J Cell Immunol. 2022;4(3):107-110.

Journal of Cellular Immunology Commentary

# Commentary on the Clinicopathological Characteristics, Prognosis and Immune Microenvironment Mapping in MSI-H/ MMR-D Endometrial Carcinomas

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**Received date:** May 24, 2022, **Accepted date:** June 14, 2022

**Citation:** Guo YE, Chen G. Commentary on the Clinicopathological Characteristics, Prognosis and Immune Microenvironment Mapping in MSI-H/MMR-D Endometrial Carcinomas. J Cell Immunol. 2022;4(3):107-110.



## Abstract

Microsatellite instability (MSI) is caused by functional defects in DNA mismatch repair in tumor tissues. The new microsatellite alleles are present at a microsatellite locus in the tumor due to the insertion or deletion of duplicate units. MSI with DNA mismatch repair defects is an important clinical tumor marker. It is usually a result of defects in the mismatch repair (MMR) system, a group of enzymes responsible for monitoring and repairing the error incorporations in microsatellites. Here, we explored MSI subtype and its correlation with the immune environment in endometrial cancer. Using unbiased single-cell RNA-seq we found that the MSI tumors were associated with improved patient survival, the closer regulation of the immune environment, and MMR-D tumors showed a higher B cells infiltration. Our study analyzed the cell types in the endometrial cancer tumor microenvironment (TME). It elucidated the diverse functional phenotypes and states of malignant, T, and myeloid cell subsets to reveal the clinicopathological characteristics prognosis and immune microenvironment mapping in MSI-H/ MMR-D endometrial carcinomas, thereby demonstrating the role of immune subsets in MSI and the relationship between immunotherapy and endometrial cancer.

**Keywords:** Single-cell RNA-seq, Endometrial cancer microenvironment, Microsatellite instability (MSI), Mismatch repair (MMR), The tumor microenvironment (TME)

**Abbreviations:** EC: Endometrial Cancer; ECC: Endometrioid Carcinoma; MMR: Mismatch Repair; PTEN: Phosphate and Tension homolog deleted on chromosome ten; POLE: DNA Polymerase ε; BMI: Body Mass Index; TME: The Tumor Microenvironment; HGF: Hepatocyte Growth Factor; FGF: Fibroblast Growth Factor

## Introduction

TME contains various cell types (malignant cells, immune cells, fibroblasts, endothelial cells, etc.) and extracellular components (cytokines, growth factors, hormones, extracellular matrix, etc.). Tumor heterogeneity, characterized by each tumor's distinct TME cellular composition and states and the interplay between these components, may play a critical role in tumor initiation, progression, therapeutic efficacy, and patient survival. Anti-tumor drugs targeting TME have gradually been developed in recent years. Endometrial cancer, a tumor originating from the endometrium, is the most common gynecological gynecologic malignancy, and its frequency is rising. There is no optimal treatment choice for endometrial cancer patients who cannot tolerate surgical operations or those with metastasis and recurrence Numerous years of research have been devoted to developing a targeted therapy for endometrial cancer, but none have been authorized as of yet. Endometrial cancer therapy still encounters many obstacles. We used the single-cell RNA-sequencing to

profile significant cell types in the endometrial cancer TME, clarifying the diversified functional phenotypes and states of malignant, T, and myeloid cell subsets, and the combination of cell experiments, mouse models, and incorporation of The Cancer Genome Atlas (TCGA) data to reveal the salient biological functions of specific subsets, thereby revealing the relationship between MSI-H and MMR-D. These investigations will provide a scientific basis for developing targeted- and immuno- therapy for endometrial cancer.

Tumors acquire unique biological functions during multiple stages of progression, continuous proliferation signals, and avoidance of growth inhibitors, which enable them to resist cell death, replicate immortality, induce angiogenesis, activate infiltration and metastasis, have heavy energy metabolism, and avoidance of immune destruction [1]. This instability leads to genetic diversity, which accelerates the acquisition and inflammation of these traits. In addition to cancer cells, tumors recruit many cells that collaborate to create a TME that helps tumors acquire their characteristic functions, and promote tumor progression [2]. Cellular components, including immune cells, interstitial cells, and vascular endothelial cells as well as signaling molecules and extracellular matrix, have a variety of phenotypic states and exist in a spatiotemporal phase of interaction. The diversity of cell composition and phenotypes in the tumor microenvironment and their interactions contribute to swelling. Tumor heterogeneity is closely related to tumor progression, metastasis, and treatment resistance [3]. The plasma cells and fibroblasts can secrete growth factors such as hepatocyte growth factor (HGF), fibroblast growth factor (FGF), and chemokine CXCL12, which can not only promote the growth and survival of malignant cells, but also attract other cells to migrate [4]. Many immune cells in the microenvironment with different functions, such as CD8+ T cells and Natural killer T cells are primarily anti-tumor cells, while tumor-associated macrophages promote tumor growth [5]. Gemcitabine and 5-fluorouracil effectively activate myeloid-derived suppressor cells (MDSCs), which produce IL-1β, weakening the drug effect [6]. However, the main biological functions of the compounds and the mechanism of their influence on tumor behavior are still poorly understood.

