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AFAP1-AS1: a rising star among oncogenic long non-coding RNAs

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Long non-coding RNAs (lncRNAs) have become a hotspot in biomedical research. This interest reflects their extensive involvement in the regulation of the expression of other genes, and their influence on the occurrence and development of a variety of human diseases. Actin filament associated protein 1-Antisense RNA 1(AFAP1-AS1) is a recently discovered oncogenic lncRNA. It is highly expressed in a variety of solid tumors, and regulates the expression of downstream genes and signaling pathways through adsorption and competing microRNAs, or by the direct binding to other proteins. Ultimately, AFAP1-AS1 promotes proliferation, chemotherapy resistance, and resistance to apoptosis, maintains stemness, and enhances invasion and migration of tumor cells. This paper summarizes the research concerning AFAP1-AS1 in malignant tumors, including the clinical application prospects of AFAP1-AS1 as a potential molecular marker and therapeutic target of malignant tumors. We also discuss the limitations in the knowledge of AFAP1-AS1 and directions of further research. AFAP1-AS1 is expected to provide an example for studies of other lncRNA molecules.

AFAP1-AS1, metastasis, proliferation, anti-cancer drug, PD-1, immunotherapy

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Introduction

After the completion of the Human Genome Project, all the human protein coding genes were annotated. This analysis revealed that all exon sequences of the protein coding genes accounted for only approximately 1% of the 3×10^9 base pairs (bp) of the human genome. The Encyclopedia of DNA Elements (ENCODE) project found that the majority of DNA sequences in the human genome can be transcribed (Ecker et al., 2012). Thus, the majority of sequences in the human transcriptome are not used to encode proteins. Transcripts that do not encode proteins are termed non-coding RNAs (ncRNAs). The vast majority of ncRNAs are longer than 200 nucleotides (nt).

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These are termed long ncRNAs(lncRNAs) (Gong et al., 2012). At present, 96,308 human lncRNA genes have been identified. They encode 172,216 transcripts that have been identified and recorded in the NONCODE database of ncRNA (www.noncode.org) (Zhao et al., 2016). The number of lncRNA genes identified in the human genome has far exceeded the number of protein coding genes (approximately 21,000).

Although lncRNAs do not code proteins, they are widely involved in regulating expression of other genes at the pre-transcription, transcription, and posttranscription levels, and can also act as signal, guide, decoy or scaffold molecules to affect the function and localization of proteins, and subsequently regulate numerous signal transduction pathways in cells. Therefore, lncRNAs are important in the development of human diseases, including malignant tumors (Fan et al., 2019; Fan et al., 2018; Fan et al., 2017; Gong et al., 2016; Gong et al., 2014; He et al., 2016; He Y. et al., 2018; Song et al., 2016; Tang L. et al., 2018; Tang Y. et al., 2018; Tang Y. et al., 2017; Wang Y. et al., 2016; Yan et al., 2015; Yang et al., 2017; Yang L. et al., 2018; Yu et al., 2017a; Yu et al., 2017b; Zeng et al., 2016; Zhang et al., 2013).

In-depth studies of the biological functions of lncRNAs and their roles in the occurrence and development of human diseases will help us understand the pathophysiology of human diseases from a new perspective. Therefore, lncRNA has become a hotspot in biomedical research in recent years. Actin filament associated protein 1-Antisense RNA 1 (AFAP1-AS1) is an oncogenic lncRNA molecule that is upregulated in a variety of malignant tumors, and is involved in tumor development. This paper summarizes the recent research progress concerning AFAP1-AS1 in malignant tumors, including the clinical application prospects of AFAP1-AS1 as a potential molecular marker and a therapeutic target of malignant tumors, the insufficiency of current research on AFAP1-AS1, and future research directions. AFAP1-AS1 is also expected to provide an example for the study of other lncRNA molecules.

AFAP1-AS1 is upregulated in various tumor tissues and is a new tumor molecular marker

Gene chip and second generation sequencing technologies can easily compile transcriptome profiles of malignant tumor tissues of different pathological types and clinical stages, corresponding normal tissue, and can screen differentially expressed lncRNAs in tumor tissues. These dysregulated lncRNAs are often involved in the development of malignant tumors. In 2013, Wu et al. performed a genome-wide DNA methylation analysis of Barrett's esophagus (BE, precancerous lesions), esophageal adenocarcinoma (EAC), and normal esophageal epithelium. The authors described that the DNA CpG islands near the AFAP1-AS1 gene were significantly hypomethylated in both BE and EAC, and that the novel lncRNA, AFAP1-AS1, was significantly upregulated in BE and EAC. This was the first report on AFAP1-AS1 (Wu et al., 2013).

