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The Role of Tumor-Associated Macrophages (TAMs) in Cancer Progression and Immunosuppression

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Abstract

Tumor-associated macrophages (TAMs) are important immunological components that influence the tumor microenvironment by inhibiting immune responses and encouraging tumor development and cellular proliferation. This study sought to assess the functional, morphological, and molecular functions of TAMs in solid tumor patients. This study used a number of methods, such as flow cytometry, quantitative polymerase chain reaction (qPCR), and immunohistochemistry. Blood samples were taken from 50 patients clinically diagnosed with solid tumors, as well as from 30 healthy individuals who served as controls. Cytological investigations revealed a considerable increase in the percentage of macrophages bearing the CD163 and CD204 markers, as well as a decrease in HLA-DR expression, indicating that the cells polarized toward the M2 immunophenotype with immunosuppressive features. Additional genetic analyses revealed elevated expression of IL-10, TGF-β, ARG1, CSF-1R, and MMP9, genes linked to the immunosuppressive tumor microenvironment (TME). Histological evaluations revealed distinct infiltration of macrophages toward tumor peripheral zones and increased PD-L1 expression by macrophages, suggesting that macrophages may participate in the regulation of immunological checkpoints in addition to the suppression of effector T lymphocytes. Statistical analyses showed an inverse correlation between PD-L1 and HLA-DR and a positive correlation with IL-10, supporting the notion of the pleiotropic immunosuppressive function of macrophages. These data underscore the importance of TAMs for tumor progression and suppression, thereby rendering them suitable targets for contemporary immunotherapeutic approaches. Research suggests that additional investigations on the potential for reprogramming or targeting these cells therapeutically to enhance the immunotherapy response in solid tumors are needed.

Keywords
CD163, gene expression, immunosuppression, microenvironment, macrophages, PD-L1, solid tumors.

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Introduction

Cancer is a complex and multifactorial disease capable of continuous adaptation and evolution. Among the critical determinants of tumor development and treatment resistance is the environment surrounding the tumor (TME). This environment consists of a diverse composition of malignant cells and nonmalignant components, including fibroblasts, immune cells, endothelial cells, and various signaling molecules, which collectively influence tumor development and progression (1,2). Within the TME, TAMs constitute a major immune cell population known for their dual and often contradictory roles. These macrophages are derived primarily from circulating monocytes that migrate to tumor sites in response to chemotactic proteins such as VEGF, CCL2, and CSF-1, where they are subsequently reprogrammed into an M2-like phenotype with tumor-promoting functions (3,4). TAMs are actively involved in diverse processes that facilitate cancer progression, including the induction of angiogenesis, tumor cell inhibition of cytotoxic immune responses, invasion, and metastasis, particularly those mediated by CD8+ T cells. The ability of tumor cells to elude immune monitoring due to this immunosuppressive action. (5–7). Furthermore, TAMs release several inhibitory cytokines and mediators, such as IL-10, TGF-β, ARG1, and PD-L1, all of which contribute to shaping the immune-evasive tumor milieu (8–9). Clinical studies have consistently demonstrated that in a number of cancer types, including breast, lung, ovarian, pancreatic, and melanoma types, a poor prognosis is linked to significant TAM infiltration. and decreased overall survival. (10,11). Genomic and proteomic profiling further revealed that the molecular signatures of TAMs and tumors are strongly related. resistance to immunotherapy, highlighting their pivotal role in promoting both immunosuppression and acquired immune resistance (12). Consequently, therapeutically targeting TAMs has become a viable strategy for cancer immunotherapy. Among the tactics being studied are blocking macrophage recruitment, blocking survival pathways (e.g., CSF-1R inhibition), repolarizing TAMs toward an M1 antitumoral phenotype, and enhancing phagocytic activity against tumor cells (13–15). A range of pharmacological agents are currently being evaluated in clinical trials, either as monotherapies combined with immunological anti-PD-1 and anti-CTLA-4 checkpoint inhibitors, although some trials have reported minimal changes in the T-cell response (16–18). The goal of this study is to offer a thorough analytical overview of the biological and functional significance of TAMs in cancer development and immune regulation, with a particular focus on their molecular mechanisms, recent therapeutic interventions, and ongoing challenges in designing effective immunotherapies targeting these immune cells. Tumor immunity and the microenvironment advanced research in cancer immunology has revolutionized our knowledge of immune system function in cancers. Cancer cells are now considered to be more than passive victims or rivals of the immune system but active in orchestrating the local immune milieu for their own benefit (19). The TME is composed of endothelial cells, fibroblasts, immune cells, cancer cells, and ECM constituents. that interact to dynamically regulate cancer growth (20). Among these immune cells, TAMs represent the most prevalent and modulatory cell type, accounting for more than 50% of the nontumor cell mass in certain cancerous tissues (21(. A growing body of research suggests that TAMs do not remain dormant in the tumor microenvironment but actively participate in the different processes involved in cancer progression, including early initiation of tumor development; subsequent promotion of metastasis; resistance to immune attack (22); and poor clinical results, enhancing the metastatic potential of several malignancies, including breast, lung, prostate, liver, and pancreatic cancers (28,29). This study aimed to assess the functional, morphological, and molecular functions of TAMs in solid tumor patients.

