Pathology - Research and Practice 247 (2023) 154549

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Review

A review on the role of LINC00472 in malignant and non-malignant disorders

Soudeh Ghafouri-Fard [a], Arian Askari [b], Bashdar Mahmud Hussen [c], Mohammed Fatih Rasul [d], Mohammad Taheri [e,f,*], Seyed Abdulmajid Ayatollahi [g,**]

[a] Department of Medical Genetics, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Department of Clinical Analysis, College of Pharmacy, Hawler Medical University, Erbil, Kurdistan Region, Iraq
[d] Department of Pharmaceutical Basic Science, Faculty of Pharmacy, Tishk International University, Erbil, Kurdistan Region, Iraq
[e] Institute of Human Genetics, Jena University Hospital, Jena, Germany
[f] Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[g] Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
LINC00472
LncRNA
Cancer
Biomarker

ABSTRACT

Long intergenic non-protein coding RNA 472 (LINC00472) has been shown to regulate diverse cellular functions and contribute to the etiology of human disorders. *LINC00472* gene is located on 6q13 and has different alternatively spliced transcripts. Expression pattern and function of LINC00472 have been evaluated in different types of cancers and some other disorders, including atherosclerosis, sepsis-induced acute hepatic injury, atrial fibrillation, neuropathic pain, primary biliary cholangitis and sepsis-induced cardiac dysfunction. This lincRNA can serve as a sponge for miR-24–3p, miR-196b-5p, miR-23a-3p, miR-93–5p, miR-4311, miR-455–3p and a number of other miRNAs. LINC00472 is able to regulate several pathways, including MEK/ERK, NF-kB, PTEN/PI3K/AKT, and STAT3 signaling pathways. This raises some concerning aspects that need to be investigated further and clarified in relation to diseases. Increasing our understanding of LINC00472's crucial roles will open new doors for creating effective therapeutic approaches against cancer and related diseases. The current study aims at providing an overview of functions of LINC00472 in malignant and non-malignant disorders.

1. Introduction

Long non-coding RNAs (lncRNAs) include a group of diverse transcripts with sizes ranging from 200 nt to hundreds of kb. These transcripts do not encode proteins [14]. LncRNAs are present in a large variety of species, from animals [2] to viruses [21]. However, compared with other types of RNAs, lncRNAs are not conserved among different species [18]. LncRNAs have usually low level of expression [6]. Although they look like transcriptional noise due to low level of expression, they exert fundamental roles in the regulation of gene expression. LncRNAs that are transcribed from intergenic regions are classified as intergenic lncRNAs and are possibly different from intronic lncRNAs in terms of regulatory mechanisms for transcriptional activation mechanisms and subcellular locations. In fact, long intergenic non-coding RNAs (lincRNAs) can act as *cis* or *trans* regulatory transcripts. They can also regulate translation, splicing or other post-transcriptional mechanisms in cancers and other diseases [20].

LINC00472 is an example of lincRNAs whose role in the regulation of cellular functions and etiology of human disorders is being elucidated in recent years. *LINC00472* gene is located on 6q13 and has 4 exons. It has at least 15 transcripts with sizes ranging from 300 bp (LINC00472–208) to 9515 bp (LINC00472–209). Expression pattern and function of LINC00472 have been evaluated in different types of cancers and some other disorders, including atherosclerosis, sepsis-induced acute hepatic injury, atrial fibrillation, neuropathic pain, primary biliary cholangitis and sepsis-induced cardiac dysfunction. This lincRNA mainly affects expression of genes that are involved in the cell proliferation and other fundamental cellular functions. The most appreciated route of participation of LINC00472 in these processes is regulation of expression of miRNAs. The current review aims at providing a concise overview of

* Corresponding author at: Institute of Human Genetics, Jena University Hospital, Jena, Germany.
** Corresponding author.
E-mail addresses: mohammad.taheri@uni-jena.de (M. Taheri), majid_ayatollahi@yahoo.com (S.A. Ayatollahi).

https://doi.org/10.1016/j.prp.2023.154549
Received 13 February 2023; Received in revised form 13 May 2023; Accepted 16 May 2023
Available online 18 May 2023

functions of LINC00472 in malignant and non-malignant disorders.

2. Malignant conditions

2.1. Cell line studies

LINC00472 has been found to be down-regulated in lung adenocarcinoma cell lines where it inhibits migration and invasiveness of cells and increases cell stiffness and adhesion. This lincRNA interacts with the transcription factor Y-box binding protein 1 (YBX1). This transcription factor could partially reverse the inhibitory effect of LINC00472 on cell migration and invasion and the stimulatory effect of this lincRNA on stiffness and adhesion of cells. In addition, LINC00472 could regulate the compactness and integrity of F-actin in lung cancer cells probably through YBX1. LINC00472 also inhibits epithelial-mesenchymal transition (EMT) process through modulation of expression of this transcription factor [5]. Expression pattern and function of LINC00472 have been evaluated in different types of cancers (Fig. 1). An independent study in lung cancer has confirmed the role of LINC00472 in modulation of cell viability, proliferation, and motility. This study has also shown differential expression of 3782 genes following LINC00472 overexpression. Differentially expressed genes have been mainly associated with intracellular metabolism. LINC00472 could also induce transcription of a quantity of tumor suppressor genes, namely PPP1R12B, RGS5, RBM5, RBL2, LDLR and PTPRM, while down-regulating SPSB1, PCNA, CD24, CDK5, CDC25A, and EIF4EBP1 [23].

Another study in pancreatic cancer cells has revealed that ZEB1 has an inhibitory effects on expression of LINC00472. Moreover, this lincRNA has been shown to exert its tumor suppressor role through modulation of miR-23a-3p/FOXO3/BID axis [1]. FOXO1 is another member of Forkhead Box Protein family whose expression is modified by LINC00472. In fact, LINC00472 can reduce carcinogenic process in the osteosarcoma through modulation of miR-300/FOXO1 axis [38].