Subsequently, multiple groups reported that AFAP1-AS1 is significantly highly expressed in nasopharyngeal carcinoma (Bo et al., 2015; He et al., 2017; Tang Y. et al., 2017), gastric cancer (Feng et al., 2017; Gao et al., 2018; Guo et al., 2017; Li et al., 2019; Mo et al., 2019; Ye et al., 2018; Zhao et al., 2018), colorectal cancer (Han et al., 2016; Li et al., 2016; Tang J. et al., 2018; Wang F. et al., 2016; Zhao et al., 2019), lung cancer (Deng et al., 2015; Ding et al., 2018; He J. et al., 2018; Huang et al., 2019; Leng et al., 2018; Li et al., 2017; Peng et al., 2017; Roth et al., 2018; Tang X.D. et al., 2018; Wang M. et al., 2016; Wei and Zhang, 2016; Yin et al., 2018; Zeng et al., 2016; Zhuang et al., 2017) and other cancer tissues (Table 1). Several groups also conducted meta-analyses on the expression of AFAP1-AS1 in various tumors and its correlation with tumor prognosis by analyzing datasets from different sources (Gao et al., 2018; Ji et al., 2018; Liu et al., 2016; Liu et al., 2018; Wang M. et al., 2016; Wang et al., 2017; Zhong et al., 2019; Zhou et al., 2018). For example, Wang et al. collected data from published papers and combined 20 sets of genechip data with clinical information from the Gene Expression Omnibus (GEO) database to extract the expression levels of AFAP1-AS1 in corresponding tumors and control tissues. The authors confirmed that AFAP1-AS1 was upregulated in most epithelial and nervous system solid tumors, and was closely related to the clinical stage of the tumors and the poor prognosis of the patients. However, AFAP1-AS1 is downregulated in blood system tumors, such as diffuse large B-cell lymphoma and lymphocytic leukemia, and patients with high expression of AFAP1-AS1 have better prognosis (Wang et al., 2017). These results suggest that the expression of AFAP1-AS1 is heterogeneous in different malignant tumors with different tissue and organ origins, and that the biological functions and molecular mechanisms of AFAP1-AS1 in tumorigenesis may also be different.

In addition to the significant increase in the expression of AFAP1-AS1 in various solid tumor tissues, which can be used as a molecular marker for predicting the efficacy of therapy and prognosis of patients, several groups have reported the expression of AFAP1-AS1 in peripheral blood samples of patients with nasopharyngeal cancer (He et al., 2017), lung cancer (Li et al., 2017), and gastric cancer (Liu et al., 2020), with no detection of AFAP1-AS1 in peripheral blood samples of normal control populations. These findings support the expectation that AFAP1-AS1 could be a serum marker of malignant tumors and may serve as an early diagnosis biomarker of these cancers.

Table 1 Functional characterization and clinical significance of AFAP1-AS1 in various cancers[a)]

