LncRNAE2F4

Subjects: Oncology
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LncRNA is a promising biomarker that predicts the prognosis of a variety of cancers, but the important role of E2F4antisense lncRNA in cancer remains unclear. E2F4as was highly expressed in ovarian cancer patients, and that the higher the expression of E2F4as, the worse the patient's prognosis.

Keywords: ovarian cancer (OC) ; long noncoding RNAs (lncRNAs) ; E2F4 antisense (E2F4as) ; epithelial–mesenchymal transition (EMT) ; biomarker

1. Introduction

Ovarian cancer is globally the sixth most common cancer in women, the second most common gynaecologic malignancy in women, and the most fatal tumour of the female reproductive system[1]. Ovarian cancer is the most fatal gynaecologic malignancy due to its aggressive metastasis, recurrence, and drug resistance[2]. The five-year survival rate of below 40% applies to late stage ovarian cancer, so an effective alternative strategy is needed to overcome tumour penetration and aggressive metastasis[3]. Therefore, an early diagnosis of ovarian cancer may play an important role in improving the prognosis and survival rate of ovarian cancer patients. In this regard, predicting the risk of ovarian cancer using patient serum could be one of the easiest methods for the early diagnosis of ovarian cancer.

Long noncoding RNAs (lncRNAs) constitute a heterogeneous group of genomic transcripts longer than 200 nucleotides without a protein-coding function[4][5]. Unlike short noncoding RNAs, such as microRNAs, the functional role of lncRNAs was underestimated because they were initially considered transcriptional noise in the genome[6]. However, recent studies showed their importance not only in normal function but also in the regulation of various biological processes such as stem cell proliferation, apoptosis, cell migration, and metastasis in cancer cells. They also supported new evidence that changes in lncRNA expression occur in a variety of human cancers, and that expression patterns are associated with cancer progression and metastasis[7].

The E2F family of transcription factors is known to be involved in the regulation of the cell cycle, proliferation, differentiation, DNA repair, and apoptosis[8][9]. E2F transcription factors are key regulators of cell cycle progression that regulate gene expression required for G1/S metastasis[10]. Among the eight members of the E2F family, E2F1-3a is a transcriptional activator, while E2F3b-7 was found to inhibit downstream gene transcription[11][12][13]. E2F4 constitutes a defined subset of the family. It was demonstrated that E2F4 accumulate sequentially in the nucleus of cycling cells and controls gene expression during cell-cycle exit. Now, little is understood about individual biochemical and biological functions[14]. This study focused on studying the "antisense" strand of the E2F4 gene cluster known as the noncoding RNA gene. This study was conducted to investigate the role of E2F4 in carcinogenesis since little is known about the function of locally present lncRNAs, and no studies have been conducted on *E2F4as* (antisense). Induction of *E2F4as* by Wnt signalling may contribute to carcinogenesis by reducing levels of the E2F4 cell cycle repressor in colorectal cancer[15]. Wnt/β-catenin signalling also promotes epithelial–mesenchymal metastasis (EMT) by inducing the expression of EMT transcription factors. EMT contributes to the invasive and metastatic spread of colorectal cancer, and is associated with chemotherapy resistance[16].

2. Role of E2F4

Recently accumulated evidence has suggested that lncRNA may play an important role in cell biology and human disease. In gynaecological cancer, several lncRNAs were identified, including *HOTAIR, SRA, MALAT-1, H19* and *LSINCT5*[17][18][19][20]. On the basis of these data, lncRNA is emerging as an early diagnosis and treatment target. Finding effective biomarkers for early diagnosis and prognosis is important, and the early diagnosis of ovarian cancer reduces mortality. Among them, liquid biopsy is currently an effective and non-invasive method. It is urgent to identify serum biomarkers with high sensitivity and specificity[21]. In this study, high-expression lncRNAs were screened using the serum

of ovarian cancer patients, among which *E2F4as* was found. However, no studies exist on the clinical prognosis importance of new lncRNA *E2F4as* in ovarian cancer. *E2F4as* expression levels in ovarian cancer were higher in blood serum, and the knockdown of *E2F4as* inhibited cell proliferation and metastasis in various ovarian cancer cell lines.

