Review

Eva Morgenstern and Markus Kretz*

The human long non-coding RNA LINC00941 and its modes of action in health and disease

https://doi.org/10.1515/hsz-2023-0183
Received April 13, 2023; accepted June 28, 2023;
published online July 10, 2023

Abstract: Long non-coding RNAs have gained attention in recent years as they were shown to play crucial roles in the regulation of cellular processes, but the understanding of the exact mechanisms is still incomplete in most cases. This is also true for long non-coding RNA LINC00941, which was recently found to be highly upregulated in various types of cancer influencing cell proliferation and metastasis. Initial studies could not elucidate the mode of action to understand the role and real impact of LINC00941 in tissue homeostasis and cancer development. However, recent analyses have demonstrated multiple potential modes of action of LINC00941 influencing the functionality of various cancer cell types. Correspondingly, LINC00941 was proposed to be involved in regulation of mRNA transcription and modulation of protein stability, respectively. In addition, several experimental approaches suggest a function of LINC00941 as competitive endogenous RNA, thus acting in a post-transcriptional regulatory fashion. This review summarizes our recent knowledge about the mechanisms of action of LINC00941 elucidated so far and discusses its putative role in miRNA sequestering processes. In addition, the functional role of LINC00941 in regulating human keratinocytes is discussed to also highlight its role in normal tissue homeostasis tissue aside from its involvement in cancer.

Keywords: cancer; ceRNA; post-transcriptional regulation; protein-RNA interaction; RNA-RNA interaction; transcriptional regulation

***Corresponding author: Markus Kretz**, Regensburg Center for Biochemistry (RCB), University of Regensburg, 93053 Regensburg, Germany; and Institute for Molecular Medicine, MSH Medical School Hamburg, 20457 Hamburg, Germany,
E-mail: markus.kretz@medicalschool-hamburg.de
Eva Morgenstern, Regensburg Center for Biochemistry (RCB), University of Regensburg, 93053 Regensburg, Germany. https://orcid.org/0009-0008-6430-5491

1 Introduction

The "RNA world hypothesis" was inspired based on RNA being a highly functional molecule which could have been the prestage of life billions of years ago (Geisler and Coller 2013). Based on this hypothesis, RNA molecules had to serve as enzymes and storage media for information until DNA and proteins have developed and taken over most of these functions. As a consequence, research initially focused on these two types of biomolecules as well as protein-coding mRNAs. Our center of attention significantly changed when next generation sequencing technologies revealed that most of the human genome is transcribed (~75 %) but only 2 % encode proteins (Djebali et al. 2012; International Human Genome Sequencing Consortium 2004). This discovery has brought scientific interest back to the world of regulatory non-coding RNAs, which affect cellular processes to an unimagined extend. Many studies have focused on elucidating the functions of small non-coding RNAs (sncRNAs) including microRNAs (miRNAs), small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs). However, another class of RNAs, the long non-coding RNAs (lncRNAs), have recently gained wide-spread attention. LncRNAs are defined as RNA transcripts longer than 200 nucleotides with little or no coding potential (Quinn and Chang 2016). In addition to the absence of translated open reading frames (ORFs), many lncRNAs show significant similarities to mRNAs since most of them are also transcribed by RNA polymerase II, often spliced, 5′-capped and polyadenylated (Guttman et al. 2009). LncRNAs were shown to be regulators of many fundamental biological processes such as X-chromosome inactivation, cell cycle control, apoptosis and epigenetic imprinting (Nagano and Fraser 2011). Their mechanisms of action, on the other hand, in many cases are less clear and appear to be highly diverse. Nevertheless, several initial approaches to categorize lncRNA mechanisms have been undertaken. This led to the division into groups based on similarities in modes of action, such as scaffolds, guides, decoys and signals interacting with DNA, RNA and proteins with an impact mainly on (post-)transcriptional regulation (Cheng et al. 2019).

As an ever-increasing number of lncRNAs are being mechanistically characterized, it is becoming apparent that

the high diversity of different lncRNA modes of action, as well as the cellular processes controlled by them, cannot be broken down to a few general categories. Correspondingly, several lncRNAs are known for regulating transcription via chromatin modulation or binding of transcription factors (Nagano and Fraser 2011), while others affect mRNA processing through splicing control or RNA editing (Beltran et al. 2008; Peters et al. 2003). Furthermore, a number of lncRNAs affect post-transcriptional pathways through regulation of translational control or mRNA stability, as well as modulation of protein activity (Carrieri et al. 2012; Gong and Maquat 2011; Yin et al. 2012). Current studies also indicate a role of lncRNAs in cell-cell communication as signaling molecules packaged in exosomes (Huang et al. 2013). Approximately 128 000 human lncRNA transcripts have currently been annotated (Volders et al. 2019). However, since most of these transcripts remain uncharacterized to date, it is unclear what portion of these annotated lncRNAs is functionally relevant. In addition to the sheer number of uncharacterized molecules, the high diversity of potential mechanisms of lncRNAs requires a clarification of their modes of action on a case-by-case basis, which is very labor-intensive. Since many lncRNAs tend to form complex secondary and tertiary structures, which then often determine their functions, efforts are being made to identify recurring lncRNA structures of functional relevance. These structures can then be used to predict the mode of action of other lncRNAs on a larger scale, thus potentially facilitating the elucidation of the mechanisms in the future (Graf and Kretz 2020). However, for a number of lncRNAs the modes of action have already been analyzed in depth – HOTAIR being one of them. The lncRNA HOTAIR appears to combine several different roles and functions in one molecule. It is capable to bind both, the Polycomb repressive complex 2 (PRC2) and the lysine-specific histone demethylase 1 (LSD1) at the same time, thus acting as a molecular scaffold for these epigenetic regulator complexes. The HOTAIR-PRC2-LSD1 complex epigenetically alters gene expression via H3K27me3 (PRC2) and H3K4 (LSD1) demethylation, thus resulting in transcriptional repression of the HOXD locus (Chu et al. 2011; Rinn et al. 2007). HOTAIR can also act on the post-transcriptional level through interaction with ribosomes, translation factors and splicing factors to modulate translation and splicing (Cantile et al. 2020).

In this review, we describe our current understanding of a lncRNA annotated as LINC00941. This non-coding RNA was identified by the ENCODE Project in 2012 (Derrien et al. 2012). Opposite to the aforementioned lncRNA HOTAIR, much less is known about the functions and modes of action of LINC00941. However, several recent studies have shed light onto potential mechanisms for this lncRNA. Therefore, we will review the current research progress of LINC00941 in terms of its modes of action in cancer cells, as well as in normal human keratinocytes and organotypic epidermis, since there are no other known studies focusing on LINC00941 in non-cancerous cells. We will also discuss the potential role of LINC00941 as a competitive endogenous RNA (ceRNA) based on the corresponding, empirical data investigating this mechanism.

2 Initial characterization of the novel human lncRNA LINC00941

The novel lncRNA LINC00941, sometimes also referred to as lncRNA-MUF or lncIAPF, is annotated on the forward strand of chromosome 12. Several transcript isoforms, including alternative splicing variants as well as different 3′ and 5′ ends, were reported. LINC00941 is currently listed in the Ensemble Genome Browser as ENST00000650286.1 containing five exons and a total length of 1355 bp. As some lncRNAs also encode small peptides (Bánfai et al. 2012; Nelson et al. 2016), it is of major importance to ensure observed functions are not induced by small peptides but solely by the lncRNA itself. In case of LINC00941, bioinformatics analyses have not predicted protein-coding potential, indicating that it likely acts as lncRNA only (Ziegler et al. 2019).

Whenever the function of a molecule is to be investigated, the elucidation of the cellular and subcellular localization can already provide first indications. LINC00941 can be detected in most human tissues, suggesting prominent, cell type independent functions (Ziegler et al. 2019). In order to gain more information about the subcellular localization, RNA-fluorescent *in situ* hybridization (FISH) and fractionation analyses were conducted in recent studies. While the findings consistently observed presence of LINC00941 in both the cytoplasm and nucleus, they differ in terms of distribution. Ziegler et al. (2019) and Wang et al. (2021) could detect this lncRNA more frequently in cytoplasm of undifferentiated keratinocytes and pancreatic cancer cells lines (PANC-1, MIA-PaCa-2), respectively. On the other hand, Lu et al. (2023) were able to demonstrate a more prevalent occurrence in the nucleus in esophageal squamous cell carcinoma (ESCC). These findings reveal that the intracellular distribution of a given lncRNA can vary between different cell types or might alternatively depend on cell state, such as differentiation status. The subcellular localization of LINC00941 is relevant for prediction of its mode of action, as nuclear accumulation suggests a primarily gene regulatory function whereas cytoplasmic lncRNAs

are susceptible to post-transcriptional processes. These tasks include modulation of mRNA stability and protein activity, respectively, as well as miRNA sequestration and intracellular protein transport, to name just a few (Karlsson and Baccarelli 2016; Morlando et al. 2015). These inconsistent data indicate that LINC00941 might have different modes of action which are differently weighted within a cell, depending on cell type condition or type of disease.

