Clinica Chimica Acta 497 (2019) 20–26

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Review

Long noncoding RNA FEZF1-AS1 in human cancers

Yuanshi Zhou[1], Shuwan Xu[1], Haoming Xia, Zewei Gao, Rongju Huang, Enyu Tang, Xingming Jiang*

Department of HPB Surgery, The 2nd Affiliated Hospital of Harbin Medical University, 246 Xuefu-ro, Harbin 150086, China

ARTICLE INFO

Keywords:
Long noncoding RNA
FEZF1-AS1
Cancer
Biomarker

ABSTRACT

Long noncoding RNAs (lncRNAs) have been shown to play key roles in various human tumors. Ectopic expression of the lncRNA FEZ finger zinc 1 antisense 1 (FEZF1-AS1) have been reported in different cancers, including colorectal cancer, gastric neoplasia, hepatocellular carcinoma and so on. Summarizing all literature correlated with FEZF1-AS1, it is obvious that FEZF1-AS1 is mainly involved in tumorigenesis and progression through competing endogenous RNA (ceRNA) which sponges tumor-suppressive microRNA (miRNA) and recruiting mechanism. Moreover, the aberrant expression of FEZF1-AS1 is related to clinical features of patients with cancers, and regulates cellular proliferation, anti-apoptosis, invasion and metastasis through diverse underlying mechanisms. The role of FEZF1-AS1 in carcinogenesis and progression suggests that it may be a potential diagnostic biomarker or a novel therapeutic target for cancers.

1. Introduction

A number of reports on global current situation of cancer from the past few years suggest that cancer is still the problem demanding prompt solution [1–3]. The potential molecular mechanisms of cancer have been extensively studied in the last few decades. Accumulating evidence indicates that noncoding RNAs (ncRNAs) have no or limited protein-coding ability on account of lacking open reading frames, but play crucial roles in molecular biology of tumors involving transcription, translation, epigenetic processes and so forth [4–9]. The ncRNAs are divided into different types according to their length, including microRNAs (miRNAs), small nucleolar RNAs (snRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs) [10–12].

LncRNAs are mainly transcribed by RNA polymerase II and longer than 200 nucleotides in length [13,14]. Increasing evidence shows that lncRNAs regulate molecular processes of tumors at transcription, translation, epigenetic levels generally *via* gene imprinting, histone modification, chromatin remodeling, transcriptional interference, alternative splicing and cell cycle control. Furthermore, certain lncRNAs show cell and tissue specific expression patterns which are critical for their functional analysis and exploring the potential of lncRNAs as diagnostic, prognostic, and therapeutic targets in cancer [15–22]. Although a mass of lncRNAs have been discovered in the past few years, many lncRNAs and its functions or mechanisms have been unknown. The role of potential thousands of lncRNAs has aroused intense scientific interest.

FEZ family zinc finger antisense 1 (FEZF1-AS1) is a novel lncRNA which is dysregulated in various human cancers and related to a lot of aspects of carcinogenesis. Recent researches have demonstrated that FEZF1-AS1 expression is upregulated in multiple types of tumors compared to matched normal tissues and knockdown of FEZF1-AS1 can suppress cellular proliferation, migration and invasion, suggesting that FEZF1-AS1 may also act as an oncogenic lncRNA in cancers. The present review summarizes current studies regarding the expression,

---

Abbreviations: AJCC, American Joint Committee on Cancer; Akt3/PKB3, protein kinase B3; BCSC, breast cancer-stem like cell; CC, cervical cancer; ceRNA, competing endogenous RNA; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; EZH2, enhancer of zeste homolog 2; FEZF1-AS1, Fez finger zinc 1 antisense 1; FEZF1/ZNF312B, Fez family zinc finger protein 1; FIGO, international federation of gynecology and obstetrics; GC, gastric cancer; HCC, hepatocellular carcinoma; LAD, lung adenocarcinoma; JAK2, janus kinase 2; lncRNAs, long noncoding RNAs; HIF-1α, hypoxia-inducible factor 1α; LSD1, lysine-specific histone demethylase 1A; MM, multiple myeloma; NUPR1, nuclear protein 1; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; OS, osteosarcoma; PC, pancreatic carcinoma; PDAC, pancreatic ductal adenocarcinoma; PKM2, pyruvate kinase 2; PRC2, polycomb repressive complex 2; Slug also known as SNAI2, snail family transcriptional repressor 2; STAD, stomach adenocarcinoma; STAT3, signal transducer and activator of transcription 3; ZO-1, zonula occludens-1

* Corresponding author.

E-mail address: xmjiang@hrbmu.edu.cn (X. Jiang).

[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.cca.2019.07.004
Received 24 April 2019; Received in revised form 27 June 2019; Accepted 1 July 2019

Table 1
Functional characterization of FEZF1-AS1 in various cancers.

Cancer type	Expression	Role	Biological functions	Related genes	Refs
Colorectal cancer	Up	Oncogenic	Proliferation, migration, invasion, cell cycle arrest	PKM2, STAT3	[23,27]
Gastric cancer	Up	Oncogenic	Proliferation, cell cycle arrest, apoptosis, EMT	p21, LSD1, β-catenin, E-cadherin, Vimentin, cyclin D1	[24,35,36]
Pancreatic carcinoma	Up	Oncogenic	Proliferation, invasion, migration	ZNF312B, miR-107, miR-142, miR-133a, HIF-1α, EGFR	[38,40]
Hepatocellular cancer	Up	Oncogenic	Proliferation, cell cycle arrest, migration, invasion, EMT	N-cadherin, Vimentin, E-cadherin, JAK2, STAT3	[42]
Lung cancer	Up	Oncogenic	Proliferation, cell cycle arrest, EMT	EZH2, LSD1, p57, FEZF1, E-cadherin, β-catenin, ZO-1, Slug, Twist, Vimentin	[43,47,48,49]
Breast cancer	Up	Oncogenic	Proliferation, migration, invasion	Nanog, miR-30a	[55]
Multiple myeloma	Up	Oncogenic	Apoptosis, cell cycle arrest	miR-610, Akt3	[58]
Nasopharyngeal carcinoma	Up	Oncogenic	Proliferation, migration, invasion, cell cycle arrest, EMT	p21, cyclin D1, N-cadherin, Vimentin, E-cadherin, β-catenin	[59]
Cervical cancer	Up	Oncogenic	–	–	[61]
Ovarian cancer	Up	Oncogenic	Proliferation, apoptosis	JAK, STAT3	[62]
Osteosarcoma	Up	Oncogenic	Proliferation, migration and invasion	miR-4443, NUPR1	[63]
Esophageal squamous cell carcinoma	Up	Oncogenic	Migration and invasion	β-catenin	[64]
Retinoblastoma	Up	Oncogenic	Proliferation, migration and invasion	–	[65]

