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Prostate Cancer and Immune Evasion Mechanisms

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Abstract: *Prosteroid cancer is a global health issue, with 1,414,259 new instances diagnosed annually and 375,304 deaths attributed to PCa globally in 2020. It is caused by genetic predisposition, inflammation, and enhanced cell proliferation. The human prostate is composed of two basic cell types: secretory luminal cells and basal epithelial cells. Lesions arise when these processes emerge in the normally functioning prostate epithelium, setting off a chain reaction that may either lead to primary PCa or proliferative inflammatory atrophy (PIA) or create an intermediate stage known as prostate intraepithelial neoplasia (PIN). Hormonal replacement helps the gland bounce back just as rapidly, while estrogenic hormones in dietary carcinogens have been linked to prostate cancer recurrence. As basal cells are not postmitotic, glandular renewal must be caused by the proliferation of surviving basal cells. Prostate adenocarcinoma is a significant clinical challenge, with 2.5 million patients worldwide surviving after being diagnosed with this type of cancer. It is based on the finding that the cytokeratin subtype composition of tumor cells always matches that of luminal cells and never that of basal cells. Cancer cells produce PSA and PAP, and have a unique phenotype known as epithelial transition in immune-like cells. The British National Cancer Institute (NHI) defines cancer survival as "the physical, psychosocial, and economic problems of cancer from diagnosis to death." After treatment for prostate cancer, most men report psychosexual difficulties. This is especially true for men over the age of 50. Prostate cancer is able to actively suppress anti-tumor immune responses due to the expression of immune cell molecules (such as heterogeneous cytokines and their receptors, transcription factors regulating immune cells signaling, Ig motifs, and immune checkpoint molecules).*

Keywords: *prostate cancer, immune evasion, signaling*

1. INTRODUCTION

More than 1,414,259 new instances of prostate cancer (PCa) are diagnosed annually and more than 375,304 deaths are attributed to PCa globally in 2020 GLOBOCAN[1]. Many predetermined elements are involved in initiating prostate cancer, including genetic predisposition, inflammation, and enhanced cell proliferation. Lesions arise when these processes emerge in the normally functioning prostate epithelium, setting off a chain reaction that may either lead straight to primary PCa or proliferative inflammatory atrophy (PIA) or create an intermediate stage known as prostate intraepithelial neoplasia (PIN), which boosts the activity of luminal secretory cells. Many variables, including age, race, genetics, employment, and infectious agents, estrogenic hormones in dietary carcinogens, have been linked to prostate cancer recurrence, as shown by molecular and pathological analyses of human prostate carcinoma samples and research using animal models of PCa. [2] [3]

Epithelial ducts and acinuses are organised in a fibromuscular stromal network of fibroblastic and myofibroblastic cells to form the human prostate, a glandular organ lying below the bladder (Figure 1A). The epithelium is composed of one layer of colonial secretory luminal cells and two layers of closely related basal cells that comprise stem cells, transit-enhancing (TA) cells, and basally engaged (CB) cells.[4] [5]

Glandular epithelium is made up of two basic cell types: secretory luminal cells and basal epithelial cells. Both prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) are released into semen by a kind of cell called a luminal cell. What exactly basal cells are supposed to do remains a mystery. They function as a pool of progenitors that can

develop into luminal cells because of their stem-cell-like properties. Male rats undergo fast involution (decrease in size and function) of the prostate after castration. Hormonal replacement helps the gland bounce back just as rapidly. Androgen deprivation is harmful to luminal cells but has a little impact on basal cells. As basal cells are not postmitotic like luminal cells, glandular renewal must be caused by the proliferation of surviving basal cells.[5]

Prostate adenocarcinoma develops when luminal cells undergo malignant transformation. This assertion is based on the finding that the cytokeratin subtype composition of tumor cells always matches that of luminal cells and never that of basal cells. Moreover, many cancer cells, like luminal cells but unlike basal cells, produce PSA and PAP. [5]

In a 1997 study, Liu and colleagues discovered that a number of basal cell markers, which are not normally found in luminal cells, are expressed by cancer cells. [5]

The British National Cancer Institute (NHI) defines cancer survival as "the physical, psychosocial, and economic problems of cancer from diagnosis to death." [6].

