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A review on the importance of LINC-ROR in human disorders

Soudeh Ghafouri-Fard [a], Ashkan Pourtavakoli [b], Bashdar Mahmud Hussen [c], Mohammad Taheri [d,e,*], Arda Kiani [f,**]

[a] Department of Medical Genetics, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran
[b] Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran
[c] Department of Clinical Analysis, College of Pharmacy, Hawler Medical University, Erbil, Kurdistan Region, Iraq
[d] Institute of Human Genetics, Jena University Hospital, Jena, Germany
[e] Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran
[f] Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran

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ABSTRACT

Long Intergenic Non-Protein Coding RNA, Regulator Of Reprogramming (LINC-ROR) is a long non-coding RNA with diverse physiological functions. The gene encoding this transcript resides on 18q21.31. Expression levels of LINC-ROR have been reported to be dysregulated in patients with diverse disorders, including cancer, autoimmune disorders and neurodegenerative and neurodevelopmental disorders. Moreover, polymorphisms within this lncRNA have been shown to be associated with a variety of disorders, such as some kinds of cancer and some aspects of systemic lupus erythematous. Abnormal expression of LINC-ROR in some other human disorders is not yet understood. Emerging evidence suggests that LINC-ROR exerts pivotal roles in most types of human disorders as an oncogene. Differentially expressed LINC-ROR contributes in the development of diseases by changing the expression of genes that control the cell cycle. It can also exert its role by affecting the activity of some cancer-related signaling pathways and sponging tumor suppressor miRNAs. Expanding our understanding of LINC-ROR functions will pave the way for developing efficient therapeutic strategies against cancer and related disorders. The current review aims at providing a concise overview of the role of LINC-ROR in diverse human disorders through providing a summary of association studies and expression assays.

1. Introduction

Long non-coding RNAs (lncRNAs) are a group of transcripts with sizes more than 200 nucleotides that regulate gene expression at different levels through acting as signal transcripts, decoy molecules, scaffolds, guide transcripts and enhancers [7,21]. These transcripts contribute to the pathogenesis of different disorders, particularly cancer [11,14,20,34]. Expression levels of these transcripts have been reported to be altered in different human disorders [12,13,35].

Long Intergenic Non-Protein Coding RNA, Regulator of Reprogramming (LINC-ROR) is an lncRNA located on 18q21.31. This lncRNA is also named as Large intergenic non-coding RNA-ROR [29,55] and lincRNA-ST8SIA3 [51]. At least 8 transcripts have been identified for LINC-ROR with sizes ranging from 2604 bp (LINC-ROR-201, ENST00000553704.3) to 532 bp (LINC-ROR-204, ENST00000644118.1) (Fig. 1). Expression levels of LINC-ROR have been reported to be dysregulated in patients with diverse disorders, including cancer [23], autoimmune disorders [15] and neurodegenerative [18] and neurodevelopmental disorders [16]. Moreover, polymorphisms within the gene encoding this lncRNA have been found to be associated with oral squamous cell carcinoma [40], colon cancer [44] and breast cancer [31] as well as some aspects of the autoimmune disorders systemic lupus erythematous (SLE) [22]. The current review aims at providing a concise overview of the role of LINC-ROR in diverse human disorders through providing a summary of association studies and expression assays.

2. Genetic association studies

The associations between LINC-ROR polymorphisms and oral squamous cell carcinoma [40], colon cancer [44] and breast cancer [31] have been assessed in different populations. Rose et al. have genotyped

* Corresponding author at: Institute of Human Genetics, Jena University Hospital, Jena, Germany.
** Corresponding author.
E-mail addresses: mohammad.taheri@uni-jena.de (M. Taheri), ardakiani@sbmu.ac.ir (A. Kiani).

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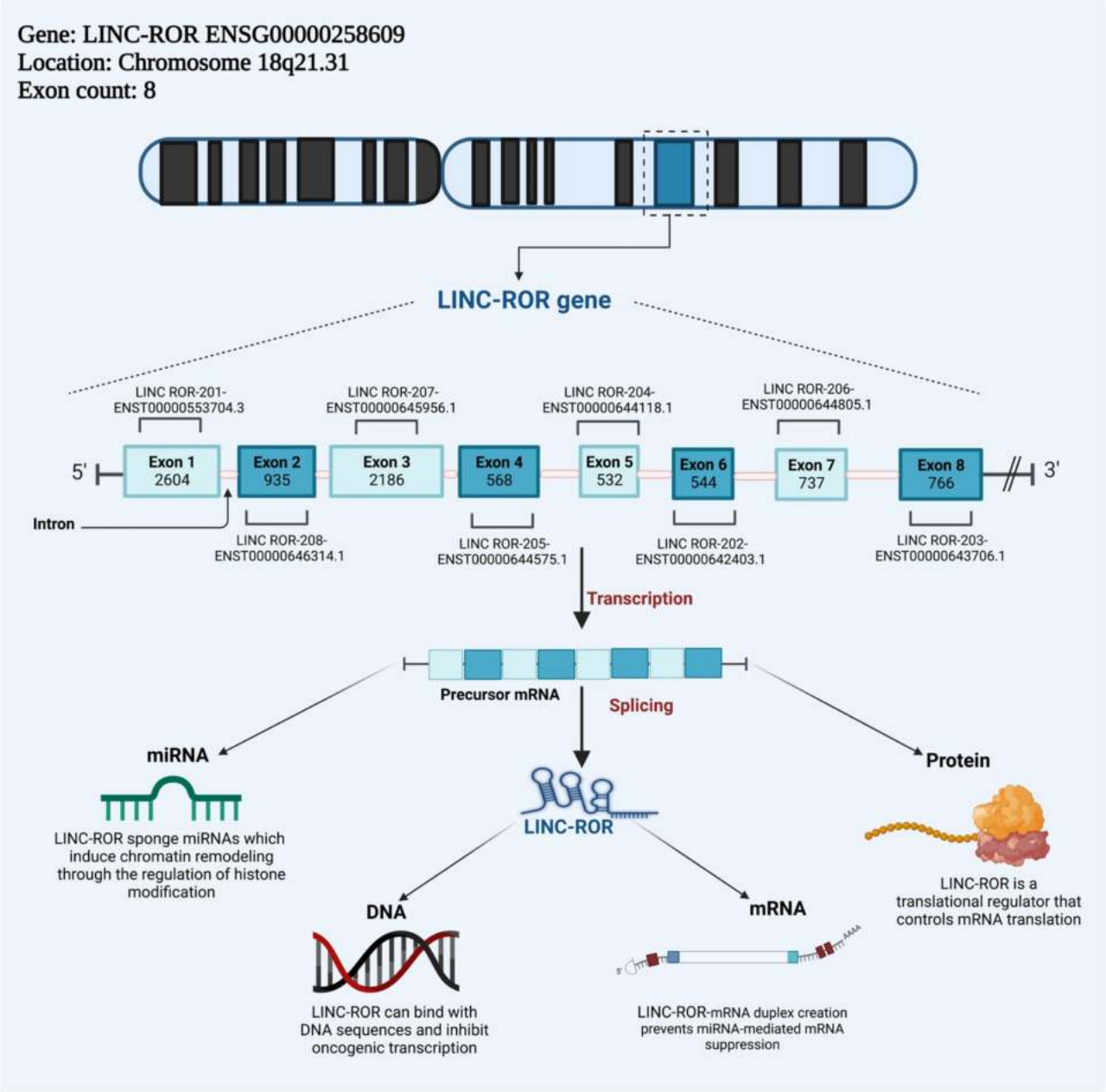

