Int. J. Morphol.,
41(5):1558-1563, 2023.

Humoral and Cellular Immunology in Human Prostate Cancer: Plasma Cells and T and B Lymphocytes

Inmunología Humoral y Celular en el Cáncer de Próstata Humano: Células Plasmáticas y Linfocitos T y B

Rodríguez Héctor[1]; Rodríguez Nicolás[2]; Gallegos Iván[3]; Arriaza Camilo[4] & Espinoza-Navarro, Omar[5]

RODRÍGUEZ, H.; RODRÍGUEZ, N.; GALLEGOS, I.; ARRIAZA, C. & ESPINOZA-NAVARRO, O. Humoral and cellular immunology in human prostate cancer: Plasma cells and t and b lymphocytes *Int. J. Morphol., 41(5)*:1558-11563, 2023.

SUMMARY: In solid and malignant tumors, innate and adaptive immunity are combined in antitumor responses. This study aimed to analyze the activation of plasma cells and the correlation between the infiltration of B and T lymphocytes with the degree of malignancy or Gleason grade in human prostate biopsies diagnosed with cancer. Prostate cancer biopsies were obtained from the Clinical Hospital of Universidad de Chile (n=70), according to the bioethical norms of the institution. Histological sections of 5µm thickness were processed for immunohistochemistry with primary antibodies against BL and total TL (HRP/DAB). Recognition and quantification were performed under a Leica DM750 optical microscope. Microsoft Excel and GraphPad software were used for the statistical study. Correlation coefficient (Pearson) and mean comparison tests (Kruskal-Wallis and Dunn) and $p \leq 0.05$ were developed. B and T lymphocyte populations were inversely interregulated in prostate cancer (Gleason) (r= -0.46). Their relationship with Gleason grade is variable according to lymphocyte type (LB vs. Gleason r= -0.0.47 and LT vs. Gleason r= -0.21). Histological diagnosis of prostate cancer correlates with a predominance of LT. The malignancy of the pathology correlates with a predominance of LTs, according to the Gleason grade. The increased knowledge of B and T lymphocyte infiltration and plasma cell activation could be used to better target clinical trials on treatments based on immune system responses. Immunotherapy could be a new paradigm to apply better antitumor therapy strategies.

KEY WORDS: Prostate Cancer; Immunomodulation; Plasma Cells; Lymphocytes; Human.

INTRODUCTION

The prostate is one of the most prominent exocrine glands in the body, both in humans and in the rest of mammals; its morphology varies widely between species concerning the development of the branching of the excretory ducts along with the close epithelium/mesenchyme relationship. The regulation of gene expression and switch-off constitutes a vital tool in the characterization and interpretation of organ pathologies that can be affected by environmental and endogenous factors causing loss of homeostasis (Timms, 2008).

The morphogenesis and initiation of branching of the prostate gland ducts are regulated by androgens (receptor/ligand), regulating their extension and function through paracrine signals (Pletcher & Shibata, 2022). Additionally, several growth factors families, such as FGF, SHH, TGF-b, and homeobox transcription factors, are involved. Prostate development and branching are generally regulated by endocrine signals: local cell-cell interactions (juxtacrine, autocrine, paracrine, and endocrine) via specific gene signals.

Plasma cells are the expression of the terminal differentiation of lymphocytes to generate humoral immune protection from the secondary lymphoid tissue and thus maintain adequate or sufficient antibody levels. They can also develop cosmopolitan behaviors and travel from the blood to tissues and vice versa by linking IgG synthesis and secretion with cytokines and interleukins. Recent research

[1] Laboratorio de Histología, Facultad de Medicina, Universidad de Chile, Santiago, Chile.
[2] Laboratorio de Morfología, ICBM, Facultad de Medicina, Universidad de Chile, Universidad de Buenos Aires, Argentina.
[3] Departamento de Anatomía Patológica, Hospital Clínico Docente de la Universidad de Chile, Facultad de Medicina, Universidad de Chile, Santiago, Chile.
[4] Laboratorio de Morfología, ICBM, Facultad de Medicina, Universidad de Chile, Santiago, Chile.
[5] Departamento de Biología, Universidad de Tarapacá, Arica, Chile.
This study was sponsored by project UTA Mayor Nº 4726-22, Universidad de Tarapacá, Arica-Chile.

