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Identification of LncRNA CASC7/ miR-26/ ASPN/TGF-β/Smad Axis in Endometrial Cancer

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XZ and JY conceived the study and wrote the article. WZ and ZC searched the literature. WW and SS and LW analyzed bioinformatics.

Key words
Endometrial cancer, lncRNA CASC7, ASPN, TGF-β/Smad pathway, Bioinformatics

ABSTRACT

Endometrial cancer is the most common gynecological malignant tumor in many countries. TGF-β regulates cell proliferation, angiogenesis and metastasis, and is an inducer of epithelial-mesenchymal transformation. Tumor cells activate the TGF-β/Smad pathway, and inhibiting its signal transduction pathway is an important strategy for tumor therapy. First, we have found lncRNA CASC7 is a poor prognostic marker of endometrial cancer. Then, ASPN was specifically expressed in endometrium and cell specific expression in basophils, among the most similar genes, we found TGF-β3. Moreover, lncRNA CASC7 acts on miR-26, and miR-26 was predicted to regulate ASPN. Next, Except for *SMAD2* and *XIAP*, the expression of *ASPN*, *TGF-β1*, *TGF-β2*, *TGF-β3*, *SMAD3* and *SMAD4* genes in normal tissues was higher than that in tumor tissues. *ASPN* was positively correlated with *TGF-β1*, *TGF-β2*, *TGF-β3*, *SMAD3* and *SMAD4*. Pathway activity shows ASPN and TGF-β1 and TGF-β3 activate EMT. Finally, we speculate that lncRNA CASC7 inhibited miR-26, inhibited ASPN, inhibited TGF-β, and promoted XIAP, to activate SMAD/XIAP pathway, improving the survival rate and invasiveness of endometrial cancer cells. Collectively, this is the first time to describe the mechanism of lncRNA CASC7/miR-26/ASPN/TGF-β/Smad axis in the proliferation and invasion of endometrial cancer cells.

INTRODUCTION

Human endometrial cancer is one of the most common female malignant tumors in the world, and the incidence is high (Morice *et al*., 2016). Although early detection significantly improved the overall survival rate, the prognosis was poor, with a median survival rate of only one year (Holub *et al*., 2020). The imbalance of apoptosis is an early event in the pathogenesis of endometrial carcinoma, this inherent resistance to various pro-apoptotic signals may be one of the reasons for the resistance of endometrial cancer to current chemotherapeutic drugs (Jayaraman *et al*., 2017). At present, there is no accurate molecular tag that can be used as a good diagnostic or prognostic biomarker for treatment resistance and disease recurrence of endometrial cancer.

A large number of studies have shown that, long noncoding RNAs (lncRNAs) is involved in the carcinogenesis of endometrial cancer by regulating proliferation, apoptosis and metastasis signal pathways and the interaction with transfer factors (Yang *et al*., 2020; Zeng *et al*., 2020; Zhang *et al*., 2021). Many studies have also shown that lncRNAs competes for endogenous RNA or molecular sponges in regulating the concentration and biological function of miRNAs. LncRNA cancer susceptibility candidate gene 7 (CASC7) is a dual-located lncRNA, that exists in nuclear components (Zhou *et al*., 2020). It is reported that lncRNA CASC7 inhibits the proliferation and migration of colon cancer cells by inhibiting miR-21 (Zhang *et al*., 2017). However, the research of lncRNA CASC7 and miR-26 in endometrial cancer has not been published so far.

As a secretory matrix protein, asporin (ASPN) plays a potential mediating role in the occurrence and development of many cancers (Rochette *et al*., 2017;

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Zhang *et al*., 2019). In the past decade, ASPN has become a potential biomarker for all types of cancer (Zhan *et al*., 2019). It is reported that ASPN is regulated by miR-26 in colorectal cancer (Wang *et al*., 2015). However, the function of ASPN in cancer cells is not clear to a large extent, and the study of ASPN in endometrial cancer has not been published so far.

