International Journal of Agriculture and Biosciences 2026 15(2): 585-593.
https://doi.org/10.47278/journal.ijab/2025.215

RESEARCH ARTICLE
eISSN: 2306-3599; pISSN: 2305-6622

Androgen Deprivation Therapy Enhances B Cells Prevalence in Lymphoid Tissues of a Prostate Cancer Mice Model: A Potential Role for the Il-7r/Il-7 Cascade

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ABSTRACT

Most prostate cancers are treated primarily with androgen deprivation therapy (ADT). However, the tumor frequently recurs in a more aggressive form shortly after, which might result in the development of androgen-independent prostate cancer (AIPC). A change in the immune system has been suggested as a mechanism for the advancement of AIPC. Thus, examining the impact of ADT on immune cell development and function in prostate cancer would be of interest. Using TRAMP mice as a model, we examined the sizes of the genitourinary (GU) organs, prostate, and spleen, as well as B cell distribution in the spleen and bone marrow following androgen ablation through castration (TRAMP-Cas). Compared to the wild-type TRAMP mice, TRAMP-Cas mice had significantly reduced prostate and GU sizes, as well as increased spleen weights ($P<0.05$). Moreover, B cell populations increased significantly in the spleen and bone marrow of the TRAMP-Cas mice compared to the TRAMP-wt mice ($P<0.01$ and $P<0.05$, respectively). Notably, we observed significant increases in immature B cells in the spleen and bone marrow of TRAMP-cas mice. In the TRAMP-cas group, IL-7R expression by bone marrow-derived immature B cells was notably higher, with significant elevations in the serum levels of IL-7. The findings of the current study highlight the possible role of the IL-7R/IL-7 signaling pathway in regulating immune cell activation and strengthening the body's defense against prostate cancer during ADT treatment. The IL-7R/IL-7 cascades show great promise, especially during the ADT period, which serves as an opportune phase for prostate cancer intervention.

Keywords: Prostate, Cancer, Interleukin-7, B cell, IL-7 receptor.

Article History
Article # 25-541
Received: 10-Sep-25
Revised: 25-Nov-25
Accepted: 30-Nov-25
Online First: 12-Dec-25

INTRODUCTION

Screening for prostate cancer is common, and it is typically detected early when an individual has tiny, minimally invasive tumors or even precancerous lesions called prostatic intraepithelial neoplasia (PIN). In such cases, the precancerous prostate lesions typically cause milder symptoms compared to the severe adverse effects associated with conventional treatments for prostate cancer. Therefore, the standard of care in these patients is a period of active surveillance that can last for years before the prostate tumor begins to pose a more serious risk to the health of the patient (Yin et al., 2003; de Vos et al., 2023; Diven et al., 2024). Throughout tumor emergence, immune cells and cancer cells interact (Dalgleish & O'Byrne, 2006). Early detection and efficient elimination of neoplastic cells in their early stages are made possible by the immune system's ability for immunosurveillance (Wang, 2006). By mimicking the immunosuppression processes linked to immune tolerance and the control of B cell responses to prevent autoimmune conditions, neoplastic cells may evade the immune system and arise as a consequence of this ongoing immunological selective pressure (Maloney, 2005). Once at the primary tumor site, activated lymphocytes exhibit their newly acquired tumor-fighting abilities (Yi et al., 2007). To promote cancer spread, the tumor microenvironment suppresses anti-tumor immune responses (Neeson & Paterson, 2006; Yi et al., 2007). It is unclear how B cell activities associate tumor growth and impaired immune responses.

Cite this Article as: Altuwaijri S and Albarrak SM, 2026. Androgen deprivation therapy enhances b cells prevalence in lymphoid tissues of a prostate cancer mice model: a potential role for the Il-7r/Il-7 cascade. International Journal of Agriculture and Biosciences 15(2): 585-593. https://doi.org/10.47278/journal.ijab/2025.215

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The main treatment for prostate cancer that cannot be cured by radiation or surgery is androgen ablation (Pope et al., 2002; Lowrance et al., 2023). When androgen elimination is used to treat prostate cancer, nearly all patients respond. However, they eventually become resistant to the treatment, a concerning clinical condition for which there is currently no reliable cure (Miyamoto et al., 2005). Transgenic mouse models, such as the TRAMP model, are utilized in studying prostate cancer development and progression in humans. The progression of prostate cancer in TRAMP mice is quite similar to that of humans, starting with precancerous PIN lesions and progressing to aggressive prostate adenocarcinoma or neuroendocrine tumors before developing into metastatic cancer (Greenberg et al., 1995; Gray et al., 2009). This model provides a useful framework for examining the impact of treatment interventions across different phases of prostate cancer evolution. Androgen deprivation in castrated healthy mice has been found to leads to a short-term increase in B cells (Olsen & Kovacs, 2001; Santana-Sánchez et al., 2024). However, in mice with prostate cancer, the distribution and functions of B cells have not been examined. According to recent research, IL-7Rα might be a useful prognostic indicator for lung adenocarcinoma (LUAD) patients. By modulating tumor size via immune cell infiltration into the tumor microenvironment, IL-7Rα inhibits tumor cell proliferation. As a result, IL-7Rα might likewise be a potential LUAD treatment target (Wang et al., 2022 a,b).

