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RESEARCH ARTICLE

PROSTATE CANCER AND THE MICROENVIRONMENT: THE ADAPTATION PROCESS

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ABSTRACT

The microenvironment of prostate cancer (PC) is considered to be the headquarters for all PC progression. The presence of the followed characteristics metastasis, drug resistance, and further functions to empower PC to adapt easily and conquer the remote organs. It is known that PCutilize their surrounding conditions to progress, but the path taken through those microenvironments to harness the surrounded cells is still unclear. Therefore, the main goal of this review is to outline three crucial tasks. Firstly, to speculate the important points that directly or indirectly influence the understanding of the PC metastasis mechanisms. Secondly, to demonstrate how animal models could influence the profiling of PC. And, thirdly, to display the limited effects of the current treatments. Furthermore, to design a personnel drugs against PC, it is important to involve animal models that could spontaneously develop PC, and share similar implications in terms of the development of this disease as it presents in men. We concluded that PC can efficiently use all molecular pathways of the body for his avail. The emotional and psychological effects could even be a crucial factor that helps PC to progress or to be treated. Besides, it is necessary to take into consideration all emotional and genetic factors of each patient to design an adaptive and adjustable treatment that fits with the profile of the individual patient.

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INTRODUCTION

Prostate cancer (PC) is diagnosed as multiple independent and heterogeneous tumor characterized by diverse environmental and genetically distinct factors. Which classified PC as a second disease develops into a lethal form of cancer in the male population (1-3). PC cells are characterized as invasive, which means that they exploit their surrounding conditions to survive in the body. However, the microenvironment is the niche of solid cancers, made up of different components that partially or fully work together to generate and maintain the cancer. In our case, the PC microenvironment is very complicated and heterogeneous (4). For example, the prostate gland is morphologically composed of parenchyma and luminal epithelial cells, providing a liquid full of calcium and simple sugars (5). The profile of luminal epithelial cells is very similar to osteocytes, which increase the affinity of PC, resulting metastasis in the bones.

Thus, Wang *et al*. (6) have explained that PC produce their own osteocytes, which secrete growth-derived factor 15 (GDF15) to promote the invasion of PC into the bones. In addition, obesity or weight gain increases the volume of adipose cells around the prostate gland, which increases the chance of developing an aggressive form of PC by stimulating the expression of pro-oxidant enzyme NAPH oxidase (NOX5), and, by consequence, intracellular reactive oxygen species, which regulate the function of the HIF1/MMP14 pathways responsible for PC metastasis (7). However, the current anti-cancer treatments cannot eliminate PC in their advanced or metastasized forms due to the resistance provided by the origin of the cancer cells (8). However, it is well known that cancer-initiating cells or cancer stem cells (CSCs) in PC may exist in various forms of cancers (9-15). Those CSCs are noted to be responsible for actual treatment failures and cancer recurrence (9). This is because CSCs are characterized by self-renewability, differentiation, and drug resistance (9, 10), and they look phenotypically similar to embryonic stem cells or tissue stem

cells (11). Furthermore, CSCs have the capacity to adapt, change phenotype, and develop their tumorigenicity even in new microenvironments, such as in *in-vitro* cultures or during relocation in animal models (9-15). The capacity of CSCs is more than enough to raise an important question about the efficiency and adaptation of PC in their surrounding environment, and further in cell culture media or in *in-vivo* models. Further, this adaptation may cause a direct influence that can result in disadvantage effects of patients. Those biological factors and another such immune-protection are the indispensable pieces of the PC' puzzle. But the diagnosis is not complete without evaluating the emotional and psychological aspects of patients. Until the present, no study could clearly explain how PC use all the molecular and cellular substances or how and when they can begin to spread through the body. Through this review, we discuss those factors which they can help to build an overview of the PC progress.