3 LINC00941 expression and regulation in cancer cells and tissues

The first studies to become aware of LINC00941, aimed to identify deregulated lncRNAs in various cancers which could be utilized as diagnostic and prognostic biomarkers. By using The Cancer Genome Atlas (TCGA) database to compare RNA sequencing data of cancer tissue and adjacent healthy tissue, LINC00941 was found to be upregulated in disorders including gastric cancer (Luo et al. 2018), lung adenocarcinoma (Wang et al. 2019), head and neck squamous cell carcinoma (Hu et al. 2020), papillary thyroid cancer (Gugnoni et al. 2021) and clear cell renal cell carcinoma (Pan et al. 2023). These publications also showed that LINC00941 expression is often negatively correlated with patient's survival, TNM stage and tumor grade, respectively. Subsequent analyses initially focused on bioinformatic methods to elucidate the underlying function of LINC00941 in cancer cells. Gene co-expression network analyses to find co-expressed mRNAs as well as functional enrichment analyses first showed its role as regulator of cancer cell proliferation, invasion, and migration. Subsequent knockdown experiments could confirm this correlation as decreased expression levels of LINC00941 led to less cancer cell proliferation and tumor growth, respectively. Ke (2022) demonstrated the underlying cause for increased expression of lncRNAs, including LINC00941 exemplified by pancreatic adenocarcinoma. It could be shown that abnormal epigenetic modifications such as H3K4me3, H3K27me3, H3K27ac, H3K9me3, H3K4me1 and H3K4me3 were responsible for deregulated lncRNA expression. Similar to the cancer studies described above, LINC00941 was also shown to be elevated in pulmonary fibrosis (PF). In this study, one specific histone modification – H3K27ac – within the promoter region of LINC00941 was demonstrated to be required for induction of LINC00941 expression (Zhang et al. 2022): Triggered by TGF-β treatment, H3K27ac induced the transcription of LINC00941 through binding of ATF3. Focusing on the binding of transcription factors after TGF-β stimulation activating LINC00941 expression, Shree et al. (2021) could observe similar relationships: TGF-β enhanced LINC00941 transcription in glioma cells through binding of SMAD2/3 to its promoter region. Another study also shed some light on the regulatory basis for the upregulation of LINC00941: In pancreatic cancer cells, the corresponding promoter region showed increased occupancy of ETS-1, a MAPK associated transcription factor, resulting in elevated levels of LINC00941 compared to healthy tissue (Ishikawa et al. 2023). These publications have unanimously demonstrated that LINC00941 is upregulated in a wide variety of cancers. Depending on the type of cancer analyzed, LINC00941 transcriptional induction in cancers appeared to be mediated by recruitment of different transcription factors and co-factors, indicating complex regulatory control mechanisms for this lncRNA.

The aforementioned studies concluded that LINC00941 may represent a diagnostic and prognostic biomarker due to its exceptionally high expression. In some cases, LINC00941 was reported to be a potential target molecule for therapeutic approaches (Ishikawa et al. 2023; Ke 2022; Shree et al. 2021; Zhang et al. 2022). However, this would require extensive knowledge of its modes of action. Below, we will summarize recent approaches to analyze the molecular mechanisms of LINC00941 and discuss respective findings.

4 Mechanisms of LINC00941 in cancer

4.1 Regulation of mRNA transcription

Even though those preceding publications did not identify the mechanism of LINC00941, some results already pointed to a role of LINC00941 as transcriptional regulator. This could be concluded based on altered gene expression of several genes, often oncogenes, as a result of LINC00941 silencing or overexpression. Several recent studies have attempted to uncover the mode of action of LINC00941 in cancer cells. Although Nishiyama et al. (2018) were the first to demonstrate an increased expression of LINC00941 in oral squamous cell carcinoma (OSCC) cell lines, Ai et al. (2020) could prove the underlying reasons for high levels of LINC00941 as well as its mode of action in OSCC. In accordance with aforementioned publications, their work showed that the LINC00941 promoter region harbored a higher level of H3K27ac modifications in OSCC, suggesting enhanced LINC00941 expression. Interestingly, LINC00941 expression positively correlates with cell growth, colony, and tumor formation, respectively. ChIP-qPCR revealed

an enriched EP300 signal in aforementioned OSCC cell lines on the LINC00941 promoter region. EP300 is a histone acetyltransferase which, in conjunction with its coactivator CBP, acetylates all four core histones in nucleosomes and thereby activates transcription (Ogryzko et al. 1996). Consequentially, silencing of EP300 reduced the amount of H3K27ac modifications on the predicted LINC00941 promoter and to decreased LINC00941 expression.

Further experiments revealed the underlying mechanism of LINC00941 in OSCC. A motif analysis showed many binding sites of CTCF between LINC00941 and its nearby gene *CAPRIN2*. CTCF is a transcriptional regulator mediating DNA looping (Eagen 2018). As LINC00941 silencing caused CAPRIN2 downregulation, a transcriptional regulation between the neighboring genes seemed possible. Correspondingly, Ai et al. hypothesized that LINC00941 regulates gene expression in cis via looping to *CAPRIN2* mediated by CTCF to influence its expression. Quantitative chromosome conformation capture (3C) analysis was conducted in HSC-3 cells and demonstrated a strong interaction between LINC00941 and *CAPRIN2* promoter regions through chromatin looping. Repeating this experiment in CTCF knockout HSC-3 cells, the LINC00941 looping signal was almost completely abolished. Functional assays revealed pivotal roles of CAPRIN2 in promoting OSCC cell proliferation and tumor formation comparable to LINC00941. CAPRIN2 phosphorylates Wnt co-receptor LRP6. Consecutive interaction of phosphorylated LRP6 with Axin led to stabilization of β-catenin and ultimately to activation of Wnt target gene transcription (Jeong and Jho 2021). Interestingly, the resulting enhanced activity of the canonical Wnt pathway is implicated with many cancer types (Ding et al. 2008; Duchartre et al. 2016). Ai et al. could therefore increase our understanding of LINC00941 mode of action for the first time: LINC00941 elevated CAPRIN2 expression through CTCF-mediated looping, which subsequently enhances activity of the Wnt signaling pathway, thus increasing cancer cell proliferation in OSCC (Figure 1A). In 2022, Qiu et al. could support the LINC00941-dependent expression of CAPRIN2 in nasopharyngeal carcinoma (NPC). Their work aimed at analyzing the CAPRIN2-dependent survival ability of extracellular matrix (ECM)-detached tumor cells to form distant metastasis without undergoing ferroptosis, a non-apoptotic cell death. As part of their studies Qiu et al. encountered LINC00941 as an upstream regulator of CAPRIN2 and confirmed LINC00941-mediated expression of CAPRIN2 regulated in cis. Contrary to Ai et al., they did not show the Wnt pathway as downstream target of CAPRIN2 but the mevalonate pathway and its key enzyme HMGCR, which mediates the regulation of ferroptosis, survival and migration of NPC cell lines 5–8F and C666-1. In summary, Qiu et al. could demonstrate that silencing of LINC00941 led to a decrease in CAPRIN2 and HMGCR expression levels in NPC causing a weakened ferroptosis resistance and an increased survival of ECM-detached NPC cells (Qiu et al. 2022).

