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REVIEW

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AFAP1-AS1: A novel oncogenic long non-coding RNA in human cancers

Fuyou Zhang[1] | Jianfa Li[1,2] | Huizhong Xiao[1,3] | Yifan Zou[1,4] | Yuchen Liu[1] | Weiren Huang[1,3,4]

[1]Key Laboratory of Medical Reprogramming Technology, Shenzhen Second People's Hospital, First Affiliated Hospital of Shenzhen University, Shenzhen 518039, Guangdong Province, China

[2]Guangdong and Shenzhen Key Laboratory of Male Reproductive Medicine and Genetics, Institute of Urology, Peking University Shenzhen Hospital, Shenzhen PKU-HKUST Medical Center, Shenzhen 518036, China

[3]University of South China, Hengyang, Hunan 421001, China

[4]Shantou University Medical College, Shantou 515041, Guangdong Province, China

Correspondence
Yuchen Liu, Key Laboratory of Medical Reprogramming Technology, Shenzhen Second People's Hospital, First Affiliated Hospital of Shenzhen University, Shenzhen 518039, Guangdong Province, China.
Email: liuyuchenmdcg@163.com

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Abstract

Long non-coding RNAs (lncRNAs), a group of non-protein-coding RNAs with more than 200 nucleotides in length, are involved in multiple biological processes, such as the proliferation, apoptosis, migration and invasion. Moreover, numerous studies have shown that lncRNAs play important roles as oncogenes or tumour suppressor genes in human cancers. In this paper, we concentrate on actin filament-associated protein 1-antisense RNA 1 (*AFAP1-AS1*), a well-known long non-coding RNA that is overexpressed in various tumour tissues and cell lines, including oesophageal cancer, pancreatic ductal adenocarcinoma, nasopharyngeal carcinoma, lung cancer, hepatocellular carcinoma, ovarian cancer, colorectal cancer, biliary tract cancer and gastric cancer. Moreover, high expression of *AFAP1-AS1* was associated with the clinicopathological features and cancer progression. In this review, we sum up the current studies on the characteristics of *AFAP1-AS1* in the biological function and mechanism of human cancers.

1 | INTRODUCTION

Nowadays, cancer is one of the major causes of death all over the world.[1,2] According to mortality data collected by the National Center for Health Statistics, it is estimated that 1 688 780 new cancer cases and 600 920 cancer deaths will take place in the United States in 2017.[3] In order to fight against cancer effectively, we should make a great effort to find more precise diagnostic biomarkers and effective therapeutic targets.

Recently, increasing evidence has shown that the non-coding portion of the genome has a crucial functional importance in both normal physiology and diseases.[4-6] Long non-coding RNAs (lncRNAs), a group of non-protein-coding RNAs with more than 200 nucleotides in length, play a vital role in regulating significant cellular functions, including cell proliferation, differentiation, apoptosis, invasion, metabolism, developmental timing and immune responses.[7-12] However, mutation of lncRNAs will cause cancer initiation and promote the metastasis of malignancy.[13-15] For instance, *lncRNA* metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) was first found in lung cancer metastasis. Many studies had demonstrated that *lncRNA*

These authors FZ, JL, HX and YZ have contributed equally to this work.

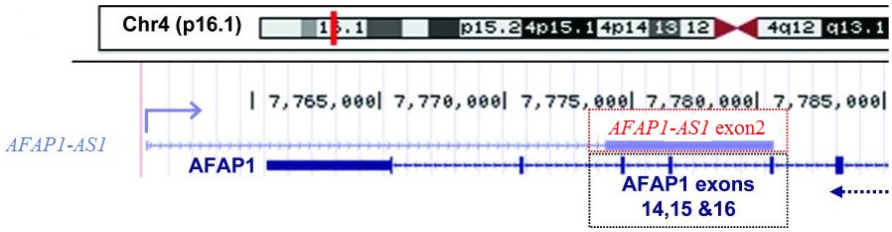

FIGURE 1 Long non-coding RNAs (*lncRNA*) actin filament-associated protein 1-antisense RNA 1 (*AFAP1-AS1*) is mapped to the 4p16.1 region of human chromosome 4. *AFAP1-AS1* is transcribed from AFAP1 gene in the antisense direction, containing several overlapping and complementary regions among the exons of *AFAP1-AS1* and AFAP1

MALAT1 was overexpressed in various cancer, and it might act as a potential biomarker and therapeutic target in cancer treatment.[16-18] *LncRNA MALAT1* might function as an oncogene through controlling alternative splicing process in breast cancer, influencing the expression of N-cadherin and E-cadherin in bladder cancer, combining with a multifunctional RNA-binding protein in colorectal cancer (CRC) and osteosarcoma.[19-22] *LncRNA* HOX antisense intergenic RNA (*HOTAIR*) induced cancer invasion and metastasis by regulating PRC2 target genes in breast cancer and epithelial-mesenchymal transition (EMT) programme in gastric cancer (GC).[23,24] *LncRNA H19* was upregulated in GC and associated with *miR-675*, p53 and Isthmin1 that improved cells proliferation, migration and invasion.[25-29] Among so many cancer-related lncRNAs, actin filament-associated protein 1-antisense RNA 1 (*AFAP1-AS1*) was initially discovered in oesophageal adenocarcinoma in 2013.[30] Then, numerous recent studies had focused on *lncRNA AFAP1-AS1* and demonstrated that it was upregulated in many cancers and played an important role in tumour progression. A meta-analysis had shown that high expression of *AFAP1-AS1* in human cancers was closely related to poor clinical outcome such as lymph node metastasis and distant metastasis.[31] Hence, we chose it as the main research object to summarize its characteristics in the biological function and mechanism of human cancers.

2 | IDENTIFICATION OF *AFAP1-AS1*

Actin filament-associated protein 1 (formerly AFAP-110), an actin cross-linking protein and a cSrc-binding partner, is a member of the AFAP family which includes AFAP1, AFAP1 like-1 and AFAP1 like-2/XB-130.[32,33] There are 2 pleckstrin homology domains in AFAP1, and one of them involves a protein kinase C-binding site and carboxy-terminal domains.[33,34] On the basis of multimerization associated with its leucine zipper and binding to actin filaments through its carboxy-terminal actin filament-binding domain, AFAP1 can crosslink actin filaments.[34]

Long non-coding RNA *AFAP1-AS1* with 6810 bp in length is mapped to the 4p16.1 region of human chromosome 4. Moreover, *AFAP1-AS1* is transcribed from the AFAP1 gene in the antisense direction, containing several overlapping and complementary regions among the exons of *AFAP1-AS1* and AFAP1[35] (Figure 1). Antisense lncRNAs like *AFAP1-AS1* are oriented in an antisense direction regard to a protein-coding gene in the opposite strand, and *AFAP1-AS1* can affect the expression of AFAP1.[36-39] Further experiments have demonstrated that *AFAP1-AS1* was overexpressed in cancer tissues and cell lines, such as oesophageal cancer, pancreatic ductal adenocarcinoma (PDAC), nasopharyngeal carcinoma (NPC) and lung cancer. In addition, overexpression of *AFAP1-AS1* was closely associated with tumour size, lymphatic metastasis, distant metastasis, tumour-node-metastasis (TNM) stage and poor prognosis of cancer patients. Using siRNA to impair the expression of *AFAP1-AS1* inhibited cell proliferation, migration and invasion and induced cell apoptosis through regulating related genes or signalling pathways.[30,35,40-58] In this review, the related clinicopathological characteristics and molecular functions of this *lncRNA* in cancers are presented in Tables 1 and 2.

