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MOLECULAR PROFILE OF MACROPHAGES IN PROSTATIC CARCINOMA

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Summary
Objectives. Tumor-associated macrophages (TAMs) are central components of the prostate cancer (PCa) microenvironment. Their molecular phenotypes influence tumor progression, immune evasion, and therapy resistance. This review synthesizes recent evidence on macrophage molecular profiles in prostatic carcinoma, emphasizing emerging biomarkers, signaling pathways, and therapeutic implications.
Methods. A comprehensive literature search was performed in PubMed, Web of Science, and Google Scholar for the years 2000–2025, following PRISMA 2020 guidelines. Eligible studies included those addressing molecular, transcriptomic, or immunohistochemical characteristics of TAMs in human or experimental PCa models. Data extraction focused on macrophage subsets, surface and intracellular markers, and pathway-level mechanisms.
Results. TAMs in PCa display heterogeneous polarization beyond the classical M1/M2 paradigm. Single-cell RNA sequencing and spatial transcriptomics have identified distinct $AR^{+}TREM2^{+}$ macrophage subpopulations expressing CD163, APOE, IL10, TGFB1, and PD-L1, which promote immune suppression and tumor growth. Regulatory pathways including CSF-1/CSF-1R, CCL2/CCR2, STAT3, PI3K/AKT, and androgen-receptor signaling coordinate macrophage recruitment and reprogramming. Lipid metabolism and hypoxic cues further reinforce an M2-like phenotype. Clinically, high infiltration of $CD163^{+}/CD206^{+}$ macrophages correlate with advanced Gleason grade, biochemical recurrence, and reduced overall survival.
Conclusions. Prostate TAMs are molecularly diverse and clinically relevant modulators of tumor behavior. Therapeutic strategies aimed at modulating TAM signaling (CSF-1R, TREM2, AR) or reprogramming macrophage metabolism may restore antitumor immunity and enhance the efficacy of immune checkpoint blockade. Integrating single-cell profiling with translational studies is crucial for identifying prognostic biomarkers and developing macrophage-targeted interventions.
Keywords: Tumor-associated macrophages, prostate cancer, single-cell RNA sequencing, androgen receptor, TREM2, immunotherapy resistance

Introduction

Prostate carcinoma (PCa) ranks among the most frequent malignancies in men worldwide, representing a major cause of cancer-related mortality and morbidity [1]. Despite advances in screening, early detection, and multimodal therapy, prostate cancer remains a heterogeneous disease, ranging from indolent localized tumors to highly aggressive, metastatic, and castration-resistant forms [2]. Understanding the biological mechanisms underlying tumor progression and therapeutic resistance is therefore essential for improving outcomes.

The tumor microenvironment (TME) has emerged as a key determinant of prostate cancer behavior, influencing tumor growth, invasion, angiogenesis, immune surveillance, and response to therapy [3, 4]. Far from being a passive bystander, the TME constitutes a dynamic and interactive network composed of tumor cells, fibroblasts, endothelial cells, immune infiltrates, and extracellular matrix components [5]. Within this complex ecosystem, immune cells—particularly tumor-associated macrophages (TAMs)—play crucial roles in orchestrating the balance between tumor suppression and tumor promotion.

Macrophages are highly plastic innate immune cells capable of adapting to microenvironmental cues such as cytokines, growth factors, and metabolic signals. In the context of cancer, macrophages undergo extensive phenotypic and functional reprogramming, acquiring either anti-tumoral or pro-tumoral functions depending on the stimuli encountered [6]. In prostate cancer, macrophages represent one of the most abundant immune populations within the tumor stroma and are increasingly recognized as prognostic biomarkers and potential therapeutic targets [7, 8].

Traditionally, macrophages have been classified into two functional extremes: classically activated, pro-inflammatory M1 macrophages and alternatively activated, immunosuppressive M2 macrophages [9]. M1 macrophages, induced by interferon-γ and microbial stimuli, produce pro-inflammatory cytokines (IL-1β, TNF-α, IL-12) and reactive oxygen species that can inhibit tumor growth and stimulate cytotoxic T-cell activity. Conversely, M2 macrophages, driven by IL-4, IL-10, and IL-13, secrete anti-inflammatory mediators such as IL-10 and TGF-β, promote tissue remodeling, angiogenesis, and tumor progression [10].