Abbreviations: FEZF1-AS1, Fez finger zinc 1 antisense 1; PKM2, pyruvate kinase 2; STAT3, signal transducer and activator of transcription 3; EMT, epithelial-mesenchymal transition; LSD1, lysine-specific histone demethylase 1A; HIF-1α, hypoxia-inducible factor 1α; EGFR, epidermal growth factor receptor; JAK, janus kinase; EZH2, enhancer of zeste homolog 2; ZO-1, zonula occludens-1; Slug also known as SNAI2, snail family transcriptional repressor 2; NUPR1, nuclear protein 1.

function, mechanism and clinical significance of FEZF1-AS1 in tumorigenesis and progression (Tables 1 and 2).

2. Characterization of FEZF1-AS1

FEZF1-AS1 is a conserved 2653 nt RNA transcribed from the plus strand of chromosome 7, on the opposite strand of its cognate gene coding Fez family zinc finger protein 1 (FEZF1), which is located on chromosome 7q31.32 and contains seven exons. There are 611 complementary nucleotides between FEZF1-AS1 first exon and FEZF1 first exon [23]. Three splice variants of FEZF-AS1 has been discovered so far, FEZF1-AS1–201 (679 bp, one exon), FEZF1-AS1-202 (2653 bp, three exons), FEZF1-AS1-203 (768 bp, one exon), respectively [24]. Researches indicate that FEZF1-AS1 is distributed in both the cytoplasm and the nucleus and plays important roles in both. The results of Human Protein Atlas project (HPA) RNA-seq normal tissues suggest that FEZF1-AS1 is higher expression in testis and brain compared with other normal human tissues [25]. Importantly, a growing body of evidence shows that FEZF1-AS1 exerts powerful functions in tumors and further studies of FEZF1-AS1 and other ncRNAs are expected to elucidate tumorigenesis and progression. Moreover, the result of a recent meta-analysis shows that increased expression of FEZF1-AS1 was significantly correlated with shorter overall survival and disease-free survival in cancer patients. FEZF1-AS1 may serve as a valuable prognostic biomarker for clinical outcomes in various solid tumors [26].

3. FEZF1-AS1 deregulation in human cancers

3.1. FEZF1-AS1 in colorectal carcinoma

FEZF1-AS1 expression was significantly elevated in 34 CRC tissues compared with adjacent non-neoplastic mucosa tissues, and upregulated expression of FEZF1-AS1 was also identified in HCT116, M5 and LOVO cell lines. Moreover, high FEZF1-AS1 expression was associated with T-stage, lymph-node invasion and distant metastasis in patient with CRC to a significant extent. Functionally, knockdown of FEZF1-AS1 inhibited cell proliferation, migration and invasion, promoted G1 arrest but did not cause apoptosis *in vitro*. Meanwhile, silence of FEZF1-AS1 repressed tumor growth and metastasis *in vivo*. Kaplan-Meier analysis suggested that the high expression of FEZF1-AS1 was significantly correlated with overall survival and disease-free survival of CRC patients. Univariate and multivariate analyses indicated that high expression of FEZF1-AS1 was considered as an independent prognostic factor for CRC patient. In addition, FEZF1-AS1 knockdown reduced its sense-cognate gene FEZF1 expression, and downregulation of FEZF1 also significantly suppressed CRC cell proliferation, migration and invasion, which showed that FEZF1-AS1 participated in CRC genesis and development through FEZF1 induction at least in part [23]. Bian et al. [27] identified FEZF1-AS1 is one of the most overexpressed lncRNAs in CRC through using lncRNA microarrays and further work confirmed this result. Mechanistically, pyruvate kinase 2 (PKM2) catalyzes the last step within glycolysis and is responsible for net ATP production. Meanwhile, energy regeneration by pyruvate kinase is independent from oxygen supply and allows survival of the organs under hypoxic conditions often found in solid tumors [28–30]. FEZF1-AS1 could bind with pyruvate kinase 2 (PKM2) and maintain its stability, resulting in increased cytoplasmic and nuclear PKM2. Increased cytoplasmic PKM2 enhanced pyruvate kinase activity and increased lactate production (aerobic glycolysis), whereas nuclear PKM2 upregulation further activated signal transducer and activator of transcription 3 (STAT3) which mediates the expression of a variety of genes in response to cell stimuli [31–33], and thus plays a key role in many cellular processes such as cell growth and apoptosis.

Table 2
Clinical significance of FEZF1-AS1 in diverse cancers.

Cancer types	Overexpression of FEZF1-AS1 and clinical features	Refs
Colorectal cancer	Advanced T stage, lymph-node metastasis, distant metastasis and poor overall survival	[23,27]
Gastric cancer	Tumor size, higher grade, advanced TNM stage and poor overall survival	[24,35,36]
Pancreatic carcinoma	Tumor size, lymph node metastasis, poor differentiation, advanced TNM stage, neural invasion and poor overall survival	[38,40]
Hepatocellular cancer	Tumor size, advanced TNM stage, venous invasion and poor overall survival	[42]
Lung cancer	Tumor size, lymph node metastasis, poor differentiation grade, advanced TNM stage, histological degree, tumor family history and poor overall survival	[43,47,48,49]
Breast cancer	ER+, HER+, distant metastases, lymphatic metastasis, advanced TNM stage and poor overall survival	[55]
Multiple myeloma	–	[58]
Nasopharyngeal carcinoma	Distant metastasis and poor overall survival	[59]
Cervical cancer	Histological grade, distant metastasis, FIGO stage and poor overall survival	[61]
Ovarian cancer	Poor overall survival	[62]
Osteosarcoma	Tumor size, metastasis, advanced clinical stage and poor overall survival	[63]
Esophageal squamous cell carcinoma	Lymphatic metastasis	[64]
Retinoblastoma	Present choroidal invasion, optic nerve invasion and unfavorable prognosis	[65]

Abbreviations: FEZF1-AS1, Fez finger zinc 1 antisense 1; ER, estrogen receptor; HER, human epidermal growth factor receptor; FIGO, international federation of gynecology and obstetrics.