LINC00472 has also been demonstrated to be down-regulated in hepatocellular carcinoma cell lines. Enforced over-expression of this lincRNA has inhibited proliferation, migratory potential and

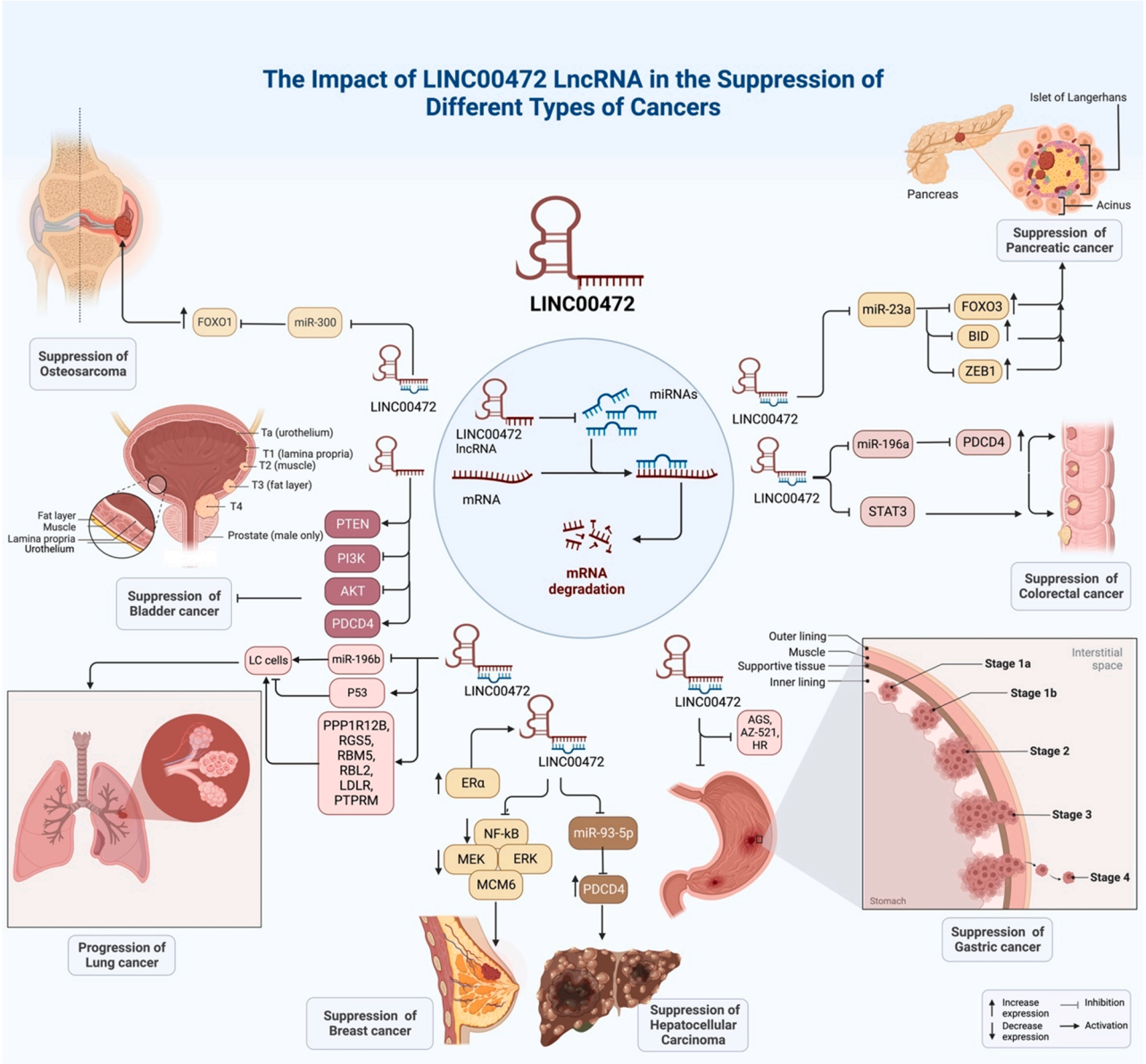

Fig. 1. This figure explains the expression pattern and function of LINC00472 in several distinct types of cancers. This type of lincRNA can serve as a sponge for miR-24–3p, miR-196b-5p, miR-23a-3p, miR-93–5p, miR-455–3p and a number of other miRNAs. LINC00472 can also regulate different pathways such as MEK/ERK, NF-kB, PTEN/PI3K/AKT and STAT3 signaling pathways.

invasiveness and enhanced their apoptosis. miR-93–5p has been acknowledged as a direct target of this lincRNA. In turn, miR-93–5p could directly target PDCD4. Therefore, miR-93–5p/PDCD4 axis mediates the tumor suppressor effect of LINC00472 in hepatocellular carcinoma cells [3].

LINC00472 has also been found to be poorly expressed in MDA-MB-231. Up-regulation of LINC00472 in these cells could inhibit proliferation, invasive properties and migratory aptitude of MDA-MB-231 cells. In contrast, minichromosome maintenance complex component 6 (MCM6) has been found to be up-regulated in these cells as a result of abnormal suppression of methylation. Mechanistically, LINC00472 prompts site-specific DNA methylation and reduces expression of MCM6 through recruitment of DNA methyltransferase into its promoter. In fact, LINC00472 serves as a tumor suppressor through suppression of MCM6 expression [24]. Table 1 reviews the tumor suppressor role of LINC00472 in different cell lines.

2.2. Animal studies

In vivo studies in different models have shown tumor suppressor role of LINC00472 (Table 2). An experiment in animal model of triple negative breast cancer has verified that the impact of LINC00472 overexpression in suppression of tumor growth and lung metastases is mediated through reduction of MCM6 levels [24]. Another study in an animal model of bladder cancer has shown that the tetracyclic quinolizidine substance extracted from *Sophora flavescens* could restrain tumor growth and metastases via increasing expression of LINC00472 [12]. Other studies in animal models of pancreatic cancer, osteosarcoma, lung cancer and oral squamous cell carcinoma have also validated the tumor suppressor role of LINC00472 (Table 2).

2.3. Studies in clinical samples

Virtually all conducted assays in clinical samples have shown down-

Table 1
Expression pattern of LINC00472 in cancer cell lines (Δ: knock-down or deletion, ↑: increase, ↓: decrease).