Lu et al. (2023) have recently made another important step forward in understanding the mechanism of LINC00941, since they not only unraveled the process of LINC00941 transcription, but they also described two functions of this lncRNA on both, the transcriptional and post-transcriptional level in ESCC. Using RNA sequencing, qRT-PCR and FISH analyses in ESCC cells, it was shown again that LINC00941 was upregulated compared to healthy cells. As in previous studies mentioned above, they could also confirm *in vivo* and *in vitro*, respectively, that LINC00941 upregulation leads to increased ESCC cell proliferation, migration and invasion leading to a poorer survival rate in affected patients. The reason for the upregulated expression was then revealed in a subsequent motif analysis in the LINC00941 promoter region. SOX2 was identified as the responsible transcription factor. A detailed analysis of the given ESCC RNA sequencing data confirmed SOX2 regulating LINC00941 transcription, since it was upregulated in ESCC cells but not in healthy ones. In SOX2 knockdown experiments, Lu et al. could verify the subsequent LINC00941 downregulation, while SOX2 overexpression led to increased levels of LINC00941. ChIP analysis finally confirmed SOX2 binding within the LINC00941 promoter region leading to the finding that SOX2 positively regulates LINC00941 expression in ESCC cell line KYSE-170. Subsequent RNA pull-down and mass spectrometry (MS) analysis then identified ILF2 and YBX1, both regulators of transcription, as potential interaction partners of LINC00941 in KYSE-170. They were also found to be upregulated in ESCC. The report describes YBX1 binding motifs in SOX2 promoter region as well as upregulated *SOX2* mRNA and protein levels as a consequence of overexpression of LINC00941, ILF2 and YBX1, respectively. Lu et al. then concluded an interaction between ILF2 and YBX1 to direct SOX2 expression mediated by LINC00941. Co-immunoprecipitation (Co-IP) verified interaction between YBX1 and ILF2 which was found to be attenuated after LINC00941 knockdown in KYSE-170. ChIP--qPCR was then applied to verify binding of YBX1 on the promoter region of SOX2 regulating its transcription. No interaction between YBX1 and SOX2 promoter region was observed when silencing LINC00941 or ILF2. Therefore, the role of LINC00941/YBX1/ILF2 complex could be identified in positively regulating SOX2 transcription. Apart from being a transcriptional regulator, ILF2 is also known to facilitate nuclear mRNA export and to inhibit exosomal degradation of *SOX2*, *NANOG* and *SALL4* (Li et al. 2021). Testing the influence of LINC00941 binding to ILF2 and YBX1 on mRNA

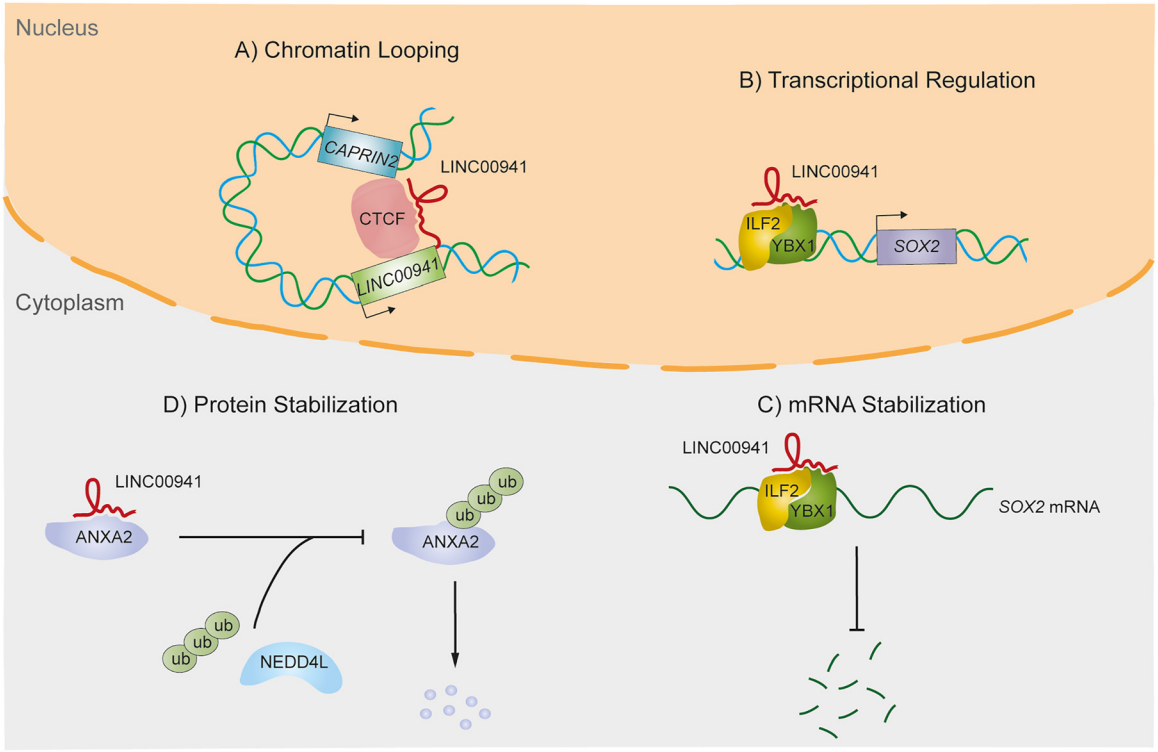

Figure 1: Schematic overview of selected LINC00941 mechanisms on transcriptional and post-transcriptional level in cancer cells. (A) LINC00941 regulates CAPRIN2 expression in cis through CTCF-mediated chromatin looping. (B) ILF2 and YBX1, recruited by LINC00941, bind to the SOX2 promotor region leading to SOX2 transcription in trans. (C) LINC00941 further promotes binding of ILF2 and YBX1 on *SOX2* mRNA to stabilize SOX2. (D) ANXA2 is bound by LINC00941 preventing NEDD4L-mediated ubiquitination and subsequent degradation of ANXA2.

stability of *SOX2*, ILF2 or YBX1 knockdown shortened the half-life of *SOX2* mRNA. This led to the hypothesis of ILF2 and YBX1 to stabilize the *SOX2* mRNA, which could be confirmed. RNA immunoprecipitation (RNA-IP) assays identified an enrichment of ILF2 and YBX1 on *SOX2* mRNA, but this interaction was also attenuated through LINC00941 knockdown in KYSE-170. ILF2 and YBX1 upregulation prolonged half-life of *SOX2* mRNA, while this effect was reversed through LINC00941 knockdown. Consequently, LINC00941 not only upregulated SOX2 through ILF2 and YBX1 interaction at the transcriptional level but also at the post-transcriptional level (Figure 1B and C). This work has not only deepened our knowledge about LINC00941 mechanisms, but it also confirmed its various possible functions within cells.

4.2 Modulation of protein stability and activity

As LINC00941 can also be found in the cytoplasm, further mechanisms at the post-transcriptional level were recently identified shedding light on its putative multilayered modes of action. Therefore, LINC00941 was not only shown to act as regulator of transcription and mRNA stabilizing component, but recent works additionally described LINC00941-mediated modulation of protein activity and stability. In 2021, Wu et al. were investigating the role of LINC00941 in epithelial-mesenchymal transition (EMT) in colorectal cancer (CRC), as EMT drives cancer cell distribution enhancing generation of metastases. They suggested that significantly increased levels of LINC00941 in CRC compared to normal control, it may promote CRC metastasis through activating EMT. Wu et al. discovered that overexpression of LINC00941 in CRC cell line HCT-116 led to upregulated mRNA and protein levels of VIM, FN1 and TWIST1, key molecular markers of cell invasion and metastasis, respectively. Simultaneously levels of ZO-1 and E-cadherin, known invasion suppressors, were decreased. This finding supports the role of LINC00941 mediating invasion and migration through regulating EMT of CRC cells. To elucidate the underlying mechanism, they performed RNA pull-down assays followed by MS analysis showing that LINC00941 interacts with SMAD4. LINC00941 suppression resulted in decreased SMAD4 protein levels and vice versa. These findings indicate that LINC00941/SMAD4 interaction

enhanced SMAD4 protein stability, which in turn leads to the assumption, that LINC00941 prevents SMAD4 degradation. Following this, Wu et al. were investigating SMAD4 poly-ubiquitination in LINC00941 overexpressing and silencing CRC cells, respectively. SMAD4 ubiquitination was significantly decreased when LINC00941 was overexpressed in HCT-116 cells, while SMAD4 ubiquitination was increased after LINC00941 knockdown in LoVo cells. These results concluded that LINC00941 could stabilize SMAD4 by suppressing its ubiquitination in CRC. Since it is known that β-TrCP is responsible for SMAD4 poly-ubiquitination and degradation (Wan et al. 2005), Wu et al. evaluated the role of β-TrCP in SMAD4 degradation. Silencing β-TrCP resulted in increased protein levels of SMAD4 and furthermore, LINC00941 knockdown caused an increased binding of SMAD4 and β-TrCP. LINC00941 overexpression caused the converse effect: Decreased binding of SMAD4 and β-TrCP. Consequently, these findings led to the hypothesis that LINC00941 suppressed SMAD4 ubiquitination and degradation by competing with β-TrCP. With the help of competitive RNA pull-down studies, they confirmed the competing relationship between LINC00941 and β-TrCP. Taken together, LINC00941 was found to enhance SMAD4 protein stability by competing with β-TrCP to prevent SMAD4 degradation. Consequentially, the lncRNA appeared to modulate the parent TGF-β1/SMAD pathway since SMAD4 binds SMAD2/3 to form complexes regulating transcription of markers for cancer cell migration and invasion causing metastases in CRC. In addition, Wu et al. discovered a putative TGF- β1 binding site in the LINC00941 promoter region. Subsequent analysis revealed that LINC00941 levels were significantly increased after addition of exogenous TGF-β1. This result and further experiments verified TGF-β1-dependent LINC00941 expression, which in turn again stabilized SMAD4 leading to EMT in CRC (Wu et al. 2021).

