Biomedicine & Pharmacotherapy 142 (2021) 111999

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

LncRNA ZFAS1: Role in tumorigenesis and other diseases

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ARTICLE INFO

Keywords:
ZFAS1
Cancer
LncRNA
Biomarker
Expression

ABSTRACT

Residing on chromosome 20q13.13, Zinc Finger NFX1-Type Containing 1 (ZNFX1) antisense RNA 1 (ZFAS1) is a transcript which has been primarily recognized as a modulator of differentiation of alveolar and epithelial cell in the mammary gland. This long non-coding RNA (lncRNA) partakes in the molecular cascades leading to several non-neoplastic conditions such as osteoarthritis, epilepsy, rheumatoid arthritis, atherosclerosis, pulmonary fibrosis, myocardial infarction, and cardiac dysfunction. More importantly, ZFAS1 is considered as an oncogene in almost all types of cancers. Using expression amounts of ZFAS1, it is possible to forecast the clinical outcome of patients with different neoplasms such as colorectal cancer, gastric cancer, cholangiocarcinoma, hepatoblastoma, and other types of cancer. We describe the role of ZFAS1 in the development of neoplastic and non-neoplastic disorders.

1. Introduction

Zinc Finger NFX1-Type Containing 1 (ZNFX1) antisense RNA 1 (ZFAS1) is a transcript whose coding gene resides on chromosome 20q13.13. This gene codes for a long non-coding RNA (lncRNA) which has been primarily recognized as a modulator of differentiation of alv eolar cells and epithelium in the mammary gland [1]. ZFAS1 has 14 transcripts created through alternative splicing (http://asia.ensembl.org/Homo_sapiens/Gene/Summary?g=ENSG00000177410;r = 20:49278178–49299600). NR_003604.3, NR_036658.2, NR_003606.3, NR_003605.2 and NR_036659.2 transcripts are 1008, 946, 860, 689 and 504 nucleotides length, respectively (https://www.ncbi.nlm.nih.gov/gene/441951).

ZFAS1 is transcribed from the antisense strand adjacent to the 5′-terminus of the protein-encoding gene *Znfx1* [1]. In its introns, ZFAS1 hosts a number of C/D box snoRNAs (SNORDs). ZFAS1 silencing in a cell line derived from mammary epithelium has enhanced cell proliferation and differentiation, without significant impact on the expression of SNORD genes [1]. The primary observed decreased amounts of ZFAS1 in breast cancer tissues have suggested a tumor suppressor role for this transcript [1]. However, subsequent studies have reported the opposite role for ZFAS1 in the development of most cancer types [2–4]. Notably, similar to some other lncRNAs, ZFAS1 has a small open reading frame and can be translated into a small peptide with pathologic functions in cancer [5]. In addition to its role in the pathogenesis of neoplasia, ZFAS1 partakes in the molecular cascades leading to a range of disorders such as osteoarthritis (OA) [6], epilepsy [7], rheumatoid arthritis (RA) [8] and atherosclerosis [9]. We have designed this study to gather all information about the role of ZFAS1 in human disorders including both neoplastic and non-neoplastic disorders.

2. ZFAS1 in neoplastic conditions

2.1. Breast cancer

Levels of ZFAS1 have been up-regulated in breast cancer cells parallel with down-regulation of miR-589, a microRNA (miRNA) that is directly targeted by ZFAS1. ZFAS1 up-regulation has suppressed proliferation, colony production ability, invasiveness, and migratory aptitude of breast cancer cells via suppressing PI3K/AKT cascade through activating PTEN. Additionally, PTEN has been shown to be targeted by miR-589 [10]. Contrary to this study, Fan et al. have demonstrated down-regulation of ZFAS1 in breast cancer cell lines compared with

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https://doi.org/10.1016/j.biopha.2021.111999
Received 23 March 2021; Received in revised form 23 July 2021; Accepted 1 August 2021

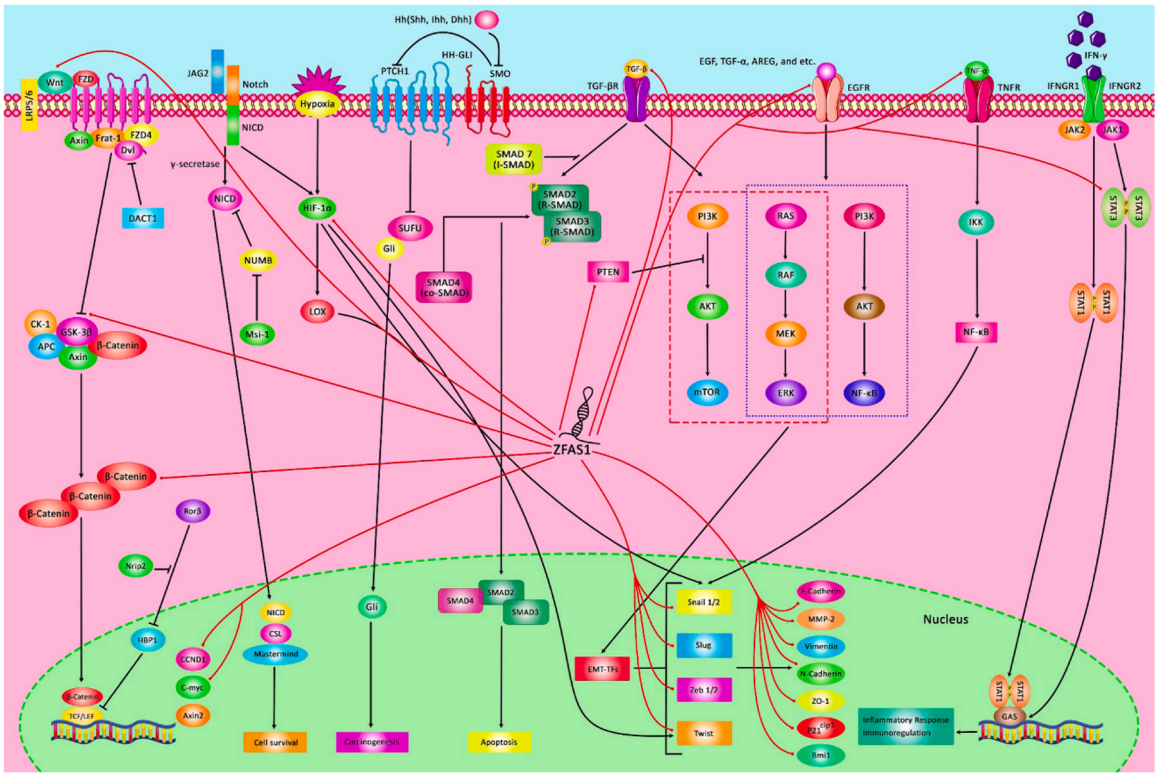

Fig. 1. A schematic representation of the regulation of PI3K/AKT, Wnt/β-catenin, Notch/Delta/Jagged, MAPK/ERK, and JAK-STAT signaling pathways via ZFAS1 in various human disorders as well as cancers. ZFAS1 via modulating EMT through target signaling cascades like MAPK/ERK, PI3K/AKT, and Wnt/β-catenin could exhibit a tumor oncogenic role in tumor progression. This lncRNA could, in turn, regulate proliferation, migration, and invasion in various human cancer cells containing glioma, breast cancer, colorectal cancer, gastric cancer as well as endometrial carcinoma via targeting E-cadherin, vimentin, MMP-2, N-cadherin, Bmi1, P21cip1, twist, snail 1/2, slug, zeb 1/2, cyclin D1, and c-myc [11,26,35,59,65,66].

control cells. Ectopic expression of ZFAS1 has inhibited cell proliferation through induction of cell cycle arrest and apoptotic pathways. Moreover, ZFAS1 has a regulatory role in epithelial-mesenchymal transition (EMT) [11].

2.2. Nasopharyngeal carcinoma

ZFAS1 has been overexpressed in nasopharyngeal carcinoma cells in association with radioresistance. ZFAS1 serves as a sponge for miR-7–5p to enhance ENO2 expression [12]. Furthermore, the expression of ZFAS1 enhanced in nasopharyngeal carcinoma tissues. Functionally, ZFAS1 regulates the expression of lysophosphatidic acid receptor 1 (LPAR1) through sequestering miR-892b. Over-expression of ZFAS1 and LPAR1 or down-regulation of miR-892b increases proliferation, migration, and invasion of nasopharyngeal carcinoma cells. Additionally, ZFAS1 silencing reduces the growth of xenograft tumors in nude mice [13].

2.3. Glioma

Over-expression of ZFAS1 has also been reported in glioma tissues and cells in association with the clinical outcome of patients. ZFAS1 silencing or over-expression of miR-1271–5p could block proliferation and migration and enhance apoptosis in the corresponding cell lines through modulating HK2 expression [14]. ZFAS1 has also been shown to increase the resistance of glioma cells to temozolomide by acting as a sponge of miR-150–5p and regulating the expression of proteolipid protein 2 (PLP2). Additionally, experiments in a xenograft model of glioma have verified the oncogenic role of ZFAS1 in vivo [15].

2.4. Ovarian cancer

Han et al. have shown higher expression of ZFAS1 ovarian cancer cells compared with normal cell lines. Yet, the expression of ZFAS1 has been lower in ovarian cancer samples compared with normal samples in the glutamic-oxaloacetic transaminase 1 (GEPIA) dataset. Stage III/IV ovarian cancer specimens have had higher amounts of ZFAS1 compared with early-stage specimens. Pathway analyses have shown an association between ZFAS1 and a number of signaling pathways/ cellular functions such as cell-cell adhesion, DNA repair, protein sumoylation, GTPase activation, and DNA replication [16].