Adaptation of prostate cancers: PC is typically described as a lazy cancer, as its growth is very slow, which is hard to identify or can gives a wrong diagnosis and conclude that the patient has a different disease than PC (16). In parallel, the speed in which PC spreads increases with its degree of severity, and it spreads very quickly compared to its slow onset; thus, making it difficult to detect early (17). Recently, it has been demonstrated that PC start with a small initial cell population, which is the origin of the severity, metastasis, and self-renewal of the cancer. The differentiation of the initial cells creates an important heterogeneity of the cancer in remote organs (18). Therefore, the current treatment methods are generally strong and extensive to eliminate PC without considering the degree of its development (18), which may open more space for PC-initiated cells to further develop (19). The described treatments may or may not increase the complication of the situation and are sometimes too late, which could result in the death of the patient (20). Therefore, the mechanism of precocious diagnosis remains the best solution to determine the most appropriate and accurate treatment method to target the tumor-initiating cells and to eliminate PC (6). PC lethality is principally correlated with the metastasis of malignant tumors, which proliferate and invade from the local site to remote organs, such as the bones or brain, to build a new microenvironment in host organ (21). Thus, the tumor microenvironment is a naturally indispensable container for PC in terms of initiation, development, and metastasis (22). PC cells have all the necessary elements to effectively adapt to new locations or survive against current treatment therapies (21). In some cases, it has been demonstrated that PC cells are associated with immune cells and implicate immune surveillance by harnessing these immune cells to regulate the immune system against tumor response and further against drugs and treatment therapies (23, 24). This association based on genetic and oncogenic landscapes stimulates the immune system to activate chronic inflammation, which is highly extensive in the adult prostate. Hence, this chronic inflammation boosts the initiation and progression of the tumor in the prostate gland (25). In 2012, Bhowmick (24) demonstrated that solid tumors such as those associated with prostate, breast, and colon cancer usually change characteristics and adapt to new remote sites, such as the bones or soft tissues. Furthermore, the tumor size and the number of circulating tumor cells in the primary sites are at the lowest level compared to the adapted ones at the new sites. However, no study has been able to explain how PC can begin the invasion of remote organs. Corn *et al*. (26), however, has confirmed the presence of a specific kind of interaction signaling pathway between normal epithelial prostate cells and the bone microenvironment in very restricted and controlled conditions via anti-tumor immune surveillance. However, in cases of cancer, this interaction is flawed and generates exorbitant cancer cells with ferocious invasive properties. The gathered data supported the positive discovery of Corn *et al*. (26), which indicates the presence of a kind of cancer cells called disseminated cancer cells that migrate from the original tumor site to remote sites in the very early stages of PC (18). Among the known circulated cancers, PC possesses a high level of tumor heterogeneity in the histological, genetic, and cell-signaling degree aspects (27). This diversity in the primary tumor composition might be the reason for the variation in androgen receptor signaling pathways and resistance against current treatments.

Accordingly, Banyard *et al*. (28), who attempted to explain that DU145–cell line dissemination is related to the rise in the expression of certain genes, such as ITGB4 (integrin β4), EpCAM (epithelial cell adhesion molecule), and uPA (urokinase-type plasminogen activator), which provide those cells with the ability to invade into the lymph nodes of mice. However, until now, no convincible explanation could clarify how the mutations differed from one patient to another within the same kind of cancer; it is more likely a 'personal fingerprint' from one patient to another. Interestingly enough, it was reported that all hallmarks and mobility properties of metastatic cells were present in the normal leukocytes (29). However, Kolonin *et al*. (30) demonstrated the direct linkage between adipocytes and PC aggressiveness. In a mouse model, they found that white Adipose Tissue (WAT) become inflamed and took the dysregulated form of fibroblasts leading to an increase in the PC aggressiveness ratio (30). Nonetheless, WAT in normal situations stocks and discharges lipids, but in the inflamed stage, WAT is differentiated from mesenchymal stromal to adipose stromal cells (ASCs) (31). Kolonin *et al*. (30) also suggested that when a patient's weight increases, the pressure from the substances produced from adipose cells incite the stromal cells to become cancer cells. Notwithstanding, ASCs release cytokines and chemokines, especially chemokine stromal cell–derived factor-1 (SDF-1, also known as CXCL12), which plays a role in PC progression and invasion by stimulating macrophages and inhibiting the function of anti-tumor T cells (32). There is evidence that macrophages belong to the range of immune cells, and are characterized by fast intra-extravasation and infiltration to all organs (33). Further, they are mostly present in tumor microenvironments to produce inflammatory factors and cause damage at the DNA level and in the mitochondria (34). However, the most logical explanation about cancer migration is that the cancer cells of the primary niche benefit from the macrophage properties through fusion and become hybridized and manipulate this hybrid to reach remote organs and establish new microenvironments (Figure 1) (29, 35). Accordingly, recent studies showed the presence of CD47 and CD163 expressed in several cancers, such as breast, colorectal, and ovarian cancers. CD47 is a surface marker whose expression inhibits the macrophages from destroying cancer cells (36). Further, CD163 is known as a macrophage-specific antigen (37). The presence of this marker in cancer cells proved the hybrid association of those cells with the macrophages, and