However, this binary paradigm has proven overly simplistic; tumor-associated macrophages often exhibit a spectrum of activation states, reflecting the diverse and dynamic nature of the tumor milieu [11].

Recent high-throughput technologies have revolutionized the understanding of TAM heterogeneity. Bulk transcriptomic profiling initially revealed enrichment of M2-like gene signatures in aggressive PCa, correlating with poor prognosis and resistance to hormonal therapy [12]. More recently, single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics have identified multiple distinct TAM subpopulations, revealing complex transcriptional landscapes beyond the conventional M1/M2 classification [13-15]. These studies demonstrated that macrophages in prostate cancer exhibit context-dependent expression of markers such as CD68, CD163, CD206, TREM2, APOE, ARG1, and PD-L1, associated with immunoregulatory and pro-tumorigenic phenotypes [16].

A particularly intriguing finding from single-cell and spatial analyses is the identification of androgen receptor–positive (AR^+) and triggering receptor expressed on myeloid cells 2–positive ($TREM2^+$) macrophages [17]. These AR^+TREM2^+ TAM subsets display transcriptional programs enriched in lipid metabolism, oxidative phosphorylation, and immune checkpoint signaling, suggesting that metabolic and hormonal cues shape macrophage function within the prostate tumor niche [18, 19]. Functionally, these macrophages exhibit potent immunosuppressive activity, inhibiting T-cell proliferation and promoting epithelial-to-mesenchymal transition (EMT) of tumor cells [20].

Mechanistically, TAM recruitment and polarization are regulated by multiple signaling pathways and cytokine networks, including CSF-1/CSF-1R, CCL2/CCR2, IL-10/STAT3, and PI3K/AKT signaling [21-23]. Tumor cells secrete macrophage colony-stimulating factor (M-CSF or CSF-1), which binds to its receptor (CSF-1R) on myeloid precursors, promoting their recruitment and differentiation into M2-like macrophages. The CCL2–CCR2 chemokine axis further amplifies macrophage infiltration, while activation of STAT3 and PI3K/AKT pathways maintains their immunosuppressive phenotype [24, 25].

Clinically, a high density of $CD163^+$ or $CD206^+$ macrophages in prostate tumor specimens correlates with adverse clinicopathologic features, including higher Gleason grade, extracapsular extension, lymph node metastasis, and biochemical recurrence [26, 27]. Meta-analyses confirm that TAM infiltration serves as an independent prognostic marker for poor recurrence-free and overall survival [28]. Moreover, TAMs contribute to therapeutic resistance: following androgen deprivation therapy (ADT), increased TAM infiltration and activation have been observed, sustaining tumor regrowth through cytokine-mediated mechanisms [29, 30].

Beyond their prognostic relevance, TAMs have attracted significant interest as therapeutic targets. Preclinical studies indicate that inhibition of CSF-1R or TREM2 can reprogram macrophages toward an inflammatory phenotype and enhance T-cell infiltration, thereby restoring sensitivity to immune checkpoint inhibitors [31, 32]. Combination therapies integrating TAM-targeted strategies with androgen receptor blockade or PD-1/PD-L1 inhibitors are currently being investigated as novel immunotherapeutic avenues [33, 34].

Altogether, the accumulating evidence underscores the crucial contribution of macrophages to prostate tumor biology. A deeper understanding of TAM heterogeneity and molecular regulation may open the path to innovative macrophage-centered therapeutic approaches capable of transforming the immunologically „cold" prostate TME into one that is „hot", inflamed, and responsive to immunotherapy [35, 36].

Aim: To comprehensively analyze the molecular characteristics and functional roles of tumor-associated macrophages (TAMs) in prostatic carcinoma, highlighting their contribution to cancer progression, immune evasion, and therapeutic resistance.

Objectives:

1. To review current evidence of the molecular and transcriptomic profiles of macrophage subpopulations within the prostate tumor microenvironment;
2. To identify key surface and intracellular markers (CD68, CD163, TREM2, AR, etc.) associated with macrophage polarization and immunosuppressive activity;
3. To explore the signaling pathways (CSF-1/CSF-1R, CCL2/CCR2, STAT3, PI3K/AKT, and AR) regulating macrophage recruitment, differentiation, and function in prostate cancer;
4. To evaluate the prognostic and therapeutic relevance of macrophage subsets, focusing on their potential as biomarkers and targets for immunomodulatory therapy;
5. To outline emerging therapeutic strategies aimed at macrophage reprogramming and integration into precision immuno-oncology for prostate carcinoma.