3 | *AFAP1-AS1* IN VARIOUS CANCERS

3.1 | Oesophageal cancer

Oesophageal cancer is the eighth most frequent types of cancer and is the sixth leading cause of tumour-related death all over the world.[59,60] There are 2 primary histological subtypes of oesophageal cancer, including oesophageal adenocarcinoma (OAC) and oesophageal squamous cell carcinoma (OSCC).[61,62] OSCC accounts for more than 95% of oesophageal cancer.[63] OAC is one of the fastest growing cancers in the Western world, while OSCC is the main subtype of oesophageal cancer in Asia.[3,64] Although different kinds of treatment have been developed, including chemotherapy, radiotherapy and surgery, the long-term survival rate of oesophageal cancer is still extremely low.[64,65] Because of the rising morbidity and poor prognosis of oesophageal cancer patients, it is urgent to look for new tumour markers and therapeutic targets for early diagnosis and advanced treatment of oesophageal cancer patients.

Wu et al[30] reported that *AFAP1-AS1* was exceedingly hypomethylated and overexpressed in Barrett's oesophagus and OAC tissues and OAC cell lines. Further functional analyses demonstrated that *AFAP1-AS1* was an oncogene in the oesophagus cancer. Inhibition of AFAPA-AS1 by siRNA in OAC cells reduced cell proliferation, colony formation, migration and invasion, increased apoptosis and induced G2/M phase arrest. However, the expression of *AFAP1-AS1* was irrelevant with AFAP1 expression. They drew a conclusion

TABLE 1 Overexpression of actin filament-associated protein 1-antisense RNA 1 (*AFAP1-AS1*) is associated with clinicopathological features

Cancer types	Clinicopathological features	References
Oesophageal cancer	Tumour size, tumour depth, lymphatic metastasis, distant metastasis, TNM stage, poor prognosis, shorter progression-free survival and overall survival chemoradioresistance	40, 41
Pancreatic ductal adenocarcinoma	Lymph node metastasis, perineural invasion, poor survival overall survival, progression-free survival	42
Nasopharyngeal carcinoma	Lymph node metastasis, distant tumour metastasis, TNM stage, poor prognosis, EBV infection poor overall survival, poor relapse-free survival	35, 43, 44
Lung cancer	Clinical stage, smoking history, infiltration degree, lymph node metastasis, distant metastasis, poor prognosis tumour progression, poor survival	46-48
Hepatocellular carcinoma	Tumour size, TNM stage, lymph-vascular space invasion poor prognosis	49, 50
Ovarian cancer	Resistance response, FIGO stage	51
Colorectal cancer	Tumour size, TNM stage, distant metastasis, poor prognosis poor overall survival and disease-free survival	52-54
Biliary tract cancers	Tumour size, vascular invasion, TNM stage, poor prognosis, poor overall survival	55-57
Gastric cancer	Poor survival	58

TNM: tumour-node-metastasis; EBV: Epstein-Barr virus; FIGO: International Federation of Gynecology and Obstetrics.

that the overexpression of *AFAP1-AS1*, which exerted functional pro-cancerous effects in oesophageal cells, was associated with hypomethylation.

Subsequent studies demonstrated that *AFAP1-AS1* was increased in OSCC, and high expression of *AFAP1-AS1* was closely associated with tumour size, tumour depth, lymphatic metastasis, distant metastasis and TNM stage. Moreover, those OSCC patients with increased *AFAP1-AS1* level have shorter progression-free survival and overall survival. Overexpression of *AFAP1-AS1* will lead to tumour resistance to radiotherapy and chemotherapy in OSCC patients who received definitive chemoradiotherapy. Furthermore, knockdown of *AFAP1-AS1* in OSCC cells suppressed cell proliferation and colony formation and induced cell apoptosis.[40,41] Therefore, *AFAP1-AS1* may work as a novel prognostic marker and potential therapeutic target for oesophageal cancer.

3.2 | Pancreatic ductal adenocarcinoma

Pancreatic ductal adenocarcinoma, one of the most aggressive solid malignancies, is the fourth leading cause of cancer-related deaths all over the world.[66,67] PDAC is characterized by a fatal disease with early metastasis and resistance to chemotherapy and radiation therapy.[7,68] Although the study of PDAC has made rapid progress in the last decades, the 5-year survival rate of PDAC patients is still only around 5%-7%.[69,70] Therefore, it is crucial to identify reliable biomarkers for early diagnosis of PDAC patients.

Ye et al[42] demonstrated that *AFAP1-AS1* was upregulated in PDAC tissues and cell lines compared with corresponding normal counterparts. Overexpression of *AFAP1-AS1* was associated with lymph node metastasis, perineural invasion, poor survival, overall survival and progression-free survival of PDAC patients. In addition, knockdown of *AFAP1-AS1* reduced proliferation and induced G2/M phase arrest in PDAC cells. Knockdown of *AFAP1-AS1* in PDAC cells inhibited migration and invasion by influencing the expression of EMT-related genes, including E-cadherin, N-cadherin, vimentin, Slug and **Snail1**. As we know, EMT is deemed to be the essential process of cancer progression, enhancing tumour migration, invasion and metastasis.[71-74] During the EMT process, epithelial cells lose epithelial status, apico-basal polarity and cell-cell adhesion so as to transform into mesenchymal cells.[74-76] In order to distinguish diverse functions, EMT is classified into 3 types: primary/type 1, secondary/type 2 and tertiary/type 3. Type 1 is associated with implantation, embryogenesis and organogenesis. Type 2 takes part in wound healing, tissue regeneration and organ development. Type 3 promotes tumour metastasis.[77-79] During cancer progression and metastasis, the expression of some EMT-related genes is changed, such as mesenchymal genes (fibronectin, N-cadherin and vimentin) are increased while epithelial genes (E-cadherin and ZO-1) are decreased.[80,81] Ye et al[42] also found that inhibition of *AFAP1-AS1* reduced PDAC cell tumorigenicity in nude mice. However, amplification of *AFAP1-AS1* produced opposite effects (Figure 2). In conclusion, *AFAP1-AS1* has potential value as a prognostic biomarker and therapeutic target in PDAC.

TABLE 2 Functional characterization of the actin filament-associated protein 1-antisense RNA 1 (*AFAP1-AS1*) in tumours

Cancer types	Expression	Effects	Related gene	Role	References
Oesophageal cancer	Upregulated	Hypomethylation proliferation colony formation, migration, invasion, apoptosis, cycle arrest	—	Oncogene	30, 40, 41
Pancreatic ductal adenocarcinoma	Upregulated	Proliferation, cycle arrest migration, invasion, EMT process	E-cadherin, N-cadherin, vimentin, Slug, **Snail1**	Oncogene	42
Nasopharyngeal carcinoma	Upregulated	Migration, invasion	AFAP1 protein, GTPase family, Pfn1, Lasp1, PD-1, *lncRNA MALAT1*, *lncRNA AL359062*	Oncogene	35, 43, 44
Lung cancer	Upregulated	Proliferation, apoptosis migration, invasion	AFAP1 protein, GTPase family, Pfn1 Lasp1	Oncogene	45-48
Hepatocellular carcinoma	Upregulated	Proliferation, migration, invasion, apoptosis, cycle arrest	PCNA, MMP-9, cyclin D1, Bax, RhoA/Rac2, Ki67, Bcl-2	Oncogene	49, 50
Ovarian cancer	Upregulated	Proliferation, apoptosis		Oncogene	51
Colorectal cancer	Upregulated	EMT process, proliferation, cycle arrest colony formation migration, invasion	E-cadherin, N-cadherin, vimentin, fibronectin, MMP-9, AFAP1	Oncogene	52-54
Biliary tract cancers	Upregulated	EMT process, proliferation colony formation, cell cycle migration, invasion	Twist1, vimentin, E-cadherin, C-myc, cyclin D1, MMP-2, MMP-9, AFAP1	Oncogene	55-57
Gastric cancer	Upregulated	Proliferation apoptosis	PTEN/p-AKT, Bcl-2, PARP, Caspase 3, Caspase 9, Bax	Oncogene	58

EMT: epithelial-mesenchymal transition; GTP: guanosine triphosphate; Pfn1: profilin 1; Lasp1: LIM and SH3 protein 1; PD-1: programmed death 1; *MALAT1:* metastasis-associated lung adenocarcinoma transcript 1; PCNA: proliferating cell nuclear antigen; MMP: matrix metalloproteinase; Bcl-2: B-cell CLL/lymphoma 2 protein; Bax: BCL2-associated X protein; RhoA: ras homologue family member A; Rac2: rac family small GTPase 2; Ki67: Antigen Ki-67; C-myc: MYC proto-oncogene, bHLH transcription factor; PTEN: phosphatase and tensin homologue; AKT: AKT serine/threonine kinase 1; PARP: poly-ADP-ribose polymerase.