explores the ability of macrophages to infiltrate into organs and avoid any excitation of the immune system (36, 37). Another alternative—that is not less important than the aforementioned—are the emotional and psychosocial challenges that a patient faces, including depression, chronic bad moods, sadness, and stress (38). All these factors are considered to be a familiar form of daily life. Some patients are able to manage them; however, others bear them as a heavy load (39). After receiving the bad news of a cancer diagnosis, most patients enter into chronic stress and bad moods that biologically influence their health outcomes and may further dysregulate the immune system (40). In addition, these biological stress responses are favorable in the emergence, progression, and metastasis of cancer (41). During stress, in which the general psychological situation of the patient is overwhelmed, the majority of cells in the body release receptors for hormones such as cortisol, epinephrine, and norepinephrine (42). Further, crucial stress factors like cytokines, interleukin-1β (IL-1β), interleukin-6 (IL-6) adrenocorticotropin (ACTH), and oxytocin are highly expressed to stimulate an inflammatory response and disturb immune surveillance (42, 43).

Unlike chronic stress, the short-term stress response is a crucial factor in the adaptation and protection over short terms (44, 45). However, Zhu *et al*. (46) have noticed that patients who suffered from cancer and received different kinds of treatments and were invited to participate in social activities and focus on hobbies such as writing, drawing, or music could reduce emotional tension, and showed a positive mood which elevated their chances of healing more rapidly (Figure 1). Despite the extreme importance of emotional and psychological effects on patients, there is very little data that could clarify the pivotal role of the emotional and psychological situation in the healing or deterioration of a patient's health conditions. Further, this emotional side of patient is barely taking into consideration in animal models.

Can mice change the characteristics of cancer?: The first experiments exploring mice for PC analysis have demonstrated that these animals present an exceptional resistance against the aggressiveness of cancer. Even PC xenografts engaged in the invasive stage in mice are very different than in humans (47). Currently, with the evolution of experimental cancer research, the development of immortalized cancer cell lines and cell culture systems are considered, such as in two-dimensional (2D) models *in vitro* (48). This simulation provides primary information, but is unable to evaluate the architectural complexity of tumors and the important physiological interactions among cancer cells and their environment *in vivo* (49, 50). Further, the predicted effectiveness of drug treatments is described to be not accurate and to have a limited efficacy and, could, therefore, fail when the experiment transitions to a clinical model. As an alternative, biologists have largely used xenografts or cell implantations in mice in an attempt to create a new, less-complex microenvironment instead of the original cancer cell microenvironment, by disrupting the function of the immune response in mice or by preventing the immune response and local specific interactions to avoid any unexpected rejection or inflammation from the characterization of the cancer development (48). Basically, three mouse models have been widely used in cancer research, which have resulted in a number of pros and cons directly related to the cancer screening or to evaluate the tested drugs. Firstly, the xenograft model is favorable for subcutaneous injection, which allows for the observation of tumor growth. But in this model, the injected cells could be completely rejected if the immune system is not compromised. Also, the injected tumor cells could completely change the tumor characteristics defined before the injection (51). The second model is known as an orthotopic xenograft, which is similar to the preceding model in terms of the injection, except it is done directly to the relevant organ instead of just under the skin (52). The third model involves genetically engineered mice, in which a strain of mice that can generate some tumors with a similar mutation found in human cancers have been genetically produced. The inconveniences of the third model could not present accurate results, which may be positively or negatively influenced by substances that exist only in mice (53).