Fig. 1. LINC-ROR is located on human chromosome 18. There are 8 transcripts (extracted from the Ensemble database). LINC-ROR transcripts play distinct roles such as epigenetic regulation, binding with the DNA sequences to inhibit or induce target gene expression, regulation of transcription, and post-transcriptional processes. Dysregulation of LINC-ROR expression is also associated with an increased risk of tumor recurrence and a worse prognosis for various tumor types.

rs6420545, rs4801078, rs1942348, and rs9636089 LINC-ROR variants in a population of South Indian patients with oral squamous cell carcinoma and healthy subjects. Moreover, authors have investigated the impact of these variants on expression levels of LINC-ROR and progression of this type of cancer. The results of association studies have revealed association between rs6420545 and rs4801078 genotypes and advanced tumor grade as well as nodal metastasis. Moreover, expression of LINC-ROR has been significantly up-regulated in this cohort of patients. Taken together, this study has revealed possible contribution of LINC-ROR genetic variants to the metastasis and progression of oral squamous cell carcinoma, particularly in the late stages of tumorigenesis. Moreover, these variants have been suggested as potential tools for establishment of personalized therapeutic management of this malignancy [40]. In addition, LINC-ROR has an intronic variant, namely rs1942347 which might affect gene regulation and disease phenotypes. A single study in colorectal cancer samples has shown association between A allele of this polymorphism and advanced pathological grade, large tumor size, distant metastasis, and high rate of mortality. Further adjustment for the effects of sex and BRAF mutation has verified that carriers of A/A genotype have 3 times higher risk of early onset of cancer compared with carriers of T/T genotype. In addition, carriers of A allele have been found to be at higher risk of mortality under four supposed inheritance models compared to carriers of T/T allele. Furthermore, stratified analyses by BRAF status have shown the protective effect of ancestor T/T allele in BRAF mutant colorectal cancer patients. Finally, Kaplan-Meier analysis has verified the impact of A/A genotype on reduction of survival time in these patients [44]. In another molecular epidemiological investigation, rs6420545, rs4801078, rs1942348 and rs9636089 polymorphisms of this lncRNA have been selected through bioinformatics methods. This study has reported association between TT

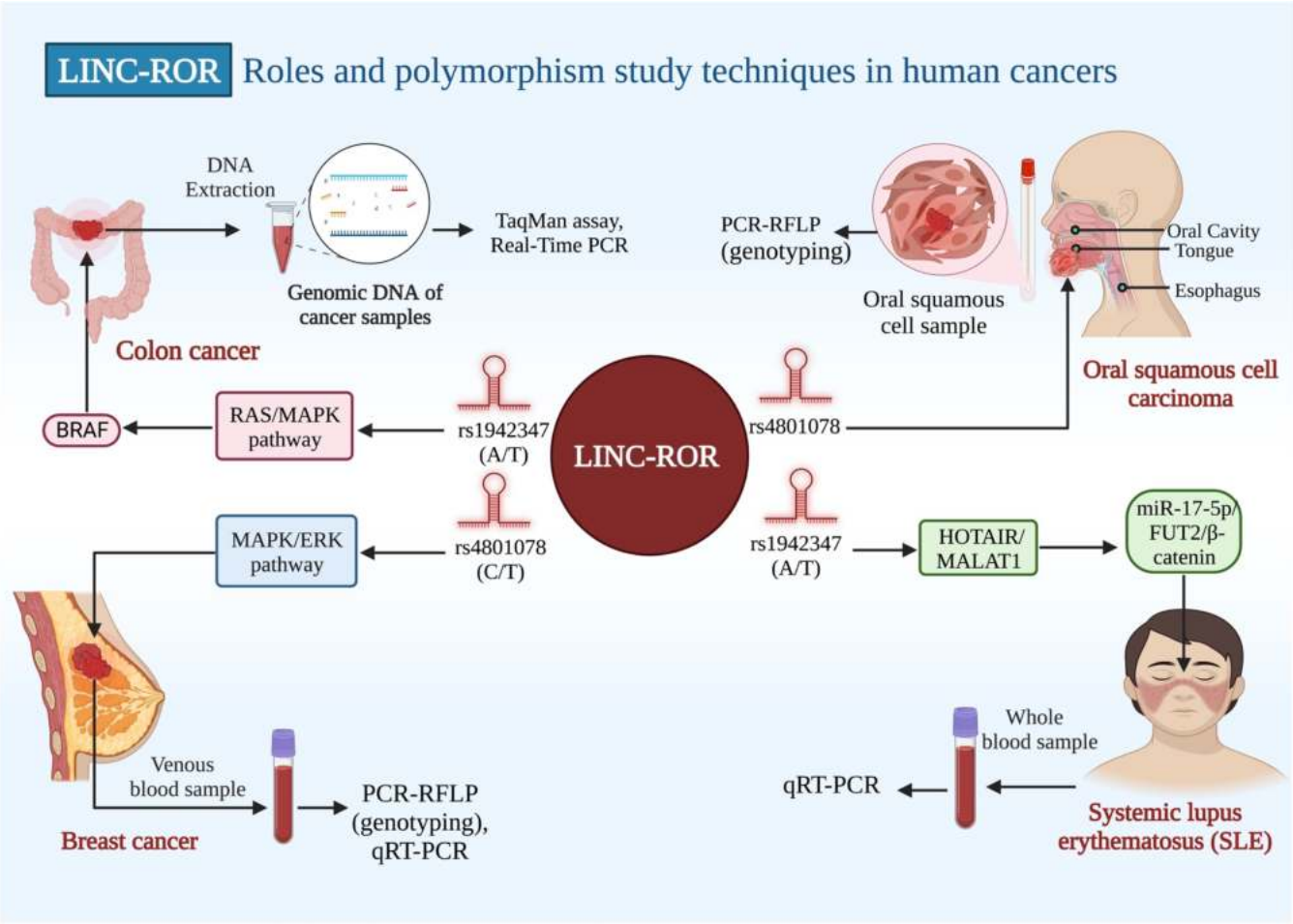

Fig. 2. The underlying mechanisms and techniques used in LINC-ROR association studies in cancer patients. LINC-ROR polymorphism seems to have a great effect on different pathways.

Table 1
The importance of LINC-ROR polymorphisms in human disorders.

Disease type	Samples	SNP	Pathway	Association Targets (Direct or Indirect)	Study Subjects	Method	Patients' outcome	Function	Ref.
Oral squamous cell carcinoma	oral squamous cell	rs4801078	–	–	178 cases and 191 controls	PCR-RFLP	Association with metastatic ability of tumors	–	[40]
Colon Cancer	genomic DNA of cancer samples	rs1942347 (A/T)	RAS/ MAPK pathway	BRAF	180 colon cancer samples	Real-Time PCR	rs1942347 A allele is associated with higher rate of death. T allele of this polymorphism confers protection in BRAF mutant cases.	Negative regulator of p53 translation	[44]
Breast Cancer	venous blood	rs4801078 (C/T)	MAPK/ ERK	–	150 participants	PCR-RFLP (genotyping), Real-Time PCR	rs4801078 TT genotype is associated with higher risk of breast cancer.	SNPs in LINC-ROR might affect expression of LINC-ROR transcript.	[31]
SLE	Whole blood	rs1942347 (A/T)	HOTAIR/ MALAT1	miR-17–5p/ FUT2/ β-catenin	163 SLE patients and 163 controls	Real-Time PCR	rs1942347 A/A genotype is associated with having a positive family history of SLE.	Regulation of chromatin structure	[22]

genotype of rs4801078 and higher risk of breast cancer. Moreover, this polymorphism has been found to affect expression of LINC-ROR (Fig. 2). Besides, authors have reported that the interaction of rs4801078, number of pregnancies and menopausal status can enhance risk of breast cancer [31]. Table 1 shows the results of association studies.

