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Research Progress and Prospects on Biomarkers for Endometrial Cancer and New Targets for Precision Diagnosis and Treatment

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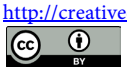

Abstract

Endometrial cancer is a common malignant tumor among women in China, with 77,000 new cases and 13,500 deaths reported in 2022. Its incidence continues to rise alongside increased lifespan and lifestyle changes such as obesity and hormone exposure, exhibiting a trend toward younger age groups. Approximately 70% of patients are diagnosed at an early stage, achieving a 5-year survival rate of 95% following surgery combined with adjuvant therapy. However, 10% - 20% of cases present with distant metastasis at initial diagnosis, with a five-year survival rate below 20%. Chemotherapy resistance is prevalent, necessitating precision treatment strategies based on molecular characteristics. This review systematically summarizes the latest evidence regarding four key molecules—P53, CD146, MMR, and Claudin18.2—in the occurrence, progression, and targeted intervention of endometrial carcinoma. The TCGA classifies endometrial carcinoma into four molecular subtypes: POLE-mutant, MSI-H, low-copy-number mutation, and high-copy-number mutation. The high-copy-number mutation subtype exhibits the poorest prognosis, with p53 mutations being particularly prominent in this subtype. Wild-type p53 inhibits invasion by maintaining the epithelial phenotype and upregulating anti-EMT miRNAs, whereas mutant p53 relieves ZEB1 inhibition, promoting EMT and distant metastasis. MMR deficiency (dMMR), accounting for 20% - 30% of endometrial carcinomas, primarily arises from MLH1 promoter methylation or germline mutations, with immunohistochemical testing now standard in clinical practice. Given the high tumor mutational burden and upregulation of PD-L1 expression in dMMR tumors, immune checkpoint inhibitors (ICIs) combined with chemotherapy demonstrate significantly superior progression-

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free survival and overall survival compared to conventional chemotherapy. MMR status has thus emerged as a companion diagnostic marker guiding the selection of immunotherapy and targeted treatments. The adhesion molecule CD146 exhibits a high positivity rate of 63.49% in endometrial carcinoma tissues, significantly higher than in normal endometrium (5.13%). Its expression correlates positively with tumor differentiation grade, FIGO stage, and myometrial invasion depth. CD146 is widely distributed in tumor vascular endothelial cells, suggesting its involvement in cancer cell proliferation, angiogenesis, and metastasis. Claudin18.2, a tight junction protein, has emerged as a novel target for solid tumors like gastric cancer due to its high selectivity and stability. Phase II trials confirmed the safety and efficacy of its targeted drugs in advanced gastric-esophageal cancer patients. Its expression and therapeutic potential in endometrial cancer warrant further investigation. In summary, p53, CD146, MMR, and Claudin18.2 not only serve as novel biomarkers for molecular subtyping and prognostic assessment in endometrial carcinoma but also provide reliable targets for overcoming drug resistance and improving survival rates in advanced patients through targeted therapy combined with chemoradiotherapy. This suggests that personalized comprehensive treatment based on molecular characteristics will become the mainstream approach in future endometrial carcinoma management.

Keywords

Endometrial Carcinoma, Molecular Markers, Research Progress

1. Introduction

Endometrial carcinoma, also known as uterine body cancer, ranks among the three most common malignant tumors of the female reproductive system. According to the "Analysis of Malignant Tumor Prevalence in China 2022" recently released by the National Cancer Center, China recorded approximately 77,000 new cases and 13,500 deaths from endometrial carcinoma in 2022, with incidence and mortality rates of 7.03/100,000 and 1.06/100,000, respectively [1]. With increasing average life expectancy and changing lifestyles, the incidence of endometrial cancer continues to rise, showing a trend toward younger age groups. Approximately 70% of patients are diagnosed at an early clinical stage, offering a favorable prognosis with a 5-year survival rate reaching 95% [2]. Surgery and adjuvant therapy form the cornerstone of treatment for endometrial cancer patients. While surgery offers significant survival benefits for early-stage patients, 10% - 20% of endometrial cancer patients present with distant metastasis at diagnosis. These patients have a poor prognosis, with a five-year survival rate < 20% [3]. Historically, treatment advances for advanced or recurrent endometrial cancer have been limited, with significant chemotherapy resistance posing urgent demands for novel therapeutic strategies. In the era of precision medicine, advances in tumor genetics and molecular biology have accelerated the development of molecularly targeted therapies. Individ-

ualized precision treatment based on molecular genetic characteristics has revolutionized the therapeutic paradigm for endometrial cancer [4]. Consequently, identifying more scientific and effective prevention and treatment methods for endometrial cancer has become a key research focus in recent years. Targeted therapy has gradually gained prominence, differing from conventional diagnostic and therapeutic approaches. Its unique cytotoxic characteristics and efficacy offer tremendous potential in reducing malignant tumor incidence, treating malignant tumors, lowering patient mortality, and improving survival prognosis. This review summarizes clinical research advances on p53 and CD146 in endometrial cancer and discusses the application prospects of the emerging target Claudin18.2 in this disease.