3.3 | Nasopharyngeal carcinoma

Nasopharyngeal carcinoma, a unique disease to Southeast Asia, is associated with the Epstein-Barr virus (EBV).[82,83] About 75%-90% of NPC cases are diagnosed at advanced stages due to the non-specific symptoms at an early stage and poor accessibility for physical examination.[84,85] The main clinical treatment of NPC is radiotherapy over the past few decades, but many patients finally die because of recurrence and distant metastasis.[86,87] Therefore, it is essential to find therapeutic targets and prognostic biomarkers for accurate early diagnosis of high-risk populations and evaluation of NPC treatment.

Bo et al[35] reported that *AFAP1-AS1* was upregulated in NPC samples compared with non-tumour nasopharyngeal epithelial samples, and amplification of *AFAP1-AS1* was associated with NPC metastasis and poor prognosis. Knockdown of *AFAP1-AS1* by siRNAs suppressed tumour cell migration and invasion. However, *AFAP1-AS1* has no effects on cell viability, cell cycle progression and apoptosis. Knockdown of *AFAP1-AS1* could increase AFAP1 protein level, induce the loss of stress filament integrity and influence the expression of many proteins related to small GTPase signalling Rho/Rac pathway in NPC cells. Hence, they suspected that *AFAP1-AS1* might promote cancer cell migration and invasion by interfering with AFAP1 expression, small GTPase signalling Rho/Rac pathway and the loss of stress filament integrity (Figure 3). They also carried out nude mouse experiments and discovered that knockdown of *AFAP1-AS1* inhibited NPC cell metastasis to mouse lungs. Based on the previous studies, Tang et al[43] found that the expression of *AFAP1-AS1* was positively correlated with programmed death 1 (PD-1), an immune escape marker. They concluded that *AFAP1-AS1* and PD-1 were co-expressed in infiltrating lymphocytes in NPC tissue and the co-expression predicted poor prognosis of NPC. Moreover, overexpression of *AFAP1-AS1* or PD-1 was correlated with distant metastasis at relapse. He et al[44] identified that 3 circulating lncRNAs (*MALAT1*, *AFAP1-AS1* and *AL359062*) may act as potential biomarkers for NPC, and the three-*lncRNA* signature could contribute to the identification of early NPC patients. Besides, high expression of these 3 lncRNAs was closely related to advanced NPC tumour node metastasis stages and EBV infection. These findings suggest that *AFAP1-AS1* may serve as a cancer-promoting gene and a potential therapeutic target in NPC.

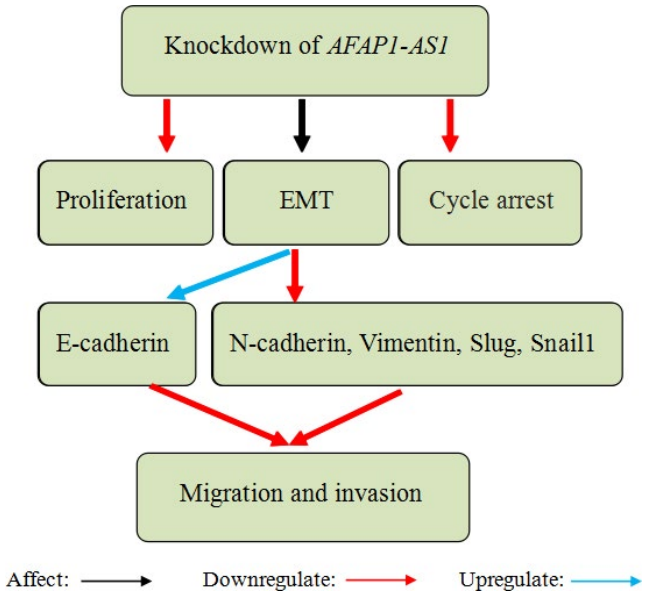

FIGURE 2 Knockdown of actin filament-associated protein 1-antisense RNA 1 (*AFAP1-AS1*) reduced proliferation and induced G2/M phase arrest in pancreatic ductal adenocarcinoma (PDAC) cells. Knockdown of *AFAP1-AS1* in PDAC cells inhibited migration and invasion by influencing the expression of epithelial-mesenchymal transition (EMT)-related genes (E-cadherin, N-cadherin, vimentin, Slug, **Snail1**)

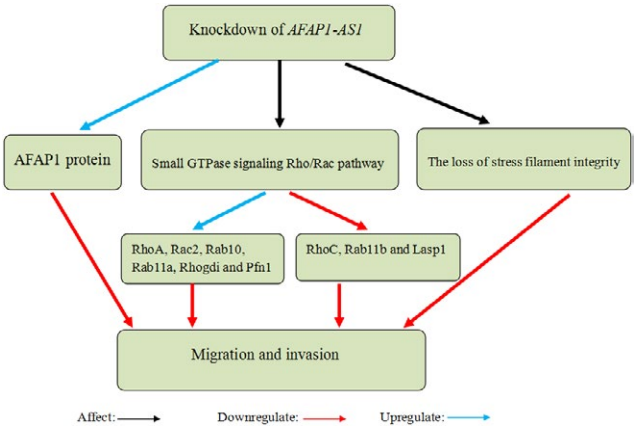

FIGURE 3 Knockdown of actin filament-associated protein 1-antisense RNA 1 (*AFAP1-AS1*) in nasopharyngeal carcinoma (NPC) cells suppressed migration and invasion by increasing AFAP1 protein levels, inducing the loss of stress filament integrity and influencing the expression of many proteins in the small GTPase signalling Rho/Rac pathway (RhoA, Rac2, Rab10, Rab11a, Rhogdi and Pfn1 were significantly upregulated, but RhoC, Rab11b and Lasp1 were significantly downregulated)

3.4 | Lung cancer

Lung cancer is the leading cause of cancer-related mortality all over the world.[88,89] According to histopathological presentation, lung cancer is divided into 4 primary histological subtypes: small cell lung cancer, squamous cell carcinoma (SCC), adenocarcinoma (ADC) and large cell carcinoma (LCC).[90] SCC, ADC and LCC are collectively called non-small cell lung cancer (NSCLC) that accounts for almost 80% of lung cancer.[91] Despite recent progresses of surgical resection, chemoradiotherapy or target drugs, lung cancer patients have a poor prognosis due to metastasis and recurrence.[92-94] The 5-year overall survival rate of advanced lung cancer patients is less than 15%.[95] Hence, it is very important to find adequate tumour biomarkers for early diagnosis and metastasis identification in lung cancers.

Yu et al[45] used microarray gene expression analysis and quantitative real-time polymerase chain reaction analysis to identify that 551 lncRNAs were upregulated in NSCLC tissues, and *AFAP1-AS1* expression changed the most among the upregulated lncRNAs. Deng et al[46] confirmed the above results. They also found that augmented expression of *AFAP1-AS1* was closely associated with clinical stage, smoking history, infiltration degree, lymph node metastasis, distant metastasis and poor prognosis in NSCLC patients. Next, Zeng et al[47] found that *AFAP1-AS1* was significantly upregulated in lung cancer, and *AFAP1-AS1* upregulation was associated with tumour progression and poor survival. In vitro experiments demonstrated that knockdown of *AFAP1-AS1* suppressed tumour cell migration and invasion. Silence of *AFAP1-AS1* also increased the levels of its antisense protein-coding gene, AFAP1, but had no significantly effect on AFAP1 mRNA. In addition, repression of *AFAP1-AS1* influenced some Rho/Rac GTPase family members and actin cytokeratin signalling pathway. Therefore, they speculated that *AFAP1-AS1* might promote migration and invasion in lung cancer by interfering with the expression of AFAP1 and some small GTPases (Figure 4). Recently, Zhuang et al[48] reported that *AFAP1-AS1* was overexpressed in ADC and associated with survival time. Knockdown of *AFAP1-AS1* suppressed cell growth, induced apoptosis and inhibited invasion. Taken together, these results suggest that *AFAP1-AS1* may function as an oncogenic *lncRNA* and a potential prognostic biomarker and therapeutic target in lung cancer.