The aim of the current study was to investigate the effects of androgen elimination on B cell development and distribution in an ADT-treated prostate cancer model. Wild-type and castrated TRAMP mice were used to characterize B-cell distribution in the spleen and bone marrow. Furthermore, we have measured IL-7 production in the circulation and IL-7R expression in bone marrow immature B cells. The results of the current study will shed light on the potential effects of androgen ablation on the control of B cell development and function as well as the role of IL-7-IL-7R pathway during ADT treatment in the prostate cancer mice model.

MATERIALS & METHODS

Animals

Jackson Laboratory (Bar Harbor, ME, USA) was the source of the TRAMP (C57BL/6-TRAMPxFVB) mice. Male TRAMP mice (9–15 per group) were used, initially aged 12–14 weeks (average weight of 30±1.9g), with most experiments conducted when mice reached 24–30 weeks. Animals were housed under controlled conditions (23–24°C, 40–55% humidity, 50–150 Lux light), with weekly food replacement and continuous cleaning availability (24h/7d). Mice were put unconscious by intraperitoneal administration of 40mg/kg sodium pentobarbital (Abbot Laboratories; Chicago, IL). Through a midline scrotal incision, surgical castration was carried out, providing bilateral access to the contents of the hemisphere. Each testicle was exposed, and the spermatic cord was tied off with a 3-0 Vicryl suture before the testicle was extracted.

Blood Collection and Serum Extraction

Blood was drawn from the submandibular vein in the face, placed in red-top serum tubes, and centrifuged for 10min at 1500 x g to separate the serum. Serum samples were stored at -20°C for further examination.

Spleen Removal and Splenocytes Isolation

The spleens of the mice were taken out and weighed after mice were put into unconsciousness by CO_2 asphyxia. Using 5mL of cold media (RPMI 1640 Medium, Life Technologies, Inc., Grand Island, NY), the spleens were homogenized on a cell culture plate filter. They were then kept on ice until the cells were tagged with antibodies for phenotypic analysis.

Isolation of Bone Marrow-Derived Immune Cells

Each animal's tibia and femur had its bone marrow cells removed using a syringe with a 26-gauge needle after the marrow cavity had been cleaned with Gibco RPMI 1640 medium (Thermo Fisher Scientific, Waltham, MA, USA). Tissues were either homogenized using a powdered glass homogenizer to produce single-cell suspensions. After centrifugation (350 x g for 10min), the cell suspensions were transferred to a 50mL conical tube, combined with 5mL of RBC lysis buffer (Cat#: 11814389001, Sigma-Aldrich, St. Louis, MO, USA), and left to stand for 3min at room temperature. Following two centrifugations with 15mL of RPMI 1640 medium at 350 x g for 5min, cells were suspended in RPMI 1640 medium and kept on ice until tagged with antibodies for phenotypic analysis by flow cytometry.

Cell Staining for FACS Analysis

Fluorochrome-conjugated antibodies, such as PE-Cyanine 7 anti-IgM and APC anti-B220 (Cat# SA-DA4 and RA3-6B2, respectively), which we acquired from eBiosciences (San Diego, CA, USA), along with FITC anti-CD127 from Pharmingen (Cat# 555288, San Diego, CA, USA), were used for flow cytometry analysis. To analyze the phenotypic of spleen/bone marrow cells, 1–5 x 10^5 cells were labeled through the incubation in FACS buffer (PBS, 0.1% sodium azide, and 1% heat-inactivated fetal bovine serum) containing ideal concentrations of labeling antibodies for 30min at 4°C. After staining, cells were washed a couple of times with FACS buffer (350 x g for 5min), followed by fixation with 3% paraformaldehyde for 30min. Ready-to-use 7-AAD (7-aminoactinomycin D) viability Staining Solution from eBiosciences (Cat# 00-6993, San Diego, CA, USA) was used to assess cell viability using flow cytometry analysis. Flow cytometry analysis was performed using the FACSCanto II Flow Cytometry instrument (Becton Dickinson and Co., Franklin Lakes, NJ, USA). Flow cytometry data were analyzed using FlowJo V7.5.5 (Tree Star, Inc., Ashland, OR, USA).

Androgen and IL-7 Quantification

The serum levels of androgen and IL-7 were quantified using a commercially available ELISA kit (Cat# NB-06-1068, Alpha Diagnostic International, San Antonio, Texas, USA) following the manufacturer's protocol.

Histological Examination

Spleen samples were fixed in 10% neutral buffered formalin, carefully washed, dehydrated in enhanced ethyl alcohol, clarified in xylene, embedded in paraffin wax, and sectioned. The blocks were sectioned (4-5µm) and stained with standard Harris hematoxylin and eosin (H&E) (Bancroft & Gamble, 2008).

Statistical Analysis

Differences of statistical significance ($P<0.05$) were detected using the two-tailed Student's t-test. Data were shown as mean±SD.

RESULTS

Castration Decreased Prostate Tumorigenesis and Improved Survival Rate

The majority of patients with early stages of prostate cancer respond well to ADT, which suppresses androgen functions (Best et al., 2005). Mice were castrated at twelve weeks of age to see if they mirrored this clinical presentation in humans. All uncastrated TRAMP mice (TRAMP-wt) developed prostate cancer by the time they were 6.5 months old. Prostate cancer, however, was seen in around half of the TRAMP-cas mice. There were apparent malignancies in two castrated mice, which ultimately caused their deaths. Although androgen deprivation before the development of prostate cancer can decrease the occurrence of this disease in male mice, the androgen-independent prostate cancer was observed in some cases. As a result, compared to wild-type TRAMP mice, TRAMP mice subjected to castration had a greater survival rate and lower levels of serum androgen (Fig. 1A and 1B). Therefore, we were able to reproduce the clinical scenario where androgen restriction therapy benefited patients with prostate cancer through the use of the TRAMP mice model.