Table 2
Altered expression of LINC-ROR in cancer.

Disease	Cell line	pathway	Targets (Direct or Indirect)	Study Subjects	Method	Expression pattern	Patients' outcome	Function	Ref.
Ovarian cancer	SKOV3 and A2780	–	–	39 high-grade ovarian serous cancer tissues, 20 normal ovarian samples	Real-Time PCR	Up-regulated	Associated with FIGO stage and lymph node metastasis	Promotes EMT	[30]
Thyroid cancer	TPC	–	miR-145	129 benign and malignant tissues	Real-Time PCR	Up-regulated	–	Acts as a sponge for miR-145	[53]
Osteosarcoma	Saos-2, U2OS, MG-63, 143B, hFOB 1.19	–	miR-206	48 patients	Real-Time PCR	Up-regulated	Associated with advanced TNM stage and lymph node metastasis and poor overall survival	Acts as a sponge for miR-206	[9]
Glioblastoma	–	G2/M phase of the cell cycle	genes involved in the regulation of mitosis	12 GBM patients (Glioblastoma and normal adjacent brain tissue)	Real-Time PCR	Up-regulated	Increases cancer stem cell population in GBM	Undefined	[23]
	–	Apoptosis	p53	332 FFPE brain cancer tissue and normal adjacent brain tissue	Real-Time PCR, Methylation-specific PCR	Up-regulated	Poor survival	Suppresses p53 through binding to hnRNP	[48]
Non-small-cell lung Cancer	–			229 patients diagnosed with NSCLC (NSCLC tissue and normal adjacent tissue)	Real-Time PCR	Up-regulated	Prognostic factor and a therapeutic target	Undefined	[38]
Lung adenocarcinoma	human LAD cell lines SPC-A1 and H1299	miR-145/ FSCN1 signaling	miR-145, miR-205 and miR-133	-	Real-Time PCR, Immunofluorescence, Western bolt	Up-regulated	Enhances the capacity of proliferation and chemotherapy resistance	Induces cell percentage reduction in G2/M phase and increases S phase percentage	[37]
Esophageal squamous cell carcinoma	–	–	–	30 tumor samples and 30 normal tissues	Real-Time PCR	Up-regulated	AB844432 (variant 4) has a moderate sensitivity and specificity in discriminating between tumor and non-tumor ESCC samples	Might have a potential role in tumor initiation and/or progression of esophagus cancer.	[43]
Oral cancer	–	Apoptosis	miR-145, Oct4, Nanog, Sox4, Klf4, and c-Myc and p53	60 oral SCC tissue samples and adjacent normal tissues	Real-Time PCR	Up-regulated	LINC-ROR ceRNA network is associated with undifferentiated oral cancer.	Post-transcriptional control of target genes c-Myc, Klf4, Oct4, and Sox2	[2]
Endometrial Cancer	–	tumor suppressor or oncogenic pathways	Oct4, Sox2 and Nanog miR-145	17 endometrial carcinoma (EC) samples and adjacent normal tissues	Real-Time PCR, Flow cytometric analyses, Fluorescence in situ hybridization	Up-regulated	Suppression of LINC-ROR decreases the chance of CSC being the origin of cancer.	Sponges miR-145	[58]
Colonic cancer stem cells	–		Oct4, Sox2 and Nanog	52 pairs of colorectal cancer tissues and adjacent tissues	qPCR Western blot	Up-regulated	Regulates chemosensitivity	Acts as a key ceRNA to prevent function of important transcription factors	[49]
Colorectal Cancer	–	miR-6833–3p/ SMC4	miR-6833–3p SMC4	24 cancer tissues and paired normal tissues	Real-Time PCR / RNA Immunoprecipitation	Up-regulated	Poor overall survival	Sponges miR-6833–3p	[25]
	–		miR-145, OCT4 and SOX2	63 cancer tissues and paired normal tissues	Real-Time PCR	Up-regulated	Higher LINC-ROR expression in patients without distant metastases and lower AJCC stages	Acts as a repressor of p53 a sponge for the tumor suppressor miR-145	[46]

(*continued on next page*)

Table 2 (*continued*)

Disease	Cell line	pathway	Targets (Direct or Indirect)	Study Subjects	Method	Expression pattern	Patients' outcome	Function	Ref.
Renal cell carcinoma	–		SOX2, and NANOG	60 RCC samples and their paired adjacent non-cancer samples	Real-Time PCR	Up-regulated	Poor survival	LINC-ROR blocks recruitment of a histone-modifying enzyme	[8]
Breast cancer	–		vimentin and N-cadherin	142 patients BC tissue samples and normal adjacent tissue sample	Real-Time PCR, MTS assay, Western blot	Up-regulated	Invasion and resistance to chemotherapy	Decreases sensibility of 5-FU and paclitaxel with decreased E-cadherin expression	[4]
	MDA-MB-231, MCF10A	autophagy	LC3-II, Beclin 1, NOTCH1, p53, miR-34a	-	Real-Time PCR /Chromatin immunoprecipitation assay	Up-regulated	-	LINC-ROR knock-down promotes expression of autophagy-related proteins (LC3-II, Beclin 1, NOTCH1).	[5]
	-	PI3K-Akt	MTOR/ miR-194–3p and MECP2	20 tumor tissue samples and 16 para carcinoma tissues	Real-Time PCR / Next generation sequencing/ Western blot	Up-regulated	LINC-ROR promotes the proliferation, migration, and invasion of breast cancer cells	LINC-ROR decreases the sensitivity of breast cancer cells to rapamycin and downregulates the expression of mTOR and LINC-ROR may affect the biological process of breast cancer cells through a ceRNA mechanism serves as a ceRNA sponge for miR-194–3p and regulates MECP2 /	[57]
	-	TGF-β	Smad2 and α-SMA	94 breast cancer patients, Both tumor and the adjacent normal tissues	Real-Time PCR	Up-regulated	Overexpression of LINC-ROR is linked to breast cancer	Affects TGF-β signaling to induce expression of factors contributing to the progression of breast cancer	[19]
Gastric adenocarcinoma	-		miR-212–3p/ FGF7	72 patients	Real-Time PCR /Western Blotting	Up-regulated		LINC-ROR knock-down attenuates the malignant phenotypes.	[33]
	-		miR-138 and miR-145	105 GC tissues and paired adjacent nontumorous tissues	Real-Time PCR	Down-regulated	Potential as a Diagnostic and Prognostic Biomarker in GC	Acts as a miRNA sponge	[52]
Gastric Cancer (with Helicobacter pylori Infection)	-	EMT	SALL4	86 GC patients (tumor and adjacent non-cancerous tissues)	Real-Time PCR	Down-regulated	Concomitant expression of LINC-ROR and stemness transcriptional factor SALL4 with clinicopathological features	-	[1]
Pancreatic Cancer	pancreatic cancer cell lines, PANC-1 and SW1990	Wnt/beta-catenin	MS2bp miR-93–5p, miR-145–3p, miR-320a, and miR-320b	-	Real-Time PCR, RNA-binding protein immunoprecipitation	Up-regulated	knockdown of LINC-ROR dramatically reduced the invasion of PANC-1 and SW1990 cells	Suppress miRNA expression through Ago2-related RNA-induced silencing complexes (RISCs) and regulates pancreatic cancer cell migration, invasion and EMT	[10]
Nasopharyngeal carcinoma	NPC cell lines (CNE2, CNE1, 5–8 F and 6–18B)	Apoptosis	siRNA-1/ p53	-	Real-Time PCR	Up-regulated		Cell migration was inhibited in LINC-ROR-silenced cells.	[24]
Head and neck squamous cell carcinoma	-	AKT/PI3K	FOXM1/ LMO4	34 patients with HNSCC (HNSCC biopsy specimens and adjacent normal tissues)	In Situ Hybridization (ISH)/ Chromatin Immunoprecipitation (ChIP) Assay/ Real-Time PCR / Western blot	Up-regulated	LINC-ROR is over-expressed in HNSCC and enhances cell proliferation and invasion.	FOXM1 upregulates expression of LINC-ROR. LINC-ROR induces cell proliferation and through regulation of LMO4 and activation of the AKT/ PI3K signaling.	[32]
Renal cancer	-	-	-	60 paired cancerous and non-cancerous tissues	Real-Time PCR	Up-regulated	Associated with tumor recurrence and poor differentiation of tumors	-	[8]
Hepatocellular carcinoma	HepG2 cells of BALB/c nude mice		DEPDC1	-	Real-Time PCR / RNA pull-down assay / RNA immunoprecipitation	Up-regulated	LINC-ROR increase the risk of hepatocellular carcinoma by increasing DEPDC1 expression	LINC-ROR directly binds miR-130a-3p & acts as a ceRNA.	[47]