2. Research Advances on p53 in Endometrial Cancer

In 2013, the Cancer Genome Atlas (TCGA) project conducted a large-scale, comprehensive, and integrated genomic analysis of 373 endometrial carcinoma cases. Based on distinct clinical-pathological and molecular characteristics, endometrial carcinoma was classified into four molecular subtypes: POLE mutation-positive (7%), high microsatellite instability (MSI-H) subtype (28%), low copy number variation subtype (39%), and high copy number variation subtype (26%). These four molecular subtypes also convey prognostic information, with the POLE mutation subtype having the best prognosis, followed by the low copy number variation subtype and the MSI-H subtype, while the high copy number variation subtype has the poorest prognosis [5]. However, the TCGA project analyzed only endometrioid and serous carcinomas, excluding clear cell endometrial carcinomas, carcinosarcomas, or poorly differentiated carcinomas [5].

The p53 gene is the most frequently mutated gene in human cancers. The p53 protein encoded by p53 is one of the most extensively studied tumor suppressor genes over the past decades [6]. Mutations in the p53 DNA-binding domain typically activate the gene primarily during precancerous stages [7]. Reports indicate that epithelial-mesenchymal transition (EMT) is a key mechanism driving metastasis in endometrial cancer. Core epithelial markers such as E-cadherin and mesenchymal markers like vimentin during EMT show strong correlations with clinical features of endometrial carcinoma, including clinical staging, pathological grading, and lymph node metastasis. Research over the past decade has highlighted novel roles for p53 in metastasis regulation, demonstrating that wild-type p53 (WTP53) prevents EMT and the generation of various cancer-associated stem cell phenotypes. As a transcription factor, p53 helps cells maintain epithelial gene characteristics, thereby inhibiting EMT. Additionally, p53 can prevent the emergence of various cancer-associated stem cell phenotypes. WTP53 can prevent EMT occurrence and the generation of various cancer-associated stem cell phenotypes. As a transcription factor, p53 helps cells maintain epithelial gene characteristics, thereby inhibiting EMT. Additionally, p53 induces reduced levels of EMT-related factors (EMT-RFs) by enhancing the expression of EMT-inhibitory microRNAs. Conversely, EMT

modulators exhibit diminished p53 function. For instance, Snail—a key EMT inducer—directly binds and inhibits wild-type p53. This Snail-mediated p53 suppression is critical for tumor initiation and growth in breast cancer [8]-[10]. Studies have demonstrated that wild-type p53 negatively regulates EMT initiation and maintenance while inhibiting tumor cell metastasis, whereas mutant p53 promotes EMT and tumor cell metastasis by regulating several EMT-related transcription factors (EMTTFs) at transcriptional, post-transcriptional, and translational levels. In EC cells, TP53, R157H, R248Q, and R273H mutants induce ZEB1 expression by transcriptionally suppressing miR-130b, a negative regulator of ZEB, leading to EMT induction and increased EC cell invasion [11].

3. Research Progress on CD146 in Endometrial Cancer

Zhang *et al*. [12] performed immunohistochemical detection of endometrial carcinoma tissues using the anti-CD146 monoclonal antibody AA4. CD146 was detected in most tumor cells, and its expression level showed a high correlation with tumor histological differentiation and depth of invasion into the myometrium, suggesting that CD146 may be associated with the occurrence and development of endometrial carcinoma. The study also detected CD146 presence in most tumor blood vessels via immunofluorescence, suggesting potential involvement in the spread and metastasis of endometrial carcinoma. Chen Ruili employed immunohistochemistry to examine CD146 expression in endometrial tissue. Results showed a significant difference in positive rates between normal endometrium (5.13%) and endometrial carcinoma (63.49%) [13]. Furthermore, in endometrial carcinoma, CD146 expression was highly correlated with tumor differentiation grade, clinical stage, and depth of myometrial invasion, suggesting an association between CD146 and the growth and progression of endometrial cancer. Sun Min [14] measured CD146-positive microvascular density in endometrioid adenocarcinoma tissues, further confirming the upregulation of CD146 expression in this tumor type.