Androgen ablation has been reported to reduce prostate cancer size (Grabowski et al., 2013). Subsequently, the anatomy of age-matched littermates (28 weeks) was compared to evaluate tumor volume. Compared to TRAMP-wt mice, TRAMP-Cas mice had significantly smaller prostatic tumors, as seen in Fig. 1C. TRAMP-Cas mice showed significantly lower weights of the genitourinary (GU) apparatus ($P<0.01$) and prostate tissue ($P<0.05$) than their TRAMP-wt counterparts (Fig. 1C, 1D).

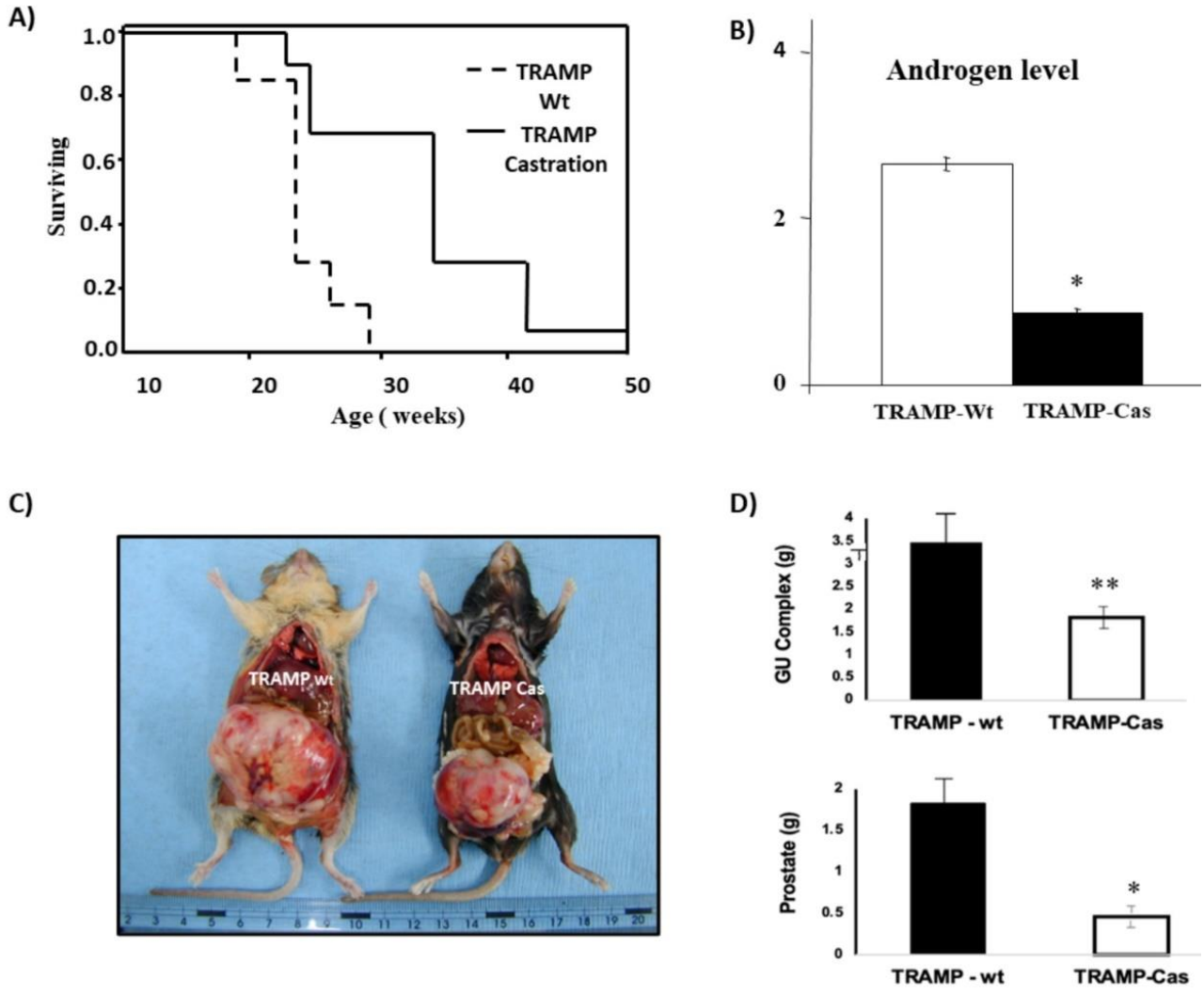

Fig. 1: Comparing TRAMP-cas with TRAMP-wt mice in terms of**:** a) Survival rate. b) The serum content of androgen. c) The growth of prostate tumors. d) The prostate and genitourinary (GU) weights. The data are shown as mean+SD. * and ** are $P<0.05$ and $P<0.01$, respectively.