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Table 2 (*continued*)

Disease	Cell line	pathway	Targets (Direct or Indirect)	Study Subjects	Method	Expression pattern	Patients' outcome	Function	Ref.
	HepG2 and PLC-PRF5 cells	TGFβ apoptosis	p53, TGFβ	-	Real-Time PCR	Up-regulated	Release of LINC-ROR may have specific roles in malignant cells	mediator of cell-to-cell communication through the transfer of extracellular vesicles	[45]
	HepG2, SMMC-7721	DAN repair	RAD18 RAD6 miR-145 ZEB2	-	Real-Time PCR, Western Blot	Up-regulated	Possible role in radioresistance	-	[3]
	L-02, HepG2, SMMC-7721, Huh-7, MHCC-97 H, Hep3B, and HCCLM3		FOXM1 miR-876–5p	-	Real-Time PCR / Western Blot	Up-regulated	intrinsic resistance to sorafenib	FOXM1 conferred sorafenib tolerance to through affecting LINC-ROR. LINC-ROR sponges miR-876–5p to regulate FOXM1 level.	[56]
	HepG2, Huh7, SMMC-7721and Bel-7402 and LO2 cells			-	Real-Time PCR /Western blot	Up-regulated	-	-	[17]
	HCC cell lines (Hep3B, Huh7, SNU387 and SNU449)		TWIST1	-	Real-Time PCR / Immunofluorescence/ Western blotting	Down-regulated	negatively associated with DOX sensitivity	LINC-ROR knockdown inhibits the EMT signaling.	[54]
Pediatric Astrocytoma	-	MAPK, Wnt, FAK, and PI3K-Akt	SOX2-OT miR-145	26 astrocytic tumors and three control tissues	Immunohistochemistry Real-Time PCR	Up-regulated	associated with cellular proliferation, evasion of apoptosis, and sustained angiogenesis	sponges miR-145	[41]
Endometrial cancer	endometrial cancer stem cells	-	miR-145	-	Fluorescence in situ hybridization		-	Acts as a sponge for miR-145	[58]

3. Expression studies

3.1. Altered expression of LINC-ROR in cancer

LINC-ROR and two of its splicing variants, namely variants 2 and 4 have been found to be over-expressed esophageal squamous cell carcinoma samples compared to their corresponding non-tumor tissues. Notably, variant 4 has been particularly up-regulated in high-grade tumor samples compared to low-grade tumors. Besides, variant 4 of LINC-ROR has been shown to have the potential to distinguish between tumors and non-tumor samples [43].

Expression studies in glioblastoma neurospheres acquired from different patients have shown high levels of this transcript in these cells parallel with up-regulation of EGFR expression. LINC-ROR silencing has led to suppression of cell proliferation, enhancement of sensitivity to DNA damage, and downregulation of the levels of cancer stem cell markers. Oppositely, up-regulation of LINC-ROR has promoted cell growth and increased the proportion of cancer stem cells. Based on the results of RNA sequencing, LINC-ROR can affect expression of genes contributing to the regulation of mitosis. In accordance with this observation, LINC-ROR has been shown to be prominently over-expressed in cells residing in G2/M phase of the cell cycle [23]. Another study has determined over-expression of LINC-ROR in about 90% of glioblastoma patients. Over-expression of LINC-ROR has been associated with poor survival of patients and their younger age of disease onset. Based on the multivariate analyses, glioblastoma patients can be clustered into two discrete groups based on expression of LINC-ROR, p53 staining level and overall survival [48].

LINC-ROR has also been reported to be over-expressed in non-small cell lung cancer specimens compared with matched nearby normal lung tissues. Moreover, higher expression levels of LINC-ROR have been correlated with advanced TNM stage and presence of distant as well as lymph node metastasis. Additionally, patients having high levels of LINC-ROR have exhibited shorter survival [38].

LINC-ROR has also been shown to be up-regulated undifferentiated oral tumors in association with recurrent cancer and poor response to therapy. Moreover, in oral squamous cell carcinoma, overexpression of LINC-ROR has been associated with under-expression of miR-145–5p, and up-regulation of c-Myc, Klf4, Oct4, and Sox2, implying the presence of LINC-ROR-mediated ceRNA network [2]. Table 2 and Fig. 3 show altered expression of LINC-ROR in cancers.

4. LINC-ROR and drug resistance in cancers

Abnormal expression of LINC-ROR has been associated with induction of resistance to anti-cancer therapies in different cancers. This is mainly mediated through induction of epithelial-mesenchymal transition (EMT). For instance, this lncRNA can facilitate resistance of hepatocellular carcinoma cells to doxorubicin through inducing TWIST1-mediated EMT [8]. Moreover, it can regulate chemoresistance in docetaxel-resistant lung adenocarcinoma cells through affecting EMT and miR-145/FSCN1 axis [36]. LINC-ROR is also involved in the resistance of HepG2 cells to arsenic trioxide through inhibition of p53 expression [27]. Moreover, up-regulation of LINC-ROR in colorectal cancer samples has been associated with radio-resistance through targeting the p53/miR-145 pathway [50].

5. Altered expression of LINC-ROR in autoimmune disorders

In an expression assay of lncRNAs in autoimmune neuropathies, LINC-ROR has been found to up-regulated in total chronic inflammatory demyelinating polyradiculoneuropathy and total Guillain-Barré syndrome cases compared with controls. However, sex-based comparisons have shown up-regulated of LINC-ROR only in male CIDP cases. AUC value of LINC-ROR has been reported to be 0.72 [15].