4. Research Progress on MMR Proteins in Endometrial Cancer

The mismatch repair (MMR) system comprises proteins encoded by genes such as MLH1, MSH2, MSH6, PMS2, and EPCAM, which are responsible for correcting base mismatches during DNA replication. Approximately 20% - 30% of endometrial carcinomas exhibit mismatch repair deficiency (dMMR), primarily due to MLH1 promoter hypermethylation (sporadic) or germline mutations in MMR genes (Lynch syndrome-associated). Immunohistochemical detection of MMR protein deficiency (dMMR) has become a clinical standard: complete absence of nuclear expression of any protein is diagnosed as dMMR; presence of all four proteins indicates pMMR. Studies show that dMMR tumors are associated with older age, higher histological grade, deeper myometrial invasion, and significantly increased peritoneal lavage cytology positivity, suggesting more aggressive biological behavior. The functional inactivation of MLH1 protein, a core component of the DNA mismatch repair (MMR) system, is closely associated with the develop-

ment and progression of various malignancies [15]. As an indispensable molecular chaperone in the MMR pathway, MLH1 primarily forms the heterodimer MutLα with PMS2. This complex identifies and binds to DNA mismatch signals initiated by either the MutSα (MSH2 - MSH6) or MutSβ (MSH2 - MSH3) complexes, thereby initiating the repair process. This system specifically corrects base mismatches and small insertions/deletions (IPDs) arising during DNA replication. When base mismatches or IPDs occur during replication, the MLH1 protein forms a heterodimer with PMS2 (MutLα), activating the subsequent repair cascade to ensure accurate transmission of genetic information. In endometrial cancer, MLH1 inactivation is the most common cause of mismatch repair deficiency (dMMR). Approximately 70% - 75% of dMMR endometrial cancer cases exhibit loss of MLH1 protein expression, with the vast majority (>95%) resulting from epigenetic silencing of the MLH1 gene promoter region [16]. When MLH1 function is lost, cells lose their ability to accurately repair DNA, leading to genomic microsatellite instability (MSI).

At the molecular subtyping level, MMR status is one of the core indicators in both the TCGA and ProMisE systems. The four-step subtyping process recommended in the latest CSCO guidelines first excludes POLE hypermutated subtypes. Patients are then classified as "MMR-deficient/MSI-high" based on MMR/MSI status. This classification, combined with p53 status, determines subsequent assignment to either the "TP53-mutated" or "non-specific molecular alteration (NSMP)" categories [17]. This classification not only replicates TCGA's prognostic curves but can also be performed using paraffin-embedded tissue, making it cost-effective and easily scalable.

dMMR endometrial carcinoma exhibits a high mutation burden, abundant neoantigens, and upregulation of PD-L1 expression, making it an ideal target for immune checkpoint inhibitors (ICIs). Multiple Phase III trials and network meta-analyses confirm that in dMMR populations, ICIs combined with chemotherapy (e.g., Dostarlimab + CP) significantly outperform conventional chemotherapy in progression-free survival (PFS) and overall survival (OS). Conversely, pMMR patients tend to benefit more from regimens such as Selinexor or Lenvatinib combined with pembrolizumab. Thus, MMR status has become a "companion diagnostic" biomarker guiding immune and targeted therapy selection. Furthermore, all endometrial cancer patients should undergo MMR protein testing to screen for Lynch syndrome, enabling dual tumor-genetic management. In the future, quantitative MLH1 methylation analysis, NGS-based multigene panel testing, and integrated models combining MMR status with TMB and PD-L1 expression will further enhance risk stratification accuracy and optimize personalized treatment decisions.

5. The Claudin Family and Tumor Association

Claudins are proteins essential for forming tight junctions and paracellular barriers [18]. To date, at least 27 distinct subtypes have been identified in humans. Claudins possess four transmembrane domains and exhibit molecular weights ranging

from 20 to 27 kDa [18]. The genetic expression and stability of claudins frequently undergo alterations within tumor cells [19]. Scientific studies have demonstrated that the overexpression of various claudin family molecules can indicate poor prognoses in cancers such as lung cancer [20], breast cancer [21], gastric cancer [22], and colorectal cancer [23]. Members of the claudin family can regulate cell proliferation by recruiting signaling proteins, thereby initiating and driving cancer development and progression [24]. It has been established that Claudin-14 protein from the claudin family is overexpressed in various malignant cancers, including prostate cancer, endometrial cancer, and breast cancer, and is significantly associated with poor patient prognosis. For instance, elevated Claudin3 expression correlates closely with poor lung cancer prognosis, while reduced Claudin2 expression is associated with poor breast cancer outcomes [23]. Overexpression of Claudin4 correlates with differentiation and prognosis in colorectal and gastric cancers [25]. This indicates that members of the claudin family play roles in cancer initiation and progression. Overexpression of claudin family members can exhibit tumor specificity, with overexpression of certain members serving as poor prognostic markers for specific cancers. As research on claudin family members and their correlates deepens, Claudin14 protein has also been identified as closely associated with the development of certain cancers through its overexpression [26].

It has been confirmed that Claudin1 to Claudin1-14 proteins in the Claudin family are overexpressed in various malignant cancers, including prostate cancer and endometrial cancer [27], and they are significantly associated with poor prognosis in patients. This indicates that members of the Claudin family can play a role in the generation and progression of cancer. The overexpression of Claudin family members can be tumor-specific [28], and the overexpression of some of its members can be a marker of poor prognosis for certain cancers [29]. With continuous in-depth research on the correlation between Claudin family members and related diseases, Claudin18.2 protein is also believed to be closely related to the occurrence of some cancers due to its overexpression.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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