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Expression and Clinical Significance of Mismatch Repair Deficiency/Microsatellite Instability and SOX2 in Endometrioid Adenocarcinoma

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Abstract: A retrospective analysis of 83 endometrioid adenocarcinoma (EA) tissue samples and 83 benign disease controls, using the EnVision method to evaluate microsatellite instability (MSI) status and SOX2 expression, revealed that SOX2 expression was significantly higher in EA tissues than in controls ($P<0.001$). Its expression correlated with higher histological grade, deeper myometrial invasion, lymph node metastasis, and advanced FIGO stage ($P<0.05$), but not with age or menopausal status. A negative correlation was observed between SOX2 expression and MSI ($P=0.025$). These findings indicate that SOX2 overexpression is associated with EA pathogenesis and negatively correlates with MSI, suggesting its potential as a biomarker for prognosis and targeted therapy.

1. Introduction

Endometrioid Adenocarcinoma (EA) is a malignant tumor originating from the endometrial epithelium, accounting for 20%-30% of female reproductive tract malignancies, with 417,000 new cases and 97,000 deaths worldwide annually[1]. In China, with the intensification of population aging and changes in lifestyle, the number of endometrioid carcinoma cases is increasing, seriously threatening women's health and quality of life. The pathogenesis of EA is complex and not yet fully elucidated. Current diagnosis and prognosis assessment of EA mainly rely on imaging examinations combined with pathological staging. Therefore, identifying key molecular markers involved in EA pathogenesis is crucial for improving diagnosis, prognostic assessment, and ultimately guiding targeted therapies to enhance patient survival.

Microsatellites are short tandem repeat DNA sequences (1-4 bp) distributed throughout the human genome. Their repetitive nature makes them prone to replication errors, which are typically corrected by the Mismatch Repair (MMR) system[2]. This highly conserved mechanism recognizes and repairs base mismatches during DNA replication and recombination. The MMR system primarily functions through four core proteins (MLH1, MSH2, MSH6, and PMS2). MMR deficiency (dMMR) causes Microsatellite Instability (MSI), characterized by altered length of

microsatellite sequences due to insertion/deletion mutations[3]. Microsatellite status is classified as MSS, MSI-L, or MSI-H. According to WHO classification, approximately 30% of endometrial carcinomas exhibit dMMR/MSI. dMMR/MSI status guides immune checkpoint inhibitor therapy, particularly for tumors with mutational burden >10 mut/Mb.

The transcription factor SOX2 (SRY-related HMG box 2) not only plays an important role in embryonic development and maintaining the undifferentiated state of embryonic stem cells, but a growing number of studies have confirmed its overexpression in various human tumor tissues. SOX2 overexpression can promote tumor progression by accelerating cell proliferation, clonal formation, invasion and migration. Currently, foreign scholars have conducted some research on the expression and role of SOX2 in EA, but relevant reports in China remain scarce.

2. Materials and Methods

2.1 Materials

This study retrospectively enrolled 83 patients with EA (experimental group) and 83 patients with uterine fibroids(control group) from The Third Affiliated Hospital of Soochow University between September 2019 and October 2024. The patients' age ranged from 32 to 70 years, with a mean of 47.95±8.62. Clinicopathological characteristics of the EA group included FIGO stage I (n=53) and II-III (n=30); myometrial invasion ≤1/2 (n=65) and >1/2 (n=18); and the presence of lymph node metastasis in 48 cases. Inclusion criteria: (1) surgically treated and pathologically confirmed EA; (2) treatment-naïve status; (3) complete medical records. Exclusion criteria: (1) recurrent EA; (2) concurrent malignancies; (3) major comorbidities, distant metastasis, or anesthesia contraindications. This study was approved by the hospital's Ethics Committee.

2.2 Methods

2.2.1 Experimental method

Clinical and pathological data of EA patients were collected. Tissue specimens from both groups were processed routinely for immunohistochemistry. The expression of MLH1, MSH2, MSH6, PMS2, and SOX2 was detected using the EnVision method on a Roche BENCHMARK XT system, with PBS serving as the negative control.