Received: 2023-06-07 Accepted: 2023-07-29

suggests the involvement of immune cells in the initiation, progression, metastasis, and treatment of prostate cancer (Weiner *et al*., 2021, Wang *et al*., 2022).

Innate and adaptive immunity in solid and malignant prostate tumors, where anti-tumor responses are combined, are currently being discussed. In prostate cancer, there is evidence of the participation of B and T lymphocytes (CD4+, CD8+, and Treg). The phenotype of these cells could be associated with the etiological role of chronic inflammatory states. Immunotherapy is a new approach to potentially treating prostate cancer (Vitkin *et al*., 2019; Saudi *et al*., 2023).

Many factors have been mentioned in the development of prostate cancer: genetic, environmental, and others (De Marzo *et al*., 2007). However, age is one of the most determining factors, with treatment even varying according to the stage of progression and degree of the disease and the patient's age. Moreover, the degree of cancer progression is defined according to histological morphometric analysis (biopsy), where the degree of tissue differentiation is estimated (Manaia *et al*., 2012; Pin *et al*., 2013; Rodríguez *et al*., 2020).

Aging is a complex process characterized by immunosenescence and the installation of chronic inflammatory processes that has a considerable adverse effect on the remodeling or differentiation of B lymphocytes of the immune system that reduces the production of immunoglobulins and increases the number of B cell clones in tissues. Therefore, studying B cells in older people is a crucial tool for monitoring immunosenescence and some chronic diseases (McEllistrim *et al*., 2017). Sfanos & De Marzo (2012), report that chronic inflammation is the enabling basis for several types of human cancer.

MATERIAL AND METHOD

Samples were collected from the Barros Luco Trudeau Hospital (2004 to 2012) and José Joaquín Aguirre Hospital (2005 to 2009). Twenty-seven biopsies were obtained from these respective databanks that were respectively anonymized. The samples with confirmed prostate cancer were formalin-fixed and paraffin-embedded for histological analysis (Gleason score).

Information on age (range 40 to 73 years) and diagnosis of prostate cancer with its minor, major, and total Gleason evaluations were obtained from the database for each patient. Previously, the samples had been fixed in 10 % formalin buffered in saline-phosphate solution pH 7.2, maintained for a minimum period of 48 hours. Subsequently, the samples were processed by routine histological techniques using Histosec of melting point between 56 and 58° Celsius. Sections of 5 µm thickness were obtained and placed on high-adherence slides. Subsequently, the slides were subjected to histological techniques of current Hematoxylin and Eosin (H&E) staining for the evaluation of plasmacytes; other sections were placed on electronically xylate slides for the development of specific immunohistochemical techniques for the recognition of total B lymphocytes (Bio SB-BSB 5193 CD20) and T lymphocytes (Bio SB-BSB 6425 CD3), using the HRP/DAB system and nuclear contrast with Hematoxylin. Finally, the samples were mounted with synthetic Canada balsam (Eukit) and were observed and quantified under the optical microscope.

Recognition, quantification and analysis. Identification of plasma cells and B and T lymphocytes in the prostate stroma was made through their typical characteristics: Plasma cells as cells of regular size with a single, central, round nucleus, chromatin organized in single centrally arranged single central and multiple peripheral heterochromatin clusters in a "cartwheel" fashion (classical histology) and displaced towards one end in a kite-like fashion, with a strongly acidophilic and abundant cytoplasm; while the lymphocytes are recognizable by the intense brown color precipitate of the immunohistochemistry technique that is observed as round cells with a central nucleus and basophilic, with cytoplasm stained intensely brown. Both cell types are distributed in the stromal connective tissue of the gland. All observations were made with a 40x objective (a diameter of 0.17 mm2).

Quantifications of 100 fields per biopsy and per patient (individual average) were performed, from which the mean was obtained and tabulated along with the other variables considered: age and Gleason grades.

Statistical Analysis. Kolmogorov-Smirnov procedures analyzed cellular variables, plasma cells, and B and T lymphocytes to determine whether they corresponded normally or non-normally distributed variables. Afterward, the correlation type relationship analysis was performed using Pearson and Spearman coefficients, always considering $p \leq 0.05$ and $p \leq 0.01$. A multiple correlation study was developed for all the variables considered under the same mathematical conditions. The results are presented in microphotographs, bar graphs, and table.