In recent years, many drugs targeting TME have been developed for chemoprophylaxis or combination including angiogenesis inhibitors (e.g., anti-VEGF-A, bevacizumab), targeted matrix medications (e.g., NAB-Paclitaxel), anti-epidemic modulation agent (PLX3397;anti-CSF-1R), Plerixafor (anti-CXCR4), S-265610 (anti-CXCR2), an immune checkpoint inhibitor Ipilimumab (anti-CTLA-4), Nivolumab (anti-PD1), etc. [7]. When PD1 inhibitors were used to treat a variety of tumors, especially melanoma, many patients developed resistance, mainly caused by the intrinsic heterogeneity of tumors [8]. The effectiveness of cancer drugs often varies from person to person, so it is crucial to select the appropriate population and administer the appropriate medications. While understanding TME in detail, cellular heterogeneity can explain the differences in patients' responses to therapeutic drugs and help develop new targeted therapies for future medicine and precision therapy.

The development of single-cell sequencing technology has enabled the in-depth study of cell heterogeneity in TME, allowing researchers to gradually refine their understanding of tumors, from the tissue level to the level of individual cells, which can provide a more direct understanding of the law of tumor genesis and growth, as well as the existence of TME between various cells and individuals for the causes of different tumor behaviors [9]. The analysis of tumor tissue cell maps based on single-cell transcriptome sequencing technology has been studied in various tumors. Researchers have utilized single-cell transcriptome analysis in breast cancer [10], colorectal cancer [11], head and neck cancer [12], and melanoma [13]. Corresponding to the gene signature, a unique gene trait often represents a unique function. In 2016, researchers performed single-cell RNA sequencing experiments on tumor samples from 19 patients with metastatic melanoma. They found that the relationship between cell cycle and spatial environment in malignant tumor cells was significant, and that interstitial cells contained drug resistance-related gene tags associated with T cell infiltration. New depletion gene tags were found in T cells [13]. Those found in subsets of cells may signify distinct functionalities associated with clinical information of cancer samples in TCGA databases. In 2018, researchers identified a CD8+ T cell gene tag related to a patient's survival in a breast cancer cell atlas study [10].

Endometrial carcinoma is an epithelial malignant tumor that develops in the endometrium. It is a frequent malignant tumor of the female reproductive tract, and its incidence rises yearly [14]. The TME of endometrial cancer stem-like cells was found to play a key role in endometrial carcinoma [15,16]. Endometrial cancer is primarily treated surgically. However, there are no effective treatment options for individuals who cannot be operated on, have metastasized, or have relapsed. Targeted therapy for endometrial cancer has been explored for many years, but none has been approved as yet [17]. Immunotherapy medicines targeting endometrial cancer are still in clinical trials [18]. High heterogeneity may result from targeted therapy for endometrial cancer and drug resistance. Not only can distinct subtypes of endometrial cancer exhibit distinct biological behaviors, but the same tissue phenotype can also exhibit variability in its spread and metastasis [19]. Chromosomal analysis mutation type, i.e., the low copy number microsatellite stable type and high copy number serious type, proposed the molecular subtypes of endometrial carcinoma; POLE strong mutant, and microsatellite unstable hyperplasia [20,21]. There are still many roadblocks in the development of therapeutic drugs, so it is necessary to comprehensively describe various types of endometrial cancer phenotypes

and interactions of cell types. In our study, we explored the relationships between the MSI status and EC clinical features, prognosis, mutation profile, and immune infiltrates using TCGA data, and explored the cellular landscape of an MMR-D/MSI-H cancer tissue using single cell-RNA analysis.

## Conclusion

In conclusion, we systematically studied the cell composition and function of the TME of endometrial cancer, the cell mapping of endometrial carcinoma, found the relationship between the distinct molecular subtypes of endometrial cancer and the clinical features, along with the mutation spectra in POLE, MSI, and other EC, the up-regulation in MSI and POLE groups compared with other groups, and the higher immune cellular composition and phenotypic diversity of MMR-D endometrial cancer. These results will be useful for the intrauterine, and provide an important basis for developing and using targeted and immunotherapy drugs for endometrial cancer.

## Ethical Approval

No ethical issues exists in the submission of this manuscript.

## Consent to Participate

We consent to participate and publish this manuscript. No objection exists in the authors contributions and submission of this manuscript.

## Funding

This study was supported by the Development Fund of Shanghai Pulmonary Hospital (fkzr2139).

## Conflict of Interest

All authors have read and approved this manuscript. Neither the submitted paper nor any similar paper, in whole or in part, has been or will be published in any other primary scientific journal. No conflict of interest exists in the submission of this manuscript.

## Availability of Data and Materials

All the data and materials are available.

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