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INVITED COMMENTARY

Prostate Cancer

Impact of IL-23 in prostate cancer

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Cytokines play an essential role in governing the overall immune response toward cancer. Recently, the role of IL-12 family cytokines in dictating immune response toward cancer has been well appreciated.[1] IL-23 is one of such heterodimeric cytokines belonging to the IL-12 family cytokine, composed of p19 and p40 subunits.[2] The role of IL-23 in regulating tumorigenesis is controversial. In some cancer settings, IL-23 activates the effector immune system and has antitumorigenic functions; on the other hand, it can support immune regulatory response and favor tumor growth.[3] In this issue of *Asian Journal of Andrology*, Liu *et al.*[4] reported the novel functions of IL-23, a cytokine that regulates both innate and adaptive immune cells; especially, it is well known to maintain Th17 cell phenotype in prostate cancer. Prostate cancer is one of the utmost challenging tumor types and is the most common cancer in men, and one man in eight will be diagnosed with prostate cancer.[5,6]

To date, prostate cancer can be diagnosed using prostate-specific antigen (PSA) testing in blood or with a digital rectal examination (DRE). Nevertheless, both tests are imperfect and sometimes give false-positive results even in the absence of cancer and *vice versa*.[7–9] It might lead to prostate surgeries even men do not have cancer, and false-negative tests can go without specific treatment even they have cancer. It demonstrates the urgent need for a different diagnostic approach for patients with prostate cancer. Recent research studies show that certain cytokine levels and prostate tumorigenesis go hand in hand and promote cancer, from low-grade prostatic intraepithelial neoplasia (PIN) to high-grade PIN, and even potentiates metastasis outgrowth of the tumor.[10–12] Infiltration of regulatory immune cells is essential in regulating prostate cancer growth and metastasis. Recent studies focused on delineating the functions of regulatory cells in directly initiating and maintaining prostate cancer progression. Several pro-inflammatory cytokines have been shown to control prostate cancer growth; mainly, IL-17–producing Th17 cells have been shown to promote prostate cancer by modulating response in a mouse model of prostate cancer.[13,14] Thus, the interplay between immune regulatory cells, cytokine signaling and initiation, and maintenance of prostate cancer growth has emerged as a crucial node in regulating prostate tumorigenesis.

Liu *et al.*[4] revealed the essential aspect of IL-23, a cytokine involved in the expansion of Th17 cells and responsible for several autoimmune and inflammatory diseases, as a prognostic factor in patients with metastatic prostate cancer. Authors showed that IL-23–positive cells were correlated with disease progression and abundantly present within prostate cancer tissue. To delineate the diagnostic potential of IL-23, the authors evaluated IL-23 expression in the TCGA-PRAD cohort and observed that it is positively correlated with the pT stage and the Gleason score. The IL-23 expression is directly related to poor survival and castration-resistant prostate cancer (CRPC)-free survival. These observations are crucial because they show the importance of proinflammatory cytokine IL-23 in the diagnosis of prostate cancer and correlate with the patient's survival. Interestingly, the authors also indicated that IL-23–secreting cells or its expression status is different in the advanced stage of the disease. In addition, using immunohistochemical analysis, authors confirmed the presence of IL-23$^+$ cells in prostate cancer tissues, and the prostate cancer patients with higher Gleason scores have enhanced IL-23$^+$ cells accumulation compared to low Gleason scores.[4]

The authors further showed that metastasis cancer lesions had increased IL-23$^+$ cells than those of nonmetastasized lesions. Patients with increased IL-23$^+$ cells infiltration have poor clinical outcomes than patients with fewer IL-23$^+$ cells infiltrated the group. These are essential findings and undoubtedly valuable for the clinical setting, where they can help design strategies for the cancer patient's treatment and guide the therapy (**Figure 1**). The authors further showed that the increased IL-23$^+$ cell infiltration is associated with a higher risk of death and CRPC grade. In addition, the authors presented the Gleason score and nerve invasion that showed the increased risk in CRPC-free survival models and revealed that IL-23$^+$ cells can self-sufficiently anticipate the prognosis of metastatic prostate cancer patients. Interestingly, the authors found that IL-23$^+$ cells predict poor clinical outcomes in the patients who received the abiraterone treatment. Inversely, it is not found in patients who received the docetaxel treatment.[4]

Although this and few other reports analyzed the role of IL-23 in cancer initiation and metastasis and provided an important aspect into its role from diagnosis to drug discovery, several questions remain. First, how IL-23$^+$ cells infiltrated and recruited at the tumor site and how IL-23 signaling affects the overall immune and cancer cell phenotype are not well studied. Second, it is also not well acknowledge how different stimuli or cytokines in the tumor environment affect IL-23$^+$ cells, and what promising intracellular signaling and transcription factors govern IL-23 expression in target cells, which might lead to tumorigenesis and worse survival. Moreover, the precise function of IL-23–producing cells in the tumor microenvironment is unclear, as they stabilize the Th17 cell phenotype; however, the role of Th17 cells in tumorigenesis, especially in human prostate cancer, is controversial.[15] In conclusion, the precise signaling and critical transcription factors dictate the fate of IL-23$^+$ cells, and target cells of IL-23 need to be evaluated. Those are crucial in prostate cancer and should be comprehensively illuminated, as these details will help design potential and novel targeted therapy for the treatment of prostate cancer.

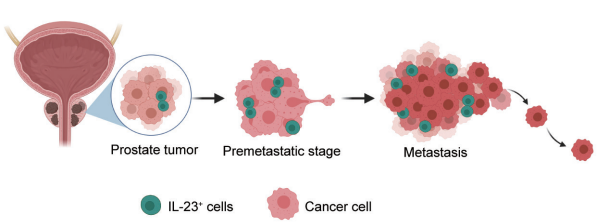

Figure 1: Higher IL-23$^+$ cells infiltration can be a good prognostic indicator in prostate cancer.

COMPETING INTERESTS

The author declared no competing interests.

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