Tumor type	Targets/Regulators and signaling pathways	Cell line	Function	References
Lung adenocarcinoma	YBX1/EMT pathway	A549, PC-9, BEAS-2B	↑LINC00472: ↓invasion ↓migration	[5]
Non-small cell lung cancer	PPP1R12B, RGS5, RBM5, RBL2, LDLR, PTPRM	-	↑LINC00472: ↓viability ↓migration	[23]
Lung cancer	miR-196b-5p	A549, H1975, 95D, Calu-3, SPC-A, 16HBE	↑LINC00472: ↑apoptosis ↓viability	[16]
	G3BP1, p53	A549, H522, PCA-1, PC9, 95 C, 95D	↑LINC00472: ↓growth of cell lines ↑Apoptosis ↑ferroptosis	[15]
Pancreatic cancer	miR-23a-3p/FOXO3/BID ZEB1	SW1990, BXPC3, Capan-2, PANC-1, hTERT-HPNE	↑LINC00472: ↓proliferation ↑apoptosis	[1]
Osteosarcoma	FOXO1 /miR-300	U2OS and MG63	↑LINC00472: ↓proliferation ↓migration	[38]
Hepatocellular carcinoma	miR-93–5p/PDCD4	HepG2, BEL7404, Hep3B, SMMC-7721, Huh-7, LO2	↑LINC00472: ↓proliferation ↑apoptosis	[3]
Triple-negative breast cancer	MEK/ERK signaling pathway, MCM6	MDA-MB-231, MDA-MB-453, HCC-1937, MDA-MB-468	↑LINC00472: ↓proliferation ↓migration ↓invasion	[24]
Breast cancer	NF-kB, ERα	MCF-7, T47D, ZR-75–1, MB231, Hs578T	↑ERα:↑LINC00472: ↓proliferation ↓migration ↓invasion	[31]
	-	SKBR3 and MCF-7	↑LINC00472 ↓proliferation ↓migration	[25]
Bladder Carcinoma	PTEN/PI3K/AKT, PDCD4	T24,5637	↑LINC00472 ↓proliferation ↓migration ↓invasion	[12]
Gastric cancer	Methylation	AGS, AZ-521, HR, TSGH, SNU1, NCI-N87	↑LINC00472 ↓cell growth	[28]
Colorectal cancer	PDCD4, miR-196a	W480, SW620, HT-29, HCT-116, NCM460	↑LINC00472: ↓proliferation ↑apoptosis	[36]
	STAT3	HCT116, HT29, SW620, and COLO-205, NCM460	↓LINC00472: ↑proliferation	[4]
Kidney Renal Clear Cell Carcinoma	-	786 O	↓LINC00472: ↑proliferation	[34]
Oral squamous cell carcinoma	miR-4311/GNG7 axis	CAL27, FADU, HN12, HSU3, SCC9, SCC25, NHOK	↑LINC00472: ↓progression ↓invasion	[40]
	miR-455–3p/ELF3 axis	SCC25, SCC-9, SCC15, and CAL27, HOK	↑LINC00472: ↓proliferation ↑apoptosis	[40]

Table 2
Role of LINC00472 in progression of cancer in animal models (Δ: knock-down or deletion, MAT: Matrine, ↑: increase, ↓: decrease).

Tumor type	Animal models	Results	References
Pancreatic cancer	Male nude mice	↑LINC00472: ↑apoptosis ↓tumorigenesis	[1]
Osteosarcoma	nude mice	↑LINC00472: ↓tumor growth	[38]
Triple-negative breast cancer	BALB/c nude mice	↑LINC00472: ↓tumor growth ↓lung metastasis	[24]
Breast cancer	BALB/c female nude mice	↑LINC00472: ↓tumor growth	[31]
Bladder Carcinoma	BALB/c nude mice	↑MAT results in ↑LINC00472 and ↓proliferation ↓migration ↓invasion	[12]
Lung cancer	SCID mice	↑LINC00472: ↓tumor size	[15]
Oral squamous cell carcinoma	BALB/c nude male mice	↑LINC00472: ↓metastasis ↓PCNA, ki-67	[40]
	BALB/c nude mice	↑LINC00472: ↓tumor size	[40]

regulation of LINC00472 in tumoral tissues compared with non-tumoral samples (Table 3). In breast cancer, expression of LINC00472 has been higher in small-sized tumors compared with larger ones [25]. In epithelial ovarian cancer, LINC00472 has been found to be over-expressed in early stage and low-grade tumors. However, its expression has not been associated with overall survival (OS) of patients [8]. In hepatocellular carcinoma tissues, expression of this lincRNA has been lower in patients with metastasis compared with those without metastasis. Moreover, expression levels of LINC00472 have been positively correlated with OS of patients with hepatocellular carcinoma [3].

In contrast to the bulk of studies, an *in silico* valuation of TCGA data has shown up-regulation of LINC00472 in renal cell carcinoma samples and association between its up-regulation and poor clinical outcome [34]. Moreover, this lincRNA has been found to be upregulated in malignant intraductal papillary mucinous neoplasms of pancreas compared with benign ones [19].

Diagnostic value of LINC00472 has been assessed in colorectal cancer (Table 4). Although its levels had appropriate sensitivity to discriminate between cancerous and non-cancerous tissues, it lacked the appropriate specificity [4].

3. Non-malignant conditions

3.1. Cell line studies

In vitro experiments have shown possible role of LINC00472 in the pathogenesis of atherosclerosis, since this lincRNA can regulate migration and proliferation of vascular smooth muscle cells through affecting expression of miR-149–3p [11] (Fig. 2). Mechanistically, miR-149–5p suppresses proliferation and other functional properties of vascular smooth muscle cells through inhibiting expression of histone deacetylase 4 [37]. Moreover, LINC00472 has a possible role in the pathophisiology of sepsis-induced hepatic [5] and cardiac dysfunction [17], through regulation of miR-373–3p/TRIM8 and miR-335–3p/Monoamine oxidase A cascades, respectively. In fact, miR-373–3p can increase viability and decrease apoptosis of liver cells [5]. Additionally, miR-335 has a protective effect against sepsis-associated myocardial damage [13]. In addition, participation of LINC00472 in the etiology of neuropathic pain has been shown to be mediated through miR-300/HMGB1 axis [35]. Finally, investigations in HiBECs cells have shown possible role of this lincRNA in the pathogenesis of primary biliary cholangitis [7]. Table 5 shows the influence of LINC00472 in the pathogenesis of non-malignant conditions according to the results of *in viro* studies.

