Journal of
Steroids & Hormonal Science
ISSN: 2157-7536

Reebye et al. J Steroids Hormon Sci 2011, S:2
DOI: 10.4172/2157-7536.S2-002

Review Article Open Access

# The Interplay between the Androgen Receptor, Soluble Factors and Tumour Microenvironment

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## Abstract

Maintaining a balanced prostate microenvironment is pivotal for normal development and homeostasis of the prostate gland. This balance however is severely disrupted during the progression of prostate cancer where the local microenvironment becomes compromised. The cellular components associated with the microenvironment, including stromal cells, immune cells, blood vessels, and the extracellular matrix, interact cooperatively with prostate cancer cells through paracrine and autocrine actions of soluble growth factors and cytokines thus creating a modified tumour microenvironment. Understanding how paracrine and autocrine factors interact in this microenvironment may lead to improved understanding of prostate cancer progression and to the development of drug combinations that might target both the primary and metastatic prostate cancer tumour microenvironments.

## Introduction

The interplay between prostate epithelial cancer cells and the surrounding stromal tissue is vital for tumour progression and metastasis. Prostate cancer cells require a sustainable microenvironment to survive and continuously grow. In the early stages, this is dependent on androgens where prostate epithelial cells express high levels of the corresponding androgen receptor (AR). Once the AR is activated, a cell signalling cascade is triggered, leading to the necessary transactivation of prostate genes specific to tumor growth. Accordingly, androgen ablation therapy is the mainstay treatment for prostate cancer. This form of therapy however only provides short-term success in patients particularly those with more advanced stages of the disease. Unfortunately, a very high number of patients treated for prostate cancer will eventually relapse as resistance to hormone treatment inevitably follows, culminating in castration-resistant disease. Several molecular mechanisms have been proposed to explain this process [1-3], but the precise events that contribute to this is still largely unknown. What is clear is that the tumor microenvironment, which includes normal stromal cells as well as transformed cells, plays a pivotal role in cancer progression, metastasis, and resistance to therapy. The survival and proliferation of primary or metastatic cancer cells is largely influenced by an intricate network of cell signaling within the tumour milieu; thus understanding the inner workings of this microenvironment remains essential in order for better and more targeted therapies to be developed. This review will identify important soluble growth factors and cytokines essential to the development of the prostate tumour microenvironment (local and metastatic), describing their functions, and highlighting their paracrine and autocrine actions on prostate cancer cells including their regulation of the androgen receptor (AR).

## The Primary Tumour Microenvironment

The elements that are crucial for establishing a nourishing microenvironment within a primary prostate tumor site includes stromal cells, blood cells, stem cells, the extracellular matrix, and soluble factors. The array of growth factors and cytokines secreted by both the prostate epithelial cancer cells and stromal cells largely determines the fate of the disease. These soluble factors perform paracrine and autocrine functions in addition to behaving as chemoattractants in the microenvironment thus dramatically enhancing tumor growth and metastasis. This effect is further exacerbated by soluble factors which communicate bidirectionally (with both the cancer cells and the stromal cells), coordinating positive and negative feedback loops to create a continuous synergistic interaction between prostate cancer cells and the surrounding tissues. The androgen receptor (AR) is expressed in both normal and abnormal prostate epithelial cells. Upon ligand activation, the AR translocates into the nucleus to activate all the necessary genes responsible for normal functioning of the gland [4]. The normal prostate microenvironment consists of prostatic ducts, epithelial cells, stem cells, and neuroendocrine cells along with the stromal components including fibroblasts, vascular endothelial cells, nerve cells, immune cells, the extracellular matrix and soluble factors such as growth factors and cytokines. These components interact either directly or indirectly by secreting autocrine or paracrine signalling molecules [5]. During the progression of prostate cancer, the homeostatic interaction between these components becomes severely disorganized leading to aberrant cell growth. The natural progression of prostate cancer varies greatly and involves multifaceted pathologies such as increased sensitivity to androgens and non androgenic steroids; and ultimately progression towards steroid independent growth. The various histological changes observed reflect this dysfunction within the tumor microenvironment where the epithelial/stromal interaction is significantly compromised and altered, favoring not only tumor survival but also metastatic growth (Figure 1). Fibroblasts within the stromal tissue also contributes to this dysfunction through the production of growth factors, cytokines and matrix metalloproteases [6-8]. This ultimately increases cell proliferation to prime the tumour cells for metastasis to secondary sites. Soluble factors are pivotal components of the tumor microenvironment and key mediators in

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**Received** August 20, 2011; **Accepted** October 20, 2011; **Published** October 24, 2011