Materials and Methods

The literature search followed the PRISMA 2020 recommendations for systematic reviews and meta-analyses. Three electronic databases—PubMed, Web of Science, and Scopus—were comprehensively screened for publications dated January 2000 to May 2025. The primary search strategy combined the keywords *„prostate cancer", „macrophages", „tumor-associated macrophages", „TREM2", „CSF1R", „single-cell RNA-seq", „immunotherapy", and „microenvironment"*, using Boolean operators and MeSH terminology where applicable.

Inclusion criteria comprised original research articles describing the molecular, immunophenotypic, or transcriptomic characterization of macrophages in human or experimental prostate cancer models. Studies reporting macrophage-related biomarkers, gene-expression profiles, or mechanistic insights into macrophage–tumor interactions were prioritized. Exclusion criteria eliminated reviews, conference abstracts, editorials, non-oncologic studies, and those lacking macrophage-specific data.

After initial identification of 678 records, duplicates were removed and titles and abstracts were independently

screened by two reviewers. Following full-text assessment, 84 studies met the eligibility criteria and were included in the final synthesis. Discrepancies were resolved through consensus. Data extraction focused on study design, macrophage markers (e.g., CD68, CD163, TREM2, AR), analytical methods (immunohistochemistry, flow cytometry, RNA-seq, scRNA-seq), and principal molecular findings.

Discussion

Macrophage Polarization in Prostate Cancer. Historically, macrophages have been classified into two functional subsets—classically activated M1 macrophages, characterized by pro-inflammatory and tumoricidal activity, and alternatively activated M2 macrophages, which promote tissue repair and immune suppression [37]. This binary model, while conceptually useful, fails to capture the complexity and plasticity of macrophage phenotypes within the TME. In reality, macrophage polarization represents a continuum of activation states, dynamically shaped by microenvironmental cues such as cytokines, hypoxia, metabolic stress, and intercellular signaling from tumor and stromal cells [38, 39].

In PCa, TAMs predominantly exhibit M2-like features, expressing markers such as CD68, CD163, CD206 (mannose receptor), and arginase-1 (ARG1) [40]. These macrophages secrete anti-inflammatory cytokines (IL-10, TGF-β), pro-angiogenic factors (VEGF, MMP9), and chemokines (CCL2, CCL18) that facilitate tumor growth, vascular remodeling, and metastatic dissemination [41]. Conversely, M1 macrophages, defined by inducible nitric oxide synthase (iNOS) and pro-inflammatory cytokines (IL-12, TNF-α), are less abundant in advanced prostate tumors but remain critical for initiating antitumor immune responses [42].

The M2-skewed macrophage profile in prostate cancer results from both tumor-derived and stromal-derived signals. Cancer cells secrete macrophage colony-stimulating factor (CSF-1) and IL-4, which polarize infiltrating monocytes toward an M2 phenotype [43, 44]. Stromal fibroblasts and endothelial cells contribute additional modulators, including TGF-β, VEGF, and CXCL12, reinforcing the immunosuppressive microenvironment [45]. Moreover, androgen receptor (AR) signaling, a hallmark of prostate tumor biology, has been shown to influence macrophage behavior directly. Studies demonstrate that AR^+ macrophages acquire a transcriptional program overlapping with M2 macrophages, characterized by the upregulation of TREM2, APOE, and CD163, and the suppression of IL-1β and HLA-DR expression [46, 47]. This AR-driven phenotype promotes EMT and tumor invasiveness through paracrine IL-10 and TGF-β signaling [48].

Recent single-cell RNA sequencing (scRNA-seq) studies have challenged the oversimplified M1/M2 paradigm, revealing extensive heterogeneity within TAM populations in PCa [49, 50]. Distinct transcriptional subclusters have been identified, including AR^+TREM2^+ macrophages, lipid-associated macrophages (LAMs) enriched for APOE and LPL, and interferon-responsive macrophages expressing IFIT1 and IRF7 [51]. Spatial transcriptomics further demonstrate that M2-like macrophages are enriched in perivascular and perineural niches, while inflammatory macrophages cluster near necrotic or hypoxic zones [21]. This spatial organization supports the hypothesis that local oxygen and nutrient gradients dictate macrophage polarization and metabolic programming.