In many tumor types, malignant progression is closely related to the loss of sensitivity to the anti-proliferative effect of transforming growth factor-β (TGF-β) (Soleimani *et al*., 2019; Efiloglu *et al*., 2020; Sano *et al*., 2020; Zhao *et al*., 2020). It is obvious that TGF-β/Smad pathway is an important tumor inhibition mechanism (Gao *et al*., 2020; Jeong *et al*., 2020; Liu *et al*., 2020; Xiong *et al*., 2020; Zhao *et al*., 2021). TGF-β1 is an anti-proliferative cytokine, especially in the early stage of tumorigenesis (Miao *et al*., 2019). Therefore, the TGF-β1 restriction point is an important obstacle that many cells must overcome in order to evolve into malignant tumors and achieve unrestricted proliferation. Interesting, TGF-β3 is expressed primarily in mesenchymal cells. TGF-β3 gene encodes a member of the TGF-β family of proteins. The encoded protein is secreted and is involved in embryogenesis and cell differentiation. Moreover, TGF-β3 increases the invasiveness of endometrial cancer cells through PI3K/XIAP or SMAD/XIAP pathway (Van Themsche *et al*., 2007).

More and more studies have reported the key functional correlation of ASPN in tumor diseases, and it is one of the most significantly differentially expressed genes. However, the mechanism of ASPN in endometrial cancer has not been reported. In addition, some studies have shown that ASPN is most likely to participate in the regulation of TGF-β pathway (Li *et al*., 2019), which has been proved to be an important pathway involved in the occurrence and development of endometrial cancer (Bokhari *et al*., 2016; Wang *et al*., 2019).

In the present study, at first, we analyze lncRNA CASC7 and ASPN through The Human Protein Atlas. Then, we discover the connection between miRNAs and lncRNAs via lncBase database, and predict the regulatory miRNAs of ASPN by miRDB database and mirDIP database and DIANA database. Then, expression levels and correlation analysis is carried out by GEPIA. Finally, Single Nucleotide Variation and Pathway Activity analysis is carried out by GSCALite.

MATERIALS AND METHODS

Analysis of protein atlas

The human protein atlas (https://www.proteinatlas.org/) is to map all the human proteins in cells, tissues and organs using integration of various omics technologies, including antibody-based imaging, mass spectrometry-based proteomics, transcriptomics and systems biology. The human protein atlas consists of six separate parts, each focusing on a particular aspect of the genome-wide analysis of the human proteins; the tissue atlas showing the distribution of the proteins across all major tissues and organs in the human body, the cell atlas showing the subcellular localization of proteins in single cells, the pathology atlas showing the impact of protein levels for survival of patients with cancer, the blood atlas, the brain atlas and the metabolic atlas.

Discovering the connection between miRNAs and lncRNAs

LncBase v.2 database (http://carolina.imis.athena-innovation.gr/diana_tools/web/index.php?r=lncbasev2%2Findex) was used to discover the connection between miRNAs and lncRNAs. Experimental module was to search for the verified targets in LncBase v.2 database. The condition we filter was that the tissue was the cervix, and the miRNA species is *Homo Sapiens*.

Regulatory miRNA prediction

MiRDB (http://mirdb.org/miRDB/index.htmL) database, mirDIP database (http://ophid.utoronto.ca/mirDIP/index.jsp#) and DIANA database (http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=microT_CDS/index) were used to identify the regulatory miRNAs for ASPN. Then, we intersected the results from the three databases to predict the regulatory miRNAs of ASPN by the Venn plotting website (http://bioinformatics.psb.ugent.be/webtools/Venn/), and get the most reliable miRNA.

Expression levels and correlation analysis

GEPIA (http://gepia2.cancer-pku.cn/#index) is a newly developed interactive web server for analyzing the RNA sequencing expression data of 9,736 tumors and 8,587 normal samples from the TCGA and the GTEx projects, using a standard processing pipeline. GEPIA provides customizable functions such as tumor/normal differential expression analysis, profiling according to cancer types or pathological stages, patient survival analysis, similar gene detection, correlation analysis and dimensionality reduction analysis.

Single nucleotide variation (SNV) and pathway activity

GSCA Lite is a web-based analysis platform for gene set cancer analysis. The alterations on DNA or RNA of cancer related genes may be contribute to the cancer initiation, progress, diagnosis, prognosis, therapy. As the cancer genomics big data available, it is very useful and urgent to provide a platform for gene set analysis in cancer.

RESULTS

LncRNA CASC7 is the prognostic marker in endometrial cancer

The Human Protein Atlas showed the expression of lncRNA CASC7 is localized to the Nucleoplasm (supported) and Cell Junctions (approved). Evidence at human protein level is showed in Figure 1A, and Evidence at human cells level is showed in Figure 1B. Thus, lncRNA CASC7 is predicted to locate in intracellular.