Based on the work of Xu et al. (2021), LINC00941 does not prevent ubiquitination but facilitates dephosphorylation of its interaction partner MST1 to maintain its stability. In this scientific study, they were investigating the role of LINC00941 in pancreatic ductal adenocarcinoma (PDAC) and initially discovered, that LINC00941 suppresses extracellular acidic production. Knocking down LINC00941, however, suppressed glycolysis in PDAC cell lines PANC-1 and SW1990, since mRNA levels of enzymes involved in glycolysis, such as GLUT1, LDHA, HK2 and PFKFB3, were downregulated. Furthermore, TEAD1, a Hippo pathway transcription factor proven to regulate glycolysis, showed impaired transcriptional activity. These results indicated the involvement of the Hippo pathway serving as a mediator of the enhanced glycolysis induced by LINC00941. To elucidate the role of LINC00941 in this signaling pathway, Xu et al. performed RNA pull-down followed by MS analysis. MST1, one of the key components of the Hippo pathway, was identified as interaction partner of LINC00941. This was further verified by RNA-IP in PADC cell line PANC-1. It was also discovered that MST1 phosphorylation levels were increased in LINC00941 silenced cells compared to controls, which is why the authors of this study concluded that LINC00941 mediates dephosphorylation of MST1. As previous studies reported PP2A-mediated dephosphorylation of MST1 (Tang et al. 2020), Co-IP was performed in LINC00941 knockdown PANC-1 and SW1990 cells. A weakened interaction between MST1 and PP2A was observed in LINC00941 silenced cells compared to control cells. Summing up they have described for the first time that LINC00941 interacts with MST1 facilitating PP2A-mediated dephosphorylation of MST1. As a result, Hippo pathway is activated, and enhanced glycolysis is triggered leading to elevated cancer cell proliferation.

Yet another study described a role of LINC00941 acting as a protective shield against degradation of its interaction partner. Using RNA pull-down assay and MS with pancreatic cancer (PC) cells, Wang et al. (2022) found that upregulated LINC00941 interacted with ANXA2. ANXA2, involved in metastasis formation in several cancer types (Anselmino et al. 2020; Mao et al. 2021), was upregulated in PC tissues. LINC00941 overexpression resulted in prolonged half-life of ANXA2, while LINC00941 knockdown decreased its stability and accelerates its degradation. Examining the underlying cause of this phenomenon, Wang et al. investigated ANXA2 ubiquitination levels. As hypothesized, LINC00941 overexpression decreased ANXA2 ubiquitination and LINC00941 knockdown caused the opposite in PANC-1 cell line. Similar to preceding studies, LINC00941 enhances protein expression of ANXA2 by suppressing its ubiquitination. Co-IP and MS identified NEDD4L, a ubiquitin ligase, as interaction partner of ANXA2 in PANC-1. In-depth analysis verified LINC00941 and NEDD4L competing to interact with ANXA2. Acting as a decoy, LINC00941 is therefore able to reduce ubiquitination of ANXA2 by NEDD4L (Figure 1D). The stabilized ANXA2 then activates the downstream FAK/AKT signaling pathway supporting tumor cell survival (Paul et al. 2020).

The above studies focusing on the mechanism of action of LINC00941 have mainly concentrated on cancer, but Zhang et al. (2022) have unraveled the mode of action of LINC00941 in PF and identified comparable functions of the lncRNA. Similar to the results in different cancer cell lines, RNA sequencing data of PF tissue revealed elevated LINC00941 expression compared to normal lung tissue. LINC00941-mediated enhanced fibroblast-to-myofibroblast differentiation accelerated PF in LINC00941 overexpression experiments. These results were supported by the upregulated fibrotic markers in LINC00941 overexpression cells identifying this lncRNA as profibrotic factor in PF.

Elucidating its regulatory mechanism, ELAVL1 was found to have an enhanced stability in cells with ectopic expression of LINC00941, but the effect was reversed when silencing LINC00941. The underlying cause was revealed using ubiquitination experiments: LINC00941 overexpression decreased ELAVL1 ubiquitination leading to elevated ELAVL1 stability. Silencing this lncRNA promoted ELAVL1 ubiquitination and degradation. Surprisingly, Zhang et al. could also show the opposite way: LINC00941 not only enhances ELAVL1 stability but ELAVL1 also influences half-life of LINC00941 suggesting that both molecules affect each other's stability. With regard to PF, LINC00941 overexpression led to increased expression of fibrotic markers including ACTA2, VIM, COL1A and COL3A causing enhanced myofibroblast proliferation and migration. These results, however, were reversed by ELAVL1 knockdown, thus suggesting that the function of LINC00941 in PF depends on ELAVL1. Searching the effects of the LINC00941/ELAVL1 interaction the fact came across that some genes related with autophagy were deregulated as a consequence of LINC00941 knockdown. Further studies revealed that overexpressing LINC00941 inhibits autophagy by blocking autophagosome and lysosome fusion, while silencing LINC00941 promoted this process. Here as well, the effect of LINC00941 depends on the presence of ELAVL1. In the further course of experiments, Zhang et al. identified mRNA of *EZH2*, *STAT1* and *FOXK1* as targets of ELAVL1 with decreasing degree of binding after LINC00941 knockdown. ELAVL1 is therefore able to influence mRNA stability depending on LINC00941 since its silencing or overexpression reduced or promoted half-life stability of those mRNAs. High levels of LINC00941 led to increased protein levels of EZH2, STAT1 and FOX1 but only in the presence of ELAVL1. It could also be revealed, that promoted expression of fibrotic proteins and decreased autophagy after EZH2, STAT1 and FOXK1 overexpression were overlapping with the same deregulated genes as detected after LINC00941 overexpression. These results reflect pro-fibrotic functions of LINC00941 mainly come from EZH2, STAT1 and FOXK1. The underlying mechanism was shown to rely on the binding of ELAVL1 protein to block its ubiquitination and degradation, respectively. As a result, increasing stability of its mRNA targets *EZH2*, *STAT1* and *FOXK1* caused attenuated autophagy and thereby accelerating pathogenesis of PF.