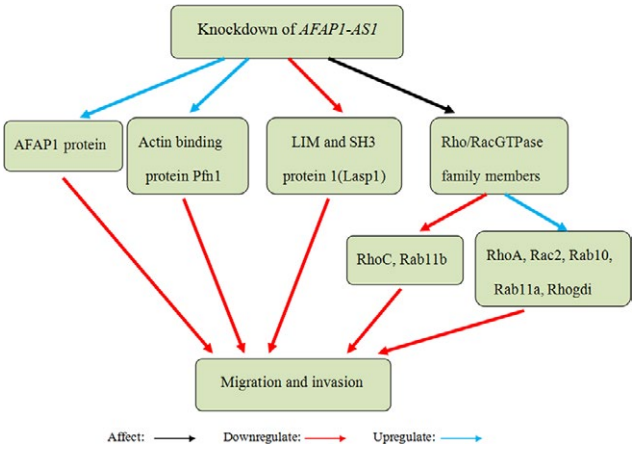

FIGURE 4 Knockdown of actin filament-associated protein 1-antisense RNA 1 (*AFAP1-AS1*) suppressed migration and invasion in lung cancer by increasing the levels of AFAP1 and influencing some Rho/Rac GTPase Rhogdi proteins and actin-binding proteins (RhoA, Rac2, Rab10, Rab11a, Rhogdi and Pfn1 were upregulated, but RhoC, Rab11b and Lasp1 were downregulated)

3.5 | Hepatocellular carcinoma

Hepatocellular carcinoma (HCC), developing on the basis of pre-existing chronic liver disease and cirrhosis, is the fifth most commonly diagnosed cancer and the third leading cause of cancer death all around the world.[96,97] Unlimited cell growth and invasion are the main characteristic of HCC. Because of delayed diagnosis and rapid metastasis, the treatment of advanced HCC is still in a dilemma, and the 5-year survival rate of HCC patients is only about 7%.[98-100] Lots of experiments have proved that HCC occurs in company with genetic or epigenetic mutation.[101-103] Therefore, it is vital to find novel tumour biomarkers and understand the pathogenesis of HCC.

Zhang et al[49] and Lu et al[50] investigated the effects of *AFAP1-AS1* in HCC. Their findings demonstrated that *AFAP1-AS1*, an independent predictor of overall survival, was apparently upregulated in HCC tissues compared with the adjacent non-tumour tissues. Overexpression of *AFAP1-AS1* was associated with tumour size, TNM stage, lymph-vascular space invasion and poor prognosis in HCC. Their results suggested that silencing of *AFAP1-AS1* impaired cell proliferation, migration and invasion through mediating some gene expressions related to proliferation and invasion in vitro. Moreover, Zhang et al[49] reported that silencing of *AFAP1-AS1* promoted cell apoptosis and cycle arrest in S phase by upregulating the expression of Bax (BCL2-associated X protein) and downregulating the expression of cyclin D1. Silencing of *AFAP1-AS1* also suppressed the activation of RhoA/Rac2 (ras homologue family member A/rac family small GTPase 2) signalling to decrease RhoA and Rac2 expression in HCC cells (Figure 5). Hence, they suspected that *AFAP1-AS1* may accelerate the progression and invasion in HCC by upregulating the RhoA/Rac2 signalling. Tumour xenograft studies showed that knockdown of *AFAP1-AS1* suppressed xenograft tumour growth in vivo. The above results suggest that *AFAP1-AS1* may play an important role in HCC development and serve as a therapeutic target of HCC.

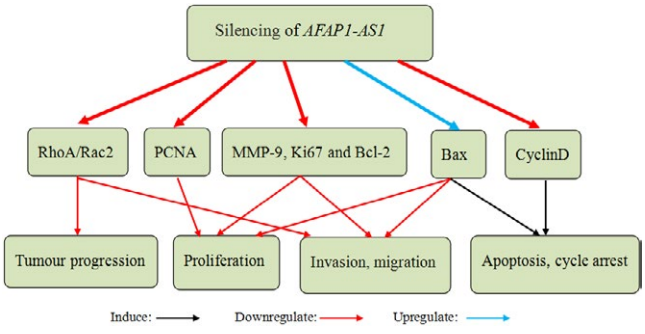

FIGURE 5 Silencing of actin filament-associated protein 1-antisense RNA 1 (*AFAP1-AS1*) in hepatocellular carcinoma (HCC) cells inhibited proliferation, migration and invasion through mediating proliferation- and invasion-related gene expression in vitro (PCNA, MMP-9, Ki67 and Bcl-2 was downregulated, but Bax was upregulated). Silencing of *AFAP1-AS1* induced cell apoptosis and cycle arrest in S phase by upregulating the expression of Bax and downregulating the expression of cyclin D1. Silencing of *AFAP1-AS1* also suppressed the expression of RhoA and Rac2 to repress the progression and invasion in HCC

3.6 | Ovarian cancer

Ovarian cancer (OC) is the third most widespread carcinoma of the female reproductive system.[104] Despite the advances in surgery, diagnostic method and new chemotherapy, OC mortality rate is still high because most patients are diagnosed at an advanced stage.[105-107] Therefore, it is exceedingly important to study its molecular mechanisms.

Yang et al[51] reported that *AFAP1-AS1* was overexpressed in OC tissue samples and cell lines compared with corresponding normal counterparts. They found that high expression of *AFAP1-AS1* was obviously associated with aggressive clinicopathological parameters of OC, including resistance response and International Federation of Gynecology and Obstetrics (FIGO) stage. Then, knockdown of *AFAP1-AS1* suppressed cell proliferation and increased cell apoptosis. Therefore, their results indicate that *AFAP1-AS1* can serve as a novel oncogene and therapeutic target for OC.

3.7 | Colorectal cancer

Colorectal cancer is the third most commonly diagnosed cancer and the second leading cause of cancer death worldwide.[104,108] Although advanced treatments, involving the combination of surgery, radiation therapy, chemotherapy and targeted therapy, are utilized to improve the prognosis of CRC patients, the recurrence and metastasis of CRC are still unavoidable.[109,110] The incidence and mortality of CRC will reduce by screening CRC from curable early stage, so we need to find a novel diagnostic and prognostic indicator for CRC.

Some experimental results proved that *AFAP1-AS1* was aberrantly overexpressed in CRC tissues and cells lines, and overexpression of *AFAP1-AS1* predicted poor prognosis of CRC patients.[52-54] Wang et al[52] found that upregulation of *AFAP1-AS1* was closely correlated with tumour size, TNM stage, distant metastasis, poorer overall survival and disease-free survival. *AFAP1-AS1* inhibition suppressed cell proliferation, colony formation, migration and invasion. Moreover, suppression of *AFAP1-AS1* enhanced G0/G1 cell cycle arrest and the protein level of AFAP1 while having no effect on the mRNA level of AFAP1.[52,53] We suspected that *AFAP1-AS1* may affect some transcription factors expression related to AFAP1 protein, and *AFAP1-AS1* is irrelevant with AFAP1 transcription. Han et al[53] found that knockdown of *AFAP1-AS1* inhibited tumour metastasis-associated genes expression associated with EMT progression. Western blot results showed that the expression of E-cadherin was elevated, but the expression of N-cadherin, vimentin, fibronectin and matrix metalloproteinase 9 (MMP-9) was reduced (Figure 6). They confirmed that knockdown of *AFAP1-AS1* inhibited tumour formation and hepatic metastasis of CRC cells in nude mice. In conclusion, these results suggest that *AFAP1-AS1* may act as an oncogene and a promising diagnostic and therapeutic target for CRC.