LINC-ROR has also been found to be under-expressed in female

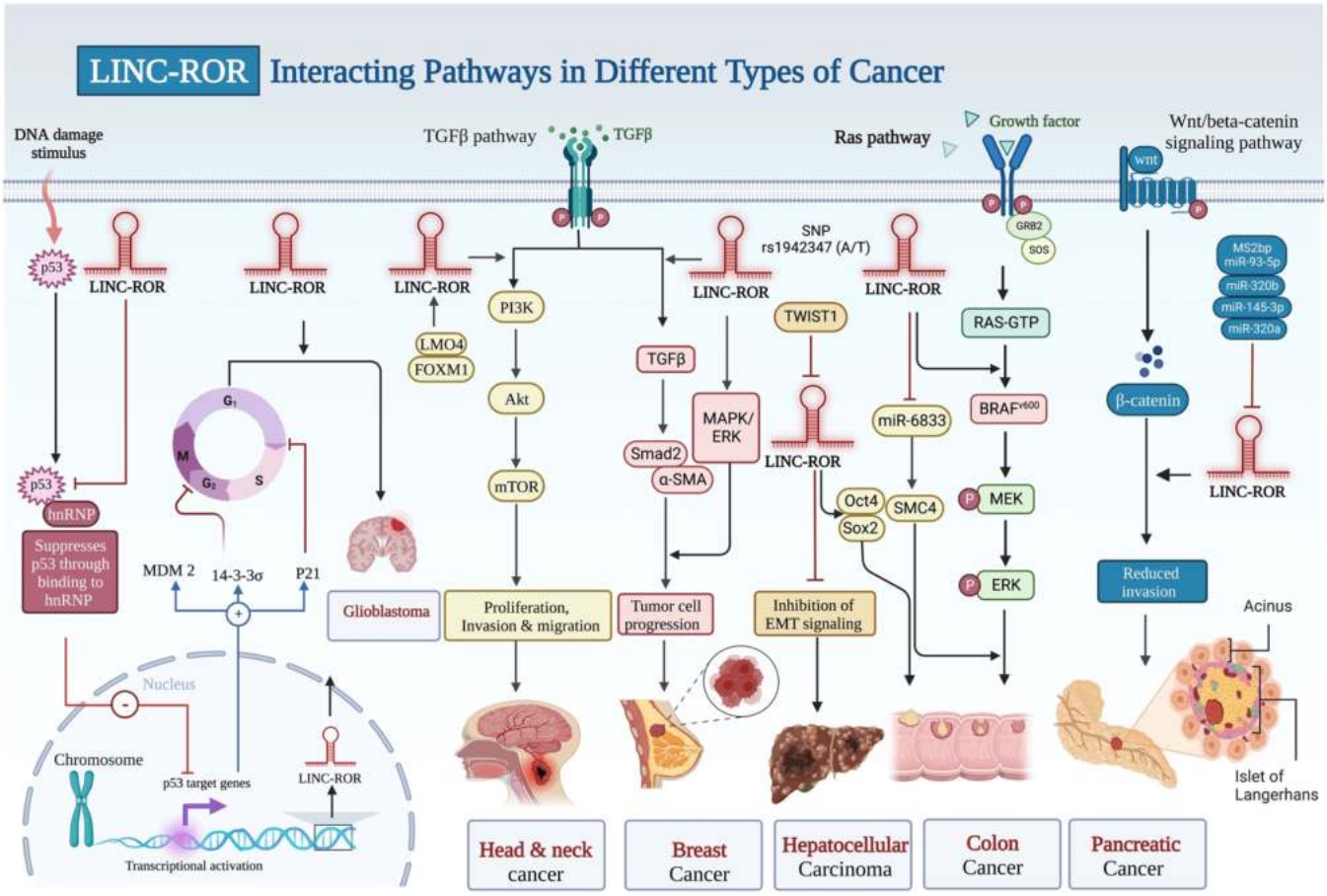

Fig. 3. Schematic representation of LINC-ROR interacting pathways. A representative of the LINC-ROR family of lncRNAs, which plays key regulatory functions in cancer cell development, invasion, and migration through interactions with targeted genes and miRNA sponging.

Table 3
Altered expression of LINC-ROR in autoimmune disorders.

Disease type	pathway	Association Targets (Direct or Indirect)	Study Subjects	Method	Expression pattern	Function	Ref.
Guillain-Barré syndrome	NF-κB pathway	miR-128–3p/ RAC1	Blood samples from 25 GBS patients, and 58 healthy controls	Real-Time PCR	Up-regulated in total patients compared with total controls	Inducing imbalance between regulatory T cells and Th17 cells	[15]
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	NF-κB pathway	miR-128–3p/ RAC1	Blood samples from 32 CIDP patients with typical type and 58 healthy controls	Real-Time PCR	Not significant (females) / Up-regulated (males)	Possible interactions between LINC-ROR and sex-related parameters	[15]
Multiple Sclerosis	TGF-β		40 RRMS patients and 40 normal individuals peripheral blood samples	Real-Time PCR	Down-regulated (females)	Downregulation of LINC-ROR might result in inhibition of TGF-β signaling and stimulation of immune responses.	[42]

patients with multiple sclerosis compared with female healthy subjects. However, no significant difference has been detected between male patients and corresponding controls [42]. Table 3 shows altered expression of LINC-ROR in autoimmune disorders.

6. Altered expression of LINC-ROR in neurodegenerative/ neurodevelopmental disorders

Expression of LINC-ROR has been reported to be elevated in total assessed Parkinson's disease cases compared with total controls and in both male and female patients compared with the corresponding controls. ROC curve analysis has revealed that LINC-ROR has diagnostic power of 0.73, which has been higher than almost all assessed lncRNAs, except for MEG3. However, expression of LINC-ROR has not been associated with any of clinical data of patients or measures of disease activity [18]. LINC-ROR has also been demonstrated to be up-regulated in total schizophrenic patients compared with total controls. Yet, when evaluating its expression in sex-based subgroups, the difference has been significant only among females. In addition, expressions of this lncRNA has been correlated with age of patients with schizophrenia [6]. Table 4 shows altered expression of LINC-ROR in neurodegenerative/ neurodevelopmental disorders.

Table 4
Altered expression of LINC-ROR in neurodegenerative/ neurodevelopmental disorders.

Disease type	pathway	Association Targets (Direct or Indirect)	Study Subjects	Method	Expression pattern	Patients' outcome	Function	Ref.
Parkinson's disease	apoptosis	miR-204–5p/ MDM2 axis	peripheral blood samples from 50 cases of PD and 58 healthy individuals	Real-Time PCR	Up-regulated	Higher expressions of LINC-ROR in total patients compared with total controls	Regulates apoptosis through influencing p53 ubiquitination via regulation of miR-204–5p/MDM2 axis	[18]
Schizophrenia		miR-138 and miR-145 and Aquaporin 4	peripheral blood samples from 60 patients with schizophrenia and 60 healthy subjects	Real-Time PCR	Up-regulated (only females) and NS (in males)	Contributes to the pathogenesis of schizophrenia through modulation of miR-145 and consequent alteration in Aquaporin 4	Acts as a sponge for miR-138 and miR-145	[6]
Epilepsy		HOXA-AS2 and SPRY4-IT1	peripheral blood samples from 40 epileptic patients and 40 normal individuals	Real-Time PCR	NS		–	[16]

NS: not significant.

Table 5
Altered expression of LINC-ROR in other disorders.