Moreover, lncRNA CASC7 is prognostic, high expression is unfavourable in endometrial cancer (Fig. 2). lncRNA CASC7 has been reported in colon cancer because of its anti-tumor effect. As far as we know, the role and mechanism of lncRNA CASC7 in endometrial cancer is not clear.

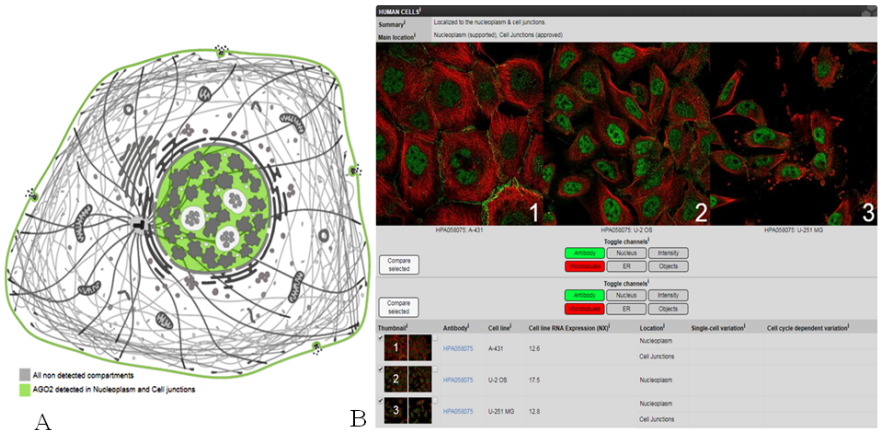

Fig. 1. lncRNA CASC7 is localized to the nucleoplasm (supported) and cell junctions (approved) at human protein level (A) and cells level (B).

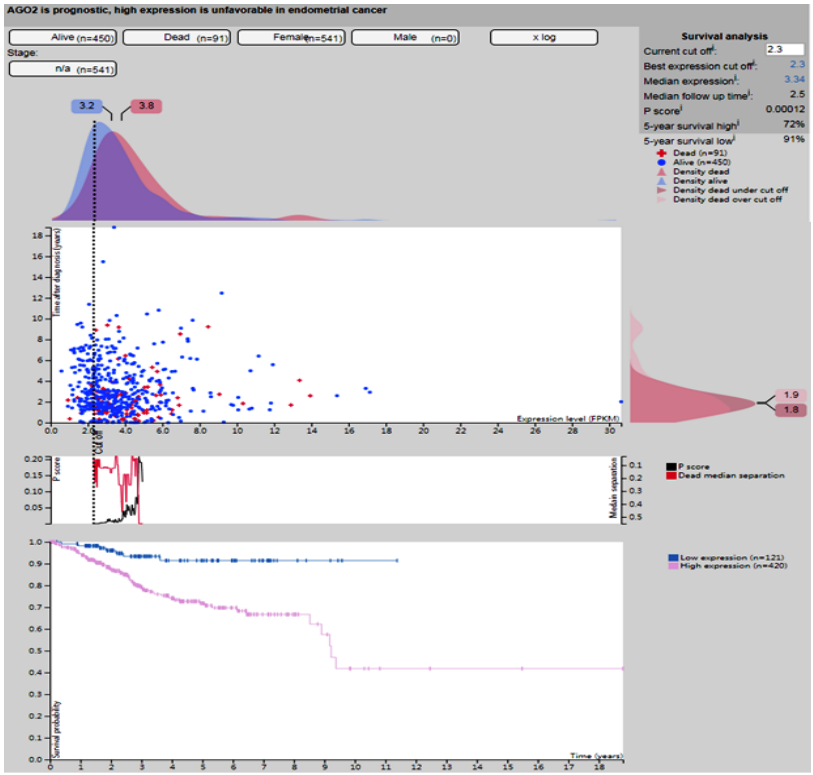

Fig. 2. lncRNA CASC7 is the prognostic marker in endometrial cancer.