Cancer types	Fold changes	Functional effects	Clinicopathological features	Related genes/miRNAs	References
Liver cancer	8.47	Cell proliferation, migration, invasion, apoptosis, cycle arrest	Tumor size, TNM stage, vascular invasion, OS, DFS, pathological stage, lymph-vascular space invasion	RhoA, Rac2	(Lu et al., 2016, Zhang et al., 2016)
Glioma	6.17	Cell invasion	Glioma grade, Karnofsky Performance Status scores, poor prognosis		(Wang Y. et al., 2018)
Pancreatic cancer	4.95	Cell proliferation, migration, invasion, stemness, cell cycle,	Tumor size, lymph node metastasis, perineural invasion, TMN stage, OS, diagnostic biomarkers	miR-384, ACVR1, miR-146b-5p, EGFR, miR-133a, IGF1R	(Chen et al., 2018, Fu et al., 2016, Wu et al., 2019, Ye et al., 2015, Zhou et al., 2019)
Breast cancer	4.65	Cell proliferation, colony formation, apoptosis, Invasion, migration	TNM stage, lymph node metastasis, poor OS, poor DFS	β-catenin, GSK3, p-GSK3, C-myc, SLUG, SNAIL, vimentin, fibronectin, N-cadherin, E-cadherin	(Ma et al., 2019, Xi et al., 2018, Zhang et al., 2018)
Pituitary adenoma	4.02	Cell proliferation, cycle progression, cell apoptosis		miR-103a-3p, PTEN	(Tang et al., 2019)
Gallbladder cancer	3.12	Cell proliferation, invasion, EMT	Tumor size, poor prognosis	Twist1, E-cadherin, Vimentin	(Ma et al., 2016)
Nasopharyngeal carcinoma	2.75	Cell migration, invasion, metastasis, stress filament integrity	Lymph node metastasis, TNM stage, distant tumor metastasis, poor OS, poor PFS, EBV infection, diagnostic marker	PD-L1, miR-423-5p, FOSL2, RAB11B, LASP1	(Bo et al., 2015, He et al., 2017, Lian et al., 2018, Tang Y. et al., 2017)
Laryngeal carcinoma	2.64	Stemness, drug resistance		miR-320a, RBPJ	(Yuan et al., 2018)
Colorectal cancer	2.45	Cell proliferation, colony formation, migration, invasion, Hepatic metastasis, cell cycle	Tumor size, TNM stage, distant metastasis, shorter OS, DFS	E-cadherin, vimentin, MMP9, ZEB1, β-catenin, ZO-1, LncRNA GAS8-AS, AFAP1, EZH2	(Bo et al., 2018, Han et al., 2016, Tang J. et al., 2018, Wang F. et al., 2016, Zhao et al., 2019)
Lung cancer	2.44	Cell proliferation, migration, invasion, apoptosis, cell cycle, EMT, chemotherapy resistance, colony formation	Greater histology type, tumor size, lymph node metastasis, distant metastasis, TNM stage, differentiation grade, diagnostic biomarkers, shorter OS, shorter recurrence-free survival, smoking, infiltration degree	AFAP1, KRT1, miR-139-5p, RRM2, HBP1, p21, AFAP1, IRF7, RIG1, MdA5, LGP2, Bcl-2, NF-κB, TNF-α	(Deng et al., 2015, He J. et al., 2018, Huang et al., 2019, Li et al., 2017, Peng et al., 2017, Tang X.D. et al., 2018, Yin et al., 2018, S. Yu et al., 2019, Zeng et al., 2016, Zhuang et al., 2017)
Gastric cancer	1.98	Apoptosis, Proliferation, Invasion, migration cell cycle, EMT	TNM stage, Lymphatic metastasis, tumor size, tumor differentiation, diagnostic biomarkers, worse OS	KLF2, PTEN	(Feng et al., 2017, Guo et al., 2017, Li et al., 2019, Liu et al., 2020, Ye et al., 2018, Yuan et al., 2020, Zhao et al., 2018)
Kidney cancer	1.75	Cell proliferation, Invasion, Migration, EMT	Shorter OS, TNM stage, lymph node metastasis	PTEN	(Mu et al., 2019)

a) OS: overall survival; PFS: relapse-free survival; DFS: disease-free survival.

Mechanisms of upregulation of AFAP1-AS1

The AFAP1-AS1 gene is located in human chromosome 4p16.1. It is on the antisense strand of the gene encoding Actin filament associated protein 1 (AFAP1). Abnormal hypomethylation of CpG islands near the AFAP1-AS1 gene was found in a genome-wide methylation profile of esophageal cancer and its precancerous lesions (BE), which led to the discovery and identification of AFAP1-AS1 as a new tumor-associated lncRNA (Wu et al., 2013). The findings indicate that the promoter region of the AFAP1-AS1 gene is hypermethylated, so that its expression level is low or not expressed under normal circumstances. In the process of carcinogenesis, the genomic DNA methylation state is dramatically changed. The promoter region of AFAP1-AS1 is demethylated, which initiates the expression of AFAP1-AS1, which is one of the mechanisms for the upregulation of the expression of AFAP1-AS1 in esophageal cancer (Wu et al., 2013), cervical cancer (Bo et al., 2019), and other malignant tumors.

