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

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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 that is responsible for monitoring and repairing the error incorporations in microsatellites. Here, we explored the MSI subtype and its correlation with the immune environment in endometrial cancer, using unbiased single-cell RNA-seq we found that the MSI tumors with better patient survival, the closer regulatory of immune environment, and the MMR-D tumors showed a higher B cells infiltration. Our study analyzed the cell types in endometrial cancer TME and clarified the diversified 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, which will uncover the role of immune subsets in MSI and the relationship of immunotherapy for 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

The tumor microenvironment (TME) contains various cell types (malignant cells, immune cells, fibroblasts, endothelial cells, etc.), in addition to extracellular components (cytokines, growth factors, hormones, extracellular matrix, etc.). Tumor heterogeneity defined by each tumor's diversified TME cellular composition and states, as well as the interplay between these components, may play critical roles in tumor initiation, progression, therapeutic efficacy, and patient survival. In recent years, anti-tumor drugs targeting TME have gradually been developed. Endometrial cancer, a tumor originating in the endometrium, is the most common gynecologic malignancy, and its incidence is increasing. For endometrial cancer patients who can't bear surgical operations or those with metastases and recurrence, there is no optimal treatment choice. Targeted therapy for endometrial cancer has been studied for many years, but up to now, no one is approved. Endometrial cancer therapy still encounters many bottlenecks. We use the single-cell RNA-sequencing to profile major cell types in 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 TCGA data

to reveal the salient biological functions of specific subsets, uncover the relationship between MSI-H and MMR-D. The above studies will provide a scientific basis for targeted- and immuno- therapy development for endometrial cancer.

Tumors acquire unique biological functions during multiple stages of progression, continuous proliferation signals, and avoidance of growth inhibitors that resist cell death, replicate immortality, induce angiogenesis, activate infiltration and metastasis, heavy energy metabolism, and avoidance of immune destruction [1]. This instability leads to genetic diversity, which in turn accelerates the acquisition and inflammation of these traits. In addition to cancer cells, tumors recruit a series of cells working together to create a tumor microenvironment (TME) to include tumors, help tumors acquire their characteristic functions, and promote tumor progression [2]. Cellular components such as 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 can not only promote the growth and survival of malignant cells, but also attract other cells to migration [4]. Many types of immune cells in the microenvironment with different functions, such as $CD8^+$ T cells and Natural killer T cells are primarily antitumor cells, while tumor-associated macrophages, mainly promote tumor growth [5]. Gemcitabine effective and 5-fluorouracil activate myeloid-derived suppressor cells (MDSCs) results in the production of IL-1β, which weakens the drug effect [6]. However, the main biological functions of the compounds and the mechanism of their influence on tumor behavior are still very limited.

In recent years, many drugs targeting the tumor microenvironment have been developed for chemoprophylaxis or combination including angiogenesis inhibitors (e.g., anti-VEGF-A, bevacizumab), and 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]. Where PD1 inhibitors have been used to treat a variety of tumors, especially melanoma, a lot of patients develop resistance, and it is 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 right population and administer the right treatment drugs. Understanding TME in detail cell heterogeneity can not only explain the differences in patients' responses to therapeutic drugs, but also help develop new targeted therapies in future medicine and precision therapy.

The development of single-cell sequencing technology has brought opportunities for in-depth study of cell heterogeneity in the tumor microenvironment, allowing researchers to gradually refine their understanding of tumors from the tissue level to the level of individual cells, which can be more direct to understand the law of tumor genesis and growth, and to understand the existence of tumor microenvironment between various cells and individuals in the causes of differences [9]. The analysis of tumor tissue cell maps based on single-cell transcriptome sequencing technology has been studied in a variety of tumors. Single-cell transcriptome analysis has been used by researchers in breast cancer [10] and 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 drug resistance-related gene tags, which were associated with T cell infiltration were found in interstitial cells. New depletion gene tags were found in T cells [13]. Those found in subsets of cells may represent specific functions of gene tags can be associated with clinical information of cancer samples in databases of TCGA. In 2018, researchers identified a $CD8^+$ T cell gene tag in a breast cancer cell atlas study associated with patient survival [10].

Endometrial carcinoma is an epithelial malignant tumor occurring in the endometrium and is a common female reproductive tract malignant tumor, its incidence is increasing year by year [14]. Tumor microenvironment of endometrial cancer stem-like cells were found to play a key role in endometrial carcinoma [15,16]. The treatment of endometrial cancer is mainly surgical treatment, but there are no good treatment options for patients who cannot be operated on or metastasized or relapsed. Endometrial cancer targeted therapy has been studied for many years, but so far there is no approved targeted therapy drug [17]. Targeting the endometrial cancer immunotherapy drugs are still in clinical trials [18]. High heterogeneity may be the result of targeted therapy for endometrial cancer and drug resistance. Not only do different endometrial cancer subtypes differ in their biological behavior, but the same tissue phenotype can also demonstrate the heterogeneity of its spread and metastasis [19]. The molecular subtypes of endometrial carcinoma, POLE strong mutant, and microsatellite unstable hyperplasia, were proposed by chromosomal analysis mutation type, low copy number microsatellite stable type, high copy number serious type [14,20]. There are still many bottlenecks 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 based on The Cancer Genome Atlas (TCGA) data, and explored the cell landscape of an MMR-D/MSI-H cancer tissue by single cell-RNA analysis.

Conclusion

In conclusion, we systematically studied the cell composition and function of tumor microenvironment of endometrial cancer, the cell mapping of endometrial carcinoma. We found the relationship between the distinct molecular subtypes of endometrial cancer and their clinical features, identified the mutation spectra in POLE, MSI, and Other EC, the upregulation 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 the development and use of targeted and immunotherapy drugs for endometrial cancer.

Ethical Approval

No ethical 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.

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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 availability.

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