The metabolic profile of M2 macrophages in PCa includes enhanced oxidative phosphorylation and fatty acid oxidation, pathways driven by PPARγ and AMPK activation [52]. In contrast, M1 macrophages rely on glycolysis and exhibit a „broken" tricarboxylic acid cycle that sustains nitric oxide production. The tumor microenvironment thus exerts metabolic pressure favoring M2-like survival, as hypoxia-inducible factor 1α (HIF-1α) and lactate accumulation further skew polarization toward pro-tumoral phenotypes [53].

Clinically, TAM polarization correlates with disease progression. A high $CD163^+$ macrophage density in prostate biopsies is associated with elevated Gleason grade, extracapsular extension, angiogenesis, and shorter biochemical recurrence-free survival [54, 55]. Conversely, patients with a higher proportion of $CD68^+iNOS^+$ M1 macrophages exhibit longer survival and improved responses to androgen deprivation therapy (ADT) [56]. Immunohistochemical analyses and meta-analyses consistently identify the M2/M1 ratio as an independent prognostic biomarker in PCa [57, 58].

Therapeutically, strategies to reprogram M2 macrophages toward a pro-inflammatory M1 state represent a promising frontier. Preclinical studies indicate that blocking CSF-1R or CCL2/CCR2 signaling reduces M2 recruitment and enhances T-cell infiltration [59]. Similarly, targeting TREM2 or modulating lipid metabolism in macrophages restores immune competence and synergizes with PD-1/PD-L1 blockade [60]. Novel approaches combining androgen receptor inhibition with TAM reprogramming agents are under evaluation to convert the immunologically „cold" prostate tumor microenvironment into a „hot," inflamed, and immunotherapy-responsive landscape [61-63].

Taken together, macrophage polarization in PCa reflects a highly plastic and context-dependent process, integrating cytokine, metabolic, and hormonal cues. The transition from inflammatory M1 to immunosuppressive M2 phenotypes underlies key aspects of tumor progression, resistance to therapy, and immune evasion. Understanding the molecular regulators of this balance is fundamental for developing macrophage-targeted interventions that could redefine the therapeutic landscape of prostate carcinoma.

Molecular Signatures and Transcriptomic Data. Advances in molecular profiling technologies—particularly bulk RNA sequencing (RNA-seq), single-cell RNA sequencing (scRNA-seq), and spatial transcriptomics—have revolutionized the understanding of TAMs heterogeneity in PCa. These integrative approaches have demonstrated that macrophages within the prostate tumor microenvironment (TME) are not a uniform population but rather comprise multiple transcriptionally distinct subclusters with specialized molecular signatures, metabolic adaptations, and

spatial organization [64-66].

Single-Cell Transcriptomic Insights. Early bulk transcriptomic analyses already hinted at an enrichment of M2-like macrophage gene signatures in aggressive or metastatic prostate tumors [67]. However, the advent of scRNA-seq enabled the dissection of macrophage diversity at single-cell resolution, revealing multiple TAM subsets coexisting within the same tumor. Studies by Chen et al. (2023) and Masetty et al. (2022) identified discrete macrophage clusters expressing unique combinations of immunomodulatory genes, including CD163, APOE, IL10, TGFβ1, and PD-L1, consistent with an immunosuppressive phenotype [65, 68].

Among these populations, a distinct subset characterized by androgen receptor (AR) and TREM2 co-expression—termed AR^+TREM2^+ TAMs—has emerged as particularly relevant to prostate tumor progression [69, 70]. Transcriptomic analyses show that these cells upregulate pathways linked to lipid metabolism (APOE, LPL, FABP5), oxidative phosphorylation, and immune checkpoint signaling (PD-L1, CD276). Functionally, this subset exhibits strong immunosuppressive capacity, downregulating antigen presentation genes (HLA-DRA, HLA-DPB1) while upregulating inhibitory ligands that suppress T-cell activation. Notably, AR^+TREM2^+ TAMs are enriched in castration-resistant prostate cancer and in tumors with poor clinical outcomes, suggesting a role in therapy resistance [71].

Lipid-Associated and Metabolically Reprogrammed TAMs. An additional macrophage population identified through transcriptomic clustering consists of lipid-loaded TAMs (LL-TAMs). These cells demonstrate metabolic reprogramming, characterized by increased expression of genes involved in fatty acid transport and oxidation (CD36, CPT1A, FABP4) and cholesterol efflux (ABCA1, APOE) [72]. Such lipid-driven remodeling supports tumor cell proliferation and maintains cancer stemness via paracrine signaling mechanisms involving VEGF, IL-6, and TGFβ1. These findings align with the broader concept of „immunometabolism," where metabolic shifts in macrophages define their functional polarization and cytokine output. In prostate cancer, LL-TAMs act as metabolic facilitators, recycling lipids from apoptotic cells and contributing to the pro-tumorigenic niche.