Prostate cancer is a significant clinical challenge. Due to advances in diagnosis and surgery, approximately 2.5 million patients worldwide survive after being diagnosed with this type of cancer. In the preceding decade, radical prostatectomy has become the surgical treatment of choice [6].Most men with prostate cancer experience psychosexual issues after surgery (during the survival phase). Men over the age of 50 have a higher risk of developing prostate cancer, with one in seven men eventually being diagnosed. More than 100 men a day are told they have prostate cancer in the United Kingdom, with over 40,000 men being diagnosed each year. When we fast forward to the year 2030, prostate cancer will have taken the top spot. Despite having one of the largest increases in incidence of any cancer over the past decade (with an age-standardized prevalence of 22% between 1999-2001 and 2008-2010), the standard age-related rate has declined. by about one tenth (11%).

By creating an immune-suppressive microenvironment, prostate carcinomas are able to actively suppress anti-tumor immune responses [7]. To support the existence of a unique phenotype of prostate cells, also known as epithelial transition in immune-like cells ("Epithelial Immune Cell-like Transition" (EIT)), Lin et al. present the expression of selected control molecules in epithelial and associated immune cells in prostate cancer. Expression of immune cell molecules (such as heterogeneous cytokines and their receptors, transcription factors regulating immune cells signaling, Ig motifs, and immune checkpoint molecules) that suppress anti-cancer immune cell activities within the tumor microenvironment is a hallmark of this epithelial transition. Immune control molecules have been linked to cancer progression, and this has been recognized by early advances in immunotherapy, which have led to the creation of new immunotherapeutic methods.

WF Whitmore Jr. once posed the following question: "Can those who need it get treatment, and do those who can get treatment really need it?"[8].

Since cancer cells can evade the anti-tumor immune response (cancer immunoediting), they become resistant to immune surveillance and the patient's immune system is unable to recognize and destroy newly developed neoplastic cell clones, leading to tumor proliferation and progression. Immune evasion is recognized as a cancer hallmark. New ground in the fight against prostate cancer with immune checkpoint inhibitors. [9] [10] [11].

Two key components of the tumor microenvironment are depicted in the figure[12] below: (a) a tumor component consisting of tumor cells, stromal cells, and cancer stem-like cells, and (b) an immune component consisting of immune system cells with immunosuppressive properties. Therapeutic strategies that target both components or reverse the immunosuppressive environment and target immune cells to target tumor cells will result in tumor-specific immunological memory and long-term regression in patients with cancer.