3.2. FEZF1-AS1 in gastric tumor

Liu et al. [24] observed that the expression of FEZF1-AS1 was upregulated in 82 gastric cancer samples, SGC-7901 and AGS cells compared with adjacent histologically normal tissues and normal gastric epithelium cells. Upregulated FEZF1-AS1 expression indicated larger tumor size, advanced clinical stage and poor prognosis. Moreover, knockdown FEZF1-AS1 significantly depressed cells proliferation by inducing G1 arrest and apoptosis, whereas increased FEZF1-AS1 expression promoted cell growth. Mechanically, FEZF1-AS1 could epigenetically repress the expression of tumor-suppressing p21 gene *via* binding with lysine-specific histone demethylase 1A (LSD1), which is the first of several protein lysine demethylases discovered and through a FAD-dependent oxidative reaction, LSD1 specifically removes histone H3K4me2 to H3K4me1 or H3K4me0 [34]. Gu et al. [35] constructed the lncRNA and mRNA expression profile of three stomach adenocarcinoma (STAD) tissues and matched adjacent non-tumor tissues through high-throughput RNA-sequencing. They found that FEZF1-AS1 expression was elevated in STAD tissues and FEZF1-AS1 had the potential diagnosis value for STAD by Hierarchical clustering analysis of expression profile. Wu et al. [36] discovered that FEZF1-AS1 was overexpressed in 104 GC tissues and MGC-803, MKN-49P cells, and related to advanced stage and higher grade to a significant extent. Suppression of FEZF1-AS1 inhibited the proliferation of GC cells and the cell cycle was arrested at a G0/G1 stage. Furthermore, downregulation of FEZF1-AS1 could suppress β-catenin, c-Myc and cyclin D1 expression, but it could promote E-cadherin expression, resulting in the silence of the Wnt/β-catenin signaling pathway.

3.3. FEZF1-AS1 in pancreatic carcinoma

Pancreatic carcinoma (PC) remains to be one of the most malignant human cancers all over the world [37]. Therefore, exploring the underlying molecular mechanisms of pancreatic carcinoma is essential for the identification of novel biomarkers and valid therapeutic targets. FEZF1-AS1 and its cognate-gene ZNF312B expression were significantly upregulated in 94 pancreatic ductal adenocarcinoma (PDAC) tissues and 5 cell lines. Both were dramatically connected with poor differentiation, advanced American Joint Committee on Cancer (AJCC) stage, and neural invasion, resulting in poorer survival in PDAD patients. Functionally, knockdown of FEZF1-AS1 suppressed tumor cells proliferation, invasion and migration. Moreover, FEZF1-AS1 primarily localized in the cytoplasm and its expression was positively related to ZNF312B expression. Furthermore, FEZF1-AS1 not its mutations acted as the competing endogenous RNA by directly binding to miR-107 in a sequence-specific manner. Meanwhile, ZNF312B was also a target gene of miR-107 and was regulated by FEZF1-AS1. In other words, FEZF1-AS1 functioned as an endogenous sponge by sequestering miR-107 and thus abolishing the miRNA-induced repressing effect on the ZNF312B. Furthermore, the Warburg effect is also known as aerobic glycolysis, which is a key point in cancer research, including pancreatic carcinoma. FEZF1-AS1/miR-107/ZNF312B pathway was able to maintain Warburg effect of PDAC cells [38,39]. Qu et al. [40] discovered that FEZF1-AS1 could promote PC cells proliferation and invasion through miR-142/HIF-1α (hypoxia-inducible factor 1α) axis under hypoxic condition and exert its oncogenic effect on PC cells through miR-133a/EGFR (epidermal growth factor receptor) axis under the normoxic condition. As mentioned above, FEZF1-AS1 as a tumor-promoting factor, may be a potential prognostic biomarker and therapeutic target for PC patients.

3.4. FEZF1-AS1 in hepatocellular carcinoma

Hepatocellular carcinoma (HCC), which leads to nearly 600,000 deaths yearly, is one of the common diagnosed cancers and one of the leading etiologies of cancer-related deaths worldwide [41]. Wang et al. [42] observed remarkable upregulation of FEZF1-AS1 expression in 139 HCC tissues and HepG2 and Huh7 cells. Meanwhile, its overexpression was significantly correlated with tumor size, TNM stage and venous invasion. Kaplan-Meier analysis revealed that high expression of FEZF1-AS1 was also associated with poor overall survival of HCC patients. Functionally, suppression of FEZF1-AS1 hindered HCC cell proliferation, cycle progression, migration and invasion *in vitro*, and tumor growth *in vivo*. Mechanically, FEZF1-AS1 knockdown in HCC cells suppressed the expression of N-cadherin and Vimentin, but upregulated the E-cadherin expression, resulting in repression of epithelial-mesenchymal transition (EMT) process. In terms of cellular signal pathway, obstruction of FEZF1-AS1 reduced the expression of Janus kinase 2 (JAK2) and phosphorylated STAT3. Nevertheless, JAK2 overexpression obviously restored the attenuated EMT process, migration and invasion of HepG2 and Huh7 cells following FEZF1-AS1 knockdown. In another word, FEZF1-AS1 exerted tumor-promoting action by regulating JAK/STAT3 signaling pathway. These results demonstrated that FEZF1-AS1 acts as an oncogenic lncRNA in HCC which may serve as a novel independent prognostic biomarker for patients.