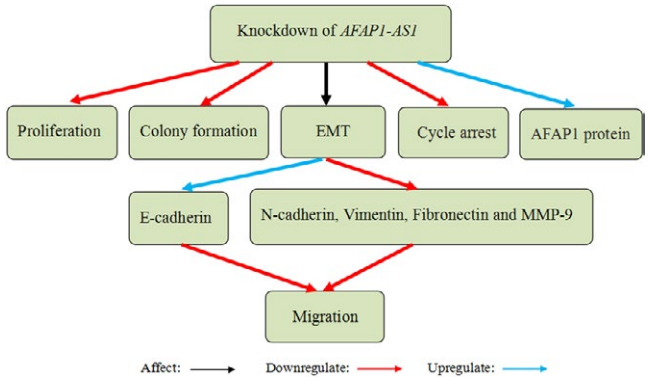

FIGURE 6 Actin filament-associated protein 1-antisense RNA 1 (*AFAP1-AS1*) knockdown in colorectal cancer (CRC) cells suppressed cell proliferation, colony formation, migration and invasion, induced G0/G1 cell cycle arrest and improved the protein level of AFAP1. Knockdown of *AFAP1-AS1* inhibited tumour metastasis-associated genes expression in terms of epithelial-mesenchymal transition (EMT; the expression of E-cadherin was elevated, but the expression of N-cadherin, vimentin, fibronectin and MMP-9 was reduced)

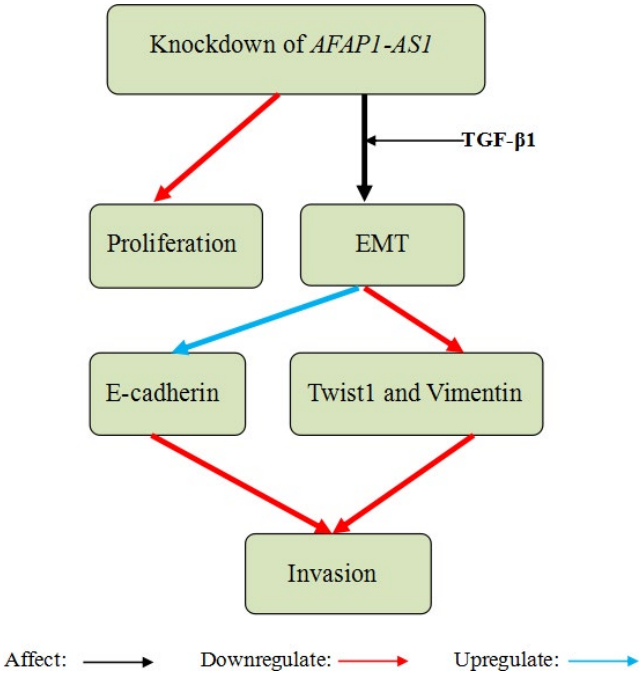

FIGURE 7 Knockdown of actin filament-associated protein 1-antisense RNA 1 (*AFAP1-AS1*) in gallbladder cancer (GBC) cells suppressed cell proliferation and inhibited cell invasion through regulating the epithelial-mesenchymal transition (EMT) process. Then, *AFAP1-AS1* was knockdown and simultaneously induced by TGF-β1 treatment in GBC cells influencing EMT process by downregulating the transcription factor Twist1 and vimentin and upregulating the E-cadherin

3.8 | Biliary tract cancers

Biliary tract cancers (BTC) consist of gallbladder cancer (GBC) and cholangiocarcinoma (CCA). GBC accounts for 80%-95% of BTC, while CCA makes up the rest. CCA is divided into intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma.[111] CCA is one of the most aggressive and lethal tumours, originating from biliary epithelial cells lining the bile duct.[112] GBC is a highly invasive malignancy neoplasm, and the overall 5-year survival of GBC is less than 5%.[113,114] It is hard to diagnose BTC at an early stage because of non-symptomatic manifestation and lack of sensitive biomarkers. Hence, finding early diagnostic markers and novel therapeutic targets is urgently needed.

Ma et al[55] found that *AFAP1-AS1* was significantly elevated in GBC tissues and GBC cell lines and associated with tumour sizes and poor prognosis. Besides, knockdown of *AFAP1-AS1* suppressed cell growth and invasion. Further experiments demonstrated that knockdown of *AFAP1-AS1* impaired the EMT process in GBC cells *via* downregulating the transcription factor Twist1 and vimentin and upregulating the E-cadherin. These findings showed that *AFAP1-AS1* may promote GBC cells invasion through accelerating EMT process (Figure 7).

Shi et al[56] and Lu et al[57] investigated the effects of *AFAP1-AS1* in CCA at the same time. Their findings demonstrated that *AFAP1-AS1* was overexpressed in CCA tissues and cell lines, and *AFAP1-AS1* overexpression was associated with tumour size, vascular invasion, advance TNM stage, poor overall survival and prognosis. In addition, *AFAP1-AS1* knockdown in vitro suppressed cell proliferation and colony formation, induced G0/G1 cell cycle arrest and inhibited S-G2/M transition. Moreover, *AFAP1-AS1* knockdown downregulated the expression of c-Myc (MYC proto-oncogene, bHLH transcription factor) and cyclin D1 that plays an important role in cell proliferation. Silence of *AFAP1-AS1* weakened cell migration and invasion by increasing AFAP1 mRNA and protein expression and reducing matrix metalloproteinase 2 (MMP-2) and MMP-9 expression in vitro. In addition, *AFAP1-AS1* inhibition reduced cell stress filament integrity and repressed CCA cell tumour growth and CCA metastasis in vivo (Figure 8). Taken together, these results suggest that *AFAP1-AS1* produces oncogenic effects in BTC and may become an effective diagnostic and therapeutic target for BTC.

3.9 | Gastric cancer

Gastric cancer, the fourth most commonly diagnosed cancer, is one of the major causes of cancer-related death all over the world.[115,116] Although surgery and chemotherapy for GC have made great progress, GC patients at an advanced stage remain a poor prognosis, having an extremely low 5-year survival rate.[117,118] Thus, it is urgent to find a new biomarkers for diagnosis and prognosis of GC.

Guo et al[58] reported that *AFAP1-AS1* was overexpressed in GC tissues and cells compared with corresponding normal counterparts. *AFAP1-AS1* suppression inhibited cell proliferation through modulating phosphatase and tensin homologue (PTEN)/p-AKT. In addition, decreased expression of *AFAP1-AS1* could impair the protein level of p-AKT (AKT serine/threonine kinase 1) and strengthen the expression of PTEN. Moreover, *AFAP1-AS1* knockdown promoted cell apoptosis through decreasing the protein level of Bcl-2 (B-cell CLL/lymphoma 2 protein) and increasing the protein level of cleaved PARP (poly-ADP-ribose polymerase), Caspase 3, Caspase 9 and Bax. In conclusion, their

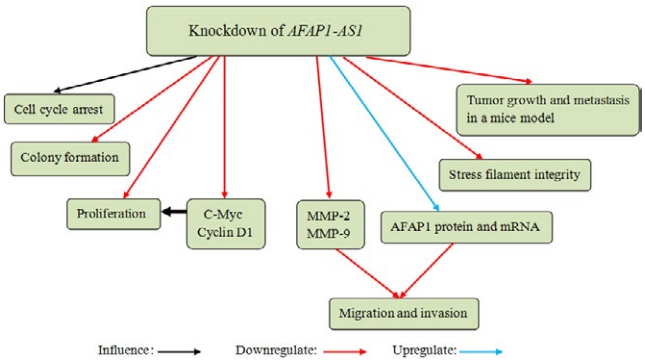

FIGURE 8 Actin filament-associated protein 1-antisense RNA 1 (*AFAP1-AS1*) knockdown in cholangiocarcinoma (CCA) cells suppressed cell proliferation and colony formation and induced cell cycle arrest. *AFAP1-AS1* knockdown downregulated the expression of c-Myc and cyclin D1, which played an important role in cell proliferation. *AFAP1-AS1* knockdown also inhibited cell migration and invasion by increasing AFAP1 protein and mRNA expression and reducing MMP-2 and MMP-9 expression. Moreover, *AFAP1-AS1* knockdown reduced cell stress filament integrity and repressed CCA cell tumour growth and CCA metastasis in a mice model

results support that *AFAP1-AS1* may play a significant role as an indicator of poor survival and a therapeutic target for GC.