Spatial Transcriptomics and Microanatomical Niches. Recent advances in spatial transcriptomics have provided spatial context to TAM heterogeneity, linking gene-expression signatures with anatomic localization within tumors [73, 74]. In PCa tissues, spatially resolved transcriptomic mapping revealed that M2-like macrophages and AR^+TREM2^+ subsets preferentially accumulate in perivascular, perineural, and stromal regions—zones associated with immune privilege, angiogenesis, and metastatic dissemination [73]. Conversely, macrophages expressing interferon-response genes (IFIT1, IRF7) are more frequent near necrotic and hypoxic areas, reflecting inflammatory adaptation to stress [26].

This microanatomical compartmentalization suggests functional specialization: perivascular TAMs promote angiogenesis through VEGF and MMP9 secretion; perineural TAMs may facilitate nerve infiltration and tumor spread; and stromal TAMs contribute to matrix remodeling and immunosuppression. The integration of spatial transcriptomics with multiplex immunofluorescence and digital pathology is expected to clarify the topographic relationships between TAM subsets and tumor cell phenotypes.

Collectively, transcriptomic evidence underscores the functional diversity and spatial organization of TAMs in PCa. By linking molecular phenotype with anatomic distribution, these studies provide a blueprint for rational targeting of macrophage subsets in future immunotherapeutic strategies.

Signaling Pathways. Multiple molecular circuits orchestrate the differentiation, polarization, and effector functions of TAMs within the prostate TME. These pathways integrate extracellular cytokine signals, metabolic cues, and hormonal stimuli, shaping macrophage phenotype and influencing tumor progression, immune evasion, and therapeutic response [72, 75].

One of the most extensively studied molecular axes is the **colony-stimulating factor-1 (CSF-1)/ CSF-1 receptor (CSF-1R)** pathway. Tumor and stromal cells secrete CSF-1, which binds to CSF-1R on myeloid precursors, promoting macrophage recruitment, survival, and M2-like polarization [21]. In prostate carcinoma, CSF-1R expression is upregulated in infiltrating macrophages, correlating with high Gleason scores and poor clinical outcomes [21]. Experimental inhibition of CSF-1R using monoclonal antibodies or small-molecule inhibitors markedly reduces macrophage infiltration, reprograms TAMs toward a pro-inflammatory phenotype, and enhances T-cell infiltration in preclinical models [72]. These findings position the CSF-1/CSF-1R axis as a therapeutic target for immunomodulation and reversal of immune suppression in prostate cancer.

Chemokine signaling networks, particularly those involving **CCL2/CCR2** and **CCL5/CCR5**, also play essential roles in TAM recruitment and M2 polarization [31]. Tumor-derived CCL2 recruits circulating $CCR2^+$ monocytes to the tumor site, where they differentiate into M2-polarized macrophages under the influence of local cytokines such as IL-4 and IL-10 [76]. In prostate cancer bone metastases, the CCL2-CCR2 axis fosters osteoclast activation and metastatic niche formation [77]. Similarly, the CCL5-CCR5 pathway reinforces macrophage-tumor cell crosstalk by promoting IL-10 production and STAT3 activation. Blocking these chemokine loops has demonstrated synergistic effects when combined with immune checkpoint inhibitors or androgen deprivation therapy (ADT) [78, 79].

Clinical Relevance and Prognosis. The clinical impact of tumor-associated macrophages in prostate carcinoma has become increasingly evident through a growing body of histopathologic, transcriptomic, and translational data. TAMs are not merely passive bystanders but active participants in tumor evolution, influencing prognosis, treatment resistance, and immune modulation. Quantitative and qualitative analyses of macrophage infiltration patterns have established TAM density and polarization state as key

prognostic biomarkers in prostate cancer [31, 56, 63].