Tissue-specific expression of ASPN in endometrium

The Human Protein Atlas showed the expression of ASPN is predicted to secreted at human protein level. Furthermore, Isoform Structure find that 2 isoforms in ASPN have different isoform structures (Fig. 3A). Li *et al*. (2019) studies shows ASPN interacts with Smad2/3 through the LRR domain, then regulating TGF-β/Smad2/3 pathway promotes cell migration in colorectal cancer. ASPN was initially identified as an exocrine protein in the study of bone and joint diseases. In many other studies, the subcellular localization of ASPN in the cytoplasm and even nucleus has been observed, but its exact biological function in cancer cells is completely unknown. May be this was related to ASPN isoform structures.

In addition, the expression of *ASPN* is tissue-specific in endometrium, and the cell type specially is basophil (Fig. 3B). It is consistent with the expression level of HPA dataset, GTEx dataset and FANTOM5 dataset. Combined with the results mentioned above, we speculate that there is a certain relationship between lncRNA CASC7 and ASPN.

LncRNA CASC7 acts on miR-26

In order to discover the connection between miRNAs and lncRNAs, we use LncBase v.2 to analyze lncRNA CASC7. The result shows that lncRNA CASC7 acts on miR-26 in human cervical tissue and HeLa cell (Fig. 4A). Whereas, miR-26 is tumor suppressive miRNA in endometrial cancer, and its expression is decreased. Therefore, there is a negative correlation between lncRNA CACS7 and miR-26. Then, we further speculate whether there is a connection between miR-26 and ASPN? Maybe miR-26 is the bridge between CASC7 and ASPN.

MiR-26 was predicted to regulate ASPN

More and more studies have reported the key functional correlation of ASPN in tumor diseases, and it is one of the genes that show the most significant differential expression. However, there are no articles about the mechanism of ASPN in endometrial carcinoma. In order to further understand the upstream regulation mechanism of ASPN, such as miRDB databases, mirDIP databases and DIANA databases are used to predict the regulated miRNAs and intersect the predicted results. The intersection determines the only accommodative miRNA miR-26 in the three databases (Fig. 4A).