2.5. Lung cancer

Over-expression of ZFAS1 has also been detected in lung adenocarcinoma samples and cells. ZFAS1 silencing has blocked cell proliferation, migration, and invasion in lung adenocarcinoma cells. This lncRNA binds with miR-1271–5p to increase the expression of fibroblast growth factor receptor substrate 2 (FRS2) [17]. Another experiment in non-small cell lung cancer has demonstrated up-regulation of ZFAS1 expression in tissues obtained from the advanced stage. ZFAS1 silencing has attenuated the proliferation and invasive aptitude of these cells while increasing the apoptotic rate. Notably, ZFAS1 silencing has also diminished tumor growth in the animal model. Functionally, ZFAS1 regulates expressions of miR-150–5p and high mobility group AT-hook 2 (HMGA2) [18].

2.6. Gastrointestinal cancers

ZFAS1 up-regulation has also been detected in pancreatic adenocarcinoma. ZFAS1 knock-down has suppressed metastatic aptitude of

Table 1
Expression of ZFAS1 in neoplastic conditions (NNCTs: nearby non-cancerous tissues).

Type of Disease	Expression Patterns	Samples	Cell Line	Target	Pathway	Function	Refs.
Breast Cancer (BC)	Up	–	MCF-10A, T47D, MCF-7, BT-549, MDA-MB-435	miR-589, MMP2, MMP9, Bcl2, Bax, Caspase-3, PTEN	PI3K/AKT	ZFAS1 by targeting miR-589 through regulating the PTEN/PI3K/AKT signal pathway could inhibit the proliferation, invasion, and migration of BC cells.	[10]
BC	Down	4 pairs of BC and NNCTs	MDA-MB-231, MCF-7, T-47D, SK-BR-3, MCF-10 A	N-cadherin, E-cadherin, Vimentin	–	Overexpression of ZFAS1 by regulating EMT could inhibit cell migration and invasion.	[11]
Nasopharyngeal Carcinoma (NPC)	Up	55 pairs of NPC and NNCTs	SUNE-1, 5–8 F, C666–1, NP-69	miR-7–5p, ENO2, HIF-1	–	ZFAS1 by inhibiting hsa-miR7–5p/ENO2 could contribute to irradiation resistance in NPC.	[12]
NPC	Up	male BALB/c nude mice/human; 53 pairs of NPC and NNCTs	NP69, HONE1, CNE, HNE1, C666–1	miR-892b, LPAR1	–	ZFAS1 by upregulating LPAR1 via sponging miR-892b could promote tumorigenesis and metastasis in NPC.	[13]
NPC	Up	31 pairs of NPC tissues and NNCTs, GEO database	5–8 F, CNE1, CNE2, C666, NP69	P21, p53, Bcl-2, E-cadherin, Vimentin, N-cadheri	PI3K/AKT	ZFAS1 via the PI3K/AKT pathway could inhibit apoptosis in NPC cells.	[22]
NPC	Up	29 pairs of NPC and NNCTs	NP69, CNE1, CNE2, HNE1, HONE1	miR-135a	–	The knockdown of ZFAS1 via sponging miR-135a could inhibit the progression of NPC.	[23]
NPC	Up	76 pairs of NPC and NNCTs	NP-69, CNE-1, CNE-2, HONE-1, SUNE-1, HNE-1	Cyclin-D1, c-myc	Wnt/β-catenin	ZFAS1 via activating the Wnt/β-catenin pathway could promote NPC.	[24]
Glioma	Up	59 pairs of glioma and NNCTs	T98G, A172, HA, LN229, U251, HS683	HK2, miR-1271–5p	–	ZFAS1 by regulating miR-1271–5p and HK2 could promote the development of glioma.	[14]
Glioma	Up	male nude mice/human; glioma tissues (n = 27), normal brain tissues (n = 10)	NHAs, U87, U251, LN229, T98G	miR-150–5p, PLP2	–	ZFAS1 by regulating the miR-150–5p/PLP2 axis could promotes the progression of glioma.	[15]
Glioma	Up	25 pairs of glioma and NNCTs	NHA, U87, U251, A172, LN299, U251/CDD, LN299/CDD	miR-432–5p	–	The knockdown of ZFAS1 via upregulating miR-432–5p could enhance cisplatin cytotoxicity in glioma cells.	[25]
Glioma	Up	46 pairs of glioma and NNCTs	U87, U251	N-cadherin, E-cadherin, Snail	Wnt/β-catenin, Notch	ZFAS1 via regulating EMT and Notch signaling could exhibit a tumor oncogenic role in glioma progression.	[26]
Ovarian Cancer (OC)	Up	BALB/c nude mice/human; 16 pairs of OC and NNCTs	SKOV3, Caov3, OVCAR3, A2780 COV644, 293 T, SKOV3/DDP	miR-548e, let-7a, E-cadherin, CXCR4, N-cadherin, Vimentin, MMP-2, Slug, BCL-XL	–	ZFAS1 by sponging miR-548e could regulate metastasis and cisplatin chemoresistance via targeting let-7a/BCL-XL/S/CXCR4 axis.	[27]
OC	Up/down	TCGA	OVCA429, SKOV3, A2780, COV644, HOSE	miR-150–5p, KLF2, NKD2	–	ZFAS1 could be considered as a prognostic indicator of the survival of patients with OC.	[16]
Cervical Cancer (CC)	Up	Female B ALB/c nude mice /human; 85 pairs of CC and NNCTs	CaSki, HeLa, C33A, HaCat	–	–	Knockdown of ZFAS1 could enhance cisplatin chemosensitivity and inhibit cell proliferation, migration, and invasion.	[28]
Lung Adenocarcinoma (LAD)	Up	46 pairs of LAD and NNCTs	BEAS-2B, A549	miR-1271–5p, FRS2		Overexpression of ZFAS1 by sponging miR-1271–5p and upregulating FRS2 could promote LAD progression.	[17]
Non-Small Cell Lung Carcinoma (NSCLC)	Up	22 pairs of NSCLC and matched tumor-adjacent tissues	A549, HCC827, 16HBE	miR-590–3p, Cdc42	–	ZFAS1 via regulating miR-590–3p could promote progression of NSCLC.	[29]
NSCLC	Up	male BALB/c nudemice/human; 50 pairs of NSCLC and NNCTs	NHBE, H838, H1299, A549,	miR-150–5p, HMGA2	–	Knockdown of ZFAS1 via targeting the miR-150–5p/HMGA2 axis could suppress NSCLC progression.	[18]
NSCLC	Up	173 pairs of NSCLC and NNCTs	–	–	–	Overexpression of ZFAS1 could reduce survival in patients with NSCLC.	[4]
Pancreatic Adenocarcinoma (PAAD)	Up	nude BALB/c mice/human; GSE14245, GSE15471, GSE21654, GSE27890, GSE32676, GSE42252,	SW1990, PANC1, BXPC3, 293 T, HPDE6C7	miR-3924, ROCK2, FAK, RHOA	–	ZFAS1 via the RHOA/ROCK2 pathway by sponging miR-3924 could promote PAAD metastasis.	[19]

(*continued on next page*)

Table 1 (*continued*)