Disease type	Tissue/Cell line	Pathway	Association Targets (Direct or Indirect)	Method	Expression pattern	Function	Ref.
Arsenite toxicity	Human bronchial epithelial (HBE) cell line and Human lung adenocarcinoma A549 cell line	Oxidative stress	ZEB1, ZEB2/ HECTD4, CDK12, and HUWE1	Real-Time PCR, Comet Assay, Western Blot	Up-regulated	LINC-ROR over-expression might be involved in the occurrence of cancers through interaction with pathways regarding RNA metabolism, stress response, and DNA repair.	[28]
	Human liver cancer HepG2 cells	Apoptosis	CASP3 P53	Real-Time PCR, MTT assay, Western blot	Up-regulated	LINC-ROR silencing enhances ATO-induced apoptosis by increasing P53 levels.	[26]
Toxoplasma gondii	Müller cells (MIO-M1)	Apoptosis Cell cycle	c-Myc p53	Real-Time PCR, PCR	Up-regulated	Increases c-Myc expression and interacts with p53 to generate an autoregulatory feedback loop	[39]

7. Altered expression of LINC-ROR in other disorder

Arsenite has been shown to increase expression of LINC-ROR in human bronchial epithelial cells in a dose dependent manner. Up-regulation of this lncRNA has been accompanied by elevation of oxidative stress as evident by high levels of intracellular reactive oxygen species and DNA damage, in addition to reduction of antioxidant glutathione and superoxide dismutase levels. Additional studies have shown that oxidative stress is an important element for induction of expression of LINC-ROR in arsenite-exposed cells. Besides, bioinformatics assays has demonstrated that arsenite-induced oxidative stress can affect expression of LINC-ROR expression though modulation of 3 genes [28]. LINC-ROR has also been among dysregulated lncRNAs in Müller cells infected with some virulent strains of *T. gondii* strains [39]. Table 5 shows altered expression of LINC-ROR in other disorders.

7.1. Conclusions and future perspectives

LINC-ROR is a long intergenic transcript with essential roles in the pathogenesis of human disorders, particularly cancer. This lncRNA has a number genetic polymorphisms that can affect its activity. However, few studies have assessed the importance of these polymorphisms in human disorders. Moreover, LINC-ROR has several splice variants, some of them being over-expressed in certain disorders.

The majority of conducted studies have assessed expression profile of LINC-ROR in clinical samples without functional verification in cell lines or animal models of cancer. This is particularly true in non-malignant conditions. Thus, the exact function of this lncRNAs remains to be explored in future studies. Besides, the physiological role of LINC-ROR has not been assessed completely. Clues from few functional studies have revealed the importance of this lncRNA in mitotic division and stemness. In non-malignant conditions, the role of LINC-ROR has been less studied. Notably, expression assays in different autoimmune disorders have identified dissimilar pattern of expression of this lncRNA. These observations add to the complexity of the role of this lncRNA in this context. An important finding in these disorders is the sex-biased expression of LINC-ROR which possibly indicates different sex-based roles of LINC-ROR in autoimmune disorders. The importance of hormone-related effects should be assessed in this context.

Besides, the observed dysregulated expression of LINC-ROR in the peripheral blood of patients with autoimmune and neurological disorders such as Parkinson's disease and schizophrenia shows the possibility of application of this lncRNA as a peripheral marker for follow-up of these patients.

Functionally, LINC-ROR can act as a molecular sponge for some miRNAs, including miR-212–3p, miR-138, miR-145, miR-93–5p, miR-320a, miR-320b and miR-876–5p. This function is the most appreciated route of function of LINC-ROR in human disorders.

LINC-ROR has the potential to be used as a diagnostic and prognostic marker in diverse cancers. Generally, over-expression of LINC-ROR has been associated malignant behavior of cancer cells, thus indicating poor clinical outcome.

Taken together, LINC-ROR is a possible oncogenic lncRNA that affects activity of some cancer-related signaling pathways and sponges tumor suppressor miRNAs. It can also affect response of cancer cells to anti-cancer modalities. Moreover, LINC-ROR can participate in the pathogenesis of autoimmune and neurodegenerative disorders. Thus, it is a possible target for design of novel therapeutics in diverse disorders.

However, it is necessary to find the exact physiological role of LINC-ROR to avoid side effects of these types of therapies in normal tissues.

Ethics approval and consent to Participant

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CRediT authorship contribution statement

SGF wrote the manuscript and revised it. MT supervised and designed the study. AK, AP and BMH collected the data and designed the figures and tables. All authors read and approved the submitted version.

Conflict of interest

The authors declare they have no conflict of interest.

Data Availability

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

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Consent of publication

Not applicable.