Castration Enlarged the Spleen in TRAMP Mice

Gross and histological examinations of the spleen are shown in Fig. 2. The spleen in the TRAMP-wt mice had sharp, narrow borders and appeared reddish brown and thin in thickness, with an average diameter of 2.7 x 0.3cm. On the other hand, the TRAMP-cas mice exhibited splenomegaly, 2-3 times larger than the wild-type, with rounded borders, uneven thickness, dark brown in color, and approximately 4.1 x 1.0 cm in diameter (Fig. 2A). The spleen average size in the TRAMP-wt was significantly reduced ($P<0.01$) compared to the TRAPM-cas mice (Fig. 2B). As shown in Fig. 2C, the histological examination of the spleen in the TRAMP-wt mice revealed lymphoid follicles of white pulp interspersed with widened blood sinusoid of red pulp. In contrast, the spleen of TRAMP-cas revealed hyperplasia of lymphoid follicles of white pulp at the expense of red pulp, which appeared narrower and condensed. The hyperplastic lymphoid follicles appeared with eccentric arterioles and sometimes coalesced to form a larger mass of lymphoid tissue. Together, our results indicated changes in the Secondary Lymphoid Organs (spleen) following androgen ablation in TRAMP mice, leading to alterations in the immune system.

Castration Increases Splenic Immature and Mature B Cells

A flow Cytometric technique was used to determine the prevalence of B cells in the spleen of TRAMP-wt and TRAMP-Cas mice (Fig. 3A). Splenocytes were stained with antibodies specific to the B220 molecule, a marker for B cells. This allowed the identification of B cells ($B220^{+}$) and the discrimination between immature ($B220^{low}$) and mature ($B220^{high}$) B cell subpopulations. The B cells population within the spleen lymphocytes was significantly reduced ($P<0.01$) in the TRAMP-wt mice compared to their TRAMP-cas counterparts (Fig. 3B). The immature B cells papulation ($B220^{low}$) was significantly increased ($P<0.001$) in the TRAMP-cas mice compared to the TRAMP-wt mice (Fig. 3C). The mature B cells population ($B220^{high}$) were significantly elevated in the TRAMP-Cas mice ($P<0.01$) compared to the TRAMP-wt mice (Fig. 3D). These findings indicate that the formation of B cells may be directly impacted by androgen ablation, this could potentially impact B cell activity in secondary lymphoid tissues.

Castration Increases the Frequency of Immature B Cells in the Bone Marrow

Immune cells originate and develop in the bone marrow, a primary lymphoid organ. We used flow cytometry to examine the prevalence of B cell subpopulations in the bone marrow to gain a better understanding of the role that B cells play to extending the survival rate in TRAMP-cas mice (Fig. 4A). The mean percentage of B cells ($B220^{+}$) with the bone marrow isolated lymphocytes was significantly higher ($P<0.05$) in the TRAMP-cas mice compared to the TRAMP-wt counterparts (Fig. 4B). Within the B cell population, immature B cells ($B220^{low}$) were significantly elevated ($P<0.01$) in the TRAMP-cas group compared to the TRAMP-wt group. Mature B cells ($B220^{high}$) were slightly increased, though not significantly, in TRAMP-Cas mice compared to TRAMP-wt. mice. These findings imply that androgen ablation may directly and intrinsically affect B cell generation in the bone marrow, which may have an impact on B cell functions during prostate cancer. It suggests that androgen may play a dual function in TRAMP-wt mice, suppressing the B cell population and function as well as increasing prostate cancer proliferation.