4.3 Regulation of mRNA post-transcriptional pathway

In addition to studies that have primarily demonstrated interaction between LINC00941 and chromatin or proteins, interaction with RNA molecules, mainly miRNAs, was also uncovered. Chang et al. (2021) aimed to reveal the role of upregulated LINC00941 in colon cancer (CC) cells since it is related to CC progression. Because LINC00941 is mainly localized in the cytoplasm of CC cells, they have concluded and focused exclusively on LINC00941 acting as ceRNA. A potential target was bioinformatically predicted and identified as miR-205-5p. Dual luciferase reporter assay was used to examine the interaction between LINC00941 and miR-205-5p. The luciferase activity decreased when miR-205-5p was overexpressed while increased when miR-205-5p was inhibited. Thus, the interaction was supposedly proven. Further experiments in the CC LoVo cell line showed, among others, that LINC00941 knockdown led to increased miR-205-5p levels, which led to their hypothesis that LINC00941 participated in CC development by targeting miR205-5p. *In situ*, the oncogene MYC was predicted to be the target gene of miR-205-5p verified through dual luciferase reporter assay. The effect of LINC00941 sequestering miR-205-5p was supposed to be revealed in a subsequent LINC00941 overexpression experiment: Increased LINC00941 levels caused decreased MYC expression levels in CC. Summarizing, exceptional high LINC00941 levels in CC led to sponging of miR-205-5p and thus upregulating MYC expression accelerating cancer cell proliferation and migration. Several publications followed discovering similar LINC00941-mediated miRNA sequestration mechanisms by performing experiments comparable to those previously described. These studies have supposedly elucidated the role of LINC00941 as ceRNA. This lncRNA was also found to sponge miR-873-3p in pancreatic adenocarcinoma and thereby upregulating gene expression of oncogene ATXN2 (Fang et al. 2021) as well as modulating post-transcriptional gene expression of VEGFA through binding of the corresponding miR-877-3p in non-small cell lung cancer (Ren et al. 2021). Wang et al. (2021) and Zhang et al. (2021) also described the function of LINC00941 as ceRNA for miR-335-5p affecting ROCK1 and miR-877-3p in PC cells and its downstream target PMEPA1 in ESCC cells, respectively. The proposed role of LINC00941 as ceRNA is described as oncogene causing enhanced cell proliferation and migration in cancer, since its significant upregulation binds exceptionally many corresponding miRNAs. Consequently, this leads to the enhanced expression of their downstream, oncogenic mRNAs. The resulting proteins are the actual oncogenes accelerating cell proliferation and migration.

4.4 Putative function of lncRNAs as ceRNAs

Once described as "Rosetta stone of hidden RNA language", the ceRNA hypothesis provided an additional layer of gene

regulation to describe "communication" between all types of RNA transcripts (Salmena et al. 2011). Competing with mRNAs for the same pool of miRNAs, ceRNAs – which include pseudogenes, lncRNAs, circRNAs and other mRNAs – might be able to titrate away miRNAs. The resulting inhibition of miRNA activity is therefore correlated with positive gene expression of the respective target mRNAs. This "new language" is largely enabled through the existence of miRNA responsive elements (MREs), a partial complementarity between 3′ UTR of mRNAs and ceRNAs, respectively, and the 5′ region of the corresponding miRNAs (Salmena et al. 2011). Nevertheless, to date it remains largely unclear whether it is stoichiometrically possible for miRNAs to be intercepted by ceRNAs in a functionally meaningful manner. Several studies and hypotheses aim at approaching this question. A number of mathematical models see miRNA sequestration as a possibility, if the RNA molecules involved are present in equimolar concentrations (Ala et al. 2013; Bosia et al. 2013; Figliuzzi et al. 2013). Another model was established by Denzler et al. (2014; 2016): Only a high abundance of miRNA binding sites in the ceRNA network could in principle reduce inhibitory effects of miRNAs. However, Denzler et al. state that no transcript or global transcription variation within physiological range can provide enough miRNA binding sites to reverse miRNA-mediated mRNA inhibition and degradation. The postulated model of Bosson et al. (2014) offers a third possible explanation: They assume that miRNAs preferentially bind to mRNAs with high-affinity target sites compared to more abundant, but lower affinity sites. According to this hypothesis and following studies, the number of putative target mRNAs is less than expected. If the ratio between miRNA and their target mRNA is small enough, ceRNAs with high-affinity binding sites are able to bind miRNAs – even under physiological conditions (Bosson et al. 2014; Smillie et al. 2018). However, knowing the stoichiometric relationship between lncRNAs putatively functioning as ceRNAs, their target miRNAs and the downstream affected mRNAs would be of great importance. Unfortunately, this analysis is technically challenging and often not included in respective studies. Nevertheless, even critics have to admit that there is an overwhelming amount of empirical evidence for the ceRNA hypothesis. This also applies to LINC00941, whose function as a ceRNA has been investigated and proposed in the above-mentioned studies. The commonalities between these publications supporting the ceRNA hypothesis include the fact that interaction between LINC00941 and various miRNAs was found to be predicted in different publicly available cross-linking immunoprecipitation high-throughput (CLIP) sequencing databases. Since miRNAs occur mainly bound to AGO2 within the cell (Jonas and Izaurralde 2015), these studies usually include AGO2-IPs followed by qRT-PCR to detect LINC00941 association. Therefore, we verified interaction of the lncRNA with AGO2, as exemplarily shown in human primary keratinocytes in Figure 2A, which provides a first, indirect indication of a putative association between LINC00941 and miRNAs (unpublished data). However, since this kind of experiment does not prove direct interaction between LINC00941 and a miRNA of interest, dual luciferase reporter assays give at least one more hint to detect interaction. For this purpose, either a wild-type (WT) or mutated (MUT) putative binding site of LINC00941 predicted by CLIP sequencing was cloned into the 3′ UTR of a luciferase gene. As shown in HeLa cells to verify binding of miR-335-5p to LINC00941 (Figure 2B), reduced luciferase activity with constructs harboring a mutated LINC00941 binding site strongly indicate direct association of the miRNA with the wildtype binding region (unpublished data). Finally, the effects of miRNA sequestration on downstream mRNA targets could also be examined with LINC00941 depletion. Provided LINC00941 acts as ceRNA, its knockdown would cause decreased levels of the corresponding mRNAs, as the miRNAs bind them and inhibit their translation since they are not bound by LINC00941. This assumption was verified in the studies discussed above. Correspondingly, the collective data indicates that LINC00941 might mediate sequestration of miRNAs, which as a result led to increased abundance of key oncogenes or related genes, thus causing enhanced proliferation and migration of the cancer cells.

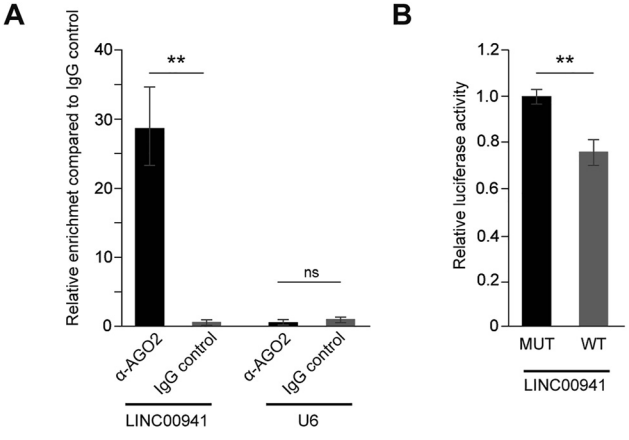

Figure 2: LINC00941 as putative ceRNA. (A) AGO2-IP and subsequent qRT-PCR detect LINC00941 bound to AGO2 in human primary keratinocytes supporting the ceRNA hypothesis. (B) Dual luciferase reporter assay verified interaction between LINC00941 and miR-335-5p in HeLa cells. CLIP sequencing predicted binding site (WT) between lncRNA and miRNA was cloned in the 3′ UTR of a luciferase and compared to luciferase activity of a mutated (MUT) binding site. Data are presented as mean ± standard deviation. Statistical significance was tested by an unpaired *t*-test (**p-value <0.01 and ns = not significant) (unpublished data).

Taken together, the studies above provide data supporting LINC00941-mediated miRNA sequestration, but additional experimentation might be required to verify that LINC00941 and other lncRNAs indeed act as ceRNAs. Partially due to limited experimental detection modes, some questions still remain open which need to be clarified to prove the final evidence of the ceRNA hypothesis. Not only is it necessary to exclude the option of AGO2/miRNA-mediated degradation of the lncRNA, it is also necessary to investigate stochiometric ratios between lncRNA and miRNA to meet the critics considerations. Furthermore, an experimental detection method is necessary to verify direct interaction between LINC00941 and the miRNA of interest *in vivo*. As there are also other ways of lncRNA-mediated regulation of mRNA levels such as influencing mRNA transcription – as already shown for LINC00941 – they should not be neglected when considering a ceRNA function. Instead, it should be taken into account that different mechanisms occur in parallel as seen by Yan et al. (2017) and Shree et al. (2021). They described LINC00941 not only acting as ceRNA but also as modulator of protein stability and regulator of mRNA transcription. Moreover, it may be likely that influence of LINC00941 on cellular processes can vary depending on focusing on cancerous or healthy tissue as LINC00941 level and subcellular localization vary as previously described.