3.5. FEZF1-AS1 in lung cancer

Jin et al. [43] demonstrated that FEZF1-AS1 was substantially overexpressed in 80 lung adenocarcinoma (LAD) samples compared with those in paired adjacent normal samples. Moreover, FEZF1-AS1 aberrantly overexpressed in human LAD 5 cell lines compared with the normal lung epithelial cells BEAS-2B, and high level of FEZF1-AS1 expression was associated with poor prognosis of LAD patients. Functional experiments and mechanistic investigations showed that down-regulation of FEZF1-AS1 could inhibit cell proliferation through causing cell cycle arrest at G1 and inducing cell apoptosis. Enhancer of zeste homolog 2 (EZH2) is the functional enzymatic component of the polycomb repressive complex 2 (PRC2). Meanwhile, EZH2 is responsible for embryonic healthy development through the epigenetic maintenance of genes in charge of regulating development and differentiation [44–46]. FEZF1-AS1 could epigenetically suppress p57 gene expression by recruiting EZH2 and LSD1 to the promoter region of p57 gene, thus impeded the cell cycle and proliferation. Moreover, further studies revealed that deletion of FEZF1-AS1 reduced mRNA and protein expression of its sense-cognate gene FEZF1 in LAD cells, and *vice versa*. Correlation analysis suggested that there was a positive correlation between FEZF1-AS1 expression and FEZF1 expression in LAD samples. Rescue assay confirmed that the functions of FEZF1-AS1 in LAD were mediated by FEZF1 [47]. He et al. [48] observed FEZF1-AS1 expression was significantly increased in 86 NSCLC tissues and 4 NSCLC cell lines compared with adjacent normal tissues and normal lung cell 16HBE. In addition, higher FEZF1-AS1 expression was associated with lymph node metastasis, poor differentiation and advanced TNM stage. *In vitro*, repression of FEZF1-AS1 inhibited cell proliferation and cell invasion capacities in NSCLC. Furthermore, lncRNA FEZF1-AS1 knockdown suppressed EMT process by increasing the expression of E-cadherin and zonula occludens-1 (ZO-1), whereas, decreasing the expression of snail family transcriptional repressor 2 (SNAI2 also known as Slug), Twist and Vimentin in NSCLC cells. Mechanically, FEZF1-AS1 could epigenetically repress the expression of E-cadherin *via* binding with LSD1 and EZH2 in NSCLC cells to its promoter region. As we all known, the Wnt/β-catenin signaling activity is significantly associated with tumor invasion and metastasis and He et al. found that knockdown of FEZF1-AS1 suppressed Wnt/β-catenin signaling in NSCLC. Gong et al. [49] also showed elevated FEZF1-AS1 expression in 160 NSCLC tissues compared with their adjacent non-tumor tissues, and FEZF1-AS1 high expression was correlated with advanced stages and tumor family history. Moreover, they also discovered that the expression of FEZF-AS1 was positively associated with FEZF1 expression.

3.6. FEZF1-AS1 in breast cancer

Breast cancer is a malignant tumor predominately originating from luminal epithelial cells and one of the most common cancers with increasing morbidity and mortality in women worldwide [50]. The first study focusing on FEZF1-AS1 in breast cancer was published in 2018. The authors reported that FEZF1-AS1 expression was upregulated in 30 breast cancer tissues compared with adjacent non-tumor tissue and indicated poor prognosis of breast cancer patients. Moreover, FEZF1-AS1 was significantly over-expressed in breast cancer-stem like cells (BCSC) (MDA-MB-231 CSC, MCF-7 CSC), which could generate tumors through the stem cell processes of self-renewal and differentiation into multiple cell types. Meanwhile, these cells can persist in tumors as a distinct population and cause relapse and metastasis by giving rise to new tumors [51–53]. In addition, FEZF1-AS1 expression knockdown reduced the $CD44^+/CD24^-$ rate, the mammosphere-forming ability, stem factors (Nanog, Oct4, SOX2), and inhibited the proliferation, migration and invasion *in vitro*, implying impaired BCSC properties. *In vivo*, FEZF1-AS1 expression knockdown suppressed the breast cancer cells growth. Mechanically, Nanog as a stem factor, helps embryonic stem cells maintain pluripotency by suppressing cell determination factors [54]. FEZF1-AS1 modulated Nanog expression in BCSC through sponging miR-30a which shared seven complementary binding sites with FEZF1-AS1 3'-UTR (untranslated regions), suggesting the regulation of FEZF1-AS1/miR-30a/Nanog [55]. Thus, FEZF1-AS1, a potential oncogenic lncRNA in breast cancer, may offer a hopeful diagnostic and therapeutic choice for the treatment of breast cancer.

3.7. FEZF1-AS1 in multiple myeloma

FEZF1-AS1 expression was significantly increased in 27 multiple myeloma (MM) samples and 5 MM cells compared with 11 healthy donors' tissues and normal plasma cells. Biologically, suppression of FEZF1-AS1 significantly promoted MM cells apoptosis and arrested cell cycle transition from G1 to S phase. Moreover, bioinformatics analysis and dual luciferase reporter assay confirmed that miR-610 could directly combine with FEZF1-AS1 3′-UTR. Subsequently, Protein kinase B3 (PKB3, also known as Akt3) which is a serine/threonine-specific protein kinase, which plays a key role in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription and cell migration. In this research, it was verified as a target of miR-610 and positively related to FEZF1-AS1 in MM [56,57]. FEZF1-AS1 knockdown reduced Akt3 expression both in mRNA and protein, whereas miR-610 inhibitors reversed the effects of FEZF1-AS1 repression on Akt3. In conclusion, these results indicated that FEZF1-AS1 served as an oncogenic lncRNA by regulating FEZF1-AS1/miR-610/Akt3 axis in MM oncogenesis [58].

