Serican Journal of Medicine
2026, VOL. 3, NO. 4, 26312
https://doi.org/10.17161/sjm.v3i4.26312

B7-H3-induced Myeloid–Stromal Circuit Enables Combinatorial Immunotherapy in Advanced Prostate Cancer

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ABSTRACT

Advanced prostate cancer remains largely refractory to immune-checkpoint blockade, highlighting the need to understand the cellular networks that sustain immune exclusion. In a recent study, Shi and colleagues identify tumor-cell B7-H3 as a key organizer of a myeloid–stromal circuit in prostate cancer. B7-H3 activates MEK–ERK signaling in monocytic myeloid-derived suppressor cells (M-MDSCs), inducing senescence and a CXCL2/3-rich secretory phenotype that recruits immunosuppressive granulocytic MDSCs (Gr-MDSCs) through CXCR2. However, genetic deletion or therapeutic blockade of B7-H3 produces a compensatory response: proliferating, non-senescent M-MDSCs accumulate and secrete SPINK1, which activates EGFR–MEK–ERK signaling in cancer-associated fibroblasts (CAFs), promotes extracellular-matrix remodeling and collagen deposition, and restricts T-cell access. Thus, B7-H3 activity and its inhibition engage complementary mechanisms of immune suppression, helping explain the limited efficacy of B7-H3 monotherapy. Combining a B7-H3 monoclonal antibody with the MEK inhibitor trametinib disrupts this adaptive immunosuppressive network, producing more durable tumor control in castration-resistant prostate cancer. These findings broaden B7-H3 from a tumor-associated surface antigen to a hub of cancer–myeloid–fibroblast communication and provide a mechanistic rationale for combined B7-H3 and MAPK pathway inhibition. More broadly, they show that effective immunotherapy may require targeting both the initiating checkpoint and the compensatory mechanisms to achieve durable therapeutic effects.

ARTICLE HISTORY
Received: Oct. 19, 2026
Accepted: Oct. 20, 2026

KEYWORDS
B7-H3, prostate cancer, immunotherapy, myeloid cell, stromal cell

Advanced prostate cancer remains remarkably resistant to immune-checkpoint blockade. Although a small subset of patients with mismatch-repair deficiency or other selected molecular features can benefit, most men with metastatic castration-resistant prostate cancer (mCRPC) do not achieve durable responses to therapies targeting CTLA-4 or PD-1/PD-L1 [1, 2]. This limited activity has often been attributed to low tumor immunogenicity, sparse T-cell infiltration, and a strongly immunosuppressive tumor microenvironment. Growing evidence suggests that overcoming this resistance requires releasing a single brake on T cells and disrupting the myeloid and stromal networks that prevent productive antitumor immunity.

B7-H3, encoded by the *CD276* gene, is an appealing candidate for cancer immunotherapy. It is highly expressed in prostate cancer and many other solid tumors but is relatively poorly expressed in normal tissues, supporting the development of B7-H3-directed monoclonal antibodies, antibody–drug conjugates (ADC), bispecific molecules, and CAR-T therapies [3]. In a phase 2 study, the Fc-optimized antibody enoblituzumab showed biological and clinical activity in localized prostate cancer [4]. Nevertheless, B7-H3-targeted monotherapy has generally produced incomplete responses, and a major biological question has remained unresolved: beyond its association with T- and NK-cell suppression, how does tumor-cell B7-H3 organize the broader immune and stromal microenvironment?

In a recent study published in Cancer Discovery, we address this question by identifying a B7-H3–MAPK signaling circuit that links cancer cells, myeloid-derived suppressor cells (MDSCs), and cancer-associated fibroblasts (CAFs) [5]. Using prostate-specific Pten/Trp53-deficient genetically engineered mouse models (GEMM) with or without *Cd276* deletion, syngeneic CEPC models, single-cell transcriptomics, spatial immunophenotyping, primary human

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MDSC/CAF co-culture assays, and prostate cancer patient datasets, we show that B7-H3 has dual functions in modulating MDSCs and CAFs, which are complementary but therapeutically important. When B7-H3 is present, it promotes granulocytic MDSC (Gr-MDSC) recruitment by inducing senescence and associated chemokine production in monocytic MDSCs (M-MDSC); while when B7-H3 is depleted, a compensatory MDSC-to-CAF signaling emerges and limits the efficacy of B7-H3-directed therapy (**Figure 1**).

