World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/2218-4333office
wjco@wjgnet.com
doi:10.5306/wjco.v2.i12.384

World J Clin Oncol 2011 December 10; 2(12): 384-396
ISSN 2218-4333 (online)

IL-6/IL-6R as a potential key signaling pathway in prostate cancer development

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Supported by Calouste Gulbenkian Foundation (Oncology/2008/Project n 96736) and Science and Technology Foundation (FCT/PTDC/SAU-FCF/71552/2006)
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Received: September 9, 2011 Revised: November 8, 2011
Accepted: November 15, 2011
Published online: December 10, 2011

Abstract

Interleukin-6 (IL-6) is a pleiotropic cytokine involved in prostate regulation and in prostate cancer (PC) development/progression. IL-6 acts as a paracrine and autocrine growth stimulator in benign and tumor prostate cells. The levels of IL-6 and respective receptors are increased during prostate carcinogenesis and tumor progression. Several studies reported that increased serum and plasma IL-6 and soluble interleukin-6 receptor levels are associated with aggressiveness of the disease and are associated with a poor prognosis in PC patients. In PC treatment, patients diagnosed with advanced stages are frequently submitted to hormonal castration, although most patients will eventually fail this therapy and die from recurrent castration-resistant prostate cancer (CRPC). Therefore, it is important to understand the mechanisms involved in CRPC. Several pathways have been proposed to be involved in CRPC development, and their understanding will improve the way to more effective therapies. In fact, the prostate is known to be dependent, not exclusively, on androgens, but also on growth factors and cytokines. The signaling pathway mediated by IL-6 may be an alternative pathway in the CRPC phenotype acquisition and cancer progression, under androgen deprivation conditions. The principal goal of this review is to evaluate the role of IL-6 pathway signaling in human PC development and progression and discuss the interaction of this pathway with the androgen recepto pathway. Furthermore, we intend to evaluate the inclusion of IL-6 and its receptor levels as a putative new class of tumor biomarkers. The IL-6/IL-6R signaling pathway may be included as a putative molecular marker for aggressiveness in PC and it may be able to maintain tumor growth through the AR pathway under androgen-deprivation conditions. The importance of the IL-6/IL-6R pathway in regulation of PC cells makes it a good candidate for targeted therapy.

Key words: Androgen receptor; Castration-resistant prostate cancer; Hormonal castration; Inteuleukin-6; Inteuleukin-6 receptor; Prostate cancer; Tumor biomarker

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Azevedo A, Cunha V, Teixeira AL, Medeiros R. IL-6/IL-6R as a potential key signaling pathway in prostate cancer development. *World J Clin Oncol* 2011; 2(12): 384-396 Available from: URL: http://www.wjgnet.com/2218-4333/full/v2/i12/384.htm DOI: http://dx.doi.org/10.5306/wjco.v2.i12.384

INTRODUCTION

Prostate cancer (PC) is the most common cancer among men in Western populations[1]. Ethnicity, advanced age and family history are well known risk factors for this disease[1]. Furthermore, circulating androgen levels, chronic prostate inflammation and obesity are also risk factors frequently described in the literature[2,3]. Currently, prostate-specific antigen (PSA) is the putative biomarker for PC screening. Two consecutive rises in PSA value over 0.5 ng/mL or one single value ⩾ 4 ng/mL are indications for biopsy[4]. However, although PSA testing has high sensibility, its specificity is rather low, causing clinicians to have doubts with regard to biopsying, since increased false-positive rates, overdiagnosis and overtreatment have been reported to be associated with PSA testing[5-8]. Therefore, novel biomarkers are needed to improve identification of men at risk of having PC and to predict the natural behavior of the prostate tumor. The use of more sensitive and specific biomarkers will be an appropriate strategy for disease diagnosis, disease staging, disease prognosis, predicting and monitoring clinical response to therapy. In consequence of the high heterogeneity of PC, it is relevant to study molecular and cellular pathways involved in its development and progression to identify key genes and molecules implicated in different stages of the disease[9].

In several diseases, a deregulation of cytokine levels can be observed. Numerous pro-inflammatory cytokines play an important role in the pathogenesis/carcinogenesis of many cancers. One of the most important cytokine associated with inflammation, interleukin-6 (IL-6), will be discussed in this manuscript.

Recent evidence suggests that the presence of inflammatory factors and cytokines at the tumor site results in tumor cell survival, proliferation, invasion and metastasis[10]. The expression and function of pro-inflammatory cytokines in PC have been extensively investigated because of their role in the regulation of proliferation, apoptosis, migration, invasion, and angiogenesis[11]. Recent studies have focused on the role of cytokines, including IL-6, in the etiology and progression of PC[12-16]. Elevated levels of IL-6 in men with local PC and advanced disease made IL-6 a candidate biomarker for PC development and progression[17].