Histopathologic Correlations and Patient Outcomes. Immunohistochemical studies demonstrate that infiltration by $CD68^+$ (pan-macrophage) and $CD163^+$ (M2-type) macrophages is strongly associated with adverse pathological features, including high Gleason grade, extracapsular extension, and seminal vesicle invasion [30]. Elevated densities of $CD163^+$ macrophages at the invasive tumor front or perivascular niches correlate with increased microvessel density, consistent with the pro-angiogenic activity of M2 macrophages through secretion of VEGF, MMP9, and IL-8 [79, 80]. Several cohort studies and meta-analyses have confirmed that high TAM infiltration independently predicts shorter biochemical recurrence-free and overall survival following radical prostatectomy [32]. Conversely, tumors containing a higher fraction of M1-polarized macrophages ($CD68^+iNOS^+$) tend to exhibit slower progression and better responses to androgen deprivation therapy (ADT).

Therapeutic Targeting of Macrophage Pathways. Given their multifaceted roles, TAMs are increasingly recognized as therapeutic targets. CSF-1R inhibitors (e.g., pexidartinib, emactuzumab) have shown preclinical success in reducing macrophage infiltration, reprogramming M2 phenotypes toward inflammatory M1 states, and restoring $CD8^+$ T-cell activity within prostate tumors [58, 81]. Similar outcomes are reported for TREM2 blockade, which disrupts lipid-driven immunosuppression and enhances responsiveness to immune checkpoint therapy [70]. Combination regimens incorporating CSF-1R or TREM2 inhibition with PD-1 blockade or androgen receptor antagonists represent a promising strategy under current investigation. These combinatorial approaches aim to overcome resistance by simultaneously targeting immune suppression and tumor-intrinsic survival pathways.

Translational and Clinical Perspectives. The incorporation of TAM-related markers into clinical practice is an evolving frontier. Quantitative immunohistochemistry and spatial transcriptomic scoring could aid in risk stratification, identifying patients likely to benefit from TAM-modulating therapies. Moreover, monitoring circulating macrophage-derived exosomes or soluble CD163 levels may provide minimally invasive biomarkers for disease progression. Continued integration of immunopathology, molecular profiling, and therapeutic trials is expected to refine the clinical utility of TAM signatures in prostate cancer prognosis and management.

In summary, the density, phenotype, and molecular signature of tumor-associated macrophages serve as powerful predictors of prognosis and determinants of therapy response in prostate carcinoma. Targeting macrophage signaling pathways such as CSF-1R and TREM2 offers a rational path to sensitize the tumor microenvironment to immunotherapy, paving the way toward precision immuno-oncology in prostate cancer [21, 60].

Future Directions. Despite substantial advances in the understanding of tumor-associated macrophages (TAMs) in prostate carcinoma (PCa), numerous mechanistic and translational questions remain unresolved. Future research must focus on integrating multi-omic technologies to construct a comprehensive taxonomy of TAM subsets and decipher their functional states in distinct tumor microenvironments [75].

From a translational perspective, future therapeutic strategies should aim not only to deplete macrophages but to reprogram them toward an anti-tumoral phenotype. The combination of CSF-1R or TREM2 blockade with immune checkpoint inhibition has shown strong preclinical synergy, suggesting a promising avenue for clinical translation [21]. Incorporating TAM modulators into multi-agent regimens—including androgen receptor antagonists, PARP inhibitors, or radioligand therapies—could reshape the immune landscape of prostate cancer, converting its immunologically „cold" microenvironment into a „hot", T-cell-inflamed one [82].

Ultimately, the integration of multi-omics technologies, systems immunology, and computational modeling will be essential to delineate the complex crosstalk between TAMs and other immune or stromal components. These efforts are expected to yield a precision immunotherapy framework where macrophage signatures guide patient selection and therapeutic design, redefining the future of prostate cancer management.

Conclusions

Tumor-associated macrophages (TAMs) represent a highly dynamic and molecularly diverse component of the prostate tumor microenvironment. Their transcriptional heterogeneity, spatial localization, and signaling complexity drive tumor progression, immune evasion, and therapeutic resistance. Advances in single-cell and spatial omics have revealed that subsets such as AR^+TREM2^+ macrophages, lipid-associated macrophages, and STAT3-activated macrophages play distinct roles in immunosuppression and disease progression. Therapeutic strategies targeting TAM signaling (CSF-1R, PI3K/AKT, TREM2, AR) or metabolic reprogramming hold significant promise for sensitizing prostate cancer to immunotherapy. Integrating multi-omics approaches with clinical translation will be crucial to transform macrophage biology into actionable therapeutic innovation.

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