3.2. Animal studies

Studies in animal models of sepsis-induced acute hepatic injury [5], neuropathic pain [35] and sepsis-induced cardiac injury [17] have shown that down-regulation of LINC00472 reduces inflammation and ameliorates the pathogenic processes. LINC00472 could also promote osteogenic differentiation and alleviate osteoporosis in animal models of this disorder [10]. Table 6 shows the results of these studies.

3.3. Studies in clinical samples

Dysregulation of LINC00472 has also been reported in a variety of non-neoplastic disorders (Table 7). This lincRNA has been found to be up-regulated in clinical samples from patients with atherosclerosis [11], pterygium [33] and primary biliary cholangitis [7]. On the other hand, its down-regulation has been reported in osteoporosis [10], atrial fibrillation [29] and diabetic kidney disease [30] Fig. 3.

Expression levels of LINC00472 have been shown to discriminate patients with atrial fibrillation from normal controls with AUC value of 0.86 [29]. In primary biliary cholangitis, this lincRNA could differentiate between different stages of disorder with AUC value of 0.84 [7]. Table 8 summarizes the results of these studies.

4. Discussion

LINC00472 has been shown to be down-regulated in a diversity of cancers. Results of in vitro and in vivo studies support a tumor suppressor role for this lncRNA. This lincRNA can serve as a sponge for a number of putative oncogenic miRNAs, such as miR-24–3p, miR-196b-5p, miR-23a-3p, miR-93–5p, miR-4311 and miR-455–3p, thus enhancing expression of their targets. LINC00472 can also regulate a number of signaling pathways with possible roles in the oncogenesis, including MEK/ERK, NF-kB, PTEN/PI3K/AKT and STAT3 pathways. Consistent with the supposition of a tumor suppressor effect for LINC00472, down-regulation of this lincRNA predicts poor survival of patients in almost all types of cancers, including lung, pancreatic, liver and kideney cancers as well as tongue squamous cell carcinoma. Therefore, LINC00472 is regraded as a prognostic factor in diverse types of cancers, particularly lung and renal cell carcinomas.

In addition to suppression of tumor growth, LINC00472 participates in the pathoetiology of diverse non-malignant conditions such as atherosclerosis, osteoporosis, atrial fibrillation, diabetic kidney disease, pterygium, autism spectrum disorder and primary biliary cholangitis. Studies in non-malignant conditions have identified the sponging effect of LINC00472 on some miRNAs, namely miR-149–3p, miR-373–3p, miR-24, miR-300 and miR-335–3p. Therefore, miR-24 is a common target of LINC00472 in both malignant and non-malignant conditions.

In spite of the presence of a bulk of evidence pointing to the dysregulation of LINC00472 in diverse conditions, diagnostic value of this lncRNA has been assessed in few situations. Threfore, the importance of identification of diagnostic markers for human disorders necessitates conduction of additional studies for unraveling the potential of LINC00472 as a diagnostic marker for human disorders, particularly cancers.

Ethics approval and consent to participant

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent forms were obtained from all study participants. The study protocol was

Table 3
LINC00472 profile in clinical specimens (OS: overall survival, DFS: disease- free survival, RFS: relapse-free survival, PTAS: paired tumor and adjacent samples).

Tumor type	Tissues	Expression (tumor vs. normal)	Kaplan-Meier Analysis (impact of LINC00472 dysregulation)	Univariate/Multivariate cox regression	Association of LINC00472 expression with clinicopathologic characteristics	References
Lung adenocarcinoma	Geo datasets: (GSE27262 and GSE31210)	Downregulated	Poorer OS and RFS	-	-	[5]
	24 PTAS	Downregulated	-	-	-	[26]
	53 PTAS	Downregulated	Poor OS	-	lymph node metastasis	[27]
Pancreatic cancer	70 PTAS	Downregulated	Poorer OS	-	TNM stage and lymph node metastasis	[1]
Osteosarcoma	20 PTAS	Downregulated	-	-	-	[38]
Hepatocellular carcinoma (HCC)	35 fresh neighboring non-tumor hepatic tissues and 109 fresh HCC samples	Downregulated	Low OS	-	-	[3]
Triple-negative breast cancer (TNBC)	42 PTAS	Downregulated	-	-	histological grading, lymph node metastasis, clinical grading and the Ki-67 expression	[24]
Breast cancer	348 tumor samples with different grades	Upregulated in smaller tumors compared with larger ones	Smaller tumors were related with better OS	-	-	[25]
Bladder Carcinoma	20 PTAS	Downregulated	-	-	-	[12]
Lung cancer	47 PTAS	Downregulated	Lower OS	-	-	[15]
Clear cell renal cell carcinoma	TCGA database of 523 cancer samples and 72 neighboring normal tissues	Downregulated Downregulated	Higher expression contributes to better OS and DFS	-	-	[9]
	22 PTAS		-			
	TCGA-ccRCC (530 RCC samples and 72 control samples)	Downregulated	Higher expression: better OS	Diagnostic value in differentiating patients with early stages from advanced stages of cancer		[32]
Kidney Renal Clear Cell Carcinoma (KIRC)	TCGA database (505 samples from KIRC patients and 106 sample from healthy individuals)	Upregulated	-	-	-	[34]
Colorectal cancer	46 PTAS	Downregulated	No significant association between LINC00472 and OS	-	-	[36]
	130 PTAS	Downregulated	-	-	Invasion, lymph node metastasis, distant metastasis, TNM stage	[4]
Oral squamous cell carcinoma	15 PTAS	Downregulated	-	-	-	[40]
Gastric cancer	42 PTAS	Downregulated	-	-	-	[28]
Epithelial ovarian cancer	266 epithelial ovarian cancer (I–II III–IV stages)	Higher expression in early stages and low-grade tumors	Not associated with OS	-	Disease stage and tumor grade	[8]
Intraductal papillary mucinous neoplasms (IPMNs)	30 malignant and 21 benign IPMNs	Upregulated in malignant neoplasms	-	-	-	[19]
Tongue squamous cell carcinoma (TSCC)	TCGA database: 122 TSCC patients and 15 normal controls	Downregulated	Poor OS	-	-	[39]

Table 4
Diagnostic value of LINC00472 in cancers.

