Inhibition of WHSC1, Prostate Cancer

Subjects: Oncology

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Immunotherapy initially demonstrated promising results in prostate cancer (PCa), but the modest or negative results of many recent trials highlight the need to overcome the poor immunogenicity of this cancer. The design of effective therapies for PCa is challenged by the limited understanding of the interface between PCa cells and the immune system in mediating therapeutic resistance. Prompted by our recent observations that elevated WHSC1, a histone methyltransferase known to promote progression of numerous cancers, can silence antigen processing and presentation in PCa.

Keywords: tumor microenvironment ; prostate cancer ; immunotherapy ; WHSC1 ; Epigenetics

1. Introduction

Modulating the immune landscape of prostate cancer (PCa) to promote anti-tumor immunity has gained enthusiasm following the initial clinical success of trials testing Provenge and Prostvac VF to stimulate immune responses against prostate acid phosphatase (PAP) and prostate specific antigen (PSA), respectively. While several studies have reported favorable clinical outcomes, especially in patients with therapy-induced immune infiltration, PCa tumors typically show only low-level immune cell infiltration in the tumor microenvironment (TME).

WHSC1 is a histone methyltransferase that targets histone 3 lysine 36 (H3K36) and, to a lesser extent, histone 4 lysine 20 (H4K20). Elevated WHSC1 expression correlates with worse prognosis in a number of cancers [1][2][3][4][5][6][7] due to its oncogenic role in promoting cell growth and metastases; however, the magnitude of the effect and mechanism(s) of action of WHSC1 remain poorly understood. In studies designed to understand the interplay between PCa cells and the immune system, we recently demonstrated that elevated levels of the WHSC1 enzyme limit lymphocyte infiltration in PCa tumors, reduce antigen processing and presentation, as well as repress local activation of immune pathways [8].

We previously reported that WHSC1 inhibition increases the frequency of intratumoral $CD8^+$ T cells [8]; however, the changes associated with the overall immune composition of the TME following WHSC1 blockade remain unknown. Here, we broadly investigate the immunological changes in the TME in vivo following pharmacological inhibition of WHSC1and report a phenotypic shift in infiltrating immune cells that reflects both increased cytotoxic T cell activity and local modulation of diverse myeloid cell subsets present within the tumor. Lastly, using pathway analysis of changes resulting from WHSC1 inhibition, we propose a signaling circuitry that defines immune activation and favors a potent anti-tumor response.

2. Discussion

We recently demonstrated that WHSC1 inhibition potently increases antigen processing and presentation via an elegant epigenetic remodeling of prostate cancer cells that increases MHC expression and antigen presentation, accompanied by an increase in tumor-infiltrating $CD8^+$ T cells [8]. Interestingly, we also observed that when tumors were grafted in immunodeficient NSG mice, no tumor growth inhibition was observed [8], suggesting that at least part of the anti-tumor effect of MCTP39 was mediated through the activity of a functional immune system. While recognizing that both mouse models were grafted subcutaneously (SQ), it is well established that SQ tumors are still subject to the immune-driven anti-tumor effect in numerous cancer indications [8][9][10][11][12][13][14][15] and include a rich and heterogeneous immune compartment reshaped by therapeutic interventions. For these studies, we used the syngeneic prostate cancer cell line TRAMP C2 [16] that can be grafted in immunocompetent mice, thus permitting tumor-infiltrating immune cells to be broadly profiled in response to therapy.

Previous studies employing single-cell analyses identified large myeloid and lymphoid infiltrates in the prostate tumors of 13 patients [17], suggesting an interconnected cellular network between tumors and the immune system that may define

disease progression. However, on the therapeutic side, there is still limited knowledge regarding the immune signaling events that accompany prostate cancer regression following effective treatment.