Materials and Methods

Study Design

This study was designed as an exploratory pan–solid tumor observational analysis design and was carried out at the Immunological Research Unit, College of Science, University of Wasit, in coordination with the Oncology Center, Kut Teaching Hospital. Patients with different solid tumors (breast, colon, and lung cancer) were analyzed collectively to investigate shared immunological patterns related to tumor-associated macrophage polarization rather than tumor-specific differences.

Participants and Sample Collection

The study included two groups:

Fifty individuals who had been diagnosed with a solid tumor both clinically and histologically (such as breast, colon, or lung cancer) and who had not received prior chemotherapy or immunotherapy were included.

Thirty apparently healthy individuals represented the control group and were matched for sex and age. Five milliliters of venous blood was obtained from each participant via sterile instruments under the supervision of a specialized medical team. The amount was distributed as follows: Three milliliters were collected in EDTA (violet cap) tubes for the isolation of mononuclear cells (PBMCs) and analysis of cellular immune markers via flow cytometry. 2 mL were collected in plain tubes (without anticoagulant) for serum separation and subsequent analysis. The samples were stored in a refrigerated container (2–8°C) after withdrawal and transported to the laboratory within a maximum of one hour.

In the laboratory, the samples were centrifuged at 3,000 rpm for 10 minutes to extract the serum, which was then stored in tiny tubes at -20°C until needed. Mononuclear cells were isolated via Ficoll-Paque solution and used immediately or stored in cryoprotective medium at –80°C for subsequent analysis.

Inclusion and Exclusion Criteria

Inclusion: Patients who were diagnosed with a primary solid

tumor, aged 18-70 years, and were not treated.

Exclusion criteria: Chronic immune diseases, acute infections, hematologic malignancies, or the use of immunosuppressive medications.

Laboratory Methods

Isolation of peripheral blood mononuclear cells (PBMCs)

Flow cytometry findings reflect systemic immune alterations in circulating monocyte/macrophage populations, whereas immunohistochemistry reveals tissue-resident TAM localization and density.

• Flow cytometry = circulating monocyte/macrophage-like cells

• IHC = tumor-resident TAMs

Flow cytometric characterization

For immunophenotypic profiling, multicolor flow cytometry was performed using a BD FACSCanto™ II system (BD Biosciences, San Jose, CA, USA). The cells were stained with fluorochrome-conjugated monoclonal antibodies specific for CD68 (FITC, Clone Y1/82A), CD163 (PE, Clone GHI/61), CD204 (APC, Clone 2G11), PD-L1 (BV421, Clone 29E.2A3), and HLA-DR (PerCP-Cy5.5, Clone L243), all of which were purchased from BD Biosciences (San Jose, CA, USA).

Data acquisition and analysis were performed via FlowJo software (version 10; BD Biosciences, Ashland, OR, USA) to identify and distinguish M1- and M2-like TAM subsets. The gating strategy included initial forward scatter (FSC) and side scatter (SSC) selection to exclude debris, followed by gating on $CD68^+$ macrophages. PD-L1 expression was subsequently analyzed within the $CD68^+$ population. The compensation settings and isotype-matched controls were applied in accordance with the manufacturer's recommendations.

Gene expression analysis (RT–qPCR)

Total RNA was extracted from isolated human cells via the RNeasy Mini Kit (Qiagen, Hilden, Germany) and reverse-transcribed into complementary DNA (cDNA). Quantitative real-time PCR (RT-qPCR) was performed to evaluate the mRNA expression levels of ARG1, CSF-1R, MMP9, TGF-β1, and IL-10. Relative gene expression was calculated via the $2^{-}\Delta\Delta Ct$ method, with GAPDH used as the housekeeping gene for normalization.