In addition to DNA methylation, modification of histones can also affect the expression of nearby genes. Xi et al. used eight different histone modification specific antibodies to pull-down their nearby DNA, and then performed chromatin immuno-precipitation sequencing (ChIP-Seq) in 13 different types of breast cancer cell lines. The authors used this analysis combined with whole transcriptome RNA-Seq to demonstrate specific chromatin modification signals in triple

negative breast cancer (TNBC) cell lines. For example, there was an active promoter signal (H3K4me3 and H3K79me2 ChIP-Seq peaks) around the AFAP1-AS1 gene and AFAP1-AS1 was also significantly upregulated in RNA-Seq data of TNBC cell lines (Xi et al., 2018). The findings implied that chromatin remodeling caused by histone modifications also plays an important role in the upregulation of AFAP1-AS1.

Except for the DNA methylation and the opening of chromatin (including histone modifications), the nucleus transcriptional regulatory proteins also play important roles in gene transcriptional regulation. Wei et al. predicted the potential promoter region of the AFAP1-AS1 gene, and gradually reduced the promoter region of AFAP1-AS1 to the –359 to –28 bp region of the transcription start site of AFAP1-AS1. The authors identified a c-Myc binding site in this promoter, and verified that the oncoprotein c-Myc could activate transcription of AFAP1-AS1 (F. Wei et al., 2019). The data support the view that the hypomethylation of the AFAP1-AS1 promoter region, H3K4me3 and H3K79me2 modifications of the nearby histones, and the co-regulation of transcription regulatory proteins, such as c-Myc, may be mechanisms for the upregulation of AFAP1-AS1 expression in various malignant tumors (Figure 1).

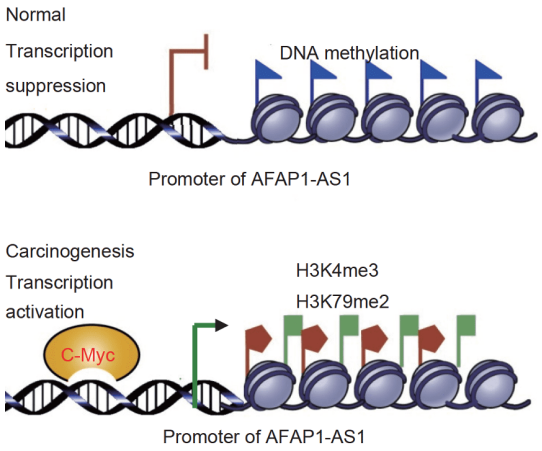

Figure 1 Mechanism of upregulation of AFAP1-AS1 expression in malignant tumors. In normal tissues, the AFAP1-AS1 promoter region is hypermethylated and AFAP1-AS1 is not transcribed. In the progress of carcinogenesis, the AFAP1-AS1 promoter is de-methylated, and the nearby histones H3K4me3 and H3K79me2 are modified. The chromatin opens and transcription factors, such as c-myc, enter and bind to the AFAP1-AS1 promoter, initiating the expression of AFAP1-AS1.

AFAP1-AS1 regulates downstream gene expression through competing miRNAs

The competing endogenous RNA (ceRNA) mechanism is a major way that lncRNAs regulate expression of other mRNAs and exert their biological functions (Lian et al., 2016). The ceRNA hypothesis posits that if long chain RNAs, including lncRNAs and mRNAs, have the same miRNA binding site (termed the miRNA response element, MRE), these RNAs could compete for the absorption of miRNA, thus regulating the expression of each other. Thus, lncRNAs, miRNAs, and mRNAs form a large and complex ceRNA regulatory network in eukaryotic cells (Tay et al., 2011). AFAP1-AS1 is 6,810 nt in length and harbors many potential miRNA binding sites. AFAP1-AS1 can regulate the expression of different mRNAs by competing with multiple miRNAs, and in turn regulates downstream signaling pathways and affects the malignant biological phenotype of tumors.