Tumor type	Samples	Distinguish between	Area under curve	Sensitivity (%)	Specificity (%)	References
Colorectal cancer (CRC)	130 pairs of CRC and nearby normal tissues	CRC tissues from normal tissues	0.680	0.823	0.439	[4]

approved by the ethical committee of Shahid Beheshti University of Medical Sciences. All methods were performed in accordance with the relevant guidelines and regulations.

Consent of publication

Not applicable.

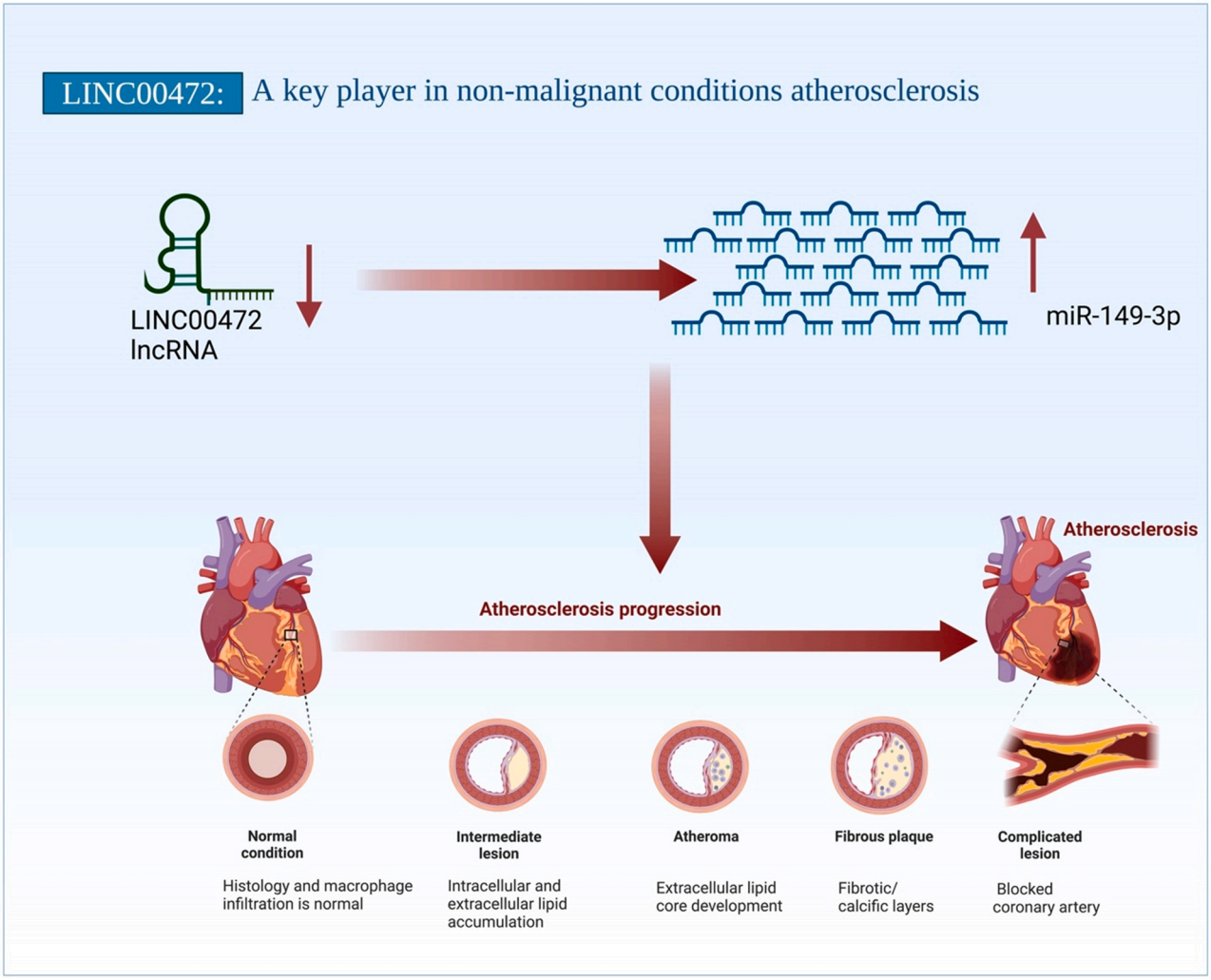

Fig. 2. Atherosclerosis is associated with a decrease in LINC00472 expression in vascular smooth muscle cells (VSMCs) in the arteries caused by TNF- and PDGF-BB. Ectopic expression of LINC00472 promoted VSMC migration and proliferation by inhibiting miR-149–3p [11].

Table 5
Role of LINC00472 in non-malignant conditions (Δ: knock-down or deletion, ↑: increase, ↓: decrease).

Disease type	Interactions	Cell line	Function	Reference
Atherosclerosis	miR-149–3p	VSMCs	↑LINC00472: ↑migration ↑invasion	[11]
Sepsis-induced acute hepatic injury	miR-373–3p/ TRIM8	THLE-3	↑LINC00472: ↓viability ↑apoptosis	[5]
Atrial fibrillation	P2, RyR2, miR-24	HCM, H9C2	↑mir-24 contributes to LINC00472 downregulation and results in Poorer conditions	[29]
Neuropathic pain	HMGB1, miR-300	PC12	↓LINC00472: reduces inflammation and hinders neuropathic pain	[35]
Primary biliary cholangitis	-	HiBECs	Upregulated	[7]
Sepsis-induced cardiac dysfunction	YY1, miR-335–3p/ MAOA cascade	AC-16	ΔLINC00472: reduces inflammation	[17]

Table 6
Animal studies on the role of LINC00472 in non-malignant conditions (Δ: knock-down or deletion, ↑: increase, ↓: decrease).

Disease type	Animal model	Results	Reference
Osteoporosis	female mice	↑LINC00472: ↑Osteogenic Differentiation	[10]
Sepsis-induced acute hepatic injury	Sprague Dawley rats	ΔLINC00472: ↓IL-6, IL-10, and TNF-α	[5]
Neuropathic pain	Specific pathogen-free Sprague Dawley (SD) rats	↓LINC00472: reduces inflammation and hinders neuropathic pain	[35]
Primary biliary cholangitis	Male C57BL/6 J mice	Upregulated	[7]
Sepsis-induced cardiac dysfunction	male C57BL/6 J mice	ΔLINC00472: Inflammation reduction	[17]

Table 7
Human studies on the role of LINC00472 in non-malignant conditions.

