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Review article

FAL1: A critical oncogenic long non-coding RNA in human cancers

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ABSTRACT

Long noncoding RNAs (lncRNAs) are characterized as a group of endogenous RNAs that are more than 200 nucleotides in length and have no protein-encoding function. More and more evidence indicates that lncRNAs play vital roles in various human diseases, especially in tumorigenesis. Focally amplified lncRNA on chromosome 1 (FAL1), a novel lncRNA with enhancer-like activity, has been identified as an oncogene in multiple cancers and high expression level of FAL1 is usually associated with poor prognosis. Dysregulation of FAL1 has been shown to promote the proliferation and metastasis of cancer cells. In the present review, we summarized and illustrated the functions and underlying molecular mechanisms of FAL1 in the occurrence and development of different cancers and other diseases. FAL1 has the potential to appear as a feasible diagnostic and prognostic tool and new therapeutic target for cancer patients though further investigation is needed so as to accelerate clinical application.

1. Introduction

Cancer is chiefly a result of genetic mutations that dysregulate the gene networks and cellular homeostasis. Such mutations often take place in genome regions with no protein-coding ability, which are usually transcribed into noncoding RNAs [1,2]. Long noncoding RNAs (lncRNAs), a group of RNA transcripts with a minimum length of 200 nucleotides, are known to participate in various cell events such as differentiation, proliferation, invasion, apoptosis, and migration [3]. Emerging evidence has identified lncRNAs as important regulators of multiple biological and disease processes, from gene transcription and translation, to posttranslational modification [4,5]. Particularly in tumorigenesis, lncRNAs could serve as tumor suppressor genes or oncogenes, and are correlated with tumor proliferation and metastasis in assorted types of cancers [6–8].

Some noncoding RNAs are transcribed from enhancer DNA elements and have enhancer-like activity, namely enhancer RNAs (eRNAs) [9,10]. They display similar transcription rates to common lncRNAs but generate fewer stable transcripts [11]. Silencing of eRNAs could lead to reduced expression of target or nearby genes through *cis*-regulation [12,13].

Focally amplified lncRNA on chromosome 1 (FAL1), also known as FALEC, is a 566-nucleotides-long eRNA located at 1q21.2, next to the tumor metastasis-associated gene ECM1 (extracellular matrix protein 1) [13–15]. It was first discovered to have oncogenic potential through genetic sequencing [14]. Subsequent studies revealed the regulative role of FAL1 in various types of human cancers and other diseases including Hirschsprung's disease [16], diabetic arteriosclerosis [17]. The elevated expression levels have been proved to affect the proliferation, metastasis and apoptosis of different cancer cells and hereby promote the cancer progression [14,18–20]. Meanwhile, FAL1 was also highlighted as potential diagnostic and prognostic approach in cancer. In this review, we will summarize the current evidence on mechanisms and function of FAL1 in human diseases and discuss its diagnostic and therapeutic values for clinical application.

2. Discovery of FAL1

Hu et al. first identified FAL1 when they conducted a large-scale analysis of SNP arrays of over 2000 tumor specimens involving 12 types of cancers [14]. They examined the oncogenicity of FAL1 in seven different cancer cell lines including ovarian cancer, breast cancer, colorectal cancer, almost all of which showed that their growth somewhat depended on the expression of FAL1. Interestingly, they also disclosed that FAL1 regulates the stability of a core protein of polycomb repressive complex 1 (PRC1) and the transcription of a large set of genes

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including p21 [14]. This research has inspired numerous more detailed studies of FAL1 on specific cancer types subsequently. Pan et al. [18] validated the protective effects of FAL1 on PRC1 core subunit BMI1, and more studies proved that such stabilization is mediated by p21 in some cancers [21,22]. Wu et al. [23] further revealed that FAL1 could regulate its adjacent gene and exert enhancer-like function as an eRNA. On the other hand, women who went on to deliver preterm also exhibited higher FAL1 expression in the cervix, and particularly, higher levels of FAL1 expression is associated with shorter lengths of gestation at delivery [24]. Yet further investigation is required to elucidate the molecular mechanism behind this change. In all, current evidence strongly indicates that upregulation of FAL1 is positively correlated with poor clinicopathological features and prognosis in cancers, including advanced TNM stages, positive lymph-node metastasis, poorer survival rate, and higher recurrence rate.