3.8. FEZF1-AS1 in nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC), which occurs at the top and side of the nasopharyngeal cavity, is one of the most common head and neck malignant tumor in southern China and Southeast Asia [59]. But the exact molecular mechanism for the development and progression of NPC is not fully clear yet. Cheng et al. [60] reported that FEZF1-AS1 expression was remarkably raised in 71 NPC samples and 5 NPC cell lines compared with 10 normal nasopharyngeal epithelium tissues from healthy people and immortalized normal nasopharyngeal epithelial cell line NP69. On the other hand, high FEZF1-AS1 expression was closely correlated with distant metastasis, poor overall survival and disease-free survival of NPC patients. Functionally, FEZF1-AS1 deletion repressed NPC cell proliferation, migration and invasion, induced G0/G1 cell arrest in NPC cells. Mechanically, p21 gene expression was increased, whereas Cyclin D1 expression was decreased after FEZF1-AS1 knockdown in NPC cells. Moreover, deletion of FEZF1-AS1 inhibited tumors' growth *in vivo*. In mechanism, E-cadherin expression was significantly increased while the expression levels of N-cadherin and Vimentin were obviously decreased in NPC cells following FEZF1-AS1 knockdown. In other words, FEZF1-AS1 induced EMT process in NPC cells. FEZF1-AS1 suppression decreased, whereas FEZF1-AS1 overexpression increased β-catenin accumulation in NPC cells, and FEZF1-AS1 could activate Wnt/β-catenin signaling in NPC cells.

3.9. FEZF1-AS1 in other cancers

FEZF1-AS1 expression was significantly upregulated in 196 cervical cancer (CC) tissues compared with their paired normal cervical tissues and greatly associated with histological grade, distant metastasis and International Federation of Gynecology and Obstetrics (FIGO) stage. A cohort of CC patients was followed up for 5 years and Kaplan-Meier curve with long-rank analysis showed that patients with high expression of FEZF1-AS1 had poorer overall survival compared with those with low expression of FEZF1-AS1 group. Besides these, univariate and multivariate analysis confirmed that FEZF1-AS1 expression was an independent prognostic factor for overall survival [61]. Zhao et al. [62] found that the expression of FEZF1-AS1 markedly elevated in 45 ovarian cancer tissues and 5 cell lines compared with adjacent normal tissues and fallopian tube epithelial FTE187. Moreover, increased FEZF1-AS1 expression was significantly correlated with poor prognosis in ovarian cancer patients. Functionally, FEZF1-AS1 knockdown suppressed ovarian cancer cell proliferation and induced apoptosis. Mechanically, FEZF1-AS1 expression was positively correlated with STAT3 expression in ovarian cancer cell and FEZF1-AS1 inhibited ovarian cancer proliferation and apoptosis through JAK-STAT3 signaling

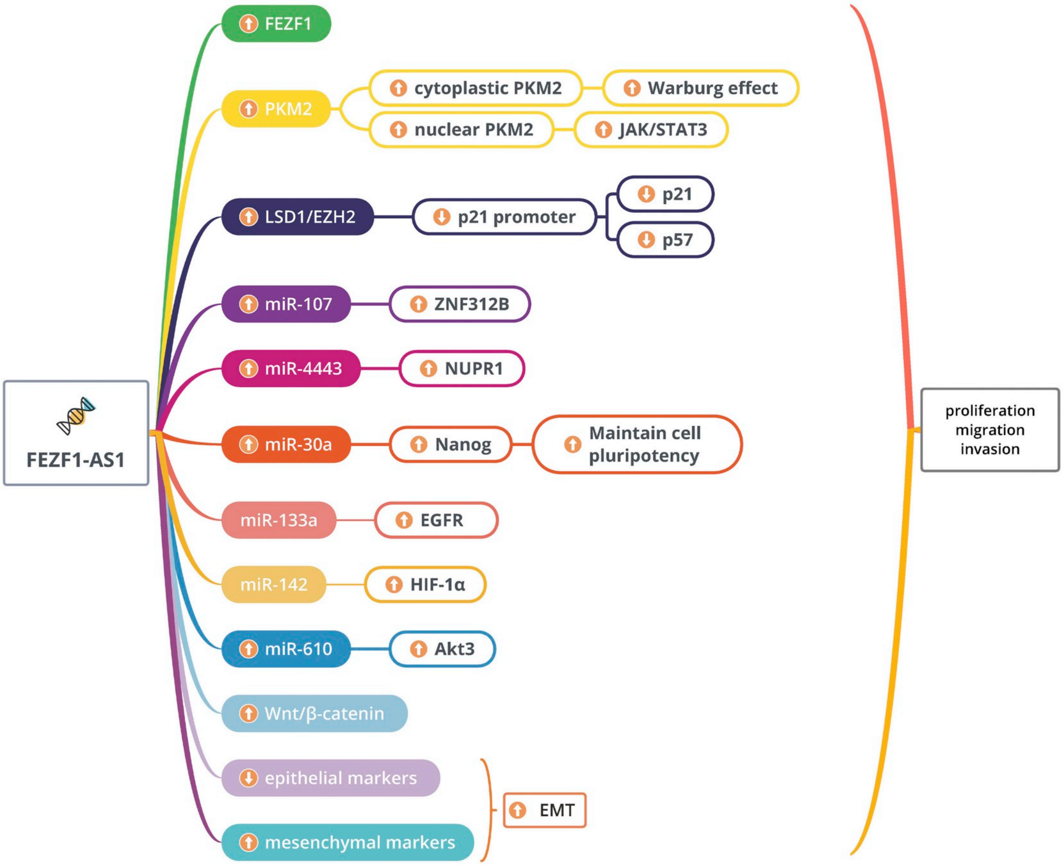

Fig. 1. Overview of the regulatory mechanisms of FEZF1-AS1 in tumorigenesis and progression. FEZF1-AS1 interacts with different types of molecules to exert multiple biological effects on proliferation, invasion, metastasis, cell cycle and apoptosis. FEZF1-AS1 can promote PKM2 expression to activate JAK/STAT3 signaling pathway and increase Warburg effect. FEZF1-AS1 can bind with EZH2 and LSD1 to repress expression of tumor suppressors p21 and p57. EZF1-AS1 also facilitates tumor progression by acting as a ceRNA. FEZF1-AS1 promotes migration and invasion by inducing the EMT through reduced expression of epithelial markers and increasing levels of mesenchymal markers. FFEZF1-AS1 functions as an oncogene *via* activating Wnt/β-catenin signaling pathway.