This review is a summary of several studies outlining the potential role of the IL-6 signaling pathway in human PC development and progression, an interesting area of scientific and clinical research.

IL-6 AND RECEPTORS IN CANCER

IL-6 is involved in the regulation of various cellular functions, among them proliferation, apoptosis, angiogenesis, differentiation and regulation of immune response[12]. This protein is a pleiotropic cytokine synthesized by different cell types, such as B and T-cells, macrophages, monocytes, fibroblasts, endothelial and mesothelial cells, keratinocytes, mast cells, stromal cells, some nerve cells and certain tumor cells[18]. Adipose tissue is another main source of IL-6[19].

The biological activity of IL-6 is initiated when the cytokine binds to a receptor complex: an 80-kDa component receptor, non-signaling α-receptor subunit (IL-6R or 80gp) and two signal-transduction components of 130 kDa (gp130) (Figure 1)[20,21]. IL-6R is expressed only by hepatocytes, neutrophils, monocytes/macrophages and some lymphocytes, while gp130 is expressed by all body cells[22]. Dimerization of IL-6/IL-6R/gp130 lead to the initiation of intracellular signaling, through Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT), Mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase/Akt kinase (PI3-K/AKT) pathways[23] and consequently activate the expression of different genes with crucial roles in inflammation and cancer development. This mechanism is the classical signaling pathway[24]. When IL-6 binds to the receptor, STAT3 is activated in a JAK-dependent manner that leads to increased receptor activator of nuclear factor κB ligand (RANKL) expression. IL-6 may also activate AKT *via* increased JAK-dependent PI3K activity and results in cell survival and anti-apoptosis signaling. Concomitantly, increased MAPK activity downstream of JAK activation can lead to up-regulated cell growth, proliferation, and mitosis (Figure 1)[25].

Some cells express lower levels of IL-6 transmembrane receptor, in this case IL-6 can bind to a soluble form of the IL-6R (sIL-6R). Then, through a process denominated trans-signaling, the IL-6/sIL-6R complex binds to gp130 and subsequently signal transduction pathways are activated (Figure 1)[24,26]. Due to the fact that the sIL-6R lacks a membrane signaling domain, there appears to be significant differences in the intracellular signaling pathways. While IL-6 trans-signaling also leads to phosphorylation and activation of STAT3, increased cell survival, proliferation, and mitosis occurs in an AKT- and MAPK-independent manner. The exact mechanisms for IL-6 trans-signaling leading to increased cell survival, proliferation, and mitosis are not yet known (Figure 1)[25].

In humans, sIL-6R can be generated by proteolytic cleavage (90%) of the transmembrane receptor mediated by metalloproteinases such as a disintegrin and metalloproteinase 10 and 17[27,28] or by an alternative mRNA splicing (10%)[29].