5 LINC00941 as regulator in healthy tissue

In previously mentioned studies, LINC00941 stood out because it is upregulated in the respective cancer tissue compared to healthy controls. Therefore, its mode of action was of interest to get a better understanding of the particular type of cancer and its cause. However, the impact of LINC00941 in healthy cells has not yet been considered although it has been demonstrated that it plays an important role, at least in the human epidermis. So far, some lncRNAs have been shown to be involved in normal human epidermal homeostasis such as ANCR, TINCR and SMRT-2 (Kretz et al. 2012, 2013; Lee et al. 2018). Ziegler et al. (2019) could recently show that LINC00941 also plays an important role in regulating epidermal tissue homeostasis. This lncRNA LINC00941 was proven to be highly expressed in undifferentiated keratinocytes but repressed upon onset of differentiation, which was shown in qRT-PCR of calcium-induced differentiation of human keratinocytes. Consistent with other work on LINC00941, this lncRNA does not occur exclusively in the nucleus or cytoplasm but is almost equally distributed to both compartments (Ziegler et al. 2019). Moreover, LINC00941 knockdown resulted in increased mRNA level of early and late differentiation genes. Both findings - suggested a role of LINC00941 in non- and poorly differentiated keratinocytes suppressing premature differentiation of keratinocytes. Gene ontology analysis of deregulated genes identified in LINC00941 knockdown tissue showed an enrichment of genes crucial for processes of epidermal differentiation, including keratinization, keratinocyte differentiation and generation of a cornified envelope (Ziegler et al. 2019). Furthermore, a strong enrichment of deregulated genes could be observed within the epidermal differentiation complex (EDC) on chromosome 1, which harbors genes for many proteins involved in keratinocyte differentiation (Kypriotou et al. 2012; Mischke et al. 1996). The affected genes within the EDC include Loricrin, SPRR4 and most of the LCE genes, which were significantly upregulated upon LINC00941 knockdown (Figure 3). Since LINC00941 is able to regulate the expression of genes in trans, a role of this lncRNA as regulator of mRNA transcription in keratinocytes is currently considered. Beyond that, a LINC00941-mediated mechanism on the post transcriptional level is taken into account since interaction

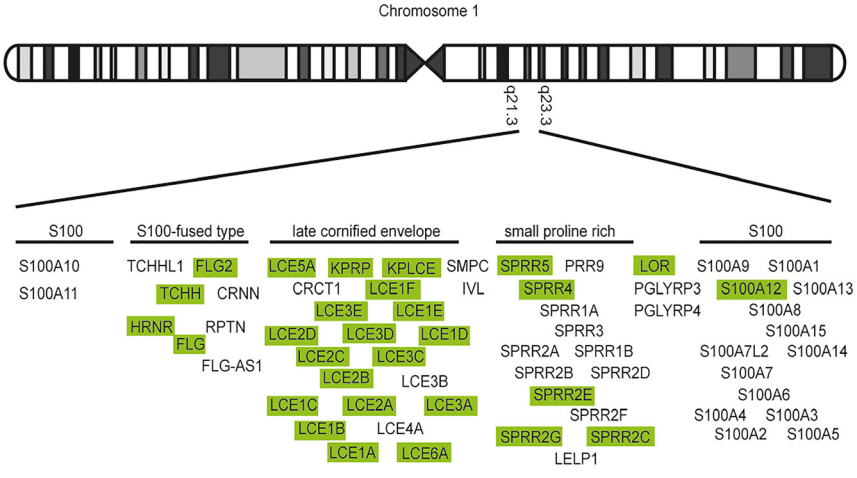

Figure 3: Upregulated genes in the epidermal differentiation complex (EDC) upon LINC00941 knockdown. LINC00941 silencing led to enhanced mRNA abundance of differentiation genes within the EDC (highlighted in green) indicating a role of LINC00941 as epigenetic regulator (Ziegler et al. 2019).

between LINC00941 and AGO2 was revealed that refers to a putative function of this lncRNA as ceRNA. MiR-335-5p is the putative miRNA bound by LINC00941 and known to be a positive regulator of keratinocyte differentiation (Liew et al. 2020). As stoichiometric relationships between LINC00941 and miR-335-5p remain unclear current data point to LINC00941 as negative regulator of keratinocyte differentiation mainly at the level of transcription and less at post-transcriptional level.

6 Conclusions

LncRNAs have versatile functions within cells in both, healthy and diseased tissue. They fulfill tasks as regulators and modulators on transcriptional and post-transcriptional level to influence various cellular processes. This review article focused on LINC00941, a lncRNA that has attracted attention over the last decade by being significantly upregulated in many cancers. LINC00941 has frequently been referred to as diagnostic marker and potential therapeutic target. Correspondingly, recent studies devoted to elucidate its mechanism in different cancer cells. It could be shown that LINC00941 acts on different level through different modes of action – maybe even depending on the type of cancer analyzed. LINC00941-mediated modulation of epigenetic regulation was often shown in various cancer tissues and is currently hypothesized for healthy keratinocytes. However, other modes of action were also found in a subset of model systems investigated to date: Some studies have been able to demonstrate that LINC00941 enhances stability of mRNAs and proteins in cancers of the pancreas and digestive tract by preventing degradation through binding to the affected molecule. Apart from the role of LINC00941 as epigenetic regulator and modulator of stability, there is empirical evidence that it could act as ceRNA. However, the final proof of direct interaction between LINC00941 and miRNAs *in vivo* is still pending. In summary, it seems likely that the lncRNA LINC00941 exerts three superordinate functions within the cell in diseased tissue. The mechanisms of LINC00941 in normal tissue are not clear as of now, but are under active investigation.

Acknowledgments: This work was supported by the Deutsche Forschungsgemeinschaft (DFG) as part of the Sonderforschungsbereich SFB 960.
Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: This research was funded by Deutsche Forschungsgemeinschaft (SFB960).
Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

References

Ai, Y., Wu, S., Zou, C., and Wei, H. (2020). LINC00941 promotes oral squamous cell carcinoma progression via activating CAPRIN2 and canonical WNT/β-catenin signaling pathway. J. Cell. Mol. Med. 24: 10512–10524.

Ala, U., Karreth, F.A., Bosia, C., Pagnani, A., Taulli, R., Léopold, V., Tay, Y., Provero, P., Zecchina, R., and Pandolfi, P.P. (2013). Integrated transcriptional and competitive endogenous RNA networks are cross-regulated in permissive molecular environments. Proc. Natl. Acad. Sci. U.S.A. 110: 7154–7159.

Anselmino, N., Bizzotto, J., Sanchis, P., Lage-Vickers, S., Ortiz, E., Valacco, P., Paez, A., Labanca, E., Meiss, R., Navone, N., et al. (2020). HO-1 interactors involved in the colonization of the bone niche: role of ANXA2 in prostate cancer progression. Biomolecules 10: 467.

Bánfai, B., Jia, H., Khatun, J., Wood, E., Risk, B., Gundling, W.E., Kundaje, A., Gunawardena, H.P., Yu, Y., Xie, L., et al. (2012). Long noncoding RNAs are rarely translated in two human cell lines. Genome Res. 22: 1646–1657.

Beltran, M., Puig, I., Peña, C., García, J.M., Alvarez, A.B., Peña, R., Bonilla, F., and de Herreros, A.G. (2008). A natural antisense transcript regulates Zeb2/Sip1 gene expression during Snail1-induced epithelial-mesenchymal transition. Genes Dev. 22: 756–769.

Bosia, C., Pagnani, A., and Zecchina, R. (2013). Modelling competing endogenous RNA networks. PloS One 8: e66609.

Bosson, A.D., Zamudio, J.R., and Sharp, P.A. (2014). Endogenous miRNA and target concentrations determine susceptibility to potential ceRNA competition. Mol. Cell 56: 347–359.

Cantile, M., Di Bonito, M., Cerrone, M., Collina, F., de Laurentiis, M., and Botti, G. (2020). Long non-coding RNA HOTAIR in breast cancer therapy. Cancers 12: 1197.

Carrieri, C., Cimatti, L., Biagioli, M., Beugnet, A., Zucchelli, S., Fedele, S., Pesce, E., Ferrer, I., Collavin, L., Santoro, C., et al. (2012). Long non-coding antisense RNA controls Uchl1 translation through an embedded SINEB2 repeat. Nature 491: 454–457.