4 | CONCLUSION

Long non-coding RNA *AFAP1-AS1* plays an important role in cancer development and serves as an oncogenic *lncRNA*, which is overexpressed in all kinds of cancers, including oesophageal cancer, PDAC, NPC, lung cancer, HCC, OC, CRC, BTC and GC. High expression level of *AFAP1-AS1* in tumour tissues is correlated with clinicopathological characteristics, such as tumour size, lymphatic metastasis, distant metastasis, TNM stage, poor prognosis, overall survival and disease-free survival. However, the precise concentration and detection method of *AFAP1-AS1* in the blood of cancer patients and healthy person are still unclear, impeding the clinical applications of *AFAP1-AS1*. In order to carry out more deeper research and draw a more accurate conclusion, more cancer patients should be involved in the *AFAP1-AS1* study. Functional experiments demonstrated that *AFAP1-AS1* could promote tumour cell proliferation, migration and invasion and inhibit apoptosis. In addition, the involvement of some related genes or signalling pathways in the oncogenic function of *AFAP1-AS1* has been proved, such as EMT-related genes and small GTPase signalling Rho/Rac pathway, but its particular upstream and downstream molecular mechanisms need to be systematically analysed in the future. Compared with other well-studied lncRNAs such as *MALAT1* and *H19*, the studies of *AFAP1-AS1* are not enough. So far, none of *AFAP1-AS1*-related miRNAs or mRNAs was found, and *AFAP1-AS1* research is still at an early stage. The relationship between *AFAP1-AS1* and proteins, miRNAs, mRNAs, ceRNAs and other lncRNAs should be better understood and investigated. Moreover, what is the role of *AFAP1-AS1* in the common pathogenesis of cancer such as chromosome abnormalities, DNA modification and histone modification? Previous studies also showed that knockdown of *AFAP1-AS1* increased the expression of AFAP1 in some cancers, but the combined actions, specific functions and regulatory molecules in tumour progression should be explored in great depth.

In conclusion, the recent studies suggest that *lncRNA AFAP1-AS1* produces oncogenic effects in human cancer and may become an effective diagnostic and therapeutic target for human cancer. With the development of *AFAP1-AS1* study, *lncRNA AFAP1-AS1* may be applied in clinical detection and treatment in the future.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

ORCID

Fuyou Zhang http://orcid.org/0000-0002-5197-1523
Jianfa Li http://orcid.org/0000-0002-2595-3073

REFERENCES

1. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66:115-132.
2. Simard EP, Ward EM, Siegel R, Jemal A. Cancers with increasing incidence trends in the United States: 1999 through 2008. *CA Cancer J Clin*. 2012;62:118-128.
3. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin*. 2017;67:7-30.
4. Mercer TR, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. *Nat Rev Genet*. 2009;10:155-159.
5. Zheng Y, Liu L, Shukla GC. A comprehensive review of web-based non-coding RNA resources for cancer research. *Cancer Lett*. 2017;407:1-8.
6. Li J, Zhuang C, Liu Y, et al. Synthetic tetracycline-controllable shRNA targeting long non-coding RNA HOXD-AS1 inhibits the progression of bladder cancer. *J Exp Clin Cancer Res*. 2016;35:99.
7. Ponting CP, Oliver PL, Reik W. Evolution and functions of long non-coding RNAs. *Cell*. 2009;136:629-641.
8. Seton-Rogers S. Non-coding RNAs: the cancer X factor. *Nat Rev Cancer*. 2013;13:224-225.
9. Chen Y, Xie H, Zou Y, et al. Tetracycline-controllable artificial microRNA-HOTAIR + EZH2 suppressed the progression of bladder cancer cells. *Mol BioSyst*. 2017;13:1597-1607.
10. Hung T, Chang HY. Long noncoding RNA in genome regulation: prospects and mechanisms. *RNA Biol*. 2010;7:582-585.
11. Zhang H, Chen Z, Wang X, Huang Z, He Z, Chen Y. Long non-coding RNA: a new player in cancer. *J Hematol Oncol*. 2013;6:37.