Immunohistochemical (IHC) analysis

Formalin-fixed, paraffin-embedded tissue sections were subjected to immunohistochemistry with specific antibodies against CD68, CD163, and PD-L1. The stained sections were semiquantitatively evaluated by qualified pathologists to determine the distribution and density of TAMs within tumor tissues.

IHC staining was evaluated via a semiquantitative scoring system on the basis of the percentage of positive cells and the staining intensity. The slides were independently evaluated by two blinded pathologists.

Statistical analysis

Every statistical analysis was conducted via the Shapiro–Wilk test. Pearson or Spearman correlation was applied accordingly, and Student's t test was employed for comparisons between two groups.

Results

Demographic and Clinical Characteristics of the Participants

This study included a total of 50 patients who were clinically and histopathologically diagnosed with breast cancer, colorectal cancer, or lung cancer, as well as 30 apparently healthy individuals who served as the control group. Demographic and clinical data, including age, sex, disease status, and relevant medical history, were collected via a structured questionnaire. The mean age of the patients was 54.3 ± 9.6 years, whereas it was 52.1 ± 8.7 years in the control group, with no statistically significant difference between the two groups ($P > 0.05$), indicating appropriate comparability. The distributions of males and females were comparable between patients and controls, minimizing potential sex-related bias.

Analysis of Tumor-Associated Macrophages (TAMs) in Peripheral Blood

Mononuclear cells isolated from peripheral blood were analyzed via multicolor flow cytometry. A set of surface markers, including CD68 as a general marker for macrophages, CD163 and CD204 as markers for M2 inhibitory macrophages, and HLA-DR as a marker for M1 stimulatory macrophages, was used to identify different macrophage subtypes. Compared with those in healthy controls, the proportions of CD163+ and CD204+ cells in patient samples were significantly greater ($P < 0.001$), indicating increased activation of tumor-associated inhibitory macrophages (Table 5). A significant decrease in the proportion of HLA-DR+ cells was detected in the patient group ($P < 0.01$), reflecting the suppression of immunostimulatory activity. These data suggest that the tumor environment contributes to the reprogramming of macrophages toward an inhibitory (M2) phenotype, which promotes tumor progression by suppressing cellular immune responses.

Gene expression analysis of regulatory immune molecules

Isolation of total cellular RNA and cDNA synthesis Total cells were harvested for RNA isolation and reverse transcribed to cDNA. Genetic testing was carried out via qPCR. The results revealed dramatically increased gene expression levels of the genes encoding IL-10, TGF-β, ARG1 and CSF-1R, which are associated with the induction of suppressive immunity and the stimulation of M2 TAMs. MMP9, a distegrating enzyme of the extracellular matrix that enables the invasion of tumors and metastasis, was highly overexpressed.

These results indicate that TAMs play a pivotal role in creating an immunosuppressive tumor environment that promotes tumor progression via these molecular pathways.

Pearson correlation analysis of HLA-DR and PD-L1 expression

Pearson's correlation analysis revealed a significant inverse

association between HLA-DR$^+$ and PD-L1 expression ($r = -0.61$, $P < 0.01$). Conversely, PD-L1 levels were strongly and positively correlated with IL-10 expression ($r = 0.74$, $P < 0.001$), indicating a key role of TAMs in promoting an immunosuppressive TME.

Table 1: Demographic and Clinical Characteristics of the Participants

Parameter	Patients (n=50)	Controls (n=30)	P value
Age (years, mean ± SD)	54.3 ± 9.6	52.1 ± 8.7	> 0.05
Gender (Male/Female)	21/29	12/18	0.67
Tumor Types	Breast, Colon, Lung	N/A	—
Clinical Stage	I-IV	N/A	—

Table 2. Flow cytometric analysis of TAM-associated markers in peripheral blood

Marker	Patients (% ± SD)	Controls (% ± SD)	P value
CD68+	28.4 ± 4.2	14.6 ± 3.1	< 0.001
CD163+	21.7 ± 3.9	9.8 ± 2.6	< 0.001
CD204+	17.5 ± 2.8	7.1 ± 1.7	< 0.001
HLA-DR+	8.9 ± 2.4	15.2 ± 2.9	< 0.001

Table 3. Gene expression of immunoregulatory molecules (fold change)

Gene	Fold Change (Patients vs Controls)	P value
IL-10	4.3	< 0.01
TGF-β	3.7	< 0.01
ARG1	5.1	< 0.001
CSF-1R	2.9	< 0.05
MMP9	3.5	< 0.01