Type of Disease	Expression Patterns	Samples	Cell Line	Target	Pathway	Function	Refs.
		GSE46385, GSE51798, GSE106189 datasets					
Hepatocellular Carcinoma (HCC)	Up	BALB/c nude mice/human; 94 pairs of HCC and NNCTs	SMMC-7721, Bel-7402, MHCC97, HepG2, L02	miR-624, MDK, P38, Vimentin, E-cadherin	ERK/JNK	ZFAS1 via the miR-624/MDK/ERK/JNK/P38 pathway could potentiate the development of HCC.	[2]
HCC	Up	Human RPF-Seq datasets	U2OS, HeLa		–	Translated ZFAS1 by elevating ROS production in HCC could promote cancer cell migration.	[5]
HCC	Up	60 pairs of HCC and NNCTs	Bel-7402, HepG2, L02	miR-193a-3p	–	ZFAS1 via epigenetically repressing miR-193a-3p could promote HCC proliferation.	[30]
HCC	Up	22 pairs of HCC and NNCTs	–	–	–	ZFAS1 could be considered as a biomarker for the diagnosis of HCC.	[20]
HCC	Up	The athymic BALB/C mice/human; GSE55191, GSE58043	Huh7, HepG2, Hep3B, LM3, SMMC7721, LO2, QSG7701	MMP14, MMP16, ZEB1	–	Overexpression of ZFAS1 could promote metastasis in HCC.	[31]
Colorectal Cancer (CRC)	Up	BALB/c-nu mice/human; 157 pairs of CRC and NNCTs	HIEC, HCT116, SW480, SW620, HT29, 293 T	NOP58	–	ZFAS1 via recruiting NOP58 could promote small nucleolar RNA-mediated 2′-O-methylation in CRC.	[32]
CRC	Up	40 pairs of CRC and NNCTs	SW-620, HCT-116, DLD-1, SW480, H29, NCM460	miR-7–5p,	–	ZFAS1 via targeting miR-7–5p could regulate proliferation, migration, and invasion in CRC	[33]
CRC	Up	Male BALB/c nude mice/human; 49 pairs of CRC and NNCTs	HCT116, SW480, SW620, HT-29, LOVO, HCoEpiC	miR-484	–	ZFAS1 by sponging miR-484 could promote cell proliferation and invasion in CRC.	[34]
CRC	Up	nude mice/human; 112 pairs of CRC and NNCTs	HCT116, HCT8, HT29, SW620, SW480, DLD-1, FHC	miR-150–5p, VEGFA, VEGFR2, E-cadherin, Vimentin, N-cadherin	Akt/mTOR	SP1-induced ZFAS1 via regulating the miR-150–5p/VEGFA axis could contribute to CRC progression.	[35]
CRC	Up	159 pairs of CRC and NNCTs	HCT8, HCT116, HT29, LoVo, SW480, SW620, 293 T	–	–	Overexpression of ZFAS1 could prompt invasion and metastasis in CRC.	[36]
Colon Cancer (CC)	Up	73 pairs of CC and NNCTs	SW480, CaCO-2, RKO, HCT8, HCT116, SW620, FHC	PARP, Caspase-3, ZEB1, Vimentin, E-cadherin, ZO-1 N-cadherin	–	ZFAS1 via modulating ZEB1 expression could promote the progression of CC	[21]
Prostate Cancer (PCa)	Up	TCGA, GEPIA, GSE21032 datasets	LNCaP, 22RV1, DU145, PC-3	miR-150–5p, PRMT5	–	The ZFAS1/miR-150–5p axis by regulating PRMT5 could promote androgen-independent PCa invasion and migration.	[37]
PCa	Up	TCGA database	–	miR-940, RPL28	–	ZFAS1 by targeting miR-940 could be considered as a prognostic marker in PC.	[38]
Oral Squamous Cell Carcinoma (OSCC)	Up	Male BALB/c nude mice/human; 45 pairs of OSCC and NNCTs	NHOK, Tca8113, SCC-9/DDP, CAL-27/DDP, CAL-27, SCC-9, TSCCA	miR-421, MEIS2, BCL2, Bax, HSP70	–	ZFAS1 via suppressing miR-421 could promote cisplatin resistance in OSCC.	[3]
Esophageal Squamous Cell Carcinoma (ESCC)	Up	female BALB/c nude mice/human; 136 pairs of ESCC and NNCTs	EC9706, Eca109, TE-13, TE-1, TTN	miR-124, STAT3	–	Exosomal ZFAS1 via targeting the miR-124/STAT3 axis could regulate ESCC cell proliferation, invasion, and migration.	[39]
ESCC	Up	246 pairs of ESCC and NNCTs	–	–	–	ZFAS1 expression predicts the prognosis of lymph node-negative cancers.	[40]
Osteosarcoma (OS)	Up		U2OS, Saos-2, MG-63, NHOst	miR-646, Raf1, NOB1	MAPK, MEK/ERK	ZFAS1 via interacting with miR-646 could regulate NOB1 and promote tumorigenesis in OS.	[41]
OS	Up	35 BALB/c nude mice/human; 34 pairs of OS and NNCTs	143B, U2OS, Saos2, MG63, hFOB1.19,	miR-135a, APEX1, Bax, Bcl-2, MMP9, MMP2, Cyclin-D1	–	The knockdown of ZFAS1 via targeting miR-135a could repress proliferation, migration, and invasion of OS cells.	[42]
OS	Up	nude mice/human; 50 pairs of OS and NNCTs	KHOS, 143b, LM7, U2OS, MG-63, Nhost	BMI1, ZEB2, miR-200b, miR-200c	–	ZFAS1 via regulating BMI1 and ZEB2 could promote growth and metastasis in OS.	[43]
OS	Up	Male BALB/c nude mice /human; 53 pairs of OS and NNCTs	U2OS, Saos- 2, HOS, MG-63, NHOst	miR-486	–	ZFAS1 by sponging miR-486 could promote OS cell metastasis.	[44]
Thyroid Cancer (TC)	Up		CAL62, SW579		–		[45]

(*continued on next page*)

Table 1 (*continued*)

Type of Disease	Expression Patterns	Samples	Cell Line	Target	Pathway	Function	Refs.
		TCGA, GSE50901, GSE33630, GSE29265		miR-150–5p, miR-590–3p		ZFAS1 could be considered as a biomarker for predicting TC prognosis.	
TC	Up	30 pairs of TC and NNCTs	Nthy-ori3–1, MDA-T68, TPC-1 SW579, B-CPAP	miR-302–3p, Cyclin-D1, N-cadherin, E-cadherin, MMP2, MMP9	–	Downregulation of ZFAS1 via regulating miR 302 3p on cyclin-D1could inhibit the hallmarks of TC.	[46]
Papillary Thyroid Carcinoma (PTC)	Up	male BALB/c nude mice/human; 80 pairs of PTC and NNCTs	IHH-4, TPC-1, K-1, BCPAP, Nthy-ori 3–1	miR-590–3p, HMGA2, Bax, Bcl-2	–	ZFAS1 via sponging miR-590–3p and upregulating HMGA2 could promote progression of PTC.	[47]
Head & Neck Squamous Cell Carcinomas (HNSCC)	Up	TCGA	DOK, SCC-040, SCC-25, FaDu	miR-150–5p,	–	ZFAS1 via regulating miR-150–5p could display oncogenic properties.	[48]
clear cell Renal Cell Carcinoma (ccRCC)	Up	ccRCC tissue (n = 60), adjacent non-tumor tissue (n = 20)	786-O, Caki-1, ACHN, HK-2, 293 T	miR-10a, SKA1	–	ZFAS1 via targeting the miR-10a/SKA1 axis could promote proliferation and metastasis of ccRCC.	[49]
Acute Myeloid Leukemia (AML)	Up	mice NOD/SCID/human; bone marrow samples from AML (n = 40), ALL (n = 23), NNCTs (25)	NB4, Kasumi-1	miR-150, Myb, Sp1, Cyclin-D1, p27, Bcl-2, Bax, PCNA	–	The knockdown of ZFAS1 via regulating miR-150/Sp1 and miR-150/Myb axes could suppress the progression of AML.	[50]
AML	Up	pediatric AML (n = 30) patients and after treatment with ADR-based chemotherapy	HL60, THP-1, HL60/ADR, THP-1/ADR	miR-195, Myb, MRP1, MDR1	–	ZFAS1 via the miR-195/Myb axis could enhance adriamycin resistance in pediatric AML.	[51]
AML	Up	–	HL-60, KG-1, ML-1, SKNO-1, Jurkat, Raji	–	–	Overexpression of ZFAS1 in AML cells could influence apoptosis. Knockdown of ZFAS1 could induce AML cell cycle G1 phase arrest.	[52]
Acute Lymphoblastic Leukemia (ALL)	Up	nude mice/human; T-ALL (n = 46)	CCRF-CEM, JK, CCRF-CEM/ADR, JK/ADR	miR-150, EGFR, ST6GAL1, Caspase-3, PARP	PI3K/AKT	ZFAS1/miR-150/ST6GAL1 crosstalk via the PI3K/Akt pathway could modulate the sialylation of EGFR in T cell ALL.	[53]
Cholangiocarcinoma	Up	BALB/c nude mouse /human; 64 pairs of CCA and NNCTs	CCLP-1, RBE, QBC939, HuCCT1	miR-296–5p, USF1, PCNA, E-cadherin, Snail, Vimentin, Bax	–	Overexpression of ZFAS1 via modulating USF1 via miR-296–5p could promote proliferation and metastasis and indicate a dismal prognosis for CCA.	[54]
Melanoma (M)	Up	BALB/c nude mice /human; 45 pairs of M and NNCTs	CHL-1, UACC904, A375, 1205Lu, HEM	miR-150–5p, RAB9A	–	ZFAS1 via regulating miR-150–5p/RAB9A could promote tumorigenesis in M.	[55]
Malignant Melanoma (MM)	Up	88 pairs of MM and NNCTs	sk-mel-1, A375	PCNA, Cyclin-D1, Ki67	–	Up-regulation of ZFAS1 enhances cell proliferation and invasion in MM.	[56]
Hepatoblastoma (HB)	Up	male nude mice/human; GSE75271, GSE75283, 70 pairs of HB and NNCTs	HepG2, HuH-6, L02, 293 T, Chang	miR-193a-3p, RALY, HGF, c-Met	–	ZFAS1 by sponging miR-193a-3p via targeting RALY via the HGF/c-Met axis could modulate HB growth.	[57]
Gastric Cancer (GC)	Up	BALB/c nude mice/human; 30 pairs of GC and NNCTs	BGC823, SGC7901	miR-200b, Wnt1, cyclin B1, GSK3β, β-catenin, Histone H3	–	ZFAS1 via the miR-200b-3p/Wnt1 axis could regulate the malignant progression of GC.	[58]
GC	Down	20 pairs of GC and NNCTs	SGC7901,	Cyclin-D1, Cyclin-E, Cyclin-B1, E-cadherin, N-cadherin, Vimentin, MMP-2, MMP-14, GSK3β, NKD2, H3	Wnt/β-catenin	The knockdown of ZFAS1 via blocking the Wnt/β-catenin pathway could inhibit malignancies in GC cells.	[59]
GC	Up	94 pairs of GC and NNCTs	BGC-823, GES-1, MGC-803, AGS, SGC-7901, MKN-28	Cyclin-D1, Bcl-2, Bax, E-cadherin, N-cadherin, Slug, Twist	EPK	Exosome-mediated transfer of ZFAS1 by promoting EMT and cell cycle progression could promote tumor metastasis in GC.	[60]
GC	Up	female athymic BALB/c nude mice/human; GEO databse	BGC823, SGC7901, MGC803, AGS, HGC27, GES-1	KLF2, NKD2	–	ZFAS1 via epigenetically repressing KLF2 and NKD2 could promote the proliferation of GC cells.	[61]
GC	Up	Plasma samples of GC (n = 77) and NC (n = 60)	GES-1, BGC-823, AGS, SGC-7901		–	Overexpression of ZFAS1 was associated with EMT of GC.	[62]