3. FAL1 in human cancers

Mounting evidence has revealed the dysregulation of FAL1 in multiple cancers, including non-small lung cancer, ovarian cancer, esophageal cancer, colorectal cancer, thyroid cancer, hepatocellular cancer, gastric cancer, prostate cancer, osteosarcoma, melanoma, cervical cancer, and oral squamous cell carcinoma. The involved molecular mechanisms are summarized in Table 1 and depicted in Fig. 1.

3.1. Non-small lung cancer

Lung cancer has been the leading cause of cancer related death for decades [25]. Non-small lung cancer (NSCLC) accounts for over 80% of all lung cancer cases and causes more than 1 million cancer related death worldwide each year [26]. Without effective early-stage detection tools, there could be a huge delay in diagnosis as symptoms often are not recognized until late stages, and therefore even when diagnosis is confirmed, most patients are already ineligible for surgical treatment [27]. Therefore, discovering novel biomarkers and therapeutic targets is critical so as to better understand the underlying molecular mechanisms involved in the initiation and progression and to abate the mortality.

Pan et al. [18] observed elevated expression of FAL1 in NSCLC tissues compared to paired normal tissues, and overexpression of FAL1 was correlated with poor outcomes in terms of lymph node metastasis, histological grade, and TNM stage. Furthermore, FAL1 was proved to promote cell proliferation, invasion, migration and lower G0/G1 arrest in NSCLC cells. Besides, epithelial–mesenchymal transition (EMT), a critical process associated with cancer metastasis, could also be facilitated by upregulation of FAL1 while downregulation exhibited reverse effects. Previously Hu et al. [14] demonstrated that FAL1 could function as a protective factor of polycomb repressive complex 1 (PRC1) by stabilizing PRC1 core protein BMI1 in ovarian cancer. Similar results were also observed in NSCLC and what's more, FAL1 was discovered to exert such effects by facilitating EMT through the PTEN/AKT pathway. Tumorigenicity assay further validated that upregulated FAL1 can promote tumor growth and metastasis in vivo. These findings demonstrate that FAL1 acts as an oncogenic lncRNA and could potentially serve as a biomarker and therapeutic target in NSCLC.

3.2. Ovarian cancer

Epithelial ovarian cancer, often present at advanced stages, is the most lethal gynecological malignancy [28,29]. Hu et al. [14] discovered that frequent occurrence of gene amplification and RNA overexpression of FAL1 in ovarian cancer tissues and both were significantly correlated with reduced survival in patients. Functional experiments validated that downregulated of FAL1 inhibits the ovarian cancer cell proliferation, migration, and invasion in vitro and in vivo. Further research showed that FAL1 could stabilize BMI1 and hereby function as a protective factor of PRC1, and also could regulate cell cycle progression and senescence through downregulating p21 expression. Together, these findings revealed that FAL1 may play a vital role in ovarian cancer.