12. Ulitsky I, Bartel DP. lincRNAs: genomics, evolution, and mechanisms. *Cell*. 2013;154:26-46.
13. Yu X, Li Z, Zheng H, Chan MT, Wu WK. NEAT1: a novel cancer-related long non-coding RNA. *Cell Prolif*. 2017;50. https://doi.org/10.1111/cpr.12329.
14. Liu Y, Zeng Y, Liu L, et al. Synthesizing AND gate genetic circuits based on CRISPR-Cas9 for identification of bladder cancer cells. *Nat Commun*. 2014;5:5393.
15. Li J, Zhuang C, Liu Y, et al. shRNA targeting long non-coding RNA CCAT2 controlled by tetracycline-inducible system inhibits progression of bladder cancer cells. *Oncotarget*. 2016;7:28989-28997.
16. Ji P, Diederichs S, Wang W, et al. MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene*. 2003;22:8031-8041.
17. Gutschner T, Hammerle M, Diederichs S. *MALAT1*–a paradigm for long noncoding RNA function in cancer. *J Mol Med (Berl)*. 2013;91:791-801.
18. Wu Y, Huang C, Meng X, Li J. Long noncoding RNA *MALAT1*: insights into its biogenesis and implications in human disease. *Curr Pharm Des*. 2015;21:5017-5028.
19. Ellis MJ, Ding L, Shen D, et al. Whole-genome analysis informs breast cancer response to aromatase inhibition. *Nature*. 2012;486:353-360.
20. Fan Y, Shen B, Tan M, et al. TGF-beta-induced upregulation of malat1 promotes bladder cancer metastasis by associating with suz12. *Clin Cancer Res*. 2014;20:1531-1541.
21. Ji Q, Zhang L, Liu X, et al. Long non-coding RNA *MALAT1* promotes tumour growth and metastasis in colorectal cancer through binding to SFPQ and releasing oncogene PTBP2 from SFPQ/PTBP2 complex. *Br J Cancer*. 2014;111:736-748.
22. Fang D, Yang H, Lin J, et al. 17beta-estradiol regulates cell proliferation, colony formation, migration, invasion and promotes apoptosis by upregulating miR-9 and thus degrades MALAT-1 in osteosarcoma cell MG-63 in an estrogen receptor-independent manner. *Biochem Biophys Res Commun*. 2015;457:500-506.
23. Gupta RA, Shah N, Wang KC, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature*. 2010;464:1071-1076.
24. Xu ZY, Yu QM, Du YA, et al. Knockdown of long non-coding RNA HOTAIR suppresses tumor invasion and reverses epithelial-mesenchymal transition in gastric cancer. *Int J Biol Sci*. 2013;9:587-597.
25. Song H, Sun W, Ye G, et al. Long non-coding RNA expression profile in human gastric cancer and its clinical significances. *J Transl Med*. 2013;11:225.
26. Li H, Yu B, Li J, et al. Overexpression of lncRNA H19 enhances carcinogenesis and metastasis of gastric cancer. *Oncotarget*. 2014;5:2318-2329.
27. Zhuang M, Gao W, Xu J, Wang P, Shu Y. The long non-coding RNA H19-derived miR-675 modulates human gastric cancer cell proliferation by targeting tumor suppressor RUNX1. *Biochem Biophys Res Commun*. 2014;448:315-322.
28. Yang F, Bi J, Xue X, et al. Up-regulated long non-coding RNA H19 contributes to proliferation of gastric cancer cells. *FEBS J*. 2012;279:3159-3165.
29. Xiang W, Ke Z, Zhang Y, et al. Isthmin is a novel secreted angiogenesis inhibitor that inhibits tumour growth in mice. *J Cell Mol Med*. 2011;15:359-374.
30. Wu W, Bhagat TD, Yang X, et al. Hypomethylation of noncoding DNA regions and overexpression of the long noncoding RNA, *AFAP1-AS1*, in Barrett's esophagus and esophageal adenocarcinoma. *Gastroenterology*. 2013;144:956-966.
31. Liu FT, Xue QZ, Zhu PQ, Luo HL, Zhang Y, Hao T. Long noncoding RNA *AFAP1-AS1*, a potential novel biomarker to predict the clinical outcome of cancer patients: a meta-analysis. *Onco Targets Ther*. 2016;9:4247-4254.
32. Flynn DC, Leu TH, Reynolds AB, Parsons JT. Identification and sequence analysis of cDNAs encoding a 110-kilodalton actin filament-associated pp60src substrate. *Mol Cell Biol*. 1993;13:7892-7900.
33. Qian Y, Baisden JM, Zot HG, Van Winkle WB, Flynn DC. The carboxy terminus of AFAP-110 modulates direct interactions with actin filaments and regulates its ability to alter actin filament integrity and induce lamellipodia formation. *Exp Cell Res*. 2000;255:102-113.
34. Qian Y, Baisden JM, Cherezova L, et al. PC phosphorylation increases the ability of AFAP-110 to cross-link actin filaments. *Mol Biol Cell*. 2002;13:2311-2322.
35. Bo H, Gong Z, Zhang W, et al. Upregulated long non-coding RNA *AFAP1-AS1* expression is associated with progression and poor prognosis of nasopharyngeal carcinoma. *Oncotarget*. 2015;6:20404-20418.
36. Carrieri C, Cimatti L, Biagioli M, et al. Long non-coding antisense RNA controls Uchl1 translation through an embedded SINEB2 repeat. *Nature*. 2012;491:454-457.
37. Sehgal L, Mathur R, Braun FK, et al. FAS-antisense 1 lncRNA and production of soluble versus membrane Fas in B-cell lymphoma. *Leukemia*. 2014;28:2376-2387.
38. Wang Y, Pang WJ, Wei N, et al. Identification, stability and expression of Sirt1 antisense long non-coding RNA. *Gene*. 2014;539:117-124.
39. Yuan SX, Tao QF, Wang J, et al. Antisense long non-coding RNA PCNA-AS1 promotes tumor growth by regulating proliferating cell nuclear antigen in hepatocellular carcinoma. *Cancer Lett*. 2014;349:87-94.
40. Zhou XL, Wang WW, Zhu WG, et al. High expression of long non-coding RNA *AFAP1-AS1* predicts chemoradioresistance and poor prognosis in patients with esophageal squamous cell carcinoma treated with definitive chemoradiotherapy. *Mol Carcinog*. 2016;55:2095-2105.
41. Luo HL, Huang MD, Guo JN, et al. *AFAP1-AS1* is upregulated and promotes esophageal squamous cell carcinoma cell proliferation and inhibits cell apoptosis. *Cancer Med*. 2016;5:2879-2885.
42. Ye Y, Chen J, Zhou Y, et al. High expression of *AFAP1-AS1* is associated with poor survival and short-term recurrence in pancreatic ductal adenocarcinoma. *J Transl Med*. 2015;13:137.
43. Tang Y, He Y, Shi L, et al. Co-expression of *AFAP1-AS1* and PD-1 predicts poor prognosis in nasopharyngeal carcinoma. *Oncotarget*. 2017;8:39001-39011.
44. He B, Zeng J, Chao W, et al. Serum long non-coding RNAs *MALAT1*, *AFAP1-AS1* and AL359062 as diagnostic and prognostic biomarkers for nasopharyngeal carcinoma. *Oncotarget*. 2017;8:41166-41177.
45. Yu H, Xu Q, Liu F, Ye X, Wang J, Meng X. Identification and validation of long noncoding RNA biomarkers in human non-small-cell lung carcinomas. *J Thorac Oncol*. 2015;10:645-654.
46. Deng J, Liang Y, Liu C, He S, Wang S. The up-regulation of long non-coding RNA *AFAP1-AS1* is associated with the poor prognosis of NSCLC patients. *Biomed Pharmacother*. 2015;75:8-11.
47. Zeng Z, Bo H, Gong Z, et al. *AFAP1-AS1*, a long noncoding RNA upregulated in lung cancer and promotes invasion and metastasis. *Tumour Biol*. 2016;37:729-737.
48. Zhuang Y, Jiang H, Li H, et al. Down-regulation of long non-coding RNA *AFAP1-AS1* inhibits tumor cell growth and invasion in lung adenocarcinoma. *Am J Transl Res*. 2017;9:2997-3005.
49. Zhang JY, Weng MZ, Song FB, et al. Long noncoding RNA *AFAP1-AS1* indicates a poor prognosis of hepatocellular carcinoma and promotes cell proliferation and invasion via upregulation of the RhoA/Rac2 signaling. *Int J Oncol*. 2016;48:1590-1598.
50. Lu X, Zhou C, Li R, et al. Critical role for the long non-coding RNA *AFAP1-AS1* in the proliferation and metastasis of hepatocellular carcinoma. *Tumour Biol*. 2016;37:9699-9707.