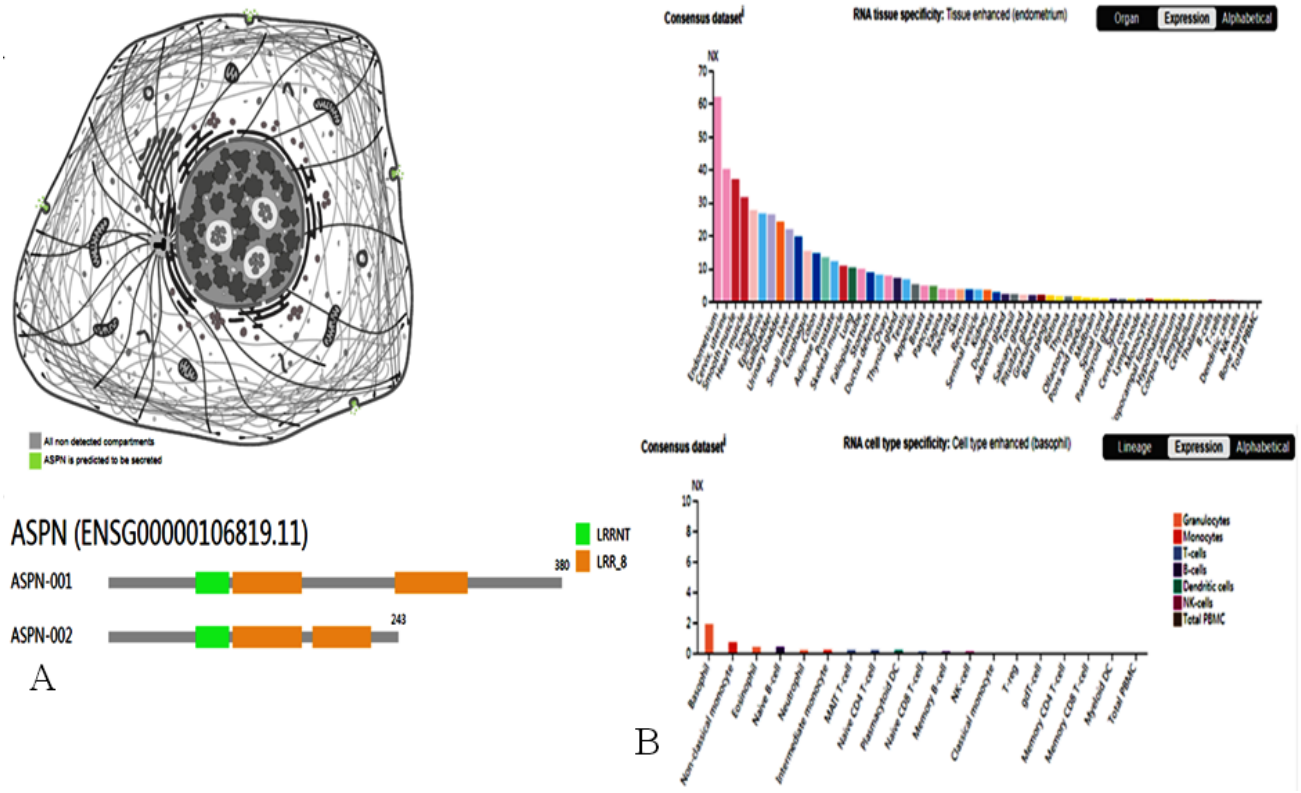

Fig. 3. Expression characteristics of ASPN. ASPN is predicted to secreted at human protein level, and there are 2 isoforms in ASPN (A). Tissue-specific expression of ASPN in endometrium and cell-specific is basophil (B).

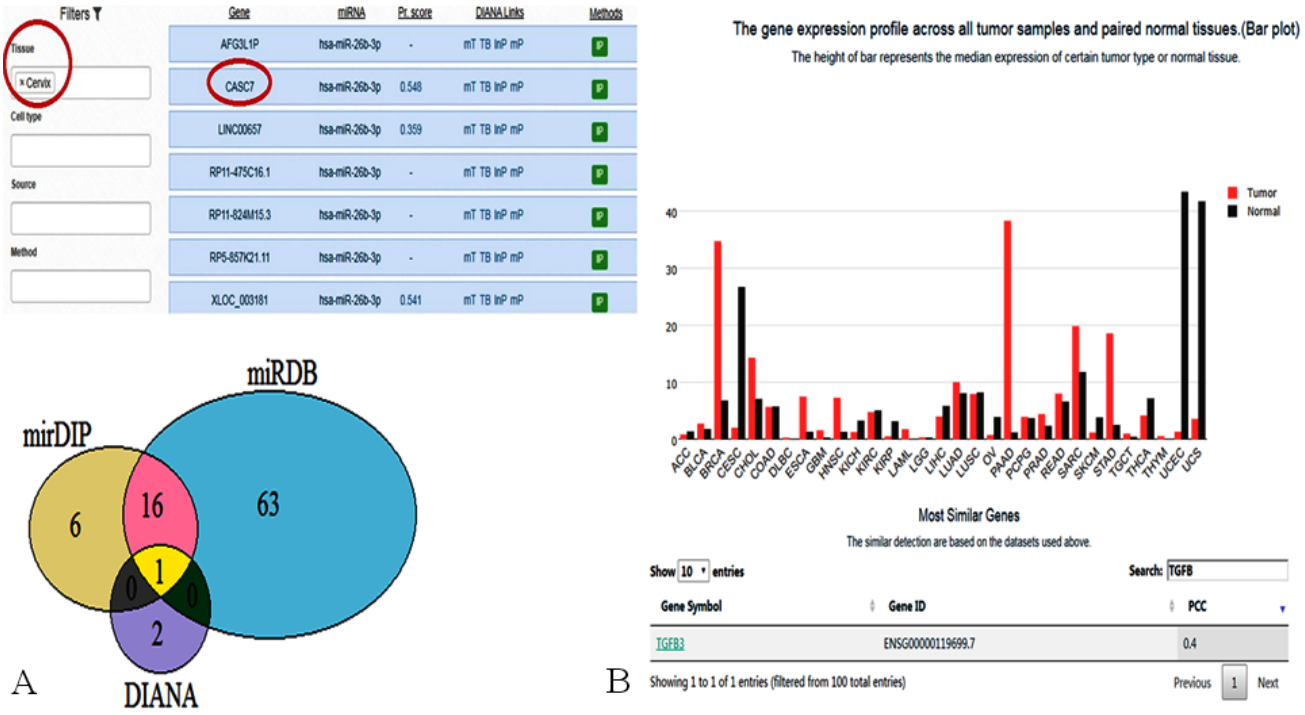

Fig. 4. Analysis of the relationship between lncRNA CASCA7, miR-26 and ASPN. lncRNA CASC7 acts on mir-26, and miR-26 regulates ASPN (A). ASPN gene expression profile across all tumor samples and paired normal tissues, and the Most Similar Genes (B).