Ethics and Informed Consent: The use and access to biopsies was authorized by the Department of Pathology of the Clinical Hospital of the University of Chile, with clinical information on age and Gleason grade. The group of researchers did not have direct access to the patients' clinical records.

RESULTS

The results are expressed in microphotographs and statistical analysis of prostate biopsies from patients with confirmed cancer versus healthy people without prostate cancer.

Figure 1A shows the normal histology in tissue composition and organization of the prostate gland. Glandular parenchyma is formed by glandular alveoli lined by a pseudostratified epithelium of variable height. Subsequently, the stroma is formed by abundant smooth muscle fibers (strongly acidophilic, red color) and connective tissue (soft red). The typical mesothelium consists of a simple flat epithelium, accompanied by the glandular capsule of connective tissue of variable density and irregularly organized. Strongly acidophilic saline concretions (intense red) are also observed inside the glandular alveoli.

Figure 1B shows the composition and organization of the prostate gland wall, mainly consisting of abundant smooth muscle fibers and scant stromal connective tissue. There are multiple and repetitive perpendicular bidirectional and repetitive bidirectional smooth muscle fibers in longitudinal and transverse directions.

Figure 2 shows a Prostate biopsy with a confirmed cancer diagnosis where many plasmacytes can be observed (arrows). The plasma cells have a typical comet shape: a laterally displaced nucleus with cartwheel chromatin (single central clusters and multiple clusters towards the periphery) and an abundant and strongly acidophilic cytoplasm.

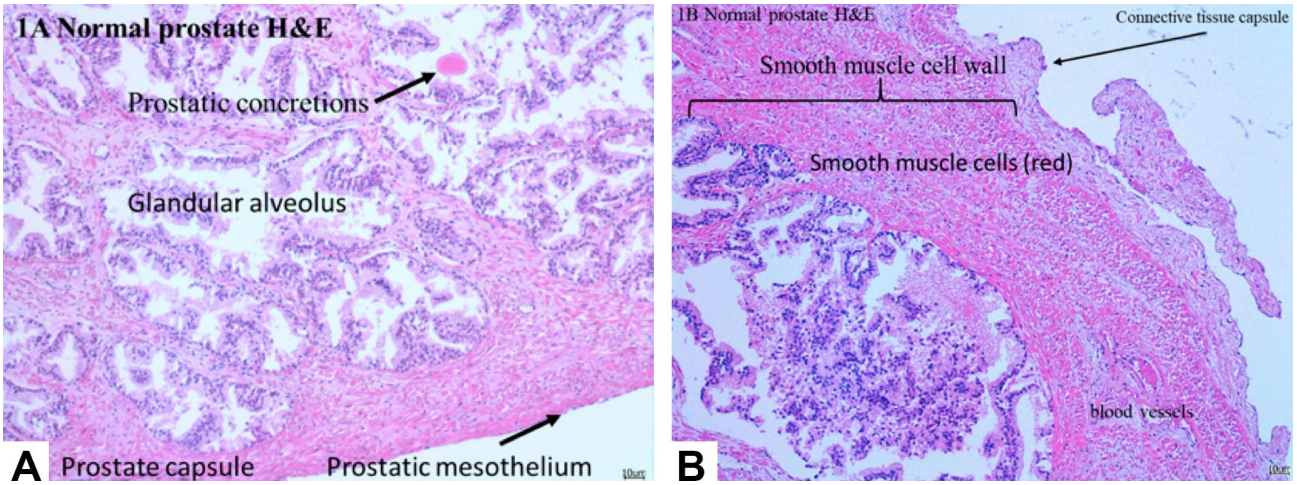

Fig. 1 (A and B). Figure A and B correspond to microphotographs of normal prostate biopsies. The histological composition of the capsule, stroma, and parenchyma (hematoxylin and Eosin stain) can be observed.