References

[1] R. Alsadat Mahmoudian, M. Lotfi Gharaie, R. Abbaszadegan, M.M. Forghanifard, M.R. Abbaszadegan, Interaction between LINC-ROR and stemness state in gastric cancer cells with helicobacter pylori infection, Iran. Biomed. J. 25 (2021) 157–168.
[2] G. Arunkumar, A.K. Deva Magendhra Rao, M. Manikandan, K. Arun, V. Vinothkumar, S. Revathidevi, K.S. Rajkumar, R. Rajaraman, A.K. Munirajan, Expression profiling of long non-coding RNA identifies linc-RoR as a prognostic biomarker in oral cancer, Tumour Biol. 39 (2017), 1010428317698366.
[3] Y. Chen, Z. Shen, Y. Zhi, H. Zhou, K. Zhang, T. Wang, B. Feng, Y. Chen, H. Song, R. Wang, X. Chu, Long non-coding RNA ROR promotes radioresistance in hepatocelluar carcinoma cells by acting as a ceRNA for microRNA-145 to regulate RAD18 expression, Arch. Biochem. Biophys. 645 (2018) 117–125.
[4] Y.M. Chen, Y. Liu, H.Y. Wei, K.Z. Lv, P. Fu, Linc-ROR induces epithelial-mesenchymal transition and contributes to drug resistance and invasion of breast cancer cells, Tumour Biol. 37 (2016) 10861–10870.
[5] Y.M. Chen, Y. Liu, H.Y. Wei, K.Z. Lv, P.F. Fu, Large intergenic non-coding RNA-ROR reverses gemcitabine-induced autophagy and apoptosis in breast cancer cells, Oncotarget 7 (2016) 59604–59617.
[6] H. Fallah, I. Azari, S.M. Neishabouri, V.K. Oskooei, M. Taheri, S. Ghafouri-Fard, Sex-specific up-regulation of lncRNAs in peripheral blood of patients with schizophrenia, Sci. Rep. 9 (2019) 12737.
[7] Y. Fang, M.J. Fullwood, Roles, functions, and mechanisms of long non-coding RNAs in cancer, Genom. Proteom. Bioinforma. 14 (2016) 42–54.
[8] M.S. Fawzy, E.A. Toraih, A. El-Wazir, M.M. Hosny, D.I. Badran, A. El, Kelish, Long intergenic non-coding RNA, regulator of reprogramming (LINC-ROR) over-expression predicts poor prognosis in renal cell carcinoma, Arch. Med. Sci. 17 (2021) 1016–1027.
[9] D. Fei, G. Sui, Y. Lu, L. Tan, Z. Dongxu, K. Zhang, The long non-coding RNA-ROR promotes osteosarcoma progression by targeting miR-206, J. Cell. Mol. Med. 23 (2019) 1865–1872.
[10] Z. Fu, G. Li, Z. Li, Y. Wang, Y. Zhao, S. Zheng, H. Ye, Y. Luo, X. Zhao, L. Wei, Y. Liu, Q. Lin, Q. Zhou, R. Chen, Endogenous miRNA Sponge LincRNA-ROR promotes proliferation, invasion and stem cell-like phenotype of pancreatic cancer cells, Cell Death Discov. 3 (2017) 17004.
[11] S. Ghafouri-Fard, S. Dashti, B.M. Hussen, M. Farsi, M. Taheri, BCYRN1: an oncogenic lncRNA in diverse cancers, Pathol. - Res. Pract. 220 (2021), 153385.
[12] S. Ghafouri-Fard, M. Esmaeili, M. Taheri, H19 lncRNA: roles in tumorigenesis, Biomed. Pharmacother. = Biomed. Pharmacother. 123 (2020), 109774.
[13] S. Ghafouri-Fard, M. Taheri, Nuclear enriched abundant transcript 1 (NEAT1): a long non-coding RNA with diverse functions in tumorigenesis, Biomed. Pharmacother. = Biomed. Pharmacother. 111 (2019) 51–59.
[14] S. Ghafouri-Fard, K.H. Tamizkar, B.M. Hussen, M. Taheri, An update on the role of long non-coding RNAs in the pathogenesis of breast cancer, Pathol. - Res. Pract. 219 (2021), 153373.
[15] M. Gholipour, M. Taheri, J. Mehvari Habibabadi, N. Nazer, A. Sayad, S. Ghafouri-Fard, Dysregulation of lncRNAs in autoimmune neuropathies, Sci. Rep. 11 (2021) 16061.
[16] F. Hashemian, S. Ghafouri-Fard, S. Arsang-Jang, S. Mirzajani, H. Fallah, J. Mehvari Habibabadi, A. Sayad, M. Taheri, Epilepsy is associated with dysregulation of long non-coding RNAs in tHe Peripheral Blood, Front. Mol. Biosci. 6 (2019) 113.
[17] X. He, J. Yu, L. Xiong, Y. Liu, L. Fan, Y. Li, B. Chen, J. Chen, X. Xu, Exosomes derived from liver cancer cells reprogram biological behaviors of LO2 cells by transferring Linc-ROR, Gene 719 (2019), 144044.
[18] K. Honarmand Tamizkar, P. Gorji, M. Gholipour, B.M. Hussen, M. Mazdeh, S. Eslami, M. Taheri, S. Ghafouri-Fard, Parkinson's disease is associated with dysregulation of circulatory levels of lncRNAs, Front. Immunol. 12 (2021), 763323.
[19] L. Hou, J. Tu, F. Cheng, H. Yang, F. Yu, M. Wang, J. Liu, J. Fan, G. Zhou, Long noncoding RNA ROR promotes breast cancer by regulating the TGF-β pathway, Cancer Cell Int. 18 (2018) 142.
[20] B.M. Hussen, H.J. Hidayat, S. Ghafouri-Fard, Identification of expression of CCND1-related lncRNAs in breast cancer, Pathol. - Res. Pract. 236 (2022), 154009.
[21] B.M. Hussen, R.K. Kheder, S.T. Abdullah, H.J. Hidayat, H.S. Rahman, A. Salihi, M. Taheri, S. Ghafouri-Fard, Functional interplay between long non-coding RNAs and Breast CSCs, Cancer Cell Int. 22 (2022) 233.
[22] N.M. Ismail, E.A. Toraih, A.I. Almars, E. Al Ageeli, M.S. Fawzy, S.A. Maher, Genotype triad for HOTAIR rs10783618, LINC-ROR rs1942347, and MALAT1 rs3200401 as molecular markers in systemic lupus erythematous, Diagnostics 12 (2022).
[23] T.F. Kovalenko, B. Yadav, K.S. Anufrieva, Y.P. Rubtsov, T.S. Zatsepin, E. Y. Shcherbinina, E.M. Solyus, D.B. Staroverov, T.D. Larionova, Y.A. Latyshev, M. I. Shakhparonov, A.K. Pandey, M.S. Pavlyukov, Functions of long non-coding RNA ROR in patient-derived glioblastoma cells, Biochimie 200 (2022) 131–139.
[24] L. Li, M. Gu, B. You, S. Shi, Y. Shan, L. Bao, Y. You, Long non-coding RNA ROR promotes proliferation, migration and chemoresistance of nasopharyngeal carcinoma, Cancer Sci. 107 (2016) 1215–1222.
[25] X. Li, W. Chen, J. Jia, Z. You, C. Hu, Y. Zhuang, Z. Lin, Y. Liu, C. Yang, R. Xu, The long non-coding RNA-RoR promotes the tumorigenesis of human colorectal cancer by targeting miR-6833-3p through SMC4, Onco Targets Ther. 13 (2020) 2573–2581.
[26] X. Li, D. Sun, T. Zhao, Z. Zhang, Long non-coding RNA ROR confers arsenic trioxide resistance to HepG2 cells by inhibiting p53 expression, Eur. J. Pharmacol. 872 (2020), 172982.
[27] X. Li, D. Sun, T. Zhao, Z. Zhang, Long non-coding RNA ROR confers arsenic trioxide resistance to HepG2 cells by inhibiting p53 expression, Eur. J. Pharmacol. 872 (2020), 172982.
[28] X. Li, C. Zuo, D. Sun, T. Zhao, Z. Zhang, Arsenite increases Linc-ROR in human bronchial epithelial cells that can be inhibited by antioxidant factors, Biol. Trace Elem. Res. 198 (2020) 131–141.
[29] S. Loewer, M.N. Cabili, M. Guttman, Y.H. Loh, K. Thomas, I.H. Park, M. Garber, M. Curran, T. Onder, S. Agarwal, P.D. Manos, S. Datta, E.S. Lander, T.M. Schlaeger, G.Q. Daley, J.L. Rinn, Large intergenic non-coding RNA-RoR modulates reprogramming of human induced pluripotent stem cells, Nat. Genet. 42 (2010) 1113–1117.
[30] Y. Lou, H. Jiang, Z. Cui, L. Wang, X. Wang, T. Tian, Linc-ROR induces epithelial-to-mesenchymal transition in ovarian cancer by increasing Wnt/β-catenin signaling, Oncotarget 8 (2017) 69983–69994.
[31] C. Luo, J. Cao, R. Peng, Q. Guo, H. Ye, P. Wang, K. Wang, C. Song, Functional variants in Linc-ROR are associated with mRNA expression of Linc-ROR and breast cancer susceptibility, Sci. Rep. 8 (2018) 4680.
[32] X. Ma, H. Zhang, Q. Li, E. Schiferle, Y. Qin, S. Xiao, T. Li, FOXM1 promotes head and neck squamous cell carcinoma via activation of the Linc-ROR/LMO4/AKT/PI3K axis, Front. Oncol. 11 (2021), 658712.
[33] Y. Mi, Y. Li, Z. He, D. Chen, Q. Hong, J. You, Upregulation of Linc-ROR promotes the proliferation, migration, and invasion of gastric cancer cells through miR-212-3p/FGF7 axis, Cancer Manag. Res. 13 (2021) 899–912.
[34] A. Mohammadzadeh, N. Dastmalchi, B.M. Hussen, M.A. Shadbad, R. Safaralizadeh, An updated review on the therapeutic, diagnostic, and prognostic value of long non-coding RNAs in gastric cancer, Curr. Med Chem. 29 (2022) 3471–3482.
[35] E. Nikpayam, B. Tasharrofi, S. Sarrafzadeh, S. Ghafouri-Fard, The role of long non-coding RNAs in ovarian cancer, Iran. Biomed. J. 21 (2017) 3–15.
[36] Y. Pan, J. Chen, L. Tao, K. Zhang, R. Wang, X. Chu, L. Chen, Long noncoding RNA ROR regulates chemoresistance in docetaxel-resistant lung adenocarcinoma cells via epithelial mesenchymal transition pathway, Oncotarget 8 (2017) 33144.
[37] Y. Pan, J. Chen, L. Tao, K. Zhang, R. Wang, X. Chu, L. Chen, Long noncoding RNA ROR regulates chemoresistance in docetaxel-resistant lung adenocarcinoma cells via epithelial mesenchymal transition pathway, Oncotarget 8 (2017) 33144–33158.
[38] C.H. Qu, Q.Y. Sun, F.M. Zhang, Y.M. Jia, Long non-coding RNA ROR is a novel prognosis factor associated with non-small-cell lung cancer progression, Eur. Rev. Med. Pharmacol. Sci. 21 (2017) 4087–4091.