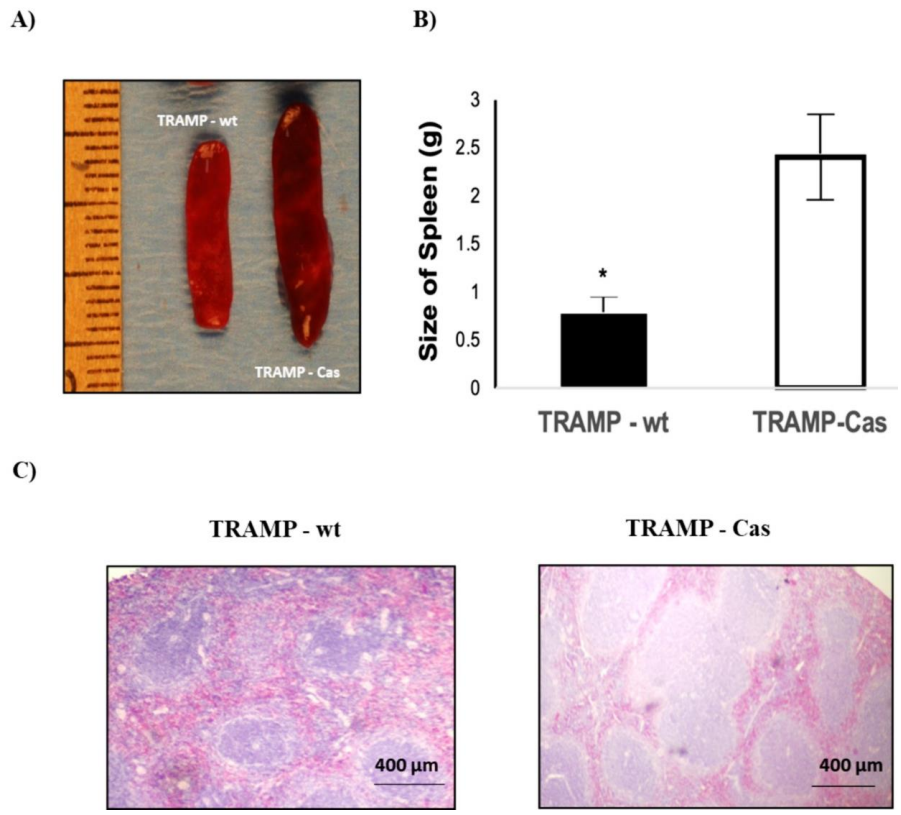

Fig. 2: Gross/histological examination of the spleen. a) Representative images of the spleens: the spleen in the TRAMP-wt mice had sharp, narrow borders and appeared reddish brown and thin in thickness, with an average diameter of 2.7 x 0.3 cm. On the other hand, the TRAMP-cas exhibited splenomegaly, 2-3 times larger than the wild-type, with rounded borders, uneven thickness, dark brown in color, and approximately 4.1 x 1.0 cm. b) The average size of the spleen in the TRAMP-wt and TRAPM-cas mice. Data are presented as mean+SD. *P<0.05. c) The spleen's microscopic appearance in TRAMP-wt mice showed enlarged blood sinusoids of red pulp scattered with lymphoid follicles of white pulp. The spleen of TRAMP-cas mice, on the other hand, showed hyperplasia of white pulp lymphoid follicles at the expense of red pulp, which seemed more condensed and narrower. The hyperplastic lymphoid follicles manifested as eccentric arterioles that occasionally merged to form a larger mass of lymphoid tissue.

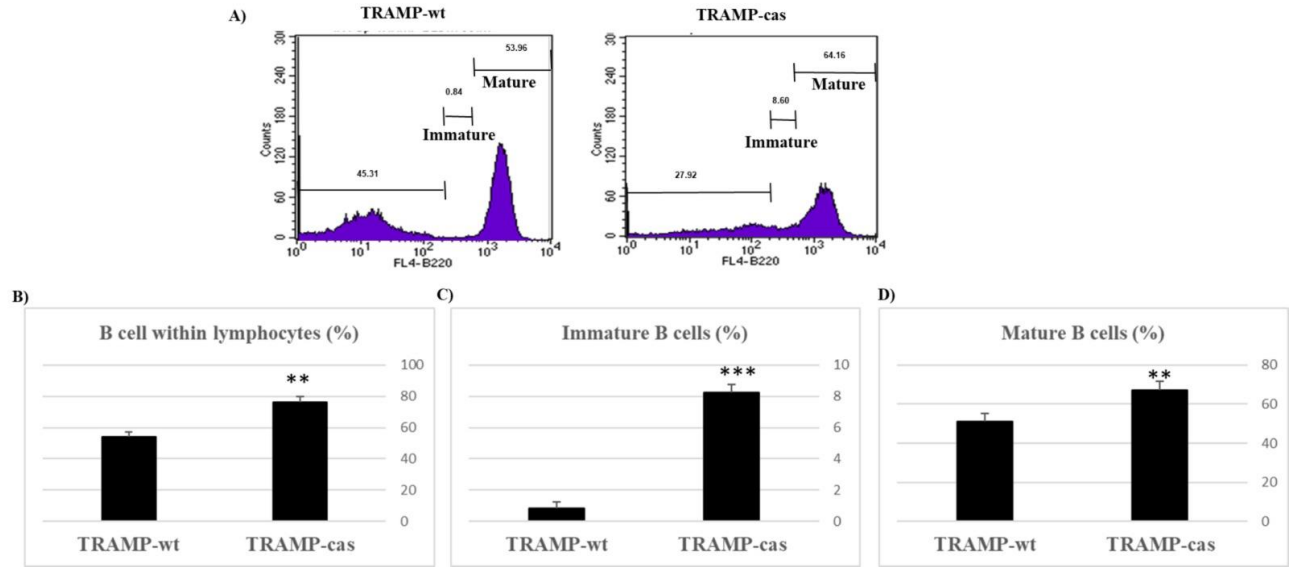

Fig. 3: B cells prevalence (percentages) in the spleen of TRAMP-wt and TRAMP-cas mice. a) Flow Cytometry measurement of the frequency of splenic B cells subpopulations ($B220^{+}$) illustrating immature B cells ($B220^{low}$) mature B cells ($B220^{high}$) TRAMP-wt and TRAMP-cas mice. b) The mean percentage of total B cells ($B220^{+}$). c) The percentages of immature B cells ($B220^{low}$). d) The mean percentage of mature B cells ($B220^{hig}$). Data are presented as mean+SD. **P<0.01 and ***P<0.001.