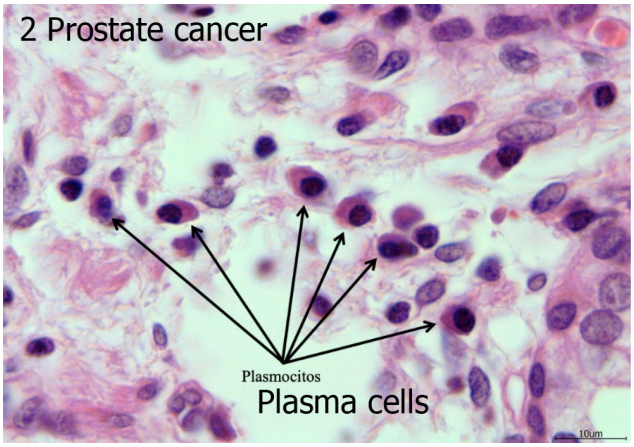

Fig. 2. Photomicrograph of prostate biopsy with a confirmed cancer diagnosis. Presence of plasma cells, with nuclei comet-shaped (arrows). Hematoxylin/ Eosin staining.

Figures 3A and 3B show prostate cancer biopsies treated with immunocytochemistry technique with specific monoclonal antibodies, detecting the presence of positive lymphocytes B and positive lymphocytes T. The arrows indicate each type of lymphocyte distributed in the stroma of the gland: recognized cells positive to the immunocytochemistry reaction are observed with a rounded basophilic nucleus and a scarce cytoplasm of intense brown color.

Figure 4. Bar graph representing B and T lymphocytes concentration variables in Patients with a Diagnosis of Prostatic Cancer. Both populations of immune cells are present in the prostate with a diagnosis of prostate cancer. Quantitatively, a more significant number of T lymphocytes stands out, although this does not necessarily mean that they have more importance in the pathological picture of the diagnosis. Essentially, the high concentrations of general and

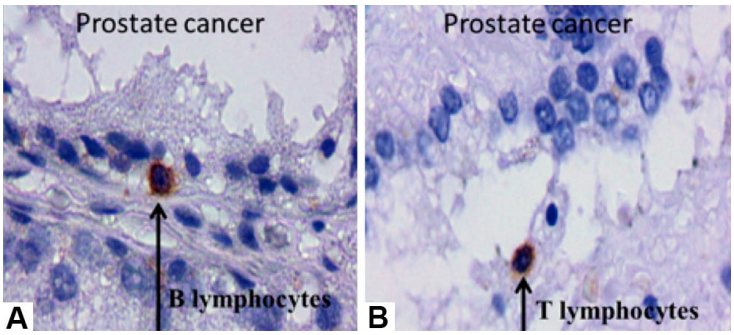

Fig. 3. A and B. Prostate cancer biopsies treated with immunocytochemistry technique with specific monoclonal antibodies. Presence of positive lymphocytes B and positive lymphocytes T.

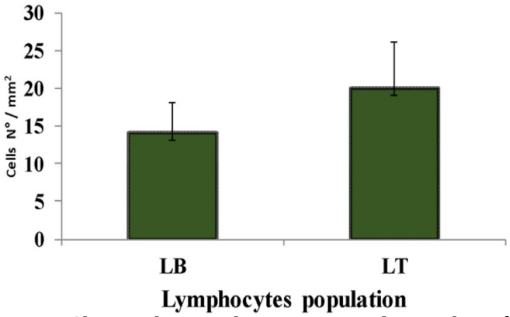

Fig. 4. Shows a bar graph representing the number of cells (B lymphocytes or T lymphocytes) per area (mm2) of prostate tissue in prostate biopsies with a diagnosis of cancer (Mean ± standard deviation).

differentiated B lymphocytes to plasmacytes and T lymphocytes (cellular immunity) means that the inflammatory process and the immune response are relevant factors in the installation and progression of cancer in the human prostate.