However, to avoid the complexity of the mice's immune systems and their unsteady and unexpected reactions to xenografts, an *ex-vivo* model was established as a replacement, in which tissue or organs are taken from the mouse's body and cultured in platforms (54). The *ex-vivo* model is defined as a three-dimensional (3D) tumor culture platform (55). It is considered to be a miniature model from the experimental animal, a transitional step between *in vitro* and *in vivo*, which genetically maintains cancer cells that are identical to the original cancer cells, but the phenotypes can be changed due to the influence of the environment exercised via parts of the tissue or organs cultured in the 3D space (56). This method allows the researchers to expedite the screening of anti-tumor reactions in real-time, as well as personalizing the parameters of the therapeutic approaches for each patient in very short time periods (57). Interestingly, Zhang *et al*. (48) have tested numerous cultures to define the optimal conditions to keep the viability and proliferation capacities of PC cells for up to 6 days. In the *ex-vivo* method, they could show better 3D matrices in which enzalutamide treatment of apoptosis, AR-expression, and PSA were significantly increased.

Similarly, Van de Merbel *et al*. (57), after their success in establishing and maintaining an *ex-vivo* culture system for prostate and bladder cancer for up to 10 days, considered this system to be a very close model to explain the evolution of prostate and bladder cancers in patients, allowing them to define tumor targets and closely observe the development of anti-neoplastic responses. However, the tumor cells in the body grow in a natural environment supported by other tissues, such as blood precursor, as well as the presence of the immune system and mood of the patients (58). Therefore, Frohlich *et al*. (59) described that the aim behind the *ex-vivo* model is mimicking and simulating this natural environment in order to closely study the conduction of those cells by providing an authentic and functional envelope with conditions similar to those in the body. Unlike 2D culturing, where the cells are surrounded via medias full of nutrition and cell's waist. However, the *ex-vivo* media can be supplied from different organic sources (e.g. mouse or animal organs, tissues components, viruses) or gel sources (e.g. Gibco's AlgiMatrix 3D culture system) (59). A set of studies have demonstrated that the cell culture in media has several drawbacks, may be sorted from organic