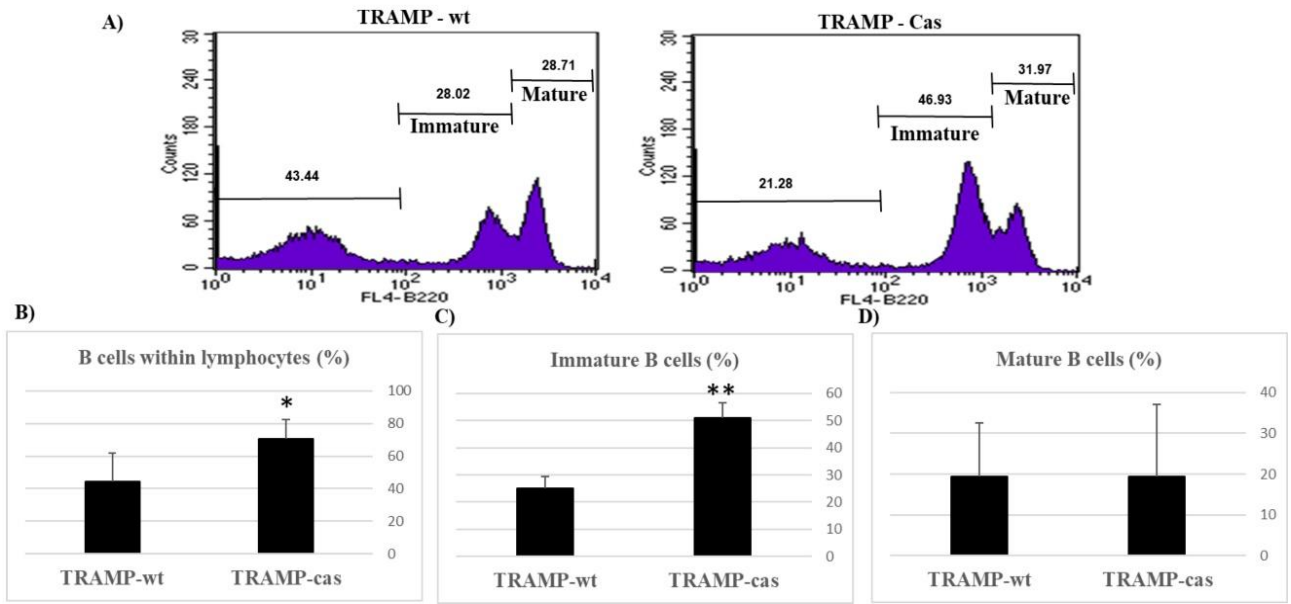

Fig. 4: B cells distribution (percentages) in the bone marrow of TRAMP-wt and TRAMP-cas mice. a) Flow Cytometry analysis of the distribution of B cells subpopulations ($B220^{+}$) within bone marrow isolated lymphocytes illustrating immature B cells ($B220^{low}$) mature B cells ($B220^{high}$) TRAMP-wt and TRAMP-cas mice. b) The mean percentage of total B cells ($B220^{+}$). c) The percentages of immature B cells ($B220^{low}$). d) The mean percentage of mature B cells ($B220^{high}$). Data are presented as mean+SD. *P<0.05 and **P<0.01.

Next, we examined the viability (apoptosis rate) of immature B cells via 7-AAD staining, a marker for apoptosis. Fig. 5A shows representative flow cytometry blots of immature B cells ($B220^{low}$) stained with 7-AAD. As shown in Fig. 5B, there was a notable reduction in bone marrow-derived viable immature B cells ($B220^{low}$ $7AAD^{-}$) in TRAMP-wt mice as compared to the TRAMP-cas mice. The mean value of viable immature B cells in the TRAMP-wt mice was 50.2% compared to the mean value of viable immature B cells in the TRAMP-cas, which was 74.16%. This data indicated the direct effects of androgen on the immature B cells (B cell development stage) in the bone marrow of a prostate cancer model (TRAMP mice). Further studies are necessary to elucidate the role of androgens in the signaling pathways involved in B-cell development and function.

Androgen Ablation Alters the IL-7R/IL-7 Pathway in Prostate Cancer

IL-7 is a crucial cytokine for both T cells and B cells development (Wang et al., 2022a; Wang et al., 2022b). We hypothesized that androgen may impacts B cells development and functions in prostate by suppressing the IL-7/IL7-R signal pathway. As shown in Fig. 6A, flow cytometry analysis shows that the percentage of immature B cells (B220low IgM-) expressing the CD127 marker (IL-7Rα) was higher in TRAMP-Cas compared to their wild-type counterparts (21.03 and 11.6%, respectively).

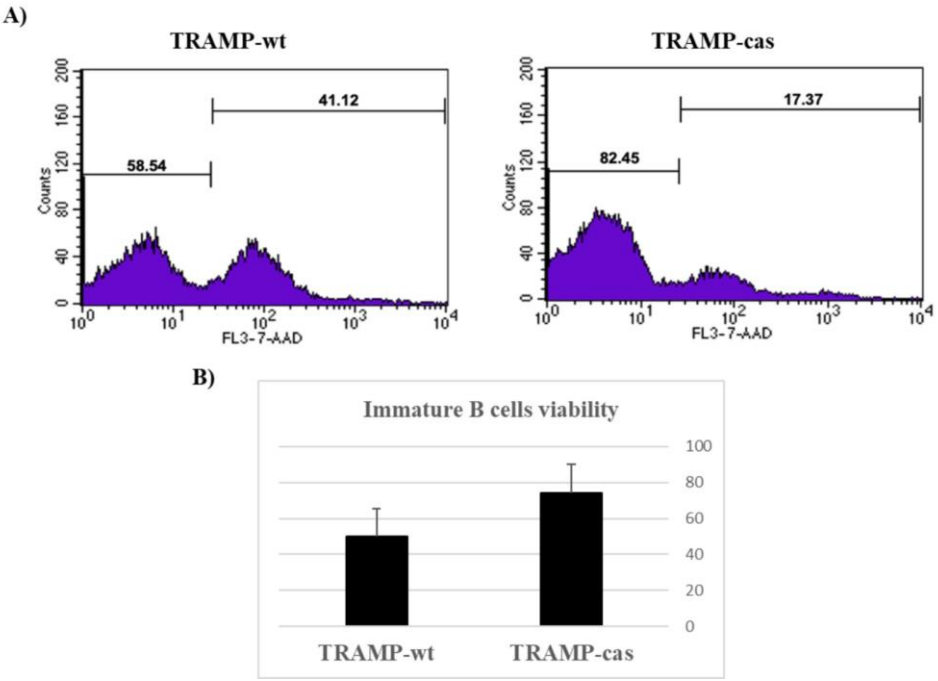

Fig. 5: Viability of the bone marrow isolated immature B cells. a) Flow Cytometric analysis of immature B cells ($B220^{low}$) stained with 7-AAD. b) The mean of viable B cells within the bone marrow-derived immature B cell subpopulation. Data are presented as Mean±SD.