(*continued on next page*)

Table 1 (*continued*)

Type of Disease	Expression Patterns	Samples	Cell Line	Target	Pathway	Function	Refs.
				Vimentin, ZEB1, Snail, MMP14, Twist			
Gastric-Cardia Adenocarcinoma (GCA)	Up	NOD/SCID mice/human; 762 pairs of GCA and NNCTs	GCA-H008, GCAL084	EPAS1, HIF-1α	–	ZFAS1 by targeting EPAS1 could lead to the epigenetic silencing of the HIF-1α and promote cancer cell proliferation and metastasis.	[63]
Bladder Cancer (BLC)	Up	172 pairs of BLC and NNCTs	T24, RT4, 5637, SW780, SE780, UM-UC-3, SV-HUC-1	miR-329	–	ZFAS1 via sponging miR-329 could facilitate BLC tumorigenesis.	[64]
Endometrial Carcinoma (EC)	Up	64 pairs of EC and NNCTs	HEC-1B, RL95–2, Ishikawa, hEEC	CDK4, Cyclin-D1, N-cadherin, E-cadherin	–	ZFAS1 could promote EMT and cell proliferation in EC.	[65]

pancreatic adenocarcinoma both in cell line assays and in vivo. In this type of cancer, ZFAS1 has a regulatory role on the miR-3924/ROCK2 axis [19]. Plasma levels of ZFAS1 have been higher in patients with hepatocellular carcinoma compared with normal subjects as well as cirrhotic patients and those affected by hepatitis B. Notably, plasma levels of ZFAS1 have been associated with serum α-fetoprotein [20]. Up-regulation of ZFAS1 has also been reported in colon cancer tissues compared with neighboring tissues in association with teneurin transmembrane protein 1 (TNM) stage, vascular invasion, and lymph node involvement. The expression of ZFAS1 and zinc finger E-box binding homeobox 1 (ZEB1) has also been elevated in plasma samples of these patients. ZFAS1 silencing has diminished levels of ZEB1 and the mesenchymal markers, vimentin, and N-cadherin while enhancing E-cadherin and ZO-1. Therefore, ZFAS1 can activate EMT via enhancing ZEB1 expression [21]. Fig. 1 represents the regulation of EMT by ZFAS1 in several human cancers that plays an effective role in triggering malignancies and metastasis through modulating various signaling pathways including MAPK/ERK and PI3K/AKT. Table 1 displays the results

Table 2
Prognostic role of ZFAS1 in cancers (CRC: colorectal cancer, NNCT: nearby non-cancerous tissues, OS: overall survival, DFS: disease-free survival).

Samples	Kaplan Meier	Multivariate Cox analysis	Refs.
46 pairs of glioma and NNCTs	Higher expression of ZFAS1 was associated with a poorer OS.	–	[26]
TCGA	Higher expression of ZFAS1 was associated with poorer OS and DFS.	–	[16]
173 pairs of non-small cell carcinoma and NNCTs	Higher expression of ZFAS1 was associated with a poorer OS.	Higher expression of ZFAS1 was associated with differentiation, lymph node metastasis, and TMN stage.	[4]
94 pairs of hepatocellular carcinoma and NNCTs	Higher expression of ZFAS1 was associated with a poorer OS.	Higher expression of ZFAS1 was associated with lymph node metastasis and clinical stage.	[2]
GSE55191, GSE58043	Higher expression of ZFAS1 was associated with poorer OS and DFS.	Higher expression of ZFAS1 was associated with microvascular invasion and recurrence.	[31]
40 pairs of CRC and NNCTs	Higher expression of ZFAS1 was associated with a poorer OS.	–	[33]
49 pairs of CRC and NNCTs	Higher expression of ZFAS1 was associated with a poorer OS.	Higher expression of ZFAS1 was associated with helicobacter pylori, lymph nodes metastasis, and TNM stage.	[34]
112 pairs of CRC and NNCTs	Higher expression of ZFAS1 was associated with a poorer OS.	Higher expression of ZFAS1 was associated with TNM stage and distant metastasis.	[35]
159 pairs of CRC and NNCTs	Higher expression of ZFAS1 was associated with poorer OS and DFS.	Higher expression of ZFAS1 was associated with lymphatic invasion and TNM stage.	[36]
50 pairs of osteosarcoma and NNCTs	Higher expression of ZFAS1 was associated with a poorer OS.	–	[43]
53 pairs of osteosarcoma and NNCTs	Higher expression of ZFAS1 was associated with poorer OS and DFS.	Higher expression of ZFAS1 was associated with tumor size and recurrence.	[44]
TCGA, GSE50901, GSE33630, GSE29265	Higher expression of ZFAS1 was associated with a poorer OS.	Higher expression of ZFAS1 was associated with lymph node metastasis, TNM stage and recurrence status.	[45]
TCGA	Higher expression of ZFAS1 was associated with poorer OS and DFS.	Higher expression of ZFAS1 was associated with cancer stage.	[48]
60 renal cell carcinoma tissues and 20 NNCTs	Higher expression of ZFAS1 was associated with poorer OS.	Higher expression of ZFAS1 was associated with tumor size and lymph node metastasis.	[49]
64 pairs of cholangiocarcinoma and NNCTs	Higher expression of ZFAS1 was associated with a poorer OS.	Higher expression of ZFAS1 was associated with lymph node invasion, TNM stage, and postoperative recurrence.	[54]
45 pairs of melanoma and NNCTs	Higher expression of ZFAS1 was associated with poorer OS and DFS.	Higher expression of ZFAS1 was associated with invasion, TNM stage, distal metastasis, and lymph node metastasis.	[55]
88 pairs of malignant melanoma and NNCTs	Higher expression of ZFAS1 was associated with poorer OS and DFS.	Higher expression of ZFAS1 was associated with tumor thickness, lymph node metastasis, and clinical stage.	[56]
GSE75271, GSE75283, 70 pairs of hepatoblastoma and NNCTs	Higher expression of ZFAS1 was associated with a poorer OS.	Higher expression of ZFAS1 was associated with vascular invasion, metastasis, and COG stage.	[57]
GEO database	Higher expression of ZFAS1 was associated with poorer OS and DFS.	Higher expression of ZFAS1 was associated with tumor size and TNM stage.	[61]
762 pairs of gastric cardia adenocarcinoma and NNCTs	Higher expression of ZFAS1 was associated with poorer OS and DFS.	Higher expression of ZFAS1 was associated with TNM stage, distant metastasis, and differentiation.	[63]
64 pairs of endometrial cancer and NNCTs	Higher expression of ZFAS1 was associated with a poorer OS.	Higher expression of ZFAS1 was associated with FIGO stage and histological grade.	[65]