When evaluating the expression of a focused panel of immune genes from bulk data, we identified a significant enrichment in antigen presentation pathways, lymphocyte activation, and migration. Among the most upregulated genes, we saw the ligands Cxcl13, Ccl21a, and Ccl22 and the chemokine receptors Cxcr4 and Ccr7. CCL22 is a homeostatic cytokine that can be produced in response to inflammation and acts through its receptor CCR4 to control immune activation in the lymph node [18][19]. The CCL21/CCR7 axis has a dual role, since it can both regulate the homing of immune cells to the lymph node to prime and activate T cells, B cells, and dendritic cells [20] and be involved in a metastatic tumor phenotype by promoting cancer cells migration [21][22]. In parallel to these functions, CXCL13 plays a key role in promoting immune infiltration in the tumor via binding to CXCR5 and controlling tumor behavior by binding to receptors on the tumor surface [23]. While overall pathway analysis suggested that treatment with MCTP39 enriched gene signatures related to immune functions, immune cell recruitment, and antigen processing and presentation, the origin of the signal and the location of the receptor can determine whether the resulting signaling cascade will lead to a pro-tumorigenic or anti-tumor response. Single cell RNASeq analyses revealed a large infiltrating myeloid cell component, consistent with previous studies of $CD45^+$ cells infiltrating prostate tumors [24][25], and suggested that improving the function of T cells within prostate cancer will necessitate successfully reprogramming the more abundant myeloid cells to promote local inflammation and anti-tumor immunity [26]. Based on our data and the broad and pleiotropic effects of MCTP39 on myeloid cell reprogramming, we propose that MCTP39 has previously underappreciated activity in targeting and modulating multiple simultaneous attributes of myeloid cell biology, which warrants additional investigation.

To maximize the anti-tumor immune response, the presence and activation of cytotoxic cells is required. Mice that were treated with MCTP39 had a higher frequency of cytotoxic $CD8^+$ T cells and NK cells, positive for Granzyme K, Ifn-γ, and Lamp1/Cd107a. The latter plays a key role in forming cytotoxic granules to be released upon antigen recognition, potentially indicating an ongoing anti-tumor response. The expression of Pdcd1/Cd279/Pd-1 was also increased in $CD8^+$ T cells, and while elevated PD-1 is a marker for exhausted $CD8^+$ T cells, it also defines tumor- and neoantigen-specific T cells. In this case, we also observed a significant reduction in the frequency of $CD8^+$ T cells expressing exhaustion markers including Lag3 [27][28][29], Btla [30], Cd244 [31], and Cd160 [32][33], while coexpressing granzymes and IFN-γ, suggesting the presence of activated, rather than exhausted, T cells. Furthermore, MCTP39 did not appear to play a direct role in enhancing $CD8^+$ T cells activation, supporting the hypothesis that the observed increase in T cell activation was driven by tumor antigens recognition in addition to immunostimulatory cues in the TME that were driven by MCTP39 treatment. Additionally, it is possible that the effects of MCTP39 on T cells may be unique, in that MCTP39 is able to directly diminish T cell exhaustion, although whether this effect is sustained over time is currently unknown and may necessitate blockade of key inhibitory pathways to produce durable T cell responses. In light of this, further efforts to bolster T cell activity in the tumor following MCTP39 may benefit from either combination therapy using checkpoint blockade or through targeting T cell co-stimulatory pathways. Combination therapies usinganti-PD1/PD-L1 could be particularly beneficial, as MCTP39 appears to enhance anti-tumor immunity in vivo, and WHSC1 knockdown in vitro downregulates PD-L1 expression in PCa cancer cells [8]. Since the expression of CD274/PD-L1 by immune cells was maintained following MCTP39 treatment (with the exception of a modest reduction in M1_Committed macrophages expressing CD274/PD-L1 (Figure S3)), combination with anti-PD-L1 therapy could help to reduce the inhibitory signals arising from tumor-infiltrating immune cells and enhance the duration of anti-tumor immunity. Interestingly, recent studies indicate that NK cells appear to benefit from checkpoint blockade therapy, with NK cell responses having a fundamental role in generating maximal anti-tumor immunity [34]. In our system, the pattern of expression of cytotoxic markers in $CD8^+$ T cells and NK cells following treatment indicates that these cell subsets have complementary but different polyfunctional phenotypes, suggesting that a combination of WHSC1 inhibition with checkpoint blockade could optimally activate both cell types, resulting in a potent anti-tumor response. Lastly, because of the increased levels of antigen presentation after MCTP39 treatment [8], we speculate that combination with WHSC1 inhibition could benefit PCa patients who receive vaccines (such as Provenge or Prostvac VF) by preferentially augmenting antigen processing and presentation following vaccination to bolster anti-tumor immunity.