Disease	Number of clinical samples	Expression (case vs. control)	Expression assay	Reference
Atherosclerosis	20 samples from normal coronary artery+ atherosclerotic coronary tissues	Upregulated	SYBR Ex Taq	[11]
Osteoporosis	Blood samples of 55 female patients with osteoporosis and 50 normal females	Downregulated	SYBR Premix Ex Taq	[10]
Atrial fibrillation (AF)	Peripheral blood of 125 Patients with AF and 168 healthy subjects free of AF	Downregulated	SYBR Premix EX Taq	[29]
Diabetic kidney disease	Geo datasets GSE30528 and GSE30529	Downregulated	-	[30]
Pterygium	Geo datasets GSE83627, GSE21346, GSE51995, and GSE2513	Upregulated (upregulates 6 hub genes and 8 miRNAs)	-	[33]
Autism Spectrum Disorder	Geo dataset GSE89594	LINC00472/hsa-miR-221–3p/PTPN11 and LINC00472/hsa-miR-132–3p/S100A2 are involved in immune-related phenomena.	-	[22]
Primary biliary cholangitis (PBC)	145 PBC patients and 110 healthy subjects	Upregulated	SYBR® Premix Ex TaqTM II	[7]

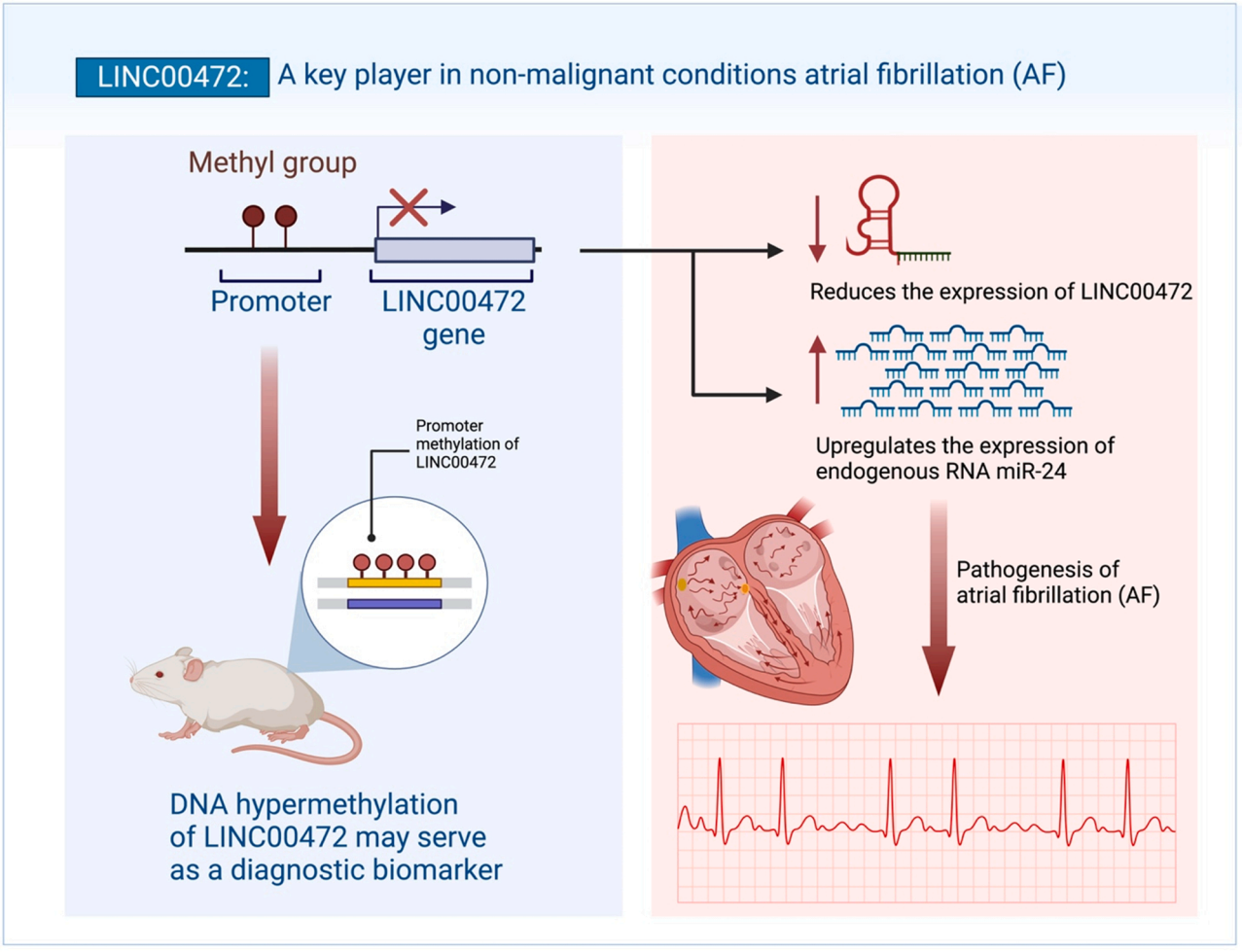

Fig. 3. When the promotor of the LINC00472 gene is hypermethylated, the activity of the LINC00472 gene is inhibited, leading to upregulation of the expression of some endogenous miRNAs, such as miRNA-24, which is known to induce atrial fibrillation and can also be used as a diagnostic biomarker for the condition.

Table 8
Diagnostic value of LINC00472 in non-malignant conditions.

Disease	Specimens	Distinguishing ability	Area under curve	Sensitivity (%)	Specificity (%)	References
Atrial fibrillation (AF)	Peripheral blood of 125 Patients with AF and 168 healthy subjects free of AF	Patients with AF and healthy controls	0.86	-	-	[29]
Primary biliary cholangitis (PBC)	A total of 145 PBC	Different stages of the disease	0.84	77.27%	77.78%	[7]

Funding

Not applicable.

CRediT authorship contribution statement

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

Declaration of Competing Interest

No conflicts of interest exist.

Data Availability

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

Acknowledgement

The authors would like to thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their support, cooperation and assistance throughout the period of study.