For example, Lian et al. performed bioinformatics analysis and experimentally verified that AFAP1-AS1 can competitively bind miR-423-5p (Lian et al., 2018). There are multiple miR423-5p binding sites in the 3′-untranslated region (3′-UTR) of LIM and SH3 domain protein 1 (LASP1) and Ras-related protein Rab-11B (RAB11B), the key proteins in the Rho/Rac pathway. Thus, AFAP1-AS1 can directly regulate the Rho/Rac pathway by adsorbing to miR423-5p and then upregulating the expression of LASP1 and RAB11B. AFAP1-AS1 also acts as a ceRNA to regulate Fos-related antigen 2 (FOSL2) expression. As a transcriptional factor of the AP-1 family, FOSL2 can transcriptionally regulate the expression of LASP1, which can further enhance the activation of the Rho/Rac pathway (Lian et al., 2018) (Figure 2). The Rho/Rac pathway regulates cytoskeletal remodeling by affecting the rearrangement and stability of microtubules and filaments, thus playing an important role in the maintenance of cell polarity and morphology, as well as cell adhesion, invasion, and migration (Tang Y. et al., 2018). Therefore, the activation of Rho/Rac pathway is the mechanism by which AFAP1-AS1 promotes the invasion and migration of nasopharyngeal carcinoma. This mechanism has also been verified in liver cancer (Zhang et al., 2016), cervical cancer (Bo et al., 2019), osteosarcoma (Shi et al., 2019), and other tumors.

In addition to competing for miR423-5p, AFAP1-AS1 can also competitively bind miR-133a (Chen et al., 2018), miR-139-5p (Huang et al., 2019), miR-384 (Wu et al., 2019), miR-103a-3p (Tang et al., 2019), miR-320a (Yuan et al., 2018), miR-146b-5p (Zhou et al., 2019), miR-4695-5p (Li et al., 2018), and other miRNAs. This can up-regulate the expression of IGF1R (Chen et al., 2018), RRM2 (Huang et al., 2019), activin A receptor, type I (ACVR1) (Wu et al., 2019), GH3/MMQ (Tang et al., 2019), RBPJ (Yuan et al., 2018), epidermal growth factor receptor (EGFR) (Zhou et al., 2019), β-catenin (Li et al., 2018), and other mRNAs. Thus, these proteins and their downstream signaling pathways promote malignant phenotypes, such as tumor proliferation, invasion, migration and stemness, and stimulate the occurrence and development of tumors (Figure 2). AFAP1-AS1 is a long non-coding RNA with a sequence length of 6,810 nt.

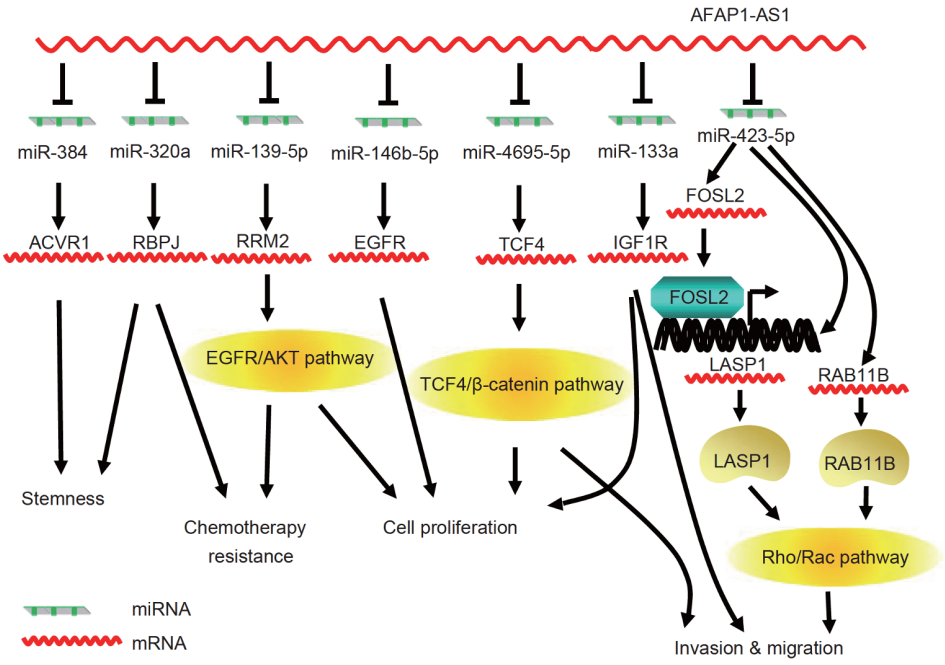

Figure 2 AFAP1-AS1 competitively binds miRNAs to regulate the expression of other mRNAs to promote tumor development. AFAP1-AS1 competitively bind miRNAs miR-423-5p, miR-133a, miR-139-5p, etc. and up-regulate the expression of FOSL2, LASP1, RAB11B, IGF1R, RRM2, and other mRNAs. Thus, these proteins and their downstream signaling pathways promote malignant phenotypes, such as tumor proliferation, invasion, migration and stemness, and stimulate the occurrence and development of tumors.

