Editorial Commentary

Exploiting pre-dormancy tumor immune microenvironment induced by androgen deprivation in prostate cancer

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Androgen deprivation therapy (ADT) is a mainstay of prostate cancer (PCa) treatment (1). It is often prescribed to patients with high-risk or advanced PCa to prevent relapse. The effectiveness of ADT is dependent on the reliance of PCa cells on androgen receptor (AR) signaling for survival or proliferation (2). Most of the PCa cells do respond to androgen deprivation, leading to cytostasis or cell death (1,3). However, with unclear mechanisms, some PCa do relapse in the form of castration-resistant PCa (CRPC), leading to eventual fatality (1). Therefore, preventing the development of relapse disease of PCa is a critical unmet need.

The advent of immune checkpoint inhibitors has significantly impacted the landscape of cancer treatments (4). PCa was, in fact, the first cancer to have approved cellular immune therapy, Sipuleucel-T (5), although it is generally considered as immune-cold (6). The clinical benefit brought about by Sipuleucel-T for managing metastatic CRPC speaks to the possibility of garnering the patient's immune system to fight PCa. In the same vein, a clinical trial was conducted to evaluate the utility of immune checkpoint inhibitor pembrolizumab in addition to enzalutamide, an androgen receptor pathway inhibitor, and ADT for treating patients with metastatic hormone-sensitive PCa; however, the addition of pembrolizumab did not improve the progression-free or overall survival of the patients (7). In addition, treatment of programmed death ligand 1 (PD-L1)-positive and PD-L1-negative disease with pembrolizumab as a monotherapy did not produce meaningfully different outcomes, suggesting that the suppressive interaction of programmed cell death protein 1 (PD1): PD-L1 may not play a crucial role or is not the sole crucial mechanism in the immunosuppressive PCa tumor immune microenvironment (TIME) (8). These observations suggest that better understanding of the interactions between the patients' immune system and PCa is required to effectively utilize immunotherapy against PCa.

Dallos *et al.* recently published a study examining the early changes in the TIME in primary PCa after ADT (9). The authors compared the transcriptomic and cellular changes in the primary PCa that were treated with degarelix, a selective gonadotropin-releasing hormone (GnRH) antagonist, for 14 days or fewer with those that were untreated. The results revealed that most of the primary PCa exhibited an active TIME after treatment with degarelix, which was supported by the upregulation of

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immune-related messenger RNA (mRNA) species, such as those that encodes immune checkpoints as well as the major histocompatibility complex (MHC) I and II. In addition, the transcriptomic profiles and immunofluorescent staining were consistent in showing the increase of cytotoxic T lymphocytes, M1 macrophages, and regulatory T (Treg) cells in the TIME of degarelix-treated PCa. Intriguingly, there was a reduction of CD47 on the PCa after ADT. Long *et al.* reported similar findings when comparing the transcriptomic profiles of 6 paired pre- and post-ADT PCa samples (10). Their results also support the increase of immune-related activity after ADT in PCa, including upregulation of antigen presentation, IFNγ signaling, immune checkpoint genes as well as infiltration of immune cells. These observations were consistent with what was reported by Dallos *et al.*, although the duration of ADT was longer in the study conducted by Long *et al.* These observations are also consistent with ADT-induced changes in a preclinical model reported by Shen *et al.*, including upregulation of immune activity, infiltration of Treg cells, and upregulation of immune checkpoints (11).

The strength of this study is that the authors were able to collect and analyze clinical samples of PCa that were treated with degarelix as well as untreated clinical samples. These samples are very difficult to obtain due to logistics reasons. The results of their study suggest that degarelix can cause dynamic changes of the TIME in PCa, at least shortly after ADT. However, since the treated and the untreated samples were not from the same patients, it is difficult to definitively conclude the increase in immune-related transcripts and expansion of immune cells were resultant of the conversion of immunologically cold PCa into hot tumor microenvironment. Nonetheless, as mentioned above, their observations were consistent with what was observed with the paired samples (10). Additionally, while the genetic aberrations of the samples were characterized, the small sample size limited the ability to determine how these aberrations influence or correlate with the immune response in relation to degarelix treatment. This limitation was acknowledged by the authors. Further, it remains unclear whether other forms of ADT, such as surgical castration, GnRH agonists, or antiandrogen therapies, such as enzalutamide, may produce the same immune response as the one induced by degarelix. As noted by the authors, the degarelix-treated samples were short-term—all collected within 2 weeks of treatment, leaving unanswered questions about how the TIME will change after 2 weeks of treatment. Moreover, whether the changes observed in TIME of the primary tumor reflect similar changes in metastatic sites remains to be determined. Finally, the increase of MHC I and II molecules expression by PCa cells is intriguing. Whether this implies a diminished role of natural killer cells in targeting the PCa cells, or whether efforts should focus on enhancing T-cell mediated killing for more effective elimination of the PCa cells, are yet to be determined. Addressing these questions will provide deeper insights as to how the immune system can be strategically manipulated to fight PCa more effectively.