**Citation:** Reebye V, Kim J, Frilling A, Nicholls JP, Habib NA, et al. (2011) The Interplay between the Androgen Receptor, Soluble Factors and Tumour Microenvironment. J Steroids Hormon Sci S2:002. doi:10.4172/2157-7536.S2-002

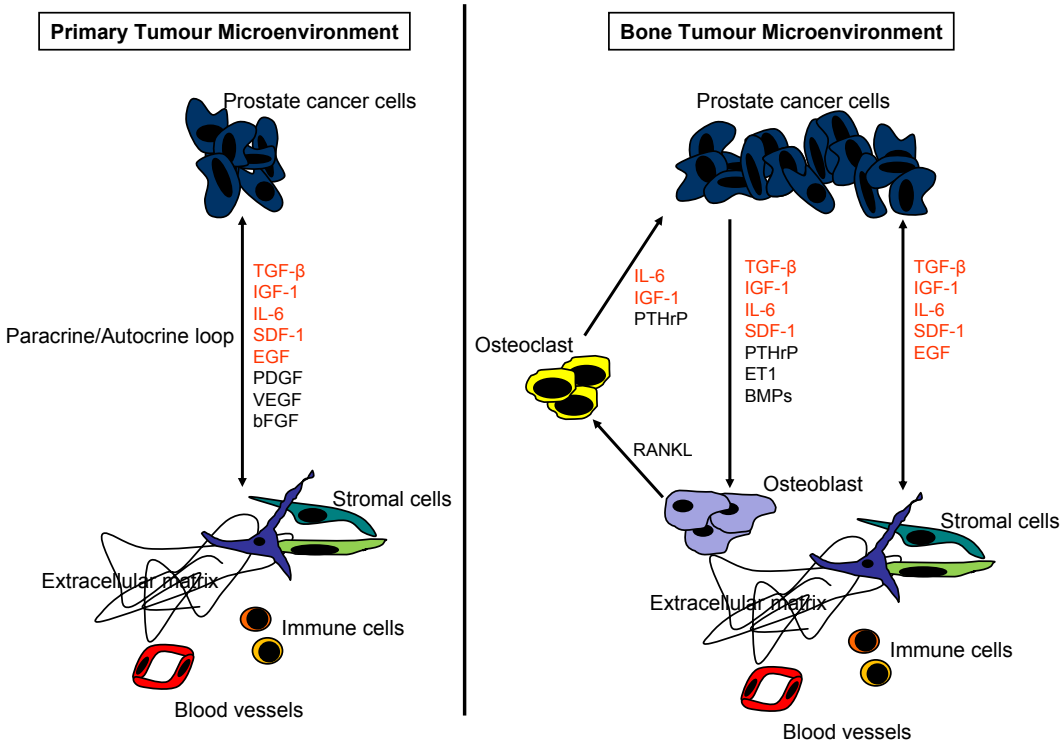


**Figure 1:** Primary tumour and and bone tumor microenvironments. Similar soluble growth factors and cytokines (highlighted in red colour) are used in the two different tumour microenvironments.

tumor development and progression. These factors are secreted by many cell types including cancer cells to collectively have a profound effect on many biological functions such as proliferation, apoptosis, angiogenesis, differentiation, immune regulation, and survival. Because of their diverse biological roles, growth factors and cytokines have been excellent targets for developing novel therapeutic drugs against autoimmune disease and tumor growth.

In the early stages of prostate cancer, growth factors and cytokines that are secreted by the stroma greatly contribute to the severity and unpredictable behaviour of the disease by enhancing activity of the AR and ultimately increasing tumour mass [1,9-11]. Eventually, the presence of androgens no longer becomes a necessity to activate the AR as parallel signaling networks from the tumour microenvironment converge to support a hormone independent pathway involving MAPK (mitogenic activated protein kinase) and AKT (protein kinase B) amongst others [1,11].

There are several important growth factors and cytokines essential to prostate cancer development, including epidermal growth factor (EGF), insulin-like growth factor-1 (IGF-1), stromal-derived factor-1 (SDF-1), interleukin 6 (IL-6), and transforming growth factor beta (TGF-β). Studies have demonstrated that these soluble factors are able to maintain AR activity in order to propagate cell survival and proliferation within the primary tumour microenvironment. This review will discuss how these factors contribute to communication across the tumour microenvironment [1,12-14]. Other important growth factors such as bFGF, PDGF and VEGF have been extensively reviewed elsewhere [15,16]. EGF is an abundant growth factor present in prostate tissue, where its primary function is in promoting cell proliferation and invasion [17,18]. A recent study showed that EGF could activate and phosphorylate the AR at key functional residues independent of hormone stimulation [19]. Moreover, in patients undergoing androgen ablation therapy, the expression level of the EGF receptor (EGFR) increases as castration-resistant prostate cancer develops. This observation suggests that EGF plays a crucial role within the primary tumor microenvironment where its production is amplified through both paracrine and autocrine pathways. This regulatory mechanism possibly promotes prostate tumour growth and expansion by maintaining activity of the AR even in the absence of androgen stimulation [20-23].