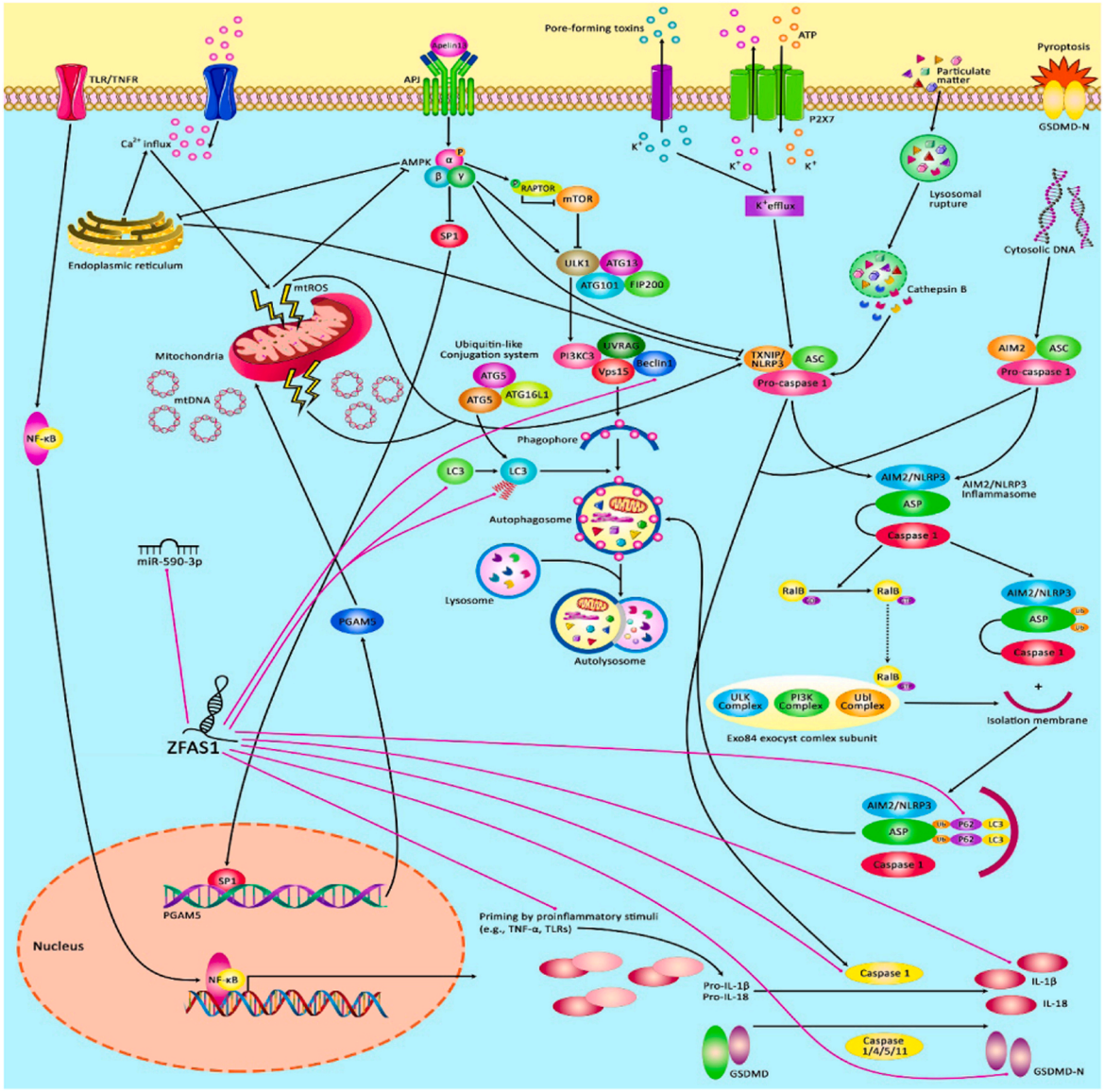

Fig. 2. A schematic diagram of the regulation of miR-590–3p/AMPK/mTOR signaling via ZFAS1 in sepsis-induced cardiac dysfunction. LncRNA ZFAS1, which is positively regulated by SP1, could play a remarkable role as a ceRNA for miR-590–3p and contributes to triggering the AMPK/mTOR signaling cascade. Consequently, this could in turn lead to autophagy inhibition as well as pyroptosis induction of cardiomyocytes. Therefore, ZFAS1 could elevate sepsis-induced cardiac dysfunction considerably.

of researches that reported aberrant expression of ZFAS1 in neoplastic conditions.

Expression of ZFAS1 can distinguish patients with neoplastic conditions from healthy subjects. For instance, plasma levels of ZFAS1 could differentiate patients with hepatocellular carcinoma from healthy subjects with the area under the receiver operating characteristic curve (AUC) value of 0.801. The combination of ZFAS1 and AFP has enhanced this value to 0.891. Thus, ZFAS1 has been suggested as a biomarker for the diagnosis of hepatocellular carcinoma [20]. In oral squamous cell carcinoma and colorectal cancers, expression levels of ZFAS1 have been shown to have AUC values of 0.82 and 0.837, respectively [3,34]. ZFAS1 levels can also predict the clinical course and prognosis of patients. In glioma, non-small cell carcinoma, hepatocellular carcinoma, colorectal cancer, cholangiocarcinoma, melanoma, hepatoblastoma, and gastric cancer, over-expression of ZFAS1 has been associated with poor clinical outcome. Table 2 shows the results of investigations that appraised the prognostic role of ZFAS1.

3. ZFAS1 in non-neoplastic conditions

3.1. Osteoarthritis (OA)

ZFAS1 levels are reduced in OA chondrocytes versus normal chondrocytes. Forced up-regulation of ZFAS1 has increased cell viability, proliferation rate, and migratory potential of chondrocytes, and suppressed apoptosis and matrix production in these cells. Moreover, ZFAS1 up-regulation has remarkably diminished Wnt3a factors. The protective impact of ZFAS1 against OA has been exerted through the modulation of Wnt3a signaling. Taken together, ZFAS1 might be a probable therapeutic candidate for the management of OA [6].

3.2. Epilepsy

ZFAS1 expression has been increased in the hippocampus and hippocampal neurons in the animal model of status epilepticus. ZFAS1 silencing has enhanced the survival of hippocampal neurons in these

Table 3
Expression of ZFAS1 in non-neoplastic conditions.

Type of Disease	Expression Patterns	Samples	Cell Line	Target	Pathway	Function	Ref
Osteoarthritis (OA)	Down	15 samples of OA chondrocytes and normal chondrocytes		MMP1, MMP13, p53, Caspase-3, BAX, Bcl-2, Wnt3a, β-catenin	–	ZFAS1 via targeting Wnt3a signaling could decrease matrix synthesis and apoptosis in OA.	[6]
Epilepsy	Up	C57BL/6 mice	Primary hippocampal neurons	miR-421, Bcl-2, Bax, Caspase-3, LC3-II/I, Beclin-1	PI3K/AKT	Knockdown of ZFAS1 by enhancing miR-421 and inducing the PI3K/AKT pathway could attenuate hippocampal neurons apoptosis and autophagy.	[7]
Rheumatoid Arthritis (RA)	Up	RA (n = 30), normal (n = 30)	fibroblast-like synoviocytes (FLR)-normal, FLS-RA	miR-2682–5p, LC3-I, LC3-II, ADAMTS9, Bcl-2, Bax, Caspase-3, TNF-α, IL-6, IL-10, p62	–	ZFAS1 via targeting the miR-2682–5p/ADAMTS9 axis could regulate the inflammation, apoptosis, and autophagy of FLR in RA.	[8]
RA	Up	Synovial tissues from RA patients (n = 40) and healthy persons (n = 40)	Fibroblast-like synoviocytes (FLS)	miR-27a, MMP-9, MMP-2	–	ZFAS1 via suppressing miR-27a could promote cell migration and invasion of FLS in RA.	[70]
Atherosclerosis	Up	–	THP-1	miR-654–3p, ADAM10, RAB22A, IL-1β, IL-6, TNF-α		ZFAS1 via regulating the miR-654–3p-ADAM10/RAB22A axis could confer inflammation and reduce cholesterol effluence.	[9]
Sepsis-Induced Cardiac Dysfunction	Up	C57BL/6 mice	Primary cardiomyocytes	Beclin 1, LC3II, LC3I, p62, miR-590–3p, IL-1β, TNF-α, GSDMD-N, Caspase-1	AMPK/mTOR	SP1-induced ZFAS1 via miR-590–3p/NLRP3-mediated autophagy and pyroptosis could aggravate sepsis-induced cardiac dysfunction.	[71]
Cerebral I/R Injury	Down	a rat model of cerebral I/R injury	PC12	miR-582, Bax, Bcl-2, Caspase-3, SOD, MDA, LDH, GSH-px, TNF-α, IL-1β, MCP-1	NOS/NO	ZFAS1 by sponging miR-582 and upregulating NOS3 could inhibit inflammation, oxidative stress, and apoptosis and also improve neuronal injury in cerebral I/R injury.	[72]
Pulmonary Fibrosis (PF)	Up	Sprague-Dawley rats	HFL1	miR-150–5p, SLC38A1, TGF-β1, E-cadherin, collagen-I, N1, α-SMA, MDA, GPX4	–	ZFAS1 via functioning as a ceRNA by the miR-150–5p/SLC38A1 axis could promote lung fibroblast-to-myofibroblast transition.	[73]
Acute Myocardial Infarction (AMI)	Down	C57BL/6 mice/ human; AMI patients (n = 138), NC (n = 95), Non-AMI control (n = 149)	–	–	–	Circulating ZFAS1 could be considered as a novel biomarker of AMI.	[74]
AMI	Up (1–48 h), Down (at 1 week and 2 weeks)	Sprague Dawley Rats	H9C2	miR-150, CRP	–	Knockdown of ZFAS1 by regulating the miR-150/CRP axis could protect cardiomyocytes against AMI.	[69]
Myocardial I/R Injury	Up	–	H9c2	miR-590–3p, TNF-α, IL-6, Bax, Caspase-3, Bcl-2, p50, NF-kB	–	Downregulation of ZFAS1 via the miR-590–3p/NF-kB pathway could protect H9c2 cells from I/R-induced apoptosis.	[75]
Myocardial Infarction (MI)	Up	C57BL/6 mice	NMCMs	Bax, Bcl2, Caspase-3, Caspase-9, SERCA2a	–	ZFAS1 via causing cytosolic Ca^{2+} overload could induce mitochondria-mediated apoptosis in mice model of MI.	[76]
MI	Up	C57BL/6 mice/human; patients with MI and without MI (n = 3)	AC16	SERCA2a	–	ZFAS1 via inhibiting SERCA2a led to intracellular Ca^{2+} overload and could impair cardiac contractile function in MI.	[77]
Ischemic Stroke (IS)	Down	176 patients and 111 healthy controls	–	–	–	ZFAS1 could be used as a biomarker for the diagnosis of stroke.	[78]

animal models and reduced their apoptosis and autophagy. Mechanistically, ZFAS1 serves as a sponge for miR-421. ZFAS1 knock-down has activated the PI3K/AKT pathway by enhancing miR-421 levels. Suppression of the PI3K/AKT pathway overturned the impact of ZFAS1 silencing on apoptosis/autophagy of neurons [7].

3.3. Rheumatoid arthritis

Expression assays in synovial tissues and fibroblast-like synoviocytes of patients with rheumatoid arthritis have demonstrated over-expression of ZFAS1 and ADAMTS9, while down-regulation of miR-2682–5p. ZFAS1 silencing has decreased proliferation, inflammation, autophagy, and enhanced apoptosis in fibroblast-like synoviocytes of these patients. Functionally, ZFAS1 accomplished this function via miR-2682–5p/ADAMTS9 axis [8].

3.4. Atherosclerosis

ZFAS1 levels have been remarkably increased in the cell line model of atherosclerosis. ZFAS1 silencing has diminished inflammatory responses and enhanced cholesterol effluence. On the other hand, ZFAS1 up-regulation has increased inflammatory responses and hindered cholesterol effluence. ZFAS1 participates in this process through sponging miR-654–3p and increasing ADAM10 and RAB22A expressions [9].