Abbreviations: FEZF1-AS1, Fez finger zinc 1 antisense 1; FEZF1/ZNF312B, Fez family zinc finger protein 1; PKM2, pyruvate kinase 2; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; EZH2, Enhancer of zeste homolog 2; LSD1, Lysine-specific histone demethylase 1A; HIF-1α, hypoxia-inducible factor 1α; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition.

pathway. Zhou et al. [63] verified that FEZF1-AS1 expression was obviously increased in 58 osteosarcoma (OS) tissues and 4 OS cells compared with that in adjacent normal tissues and fetal osteoblastic cell line hFOB. Kaplan-Meier analysis indicated that the down-regulated FEZF1-AS1 expression means poor survival of patients and advanced phenotype of OS. Gain and loss of function analyses demonstrated that FEZF1-AS1 depletion significantly reduced the proliferation, migration and invasion in OS cells. *In vivo*, FEZF1-AS1 knockdown inhibited tumor growth in lung and metastasis. In mechanism, FEZF1-AS1 sponged miR-4443 to enhance nuclear protein 1 (NUPR1) expression in OS cells and the formation and development of OS. Recently, Yang et al. [64] reported that FEZF1-AS1 was remarkably upregulated in esophageal squamous cell carcinoma (ESCC) tissues and cell lines. Silencing of FEZF1-AS1 significantly inhibited the migration and invasion of ESCC cells by decreasing the mRNA and protein expression of β-catenin, while FEZF1-AS1 had no effect on ESCC cell proliferation and cell cycle. In addition, FEZF1-AS1 was discovered that it functioned as an oncogenic lncRNA in retinoblastoma. FEZF1-AS1 expression was elevated in retinoblastoma tissue specimens and cell lines and significantly correlated with present choroidal invasion and optic nerve invasion. Meanwhile, and high FEZF1-AS1 expression was an independent unfavorable prognostic factor for disease-free survival in retinoblastoma patients. Moreover, silencing FEZF1-AS1 expression could inhibit retinoblastoma cell proliferation, invasion and migration [65].

4. Conclusion and future perspectives

Accumulating data have identified dysregulated lncRNAs as potential oncogenes or tumor suppressor that play crucial regulatory roles in tumorigenesis and tumor progression. LncRNAs will have a potential application prospect as tumor biomarkers or therapeutic targets in diagnosis and treatment of cancers by understanding these underlying mechanisms. There has been a great deal of studies on lncRNAs so far, such as PCAT-1, GAPLINC and SNHG15 which have been firstly discovered in prostate cancer and gastric carcinoma, respectively. FEZF1-AS1 as a novel lncRNA, its expression is upregulated in CRC, GC, PDAC, HCC, lung cancer, breast cancer, CC, ovarian cancer, OS, MM, NPC, ESCC and retinoblastoma, which is associated with clinical and pathological characteristics, including tumor stage, lymph node metastasis, and survival of cancer patients. As a tumor promoter, FEZF1-AS1 is involved in regulating cellular biological functions, such as cell proliferation, migration, invasion, and anti-apoptosis by complicated regulatory mechanisms. FEZF1-AS1 could competitively binds with endogenous miRNAs (such as miR-107 and miR-4443), resulting in the ectopic expression of their downstream target gene (such as ZNF312B and NUPR1), or modulation of some classical signaling pathways (Fig. 1). The above studies indicate that FEZF1-AS1 exerts significant regulatory functions in tumor development. Hence, FEZF1-AS1 may be considered as a novel diagnostic/prognostic biomarker or a promising therapeutic target for cancers. Although the role of FEZF1-AS1 has been studied in many cancers, it has not been reported in some of the more common cancers, such as esophageal cancer and bladder carcinoma. Furthermore, the detailed molecular mechanisms upstream and downstream of FEZF1-AS1 remain in the early stages. Further research should be focused on investigating the precise molecular regulatory mechanisms of FEZF1-AS1, and a larger cohort of cancer samples also should be included in the study to facilitate the clinical application of FEZF1-S1 as early as possible.

Declaration of Competing Interests

None.

Acknowledgements

This work was supported by National Natural Science Foundation of China [No. 81602088]; HMU College Students' Innovation and Entrepreneurship Training Program [No. 201810226105], China; China Postdoctoral Science Foundation [No. 2017M621305]; Heilongjiang Postdoctoral Science Foundation [No. LBH-Z16096], China; Health and Family Planning Commission Research Project of Heilongjiang Province [No. 2016-049], China and Innovative Science Foundation of Harbin Medical University [No. 2016LCZX09], China.

