apoptosis	[24]
Oncogene	miR-608/*FOXO6*	Promotes cell growth	[25]
Oncogene	miR-204-5p/*KMT2D*	Promotes cell proliferation	[26]
Oncogene	miR-433-3p/ATG5 and ATG12	Promotes autophagy	[27]
Esophageal Cancer			
Oncogene	N/A	This correlates with a poor prognosis in patients with esophageal cancer	[28,29]
Oncogene	miR-224-3p/MTDH	Promotes CDDP resistance	[30]
Oncogene	miR-30a-5p/WNT	Promotes EMT and metastasis	[31]
Liver cancer			
Oncogene	miR-202-5p/TGFβ	Promote migration and invasion	[32]
Oncogene	miR-424/*PD-L1*	Promote migration and invasion	[33]
Oncogene	miR-211-5p/*VEGF-A*	Promote cell proliferation, migration, and angiogenesis	[34]
Oncogene	miR-556-3p/*MIEN1*	Promote cell proliferation and EMT	[35]
Pancreatic cancer			
Oncogene	miR125a-3p/*RhoA*	Promote EMT, under hypoxic conditions	[36]
Oncogene	miR-202-5p/*ANP32E*	Promote the viability, proliferation, and self-renewal capacity of PC cells	[37]
Oncogene	miR-532-3p/Nectin-4	Promote cell proliferation and angiogenesis	[38]
Colorectal cancer			
Oncogene	miR-202-5p and miR-203a	Promote proliferation, migration, and invasion	[39,40]
Oncogene	miR-495-3p/*HIF1A*	Promotes VM formation and resistance to therapy	[41]

Akt: Serine/Threonine Kinase; ANP32E: Acidic Leucine-rich Nuclear Phosphoprotein 32 Family Member E; ATG5: Autophagy Related 5; ATG12: Autophagy Related 12; EMT: epithelial-mesenchymal transition; FOXO6: Forkhead Box O6; HIF1A: Hipoxia-inducible factor 1A; KMT2D: Lysine Methyltransferase 2D; MIEN1: Migration and Invasion Enhancer 1; MTDH: Metadherin; RhoA: Ras Homolog family member A; mTOR: Mechanistic Target Of Rapamycin Kinase; Nectin-4: Nectin Cell Adhesion Molecule 4; PD-L1: Programmed Cell Death 1 Ligand 1; RHOA: Ras Homolog Family Member A; ROCK1: Rho-associated coiled-coil containing protein kinase 1; TGFβ: Transforming Growth Factor Beta; VEGF-A: Vascular Endothelial Growth Factor A; WNT: Proto-Oncogene Wingless-related integration site; VM: Vasculogenic Mimicry.