3.3. Esophageal cancer

Esophageal cancer is one of the most common cancers with poor prognosis and high mortality [30]. Esophageal squamous cell carcinoma (ESCC), derived from esophageal epithelial cells, is the predominant subtype of esophageal cancer [31,32]. Both Yang et al. [33] and Liang et al. [34] discovered that FAL1 was overexpressed in esophageal cancer tissues and cell lines, and cell experiments showed that knockdown of FAL1 impeded cell proliferation, migration, and invasion in vitro. According to Yang et al. [33], FAL1 regulates the expression of multiple cell cycle proteins (cycline D1, cyclin E, and c-Myc), and the knockdown of FAL1 could lead to a significant cell arrest at G0/G1 phase and a remarkable decrease at S phase. Further research revealed that silencing of FAL1 resulted in increased expression of PTEN but reduced AKT phosphorylation in esophageal cancer cell lines. Liu et al. [35] also confirmed the elevated expression of FAL1 in esophageal cancer tissues and cell lines, and found that knockdown of FAL1 could promote mitochondrial fission and mitochondrial dysfunction via increasing the expression of mitochondrial fission protein dynamin-related protein 1 (DRP1). Inhibition of FAL1 leads to mitochondrial dysfunction, which can be prevented by silencing DRP1. Similarly, they also disclosed that inhibition of FAL1 facilitates apoptosis while knockdown of DRP1 could rescue such inhibition effects on FAL1-induced apoptosis. These results present a new therapeutic target that is potentially promising and effective for treating esophageal cancer

Table 1
Functional characterization of FAL1 in cancers.

Cancer Type	Expression	Functional effects	Related genes	Role	Reference
Non-small lung cancer	Upregulated	Promote cell proliferation, invasion, migration; facilitate EMT; regulate cell cycle	BMI1, PTEN, AKT	Oncogenic	[18]
Ovarian cancer	Upregulated	Promote cell proliferation, invasion, migration; regulate cell cycle	BMI1, p21	Oncogenic	[14]
Esophageal cancer	Upregulated	Promote cell proliferation, invasion, migration; regulate cell cycle	PTEN, AKT, DRP1	Oncogenic	[33–35]
Colorectal cancer	Upregulated	Promote cell proliferation, invasion, migration	STAT3, miR-637, NUPR1, HIF-1α	Oncogenic	[19,39]
Thyroid cancer	Upregulated	Regulate cell cycle		Oncogenic	[45,46]
Hepatocellular cancer	Upregulated	Promote cell proliferation, invasion, migration; facilitate EMT	miR-1236, ZEB1, AFP	Oncogenic	[20]
Gastric cancer	Upregulated	Promote cell proliferation; regulate cell cycle	PTEN	Oncogenic	[23,50]
Prostate cancer	Upregulated	Promote cell proliferation, invasion, migration	HIF-1α	Oncogenic	[53]
Osteosarcoma	Upregulated	Promote cell proliferation, invasion, migration; facilitate EMT	p21, GSK-3β	Oncogenic	[21]
Melanoma	Upregulated	Promote cell proliferation, invasion, migration	EZH2, p21	Oncogenic	[22]
Cervical cancer	Upregulated	Promote cell proliferation, invasion		Oncogenic	[57]
Oral squamous cell carcinoma	Upregulated	Promote cell proliferation	miRNA-761, CRKL	Oncogenic	[59]