References

[1] C. Bi, G. Wang, LINC00472 suppressed by ZEB1 regulates the miR-23a-3p/FOXO3/BID axis to inhibit the progression of pancreatic cancer, J. Cell Mol. Med 25 (2021) 8312–8328.
[2] C.J. Brown, B.D. Hendrich, J.L. Rupert, R.G. Lafreniere, Y. Xing, J. Lawrence, H. F. Willard, The human XIST gene: analysis of a 17 kb inactive X-specific RNA that contains conserved repeats and is highly localized within the nucleus, Cell 71 (1992) 527–542.
[3] C. Chen, Q. Zheng, W. Kang, C. Yu, Long non-coding RNA LINC00472 suppresses hepatocellular carcinoma cell proliferation, migration and invasion through miR-93-5p/PDCD4 pathway, Clin. Res Hepatol. Gastroenterol. 43 (2019) 436–445.
[4] L. Chen, W. Zhang, D.Y. Li, X. Wang, Y. Tao, Y. Zhang, C. Dong, J. Zhao, L. Zhang, X. Zhang, J. Guo, X. Zhang, Q. Liao, Regulatory network analysis of LINC00472, a long noncoding RNA downregulated by DNA hypermethylation in colorectal cancer, Clin. Genet 93 (2018) 1189–1198.
[5] X. Deng, W. Xiong, X. Jiang, S. Zhang, Z. Li, Y. Zhou, B. Xiang, M. Zhou, X. Li, G. Li, Z. Zeng, Z. Gong, LncRNA LINC00472 regulates cell stiffness and inhibits the migration and invasion of lung adenocarcinoma by binding to YBX1, Cell Death Dis. 11 (2020) 945.
[6] T. Derrien, R. Johnson, G. Bussotti, A. Tanzer, S. Djebali, H. Tilgner, G. Guernec, D. Martin, A. Merkel, D.G. Knowles, The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression, Genome Res. 22 (2012) 1775–1789.
[7] X.H. Dong, D. Dai, Z.D. Yang, X.O. Yu, H. Li, H. Kang, S100 calcium binding protein A6 and associated long noncoding ribonucleic acids as biomarkers in the diagnosis and staging of primary biliary cholangitis, World J. Gastroenterol. 27 (2021) 1973–1992.
[8] Y. Fu, N. Biglia, Z. Wang, Y. Shen, H.A. Risch, L. Lu, E.M. Canuto, W. Jia, D. Katsaros, H. Yu, Long non-coding RNAs, ASAP1-IT1, FAM215A, and LINC00472, in epithelial ovarian cancer, Gynecol. Oncol. 143 (2016) 642–649.
[9] S. Gao, Z. Wang, Comprehensive Analysis of Regulatory Network for LINC00472 in Clear Cell Renal Cell Carcinoma, J. Health Eng. 2021 (2021) 3533608.
[10] H.L. Guo, X. Wang, G.Y. Yang, Y.Y. Wu, Y.C. Chen, H.S. Zhan, Y.F. Zhao, LINC00472 promotes osteogenic differentiation and alleviates osteoporosis by sponging miR-300 to upregulate the expression of FGFR2, Eur. Rev. Med Pharm. Sci. 24 (2020) 4652–4664.
[11] R. Jing, W. Pan, T. Long, Z. Li, C. Li, LINC00472 regulates vascular smooth muscle cell migration and proliferation via regulating miR-149-3p, Environ. Sci. Pollut. Res Int 28 (2021) 12960–12967.
[12] L. Li, F. Qi, K. Wang, Matrine restrains cell growth and metastasis by up-regulating LINC00472 in bladder carcinoma, Cancer Manag Res 12 (2020) 1241–1251.
[13] X. Long, Y. Huang, J. He, X. Zhang, Y. Zhou, Y. Wei, Y. Tang, L. Liu, Upregulation of miR-335 exerts protective effects against sepsis-induced myocardial injury, Mol. Med. Rep. 24 (2021).
[14] L. Ma, V.B. Bajic, Z. Zhang, On the classification of long non-coding RNAs, RNA Biol. 10 (2013) 925–933.
[15] C. Mao, X. Wang, Y. Liu, M. Wang, B. Yan, Y. Jiang, Y. Shi, Y. Shen, X. Liu, W. Lai, R. Yang, D. Xiao, Y. Cheng, S. Liu, H. Zhou, Y. Cao, W. Yu, K. Muegge, H. Yu, Y. Tao, A G3BP1-interacting lncRNA promotes ferroptosis and apoptosis in cancer via nuclear sequestration of p53, Cancer Res. 78 (2018) 3484–3496.
[16] X. Mao, X. Zhou, J. Liu, Y. Mao, H. Zhou, Up-regulated Linc00472 suppresses development of lung cancer cell via inhibition of MiR-196b-5p, Biosci. Biotechnol. Biochem (2019) 1–13.
[17] G. Mo, J. Mo, X. Tan, J. Wang, Z. Yan, Y. Liu, Yin Yang 1 (YY1)-induced long intergenic non-protein coding RNA 472 (LINC00472) aggravates sepsis-associated cardiac dysfunction via the micro-RNA-335-3p (miR-335-3p)/Monoamine oxidase A (MAOA) cascade, Bioengineered 13 (2022) 1049–1061.
[18] K.C. Pang, M.C. Frith, J.S. Mattick, Rapid evolution of noncoding RNAs: lack of conservation does not mean lack of function, Trends Genet. 22 (2006) 1–5.
[19] J.B. Permuth, D.T. Chen, S.J. Yoder, J. Li, A.T. Smith, J.W. Choi, J. Kim, Y. Balagurunathan, K. Jiang, D. Coppola, B.A. Centeno, J. Klapman, P. Hodul, F. A. Karreth, J.G. Trevino, N. Merchant, A. Magliocco, M.P. Malafa, R. Gillies, Linc-ing circulating long non-coding RNAs to the diagnosis and malignant prediction of intraductal papillary mucinous neoplasms of the pancreas, Sci. Rep. 7 (2017) 10484.
[20] J.D. Ransohoff, Y. Wei, P.A. Khavari, The functions and unique features of long intergenic non-coding RNA, Nat. Rev. Mol. Cell Biol. 19 (2018) 143–157.