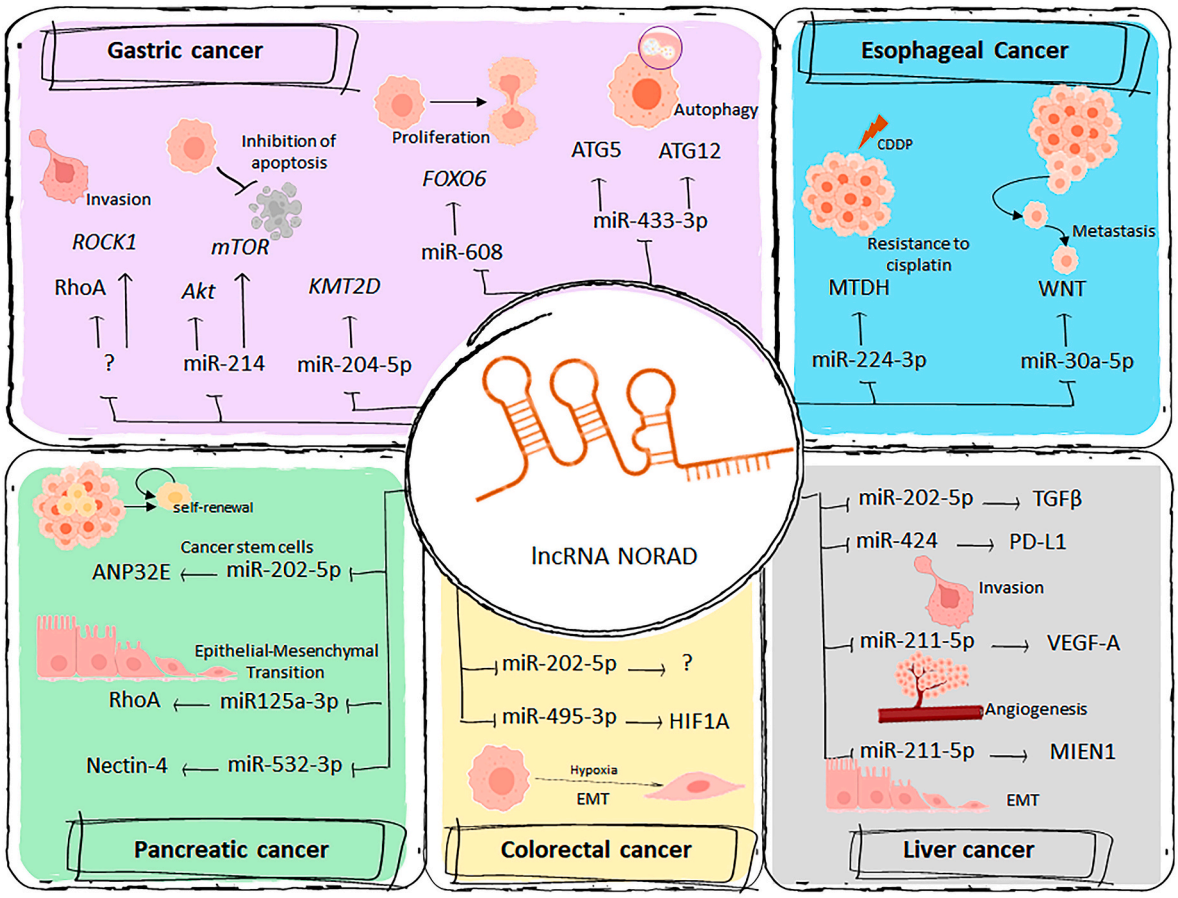

Fig. 3. Molecular interactions of NORAD in different types of cancers within the digestive system. The core of this scheme is lncRNA NORAD, acting as the central key player of regulation. Around it, different colored panels are arranged representing different types of cancer: gastric (purple), esophageal (blue), liver (grey), pancreatic (green), and colorectal (yellow). Each panel details specific regulatory pathways involved in carcinogenesis, such as interactions between different miRNAs and their respective molecular targets, which influence critical processes such as cell proliferation, migration, invasion, and resistance to therapy.

regulates metadherin (*MTDH*) to promote cis-diaminodichloroplatinum (CDDP) resistance and EC progression, through miR-224- 3p regulation [30]. It is of particular relevance in cancer that NORAD is able to promote EMT, which is a critical process by which epithelial cells acquire mesenchymal properties, facilitating invasion and metastasis. This process is mediated, in part, by the interaction of NORAD with specific miRNAs, such as miR-30a-5p, involved in the regulation of key pathways such as WNT/β-catenin, essential for EMT and metastasis (Fig. 3. Blue panel) [31].

Taken together, these findings highlight the importance of NORAD not only as a marker of tumor progression, but also as a potential therapeutic target in EC. The manipulation of NORAD expression or function could offer new strategies to combat this devastating disease. However, more research is required to fully unravel the complex mechanisms by which NORAD contributes to the pathogenesis of EC and to validate its clinical utility as a therapeutic target.

3.3. Molecular mechanisms of lncRNA NORAD in liver cancer

Liver cancer represents a significant public health concern, particularly hepatocellular carcinoma (HCC), which represents one of the primary forms of liver neoplasms. According to GLOBOCAN data from 2022, there were 866,136 reported cases of liver cancer globally [2,49]. HCC is a multifactorial disease with a complex aetiology that encompasses a range of underlying factors, including chronic hepatitis induced by viral infections such as hepatitis B and C, alcohol consumption, and cirrhosis [50,51]. Yang and collaborators [32], demonstrated that NORAD is overexpressed in liver cancer patient tissues, and its positive upregulation was directly correlated with *TGFβ* expression levels and shorter overall survival of HCC patients. Furthermore, they found that NORAD overexpression induces HCC cell migration and invasion through the NORAD/miR-202-5p/*TGFβ* regulatory axis [32]. Similarly, lncRNA NORAD promotes HCC progression through miR-424/*PD-L1* regulation [33].

Indeed, as the process of hepatocellular carcinoma (HCC) cell metastasis is highly dependent on angiogenesis, most of the currently approved first- and second-line therapies for HCC focus on inhibiting the formation of new blood vessels [52]. The NORAD overexpression in HCC was demonstrated that NORAD in hepatocellular carcinoma tissues and cell lines, and positively correlates with the angiogenic protein VEGFA. Interestingly, they found that silencing of lncRNA inhibits proliferation, migration, and angiogenesis through the NORAD/miR-211-5p/*VEGF-A* regulatory axis [34]. Another cellular process, which promotes metastasis, is the EMT. Recently, propofol has been shown to inhibit EMT and decrease NORAD levels in the hepatocellular carcinoma cell lines Hep3B and SNU449. Low NORAD expression levels correlate with migration and invasion enhancer 1 (MIEN1) expression levels, mediated by miR-556-3p. Therefore, these data indicate that propofol inhibits HCC cell proliferation and EMT progression through the NORAD/miR-556-3p/*MIEN1* axis (Fig. 3. Grey panel) [35].