A soluble form of gp130 (sgp130) is present at con-

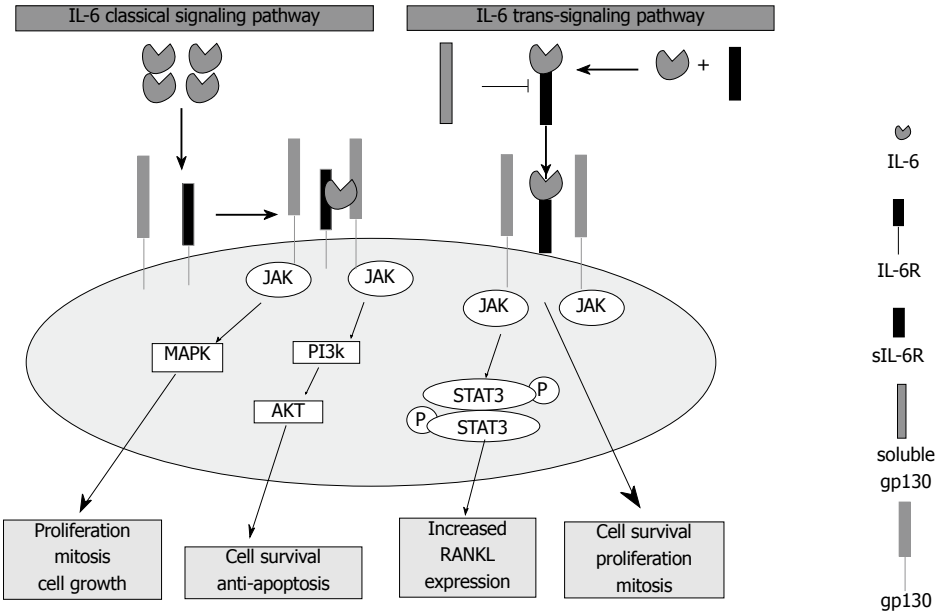

Figure 1 Schematic of IL-6 classical and trans-signaling pathway. IL-6: Interleukin 6; JAK: Janus kinase; MAPK: Mitogen-activated protein kinase; PI3K; Phosphatidylinositol 3-kinase; RANKL: Receptor activator of nuclear factor κB ligand; sIL-6R: Soluble IL-6 receptor; STAT3: Signal transducer and activator of transcription 3.

centrations between 100-400 ng/mL (1-4 nmol/L) in healthy human serum[30]. Jostock *et al*[31] reported that IL-6 alone does not interact with sgp130. Thus, signaling *via* the membrane-bound IL-6R is not inhibited by sgp130[31]. Based on their results, it was suggested that endogenous sgp130 may be a natural antagonist of the IL-6/sIL-6R complex *in vivo*, probably to prevent systemic IL-6 trans-signaling during inflammatory diseases[31]. Sgp130 inhibits the activity of the IL-6/sIL-6R complex and is in competition with gp130 for this complex without interfering with the classical IL-6 signaling pathway (Figure 1)[31-33]. A schematic of IL-6 classical and trans-signaling pathway is shown in Figure 1. In classical signaling, IL-6 binds first to the membrane-bound non-signaling IL-6R. After recruitment of two gp130 molecules the complex is formed and signal transduction is induced; in trans-signaling, IL-6 binds to the sIL-6R, which is generated by ectodomain shedding of the surface receptor or alternative splicing. The IL-6/sIL-6R can bind to both membrane-bound or sgp130 and a molar excess of sgp130 leads to competitive inhibition of the IL-6/sIL-6R response. Sgp130 has no access to the IL-6/IL-6R complex of the classical signaling pathway. Figure 1 was adapted from[25,34,35].

IL-6 may have a crucial role in the growth and differentiation of malignant tumors. IL-6 has multiple effects on tumor progression, some are the result of autocrine activity on tumor cells and others are a consequence of paracrine action on normal cells in the tumor microenvironment, particularly osteoblasts, osteoclasts, endothelial cells and immune cells[36]. For example, tumor cells from prostate, breast and colon cancer produce large amounts of IL-6 and express its receptors, IL-6R (gp80) and gp130, allowing them to respond in an autocrine manner to IL-6[28]. Moreover, multiple myeloma and neuroblastoma cells do not produce IL-6R but express IL-6. These cells respond in a paracrine manner to IL-6 present in the tumor microenvironment[36].

IL-6 can also modulate the metastatic process. High IL-6 expression in specific organs such as lung, liver or brain may attract circulating tumor cells to these organs, promoting the development of metastases[28]. Recently, it was demonstrated that the production of IL-6 and IL-8 in the primary tumor was responsible for the recruitment of circulating tumor cells to the primary site, resulting in a process called self-seeding which would lead to rapid tumor growth, angiogenesis, as well as stromal cell recruitment[29].

An elevated serum IL-6 level has been correlated with adverse prognosis in patients with several different types of cancer, such as multiple myeloma[37], lymphoma[38], ovarian cancer[39-41], PC[42], metastatic renal carcinoma[43], lung cancer[44], and breast cancer[45,46]. Hence, the interest in using serum IL-6 as a specific prognostic factor for PC and breast cancer has increased[45,47].

On the other hand, trans-signaling through the IL-6/sIL-6R complex has been shown to have an important role in inflammatory diseases and in the development and progression of various malignant tumors[34].

IL-6 trans-signaling has become a new area of research, and it was shown that sIL-6R is produced by various cancer cells, the serum concentration of sIL-6R is associated with decreased survival and increased aggressiveness of metastases in breast, prostate and colorectal cancers[48-50]. The source of sIL-6R is not known, but it is shed by inflammatory cells including neutrophils, monocytes/macrophages and T cells[51,52]. On the other hand, several tumor cells can shed IL-6R or produce it as a result of alternative splicing[53]. Some data suggest that IL-6 trans-signaling causes various effects that promote cancer metastases including, increased detachment, proliferation

and migration[54].

IL-6 has emerged as an important cytokine in the tumor microenvironment, which may contribute to the development and progression of various malignant tumors. Currently, little is known about the IL-6 trans-signaling pathway, and we suggest more studies to improve knowledge on the sIL-6R as a potential therapeutic target.