2.2.2 Result Judgment

SOX2 expression was semi-quantitatively assessed by multiplying the staining intensity score (0-3) by the proportion of positive cells score (0-4). Staining intensity was graded as: 0 (negative), 1 (light yellow), 2 (brownish-yellow), or 3 (tan-brown). The percentage of positive cells was scored as: 0 (≤5%), 1 (6-25%), 2 (26-50%), 3 (51-75%), or 4 (>75%). A final score ≥4 was considered positive. For MLH1, MSH2, MSH6, and PMS2, nuclear staining was assessed, with loss of any protein considered indicative of microsatellite instability. All assessments were made independently by two blinded pathologists.

2.2.3 Statistical Analysis

Data were analyzed using SPSS 25.0. Count data were expressed as n (%), and the χ^2 test was used. The correlation between SOX2 and MSI was assessed by Spearman's analysis. The test level $\alpha=0.05$, and $P<0.05$ was considered statistically significant.

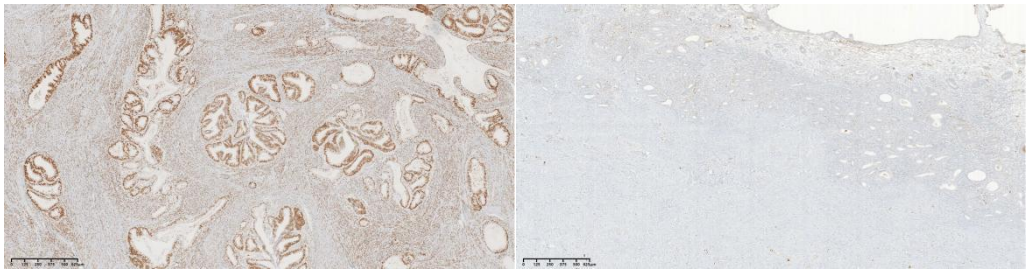
3. Results

3.1 Expression of SOX2 in Experimental and Control Groups

Immunohistochemical detection results showed that the positive expression of SOX2 in the experimental group was higher than that in the control group (P < 0.001) (Table 1 and Figure 1).

Table 1: Expression of SOX2 in EA Tissues and Normal Tissues[n (%)].

Group	n	SOX2	
		Positive	Negative
EA Tissue	83	56	27
Normal Tissue	83	31	52
χ^2	15.095		
p	<0.001		



a b

Figure 1 Representative images comparing SOX2 expression in (a) EA versus (b) normal endometrium (EnVision method, ×100).

3.2 Relationship between SOX2 Protein Expression and Clinicopathological Characteristics of EA

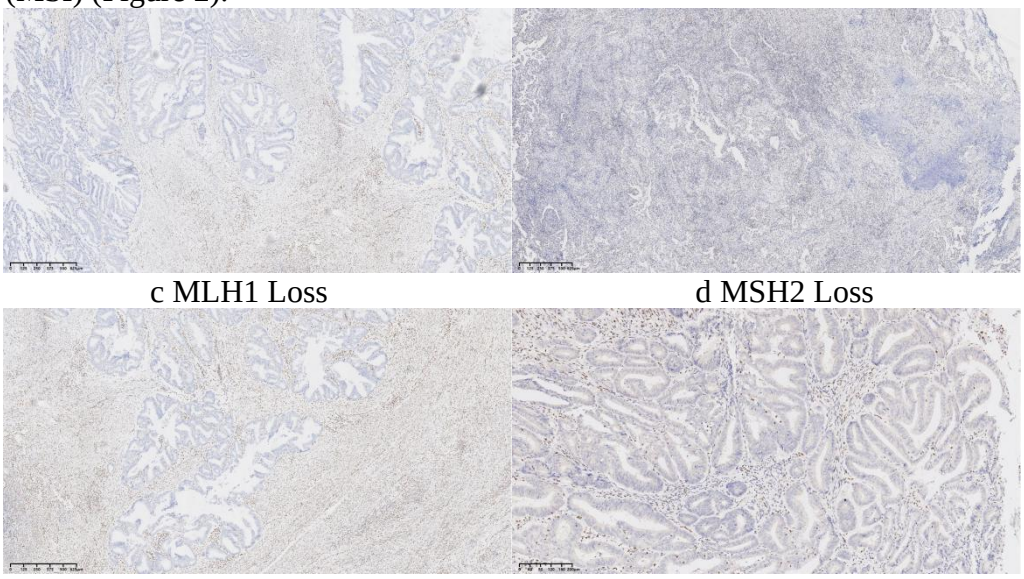
Positive SOX2 expression in cancer tissue was correlated with histological grade, depth of myometrial invasion, lymph node metastasis, and FIGO clinical stage (P<0.05), but not with age or menopausal status (P>0.05) (Table 2).