The long sequence of AFAP1-AS1 may provide more miRNA binding sites that need to be explored.

AFAP1-AS1 regulates downstream gene expression by directly binding to proteins

In addition to competing with miRNAs and regulating the stability of mRNAs, lncRNAs can also bind to corresponding proteins. These RNA binding proteins can affect the stability, intracellular localization and function of proteins, and have biological functions. Zhong et al. captured AFAP1-AS1 binding protein in an RNA pull-down experiment, and identified the captured proteins through liquid chromatography tandem mass spectrometry (LC-MS). The authors found that AFAP1-AS1 had a high affinity with Smad nuclear interacting protein 1 (SNIP1). This was confirmed by an RNA binding protein immunoprecipitation (RIP) experiment. It was subsequently verified that AFAP1-AS1 can promote the binding of SNIP1 and c-Myc, and the combination of SNIP1 and c-Myc can inhibit the ubiquitination and degradation of c-Myc, leading to the upregulation of c-Myc expression. As a transcription factor, c-Myc then promotes expression of downstream target genes, such as ZEB1, ZEB2, and Snail, thereby promoting EMT of tumor cells and ultimately promoting tumor invasion and metastasis (Zhong et al., 2021) (Figure 3A).

Tang et al. found that AFAP1-AS1 can bind to enhancer of zeste homolog 2 (EZH2) protein. The binding promotes tumor growth (Tang J. et al., 2018). EZH2 is a member of polycomb repressive complex 2 (PRC2). The PRC2 complex can inhibit transcription of target genes by methylating lysine residues at positions 9 and 27 of histone H3 (H3K9me and H3K27me of histone H3). Yin et al. also reported that AFAP1-AS1 can bind to EZH2, recruit EZH2 to the promoter of p21 gene, and inhibit the expression of p21 through epigenetic regulation to promote tumor cell proliferation (Yin et al., 2018). In addition, AFAP1-AS1 can also bind to another important enzyme involved in epigenetic modification, lysine-specific demethylase 1 (LSD1), and inhibit the expression of HMG box-containing protein 1 (HBP1) through LSD1 (Yu et al., 2019), thereby promoting tumor proliferation (Figure 3B). In addition to that the interaction between AFAP1-AS1 and protein is related to the malignant phenotype of tumor cells, Han et al. found that AFAP1-AS1 up-regulates the expression of HER-2 in breast cancer cells by interacting with AU-binding factor 1 (AUF1) to activate the translation of ERBB2 mRNA, and ultimately cause the breast cancer cells to develop resistance to trastuzumab (Han et al., 2020) (Figure 3C).

Different RNA domains can recruit different proteins or histone modification molecules to participate in the regulation of physiological or pathological activities in organisms (Yang X. et al., 2018). For example, the 911–1,190 nt sites of AFAP1-AS1 form a stem-loop structure that can bind to the AUF1 (Han et al., 2020). The sequence of AFAP1-AS1 is