Despite the yet-to-be-answered questions, the results of this study point to the possibility of exploiting the early immune response to degarelix treatment to eliminate the PCa cells, reducing the frequency of recurrence. As mentioned above, pembrolizumab was ineffective in improving the outcomes of PCa patients with metastatic CRPC, suggesting the presence of more dominant immunosuppressive mechanism(s) in the PCa TIME. Dallos *et al.* reported the increase of other immune checkpoints, including LAG3, HAVCR2, and TIGIT. At present, there are checkpoint inhibitors targeting these molecules at preclinical and clinical stage development (12). According to the data presented by Dallos *et al.*, there seems to be co-upregulation of LAG3 and MHC II molecules in the same samples. Since one of the major ligands of LAG3 is MHC II molecules, the observations suggest that LAG3:MHC II interaction may be one of the dominant immunosuppressive mechanism during the early ADT-induced TIME change, and LAG3 maybe a viable alternative target to PD1:PD-L1 interaction. In addition, combination therapy with immune checkpoint inhibitors have shown early successes in clinical trials, particularly the combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA4) in treating melanoma and renal cell carcinoma (13). Although not all trials with immune checkpoint inhibitor combinations lead to encouraging results, the lessons learned are valuable, for example, the heterogeneity of the immune suppressive mechanisms that a cancer can utilize and the need of biomarkers to identify the effective combination(s) to immune checkpoint inhibitors to be utilized.

Our lab has been interested in studying ADT-induced PCa dormancy (14). We believe the time window before and during ADT-induced dormancy should be exploited to prevent relapse, this includes the early changes induced by ADT. We have previously reported that the dynamic changes of B7-H3 and B7-H4 expression immediately after ADT, during PCa dormancy, and upon relapse. Notably, the observed changes in B7-H3 and B7-H4 expression

highlight that immunomodulatory molecules can have different expression levels at different time points after ADT (15,16). This dynamic regulation may extend to other immune checkpoint molecules as well. Therefore, longer longitudinal studies are required to better understand the dynamic regulations and target the immune checkpoints at the optimal time window.

Paired clinical samples of PCa from the same patients prior to or after ADT are very difficult to collect. Due to the heterogeneity of PCa, information gained from paired samples are invaluable. To overcome such hurdle, patient-derived xenografts (PDXs) are good options (17). Although PDXs are carried by immunocompromised mice and human immune system is absent, we argued that expression changes of immunomodulatory molecules in response to ADT can be hardwired, presumably due to particular genetic aberrations or epigenetic states. With this hypothesis, we reported the changes of the transcriptomic landscape of immunomodulatory molecules during ADT-induced PCa dormancy. Interestingly, we also observed upregulation of MHC I, MHC II, and β2 microglobulin (18). Our observations are consistent with those of Dallos *et al*. This increase of the capacity for antigen presentation induced by ADT deserves further study and perhaps it can be manipulated for the effective eradication of the PCa cells.

Overall, the report from Dallos *et al.* provided essential information on the short-term TIME change in response to ADT. These observations prompt for further studies to better understand how ADT-induced response can be exploited for the effective elimination of PCa cells. The current challenges of immunotherapy are of two-fold: achieving specificity and managing toxicity. Efforts to enhance the effectiveness and minimize the toxic effects of immunotherapy include targeting novel immune checkpoints and combinations of immune checkpoint inhibitors as well as cellular therapy, such as CAR-T or natural killer (NK) cells (19). However, these approaches have largely resulted in only incremental improvement, their overall impact remains limited (20).

The primary hurdle in advancing immunotherapy, however, lies in the complexity and adaptability of immune evasion mechanisms. Cancer cells exploit an increasing number of immunosuppressive strategies, including alterations in immune checkpoint expression, metabolic reprogramming, and cytokine and chemokine signaling (21-23). Additionally, these mechanisms are highly dynamic, evolving over time and contributing to therapy resistance. This adaptability not only complicates the development and selection of effective immunotherapies but also reduces their long-term efficacy.

To achieve transformative progress, it may be necessary to shift focus toward targeting fundamental immunosuppressive mechanisms. For example, addressing cancer's aberrant metabolism, such as the Warburg effect, and its role in creating an acidic, immunosuppressive environment, could present a pivotal strategy (24,25). Such approaches have the potential to enhance immune system functionality and improve the durability of immunotherapy responses, ultimately overcoming the challenges posed by the dynamic and complex nature of immune evasion mechanisms.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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