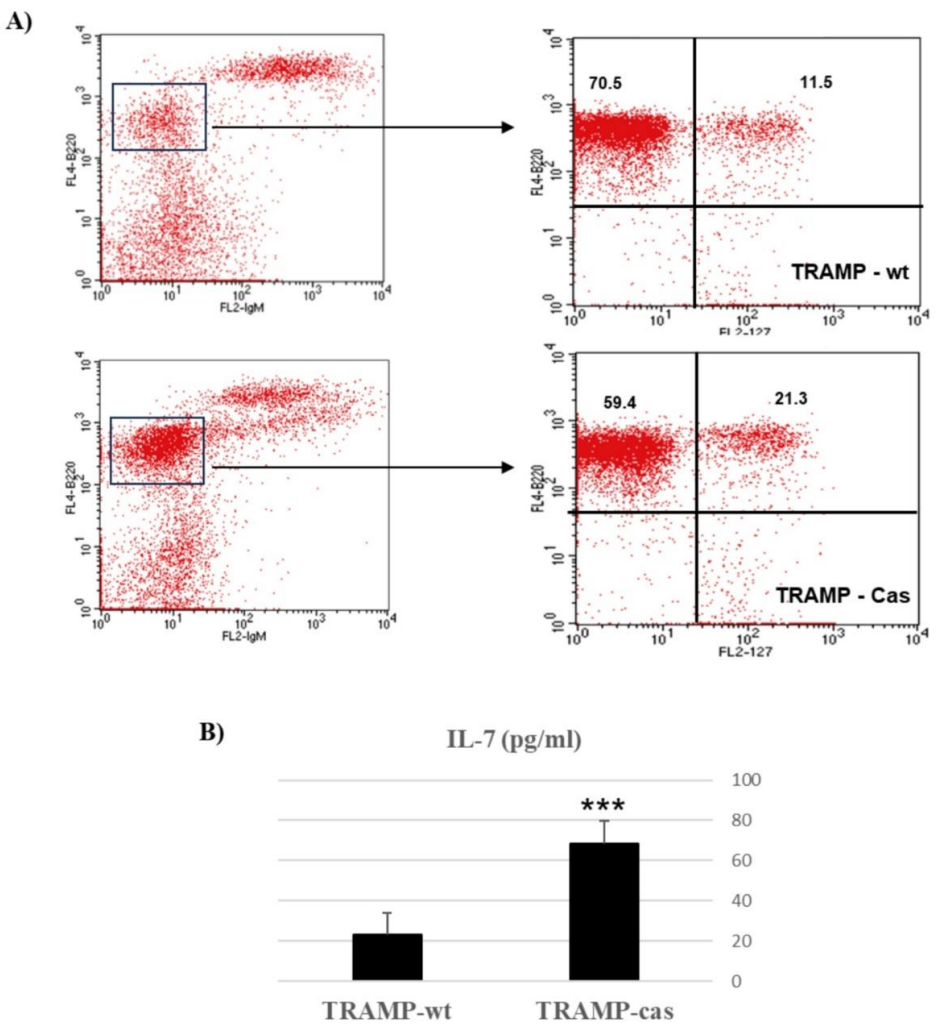

Fig. 6: Androgen ablation impacts on the IL-7R/IL-7 pathway. a) Flow cytometric analysis showing the percentages of bone marrow-derived immature B cells ($B220^{low}$ IgM^{-}) expressing IL-7R (CD127). **b)** Histogram showing the mean value of IL-7 concentrations in the sera of wild-type and castrated TRAMP mice. Data are presented as Mean+SD. ***P<0.001.

To further investigate the role of immune signaling in androgen ablation, we measured interleukin-7 (IL-7) levels in the sera of TRAMP-Cas and TRAMP-wt mice. As depicted in Fig. 6B, the IL-7 levels were approximately two-fold higher in TRAMP-Cas mice compared to TRAMP-wt mice (P<0.001). This elevation suggests a significant impact of androgen deprivation on the IL-7 signaling pathway, potentially influencing immune responses and B cell development in the prostate cancer model used in the current study.

DISCUSSION

Most prostate cancers are treated primarily with androgen deprivation therapy (ADT), which, in the current investigation, increased the survival rate of TRAMP-cas mice. Using the TRAMP-wt mice as a model, we have examined the morphology and sizes of the spleen, genitourinary (GU) organs, and the prostate, as well as B cell distribution and function in the spleen and bone marrow following androgen ablation through castration (TRAMP-Cas). We observed increased spleen size and significant decreases in prostate and GU weight in TRAMP-Cas mice compared to TRAMP-wt mice. Our findings are in agreement with human prostate cancer results during androgen deprivation therapy (ADT) (Bosch et al., 1989; Grabowski et al., 2013). Female sex hormones, such as androgens, have been linked to many autoimmune disorders and have been shown to have immune-regulatory properties (Jacobson et al., 1997; Whitacre, 2001; Lai et al., 2012; Sciarra et al., 2023; Altuwaijri & Albarrak, 2025). The discovery that male rheumatoid arthritis patients exhibit a reduced amount of androgens lines up with the causative connection between sex hormones and vulnerability to autoimmunity (Altuwaijri et al., 2009). Rheumatoid arthritis was shown to be more common among men with prostate cancer receiving androgen-deprivation treatment (Rittirsch et al., 2008).