3.5. Sepsis-induced cardiac dysfunction

Over-expression of ZFAS1 has also been detected in sepsis-associated cardiac dysfunction in cell and animal models. ZFAS1 silencing has strongly stopped LPS-induced pyroptosis and decreased the suppression of autophagy. Expression of ZFAS1has been induced by the transcription factor SP1. Besides, miR-590–3p has been reported to be the downstream effector reversing ZFAS1-associated sepsis-induced cardiac dysfunction. AMPK/mTOR cascade has been identified as the molecular mediator of these effects [68]. Fig. 2 depicts an overview of SP1-induced ZFAS1 which deteriorates sepsis-induced cardiac dysfunction through miR-590–3p/NLRP3-modulated autophagy and pyroptosis. Up-regulation of ZFAS1 has also been reported in the myocardium infarcted zone and border zone of acute myocardial infarction (AMI). Levels of this lncRNA have been decreased 1 week and 2 weeks after AMI. ZFAS1 interacts with miR-150 to regulate levels of C-reactive protein (CRP) and increase apoptosis of cardiomyocytes [69]. Table 3 shows the role of ZFAS1 in non-neoplastic conditions.

4. Discussion

ZFAS1 partakes in the pathogenesis of diverse human disorders. This lncRNA mostly exerts its effect through sponging miRNAs. In the context of cancer, ZFAS1 mostly sequesters tumor suppressor miRNAs, thus increasing the expression of a number of oncogenes. Diverse studies have demonstrated that ZFAS1 acts as a molecular sponge for many miRNAs such as miR-589, miR-7–5p, miR-892b, miR-135a, miR-1271–5p, miR-432–5p, miR-548e, miR-150p, miR-590–3p, and miR-3924.

This lncRNA contributes to the regulation of PTEN/PI3K/AKT, Wnt/β-catenin, ERK/JNK, AKT/mTOR, and Notch pathway. In almost all types of cancers, ZFAS1 acts as an oncogene. In breast cancer, the results of different studies are inconsistent reporting both oncogenic and tumor suppressor roles for ZFAS1. ZFAS1 might also alter the response of cancer cells to radiotherapy and chemotherapy representing a possible target for improvement of the response of cancer cells to conventional treatment options. ZFAS1 might also affect the EMT process, thus influencing the metastatic aptitude of cancer cells. Plasma and tissue levels of ZFAS1 not only can distinguish patients with neoplastic conditions from healthy subjects, but they can also forecast the clinical outcome of cancer patients. Preliminary results have indicated the translation of ZFAS1 into a small peptide with functional roles in the carcinogenic processes in certain types of cancer. Upcoming studies should appraise the presence and functionality of translated ZFAS1 in other tissues.

Assessment of expression levels of ZFAS1 by quantitative real-time PCR method has led to proposing this lncRNA as a diagnostic marker for several neoplastic and non-neoplastic conditions. The data summarized above has also demonstrated a prognostic role for ZFAS1 in different cancers. A previous metanalysis of the prognostic role of ZFAS1 in different cancers has indicated an association between over-expression of ZFAS1 and poor overall survival as well as relapse-free survival of cancer patients. Notably, over-expression of ZFAS1 has also been associated with vascular invasion, lymph node involvement, and higher TNM stage [67].

Moreover, ZFAS1 is involved in the pathophysiology of a number of immune-related disorders such as RA and ischemic conditions such as ischemic stroke and myocardial infarction. The impact of ZFAS1 on immune-related genes has not been elucidated. Yet, apoptosis and autophagy-related pathways might also affect the pathogenic processes during these disorders.

Similar to other lncRNAs, expression levels of ZFAS1 in the peripheral blood can reflect the tissue-specific expression levels of this lncRNA, thus being applied as a non-invasive disease marker. An experiment in gastric cancer patients has verified this note [62]. However, data regarding the correlation between its circulatory levels and its tissue levels is not enough. In cases such as epilepsy in which tissue biopsy is not available, appraisal of this point is more difficult.

Finally, the correlation between ZFAS1 and its sense transcript should be assessed in different tissues to find the relevance of its sense transcript in this regard. Future studies should also focus on the evaluation of the diagnostic and prognostic roles of ZFAS1 in non-neoplastic disorders, particularly in immune-related conditions. The contribution of genetic variants of ZFAS1 in the pathogenesis of neoplastic or non-neoplastic conditions should also be appraised in future investigations.

CRediT authorship contribution statement

SGF and MT wrote the draft and revised it. AB, HS and MJK performed the data collection and designed the tables and figures. All the authors read and approved the submitted version.

Acknowledgements

This study was financially supported by shahid beheshti university of medical sciences.

References

[1] M.E. Askarian-Amiri, J. Crawford, J.D. French, C.E. Smart, M.A. Smith, M.B. Clark, K. Ru, T.R. Mercer, E.R. Thompson, S.R. Lakhani, A.C. Vargas, I.G. Campbell, M. A. Brown, M.E. Dinger, J.S. Mattick, SNORD-host RNA Zfas1 is a regulator of mammary development and a potential marker for breast cancer, RNA (N.Y.) 17 (5) (2011) 878–891.
[2] R. Duan, C. Li, F. Wang, F. Han, L. Zhu, The long noncoding RNA ZFAS1 potentiates the development of Hepatocellular carcinoma via the microRNA-624/MDK/ERK/JNK/P38 signaling pathway, OncoTargets Ther. 13 (2020) 4431–4444.
[3] X. Wang, R. Hao, F. Wang, F. Wang, ZFAS1 promotes cisplatin resistance via suppressing miR-421 expression in oral squamous cell carcinoma, Cancer Manag. Res. 12 (2020) 7251–7262.
[4] F. Tian, F. Meng, X. Wang, Overexpression of long-noncoding RNA ZFAS1 decreases survival in human NSCLC patients, Eur. Rev. Med. Pharm. Sci. 20 (24) (2016) 5126–5131.
[5] Z. Guo, Y. Meng, C. Xie, N. Zhao, M. Li, X. Zhai, C. Zhou, K. Li, T. Liu, X. Yang, Translated long non-coding ribonucleic acid ZFAS1 promotes cancer cell migration by elevating reactive oxygen species production in Hepatocellular carcinoma, Front. Genet. 10 (2019) 1111.
[6] D. Ye, W. Jian, J. Feng, X. Liao, Role of long noncoding RNA ZFAS1 in proliferation, apoptosis and migration of chondrocytes in osteoarthritis, Biomed. Pharmacother. 104 (2018) 825–831.
[7] F. Hu, L. Shao, J. Zhang, H. Zhang, A. Wen, P. Zhang, Knockdown of ZFAS1 Inhibits hippocampal neurons apoptosis and autophagy by activating the PI3K/AKT pathway via up-regulating miR-421 in epilepsy, Neurochem. Res. 45 (10) (2020) 2433–2441.
[8] S. Yang, W. Yin, Y. Ding, F. Liu, Lnc RNA ZFAS1 regulates the proliferation, apoptosis, inflammatory response and autophagy of fibroblast-like synoviocytes via miR-2682-5p/ADAMTS9 axis in rheumatoid arthritis, Biosci. Rep. 40 (8) (2020).
[9] X. Tang, R. Yin, H. Shi, X. Wang, D. Shen, X. Wang, C. Pan, LncRNA ZFAS1 confers inflammatory responses and reduces cholesterol efflux in atherosclerosis through regulating miR-654-3p-ADAM10/RAB22A axis, Int. J. Cardio 315 (2020) 72–80.
[10] S. Zhang, J. Wang, T. Yao, M. Tao, LncRNA ZFAS1/miR-589 regulates the PTEN/PI3K/AKT signal pathway in the proliferation, invasion and migration of breast cancer cells, Cytotechnology 72 (3) (2020) 415–425.
[11] S. Fan, C. Fan, N. Liu, K. Huang, X. Fang, K. Wang, Downregulation of the long non-coding RNA ZFAS1 is associated with cell proliferation, migration and invasion in breast cancer, Mol. Med. Rep. 17 (5) (2018) 6405–6412.
[12] S. Liu, J. Peng, F. Liu, H. Zheng, Q. Wu, LncRNA ZFAS1 contributed to irradiation resistance in nasopharyngeal carcinoma by inhibiting hsa-miR-7–5p/ENO2, (2020). DOI: https://doi.org/10.21203/rs.3.rs-16630/v1.
[13] J. Peng, F. Liu, H. Zheng, Q. Wu, S. Liu, Long noncoding RNA ZFAS1 promotes tumorigenesis and metastasis in nasopharyngeal carcinoma by sponging miR-892b to up-regulate LPAR1 expression, J. Cell. Mol. Med. 24 (2) (2020) 1437–1450.
[14] B. Zhang, J. Chen, M. Cui, Y. Jiang, LncRNA ZFAS1/miR-1271-5p/HK2 promotes glioma development through regulating proliferation, migration, invasion and apoptosis, Neurochem. Res. 45 (12) (2020) 2828–2839.
[15] X. Li, Y. Luo, L. Liu, S. Cui, W. Chen, A. Zeng, Y. Shi, L. Luo, The long noncoding RNA ZFAS1 promotes the progression of glioma by regulating the miR-150–5p/PLP2 axis, J. Cell. Physiol. 235 (3) (2020) 2937–2946.
[16] S. Han, D.Z. Li, M.F. Xiao, LncRNA ZFAS1 serves as a prognostic biomarker to predict the survival of patients with ovarian cancer, Exp. Ther. Med. 18 (6) (2019) 4673–4681.
[17] G. Fan, J. Jiao, F. Shen, F. Chu, Upregulation of lncRNA ZFAS1 promotes lung adenocarcinoma progression by sponging miR-1271–5p and upregulating FRS2, Thorac. Cancer 11 (2020) 2178–2187.