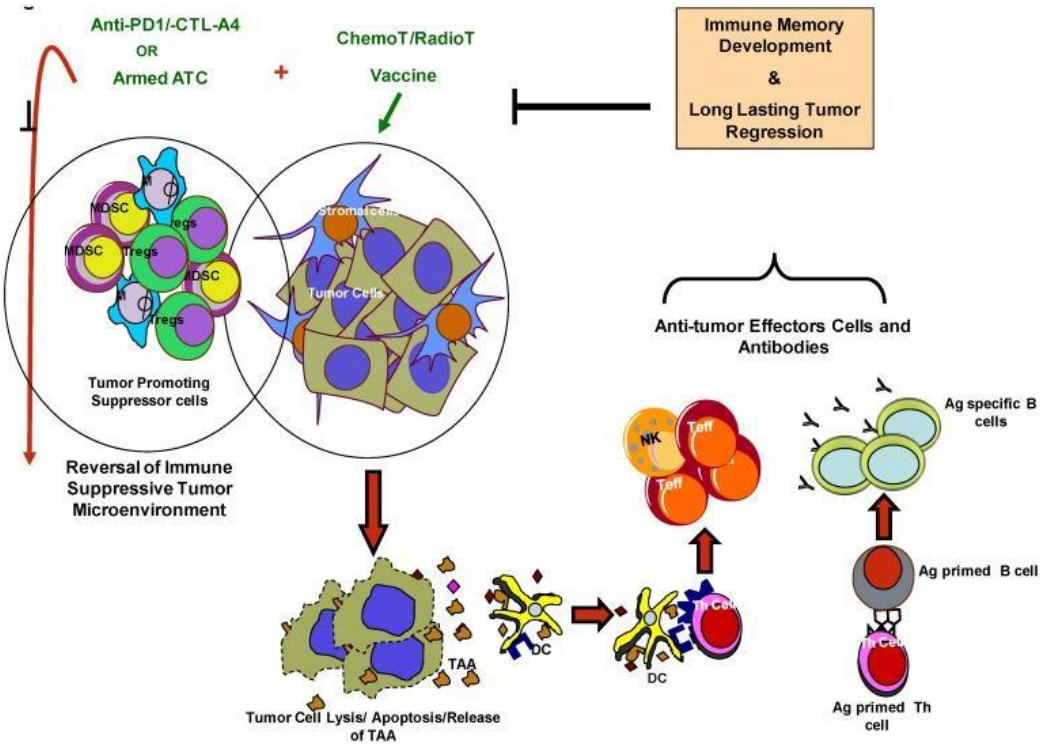

Figure1. *The tumor microenvironment's two key cellular components are depicted: (a) the tumor component, which includes tumor cells, stromal cells, and cancer stem-like cells, and (b) the immune component, which includes immune system cells with immunosuppressive properties. Therapeutic strategies that target both components or reverse the immunosuppressive environment and use immune cells to target tumor cells would result in tumor-specific immunological memory in cancer patients, allowing for long-term remission. From Thakur A et al., 2013 [12]*

2. MOLECULAR COMPONENTS INVOLVED IN PROSTATE CANCER REGULATION

The key immune inhibitors PD-1 and CTLA-4 are components of the immune synapse and function as negative regulators of the immune response. They work in tandem with other T-cell receptors (TCRs) to maintain a tolerogenic immune system that can effectively fight off infections and cancer. Through deregulation of T cell activation, their overexpression kills cancer cells.

Multiple internal and external signals, including chromosomal alterations, epigenetic modifications, abnormal oncogenic and tumor-suppressive signals, inflammatory cytokines, and other factors at the genetic, transcriptional, post-transcriptional, translational, and post-translational levels, can regulate PD-L1 expression, making it complex and variable in different tumor types[13]. Regulation of the PD-L1 molecule is discussed at various levels by Shen et al. [13]

After undergoing radical prostatectomy (RP), Gevensleben et al., found that PD-L1 expression was highly prevalent in primary prostate cancer and was also an independent prognostic factor. According to Gevensleben et al., the association of PD-L1 with aggressive behavior in primary prostate cancer suggests that activation of the PD-1 / PD-L1 pathway aids in the avoidance of the anti-tumor response and leads to tumor proliferation and progression.[14]

In the early 1990s, the inhibitory receptor in the immune response phase, programmed cell death protein-1 (PD-1, Pdcd1), was identified as a member of the CD28 / CTLA-4 family of immunoglobulin superfamilies [15]. PD-1 is a type I transmembrane protein of 50-55 kDa that is upregulated in various hematopoietic cells found in the peripheral blood. It is also widely induced in immune cells following antigen receptor signaling (T and B cells, macrophages, some dendritic cells, and so on) and in tumor cells following cytokine signaling. [15]

Programmed cell death ligands 1 and 2 (PD-L1 / PD-L2) are two of the most important PD-1 immunoregulatory ligands. PD-L1 is a 40 kDa type I transmembrane protein that is expressed on antigen-presenting cells (macrophages, dendritic cells, and others) and on all tumor cell types, as well as in lymphoid

and non-lymphoid tissues. Together, PD-1 and PD-L1 are part of a larger family of proteins called immune checkpoints that regulate immune responses (). Together, they act as co-inhibitors to control T-cell tolerance in the body's core or periphery. Complex inhibitory signals are transmitted by these cells to dampen the growth of CD8+ cytotoxic T-cells in the lymph nodes.