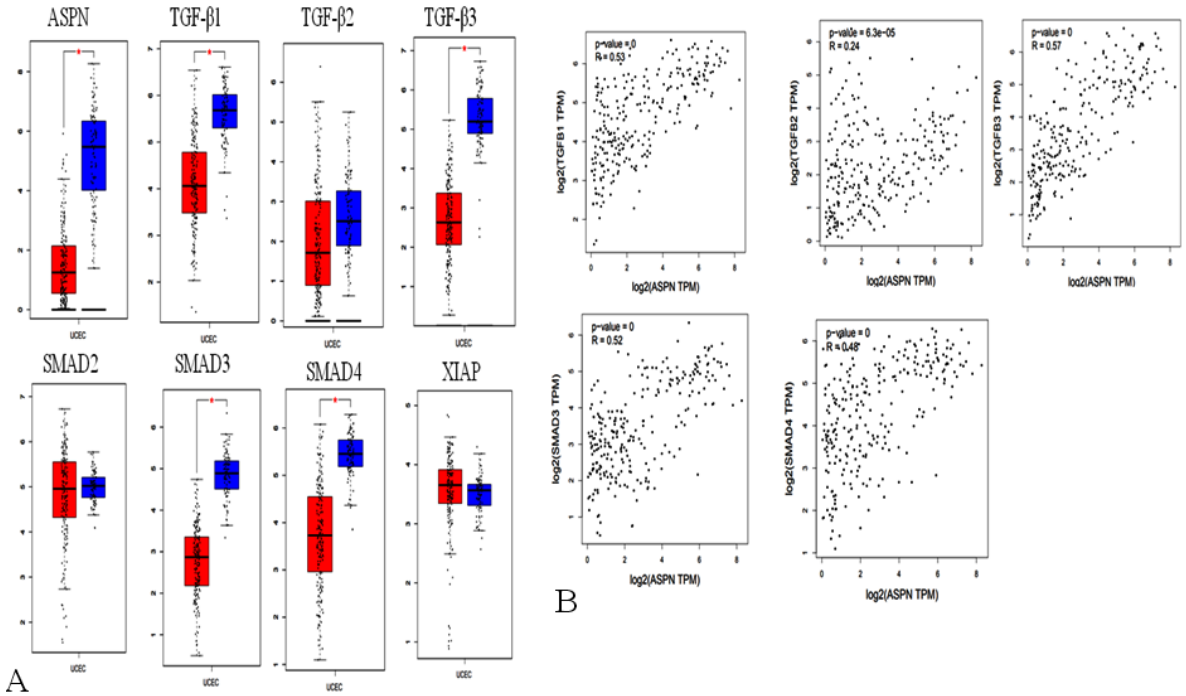

Fig. 5. Analysis of gene expression level and correlation. Expression levels of ASPN, TGF-β1, TGF-β2, TGF-β3, SMAD2, SMAD3, SMAD4 and XIAP (A). ASPN was positively correlated with TGF-β1, TGF-β2, TGF-β3, SMAD3 and SMAD4 (B).