3.4. Molecular mechanisms of lncRNA NORAD in pancreatic cancer

Pancreatic cancer (PC) represents the fourth leading cause of cancer-related mortality, and there has been an increase in both its incidence and mortality rates in recent years [53]. The primary issue is that most

patients exhibit no symptoms during the progression of the illness. As a result, diagnosis hinges on the capacity to identify and screen individuals at elevated risk before the emergence of symptoms [54]. Li and collaborators [36] demonstrated that lncRNA NORAD is overexpressed in PC patients and associated with a poor survival prognosis. In fact, this research group found that NORAD regulates RhoA expression through miR125a-3p, promoting EMT, under hypoxic conditions [36]. Previous studies have been described the role of cancer stem cells in this cancer progression. The lncRNA NORAD overexpression in PC stem cells and is correlated with the presence of acidic leucine-rich nuclear phosphoprotein 32 family member E (ANP32E), whereas the expression of miR-202-5p is negatively regulated. They demonstrated that lncRNA NORAD negatively regulates miR-202-5p, promoting the viability, proliferation, and self-renewal capacity of PC cells, through the NORAD/miR-202-5p/*ANP32E* regulatory axis [37]. In a similar way, another study showed that overexpression of NORAD promotes PC cell proliferation and angiogenesis through miR-532-3p/*Nectin-4* regulation. Finally, these studies demonstrated that NORAD silencing inhibits the proliferation and angiogenesis in PC cells through the NORAD/miR-532-3p/*Nectin-4* regulatory axis (Fig. 3. Green panel) [38].

3.5. Molecular mechanisms of lncRNA NORAD in colorectal cancer

Colorectal cancer (CRC) represents the third most prevalent cancer worldwide and the second leading cause of cancer-related mortality, with 1,142,286 new cases documented globally in 2022 [2,55]. Recently, great emphasis has been placed on developing effective methods for diagnosing and treating CRC. Therefore, it is necessary to fully understand the underlying molecular mechanism that regulates the development and CRC progression [55]. LncRNA NORAD could be a non-invasive biomarker for CRC surveillance because its expression levels in patient tissues positively correlate with its levels in blood serum. Additionally, elevated NORAD expression was found to be significantly linked to metastasis and unfavorable prognosis in patients with CRC [56]. Moreover, serum levels of NORAD can distinguish patients with adenomatous polyposis (AP) and patients with ulcerative colitis (UC) from controls [57].

LncRNA NORAD silencing suppresses proliferation, migration, and invasion, but induces cell apoptosis, through regulation of miR-202-5p in CRC cell lines [39]. Nowadays, it is known that stem cells contribute to cancer progression by inducing metastasis. Zhao and collaborators demonstrated [40], that NORAD is not only overexpressed in CRC tissues and cell lines, but is also overexpressed in cells with a stem cell phenotype, and silencing of lncRNA inhibits invasion through upregulation of miR-203a, resulting in another mechanism contributing to metastasis is the tumor microenvironment [40]. In recent decades, tumor hypoxia has been shown to promote angiogenesis, VM, and chemoresistance, leading to poor prognosis in cancer patients [58]. The correlation between the NORAD expression levels and hypoxia-inducible factor 1A (*HIF1A*), which promotes VM and 5-fluorouracil (5-FU) resistance in CRC. Interestingly, silencing NORAD reduced *HIF1A* expression and suppressed VM formation and chemoresistance through the NORAD/miR-495-3p/*HIF1A* regulatory axis in cancer (Fig. 3. Yellow panel) [41].

4. Conclusions and future perspectives

The long non-coding RNA (lncRNA) NORAD has been identified as a pivotal molecule in the progression of multiple types of digestive system cancers, including esophageal, gastric, and pancreatic cancer. It has previously been demonstrated that overexpression of NORAD is associated with an unfavorable prognosis in cancer patients, thereby underscoring its potential as a biomarker and a therapeutic target. Additionally, it has been demonstrated that NORAD can act as a "sponge" of microRNAs (miRNAs), indicating the presence of an innovative regulatory mechanism in the advancement of tumors. This mechanism is thought to control the transcription and expression levels of genes associated with cell proliferation, invasion, and metastasis.

NORAD lncRNA presents various perspectives for examining and managing digestive system tumors, including: i) Utilizing deregulated NORAD expression as a biomarker for early detection of digestive system tumors, ii) Implementing RNA-based targeted therapy by silencing NORAD to impede tumor progression, iii) Recognizing the significance of understanding the regulatory networks (lncRNA/miRNA/mRNA) detailed in this review to pinpoint new treatment targets and strategies. However, further research is necessary to fully comprehend their role in cancer biology and address the technical challenges linked to their clinical application.

5. Limitations

The lncRNA NORAD, plays a crucial role in regulating various cellular processes in digestive system tumors, such as cell proliferation, invasion, apoptosis, and metastasis. However, utilizing NORAD as a therapeutic target and biomarker for digestive system tumors is constrained by: i) its intricate regulation: since NORAD regulates the stability of several mRNAs through interactions with proteins and other RNA molecules (miRNA), making its role in cancer complex and often difficult to decipher, and ii) the inherent challenges of RNA-based treatments. More investigation is required to address these constraints and gain a deeper understanding of NORAD's involvement in cancer biology.

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CRediT authorship contribution statement

Yussel Pérez-Navarro: Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Yarely M. Salinas-Vera:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Cesar López-Camarillo:** Writing – review & editing, Resources, Formal analysis. **Elisa Elvira Figueroa-Angulo:** Writing – review & editing, Formal analysis. **María Elizbeth Alvarez-Sánchez:** Writing – review & editing, Writing – original draft, Resources, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ncrna.2024.09.002.

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