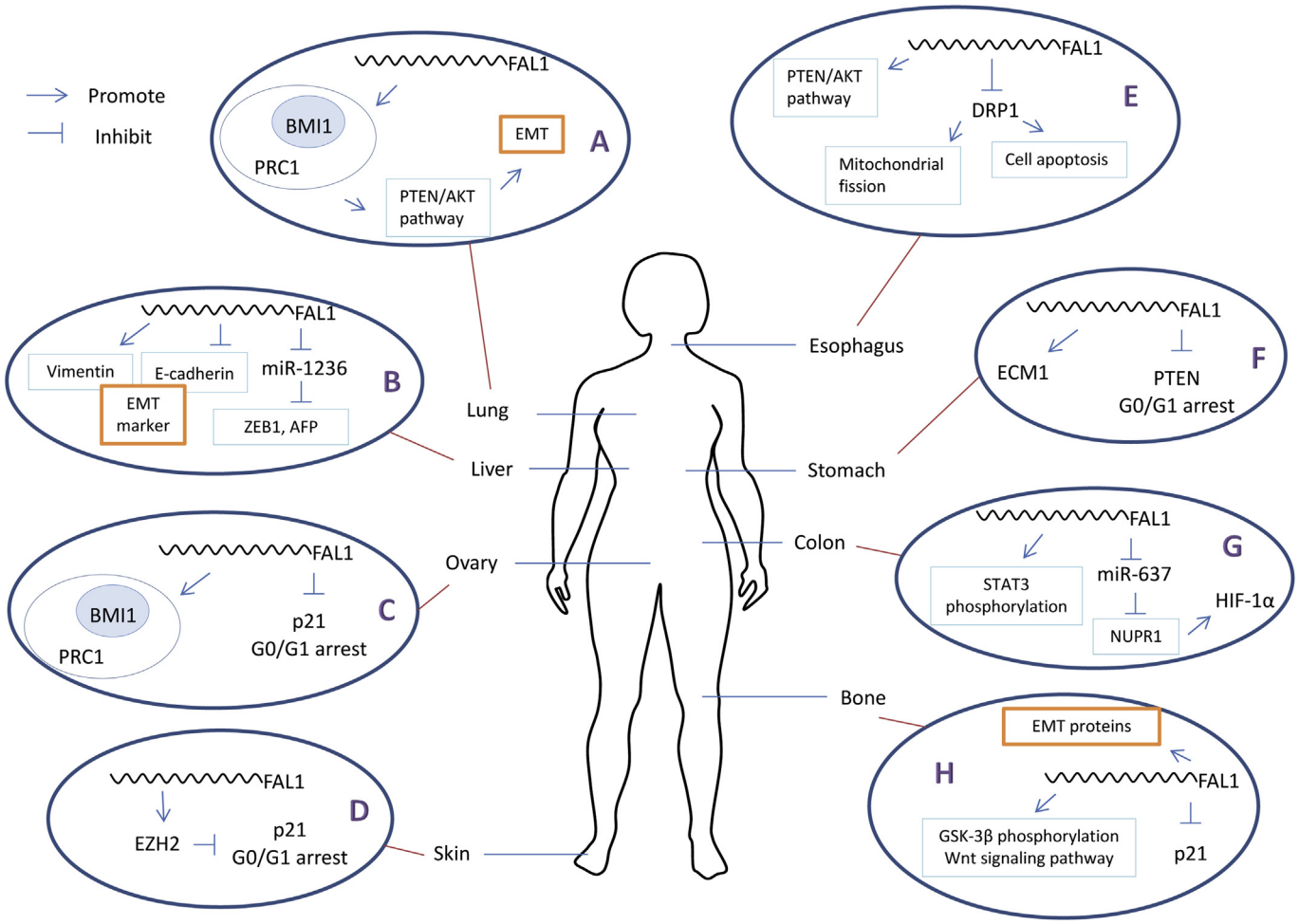

Fig. 1. Underlying molecular mechanisms of FAL1 in multiple cancers. (A), FAL1 stabilizes BMI1 and facilitate EMT through PTEN/AKT pathway. (B), FAL1 binds to miR-1236 to upregulate ZEB1 and AFP, while it also regulates the expression of EMT markers. (C), FAL1 stabilizes BMI1 and regulates cell cycle via repressing p21 expression. (D), FAL1 represses p21 by recruiting E2H2 to the promoter of p21. (E), FAL1 downregulates DRP1 to attenuate mitochondrial fission and mitochondrial dysfunction while it increased expression of PTEN and reduced AKT phosphorylation. (F), FAL1 downregulates PTEN expression and decreases G0/G1 arrest while it promotes ECM1 expression. (G), FAL1 facilitates the phosphorylation of STAT3 and regulates NUPR1 by competitively binding to miR-637, and NUPR1 overexpression leads to increased HIF-1α expression. (H), FAL1 upregulates EMT-associated proteins and represses p21 while it facilitates GSK-3β phosphorylation. The detailed mechanisms of FAL1 in other cancers are illustrated in the review.

patients.