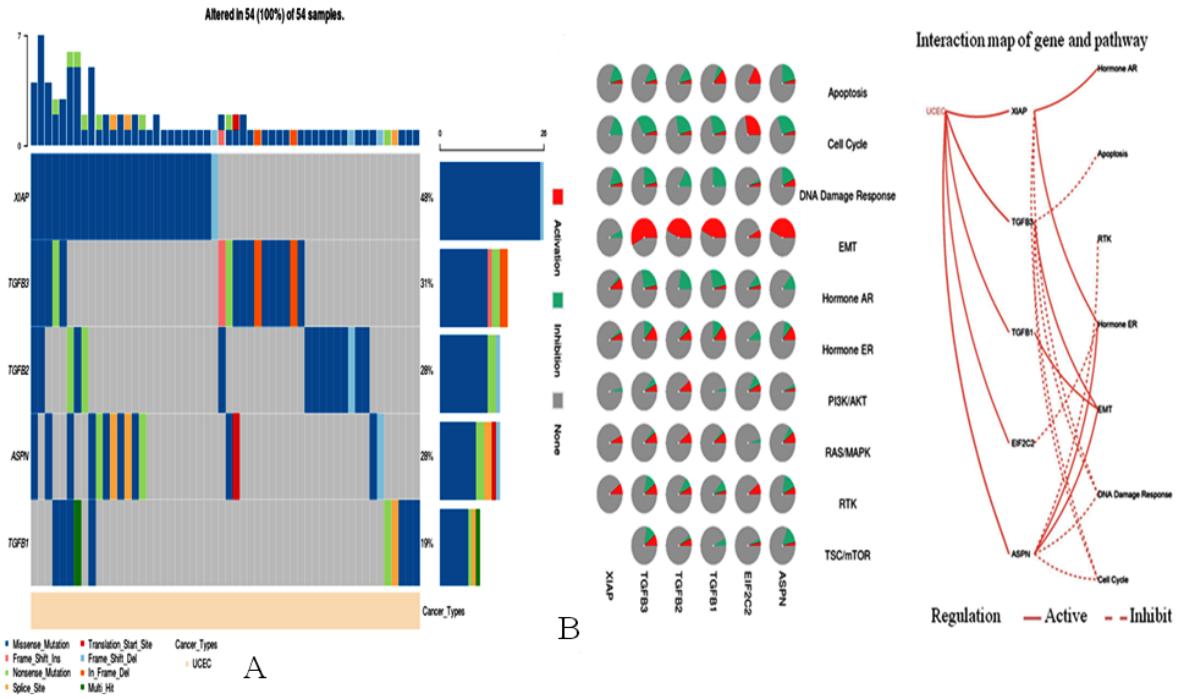

Fig. 6. Analysis of SNV and Pathway Activity. (A) SNV analysis of *ASPN*, *TGFB1*, *TGFB2*, *TGFB3*, *XIAP*. (B) Pathway Activity analysis of lncRNA CASC7, ASPN, TGFB1, TGFB2, TGFB3, XIAP.

Expression levels and correlation analysis

GEPIA analysis shows *ASPN* gene expression profile across all tumor samples and paired normal tissues, and in the most similar genes, we found TGF-β3 (Fig. 4B). In normal endometrium, ASPN expression in normal tissues was significantly higher than that in cancer tissues. Moreover, TGF-β3 expression is similar to ASPN.

Expression levels of *ASPN*, *TGF-β1*, *TGF-β2*, *TGF-β3*, *SMAD2*, *SMAD3*, *SMAD4* and *XIAP* genes are displayed in Figure 5A. Except for *SMAD2* and *XIAP*, the expression of *ASPN*, *TGF-β1*, *TGF-β2*, *TGF-β3*, *SMAD3* and *SMAD4* genes in normal tissues was higher than that in tumor tissues. Furthermore, Pearson correlation analyses between the genes are presented in Figure 5B. Results revealed that *ASPN* was positively correlated with *TGF-β1*, *TGF-β2*, *TGF-β3*, *SMAD3* and *SMAD4* (all $R > 0$, $P < 0.05$).

SNV and pathway activity

SNV shows SNV frequency of *XIAP*, *TGF-β1*, *TGF-β2*, *TGF-β3*, *ASPN*, and SNV frequency of *XIAP* is the most (Fig. 6A). Pathway activity shows ASPN and TGF-β1 and TGF-β3 activate EMT (Fig. 6B). Based on literature materials, we speculate that lncRNA CASC7 inhibited miR-26, inhibited ASPN, inhibited TGF-β, and promoted XIAP, to activate SMAD/XIAP pathway, improving the survival rate and invasiveness of endometrial cancer cells (Fig. 7). Collectively, this is the first time to describe the mechanism of lncRNA CASC7/miR-26/ASPN/TGF-β/Smad axis in the proliferation and invasion of endometrial cancer cells.