The increase in B cells has been associated with several autoimmune disorders and malignancies. In the current investigation, we have demonstrated significant increases in B cell prevalence in peripheral lymphoid organs (spleen) of castrated TRAMP mice as compared to the non-castrated TRAMP mice. Androgen deprivation has led to significant increases in both immature and mature B cells in splenocytes from TRAMP-cas mice. Moreover, increases in the B cell population in primary lymphoid organs (bone marrow) were noted in TRAMP-Cas mice compared to the TRAMP-wt mice. Notably, we observed a significant increase in the bone marrow-derived immature B cell subpopulation in TRAMP-cas mice. This phenomenon may be attributed to apoptosis resistance during B-cell maturation. Together, these observations align with previous reports indicating that androgen deprivation therapy increases B-cell lymphopoiesis (Aragon-Ching et al., 2007; Morse & McNeel, 2010; Sasagawa et al., 2023). A previous study by Altuwaijri et al. (2009) has reported B cell resistance to apoptosis and vulnerability to autoimmunity in androgen receptor knockout mice. It would be intriguing for researchers to determine whether TRAMP-cas mice are more susceptible to autoimmune disorders such as rheumatoid arthritis. Men with prostate cancer who underwent androgen deprivation therapy acquired rheumatoid arthritis at greater rates (Pope et al., 2002). On the other hand, testosterone replacement treatment decreased IgM rheumatoid factor levels and improved clinical indicators in hypogonadal males with rheumatoid arthritis.

Previous studies have indicated that IL-7Rα may serve as a valuable predictive indicator for lung adenocarcinoma (LUAD) (Wang et al., 2022b). By promoting immune cell infiltration into the tumor microenvironment, IL-7Rα reduces tumor volume and suppresses tumor cell proliferation. Therefore, IL-7Rα might be a potential LUAD treatment target (Wang et al., 2022a). Sipuleucel-T (Sip-T) is the sole immunotherapy for metastatic castration-resistant prostate cancer that has received FDA approval. Sip-T is an autologous cellular immunotherapy used to treat certain men with advanced prostate cancer (Wang et al., 2022a). IL-7 significantly influences T and B lymphocyte development, proliferation, and differentiation by activating its receptor (IL-7R). IL-7 has been utilized in cancer clinical research and treatment and is strongly linked to tumor formation (Wang et al., 2022b; Hudson et al., 2025; Zeng et al., 2025). In this study, we observed higher IL-7R expression in bone marrow-derived immature B cells and increased IL-7 levels in the sera of the TRAMP-Cas mice compared to the TRAMP-wt mice. These observations highlight the vital role of the IL-7R/IL-7 signaling pathway in regulating immune cell activation and strengthening the body's defense against prostate cancer during ADT treatment. Our data suggest that IL-7R/IL-7 cascades show great promise, especially during the ADT period, a phase that offers an opportune window for prostate cancer intervention. Given that IL-7 enhances stimulation of T cells, and joint degradation in autoimmune models, the application of IL-7 in people necessitates thorough assessment (Krawczenko et al., 2005; Mackall et al., 2011; Meyer et al., 2022; Zeng et al., 2025).

Conclusion

In summary, the data of the current study demonstrated significant increases in B cell distribution in primary and secondary lymphoid organs of castrated TRAMP mice. The elevated proportions of immature B cells in the bone marrow of TRAMP-cas mice may result from their insensitivity to apoptotic deletion during B cell development. This observation is limited by the possibility that boosting immature B cells might not be the best way to promote B cell activities in the fight against prostate cancer. Another drawback is that by secreting TGF-beta and IL-10, B cells may inhibit T cell activity (B-rag). Our findings support the assertion that androgen functions as an inhibitor of IL-7/IL-7R signaling, impacting B cell development and function, particularly in the context of prostate cancer models. Our data suggest that the IL-7/IL-7R cascades may represent a potential immunotherapy for prostate cancer during ADT. A potential downside is that individuals could get autoimmune diseases like Rheumatoid Arthritis, which has been connected to elevated levels of IL-7. Further studies are necessary to confirm the direct mechanisms through which androgen modulates this pathway.

DECLARATIONS

Funding: This research was funded by Pharm Research MD. Co. LTD (Novotel Business Park, Al Khobar-Dammam Highway, Dammam 31413, Kingdom of Saudi Arabia).

Acknowledgement: The Researchers would like to thank

the Deanship of Graduate Studies and Scientific Research at Qassim University for financial support (QU-APC-2025).

Conflict of Interest: There is no conflict of interest to declare.

Data Availability: All the data is available in the article.

Ethics Statement: The animal model and animal handling practices were approved by the Institutional Animal Care and Use Committee at the University of Rochester Medical Center in Rochester (New York, USA) and previously published.

Author's Contribution: Experimental design and execution were done by SAT. SAB and SAT analyzed the data and wrote the manuscript. After reviewing the final draft, both authors approved it.

Generative AI Statement: The authors declare that no Gen AI/DeepSeek was used in the writing/creation of this manuscript.

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