Table 4. Correlation Analysis between Immune Markers and Suppressive Genes

Comparison	Correlation Coefficient (r)	P value	Interpretation
PD-L1 vs HLA-DR+	-0.61	< 0.01	Inverse correlation
PD-L1 vs IL-10	0.74	< 0.001	Strong positive correlation

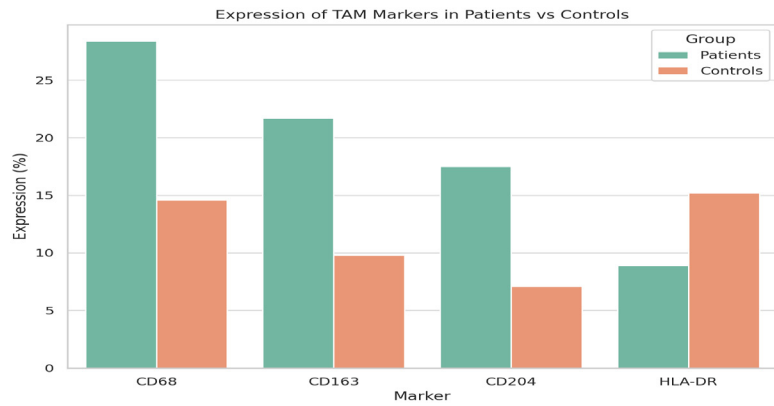

Figure 1. TAM-associated markers (CD68, CD163, CD204, and HLA-DR) in patients versus controls. Patients exhibit significantly elevated levels of M2 markers (CD163 and CD204) and reduced HLA-DR expression, suggesting a shift toward an immunosuppressive phenotype.

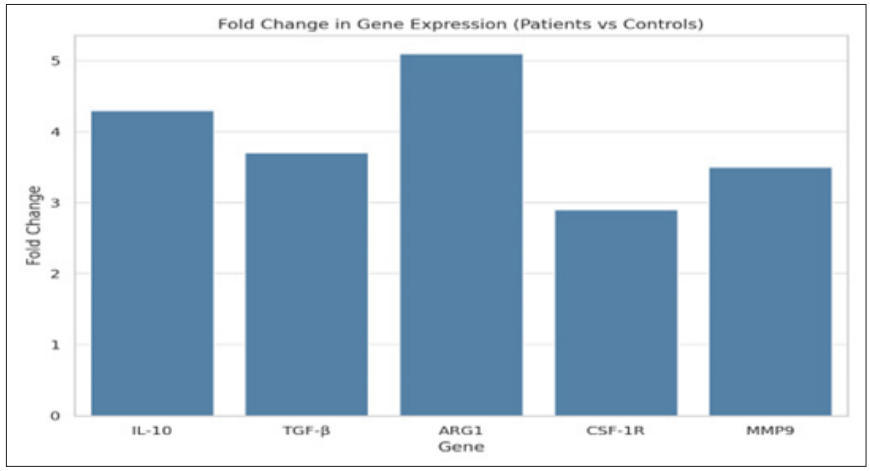

Figure 2. Fold change in the expression of key immunoregulatory genes. shows changes in the expression of IL-10, TGF-β, ARG1, CSF-1R, and MMP9 in patients compared with controls. The data indicate that the upregulation of genes associated with M2 macrophage polarization and tumor immunosuppression

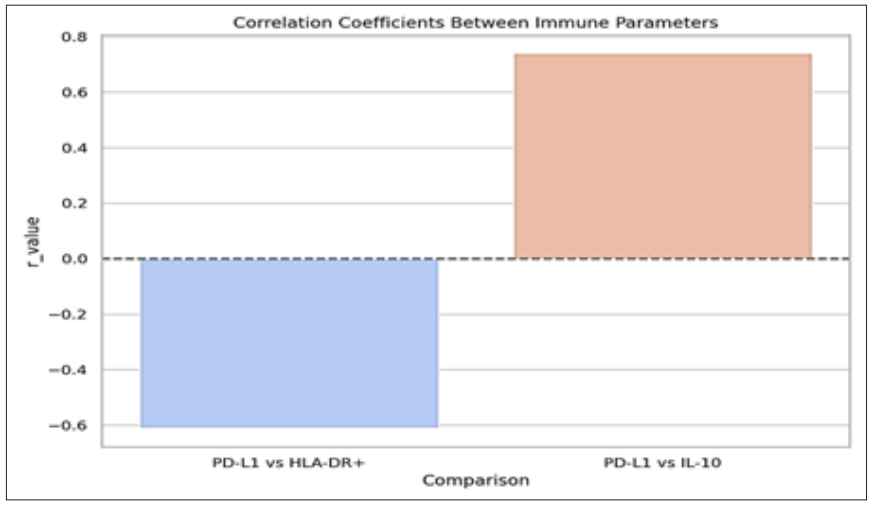

Figure 3. PD-L1 and HLA-DR expression are strongly negatively correlated, whereas PD-L1 and IL-10 expression are strongly positively correlated. These connections lend credence to the immunosuppressive role of TAMs in the TME.

