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DECODING THE UMOD GENE: IMPLICATIONS FOR CHRONIC KIDNEY DISEASE THROUGH GENETIC MECHANISMS, DIAGNOSTICS, AND THERAPEUTIC INNOVATIONS

F.G.Ulmasov[1] D.Z.Mamarasulova[2] B.S.Esankulova[1]

1. Samarkand State Medical University, Samarkand, Uzbekistan.
2. Andijan state medical institute, Andijan Uzbekistan.

Abstract.

Relevance. Ovarian cancer is one of the most lethal gynecological malignancies worldwide, with high mortality primarily due to late-stage diagnosis and the lack of effective early screening. The tumor microenvironment (TME) plays a crucial role in cancer progression, immune evasion, and resistance to therapy. Immune cells, particularly CD4+ and CD8+ T cells, along with immune checkpoint proteins like PD-L1, significantly influence tumor behavior and therapeutic response. Understanding their roles in ovarian cancer may provide insights into novel immunotherapeutic strategies. **Materials and methods of study**. A total of 135 ovarian cancer patients from the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology, Samarkand Branch, were included in this study. Tumor samples were obtained through biopsy or surgical resection, and immune profiling was performed using multiplex immunohistochemistry and flow cytometry. The expression levels of CD4+, CD8+, and PD-L1 were quantified, and their spatial distribution within the TME was analyzed. Correlations between immune profiles and clinical outcomes, including survival rates and response to immunotherapy, were assessed. **Research results**. CD4+ T helper cells exhibited functional diversity, with Th1 cells promoting anti-tumor immunity, whereas Th2 and regulatory T cells (Tregs) contributed to immune suppression in advanced tumors. High CD8+ T-cell infiltration correlated with improved survival; however, elevated PD-L1 expression was associated with T-cell exhaustion (PD-1, TIM-3, LAG-3) and immune evasion. Increased PD-L1 levels were linked to poor prognosis, reinforcing its role as a key immune checkpoint regulator. **Conclusion**. This study highlights the prognostic significance of CD4+, CD8+, and PD-L1 expression in ovarian cancer. Immune profiling may aid in personalized treatment strategies, optimizing immunotherapy efficacy. Future research should focus on integrating multi-omics approaches to enhance patient stratification and improve therapeutic outcomes.

Key words: Ovarian cancer, Tumor microenvironment, CD4+ T cells, CD8+ T cells, PD-L1, Immune checkpoint inhibitors, Immunotherapy, Biomarkers, Cytotoxic lymphocytes.

Relevance. Ovarian cancer is one of the deadliest oncological diseases among women worldwide. Late diagnosis and the lack of effective screening methods contribute to its high mortality rate. The tumor microenvironment (TME) plays a crucial role in cancer progression and immune response suppression. Therefore, understanding the interactions between the immune system and tumor cells is vital for developing new therapeutic strategies.

Recent studies have shown that PD-L1 expression within the TME is highly heterogeneous, influencing response rates to immune checkpoint inhibitors [1,7]. The presence of tumor-infiltrating lymphocytes, particularly CD8+ T cells, is often associated with better prognosis, though their functionality is frequently compromised due to immune suppression mechanisms [12]. Additionally, natural killer (NK) cells have been identified as crucial players in ovarian cancer immunity, with their role in mediating cytotoxicity being limited by the immunosuppressive microenvironment [5,8].

Further, CD28 co-stimulation has been highlighted as a potential therapeutic target in improving T-cell responses in ovarian cancer [2]. Pharmacogenomic and epigenomic approaches have been

explored to optimize the response to IL-10 blockade, which is a key immune-modulatory factor within ovarian tumors [13]. Emerging research into exosomal non-coding RNAs also indicates their role in shaping immune responses, providing novel insights into biomarker discovery [3,4].

Thus, a comprehensive evaluation of immune cell infiltration, checkpoint expression, and novel biomarkers is critical to improving ovarian cancer immunotherapy outcomes [6,9]. Ovarian cancer is one of the deadliest oncological diseases among women worldwide. Late diagnosis and the lack of effective screening methods contribute to its high mortality rate. The tumor microenvironment (TME) plays a crucial role in cancer progression and immune response suppression. Therefore, understanding the interactions between the immune system and tumor cells is vital for developing new therapeutic strategies

Materials and methods of the study. A total of 135 patients diagnosed with ovarian cancer in Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of Samarkand Branch, were enrolled in this study. The inclusion criteria required histologically confirmed ovarian cancer and availability of tumor tissue samples. Clinical and pathological data, including tumor stage, histological subtype, and treatment history, were collected.

Sample Collection and Processing

Tumor samples were obtained through biopsy or surgical resection and immediately processed for immunohistochemical and flow cytometric analyses. Peripheral blood samples were also collected for comparative immune profiling.