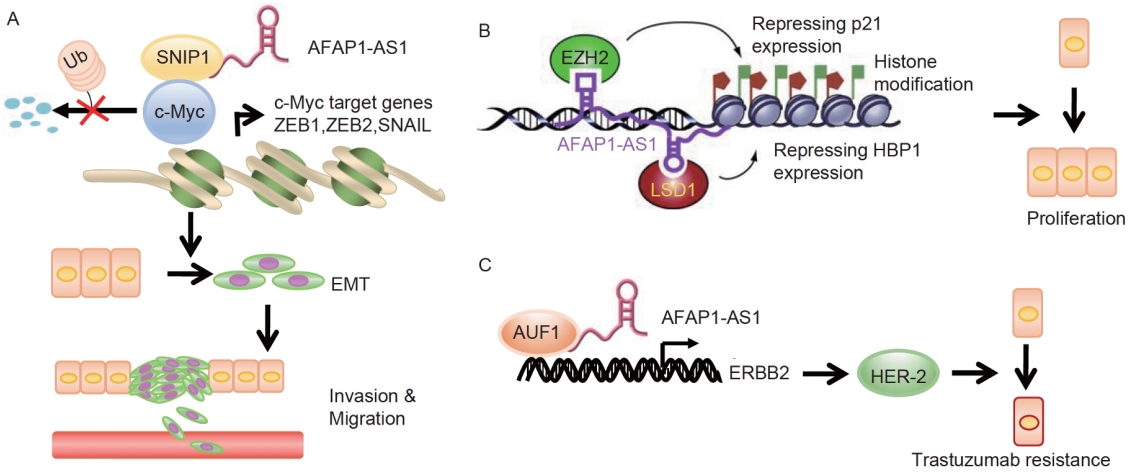

Figure 3 AFAP1-AS1 promotes tumor development by binding proteins. A, AFAP1-AS1 binds to SNIP1, promotes the binding of SNIP1 and c-Myc, and inhibits the ubiquitination of c-Myc, leading to the upregulation of c-Myc expression. Upregulation of c-Myc expression can enhance the transcription of target genes, such as ZEB1, ZEB2, and Snail, and ultimately accelerates the EMT of tumor cells and promotes tumor cell invasion and migration. B, AFAP1-AS1 can recruit epigenetic regulatory proteins, such as EZH2 and LSD1, to specific chromatin sites, regulates histone modification of chromatin, inhibits the expression of certain genes that include p21 and HBP1, and promotes the proliferation of tumor cells. C, AFAP1-AS1 up-regulates the expression of HER-2 by interacting with AUF1 to activate the translation of ERBB2 mRNA, and ultimately cause the breast cancer cells to develop resistance to trastuzumab.

relatively long and the secondary structure is complex. Moreover, the secondary structure of RNA is closely related to RNA function. By analyzing the secondary structure of AFAP1-AS1, we may discover more proteins related to AFAP1-AS1 regulating tumors. In addition, AFAP1-AS1 is located in the cytoplasm and nucleus (Han et al., 2020). In different tissues, the subcellular localization analysis of AFAP1-AS1 is also a way of exploring its mechanism to regulate tumor development.

Summary and future perspectives

AFAP1-AS1 is a recently discovered, important oncogenic lncRNA. In the above, we summarized the relevant mechanisms of AFAP1-AS1 regulating tumor development. AFAP1-AS1, as a sponge of miRNA, can relieve the silencing of cancer-promoting genes. The interaction between AFAP1-AS1 and RBPs regulates the expression of downstream related genes. In addition, some related signaling pathways are involved in the carcinogenic function of AFAP1-AS1, such as EGFR/AKT signaling pathway, PTEN/AKT pathway, TCF4/β-catenin pathway, and Rho/Rac pathway. However, it cannot be ignored that the upstream and downstream molecular mechanisms of AFAP1-AS1 still need to be explored in detail to clarify the specific role of AFAP1-AS1 in tumor regulation. Although it is generally considered that if the longest predicted open reading frame (ORF) of an RNA is less than 300 nt (i.e., the polypeptide is encoded by less than 100 amino acid residues), the coding capacity of this RNA is low, and it is defined as lncRNA. In general, progressively shorter ORF shaves progressively weaker coding ability. However, recent research has found that some lncRNAs that were previously thought not to encode proteins, actually do encode small, biologically functional peptides having less than 100 amino acids (Wu P. et al., 2020). AFAP1-AS1 is currently defined as lncRNA. The longest ORF it can predict is 588 nt (reference sequence NR_026892.1, 1,396–1,983 nt). The expected encoded polypeptide is 195 amino acids. Two other ORFs with more than 300 nt in the sense sequence are predicted (5,153–5,467 nt and 718–1,020 nt). Can AFAP1-AS1 also encode small peptides with biological functions through the encoded small peptides? This issue is interesting and worthy of further study.