Table I shows the correlation study (Spearman's r) between relevant variables. The Kolmogorov-Smirnov and Shapiro-Wilk statistics test determine that the variables considered have a non-normal distribution. The correlations calculation shows that there is a negative correlation between the concentration of B lymphocytes per area and the Gleason value, which would indicate that the concentration or presence of B lymphocytes in the prostate with a cancer diagnosis is inversely related to the malignancy of the cancer ($r= -0.468^*$) ($p<0.05$). The statistical relationship between the concentrations of B and T lymphocytes yields a statistically significant positive correlation coefficient (0.368^{**}) ($p<0.01$), indicating that in the inflammatory picture installed in the prostate with a diagnosis of cancer, B and T lymphocytes are present in a positively interdependent manner. Additionally, both lymphocytes have a negative and low correlation regarding age, i.e., the older the age, the lower the migration capacity and presence of B and T lymphocytes to the cancer site (r=-0.273 and -0.040, respectively) being more relevant and reduced the migration of B lymphocytes.

Table I. Represents the correlation analysis (Rho of Spearman, r) between the variables considered in this study: Age of the patients, Gleason Index Grade obtained from the histopathological analysis of prostate biopsies, concentration per area of B lymphocytes and T lymphocytes shown utilizing specific immunocytochemistry for each of them.

		Correlation Coefficients			
Correlation Test	Variables	BL	TL	Age	Gleason index
Rho of Spearman (r)	LB	1,000	0,368**	-0,273	-0,468*
	LT	0,368**	1,000	-0,040	-0,214
	Age	-0,273	-0,040	1,000	0,185*
	Gleason	-0,468*	-0,214	0,185*	1,000

* p≤ 0.05; ** p≤ 0.01

DISCUSSION

The tissue dynamics of the prostate range from proliferative basal epithelial cells to luminal secretory cells, organized in a glandular epithelium embedded in a relevant fibromuscular stroma forming the stroma of the gland, histologically, the epithelium is composed of two different cell sheets: 1) luminal secretory sheet of tall columnar cells responsible for the production and secretion of PSA (prostate-specific antigen), Kalikrein-2 and PAP (prostatic acid phosphatase) and 2) basal lamina that it is supported by a layer of cuboidal basal epithelial that separates them from the glandular stroma (Figs. 1A and 1B). The basal lamina, or matrix, provides mechanical support and acts as a barrier (Zhang *et al*., 2018).

Additionally, biochemical and physical dynamic signals are elements integrated into cellular behavior and tissue function, whose alterations participate in the development of prostatic disease, generating an imbalance between synthesis and degradation, leading to disease, injury, and aging (Rodríguez *et al*., 2020).

In the prostate gland, at least two tissues develop and present a delicate basal lamina, whose components are permanent targets of an autoimmune attack and whose epitopes are related to autoantibodies and T lymphocytes. Genetic and environmental factors are involved in this response (Foster, 2017).

Several hypotheses are put forward regarding the origin of prostate pathologies; however, a very preponderant factor would be aging, which would cause changes in prostatic androgen metabolism, with an abnormal accumulation of dihydrotestosterone, expressing an enlarged prostate; changes in epithelial-stromal interaction, with an inductive effect on prostatic growth and finally causing an increase in the total number of prostatic stem cells and an increase in clonal expansion of stem cells (Fig. 2) (Banerjee *et al*., 2018).

Aging is a complex process that significantly affects the remodeling or differentiation of B lymphocytes in the immune system, with a decrease in the production of immunoglobulins and an increase in the number of B cell clones in the tissues (Frasca & Blomberg, 2011). Once B lymphocytes have differentiated, they become sensitive to regulation by mitochondrial metabolic states (differential mitochondrial modulation), with a metabolism similar to T lymphocytes regarding the glycolysis and oxidative phosphorylation pathways.

Studying B cells could be crucial for monitoring immunosenescence and some chronic diseases (McEllistrim *et al*., 2017). A proper understanding of the metabolic requirements of differentiated B cell lines could be helpful for the development of new therapeutic strategies (Sandoval *et al*., 2018; Saudi *et al*., 2023).

Schweighoffer & Tybulewicz (2018), determined that the number of mature lymphocytes is tightly controlled via cell survival membrane receptors. It is suggested that in prostate cancer onset, progression, and metastasis processes, the involvement of adaptive or innate infiltrating immune cells are determinant (Wang *et al*., 2018). The deformation of the tissue matrix by the action of cells, expected or not, affects the behavior of participating and neighboring cells and induces intracellular biochemical changes with downstream effects on the basal lamina's composition, structure, and function (Miller, 2017) (Figs. 3, 4 and Table I).