Another important growth factor involved in prostate cancer development is transforming growth factor β (TGF-β). TGF-β is part of a superfamily of secreted proteins of which the members include inhibins, activin, anti-müllerian hormone and bone morphogenetic protein. Expressed in normal as well as malignant prostate tissues [24], TGF-β is highly conserved and is involved in multiple biological effects including angiogenesis [25], synthesis of components within the extracellular matrix [26], and immune T cell regulation [27]. Similar to EGF, TGF-β also cross-talks with the AR axis to promote development of androgen independent cancer growth [28]. Since TGF-β regulates cell cycle progression, apoptosis and modulation of immune T cells [5,29,30] its expression levels could be indicative of the fate the local tumour mass might take. In addition to inducing angiogenesis TGF-β also works with membrane metalloproteases and collagenase to induce tissue remodeling [4]. The overall effect thus involves enhanced TGF-β levels and its accessory protein endoglin [31] within the prostate tumour microenvironment to maintain deregulated AR signalling in epithelial cells [28] and to facilitate tumour growth and metastasis to secondary sites [29,32]. Since the most common site of prostate cancer mestastasis is the skeleton, it is now recognized that TGF-β also plays a strong part in promoting osteoblastic lesions. *In vivo* experiments with nude mice

have demonstrated that targeted knockdown of TGF-β significantly decreases osteoblastic bone formation and tumour incidence [33]. Since the prostate tumor microenvironment constantly changes during progression of the disease, these associated changes in autrocine and paracrine signalling are reflected by how cancer cells respond to this. Whilst EGFR signaling potentially enhances aberrant growth factor induced hormone-independent activation of the AR; TGF-β is believed to contribute to prostate cancer induced bone metastasis.

In addition to TGF-β, stromal-derived factor 1 (SDF-1) also participates in facilitating bone metastasis. SDF-1 belongs to the chemokine family known as chemokine (C-X-X motif) ligand 12 or CXCL12. CXCL12 is known for is strong chemoattraction for lymphocytes during embryogenesis where it directs migration of hematopoietic cells from the foetal liver to the bone marrow for the formation of large blood vessels [34,35]. In adults, SDF-1/CXCL12 maintains a similar role in angiogenesis and this is observed in prostate cancer cell metastasis to the bone where CXCL12 initiates its signaling through the CXCR4 receptor to activate expression of alpha-vβ3-integrins (cell surface receptors that play a role in adhesion, migration, invasion, growth and angiogenesis) [36] and CD164 (an adhesive factor involved in haematopoiesis) [37]. This causes down regulation in the expression of the glycolytic enzyme phosphoglycerate kinase 1 (PGK1) and angiostatin in parallel to secretion of VEGF and tissue inhibitor of metalloproteases 2 (TIMP2) via the PI3K/Akt pathway [38]. Secretion of interleukin-6 (IL-6) and interleukin 8 (IL-8) is then initiated via the MAPK/Erk pathway to collectively promote growth of the cancer cells within the bone microenvironment [38]. The contribution of CXCL12 in this setting is highlighted when inhibition of its signalling almost completely stops the growth of prostate cancer in bone [39].

The cytokine interleukin-6 (IL-6) is an interesting molecule because of its diverse biological roles in many diseases. Its importance in cell proliferation, inhibition of apoptosis, inflammatory response, and osteoclast resorption of bone reflects the ubiquity of its expression in many tumor cells including prostate cancer [40-42]. Studies have shown that IL-6 can induce AR activity independent of androgens [43-45] where it is able to induce the AR to activate several androgen response promoters including PSA in the absence of steroidal hormones [43]. Since EGF, TGF-β and CXCL12 appear to contribute towards regulation of IL-6 secretion within the tumor microenvironment [46,47], a pattern of synergistic interaction between these factors and perhaps many more will eventually emerge to give us a better understanding of the key players involved in maintaining activity of the AR and promotion of tumour growth along a non-conventional signaling pathway.