E2F4 constitutes a subset of the E2F family and the E2F family is only known to be involved in the regulation of cell cycle and apoptosis[8][10][14][22]. E2F4 transcription factors is critical to maintain cell cycle arrest in G0/G1 in conjunction with members of the retinoblastoma (RB) family. E2F4 are “repressors” that prevent uncontrolled proliferation. To date, the role of *E2F4as* is unclear with E2F4, and cell cycle and apoptosis studies have been conducted to clarify the role of *E2F4as* in ovarian cancer cell lines. This study showed that *E2F4as* expression may contribute to the development of ovarian cancer by reducing E2F4 expression, reducing the level of cell cycle inhibitors, and mediating the proliferation of ovarian cancer cells.

Questions were raised as to whether *E2F4as* promotes ovarian cancer metastasis by regulating the expression of genes encoding metastasis-related proteins. EMT was thought to be one of the manual mechanisms. EMT properties were reported to contribute to cell proliferation, invasion, migration, and metastasis in various malignant tumours [23][24]. These findings highlighted the clinical relevance of *E2F4as* in predicting the detrimental prognosis of ovarian cancer, and suggest the possibility of promoting tumour aggression through the regulation of EMT-related mechanisms[25]. To date, many noncoding RNAs (ncRNAs) were recognized to control almost all levels of gene expression and pathway activation, including the activation and inhibition of EMT processes. lncRNA *XIST* was found to promote EMT through the regulation of ZEB2 by acting as a miRNA-367/141 ceRNA in non-small cell lung cancer [26]. However, the role and mechanisms of other lncRNAs in EMT, and their effect on cell invasion and metastasis in ovarian cancer are still not well understood. Our results highlighted the predictive prognosis of ovarian cancer and the clinical relevance of *E2F4as*, and suggested the possibility of promoting tumour aggression through the regulation of EMT-related mechanisms. In vitro and in vivo observations of lncRNAs showed reduced cell growth, invasion, and migration when downregulated as in this study. Taken together, the regulatory abnormal expression of EMT-related genes appears to participate in ovarian cancer cell invasion and migration in relation to *E2F4as*.

Taken together, these results suggested that *E2F4as* may play an important role in the development of ovarian cancer. However, the relatively small clinical sample size was a limitation of this study and may have reduced the power of clinical analysis. Another limitation is that only subcutaneous xenograft models had been used to investigate cancer cell behaviour in vivo. Cancer cells implanted subcutaneously allow rapid and quantitative tumour formation, making them more suitable for use in studies involving continuous measurement of tumours. In contrast, with intraperitoneal and orthotopic xenograft models it is inherently difficult to quantitatively monitor tumour growth, but these models can reveal a more relevant tumour microenvironment.

Many researchers have persevered to detect ovarian cancer early, but details of markers are not available in literature[27]. The low sensitivity of CA125 as a serum marker to detect early ovarian cancer and monitor the patient’s clinical progression remains the biggest obstacle to improving patient outcomes[27][28]. For the first time, we demonstrated the usefulness of *E2F4as* as a less invasive prognostic marker using serum samples collected from ovarian cancer patients. The findings emphasize the clinical importance of *E2F4as* in early diagnosis and prognosis prediction using the serum of ovarian cancer patients, and suggest the potential of promoting tumour aggression by the regulation of EMT-related mechanisms. This potentially yields a less invasive and inexpensive diagnostic test that can be used in combination with other outcome factors to improve patient outcomes and provide optimal treatment. Therefore, lncRNA *E2F4as* was related to the abnormal proliferation and migration of ovarian cancer, indicating that lncRNA *E2F4as* might be a promising target in treating ovarian cancer.

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