While a high abundance of intratumoral myeloid cells can be associated with an immunosuppressive TME, macrophages and classical monocytes can promote a sustained inflammatory response and favor T cell homing to the tumor. In our model, inhibition of WHSC1 altered the transcriptional programs of M1 and M2 macrophages, upregulating genes in both antigen processing and presentation and leukocytes migration pathways. These results are in line with the increased frequency of cytotoxic immune cells in the treated group and suggest that myeloid cell reprogramming through MCT39 actively enhances the anti-tumor immune response.

Due to the coordinated action of chemokine ligands and receptors, immune cells are able to recruit cytotoxic T and NK cells to the target sites [35][36] or, conversely, they can ameliorate an ongoing inflammation process. We surveyed the ligand–receptor pairs for each classified cell type in an attempt to profile the mechanism(s) by which autocrine and paracrine signaling from cytokines and chemokines can rewire the immune behavior in tumors. For example, Nanostring analysis revealed a higher expression of Cd74. CD74, also named MHC II invariant chain [37], acts as chaperone for class II MHC antigen presentation and collaborates with MHC II to present surface antigens to the immune system [38]. In parallel, it is also known to bind to Cxcr4 in monocytes and T cells [39] and to Cxcr2 to promote leukocytes recruitment [40]. Our data indicate increased signaling in macrophages and DCs that promotes CD8+ T cell recruitment via Cxcr2/Cxcr4. These results are consistent with both higher $CD8^+$ T cell infiltration and MHC expression on DCs as measured by flow cytometry, suggesting a potential molecular mechanism by which WHSC1 inhibition alters paracrine signaling in myeloid cells, promoting higher T cell infiltration in the tumor and ultimately establishing an immuno-stimulatory TME. The Ccr5 receptor is uniquely expressed on activated T cells [41][42] and was upregulated in the MCTP39-treated group, in parallel with an upregulation of Ccl5 (a ligand for Ccr5) in DCs, M1, and T_M macrophages. Ccr5 was shown to promote T cell activation in concert with Cxcr4 [42], which can act as receptor for HMGB1 [43], Cxcl12 [44][45], and Cd74 [46]. While computational predictions suggest that complementary pro-inflammatory signals converge to establish a potent anti-tumor immune response, further experimental validation of the changes in cytokine and chemokine levels in each cell type would allow for a more precise interpretation of MCTP39 activity in the TME. The use of multiple prostate cancer models paired with toxicity analyses would further help to expand our current understanding of the safety and clinical applicability of the pharmacological inhibition of WHSC1, thus allowing for these findings to be translated as a clinically actionable treatment approach.

In conclusion, we present a detailed study that addresses the role of WHSC1 in altering anti-tumor cytotoxicity by rewiring the chemokine and cytokine signaling governing the communication between myeloid and lymphoid cells that infiltrate tumors. Due to the vast array of pro-tumorigenic functions shared by WHSC1 across cancer types [1][2][3][4][5][6][7], future studies that extend this approach to other tumor indications will reveal whether WHSC1 has a pan- or multi-cancer immuno-modulatory role. The downstream consequences of these findings have direct therapeutic implications, where cancer patients can be stratified based on WHSC1 expression to identify those that would benefit from WHSC1 inhibition as a complementary approach to immunotherapy.

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