Insulin-like growth factor-1 (IGF-1) is an endocrine hormone with similar molecular structure to insulin. Its primary action is mediated by binding to its receptor, the insulin like growth factor-1 receptor (IGF-1R), a receptor tyrosine kinase present on many cells that initiates intracellular signalling. Since IGF-1 is a strong activator of the Akt signaling pathway and an inhibitor of apoptosis, there are numerous studies being undertaken to elucidate the effects of inhibiting its signaling pathway for cancer therapy [48-53]. Epidemiological studies have established a link between high circulating serum IGF-1 levels and the risk of developing advanced prostate cancer [50,54]. IGF-1 has been shown to stimulate proliferation of human prostate epithelial cell by enhancing activity of the AR [55,56]. Accordingly evidence also suggests that IGF-1R is highly expressed in prostate cancer cells [57-59] where it plays an important role in AR mediated progression towards androgen independent progression of the disease by compartmentalizing the AR into the nucleus [60]. Taken together, these numerous studies show that IGF-1 has an important functional role in AR signaling by potentiating the transcriptional activity of the AR in the face of androgen ablation, through recruitment of co-activatiors and intracellular mediators such as the phosphoinositide 3-kinase (PI3K) signaling pathway. Collectively these signals invoke the action of other growth factors and cytokines from the primary and secondary tumour microenvironment for progression of the disease (Figure 1).

## The Bone Tumor Microenvironment

Greater than 90% of patients with metastatic prostate cancer will have bone metastases [61-63]. In these cases, fractures, spinal cord compression, debilitating bone pain, and other severe bone complications result [61]. By secreting soluble factors that directly affect the function of osteoblasts and other important cellular and tissue components, prostate cancer cells can severely alter bone homeostasis and establish conditions favorable not only for cell survival but also for continuous cancer growth. Some of the growth factors and cytokines secreted by prostate cancer cells within the primary tumour microenvironment are able to remodel the bone tissue where the tight regulation of osteoclasts and osteoblasts operating under normal conditions undergoes severe disruption [64,65]. The important paracrine and autocrine factors that are involved with this include parathyroid-hormone-related peptide (PTHrP), prostaglandins, bone morphogenic proteins (BMPs), TGF-β, IGF-1, endothelin-1 (ET-1) and IL-6 [66]. During alteration of the bone microenvironment, the propagation of these growth factors and cytokines attract other components including osteoblasts, osteoclasts, and stromal cells to facilitate angiogenesis and infiltration of the cancerous cells [67]. A major function of these growth factors is to stimulate osteoblasts to express RANKL, an important protein that regulates bone and stimulates growth factor secretion from osteoclasts. These secreted growth factors which include IL-6 and IGF-1 then stimulate prostate cancer cells to proliferate and expand from the primary tumour site, resulting in a perpetual cycle of interaction that creates a severely dysfunctional bone tumour microenvironment (Figure 1, Right Panel). Studies have shown that in bone metastases, osteoblasts can promote prostate cancer progression through cross-talk between prostate cancer epithelial cells and the various stromal components within the bone microenvironment [68,69]. Some of the secreted factors are unique to and more abundant in the bone, including PTHrP, BMPs, and ET-1. These factors play a central role in osteoblast development and bone infiltration of prostate cancer cells by stimulating prostate cell derived PTHrP to induce expression of nuclear factor-κβ ligand (RANKL) [70-72] and inhibit the expression of osteoprotegerin (OPG), which acts as a decoy receptor for osteoclasts [73]. This mechanism also explains why very high levels of PTHrP is observed in prostate cancer induced bone lesion sites [74,75]. The activation of RANKL on osteoblasts allows direct interaction with osteoclasts, which express its corresponding receptor RANK. This osteoblast-osteoclast interaction is then amplified by other soluble factors including IL-6 and TGF-β (both of which are also secreted by osteoclast cells), enabling continuous cross-talk with prostate cancer cells.

ET-1 is another important bone remodeling soluble factor secreted by prostate cancer cells to act as a mitogenic factor for osteoblasts at metastatic sites resulting in dysfunctional bone formation [76-78]. Interestingly, some of the gene targets of ET-1, including IL-6 and RANKL are also upregulated and collectively may perpetuate the synergistic interaction of TFG-β, IGF-1, IL-6, SDF-1/CXCL12, and EGF between the bone matrix and prostate cancer cells.

In summary, enhancing our understanding of the cooperative interaction between the stromal cells and cancer cells within the tumor microenvironment may lead to new therapeutic combinations of agents to disrupt them. It is evident that cancer cells are able to constantly interact and acquire adaptive and survival changes within the tumor microenvironment. Mechanistically, paracrine and autocrine actions of soluble factors released within this microenvironment are crucial in maintaining a perpetual interaction between the various cellular components of the surrounding tissues. Selectively targeting these growth factors and cytokines associated with the both the primary and secondary tumor microenvironment will undoubtedly produce better improved overall survival outcome for solid tumours such as prostate cancer.

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This article was originally published in a special issue, **Androgen Receptors** handled by Editor(s). Dr. Rebecca L Cunningham, University of North Texas Health Science Center, USA; Dr. Ze-hua Liu, Osaka City University, Japan