3.4. Colorectal cancer

Colorectal cancer (CRC) is the third most prevalent cancer worldwide and a leading cause of cancer-related death [36,37]. The progression of colorectal cancer can best represent the multistage transformation model of tumorigenesis, which results from genetic instability including mutational activation of oncogenes and inactivation of tumor suppressor genes [38].

It was reported that FAL1 expression was increased in human colorectal cancer tissues and cell lines, and such alternation promoted cancer growth and metastasis [19]. Western blot analysis and RNA pull-down assay indicated that overexpression of FAL1 could facilitate the phosphorylation of STAT3, which might partially explain how FAL1 participate in the development of CRC. Meanwhile, Wang et al. [39] confirmed the elevated expression of FAL1 in CRC but disclosed a different mechanism. Their studies revealed that FAL1 could act as a competing endogenous RNA (ceRNA) to bind to miR-637, which is a suppressor in CRC cells and can downregulate nuclear protein 1 (NUPR1) expression. NUPR1 is an oncogene known to be highly expressed and to promote tumorigenesis in many cancers [39,40]. In CRC specifically, upregulation of NUPR1 can lead to markedly increased expression of hypoxia inducible factor-1 alpha (HIF-1α) and its target gene LASP1. HIF-1α has been previously demonstrated to participate in cancer development and is correlated with patient's outcome in different cancers [41].

3.5. Thyroid cancer

Thyroid cancer is the most common endocrine cancer with increasing incidence globally [42]. Out of five main types of thyroid cancer, papillary thyroid carcinoma (PTC), the most common type, constitutes 80%–90% of thyroid cancers [43]. Despite conventional surgery and adjuvant radioiodine that are often effective on PTC patients, recurrence and metastases still happen to 10%–20% treated patients [44].

Jeong et al. [45] and Shams et al. [46] both revealed that FAL1 is significantly upregulated in PTC tissues but inconsistent with what was reported in ovarian cancer, Jeong et al. [45] detected a relatively higher level of p21 expression in PTC tissues, suggesting that FAL1 may exert its function in other ways. By comparing patients with higher and lower FAL1 expression, they found that high expression of FAL1 might be associated with greater chances of multifocality. It was also reported that overexpression of FAL1 could increase the expression of cell cycle regulators in PTC cells, including E2F transcription factors (E2F1,

E2F2), VEGFA, and cyclin D1, and Gene Set Enrichment Analysis (GSEA) results confirmed this correlation, but further investigation is required to unveil whether and how this pathway affects the development of PTC.

3.6. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is one of the most lethal cancers with poor prognosis and high mortality due to high metastasis rate [47,48]. A report by Li et al. [20] showed that FAL1 was overexpressed in HCC tissues and cell lines, and functioned as an oncogene that could promote cell growth and metastasis in HCC cells. They discovered that FAL1 could competitively bind to miR-1236 to upregulate its target genes, ZEB1 and AFP, hence promoting tumorigenesis in HCC. In addition, Li et al. also detected high expression level of FAL1 in the HCC serum exosomes. Through co-culture with exosomes extracted from HCC serum, HCC cells managed to gain FAL1 and cell proliferation, migration, invasion abilities were all remarkably enhanced. Moreover, these cells exhibited down-regulated miR-1236 expression and elevated expression level of ZEB1 and AFP. Interestingly, E-cadherin, an epithelial marker, was also significantly decreased while Vimentin, a mesenchymal marker was increased, both of which are important EMT markers, indicating that FAL1 might also exert its function through interfering with the EMT process in HCC.