[18] Z. Zeng, G. Zhao, C. Rao, G. Hua, M. Yang, X. Miao, J. Ying, L. Nie, Knockdown of lncRNA ZFAS1–suppressed non–small cell lung cancer progression via targeting the miR-150–5p/HMGA2 signaling, J. Cell Biochem. 121 (2020) 3814–3824.
[19] J. Liu, Y. Zhu, C. Ge, LncRNA ZFAS1 promotes pancreatic adenocarcinoma metastasis via the RHOA/ROCK2 pathway by sponging miR-3924, Cancer Cell Int. 20 (1) (2020) 249–264.
[20] P. Luo, C. Liang, X. Zhang, X. Liu, Y. Wang, M. Wu, X. Feng, J. Tu, Identification of long non-coding RNA ZFAS1 as a novel biomarker for diagnosis of HCC, Biosci. Rep. 38 (4) (2018).
[21] C. Fang, J. Zan, B. Yue, C. Liu, C. He, D. Yan, Long non-coding ribonucleic acid zinc finger antisense 1 promotes the progression of colonic cancer by modulating ZEB1 expression, J. Gastroenterol. Hepatol. 32 (6) (2017) 1204–1211.
[22] X. Wang, Q. Jin, X. Wang, W. Chen, Z. Cai, LncRNA ZFAS1 promotes proliferation and migration and inhibits apoptosis in nasopharyngeal carcinoma via the PI3K/AKT pathway in vitro, Cancer Biomark. 26 (2) (2019) 171–182.
[23] M. Wang, Y. Ji, Z. Song, X. Ma, Y. Zou, X. Li, Knockdown of lncRNA ZFAS1 inhibits progression of nasopharyngeal carcinoma by sponging miR-135a, Neoplasma 66 (6) (2019) 939–945.
[24] X. Chen, J. Li, C. Li, X. Lu, Long non-coding RNA ZFAS1 promotes nasopharyngeal carcinoma through activation of Wnt/beta-catenin pathway, Eur. Rev. Med. Pharm. Sci. 22 (11) (2018) 3423–3429.
[25] G. Yang, B. Han, T. Feng, ZFAS1 knockdown inhibits viability and enhances cisplatin cytotoxicity by up-regulating miR-432–5p in glioma cells, Basic Clin. Pharmacol. Toxicol. 125 (6) (2019) 518–526.
[26] K. Gao, Z. Ji, K. She, Q. Yang, L. Shao, Long non-coding RNA ZFAS1 is an unfavourable prognostic factor and promotes glioma cell progression by activation of the Notch signaling pathway, Biomed. Pharmacother. 87 (2017) 555–560.
[27] J. Zhang, L.-N. Quan, Q. Meng, H.-Y. Wang, J. Wang, P. Yu, J.-T. Fu, Y.-J. Li, J. Chen, H. Cheng, miR-548e Sponged by ZFAS1 regulates metastasis and cisplatin resistance of OC by targeting CXCR4 and let-7a/BCL-XL/S signaling axis, Mol. Ther. Nucleic Acids 20 (2020) 621–638.
[28] L.L. Feng, F.R. Shen, J.H. Zhou, Y.G. Chen, Expression of the lncRNA ZFAS1 in cervical cancer and its correlation with prognosis and chemosensitivity, Gene 696 (2019) 105–112.
[29] Y. Zhou, L. Si, Z. Liu, Y. Shi, B. Agula, Long Noncoding RNA ZFAS1 Promotes Progression of NSCLC via Regulating of miR-590-3p, Cell Transplant. 29 (2020), 096368972091943, 0963689720919435.
[30] H. Zhou, Y. Zhou, Z. Feng, Long noncoding RNA ZFAS1 promotes hepatocellular carcinoma proliferation by epigenetically repressing miR-193a-3p, Eur. Rev. Med. Pharm. Sci. 23 (22) (2019) 9840–9847.
[31] T. Li, J. Xie, C. Shen, D. Cheng, Y. Shi, Z. Wu, X. Deng, H. Chen, B. Shen, C. Peng, Amplification of long noncoding RNA ZFAS1 promotes metastasis in hepatocellular carcinoma, Cancer Res. 75 (15) (2015) 3181–3191.
[32] H. Wu, W. Qin, S. Lu, X. Wang, J. Zhang, T. Sun, X. Hu, Y. Li, Q. Chen, Y. Wang, Long noncoding RNA ZFAS1 promoting small nucleolar RNA-mediated 2′-O-methylation via NOP58 recruitment in colorectal cancer, Mol. Cancer 19 (2020) 1–22.
[33] D. Mo, W. Liu, Y. Li, W. Cui, Long non-coding RNA zinc finger antisense 1 (ZFAS1) regulates proliferation, migration, invasion, and apoptosis by targeting MiR-7-5p in colorectal cancer, Med. Sci. Monit. Int. Med. J. Exp. Clin. Res. 25 (2019) 5150–5158.
[34] S. Xie, Q. Ge, X. Wang, X. Sun, Y. Kang, Long non-coding RNA ZFAS1 sponges miR-484 to promote cell proliferation and invasion in colorectal cancer, Cell Cycle 17 (2) (2018) 154–161.
[35] X. Chen, K. Zeng, M. Xu, X. Hu, X. Liu, T. Xu, B. He, Y. Pan, H. Sun, S. Wang, SP1-induced lncRNA-ZFAS1 contributes to colorectal cancer progression via the miR-150-5p/VEGFA axis, Cell Death Dis. 9 (10) (2018) 982.
[36] W. Wang, C. Xing, Upregulation of long noncoding RNA ZFAS1 predicts poor prognosis and prompts invasion and metastasis in colorectal cancer, Pathol. Res. Pract. 212 (8) (2016) 690–695.
[37] H. Shen, L. Wang, L. Zhang, X.-D. Weng, D. Yang, X.-H. Liu, Triiodothyronine levels were positively correlated with opening of collateral circulation in cerebral infarction patients with large artery atherosclerosis, Arch. Med. Sci. 16 (1) (2020) 51–57.
[38] X. Chen, C. Yang, S. Xie, E. Cheung, Long non-coding RNA GAS5 and ZFAS1 are prognostic markers involved in translation targeted by miR-940 in prostate cancer, Oncotarget 9 (1) (2018) 1048–1062.
[39] Z. Li, X. Qin, W. Bian, Y. Li, B. Shan, Z. Yao, S. Li, Exosomal lncRNA ZFAS1 regulates esophageal squamous cell carcinoma cell proliferation, invasion, migration and apoptosis via microRNA-124/STAT3 axis, J. Exp. Clin. Cancer Res. 38 (1) (2019) 477.
[40] H. Shi, Z. Liu, D. Pei, Y. Jiang, H. Zhu, B. Chen, Development and validation of nomogram based on lncRNA ZFAS1 for predicting survival in lymph node-negative esophageal squamous cell carcinoma patients, Oncotarget 8 (35) (2017) 59048–59057.
[41] C. Liu, D. Liu, D. Peng, Long non-coding RNA ZFAS1 regulates NOB1 expression through interacting with miR-646 and promotes tumorigenesis in osteosarcoma, Eur. Rev. Med. Pharm. Sci. 23 (8) (2019) 3206–3216.
[42] Z. Zhao, X. Lin, Y. Tong, W. Li, Silencing lncRNA ZFAS1 or elevated microRNA-135a represses proliferation, migration, invasion and resistance to apoptosis of osteosarcoma cells, Cancer Cell Int. 19 (1) (2019) 326.
[43] G. Liu, L. Wang, H. Han, Y. Li, S. Lu, T. Li, C. Cheng, LncRNA ZFAS1 promotes growth and metastasis by regulating BMI1 and ZEB2 in osteosarcoma, Am. J. Cancer Res. 7 (7) (2017) 1450–1462.
[44] N. Li, Z.-H. Sun, M. Fang, J.-Y. Xin, C.-Y. Wan, Long non-coding RNA ZFAS1 sponges miR-486 to promote osteosarcoma cells progression and metastasis in vitro and vivo, Oncotarget 8 (61) (2017) 104160–104170.
[45] C.-G. Han, Y. Huang, L. Qin, Long non-coding RNA ZFAS1 as a novel potential biomarker for predicting the prognosis of thyroid cancer, Med. Sci. Monit. Int. Med. J. Exp. Clin. Res. 25 (2019) 2984–2992.
[46] W. Chen, L. Zhai, H. Liu, Y. Li, Q. Zhang, D. Xu, W. Fan, Downregulation of lncRNA ZFAS1 inhibits the hallmarks of thyroid carcinoma via the regulation of miR-302–3p on cyclin D1, Mol. Med. Rep. 23 (1) (2021).
[47] H. Tong, X. Zhuang, J. Cai, Y. Ding, Y. Si, H. Zhang, M. Shen, Long noncoding RNA ZFAS1 promotes progression of papillary thyroid carcinoma by sponging miR-590-3p and upregulating HMGA2 expression, OncoTargets Ther. 12 (2019) 7501–7512.
[48] T. Kolenda, K. Guglas, M. Kopczyńska, A. Teresiak, R. Bliźniak, A. Mackiewicz, K. Lamperska, J. Mackiewicz, Oncogenic role of ZFAS1 lncRNA in head and neck squamous cell carcinomas, Cells 8 (4) (2019) 366.
[49] D. Dong, Z. Mu, N. Wei, M. Sun, W. Wang, N. Xin, Y. Shao, C. Zhao, Long non-coding RNA ZFAS1 promotes proliferation and metastasis of clear cell renal cell carcinoma via targeting miR-10a/SKA1 pathway, Biomed. Pharmacother. 111 (2019) 917–925.
[50] S. Gan, P. Ma, J. Ma, W. Wang, H. Han, L. Chen, X. Li, F. Wu, H. Sun, Knockdown of ZFAS1 suppresses the progression of acute myeloid leukemia by regulating microRNA-150/Sp1 and microRNA-150/Myb pathways, Eur. J. Pharm. 844 (2019) 38–48.
[51] Q. Li, J. Wang, Long noncoding RNA ZFAS1 enhances adriamycin resistance in pediatric acute myeloid leukemia through the miR-195/Myb axis, RSC Adv. 9 (48) (2019) 28126–28134.
[52] H. Guo, L. Wu, P. Zhao, A. Feng, Overexpression of long non-coding RNA zinc finger antisense 1 in acute myeloid leukemia cell lines influences cell growth and apoptosis, Exp. Ther. Med. 14 (1) (2017) 647–651.
[53] Q. Liu, H. Ma, X. Sun, B. Liu, Y. Xiao, S. Pan, H. Zhou, W. Dong, L. Jia, The regulatory ZFAS1/miR-150/ST6GAL1 crosstalk modulates sialylation of EGFR via PI3K/Akt pathway in T-cell acute lymphoblastic leukemia, J. Exp. Clin. Cancer Res. 38 (1) (2019) 199.
[54] Z. Li, X. Jiang, L. Huang, J. Li, D. Ji, Y. Xu, K. Leng, Y. Cui, Up-regulation of ZFAS1 indicates dismal prognosis for cholangiocarcinoma and promotes proliferation and metastasis by modulating USF1 via miR-296–5p, J. Cell. Mol. Med. 23 (12) (2019) 8258–8268.
[55] L. Liang, Z. Zhang, X. Qin, Y. Gao, P. Zhao, J. Liu, W. Zeng, Long noncoding RNA ZFAS1 promotes tumorigenesis through regulation of miR-150-5p/RAB9A in melanoma, Melanoma Res. 29 (6) (2019) 569–581.
[56] Y.-H. Wei, Y. Fu, H.-J. Luo, R. Li, H.-Y. Li, Z. Zhang, Y.-H. Zhu, Y. Gao, X.-L. Liu, Higher expression of ZFAS1 is associated with poor prognosis in malignant melanoma and promotes cell proliferation and invasion, Int J. Clin. Exp. Pathol. 10 (4) (2017) 4640–4646.
[57] G. Cui, X. Cui, Z. Wang, L. lIU, X. Liu, D. Zhang, J. Li, J. Zhu, J. Pan, D. Zhang, The Long Non-coding RNA ZFAS1 sponges miR-193a-3p to modulate hepatoblastoma growth by targeting RALY via HGF/c-Met pathway, Front. Cell Dev. Biol. 7 (2019) 271.
[58] F. Zhang, Y. Li, W. Xu, L. He, Y. Tan, H. Xu, Long non-coding RNA ZFAS1 regulates the malignant progression of gastric cancer via the microRNA-200b-3p/Wnt1 axis, Biosci. Biotechnol. Biochem. 83 (7) (2019) 1289–1299.
[59] W. Xu, L. He, Y. Li, Y. Tan, F. Zhang, H. Xu, Silencing of lncRNA ZFAS1 inhibits malignancies by blocking Wnt/β-catenin signaling in gastric cancer cells, Biosci. Biotechnol. Biochem. 82 (3) (2018) 456–465.
[60] L. Pan, W. Liang, M. Fu, Z.-h Huang, X. Li, W. Zhang, P. Zhang, H. Qian, P.-c Jiang, W.-r Xu, Exosomes-mediated transfer of long noncoding RNA ZFAS1 promotes gastric cancer progression, J. Cancer Res. Clin. Oncol. 143 (6) (2017) 991–1004.
[61] F. Nie, X. Yu, M. Huang, Y. Wang, M. Xie, H. Ma, Z. Wang, W. De, M. Sun, Long noncoding RNA ZFAS1 promotes gastric cancer cells proliferation by epigenetically repressing KLF2 and NKD2 expression, Oncotarget 8 (24) (2017) 38227–38238.
[62] H. Zhou, F. Wang, H. Chen, Q. Tan, S. Qiu, S. Chen, W. Jing, M. Yu, C. Liang, S. Ye, Increased expression of long-noncoding RNA ZFAS1 is associated with epithelial-mesenchymal transition of gastric cancer, Aging (Albany NY) 8 (9) (2016) 2023–2038.
[63] T. Zhu, Z. Wang, G. Wang, Z. Hu, H. Ding, R. Li, J. Sun, Long non-coding RNA ZFAS1 promotes the expression of EPAS1 in gastric cardia adenocarcinoma, J. Adv. Res 28 (2020) 7–15.
[64] J.-S. Wang, Q.-H. Liu, X.-H. Cheng, W.-Y. Zhang, Y.-C. Jin, The long noncoding RNA ZFAS1 facilitates bladder cancer tumorigenesis by sponging miR-329, Biomed. Pharmacother. 103 (2018) 174–181.
[65] Y. Sun, X. Gao, P. Li, L. Song, L. Shi, LncRNA ZFAS1, as a poor prognostic indicator, promotes cell proliferation and epithelial–mesenchymal transition in endometrial carcinoma, Per Med. 18 (1) (2021) 43–53.
[66] S. Ghafouri-Fard, H. Shoorei, F.T. Anamag, M. Taheri, The role of non-coding RNAs in controlling cell cycle related proteins in cancer cells, Front. Oncol. 10 (2616) (2020).
[67] T. Lan, X. Lan, G. Li, Z. Zheng, M. Zhang, F. Qin, Prognostic role of long noncoding RNA ZFAS1 in cancer patients: a systematic review and meta-analysis, Oncotarget 8 (59) (2017) 100490–100498.
[68] J.-J. Liu, Y. Li, M.-S. Yang, R. Chen, C.-Q. Cen, SP1-induced ZFAS1 aggravates sepsis-induced cardiac dysfunction via miR-590–3p/NLRP3-mediated autophagy and pyroptosis, Arch. Biochem. Biophys. 695 (2020), 108611.
[69] T. Wu, D. Wu, Q. Wu, B. Zou, X. Huang, X. Cheng, Y. Wu, K. Hong, P. Li, R. Yang, Knockdown of long non-coding RNA-ZFAS1 protects cardiomyocytes against acute myocardial infarction via anti-apoptosis by regulating miR-150/CRP, J. Cell. Biochem. 118 (10) (2017) 3281–3289.