[39] E. Rochet, B. Appukuttan, Y. Ma, L.M. Ashander, J.R. Smith, Expression of long non-coding RNAs by human retinal müller glial cells infected with clonal and exotic virulent toxoplasma gondii. noncoding, RNA 5 (2019).
[40] M.M. Rose, S. Dhamodharan, G. Bharath, K. Murali, S. Subbiah, L.V.K.S. Bhaskar, A.K. Murugan, A.K. Munirajan, Linc-ROR genetic variants are associated with the advanced disease in oral squamous cell carcinoma, Arch. Oral Biol. 139 (2022), 105428.
[41] R. Ruiz Esparza-Garrido, J.M. Rodríguez-Corona, J.E. López-Aguilar, M. A. Rodríguez-Florido, A.C. Velázquez-Wong, R. Viedma-Rodríguez, F. Salamanca-Gómez, M. Velázquez-Flores, Differentially expressed long non-coding RNAs were predicted to be involved in the control of signaling pathways in pediatric astrocytoma, Mol. Neurobiol. 54 (2017) 6598–6608.
[42] A. Safa, M. Taheri, H. Fallah, T. Salmani, S. Arsang-Jang, S. Ghafouri-Fard, M. D. Omrani, Downregulation of cancer-associated lncRNAs in peripheral blood of multiple sclerosis patients, J. Mol. Neurosci.: MN 70 (2020) 1533–1540.
[43] R. Sahebi, M. Malakootian, B. Balalaee, A. Shahryari, M. Khoshnia, M. R. Abbaszadegan, A. Moradi, S. Javad, Mowla, Linc-ROR and its spliced variants 2 and 4 are significantly up-regulated in esophageal squamous cell carcinoma, Iran. J. Basic Med. Sci. 19 (2016) 1131–1135.
[44] A.A.M. Shaalan, S.H. Mokhtar, H.T. Ahmedah, A.I. Almars, E.A. Toraih, A. T. Ibrahiem, M.S. Fawzy, M.A. Salem, Prognostic value of LINC-ROR (rs1942347) variant in patients with colon cancer harboring BRAF mutation: a propensity score-matched analysis, Biomolecules 12 (2022).
[45] K. Takahashi, I.K. Yan, T. Kogure, H. Haga, T. Patel, Extracellular vesicle-mediated transfer of long non-coding RNA ROR modulates chemosensitivity in human hepatocellular cancer, FEBS Open Biol. 4 (2014) 458–467.
[46] J.A. Thiele, P. Hosek, E. Kralovcova, P. Ostasov, V. Liska, J. Bruha, O. Vycital, J. Rosendorf, A. Opattova, J. Horak, M. Kralickova, P. Vodicka, P. Pitule, lncRNAs in non-malignant tissue have prognostic value in colorectal cancer, Int J. Mol. Sci. 19 (2018).
[47] C. Tian, M. Abudoureyimu, X. Lin, X. Chu, R. Wang, Linc-ROR facilitates progression and angiogenesis of hepatocellular carcinoma by modulating DEPDC1 expression, Cell Death Dis. 12 (2021) 1047.
[48] E.A. Toraih, A. El-Wazir, M.H. Hussein, M.S. Khashana, A. Matter, M.S. Fawzy, S. Hosny, Expression of long intergenic non-coding RNA, regulator of reprogramming, and its prognostic value in patients with glioblastoma, Int J. Biol. Markers 34 (2019) 69–79.
[49] Z.Y. Yan, X.C. Sun, LincRNA-ROR functions as a ceRNA to regulate Oct4, Sox2, and Nanog expression by sponging miR-145 and its effect on biologic characteristics of colonic cancer stem cells, Zhonghua Bing. Li Xue Za Zhi 47 (2018) 284–290.
[50] P. Yang, Y. Yang, W. An, J. Xu, G. Zhang, J. Jie, Q. Zhang, The long noncoding RNA-ROR promotes the resistance of radiotherapy for human colorectal cancer cells by targeting the p53/miR-145 pathway, J. Gastroenterol. Hepatol. 32 (2017) 837–845.
[51] S. Yılmaz Susluer, C. Kayabasi, B. Ozmen Yelken, A. Asik, D. Celik, T. Balci Okcanoglu, S. Serin Senger, C. Biray Avci, S. Kose, C. Gunduz, Analysis of long non-coding RNA (lncRNA) expression in hepatitis B patients, Bosn. J. Basic Med. Sci. 18 (2018) 150–161.
[52] X. Yu, H. Ding, Y. Shi, L. Yang, J. Zhou, Z. Yan, B. Xiao, Downregulated expression of linc-ROR in gastric cancer and its potential diagnostic and prognosis value, Dis. Markers 2020 (2020) 7347298.
[53] R. Zhang, H. Hardin, W. Huang, D. Buehler, R.V. Lloyd, Long non-coding RNA Linc-ROR is upregulated in papillary thyroid carcinoma, Endocr. Pathol. 29 (2018) 1–8.
[54] Y. Zhang, W. Wu, Q. Sun, L. Ye, D. Zhou, W. Wang, linc-ROR facilitates hepatocellular carcinoma resistance to doxorubicin by regulating TWIST1–mediated epithelial-mesenchymal transition, Mol. Med. Rep. 23 (2021).
[55] T. Zhao, L. Wu, X. Li, H. Dai, Z. Zhang, Large intergenic non-coding RNA-ROR as a potential biomarker for the diagnosis and dynamic monitoring of breast cancer, Cancer Biomark.: Sect. A Dis. Markers 20 (2017) 165–173.
[56] Y. Zhi, M. Abudoureyimu, H. Zhou, T. Wang, B. Feng, R. Wang, X. Chu, FOXM1-mediated LINC-ROR regulates the proliferation and sensitivity to sorafenib in hepatocellular carcinoma. Molecular therapy, Nucleic Acids 16 (2019) 576–588.
[57] Q. Zhou, J. Guo, W. Huang, X. Yu, C. Xu, X. Long, Linc-ROR promotes the progression of breast cancer and decreases the sensitivity to rapamycin through miR-194-3p targeting MECP2, Mol. Oncol. 14 (2020) 2231–2250.
[58] X. Zhou, Q. Gao, J. Wang, X. Zhang, K. Liu, Z. Duan, Linc-RNA-RoR acts as a "sponge" against mediation of the differentiation of endometrial cancer stem cells by microRNA-145, Gynecol. Oncol. 133 (2014) 333–339.