3.7. Gastric cancer

Gastric cancer represents the second leading cause of cancer-related death [49]. Zhu et al. [50] revealed that the expression of FAL1 in gastric cancer (GC) tissues was increased compared with that of adjacent tissues, and the serum expression levels of FAL1 in stage III and IV GC patients were markedly higher than stage I and II patients, which indicates that the FAL1 level in serum might reflect the pathological grades of GC and could potentially serve as a diagnostic tool. Functional experiments showed that FAL1 could facilitate cell proliferation in gastric mucosal cell lines and in accordance with previous findings, flow cytometry showed that overexpression of FAL1 could lead to significant decrease at G0/G1 phase and increase at S phase. Furthermore, a negative correlation between FAL1 and PTEN in GC was disclosed and upregulation of PTEN can reverse the effects of FAL1 overexpression on cell proliferation and cell cycle in GC cell lines. Wu et al. [23] showed that FAL1 could exert its enhancer-like regulation in cis and promote the expression of its flanking gene ECM1, and high level of ECM1 is correlated with poor prognosis in GC.

3.8. Prostate cancer

Prostate cancer (PC) is a common malignancy in men and its prevalence in Asia (especially in China) has been on the rise over the past few decades [51,52]. Zhao et al. [53] demonstrated that expression of FAL1 was significantly higher than adjacent noncancerous tissues and the high level of FAL1 was related to deeper tumor invasion depth and higher Gleason Score. Experiments in vitro and in vivo both suggested that FAL1 might accelerate the growth and metastasis of PC. What's more, remarkably shorter biochemical recurrence time was observed in patients with higher level of FAL1 compared with those with low level of FAL1, which all indicated that upregulation of FAL1 might be associated with PC progression, but further investigation is needed to draw the conclusion. Zhao et al. [53] also discovered that hypoxia could induce a huge increase of FAL1 expression in PC cell lines and HIF-1α functioned as a transcriptional regulator of FAL1 during this process. They identified two hypoxia response elements (HREs), namely the binding sites of HIF-1α, in the promoter region of FAL1, and chromatin immunoprecipitation (ChIP) assays unveiled that HIF-1α could directly bind to one of the two sites in vitro and hereby activate FAL1 promoter.

3.9. Osteosarcoma

Osteosarcoma is the most common bone malignancy that mostly happens to children and adolescents [54]. According to the report by Wang et al. [21], FAL1 was significantly overexpressed in osteosarcoma tissues compared with adjacent normal tissues, and the high expression was associated with poor prognosis and overall survival rate. They also detected higher expression level of FAL1 in serum samples of preoperative osteosarcoma patients compared with normal controls and postoperative patients. ROC analysis exhibited an area under the curve (AUC) of 0.829, which showed that FAL1 has the potential to serve as a serum biomarker in osteosarcoma. Consistent with some of previous findings in other cancers, functional experiments showed that silencing of FAL1 could impede the growth and metastasis of osteosarcoma cells, and they further revealed that such silencing resulted in reduced expression of EMT-associated proteins and increased level of p21, and abated the phosphorylation of GSK-3β, which is a famous key element in Wnt signaling pathway.

3.10. Melanoma

Melanoma is the primary cause of skin cancer death [55]. Ni et al. [22] identified the high expression of FAL1 in melanoma tissues and cell lines, and such overexpression is associated with poor prognosis in terms of invasion, TNM stage and metastasis. When transfected with si-FAL1, melanoma cells displayed hindered proliferation, migration and invasion, and both the cell cycle and cell apoptosis were affected too. An inversed correlation between FAL1 and p21 was also detected in melanoma, and RNA immunoprecipitation (RIP) and RNA pull-down assay showed that FAL1 could directly bind to enhancer of zeste homolog-2 (EZH2), a histone methyltransferase, to regulate p21 expression in melanoma cell lines. ChIP experiments validated that downregulated FALEC impaired the binding capability of EZH2 to p21 and potentially caused methylated modification.

3.11. Cervical cancer

Cervical cancer, though preventable, remains the second most prevalent cancer among women [56]. Naizhaer et al. [57] reported that FAL1 expression was significantly higher in plasma of cervical cancer patients than normal controls, and patients at more advance stages had even higher expression in the plasma than those at early stages. Then they further confirmed the high level of FAL1 in cervical cancer cell lines and exhibited that FAL1 could promote cell proliferation and invasion in cervical cancer cells. Receiver operating characteristic analysis showed that FAL1 expression levels could distinguish cervical cancer patients from healthy controls, suggesting that FAL1 might potentially be a good plasma biomarker for cervical cancer.