51. Yang SL, Lin RX, Si LH, Cui MH, Zhang XW, Fan LM. Expression and functional role of long non-coding RNA *AFAP1-AS1* in ovarian cancer. *Eur Rev Med Pharmacol Sci*. 2016;20:5107-5112.
52. Wang F, Ni H, Sun F, Li M, Chen L. Overexpression of lncRNA *AFAP1-AS1* correlates with poor prognosis and promotes tumorigenesis in colorectal cancer. *Biomed Pharmacother*. 2016;81:152-159.
53. Han X, Wang L, Ning Y, Li S, Wang Z. Long non-coding RNA *AFAP1-AS1* facilitates tumor growth and promotes metastasis in colorectal cancer. *Biol Res*. 2016;49:36.
54. Li Q, Dai Y, Wang F, Hou S. Differentially expressed long non-coding RNAs and the prognostic potential in colorectal cancer. *Neoplasma*. 2016;63:977-983.
55. Ma F, Wang SH, Cai Q, Zhang MD, Yang Y, Ding J. Overexpression of LncRNA *AFAP1-AS1* predicts poor prognosis and promotes cells proliferation and invasion in gallbladder cancer. *Biomed Pharmacother*. 2016;84:1249-1255.
56. Shi X, Zhang H, Wang M, et al. LncRNA *AFAP1-AS1* promotes growth and metastasis of cholangiocarcinoma cells. *Oncotarget*. 2017;8:58394-58404.
57. Lu X, Zhou C, Li R, Deng Y, Zhao L, Zhai W. Long Noncoding RNA *AFAP1-AS1* Promoted Tumor Growth and Invasion in Cholangiocarcinoma. *Cell Physiol Biochem*. 2017;42:222-230.
58. Guo JQ, Li SJ, Guo GX. Long Noncoding RNA *AFAP1-AS1* Promotes Cell Proliferation and Apoptosis of Gastric Cancer Cells via PTEN/p-AKT Pathway. *Dig Dis Sci*. 2017;62:2004-2010.
59. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. *Lancet*. 2013;381:400-412.
60. Lagergren J, Lagergren P. Recent developments in esophageal adenocarcinoma. *CA Cancer J Clin*. 2013;63:232-248.
61. Rice TW, Gress DM, Patil DT, Hofstetter WL, Kelsen DP, Blackstone EH. Cancer of the esophagus and esophagogastric junction-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67:304-317.
62. Barton MK. Smoking found to increase the rate of progression of Barrett esophagus to adenocarcinoma. *CA Cancer J Clin*. 2012;62:215-216.
63. Yuequan J, Shifeng C, Bing Z. Prognostic factors and family history for survival of esophageal squamous cell carcinoma patients after surgery. *Ann Thorac Surg*. 2010;90:908-913.
64. Polednak AP. Trends in survival for both histologic types of esophageal cancer in US surveillance, epidemiology and end results areas. *Int J Cancer*. 2003;105:98-100.
65. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med*. 2003;349:2241-2252.
66. Garrido-Laguna I, Hidalgo M. Pancreatic cancer: from state-of-the-art treatments to promising novel therapies. *Nat Rev Clin Oncol*. 2015;12:319-334.
67. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. *Lancet*. 2016;388:73-85.
68. Frampton AE, Castellano L, Colombo T, et al. Integrated molecular analysis to investigate the role of microRNAs in pancreatic tumour growth and progression. *Lancet*. 2015;385(suppl 1):S37.
69. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. *Lancet*. 2011;378:607-620.
70. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet*. 2017;389:1011-1024.
71. De Craene B, Berx G. Regulatory networks defining EMT during cancer initiation and progression. *Nat Rev Cancer*. 2013;13:97-110.
72. Nakaya Y, Sheng G. EMT in developmental morphogenesis. *Cancer Lett*. 2013;341:9-15.
73. Nieto MA. Epithelial plasticity: a common theme in embryonic and cancer cells. *Science*. 2013;342:1234850.
74. Nieto MA, Huang RY, Jackson RA, Thiery JP. Emt: 2016. *Cell*. 2016;166:21-45.
75. Thiery JP, Acloque H, Huang RY, Nieto MA. Epithelial-mesenchymal transitions in development and disease. *Cell*. 2009;139:871-890.
76. Santamaria PG, Moreno-Bueno G, Portillo F, Cano A. EMT: present and future in clinical oncology. *Mol Oncol*. 2017;11:718-738.
77. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. *J Clin Invest*. 2009;119:1420-1428.
78. Gonzalez DM, Medici D. Signaling mechanisms of the epithelial-mesenchymal transition. *Sci Signal*. 2014;7:re8.
79. Singh M, Yelle N, Venugopal C, Singh SK. EMT: mechanisms and therapeutic implications. *Pharmacol Ther*. 2017. https://doi.org/10.1016/j.pharmthera.2017.08.009.
80. Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. *Nat Rev Mol Cell Biol*. 2014;15:178-196.
81. Du B, Shim JS. Targeting epithelial-mesenchymal transition (EMT) to overcome drug resistance in cancer. *Molecules*. 2016;21:E965.
82. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65:87-108.
83. Chua MLK, Wee JTS, Hui EP, Chan ATC. Nasopharyngeal carcinoma. *Lancet*. 2016;387:1012-1024.
84. Agulnik M, Epstein JB. Nasopharyngeal carcinoma: current management, future directions and dental implications. *Oral Oncol*. 2008;44:617-627.
85. Yan Q, Zeng Z, Gong Z, et al. EBV-miR-BART10-3p facilitates epithelial-mesenchymal transition and promotes metastasis of nasopharyngeal carcinoma by targeting BTRC. *Oncotarget*. 2015;6:41766-41782.
86. Zhou Y, Zeng Z, Zhang W, et al. Lactotransferrin: a candidate tumor suppressor-Deficient expression in human nasopharyngeal carcinoma and inhibition of NPC cell proliferation by modulating the mitogen-activated protein kinase pathway. *Int J Cancer*. 2008;123:2065-2072.
87. Yang Y, Liao Q, Wei F, et al. LPLUNC1 inhibits nasopharyngeal carcinoma cell growth via down-regulation of the MAP kinase and cyclin D1/E2F pathways. *PLoS ONE*. 2013;8:e62869.
88. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013;49:1374-1403.
89. Barton MK. Integration of lung cancer screening into practice is lacking. *CA Cancer J Clin*. 2015;65:255-256.
90. Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer–major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67:138-155.
91. He M, Xue Y. MicroRNA-148a suppresses proliferation and invasion potential of non-small cell lung carcinomas via regulation of STAT3. *Onco Targets Ther*. 2017;10:1353-1361.
92. Morgensztern D, Ng SH, Gao F, Govindan R. Trends in stage distribution for patients with non-small cell lung cancer: a National Cancer Database survey. *J Thorac Oncol*. 2010;5:29-33.
93. Barton MK. Encouraging long-term outcomes reported in patients with stage I non-small cell lung cancer treated with stereotactic ablative radiotherapy. *CA Cancer J Clin*. 2017;67:349-350.
94. Barton MK. Local consolidative therapy may be beneficial in patients with oligometastatic non-small cell lung cancer. *CA Cancer J Clin*. 2017;67:89-90.
95. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011;12:735-742.
96. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. *JAMA*. 2015;313:2263-2273.
97. Au JS, Frenette CT. Erratum: management of hepatocellular carcinoma: current Status and future directions. *Gut Liv*. 2015;9:811.

98. Waghray A, Murali AR, Menon KN. Hepatocellular carcinoma: From diagnosis to treatment. *World J Hepatol*. 2015;7:1020-1029.
99. Ilikhan SU, Bilici M, Sahin H, et al. Assessment of the correlation between serum prolidase and alpha-fetoprotein levels in patients with hepatocellular carcinoma. *World J Gastroenterol*. 2015;21:6999-7007.
100. Maluccio M, Covey A. Recent progress in understanding, diagnosing, and treating hepatocellular carcinoma. *CA Cancer J Clin*. 2012;62:394-399.
101. Poon RT. Prevention of recurrence after resection of hepatocellular carcinoma: a daunting challenge. *Hepatology*. 2011;54:757-759.
102. Dong QZ, Zhang XF, Zhao Y, et al. Osteopontin promoter polymorphisms at locus -443 significantly affect the metastasis and prognosis of human hepatocellular carcinoma. *Hepatology*. 2013;57:1024-1034.
103. Wang B, Fang J, Qu L, Cao Z, Zhou J, Deng B. Upregulated TRIO expression correlates with a malignant phenotype in human hepatocellular carcinoma. *Tumour Biol*. 2015;36:6901-6908.
104. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61:69-90.
105. Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology, and prognostic factors. *Semin Surg Oncol*. 2000;19:3.
106. Rustin G, van der Burg M, Griffin C, Qian W, Swart AM. Early versus delayed treatment of relapsed ovarian cancer. *Lancet*. 2011;377:380-381.
107. Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. *CA Cancer J Clin*. 2011;61:183-203.
108. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. *CA Cancer J Clin*. 2017;67:177-193.
109. Edwards BK, Noone AM, Mariotto AB, et al. Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. *Cancer*. 2014;120:1290-1314.
110. Brenner H, Kloor M, Pox CP. Colorectal cancer. *Lancet*. 2014;383:1490-1502.
111. Miyazaki M, Yoshitomi H, Miyakawa S, et al. Clinical practice guidelines for the management of biliary tract cancers 2015: the 2nd English edition. *J Hepatobiliary Pancreat Sci*. 2015;22:249-273.
112. Wang WT, Ye H, Wei PP, et al. LncRNAs H19 and HULC, activated by oxidative stress, promote cell migration and invasion in cholangiocarcinoma through a ceRNA manner. *J Hematol Oncol*. 2016;9:117.
113. Lazcano-Ponce EC, Miquel JF, Munoz N, et al. Epidemiology and molecular pathology of gallbladder cancer. *CA Cancer J Clin*. 2001;51:349-364.
114. Goetze TO. Gallbladder carcinoma: prognostic factors and therapeutic options. *World J Gastroenterol*. 2015;21:12211-12217.
115. Ang TL, Fock KM. Clinical epidemiology of gastric cancer. *Singapore Med J*. 2014;55:621-628.
116. Zong L, Abe M, Seto Y, Ji J. The challenge of screening for early gastric cancer in China. *Lancet*. 2016;388:2606.
117. Lim SM, Lim JY, Cho JY. Targeted therapy in gastric cancer: personalizing cancer treatment based on patient genome. *World J Gastroenterol*. 2014;20:2042-2050.
118. Van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. *Lancet*. 2016;388:2654-2664.

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