Knowledge about heterotypic interactions involving cancer cells and local host cells, along with variations in the tumor microenvironment (epigenetics), will enable the design of optimal therapeutic strategies and possible cures for advanced disease to attain the optimal care approaches for a given patient (Wang *et al*., 2022).

Specifically, prostate cancer secretes the TGF-B marker, which inhibits immunity and facilitates cancer progression. Blocking TGF-B signaling in T cells would enhance their ability to infiltrate, proliferate and mediate an antitumor response. Co expression of dominant negative TGF-BRII expresses increased proliferation, cytokine secretion, and long-term in vivo activity that would induce experimental tumor eradication (Kloss *et al*., 2018; Thompson-Elliott *et al*., 2021; Narayan *et al*., 2022).

The histopathological evaluation of many conditions may be prone to variation among pathologists, leading to a continuous search for biomolecular markers and other helpful variables in support of a more accurate and optimal diagnosis (Young *et al*., 2021). Additionally, new immunological molecular classifiers that indicate a close relationship with clinical prognosis have been identified, providing new immunotherapeutic strategies in patients with prostate cancer (Meng *et al*., 2021; Weiner *et al*., 2023).

CONCLUSIONS

Finally, it is concluded that B and T lymphocyte populations are inversely associated and inter-regulated in prostate cancer (r= -0.4578). Simultaneously, their relationship with the Gleason grade is variable according to the type of lymphocyte (LB vs. Gleason r= -0.9198 and LT vs. Gleason r= 0.09256). Histological diagnosis of prostate cancer correlates with a predominance of LT, and the malignancy of the pathology correlates with LB predominance, according to the Gleason grade. The increased knowledge of B and T lymphocyte infiltration and plasma cell activation could be used to better target clinical trials on treatments based on immune system responses. Immunotherapy could be a new paradigm to apply better antitumor therapy strategies

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RESUMEN: En tumores sólidos y malignos, la inmunidad innata y adaptativa se combinan en respuestas antitumorales. Este estudio tuvo como objetivo analizar la activación de células plasmáticas y la correlación entre la infiltración de linfocitos B y T con el grado de malignidad o grado de Gleason en biopsias de próstata humana diagnosticadas con cáncer. Las biopsias de cáncer de próstata se obtuvieron del Hospital Clínico de la Universidad de Chile (n=70), de acuerdo con las normas bioéticas de la institución. Secciones histológicas de 5 µm de espesor fueron procesadas para inmunohistoquímica con anticuerpos primarios contra LB y LT total (HRP/DAB). El reconocimiento y las cuantificaciones se realizaron bajo un microscopio óptico Leica DM750. Para el estudio estadístico se utilizaron los programas Microsoft Excel y GraphPad. Se desarrollaron pruebas de coefi-

ciente de correlación (Pearson) y comparación de medias (Kruskal-Wallis y Dunn) y p≤ 0.05. Los resultados muestran que las poblaciones de linfocitos B y T están inversamente interreguladas en el cáncer de próstata (r= -0,4578). Su relación con el grado de Gleason es variable según el tipo de linfocito (LB *vs* Gleason r= -0,47* y LT *vs* Gleason r= -0,21). Se concluye que la malignidad del cáncer de próstata se correlaciona con un predominio de LT, versus el grado de Gleason. El mayor conocimiento de la infiltración de linfocitos B y T y la activación de células plasmáticas podría aprovecharse para una mejor orientación de ensayos clínicos en tratamientos basados en las respuestas del sistema inmunitario. La inmunoterapia podría ser un nuevo paradigma para aplicar mejores estrategias de terapias antitumorales.

PALABRAS CLAVE: Cáncer Prostático; Inmunomodulación; Células Plasmáticas; Linfocitos; Humanos.

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Corresponding author:
Dr. Héctor Rodríguez Bustos
Laboratorio de Histología
Facultad de Medicina
Universidad de Chile
Santiago
CHILE

E-mail: hector3@uchile.cl

Corresponding author:
Dr. Omar Espinoza-Navarro
Departamento de Biología
Universidad de Tarapacá
Arica
CHILE

E-mail: oespinoz@academicos.uta.cl

ORCID: https://orcid.org/0000-0002-2666-8725