Table 2: Relationship between SOX2 Expression and Clinicopathological Characteristics in EA Patients [n (%)].

Clinicopathological Feature		n	Positive Group(n=56)	Negative Group(n=27)	χ2	p
Age	≤55	47	35(62.50)	12(44.44)	2.418	0.120
	>55	36	21(37.50)	15(55.56)		
Menopausal Status	Premenopausal	48	32(57.14)	16(59.26)	0.034	0.855
	Postmenopausal	35	24(42.86)	11(40.74)		
Histological Grade	G1	53	29(51.79)	24(88.89)	10.866	0.001
	G2+G3	30	27(48.21)	3(11.11)		
Depth of Invasion	≤1/2	65	40(71.43)	25(92.59)	4.804	0.028
	>1/2	18	16(28.57)	2(7.41)		
Lymph Node Metastasis	Yes	48	39(69.64)	9(33.33)	9.848	0.002
	No	35	17(30.36)	18(66.67)		
FIGO Stage	I	53	31(55.36)	22(81.48)	5.387	0.020
	II+III	30	25(44.64)	5(18.52)		

3.3 Expression of MSI Status in EA

Immunohistochemical detection of MMR proteins (MLH1, MSH2, MSH6, PMS2) revealed 46 cases (55.42%) with microsatellite stability (MSS) and 37 cases (44.58%) with microsatellite instability (MSI) (Figure 2).



c MLH1 Loss d MSH2 Loss

e PMS2 Loss f MSH6 Loss

Figure 2 Representative images of MMR protein expression loss indicating MSI status (EnVision method, ×100).

3.4 Correlation between Positive SOX2 Expression and MSI

Spearman correlation analysis results showed a negative correlation between positive SOX2 expression and MSI (r = -0.246, P=0.025) (Table 3).

Table 3 Correlation Analysis between SOX2 and MSI Expression in EA Tissues [n(%)].

Group	SOX2 Expression		r value	p value
	Positive	Negative		
MSI	29	8	-0.246	0.025
MSS	27	19		
Total	56	27		

4. Discussion

EA is a common malignant tumor of the female reproductive system. Currently available tumor markers for EA, such as HE4 and CA125, lack specificity. Discovering novel biomarkers that accurately predict disease progression is thus of significant clinical importance.

The transcription factor SOX2, essential for embryonic development and stem cell pluripotency, is also implicated in tumorigenesis when dysregulated [4]. Research on SOX2 in EA is limited, and its mechanism is less understood. Some studies have detected through immunohistochemistry that SOX2 expression increases sequentially in normal endometrium, EA, and metastatic EA, which may help differentiate between EA and metastatic EA. Our study show that the positive expression rate of SOX2 protein in EA tissue is significantly higher than in normal endometrial tissue, suggesting that SOX2 may be related to the carcinogenesis of endometrial glandular epithelial cells,

and SOX2 overexpression promoting cell proliferation and malignant transformation is a possible mechanism. Furthermore, positive SOX2 expression is related to histological grade. Whether SOX2 can predict the prognosis of EA patients requires further study with expanded sample size and increased follow-up to draw definitive conclusions.

MMR gene mutations cause deficient MMR protein expression, leading to accumulated DNA replication errors. This genomic instability manifests as microsatellite instability (MSI), driving uncontrolled cell proliferation and tumorigenesis. Our Spearman analysis revealed a significant negative correlation between SOX2 overexpression and MSI, suggesting interplay between these pathways in EA pathogenesis. Both SOX2 and MSI status may serve as valuable indicators for assessing tumor aggressiveness and prognosis. Furthermore, these markers show potential for guiding individualized treatment strategies, particularly in immunotherapy selection, and represent promising therapeutic targets.

In conclusion, our study demonstrates that SOX2 is significantly overexpressed in EA and associates with adverse clinicopathological features. The identified negative correlation with MSI highlights a potentially significant interplay between these two molecular pathways. Future investigations should focus on elucidating the signaling pathways connecting SOX2 and DNA repair mechanisms in EA, ultimately providing a stronger theoretical foundation for targeted therapies and prognostic assessment.

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