Immunohistochemistry and Flow Cytometry

Multiplex immunohistochemistry (mIHC) was used to evaluate the spatial distribution and co-expression of CD4+, CD8+, and PD-L1 within the tumor microenvironment. Flow cytometry was performed on dissociated tumor samples to quantify immune cell populations and assess functional markers, such as IFN-γ, TNF-α, and exhaustion markers (PD-1, TIM-3, LAG-3).

Statistical Analysis

Correlation analyses were performed to determine associations between immune markers and clinical outcomes. Kaplan-Meier survival analysis was conducted to assess the impact of immune infiltration on overall and progression-free survival.

Data Presentation

Key findings were visualized using bar graphs, heatmaps, and box plots for comparative analyses. A summary of immune profiles across different tumor stages is presented in Table 1. A total of 135 patients diagnosed with ovarian cancer were enrolled in this study. Tumor samples were obtained through biopsy or surgical resection, and immune profiling was performed using multiplex immunohistochemistry and flow cytometry. The expression levels of CD4+, CD8+, and PD-L1 were quantified, and their spatial distribution within the TME was analyzed. Correlations between immune profiles and clinical outcomes, including survival rates and response to immunotherapy, were assessed.

Research results.

Immune Cell Infiltration Across Tumor Stages

Table-1

Summary of immune cell infiltration in ovarian cancer patients

Tumor Stage	CD4+ T cells (%)	CD8+ T cells (%)	PD-L1 Expression (%)
Stage I	15.2 ± 3.4	22.5 ± 4.1	10.3 ± 2.2
Stage II	12.8 ± 2.9	19.7 ± 3.8	15.7 ± 3.4
Stage III	10.1 ± 2.6	17.3 ± 3.5	23.9 ± 4.1
Stage IV	8.3 ± 2.2	14.5 ± 3.0	32.6 ± 5.3

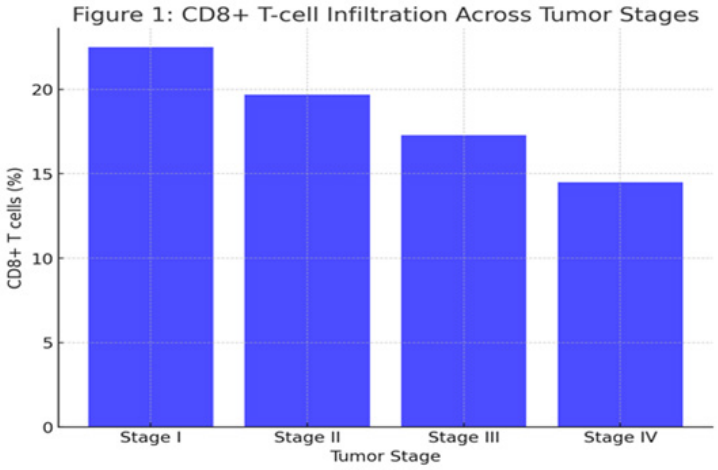
CD4+ T Cells in Ovarian Cancer TME

CD4+ T helper cells exhibited diverse functional profiles, with TH1 cells promoting anti-tumor immunity through IFN-γ secretion, while TH2 cells contributed to tumor progression via IL-4 and IL-

13. Regulatory T cells (Tregs) were frequently observed in advanced-stage tumors, correlating with immune suppression and poorer prognosis.

CD8+ T Cells and Cytotoxic Function

A higher frequency of CD8+ tumor-infiltrating cells correlated with improved general survival rates. Figure 1 depicts the infiltration density of CD8+ cells across tumor samples.



These cells exhibited cytotoxic activity through perforin and granzyme-mediated tumor cell apoptosis. However, in tumors with elevated PD-L1 expression, CD8+ T cells displayed markers of exhaustion, including PD-1, TIM-3, and LAG-3, leading to reduced anti-tumor activity.