Using data from many separate clinical cohorts, Scott et al. (2023) showed that the glycosyltransferase enzyme GALNT7 is overexpressed in prostate cancer cells. They demonstrate that GALNT7 has greater diagnostic accuracy than serum PSA alone in identifying men with prostate cancer from urine and blood samples. Furthermore, they use in vitro and in vivo models to show that GALNT7 stimulates prostate cancer growth, and they show that GALNT7 levels remain high in progression to castrate-resistant illness. GALNT7 has been shown to link with cell cycle and immunological signaling pathways and to mechanistically alter O-glycosylation in prostate cancer cells. Their findings establish GALNT7-mediated O-glycosylation as a key driver of prostate cancer progression and add a new biomarker to the diagnostic toolkit for patients with advanced illness. [16]

3. IMMUNE FUNCTION IN THE PROSTATE GLAND

Complete knowledge of the immune system permits the design of effective immunotherapies for the management of prostate cancer. Seminal fluid's immunosuppressive properties and the absence of afferent lymph vessels place the prostate in a privileged immunological position. The high immunogenicity of prostate cancer can be explained by the fact that the majority of cases progress slowly, giving the immune system enough time to mount a clinically significant response. Indeed, prostate cancer cells abnormally overexpress highly immunogenic tumor-associated antigens, making them targets for promising immunotherapies.[9]

Important signaling pathways in prostate cancer development and progression are depicted in Figure 1. Since its discovery, the role of other signaling cascades in PCa has been established through a variety of in vitro and in vivo studies. Androgen Receptor signaling pathway 18 is one of the well-known pathways[17]. Lonergan and Tindall provided a detailed picture of the primary signaling pathways active in the progression of PCa.