3.12. Oral squamous cell carcinoma

Oral squamous cell carcinoma (OSCC) is the most common head and neck cancer [58]. Ye et al. [59] corroborated that FAL1 was overexpressed in both OSCC tissues and cell lines and downregulated FAL1 could attenuate the proliferation of OSCC cells. Another ceRNA pathway was presented as they found out that FAL1 could competitively bind to miRNA-761 which could downregulate CRKL by binding to the 3′UTR of CRKL. Further experiments validated this axis and suggested that FAL1 might facilitate OSCC via the miRNA-761/CRKL pathway.

4. FAL1 in other diseases

4.1. Hirschsprung's disease

Hirschsprung's disease (HSCR), also known as congenital

megacolon, is a common malformation of the digestive tract that occurs when enteric neural crest cells fail to colonize the distal gut [60]. About 14 genes have been identified to be associated with HSCR but together can only explain a small portion of HSCR cases, and further investigation is required to better understand the pathogenesis of HSCR [61]. Li et al. [16] unveiled that FAL1 expression was significantly lowered in the HSCR aganglionic tissues compared with normal controls and knockdown of FAL1 remarkably inhibited cell proliferation and migration in HEK293T and SH-SY5Y cells. Further research showed that FAL1 could competitively bind to miR-637 and hereby regulate the expression of AKT serine/threonine kinase 1 (AKT1).

4.2. Diabetic arteriosclerosis

Diabetes mellitus is a critical health problem with growing incidence around the globe [62]. Type 2 diabetes mellitus fosters the process of arteriosclerosis and could lead to severe cardiovascular events [63]. Compared with normal arterial tissues, Shang et al. [17] discovered that FAL1 was overexpressed in arterial tissues of diabetic arteriosclerosis patients, and interestingly, HUVECs that were treated in high-dose glucose exhibited higher levels of FAL1 than those treated in low-dose glucose. Cell experiments showed that such overexpression could accelerate cell proliferation and migration. Further research suggested that upregulation of FAL1 could downregulate PTEN and upregulate AKT, and PTEN overexpression partially reversed the enhanced proliferation of HUVECs induced by FAL1 overexpression.

5. Molecular mechanisms of FAL1

Competing endogenous RNAs (ceRNAs) refer to lncRNAs that regulate the mRNA expression of genes by competitively binding to miRNAs that target both lncRNAs and genes [64,65]. Several studies have mentioned the role of FAL1 as a ceRNA to exert oncogenic effects. Li et al. [20] showed that FAL1 could bind to miR-1236 and hereby upregulate mir-1236's target genes, ZEB1 and AFP, in hepatocellular carcinoma. Wang et al. [39] reported that FAL1 regulates oncogene NUPR1 by competitively binding to miR-637 in colorectal cancer. Ye et al. [59] found that FAL1 could directly interact with miR-761 to increase the expression of its downstream gene CRKL. In HSCR, Li et al. [16] demonstrated that FAL1 modulated AKT1 by sponging miR-637, affecting cell proliferation and migration.

FAL1 is also known as an eRNA with enhancer-like activity that would impede nearby/target gene expression. Wu et al. [23] revealed the genes that are located in proximity to FAL1, including ECM1, MCL1, ADAMTSL4, TARS2, RPRD2, and ENSA. Further experiments showed that knockdown of FAL1 markedly decrease the expression of its flanking gene ECM1 in gastric cancer cells. Most recently, via inspecting the modular structures on chromosome 1, Thiel et al. [66] demonstrated that the interaction between FAL1 and ECM1 is mediated by ADAMTSL. Besides, MCL1 is also indirectly correlated with FAL1 through other transcribed enhancer elements and encoding genes.