Chang, L., Zhou, D., and Luo, S. (2021). Novel lncRNA LINC00941 promotes proliferation and invasion of colon cancer through activation of MYC. OncoTargets Ther. 14: 1173–1186.

Cheng, J.-T., Wang, L., Wang, H., Tang, F.-R., Cai, W.-Q., Sethi, G., Xin, H.-W., and Ma, Z. (2019). Insights into biological role of LncRNAs in epithelial-mesenchymal transition. Cells 8: 1178.

Chu, C., Qu, K., Zhong, F.L., Artandi, S.E., and Chang, H.Y. (2011). Genomic maps of long noncoding RNA occupancy reveal principles of RNA-chromatin interactions. Mol. Cell 44: 667–678.

Denzler, R., Agarwal, V., Stefano, J., Bartel, D.P., and Stoffel, M. (2014). Assessing the ceRNA hypothesis with quantitative measurements of miRNA and target abundance. Mol. Cell 54: 766–776.

Denzler, R., McGeary, S.E., Title, A.C., Agarwal, V., Bartel, D.P., and Stoffel, M. (2016). Impact of microRNA levels, target-site complementarity, and cooperativity on competing endogenous RNA-regulated gene expression. Mol. Cell 64: 565–579.

Derrien, T., Johnson, R., Bussotti, G., Tanzer, A., Djebali, S., Tilgner, H., Guernec, G., Martin, D., Merkel, A., Knowles, D.G., et al. (2012). The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res. 22: 1775–1789.

Ding, Y., Xi, Y., Chen, T., Wang, J., Tao, D., Wu, Z.-L., Li, Y., Li, C., Zeng, R., and Li, L. (2008). Caprin-2 enhances canonical Wnt signaling through regulating LRP5/6 phosphorylation. J. Cell Biol. 182: 865–872.

Djebali, S., Davis, C.A., Merkel, A., Dobin, A., Lassmann, T., Mortazavi, A., Tanzer, A., Lagarde, J., Lin, W., Schlesinger, F., et al. (2012). Landscape of transcription in human cells. Nature 489: 101–108.

Duchartre, Y., Kim, Y.-M., and Kahn, M. (2016). The Wnt signaling pathway in cancer. Crit. Rev. Oncol. 99: 141–149.

Eagen, K.P. (2018). Principles of chromosome architecture revealed by Hi-C. Trends Biochem. Sci. 43: 469–478.

Fang, L., Wang, S.-H., Cui, Y.-G., and Huang, L. (2021). LINC00941 promotes proliferation and metastasis of pancreatic adenocarcinoma by competitively binding miR-873-3p and thus upregulates ATXN2. Eur. Rev. Med. Pharmacol. Sci. 25: 1861–1868.

Figliuzzi, M., Marinari, E., and de Martino, A. (2013). MicroRNAs as a selective channel of communication between competing RNAs: a steady-state theory. Biophys. J. 104: 1203–1213.

Geisler, S. and Coller, J. (2013). RNA in unexpected places: long non-coding RNA functions in diverse cellular contexts. Nat. Rev. Mol. Cell Biol. 14: 699–712.

Gong, C. and Maquat, L.E. (2011). lncRNAs transactivate STAU1-mediated mRNA decay by duplexing with 3′ UTRs via Alu elements. Nature 470: 284–288.

Graf, J. and Kretz, M. (2020). From structure to function: route to understanding lncRNA mechanism. Bioessays 42: e2000027.

Gugnoni, M., Manicardi, V., Torricelli, F., Sauta, E., Bellazzi, R., Manzotti, G., Vitale, E., de Biase, D., Piana, S., and Ciarrocchi, A. (2021). Linc00941 is a novel transforming growth factor β target that primes papillary thyroid cancer metastatic behavior by regulating the expression of cadherin 6. Thyroid 31: 247–263.

Guttman, M., Amit, I., Garber, M., French, C., Lin, M.F., Feldser, D., Huarte, M., Zuk, O., Carey, B.W., Cassady, J.P., et al. (2009). Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature 458: 223–227.

Hu, Y., Guo, G., Li, J., Chen, J., and Tan, P. (2020). Screening key lncRNAs with diagnostic and prognostic value for head and neck squamous cell carcinoma based on machine learning and mRNA-lncRNA co-expression network analysis. Cancer Biomark. 27: 195–206.

Huang, X., Yuan, T., Tschannen, M., Sun, Z., Jacob, H., Du, M., Liang, M., Dittmar, R.L., Liu, Y., Liang, M., et al. (2013). Characterization of human plasma-derived exosomal RNAs by deep sequencing. BMC Genom. 14: 319.

International Human Genome Sequencing Consortium (2004). Finishing the euchromatic sequence of the human genome. Nature 431: 931–945.

Ishikawa, T., Fukushige, S., Saiki, Y., Hirose, K., Hiyoshi, T., Ogawa, T., Katori, Y., and Furukawa, T. (2023). Long non-coding RNAs associated with mitogen-activated protein kinase in human pancreatic cancer. Cancers 15: 303.

Jeong, W. and Jho, E.-H. (2021). Regulation of the low-density lipoprotein receptor-related protein LRP6 and its association with disease: Wnt/β-catenin signaling and beyond. Front. Cell Dev. Biol. 9: 714330.

Jonas, S. and Izaurralde, E. (2015). Towards a molecular understanding of microRNA-mediated gene silencing. Nat. Rev. Genet. 16: 421–433.

Karlsson, O. and Baccarelli, A.A. (2016). Environmental health and long non-coding RNAs. Curr. Environ. Health Rep. 3: 178–187.

Ke, M. (2022). Identification and validation of apparent imbalanced epi-lncRNAs prognostic model based on multi-omics data in pancreatic cancer. Front. Mol. Biosci 9: 860323.

Kretz, M., Siprashvili, Z., Chu, C., Webster, D.E., Zehnder, A., Qu, K., Lee, C.S., Flockhart, R.J., Groff, A.F., Chow, J., et al. (2013). Control of somatic tissue differentiation by the long non-coding RNA TINCR. Nature 493: 231–235.

Kretz, M., Webster, D.E., Flockhart, R.J., Lee, C.S., Zehnder, A., Lopez-Pajares, V., Qu, K., Zheng, G.X.Y., Chow, J., Kim, G.E., et al. (2012). Suppression of progenitor differentiation requires the long noncoding RNA ANCR. Genes Dev. 26: 338–343.

Kypriotou, M., Huber, M., and Hohl, D. (2012). The human epidermal differentiation complex: cornified envelope precursors, S100 proteins and the 'fused genes' family. Exp. Dermatol. 21: 643–649.

Lee, C.S., Mah, A., Aros, C.J., Lopez-Pajares, V., Bhaduri, A., Webster, D.E., Kretz, M., and Khavari, P.A. (2018). Cancer-associated long noncoding RNA SMRT-2 controls epidermal differentiation. J. Invest. Dermatol. 138: 1445–1449.

Li, Y., Wang, M., Yang, M., Xiao, Y., Jian, Y., Shi, D., Chen, X., Ouyang, Y., Kong, L., Huang, X., et al. (2021). Nicotine-induced ILF2 facilitates nuclear mRNA export of pluripotency factors to promote stemness and chemoresistance in human esophageal cancer. Cancer Res. 81: 3525–3538.

Liew, W.C., Sundaram, G.M., Quah, S., Lum, G.G., Tan, J.S.L., Ramalingam, R., Common, J.E.A., Tang, M.B.Y., Lane, E.B., Thng, S.T.G., et al. (2020). Belinostat resolves skin barrier defects in atopic dermatitis by targeting the dysregulated miR-335:SOX6 axis. J. Allergy Clin. Immunol. 146: 606–620.

Lu, J.-T., Yan, Z.-Y., Xu, T.-X., Zhao, F., Liu, L., Li, F., and Guo, W. (2023). Reciprocal regulation of LINC00941 and SOX2 promotes progression of esophageal squamous cell carcinoma. Cell Death Dis 14: 72.

Luo, C., Tao, Y., Zhang, Y., Zhu, Y., Minyao, D.N., Haleem, M., Dong, C., Zhang, L., Zhang, X., Zhao, J., et al. (2018). Regulatory network analysis of high expressed long non-coding RNA LINC00941 in gastric cancer. Gene 662: 103–109.

Mao, L., Yuan, W., Cai, K., Lai, C., Huang, C., Xu, Y., Zhong, S., Yang, C., Wang, R., Zeng, P., et al. (2021). EphA2-YES1-ANXA2 pathway promotes gastric cancer progression and metastasis. Oncogene 40: 3610–3623.