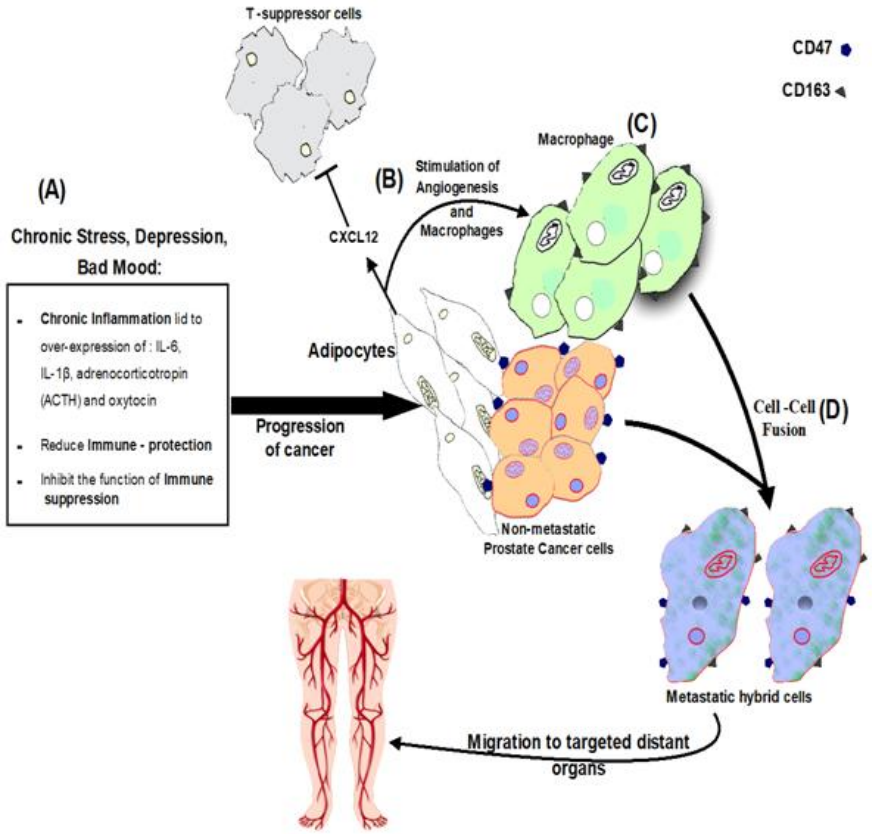

Figure 1: The complicity of several conditions in prostate cancer progression. (A): Stress and bad moods reduce the efficacy of the immune system and induce the overexpression of stress hormones, which stimulate inflammation. (B): Influenced by prostate cancer (PC) cells, adipocytes change the morphology and enhance PC cells to secrete CXCL12, which stops the function of T cells and inhibits all immune protection against the PC cells. In the meantime, adipocytes relay PC cells to the blood via the veins and stimulate the macrophages via inflammation. (C): PC cells express CD47 to stop all dissociation and digestion reactions induced from the adhered macrophages and the immune system. (D): PC cells fuse with the adhered macrophages and transfer all PC substances, such as mitochondria and nuclei to the host cells. The metastatic hybrid cells maintain the specific macrophage marker CD163 expression for camouflage and to spread to remote organs.

Table 1. Summarizing the most recent models of therapies used against prostate cancers (PC)

Different therapeutic models	Description	Features	References
Biological cargo	Drug carriers derived from organelles or extracellular vesicles such as exosomes	The cargo could be in the form of the following products: . synthetized specific genes . polypeptides . siRNAs	[66-68, 85]
	Organic nanoparticle platforms, which are natural scaffolds to carry drugs	Those organic nanoparticles may be composed of: . viruses . adenovirus . plant viruses (cowpea mosaic virus) . bacteriophage (M13, fd)	[64, 86-88]
Physical treatment	Radical prostatectomy	The surgery should be performed 4-6 weeks after the biopsy.	[73]
Nanotechnology	Inorganic: are non-viral and nanoparticular platform are designed and synthetized cargos	. nanobombs or nanoworms . micelles, liposomes, dendrimers, dendrons . iron oxide nanoparticles . gold nanoparticles and quantum dots . physical and chemical properties such as: NIR-activated polymeric nanoplatforms for the diagnosis and imaging of cancer . trucking tracking enzymes such as enzalutamide, and chemical agents such as cabazitaxel	[89-91] [92]
	Recent nanoplatforms	The nanoparticles are carried via: . The metal-organic–framework has recently been established as a capsule reporter of genes and proteins to the targeted CSCs in very short times (up to 4 days).	[93- 95]

supplies, which may contain undefined or undesirable components, such as growth factors or virus elements. Even, the cell-cell attachment may translate some signals, which may affect gene expression. Further, it is difficult to remove or separate the target cells from the rest of the support tissues. Concerning gel matrices, they are favorably elected because they make it very easy to liberate cells by dissolving buffers (58, 59). Until today, *ex-vivo* cultures provide the best conditions for screening for the effectiveness of treatments with less cost and minimum undesirable effects in animals (60).

A canine model is the closest to humans in terms of the development of maladies: Numerous studies have considered the similarities between canine and human maladies. Due to the fact that dogs share several similar malady characteristics with humans, which has elected them as a central candidate to evaluate human medical management and precautionary health protections (61). Dogs are a perfect model, because they share many characteristics with humans, such as lifestyle and nutritional habits. Dogs even participate in emotional moments with their owners. In addition, the histological features and morphological information of the prostate gland are very close between both species. Further, those both techniques showed anatomical similarities in some organs and in the development of maladies (62). Although canine PC spontaneously develop in faster and more aggressive forms than human PC. Canine PC is barely diagnosed and his incidence is limited compared to the men (63).