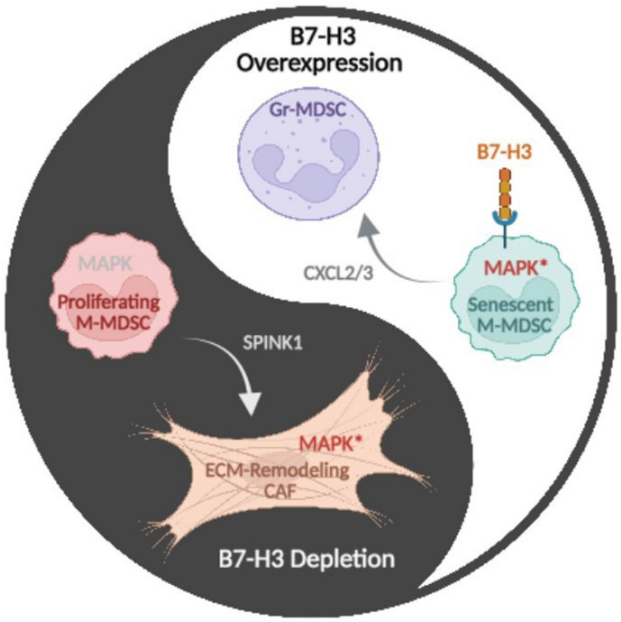
The first key observation is that tumor-cell B7-H3 controls MDSC subset switch, rather than simply changing total myeloid-cell abundance. In Pten/Trp53-deficient prostate tumors, Gr-MDSCs are the dominant MDSC population. Genetic deletion of *Cd276* reduced Gr-MDSCs while increasing M-MDSCs. Antibody-mediated depletion experiments placed M-MDSCs upstream of this shift: removing M-MDSCs reduced Gr-MDSC infiltration, whereas removing Gr-MDSCs had little effect on M-MDSCs. These data reveal that the two MDSC populations are not independent suppressive compartments. Instead, B7-H3 uses one population to control the other.

The mechanistic explanation is particularly interesting. B7-H3 protein preferentially binds to M-MDSCs and activates MEK–ERK–STAT1 signaling, driving these cells into cellular senescence. At first glance, induction of senescence might appear antitumoral because it limits M-MDSC proliferation. However, the senescent M-MDSCs acquired a senescence-associated secretory phenotype (SASP) and released CXCL2/3, which recruited immunosuppressive Gr-MDSCs into the tumor microenvironment (TME) through interaction with the CXCR2 receptor. Thus, B7-H3 converts a relatively small population of growth-arrested M-MDSCs into a signaling hub that amplifies myeloid suppression. This finding adds an important layer to recent work implicating senescent myeloid cells and the CXCL–CXCR2 axis in prostate cancer progression and treatment resistance [6, 7]. It also reframes cellular senescence in the TME: the biological consequence depends less on whether a cell stops dividing than on what the senescent cell secretes and how neighboring cells respond.

The second major finding explains why B7-H3 inhibition alone may be insufficient. Loss or pharmacological blockade of B7-H3 reduced M-MDSC senescence and Gr-MDSC recruitment, but it also increased the pool of non-senescent M-MDSCs. These cells produced more serine protease inhibitor Kazal type 1 (SPINK1), which activated EGFR–MEK–ERK signaling in fibroblasts and promoted an extracellular-matrix (ECM)-remodeling CAF state. These reprogrammed CAFs expressed collagen and matrix-remodeling molecules that can increase stromal stiffness and restrict T cell access. Depleting M-MDSCs prevented this fibroblast response, providing functional evidence that the CAF phenotype was not merely parallel to the myeloid changes but driven by them.

This MDSC–CAF connection is an important conceptual advance. CAFs are increasingly recognized as active regulators of immune exclusion rather than passive structural cells [8, 9], but the signals that connect myeloid adaptation to fibroblast state remain incompletely understood. Our study identifies SPINK1 as one such signal and places it upstream of a druggable EGFR–MEK–ERK pathway. The finding is espe-

Figure 1. Dual functions of B7-H3–MAPK signaling in modulating MDSC-CAF circuits.
Tumor-intrinsic B7-H3 has dual functions in modulating myeloid-derived suppressor cells (MDSCs) and cancer-associated fibroblasts (CAFs), which complement each other in creating the immunosuppressive TME and are therapeutically important. In B7-H3-overexpressing tumors, B7-H3 binds to monocytic MDSCs (M-MDSCs), activates MAPK signaling, and induces senescence and associated CXCL2/3 chemokine production in M-MDSCs, thereby recruiting granulocytic MDSCs (Gr-MDSCs) to prostate tumors. In the context of B7-H3 depletion, such as with B7-H3 immunotherapy, Gr-MDSCs decrease, but increased proliferating M-MDSCs produce SPINK1, which triggers EGFR-MAPK signaling to reprogram cancer-associated fibroblasts (CAFs) and promote their extracellular matrix (ECM) remodeling function.



cially relevant in prostate cancer, where SPINK1 has traditionally been studied as a tumor-cell-associated molecular subtype and therapeutic target [10]. Here, SPINK1 functions as a paracrine mediator produced by host myeloid cells, broadening its biological role from a cancer-cell marker to a key regulator of immune–stromal communication.