Discussion

The current study highlights the significant involvement of tumor-associated macrophages (TAMs) in modulating the tumor microenvironment toward an immunosuppressive state that favors tumor progression. Our findings demonstrated a clear predominance of M2-like macrophages, as reflected by the increased expression of CD163 and CD204, together with a notable reduction in HLA-DR–positive macrophages, indicating attenuation of classical M1-associated antitumor immune activity. Similar patterns of TAM polarization have been reported in several solid tumors, where M2-dominant macrophage populations are associated with poor prognosis and immune evasion (30,31).

These observations are in accordance with previous studies reporting that M2-polarized TAMs contribute to tumor immune evasion through the suppression of antigen presentation and the inhibition of cytotoxic T-cell responses (31,32). The downregulation of HLA-DR expression observed in this study suggests impaired macrophage-mediated immune activation, a feature commonly associated with advanced tumors and reduced responsiveness to immune-based therapies. At the molecular level, the upregulation of IL-10, TGF-β, and ARG1 supports the presence of a tolerogenic microenvironment driven by TAMs. These mediators have been widely implicated in immune suppression, T-cell dysfunction, and maintenance of tumor immune tolerance (32).

These findings further emphasize the functional reprogramming of TAMs toward a protumoral phenotype. The elevated expression of MMP9 detected in this study indicates an additional role for TAMs in facilitating tumor invasion through extracellular matrix remodeling. This finding is consistent with previous reports linking TAM-derived metalloproteinases to increased local invasion and metastatic potential. Histopathological examination corroborated these results by demonstrating peritumoral accumulation of $CD68^{+}/CD163^{+}$ macrophages, a distribution pattern recognized as a marker of weak local immune surveillance (33).

The observed inverse association between PD-L1 and HLA-DR expression reflects a dynamic shift toward immune checkpoint–mediated suppression, whereas the positive cor-

relation between PD-L1 and IL-10 highlights the synergistic contribution of inhibitory cytokines and checkpoint pathways in reinforcing immune tolerance within the tumor microenvironment. Taken together, these results indicate that TAMs are active regulators of tumor immune dynamics rather than passive components. Therefore, targeting TAM polarization or suppressive function may represent a rational therapeutic approach, particularly in tumors that demonstrate a limited response to current immunotherapeutic strategies (34).

Conclusion

This study provides evidence that tumor-associated macrophages (TAMs) are closely associated with the immunological landscape of the TME. The predominance of macrophages exhibiting an M2-like immunophenotype is correlated with increased expression of immunosuppressive mediators, including IL-10, TGF-β, ARG1, and PD-L1, suggesting an immune context characterized by reduced effector T-cell activity. The observed inverse correlation between HLA-DR and PD-L1 expression, together with the strong positive association with IL-10, further supports a relationship between TAM polarization and immunosuppressive signaling pathways. These findings indicate that TAMs are integrally linked to tumor immune modulation and immune escape mechanisms. Although causal relationships cannot be inferred, the data highlight TAM-related markers as potential indicators of immune suppression within the tumor microenvironment and warrant further mechanistic and interventional studies to clarify their functional significance, particularly in solid tumors with limited responsiveness to current therapeutic approaches.

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Author Declarations

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Conflict of Interest Statement

The author declares that there are no conflicts of interest related to this study.

Ethics Statement

This study received ethical approval from the Ethics Committee of the College of Science, University of Wasit, in coordination with the Wasit Health Department/Oncology Center (approval number 158, dated March 13, 2025). Written informed consent was obtained from all participants for the use of their anonymized clinical data. Patient confidentiality and data privacy were strictly adhered to throughout the study. Data were collected at Kut Hospital, which is located in Wasit Governorate, Iraq. Access to identifiable patient information was restricted, and no data was shared with individuals or entities not directly involved in the research or manuscript preparation.

Consent for Publication

Written informed consent was obtained from all participants for the use of their anonymized clinical data and publication of the study findings.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

The author confirms sole responsibility for the conception and design of the study, data acquisition, data analysis and interpretation, manuscript drafting, critical revision of the manuscript, and approval of the final version for publication.

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