References

[1] L.A. Torre, F. Bray, R.L. Siegel, et al., Global cancer statistics, 2012, CA Cancer J. Clin. 65 (2015) 87–108.
[2] C. Allemani, T. Matsuda, V.D. Carlo, et al., Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37513025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries, Lancet. 391 (2018) 1023–1075.
[3] F. Bray, J. Ferlay, I. Soerjomataram, et al., Global Cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (2018) 394–424.
[4] B.A. Sullenger, S. Nair, From the RNA world to the clinic, Science. 352 (2016) 1417–1420.
[5] F.E. Nicolas, Role of ncRNAs in development, diagnosis and treatment of human cancer, Recent Pat. Anticancer Drug Discov. 12 (2017) 128–135.
[6] M. Gandhi, M.C. Herger, S. Diederichs, RNA motifs and combinatorial prediction of interactions, stability and localization of noncoding RNAs, Nat. Struct. Mol. Biol. 25 (2018) 1070–1076.
[7] E. Anastasiadou, L.S. Jacob, F.J. Slack, Non-coding RNA networks in cancer, Nat. Rev. Cancer 18 (2018) 5–18.
[8] V.V. Sherstyuk, S.P. Medvedev, S.M. Zakian, Noncoding RNAs in the regulation of pluripotency and reprogramming, Stem Cell Rev. 14 (2018) 58–70.
[9] H. Liu, J. Luo, S. Luan, et al., Long non-coding RNAs involved in cancer metabolic reprogramming, Cell. Mol. Life Sci. 76 (2019) 495–504.
[10] E. Khurana, Y. Fu, D. Chakravarty, et al., Role of non-coding sequence variants in cancer, Nat. Rev. Genet. 17 (2016) 93–108.
[11] Z.J. Zhao, S. Li, E.W. Song, et al., The roles of ncRNAs and histone-modifiers in regulating breast cancer stem cells, Protein Cell 7 (2016) 89–99.
[12] H.D. Zhang, L.H. Jiang, D.W. Sun, et al., CircRNA: a novel type of biomarker for cancer, Breast Cancer 25 (2018) 1–7.
[13] Y.W. Fang, M.J. Fullwood, Roles, functions, and mechanisms of long non-coding RNAs in cancer, Genomics Proteomics Bioinform. 14 (2016) 42–54.
[14] T. Wu, Y. Du, LncRNAs: from basic research to medical application, Int. J. Biol. Sci. 23 (2017) 295–307.
[15] M. Huarte, The emerging role of lncRNAs in cancer, Nat. Med. 21 (2015) 1253–1261.
[16] J.H. Yoon, J. Kim, M. Gorospe, Long non-coding RNA turnover, Biochimie. 117 (2015) 15–21.
[17] M. Sun, F. Nie, Y. Wang, et al., LncRNA HOXA11-AS promotes proliferation and invasion of gastric cancer by scaffolding the chromatin modification factors PRC2, LSD1, and DNMT1, Cancer Res. 76 (2016) 6299–6310.
[18] X.M. Jiang, Z.L. Li, J.L. Li, et al., LncRNA CCAT1 as the unfavorable prognostic biomarker for cholangiocarcinoma, Eur. Rev. Med. Pharmacol. Sci. 21 (2017) 1242–1247.
[19] Z.L. Li, X.M. Jiang, Z.L. Su, et al., Current insight into a cancer-implicated long noncoding RNA ZFAS1 and correlative functional mechanisms involved, Pathol. Res. Pract. 214 (2018) 1517–1523.
[20] J.C. Wang, Z.L. Su, S.N. Lu, et al., LncRNA HOXA-AS2 and its molecular mechanisms in human cancer, Clin. Chim. Acta 485 (2018) 229–233.
[21] J.L. Li, X.M. Jiang, Z.L. Li, et al., Long noncoding RNA GHET1 in human cancer, Clin. Chim. Acta 488 (2019) 111–115.
[22] R. Esposito, N. Bosch, A. Lanzós, et al., Hacking the Cancer genome: profiling therapeutically actionable long non-coding RNAs using CRISPR-Cas9 screening, Cancer Cell 35 (2019) 545–557.
[23] N. Chen, D. Guo, Q. Xu, et al., Long non-coding RNA FEZF1-AS1 facilitates cell proliferation and migration in colorectal carcinoma, Oncotarget. 7 (2016) 11271–11283.
[24] Y.W. Liu, K. Xia, F. Yang, et al., LincRNA FEZF1-AS1 represses P21 expression to promote gastric cancer proliferation through LSD1-mediated H3K4me2 demethylation, Mol. Cancer 16 (2017) 39.
[25] L. Fagerberg, B.M. Hallström, P. Oksvold, et al., Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics, Mol. Cell. Proteomics 13 (2014) 397–406.
[26] Y. Zhang, Q.X. Yang, T.T. Peng, et al., Prognostic value of lncRNA FEZF1 antisense RNA 1 over-expression in oncologic outcomes of patients with solid tumors, Medicine (Baltimore) 98 (2019) e15982.
[27] Z.H. Bian, J.W. Zhang, M. Li, et al., LncRNA-FEZF1-AS1 promotes tumor proliferation and metastasis in colorectal cancer by regulating PKM2 signaling, Clin. Cancer Res. 24 (2018) 4808–4819.
[28] P. Vaupel, L. Harrison, Tumor hypoxia: causative factors, compensatory mechanisms, and cellular response, Oncologist. 9 (2004) 4–9.
[29] N. Azoitei, A. Becher, K. Steinestel, et al., PKM2 promotes tumor angiogenesis by regulating HIF-1α through NF-κB activation, Mol. Cancer 15 (2016) 3.
[30] Z. Zhou, M. Li, L. Zhang, et al., Oncogenic kinase-induced PKM2 tyrosine 105 phosphorylation converts nononcogenic PKM2 to a tumor promoter and induces cancer stem-like cells, Cancer Res. 78 (2018) 2248–2261.
[31] Z.L. Yuan, Y.J. Guan, L. Wang, et al., Central role of the threonine residue within the p + 1 loop of receptor tyrosine kinase in STAT3 constitutive phosphorylation in metastatic cancer cells, Mol. Cell. Biol. 24 (2004) 9390–9400.
[32] K.J. Kim, S.H. Kwon, J.H. Yun, et al., STAT3 activation in endothelial cells is important for tumor metastasis via increased cell adhesion molecule expression, Oncogene. 36 (2017) 5445–5459.
[33] Y. Wang, Y. Shen, S. Wang, et al., The role of STAT3 in leading the crosstalk between human cancers and the immune system, Cancer Lett. 415 (2018) 117–128.
[34] Y. Shi, F. Lan, C. Matson, et al., Histone demethylation mediated by the nuclear amine oxidase homolog LSD1, Cell. 119 (2004) 941–953.
[35] J.B. Gu, Y. Li, L.Q. Fan, et al., Identification of aberrantly expressed long non-coding RNAs in stomach adenocarcinoma, Oncotarget. 8 (2017) 49201–49216.
[36] X.L. Wu, P.C. Zhang, H. Zhu, et al., Long noncoding RNA FEZF1-AS1 indicates a poor prognosis of gastric cancer and promotes tumorigenesis via activation of Wnt signaling pathway, Biomed. Pharmacother. 96 (2017) 1103–1108.
[37] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2017, CA Cancer J. Clin. 67 (2017) 7–30.
[38] H.L. Ye, Q.B. Zhou, S.Y. Zheng, et al., FEZF1-AS1/miR-107/ZNF312B axis facilitates progression and Warburg effect in pancreatic ductal adenocarcinoma, Cell Death Dis. 9 (2018) 34.
[39] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell. 144 (2011) 646–674.
[40] Z.L. Ou, M. Zhang, L.D. Ji, et al., Long noncoding RNA FEZF1-AS1 predicts poor prognosis and modulates pancreatic cancer cell proliferation and invasion through miR-142/HIF-1α and miR-133a/EGFR upon hypoxia/normoxia, J. Cell. Physiol. (Epub ahead of print).
[41] A. Budny, P. Kozlowski, M. Kaminska, et al., Epidemiology and risk factors of hepatocellular carcinoma, Pol. Merkur. Lekarski 43 (2017) 133–139.
[42] Y.D. Wang, X.J. Sun, J.J. Yin, et al., Long non-coding RNA FEZF1-AS1 promotes cell invasion and epithelial-mesenchymal transition through JAK2/STAT3 signaling pathway in human hepatocellular carcinoma, Biomed. Pharmacother. 106 (2018) 134–141.
[43] S. Jin, S.Y. Chen, Y.F. Ma, et al., LincRNA FEZF1-AS1 contributes to the proliferation of LAD cells by silencing p57 expression, Oncotarget. 8 (2017) 103004–103013.
[44] L. Morey, K. Helin, Polycomb group protein-mediated repression of transcription, Trends Biochem. Sci. 35 (2010) 323–332.
[45] K.H. Kim, C.W. Roberts, Targeting EZH2 in cancer, Nat. Med. 22 (2016) 128–134.
[46] M. Yamagishi, K. Uchimaru, Targeting EZH2 in cancer therapy, Curr. Opin. Oncol. 29 (2017) 375–381.
[47] Z.J. Liu, P. Zhao, Y.P. Han, et al., LincRNA FEZF1-AS1 is associated with prognosis in lung adenocarcinoma and promotes cell proliferation, migration and invasion, Oncol. Res. 27 (2018) 39–45.
[48] R. He, F.H. Zhang, N. Shen, LncRNA FEZF1-AS1 enhances epithelial-mesenchymal transition (EMT) through suppressing E-cadherin and regulating WNT pathway in non-small cell lung cancer (NSCLC), Biomed. Pharmacother. 95 (2017) 331–338.
[49] W. Gong, Y. Cao, Y.Y. Wang, et al., Upregulation of LncRNA FEZF-AS1 is associated with advanced clinical stages and family history of cancer in patients with NSCLC, Pathol. Res. Pract. 214 (2018) 857–861.
[50] C. DeSantis, J. Ma, L. Bryan, Breast cancer statistics, 2013, CA Cancer J. Clin. 64 (2014) 52–62.
[51] S. Dawood, L. Austin, M. Cristofanilli, Cancer stem cells: implications for cancer therapy, Oncology (Williston Park) 28 (2014) 1101–7, 1110.
[52] T.B. Toh, J.J. Lim, E.K. Chow, Epigenetics in cancer stem cells, Mol. Cancer 16 (2017) 29.
[53] M. Sreepadmanabh, B.J. Toley, Investigations into the cancer stem cell niche using in-vitro 3-D tumor models and microfluidics, Biotechnol. Adv. 36 (2018) 1094–1110.
[54] K.H. Song, C.H. Choi, H.J. Lee, et al., HDAC1 upregulation by NANOG promotes multidrug resistance and a stem-like phenotype in immune edited tumor cells, Cancer Res. 77 (2017) 5039–5053.
[55] Z. Zhang, L.W. Sun, Y.X. Zhang, et al., Long non-coding RNA FEZF1-AS1 promotes breast cancer stemness and tumorigenesis via targeting miR-30a/Nanog axis, J. Cell. Physiol. 233 (2018) 8630–8638.