Current treatments: The heterogeneous aspect and the complication of prostate CSCs calls for the urgent development of a treatment with rapid efficacy and minimum toxicity, especially against the metastasis and advanced stages of this disease (64). Therefore, the treatment takes different modalities from the biological, physical, and chemical aspects, arriving at nanotechnology. All those treatments are oriented to target CSCs and to the total healing from PC and the other cancers (65).

Therapies depending on biological items: herein, biological therapies explore the developed or modified organelles or synthesized substances or sequences such as exosomes, miRNAs, and proteins (Table 1), for example, the exosomes extracted primarily from macrophage cells, cancer cell lines, or raw bovine milk (66-68). Those recipients are exploited as cargo for regulator proteins, such as protein tyrosine phosphatases (69). Also, carrying biomaterials or molecules, such as introducing siRNA to inhibit the over expression of anti-apoptotic Bcl-xL to induce apoptosis into PC. Exosomes could even be designed to carry drugs like paclitaxel to cancer cells (70).

Physical treatment: surgery, such as radical prostatectomy, which is considered as first radical solution. However, this option is supposed to be a final and radical solution for this disease before its progressions (71). Recently, radical prostatectomy has been performed via robot-assisted laparoscopy, which has increased the accuracy of the surgery and reduced complications (72). However, the impact of the interval time between the biopsy and surgery date is considered to be a very early period to prohibit further disease progression and complications. Westernam *et al*. (73) described, through a study that included 7,350 men from 1994 until 2012, that the ideal period to perform prostatectomy PR is between 4-6 weeks after the biopsy is performed. Otherwise, beyond this time period, the likelihood of biochemical recurrence will be higher in men with increasing risks of this disease (73). Logically, the surgeons will apply some conventional techniques, such as total anatomical reconstruction, which evaluates the factors that could affect the postoperative recovery and prevent suspected complications (Table 1) (74).

Treatments based on advanced evolution in the nanomedicine field: this kind of treatment is a combination between pharmaceutical, nanotechnology, and biomedical sciences (75). Basically, the treatment is depend on the description of the biomarker profile, which is used as an indicator for the pathologic process or to evaluate the therapeutic intervention (76), such that, each PC type is based on its microenvironment and heterogeneity, which are responsible for the diversity in the presented profile from one patient to another (76). However, the utility of this technology permits to exceed the limitations and failures of actual treatments, especially against advanced stages of PC (Table 1) (77). In a similar way, Qin *et al*. (78) determined the three most utilized nanotechnology systems to be: nano-platforms with physical and chemical properties, and the nano-delivery system. For example, PC have recently been diagnosed via Prostate specific Antigen (PSA) and Prostate Specific membrane Antigen (PSMA) florescent nanoprobes carried on gold nanoparticles in the blood and tissue *in vivo*, respectively (79, 80). However, the use of chemotherapy via nano-materials increases the drug efficacy and reduces toxic side-effects via the targeted penetration of drugs into the tumor microenvironment (81). Otherwise, the gene, proteins, or even RNA delivery via nano-materials is a qualitative leap in this field (82), such that a non-viral vector can transport the gene or siRNA to inhibit, for example, an anti-apoptotic effect in the tumor cells (83). Immunotherapy even rode this wave by developing novo antigenic response-induced anti-tumor immunity using tumor-associated antigen proteins based on vaccination approaches (84).

Conclusion

In conclusion, the complexity of PC is very difficult to be clarified just by the biological experiments. Further, the psychological and emotional effects of patients or mammalian models may be crucial during the study or establishment of new treatments and precocious diagnosis against PC progression. However, canine PC models are an ideal opportunity to better understand and closely evaluate the effect of recent treatments in a very short period, which is a perfect alternative to treat cancer definitively.

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