Multiple articles pointed out that FAL1 could interfere with cell cycle in different cell lines. In most cases, overexpression of FAL1 in cancer cells lead to increased cell arrest at S phase and significant decrease at G0/G1 phase, and silencing of FAL1 has the opposite effects, which was demonstrated or partially demonstrated in non-small lung cancer, gastric cancer, esophageal cancer, melanoma, and prostate cancer [18,22,33,50,53]. Meanwhile, Wang et al. [21] elucidated that in osteosarcoma cells, knockdown of FAL1 remarkably increased cell arrest at the G2/M phase. FAL1 was also shown to induce cell apoptosis in esophageal cancer, and melanoma. These effects of FAL1 on cell cycle and cell apoptosis might to some extent explain how FAL1 affects cell proliferation, but the detailed mechanism behind it is yet to be explored.

Several signaling pathways involving FAL1 have been revealed. EMT plays a fundamental role in both physiological and pathological context, from early embryogenesis to tumor metastasis [67]. PTEN/AKT is a well-known pathway that could induce and promote EMT [68,69]. At first Hu et al. [14] discovered that FAL1 could protect PRC1 by stabilizing the expression of its core protein BMI1, which has been previously proved to repress PTEN and induce EMT [70]. Subsequently, mounting evidence showed that FAL1 could regulate PTEN expression and AKT phosphorylation and alter other EMT-associated proteins in both cancer and noncancerous cells. Besides, FAL1 could downregulate p21, a member of cyclin-dependent kinase inhibitors that modulates cell proliferation, apoptosis and DNA damage response during the development and progression of multiple human diseases [71,72]. Ni et al. [22] pointed out that FAL1 might directly bind to the histone methyltransferase EZH2 and hereby repress p21. However, contrary to most reports, Jeong et al. [45] detected increased p21 expression in papillary thyroid carcinoma, suggesting that such mechanism might not apply to all cancers and further verification is necessary. FAL1 has also been linked with elements from other famous pathways such as GSK-3β from Wnt signaling pathway [21].

6. Conclusion and future perspectives

In this review, we summarized the current knowledge about FAL1. FAL1 is an oncogenic lncRNA and its overexpression has been identified in various malignancies. FAL1 could bolster the proliferation, migration and invasion of tumor cells both in vivo and in vitro, and up-regulation of FAL1 is often associated with poor prognosis in multiple cancers. FAL1 might serve as a potentially promising therapeutic target and biomarker for diagnosis in cancers, although no clinical application has been available at the moment. Specifically, to exert oncogenic effects, FAL1 can competitively bind to miRNAs or modify its adjacent gene while cell cycle and cell apoptosis were also proved to be affected when FAL1 is upregulated. PTEN/AKT and several other pathways are correlated with FAL1 but lots of links are missing to connect them in a larger map. Meanwhile, current studies have proposed quite a few unexpected findings about FAL1 that potentially deserve more attention. Within cancers, Hu et al. [14] reported that RNA overexpression of FAL1 occurs much more frequently in epithelial tumors compared with other cancers like neural and hematologic tumors. It is potentially meaningful to study the precise role of FAL1 in epithelial cells and whether FAL1 contributes to other epithelium-related diseases. Besides, FAL1 is also dysregulated in some other diseases or condition including Hirschsprung's disease, diabetic arteriosclerosis, and interestingly, women who are most likely to deliver preterm. But the underlying mechanism of how FAL1 is related to diabetic arteriosclerosis or gestation remains largely unknown and awaits more research.

Taken together, these studies of FAL1 as an oncogenic lncRNA provide new insights into the current understanding of the molecular mechanism behind tumorigenesis and also allow novel strategies for cancer treatment. But independent cohort studies and multicenter studies are necessary for further verification. Future research should also clarify the precise molecular mechanism of FAL1 in each cancer type so as to accelerate its clinical utility.

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