[56] G. Song, G. Ouyang, S. Bao, The activation of Akt/PKB signaling pathway and cell survival, J. Cell. Mol. Med. 9 (2005) 59–71.

[57] M. Palmieri, R. Pal, H.R. Nelvagal, et al., mTORC1-independent TFEB activation via Akt inhibition promotes cellular clearance in neurodegenerative storage diseases, Nat. Commun. 8 (2017) 14338.

[58] Q.Y. Li, L. Chen, N. Hu, et al., Long non-coding RNA FEZF1-AS1 promotes cell growth in multiple myeloma via miR-610/Akt3 axis, Biomed. Pharmacother. 103 (2018) 1727–1732.

[59] M.L.K. Chua, J.T.S. Wee, E.P. Hui, et al., Nasopharyngeal carcinoma, Lancet. 387 (2016) 1012–1024.

[60] Y. Cheng, FEZF1-AS1 is a key regulator of cell cycle, epithelial-mesenchymal transition and Wnt/β-catenin signaling in nasopharyngeal carcinoma cells, Biosci. Rep. 39 (2019) BSR20180906.

[61] H.H. Zhang, A.H. Li, Long non-coding RNA FEZF1-AS1 is up-regulated and associated with poor prognosis in patients with cervical cancer, Eur. Rev. Med. Pharmacol. Sci. 22 (2018) 3357–3362.

[62] X. Zhao, Z. Cheng, J. Wang, Long noncoding RNA FEZF1-AS1 promotes proliferation and inhibits apoptosis in ovarian Cancer by activation of JAK-STAT3 pathway, Med. Sci. Monit. 24 (2018) 8088–8095.

[63] C.W. Zhou, J.X. Xu, J.T. Lin, et al., Long non-coding RNA FEZF1-AS1 promotes osteosarcoma progression by regulating miR-4443/NUPR1 axis, Oncol. Res. 233 (2018) 8630–8638.

[64] L. Yang, Y. Ye, J. Chu, et al., Long noncoding RNA FEZF1-AS1 promotes the motility of esophageal squamous cell carcinoma through Wnt/β-catenin pathway, Cancer Manag. Res. 11 (2019) 4425–4435.

[65] L.J. Quan, W.J. Wang, FEZF1-AS1 functions AS an oncogenic lncRNA in retinoblastoma, Biosci. Rep. 39 (2019) (pii: BSR20190754).