Mischke, D., Korge, B.P., Marenholz, I., Volz, A., and Ziegler, A. (1996). Genes encoding structural proteins of epidermal cornification and S100 calcium-binding proteins form a gene complex ("epidermal differentiation complex") on human chromosome 1q21. J. Invest. Dermatol. 106: 989–992.

Morlando, M., Ballarino, M., and Fatica, A. (2015). Long non-coding RNAs: new players in hematopoiesis and leukemia. Front. Med. 2: 23.

Nagano, T. and Fraser, P. (2011). No-nonsense functions for long noncoding RNAs. Cell 145: 178–181.

Nelson, B.R., Makarewich, C.A., Anderson, D.M., Winders, B.R., Troupes, C.D., Wu, F., Reese, A.L., McAnally, J.R., Chen, X., Kavalali, E.T., et al. (2016). A peptide encoded by a transcript annotated as long noncoding RNA enhances SERCA activity in muscle. Science 351: 271–275.

Nishiyama, K., Maruyama, R., Niinuma, T., Kai, M., Kitajima, H., Toyota, M., Hatanaka, Y., Igarashi, T., Kobayashi, J.-I., Ogi, K., et al. (2018). Screening for long noncoding RNAs associated with oral squamous cell carcinoma reveals the potentially oncogenic actions of DLEU1. Cell Death Dis. 9: 826.

Ogryzko, V.V., Schiltz, R.L., Russanova, V., Howard, B.H., and Nakatani, Y. (1996). The transcriptional coactivators p300 and CBP are histone acetyltransferases. Cell 87: 953–959.

Pan, H., Wei, W., Fu, G., Pan, J., and Jin, B. (2023). LINC00941 promotes cell malignant behavior and is one of five costimulatory molecule-related lncRNAs that predict prognosis in renal clear cell carcinoma. Medicina 59: 187.

Paul, R., Luo, M., Mo, X., Lu, J., Yeo, S.K., and Guan, J.-L. (2020). FAK activates AKT-mTOR signaling to promote the growth and progression of MMTV-Wnt1-driven basal-like mammary tumors. Breast Cancer Res. 22: 59.

Peters, N.T., Rohrbach, J.A., Zalewski, B.A., Byrkett, C.M., and Vaughn, J.C. (2003). RNA editing and regulation of *Drosophila* 4f-rnp expression by sas-10 antisense readthrough mRNA transcripts. RNA 9: 698–710.

Qiu, L., Zhou, R., Zhou, L., Yang, S., and Wu, J. (2022). CAPRIN2 upregulation by LINC00941 promotes nasopharyngeal carcinoma ferroptosis resistance and metastatic colonization through HMGCR. Front. Oncol. 12: 931749.

Quinn, J.J. and Chang, H.Y. (2016). Unique features of long non-coding RNA biogenesis and function. Nat. Rev. Genet. 17: 47–62.

Ren, M.-H., Chen, S., Wang, L.-G., Rui, W.-X., and Li, P. (2021). LINC00941 promotes progression of non-small cell lung cancer by sponging miR-877-3p to regulate VEGFA expression. Front. Oncol. 11: 650037.

Rinn, J.L., Kertesz, M., Wang, J.K., Squazzo, S.L., Xu, X., Brugmann, S.A., Goodnough, L.H., Helms, J.A., Farnham, P.J., Segal, E., et al. (2007). Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. Cell 129: 1311–1323.

Salmena, L., Poliseno, L., Tay, Y., Kats, L., and Pandolfi, P.P. (2011). A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? Cell 146: 353–358.

Shree, B., Tripathi, S., and Sharma, V. (2021). Transforming growth factor-Beta-regulated LncRNA-MUF promotes invasion by modulating the miR-34a Snail1 axis in glioblastoma multiforme. Front. Oncol. 11: 788755.

Smillie, C.L., Sirey, T., and Ponting, C.P. (2018). Complexities of post-transcriptional regulation and the modeling of ceRNA crosstalk. Crit. Rev. Biochem. Mol. Biol. 53: 231–245.

Tang, Y., Fang, G., Guo, F., Zhang, H., Chen, X., An, L., Chen, M., Zhou, L., Wang, W., Ye, T., et al. (2020). Selective inhibition of STRN3-containing PP2A phosphatase restores Hippo tumor-suppressor activity in gastric cancer. Cancer Cell 38: 115–128.

Volders, P.-J., Anckaert, J., Verheggen, K., Nuytens, J., Martens, L., Mestdagh, P., and Vandesompele, J. (2019). LNCipedia 5: towards a reference set of human long non-coding RNAs. Nucleic Acids Res. 47: D135–D139.

Wan, M., Huang, J., Jhala, N.C., Tytler, E.M., Yang, L., Vickers, S.M., Tang, Y., Lu, C., Wang, N., and Cao, X. (2005). SCF(beta-TrCP1) controls Smad4 protein stability in pancreatic cancer cells. Am. J. Pahtol. 166: 1379–1392.

Wang, J., He, Z., Liu, X., Xu, J., Jiang, X., Quan, G., and Jiang, J. (2022). LINC00941 promotes pancreatic cancer malignancy by interacting with ANXA2 and suppressing NEDD4L-mediated degradation of ANXA2. Cell Death Dis. 13: 718.

Wang, J., He, Z., Xu, J., Chen, P., and Jiang, J. (2021). Long noncoding RNA LINC00941 promotes pancreatic cancer progression by competitively binding miR-335-5p to regulate ROCK1-mediated LIMK1/Cofilin-1 signaling. Cell Death Dis. 12: 36.

Wang, L., Zhao, H., Xu, Y., Li, J., Deng, C., Deng, Y., Bai, J., Li, X., Xiao, Y., and Zhang, Y. (2019). Systematic identification of lincRNA-based prognostic biomarkers by integrating lincRNA expression and copy number variation in lung adenocarcinoma. Int. J. Cancer 144: 1723–1734.

Wu, N., Jiang, M., Liu, H., Chu, Y., Wang, D., Cao, J., Wang, Z., Xie, X., Han, Y., and Xu, B. (2021). LINC00941 promotes CRC metastasis through preventing SMAD4 protein degradation and activating the TGF-β/SMAD2/3 signaling pathway. Cell Death Differ. 28: 219–232.

Xu, M., Cui, R., Ye, L., Wang, Y., Wang, X., Zhang, Q., Wang, K., Dong, C., Le, W., and Chen, B. (2021). LINC00941 promotes glycolysis in pancreatic cancer by modulating the Hippo pathway. Mol. Ther. Nucleic Acids 26: 280–294.

Yan, X., Zhang, D., Wu, W., Wu, S., Qian, J., Hao, Y., Yan, F., Zhu, P., Wu, J., Huang, G., et al. (2017). Mesenchymal stem cells promote hepatocarcinogenesis via lncRNA-MUF interaction with ANXA2 and miR-34a. Cancer Res. 77: 6704–6716.

Yin, Q.-F., Yang, L., Zhang, Y., Xiang, J.-F., Wu, Y.-W., Carmichael, G.G., and Chen, L.-L. (2012). Long noncoding RNAs with snoRNA ends. Mol. Cell 48: 219–230.

Zhang, J., Wang, H., Chen, H., Li, H., Xu, P., Liu, B., Zhang, Q., Lv, C., and Song, X. (2022). ATF3 -activated accelerating effect of LINC00941/lncIAPF on fibroblast-to-myofibroblast differentiation by blocking autophagy depending on ELAVL1/HuR in pulmonary fibrosis. Autophagy: 1–20, https://doi.org/10.1080/15548627.2022.2046448.

Zhang, Y., Zhu, H., Sun, N., Zhang, X., Liang, G., Zhu, J., Xia, L., Kou, Y., and Lu, J. (2021). Linc00941 regulates esophageal squamous cell carcinoma via functioning as a competing endogenous RNA for miR-877-3p to modulate PMEPA1 expression. Aging 13: 17830–17846.

Ziegler, C., Graf, J., Faderl, S., Schedlbauer, J., Strieder, N., Förstl, B., Spang, R., Bruckmann, A., Merkl, R., Hombach, S., et al. (2019). The long non-coding RNA LINC00941 and SPRR5 are novel regulators of human epidermal homeostasis. EMBO Rep. 20: e46612.