AFAP1-AS1 is upregulated in a variety of malignant tumors, but not in most normal tissues. Therefore, AFAP1-AS1 is not only a molecular marker for cancer diagnosis but also a new target for tumor treatment. AFAP1-AS1 expression is upregulated in peripheral blood samples from patients with nasopharyngeal cancer (He et al., 2017), lung cancer (Li et al., 2017), and gastric cancer (Liu et al., 2020). However, its value as a new biomarker for liquid biopsy (Ye et al., 2019) of malignant tumors has yet to be verified with a large number of clinic samples. The sensitivity and specificity of AFAP1-AS1 in other types of tumors also require further analysis. If it is verified that AFAP1-AS1 is indeed a highly sensitive and highly specific molecular marker for certain malignancies, further development of a convenient, economical and fast detection kit will help its clinical application.

At the same time, as a highly expressed lncRNA molecule in tumor cells, how does AFAP1-AS1 enter peripheral blood, and does it pass through exosomes (Han et al., 2020)? In addition to peripheral blood, can it be detected in other body fluids, such as urine and saliva? Does detecting the expres-

sion of AFAP1-AS1 in these body fluids have clinical application value? These are questions worth exploring.

Inhibiting or down-regulating the expression of AFAP1-AS1 can significantly inhibit malignant phenotypes, such as cell proliferation, invasion and migration in a variety of tumors, suggesting that AFAP1-AS1 may be an important antitumor target. Zhao et al. found that another lncRNA, GAS8-AS, can down-regulate the expression of AFAP1-AS1 and inhibit the proliferation of colorectal cancer cells (Zhao et al., 2019). Screening for small molecule compounds, especially small molecule drugs from natural products, to inhibit the expression of AFAP1-AS1, has also made some progress. Cucurbitacin B (Zhou et al., 2019) and oridonin (Lou et al., 2019) exert antitumor effects by inhibiting the expression of AFAP1-AS1. Further screening of other small molecule compounds or derivatives of cucurbitacin B and oridonin, which more specifically inhibit the expression of AFAP1-AS1 and have a better tumor suppressive effect, may eventually be used in the clinical treatment of tumors, to the benefit of the majority of cancer patients.

Recently, the expression of AFAP1-AS1 was also significantly positively correlated with the infiltration of T cells in tumor tissues and the expression of programmed cell death protein 1 (PD-1) on the surface of T cells (Tang Y. et al., 2017). Scientists have made breakthroughs using PD-1 and programmed cell death 1 ligand 1 (PD-L1) antibodies in tumor immunotherapy (Duan et al., 2019; Ge et al., 2020; Jiang et al., 2019; Jiang et al., 2018; Peng et al., 2019; Ren et al., 2020; Wang Y.A. et al., 2018). However, the antibodies are expensive and the effect is not obvious in a majority of patients with solid tumors. Thus, it is an important goal to discover molecular markers that can predict the potential efficacy of PD-1/PD-L1 blocking therapy to guide clinical applications, achieve precise treatment, and reduce treatment costs. If further research shows that AFAP1-AS1 is not only related to PD-1 expression, but also significantly related to the patient's response to PD-1 antibody treatment, then AFAP1-AS1 may also become a new molecular marker to predict the effect of tumor immunotherapy, especially anti-PD-1/PD-L1 therapy. Further exploration of the roles and mechanisms of AFAP1-AS1 in tumor immune escape and immunotherapy will open a new field for the study of AFAP1-AS1.

In addition to malignant tumors, AFAP1-AS1 is also highly expressed in endometriosis. AFAP1-AS1 can promote EMT in the endometrium by upregulating zinc finger E-box-binding homeobox 1 (ZEB1), while EMT is also an important step for tumor invasion and metastasis (Lin et al., 2019). In addition, AFAP1-AS1 is also highly expressed in Hirschsprung disease (Chen et al., 2017). These findings suggest that in addition to malignant tumors, the expression, role, and mechanism of AFAP1-AS1 in the pathogenesis of other diseases, especially some proliferation-related diseases, are also worthy of further study.

In summary, AFAP1-AS1, as an lncRNA with oncogene properties, is highly expressed in many solid tumors, and has become an intensively researched ncRNA in recent years. It has important functions in the development of malignant tumors, especially in the process of tumor cell proliferation, prevention of apoptosis, drug resistance, maintenance of stem cell characteristics, and invasion and migration. It is also a potential molecular marker and candidate target of therapy for many tumors. However, research on AFAP1-AS1 has just begun. Further in-depth and comprehensive explorations of its functional and biological significance will further the understanding of the pathogenesis of tumors. This knowledge will assist in the diagnosis and treatment of tumors.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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