These two mechanisms create a therapeutic dilemma. B7-H3 activity drives an M-MDSC senescence–CXCL–Gr-MDSC axis, but B7-H3 inhibition releases a SPINK1–CAF response. Our team resolves this problem by combining a B7-H3 monoclonal antibody with trametinib, an FDA-approved MEK inhibitor. The combination produced deeper and more durable tumor control than either agent alone in syngeneic and GEMM models of CRPC, and its activity depended substantially on CD4 and CD8 T cells, rather than NK cells. Single-cell and spatial immunoprofiling analyses further showed that combined treatment reduced Gr-MDSCs and senescent M-MDSCs, suppressed ECM-remodeling CAF programs and collagen deposition, increased cytotoxic lymphocyte infiltration, and reduced features of T-cell exhaustion. Rather than targeting a single cell population, the combination appears to interrupt communication across the cancer–myeloid–fibroblast circuit.

Several aspects of this work strengthen its translational importance. We used complementary genetic and pharmacological approaches, validated key findings in both mouse and human myeloid systems, and confirmed therapeutic activities in more than one immunocompetent CRPC model. Analysis of 44 human prostate tumors also revealed relationships consistent with the proposed model: B7-H3-high tumors showed stronger Gr-MDSC signatures, whereas lower B7-H3 expression was associated with SPINK1 and ECM-remodeling CAF programs. These human data do not establish causality, but they suggest that the circuit is not restricted to a single experimental model.

Important questions remain. First, the receptor through which B7-H3 activates MAPK signaling in M-MDSCs remains unknown. Identifying this receptor will be essential for understanding cell-type specificity, developing pharmacodynamic biomarkers, and determining whether the pathway can be interrupted without directly targeting B7-H3. Second, human M-MDSCs and Gr-MDSCs are heterogeneous and overlap phenotypically with monocytes and neutrophils. Functional validation in prospectively collected patient samples—particularly metastatic bone lesions, the major clinical site of advanced prostate cancer—will therefore be important. Third, most mechanistic experiments were performed in prostate cancers with defined tumor-suppressor alterations. Whether the same circuit operates across other prostate cancer genotypes, neuroendocrine subtypes, or B7-H3-expressing nonprostatic tumors remains to be established.

There are also treatment-specific considerations. MEK inhibition can affect cancer cells, fibroblasts, myeloid cells, and lymphocytes simultaneously; its favorable net effect may depend on dose and schedule. The therapeutic window, potential toxicity, and optimal sequencing with B7-H3-directed agents will require careful study. Moreover, it is uncertain whether the same compensatory SPINK1–CAF response will occur with every B7-H3 therapeutic modality. Naked antibodies, ADCs, bispecific engagers, and CAR-T therapies can differ substantially in target-cell killing, Fc-mediated activity, tissue penetration, and bystander effects. Biomarkers integrating tumor B7-H3, MDSC states, circulating CXCL factors, SPINK1, and ECM-remodeling CAF signatures may be needed to identify the patients most likely to benefit from combined B7-H3 and MAPK pathway inhibition in prostate cancer, among other malignancies.

Nevertheless, our study provides a compelling explanation for why targeting a highly expressed immunotherapy target may yield limited anti-tumor activity as a single treatment. B7-H3 is not simply a surface marker on prostate cancer cells or a direct suppressor of lymphocytes. It acts as an organizer of the tumor ecosystem, shifting MDSC states and triggering adaptive communication between myeloid cells and fibroblasts. By exposing both the primary immunosuppressive pathway and the compensatory escape route, this work offers a rational combination strategy and a broader lesson for immunotherapy development: effective treatment may require targeting not only a checkpoint, but also the cellular conversation that follows its blockade.

Authors' Contributions Statement: Q.G. wrote the manuscript. D.Z. revised the manuscript and provided the funding support.

Acknowledgments: D. Zhao is a CPRIT Scholar in Cancer Research and has been supported by the CPRIT Recruitment of First-Time Tenure-Track Faculty Award RR190021, NIH/NCI R01 CA275990 and

CA278889, Prostate Cancer Foundation Challenge Award FP00016492, and DoD CDMRP IDA award PC230358.

Conflicts of Interest: The authors declare no potential conflicts of interest.

#Commentary on "Shi W#, Xu P#, Gu Q#, Fan Z#, Liang X, Wang Y, Zhao Y, Meng C, Leo J, Kim J, Teng H, Zhang J, Chen F, Chen Y, Navin N, Zhao D*. Dual Functions of B7-H3-MAPK Signaling Orchestrate Tumor Immunosuppression via Regulating the Plasticity of Myeloid-derived Suppressor Cells and Fibroblasts. Cancer Discovery. 2026. Sep 18. doi: 10.1158/2159-8290.CD-25-1613. PMID: 42757853."

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