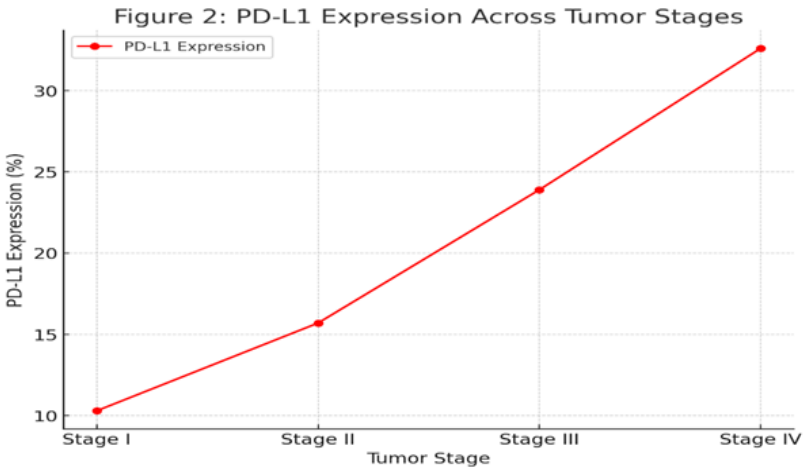
Table-2

Expression levels of exhaustion markers on CD8+ T cells

Marker	Expression Level (%)
PD-1	67.4 ± 4.2
TIM-3	52.8 ± 3.9
LAG-3	46.3 ± 3.5

PD-L1 Expression and Immune Evasion

PD-L1 expression was detected in tumor cells and infiltrating immune cells, with higher levels correlating with poor prognosis. Patients with elevated PD-L1 expression exhibited diminished CD8+ T-cell activity, suggesting that PD-L1-mediated immune evasion contributes to tumor progression. The spatial heterogeneity of PD-L1 expression highlighted its dynamic regulation in response to immune pressure, as shown in Figure 2.



Overall, the study highlights significant associations between immune infiltration, checkpoint expression, and clinical outcomes, paving the way for targeted immunotherapy approaches.

CD4+ T Cells in Ovarian Cancer TME

CD4+ T helper cells exhibited diverse functional profiles, with TH1 cells promoting anti-tumor immunity through IFN-γ secretion, while TH2 cells contributed to tumor progression via IL-4 and IL-13. Regulatory T cells (Tregs) were frequently observed in advanced-stage tumors, correlating with immune suppression and poorer prognosis.

CD8+ T Cells and Cytotoxic Function

High intratumoral CD8+ T-cell infiltration was associated with improved survival outcomes. These cells exhibited cytotoxic activity through perforin and granzyme-mediated tumor cell apoptosis. However, in tumors with elevated PD-L1 expression, CD8+ T cells displayed markers of exhaustion, including PD-1, TIM-3, and LAG-3, leading to reduced anti-tumor activity.

PD-L1 Expression and Immune Evasion

PD-L1 expression was detected in tumor cells and infiltrating immune cells, with higher levels correlating with poor prognosis. Patients with elevated PD-L1 expression exhibited diminished CD8+ T-cell activity, suggesting that PD-L1-mediated immune evasion contributes to tumor progression. The spatial heterogeneity of PD-L1 expression highlighted its dynamic regulation in response to immune pressure.

Discussion. The findings underscore the complexity of immune interactions in ovarian cancer. The immune checkpoint PD-L1 plays a dual role—facilitating immune evasion while serving as a potential target for immunotherapy. The observed heterogeneity in CD4+ and CD8+ T-cell infiltration suggests that immune profiles could serve as prognostic biomarkers and guide personalized therapeutic strategies.

Therapeutic Implications

• Immune Checkpoint Inhibitors (ICIs): Targeting the PD-1/PD-L1 axis has shown promise in clinical trials, particularly in patients with high PD-L1 expression and robust T-cell infiltration.

• Combination Immunotherapy: Strategies that enhance CD8+ T-cell activation while inhibiting suppressive pathways (e.g., targeting Tregs) could improve patient outcomes.

• Biomarker-Guided Therapy: Stratification based on immune profiles may optimize patient selection for immunotherapy, improving response rates and minimizing unnecessary treatments.

Conclusion. This study highlights the prognostic significance of CD4+, CD8+, and PD-L1 expression in ovarian cancer. Immune profiling may aid in the development of personalized treatment strategies, leveraging immunotherapy to enhance anti-tumor responses. Future research should focus on integrating multi-omics approaches to refine patient stratification and improve therapeutic efficacy.

The findings underscore the importance of a dynamic immune landscape in determining treatment responses and patient outcomes. The observed heterogeneity in immune cell infiltration and checkpoint molecule expression emphasizes the need for a more tailored approach in immunotherapy. Incorporating additional immune markers and exploring their interplay within the tumor microenvironment could yield further insights into resistance mechanisms and potential combinatorial treatment strategies.

Moreover, the development of novel therapeutic interventions, such as engineered T-cell therapies and next-generation immune checkpoint inhibitors, could significantly enhance treatment efficacy. Personalized medicine approaches, informed by detailed immune profiling, may allow clinicians to optimize treatment regimens and minimize adverse effects, ultimately improving survival rates and quality of life for ovarian cancer patients [10].

Finally, continued efforts in biomarker discovery and validation are crucial to identifying patients who will benefit most from immune-based therapies [11]. Future clinical trials should aim to incorporate comprehensive immune profiling as a standard component of patient stratification, ensuring that treatment decisions are based on a robust understanding of individual immune responses. By advancing our knowledge of immune dynamics within ovarian cancer, we can move closer to developing more effective and durable therapeutic solutions. This study highlights the prognostic significance of CD4+, CD8+, and PD-L1 expression in ovarian cancer. Immune profiling may aid in the development of personalized treatment strategies, leveraging immunotherapy to enhance anti-tumor responses. Future research should focus on integrating multi-omics approaches to refine

patient stratification and improve therapeutic efficacy.

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