[70] Y. Ye, X. Gao, N. Yang, LncRNA ZFAS1 promotes cell migration and invasion of fibroblast-like synoviocytes by suppression of miR-27a in rheumatoid arthritis, Hum. Cell 31 (1) (2018) 14–21.
[71] J.-J. Liu, Y. Li, M.-S. Yang, R. Chen, C.-Q. Cen, SP1-induced ZFAS1 aggravates sepsis-induced cardiac dysfunction via miR-590-3p/NLRP3-mediated autophagy and pyroptosis, Arch. Biochem. Biophys. 695 (2020), 108611.
[72] Y. Zhang, Y. Zhang, lncRNA ZFAS1 improves neuronal injury and inhibits inflammation, oxidative stress, and apoptosis by sponging miR-582 and upregulating NOS3 expression in cerebral ischemia/reperfusion injury, Inflammation 43 (4) (2020) 1337–1350.
[73] Y. Yang, W. Tai, N. Lu, T. Li, Y. Liu, W. Wu, Z. Li, L. Pu, X. Zhao, T. Zhang, lncRNA ZFAS1 promotes lung fibroblast-to-myofibroblast transition and ferroptosis via functioning as a ceRNA through miR-150-5p/SLC38A1 axis, Aging (Albany NY) 12 (10) (2020) 9085–9102.
[74] Y. Zhang, L. Sun, L. Xuan, Z. Pan, K. Li, S. Liu, Y. Huang, X. Zhao, L. Huang, Z. Wang, Reciprocal changes of circulating long non-coding RNAs ZFAS1 and CDR1AS predict acute myocardial infarction, Sci. Rep. 6 (2016) 22384.
[75] P. Huang, D. Yang, L. Yu, Y. Shi, Downregulation of lncRNA ZFAS1 protects H9c2 cardiomyocytes from ischemia/reperfusion-induced apoptosis via the miR-590–3p/NF-κB signaling pathway, Mol. Med. Rep. 22 (3) (2020) 2300–2306.
[76] L. Jiao, M. Li, Y. Shao, Y. Zhang, M. Gong, X. Yang, Y. Wang, Z. Tan, L. Sun, L. Xuan, lncRNA-ZFAS1 induces mitochondria-mediated apoptosis by causing cytosolic Ca2+ overload in myocardial infarction mice model, Cell Death Dis. 10 (12) (2019) 942.
[77] Y. Zhang, L. Jiao, L. Sun, Y. Li, Y. Gao, C. Xu, Y. Shao, M. Li, C. Li, Y. Lu, LncRNA ZFAS1 as a SERCA2a inhibitor to cause intracellular Ca2+ overload and contractile dysfunction in a mouse model of myocardial infarction, Circ. Res. 122 (10) (2018) 1354–1368.
[78] J. Wang, J. Ruan, M. Zhu, J. Yang, S. Du, P. Xu, Z. Zhang, P. Wang, W. Yang, M. Yu, Predictive value of long noncoding RNA ZFAS1 in patients with ischemic stroke, Clin. Exp. Hypertens. 41 (7) (2019) 615–621.