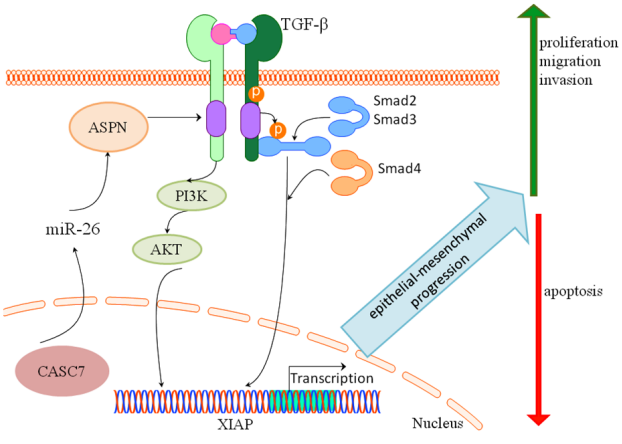

Fig. 7. Schematic representation of the underlying mechanism of lncRNA CASC7/miR-26/ASPN/TGF-β/Smad axis in endometrial Cancer. Based on literature materials, we speculate that lncRNA CASC7 inhibited miR-26, inhibited ASPN, inhibited TGF-β, and promoted XIAP, to activate SMAD/XIAP pathway, improving the survival rate and invasiveness of endometrial cancer cells.

DISCUSSION

In this study, we have found lncRNA CASC7 is the prognostic marker in endometrial cancer, and *ASPN* is tissue-specific in endometrium. Moreover, lncRNA CASC7 acts on miR-26, and miR-26 was predicted to regulate ASPN. Besides, miR-26 is also tumor suppressor miRNA, and its expression is decreased in endometrial carcinoma. Interesting, TGF-β1 is an anti-proliferative cytokine, especially in the early stage of tumorigenesis, and TGF-β3 is expressed primarily in mesenchymal cells. Besides, TGF-β3 increases the invasiveness of endometrial cancer cells through PI3K/XIAP or SMAD/XIAP pathway. A*SPN* was positively correlated with *TGF-β1*, *TGF-β2*, *TGF-β3*, *SMAD3* and *SMAD4*. SNV shows SNV frequency of *XIAP* is the most. In addition, Pathway activity shows ASPN and TGF-β1 and TGF-β3 activate EMT. Based on literature materials, we have speculated that the lncRNA CASC7/miR-26/ASPN/TGF-β/Smad axis has effect on the proliferation and migration and invasion in endometrial cancer. In endometrial cancer cells, lncRNA CASC7 inhibited miR-26, inhibited ASPN, inhibited TGF-β, and promoted XIAP, to activate SMAD/XIAP pathway, improving the survival rate and invasiveness of endometrial cancer cells. This is the first time to describe the mechanism of lncRNA CASC7/miR-26/ASPN/TGF-β/Smad axis in the proliferation and invasion of endometrial cancer cells.

X-linked inhibitor of apoptosis protein (XIAP) is often over-expressed in tumor cells, and it plays a key role in the survival and invasiveness of tumor cells. In our studies, compared with normal tissue, XIAP expression level of tumor tissue is high. Van Themsche *et al*. (2010) have observed that XIAP can protect endometrial cancer cells from a variety of pro-apoptotic drugs, including TGF-β, tumor necrosis factor-α (TNF-α) and chemotherapeutic drugs. This is also consistent with the results of our analysis, high expression of XIAP can inhibit apoptosis of tumor cells.

TGF-β regulates cell proliferation, angiogenesis and metastasis, and is an inducer of epithelial-mesenchymal transformation (EMT). Tumor cells activate the transforming growth factor-β/SMAD signal transduction pathway, and inhibiting its signal transduction pathway is an important strategy for tumor therapy. Moreover, Tumor invasion and metastasis is the key link that affects the curative effect and prognosis of endometrial cancer. This is also consistent with the results of our analysis, Pathway activity shows ASPN and TGF-β1 and TGF-β3 activate EMT.

In conclusion, we showed for the first time that lncRNA CASC7/ miR-26/ASPN/ TGF-β/Smad axis has effect on the proliferation and migration and invasion in endometrial cancer. However, this needs to be verified by subsequent experiments, and it is also worthy of further study. Because, there is no accurate molecular tag that can be used as a good diagnostic or prognostic biomarker for treatment resistance and disease recurrence of endometrial carcinoma at present. Thus, the search for a prognostic marker will benefit patients because it can be used as a predictor of treatment response and target therapy for patients who benefit more from specific adjuvant therapy. It is of great significance to explore ways to inhibit these processes to improve the prognosis and quality of life of patients with endometrial cancer.

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Statement of conflict of interest

The authors have declared no conflict interest.

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