[21] M.B. Reeves, A.A. Davies, B.P. McSharry, G.W. Wilkinson, J.H. Sinclair, Complex I binding by a virally encoded RNA regulates mitochondria-induced cell death, Science 316 (2007) 1345–1348.
[22] H. Sabaie, H. Dehghani, S. Shiva, M.R. Asadi, O. Rezaei, M. Taheri, M. Rezazadeh, Mechanistic Insight Into the Regulation of Immune-Related Genes Expression in Autism Spectrum Disorder, Front. Mol. Biosci. 8 (2021), 754296.
[23] D. Seo, J. Roh, Y. Chae, W. Kim, Gene expression profiling after LINC00472 overexpression in an NSCLC cell line1, Cancer Biomark. 32 (2021) 175–188.
[24] G. Shao, X. Fan, P. Zhang, X. Liu, L. Huang, S. Ji, Methylation-dependent MCM6 repression induced by LINC00472 inhibits triple-negative breast cancer metastasis by disturbing the MEK/ERK signaling pathway, Aging 13 (2021) 4962–4975.
[25] Y. Shen, D. Katsaros, L.W. Loo, B.Y. Hernandez, C. Chong, E.M. Canuto, N. Biglia, L. Lu, H. Risch, W.M. Chu, H. Yu, Prognostic and predictive values of long non-coding RNA LINC00472 in breast cancer, Oncotarget 6 (2015) 8579–8592.
[26] C. Su, K. Shi, X. Cheng, Y. Han, Y. Li, D. Yu, Z. Liu, Long noncoding RNA LINC00472 inhibits proliferation and promotes apoptosis of lung adenocarcinoma cells via regulating miR-24-3p/ DEDD, Technol. Cancer Res Treat. 17 (2018), 1533033818790490.
[27] J. Sui, Y.H. Li, Y.Q. Zhang, C.Y. Li, X. Shen, W.Z. Yao, H. Peng, W.W. Hong, L. H. Yin, Y.P. Pu, G.Y. Liang, Integrated analysis of long non-coding RNA-associated ceRNA network reveals potential lncRNA biomarkers in human lung adenocarcinoma, Int. J. Oncol. 49 (2016) 2023–2036.
[28] K.W. Tsai, C.Y. Tsai, N.H. Chou, K.C. Wang, C.H. Kang, S.C. Li, Y.H. Lao, H. T. Chang, Aberrant DNA hypermethylation silenced LncRNA expression in gastric cancer, Anticancer Res. 39 (2019) 5381–5391.
[29] L.Y. Wang, H. Shen, Q. Yang, J. Min, Q. Wang, W. Xi, L. Yin, S.G. Le, Y.F. Zhang, J. Xiao, Z.N. Wang, G.Y. Ji, LncRNA-LINC00472 contributes to the pathogenesis of atrial fibrillation (Af) by reducing expression of JP2 and RyR2 via miR-24, Biomed. Pharmacother. Biomed. Pharmacother. 120 (2019), 109364.
[30] Y.Z. Wang, D.Y. Zhu, X.M. Xie, M. Ding, Y.L. Wang, L.L. Sun, N. Zhang, E. Shen, X. X. Wang, EA15, MIR22, LINC00472 as diagnostic markers for diabetic kidney disease, J. Cell Physiol. 234 (2019) 8797–8803.
[31] Z. Wang, D. Katsaros, N. Biglia, Y. Shen, L. Loo, X. Yu, H. Lin, Y. Fu, W.M. Chu, P. Fei, Y. Ni, W. Jia, X. Deng, B. Qian, H. Yu, ERα upregulates the expression of long non-coding RNA LINC00472 which suppresses the phosphorylation of NF-κB in breast cancer, Breast Cancer Res Treat. 175 (2019) 353–368.
[32] Z. Xiang, E. Shen, M. Li, D. Hu, Z. Zhang, S. Yu, Potential prognostic biomarkers related to immunity in clear cell renal cell carcinoma using bioinformatic strategy, Bioengineered 12 (2021) 1773–1790.
[33] Y. Xu, C. Qiao, S. He, C. Lu, S. Dong, X. Wu, M. Yan, F. Zheng, Identification of functional genes in pterygium based on bioinformatics analysis, Biomed. Res Int 2020 (2020) 2383516.
[34] Q. Yang, W. Chu, W. Yang, Y. Cheng, C. Chu, X. Pan, J. Ye, J. Cao, S. Gan, X. Cui, Identification of RNA transcript makers associated with prognosis of kidney renal clear cell carcinoma by a competing endogenous RNA network analysis, Front Genet 11 (2020), 540094.
[35] X. Ye, Q. Lu, A. Yang, J. Rao, W. Xie, C. He, W. Wang, H. Li, Z. Zhang, MiR-206 regulates the Th17/Treg ratio during osteoarthritis, Mol. Med. 27 (2021) 1–9.
[36] Y. Ye, S. Yang, Y. Han, J. Sun, L. Xv, L. Wu, Y. Wang, L. Ming, Linc00472 suppresses proliferation and promotes apoptosis through elevating PDCD4 expression by sponging miR-196a in colorectal cancer, Aging 10 (2018) 1523–1533.
[37] B. Zhang, Y. Dong, M. Liu, L. Yang, Z. Zhao, miR-149-5p inhibits vascular smooth muscle cells proliferation, invasion, and migration by targeting histone deacetylase 4 (HDAC4), Med. Sci. Monit. Int. Med. J. Exp. Clin. Res. 25 (2019) 7581–7590.
[38] J. Zhang, J. Zhang, D. Zhang, W. Ni, H. Xiao, B. Zhao, Down-regulation of LINC00472 promotes osteosarcoma tumorigenesis by reducing FOXO1 expressions via miR-300, Cancer Cell Int 20 (2020) 100.
[39] S. Zhang, R. Cao, Q. Li, M. Yao, Y. Chen, H. Zhou, Comprehensive analysis of lncRNA-associated competing endogenous RNA network in tongue squamous cell carcinoma, PeerJ 7 (2019), e6397.
[40] C. Zou, X. Lv, H. Wei, S. Wu, J. Song, Z. Tang, S. Liu, X. Li, Y. Ai, Long non-coding RNA LINC00472 inhibits oral squamous cell carcinoma via miR-4311/GNG7 axis, Bioengineered 13 (2022) 6371–6382.