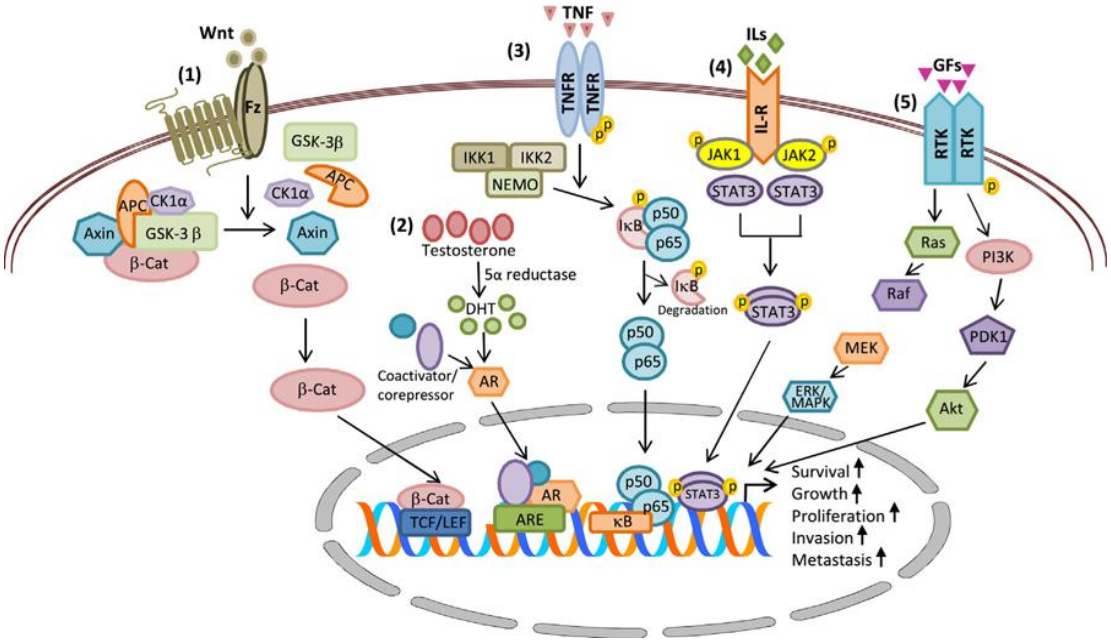

Figure2. *Important signaling pathways in the initiation, progression, and metastasis of prostate cancer. Wnt/-catenin signaling, AR signaling, NF-B signaling, JAK/STAT signaling, and receptor tyrosine kinase signaling are the five signaling pathways.[2]*

A large number of inflammatory T cells [tumor-infiltrating lymphocytes, tumor-infiltrating lymphocytes (TILs)] infiltrate the tumor and tumor microenvironment, expressing prostate cancer tissue, as reported by Modena et al., 2016[9]. Both innate and acquired immunity play a role in the body's defense mechanisms against neoplastic

prostate cells. Macrophages and antigen-presenting cells (APCs), cytotoxic lymphocytes T CD8 +, helper lymphocytes T CD4 +, and natural killer (NK) cells are all capable of recognizing and killing cancer cells. As a result, TILs lymphocyte infiltration has a favorable prognosis and is linked to longer patient survival.

Prostate cancer tumor microenvironments rely heavily on immune cells. Tumor-associated immune cells with specific phenotypes may mediate immune avoidance or tolerance of tumor prostate cells at different stages of the disease, either directly via interactions with tumor cells or indirectly via cytokine secretion to promote prostate initiation and progression. A generalized diagram of tumor-associated immune cells interacting with prostate cancer cells is shown in Figure 3. Immune vaccines and key immune inhibitors could pave the way for a new approach to treating prostate cancer, particularly metastatic castration-resistant prostate cancer.[18]

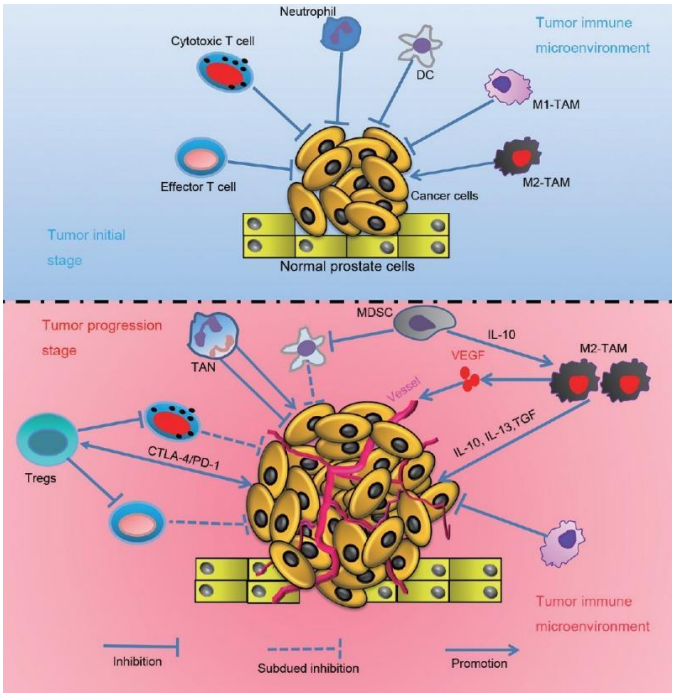

Figure3. *A graphical representation of the role that immune cells associated with tumors play in the onset and progression of prostate cancer. [18]*

4. Conclusions

Despite advances in prostate cancer treatment, there are no effective treatments for advanced prostate cancer. Although some combined clinical trials in advanced disease have yielded promising results, several issues, such as the timing and order of immunotherapy, androgen deprivation therapy, and the logic for early treatment, must still be carefully considered. A cautious assessment of current knowledge may provide a valuable resource for developing an effective treatment strategy capable of inducing tumor-specific immunological memory for long-term regression in cancer patients.

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