IL-6 PATHWAY IN PROSTATE CANCER

IL-6 serum levels and its receptors in prostate cancer patients

Involvement of IL-6 in PC development and progression has been suggested by several studies through increased IL-6 and sIL-6R levels during PC carcinogenesis and progression[12-14]. Baillargeon *et al*[15] suggested that serum and plasma IL-6 and sIL-6R levels are associated with progression and poor prognostic in PC patients.

Clinical observations have demonstrated increased IL-6 levels in plasma and serum from patients with CRPC[55,56], metastatic PC[42,48,57-59], biochemical recurrence[42] and poorer overall survival[15,60] compared to patients with earlier stages of the disease and healthy individuals.

Other studies support these findings and have shown that IL-6 can be correlated with the extension of disease, tumor size and bone metastases in PC[48,61].

Akimoto *et al*[57] found that serum levels of IL-6 were significantly higher in PC patients with bone metastasis than in PC patients without bone metastasis. These results suggested that serum levels of IL-6 were closely related to the metastatic burden of osseous tissue in PC patients[57]. Adler *et al*[58] reported that patients with metastatic PC had significantly elevated IL-6 levels when compared with those in other PC groups as well as controls. Of the 9 patients with distant metastatic disease (M1), 7 had elevated serum IL-6 levels. However, mean serum IL-6 was similar in patients with organ confined cancer (pT2) and in those with nodal metastases (N1). Eight of the 12 patients with N1 disease had decreased serum IL-6 compared to the pT2 group.

In another study, patients with metastatic PC were compared to patients with localized PC, and significant differences in IL-6 levels among the groups were observed. IL-6 levels were significantly higher in patients with metastatic disease. Patients with lymph node metastases or bone metastases had similar IL-6 levels. Serum IL-6 was significantly elevated in patients with Gleason score > 6[59]. Shariat *et al*[48] observed that the preoperative IL-6 and IL-6sR levels were elevated in patients with a final Gleason sum of 7 or greater. They reported that neither IL-6 nor IL-6sR were predictors of organ-confined disease. The mean preoperative IL-6 and sIL-6R plasma levels were higher in patients with aggressive disease than in those with non aggressive phenotype. IL-6 and sIL-6R plasma levels in patients with PC metastatic to bone were higher than those in patients with metastases in regional lymph nodes and these, in turn, were higher than those in prostatectomy patients and healthy subjects. However, the IL-6 and IL-6sR levels were not different between the prostatectomy patients and the healthy subjects.

Regarding patients with CRPC, Drachenberg *et al*[55] found that serum levels of IL-6 were significantly elevated in patients with clinically evident CRPC compared to normal controls, patients with BPH, prostatitis, and localized or recurrent disease. Wise *et al*[56] observed elevated levels of the anti-inflammatory cytokine, IL-6, in CRPC patients when compared to patients with CSPC.

The results obtained by George *et al*[60] showed that IL-6 levels were higher in patients with metastatic disease and these patients had worse survival when compared with patients who had low IL-6 levels. An analysis by Nakashima *et al*[15] verified a significantly shorter survival in patients with elevated IL-6 levels, PSA serum levels and aggressive disease.

Additionally, Shariat's[48,62,63] group demonstrated that preoperative plasma levels of IL-6, sIL-6R and transforming growth factor-beta1 (TGF-β1) predicted biochemical recurrence after surgery or radical prostatectomy, suggesting an association with occult metastatic disease at the time of radical prostatectomy. The results of Alcover *et al*[64] are in agreement with Shariat's group, as they observed that IL-6 predicts biochemical recurrence following radical prostatectomy. More recently, a predictive model was proposed that included only sIL-6R[65]. Kattan *et al*[66] developed and validated a prognostic model that added plasma sIL-6R and TGF-β1 as standard clinical predictors for biochemical recurrence. However, Baillargeon *et al*[16] found that serum IL-6 levels were not associated with PC. According to Finley *et al*[67] the differences among various studies are a consequence of systemic cytokine levels detected in peripheral blood that may not reflect local concentrations in the tumor microenvironment.

IL-6 levels can also be elevated in obese individuals[68]. The relationship between obesity, circulating IL-6 and PC may help to understand the role of this molecule and how it contributes to the molecular basis for the association between obesity and PC[3,69-71]. Adipose tissue is a highly active endocrine tissue that secretes numerous factors, including growth factors, cytokines, hormone-like molecules and many other molecules[72]. Several studies have demonstrated that the abundant number of growth factors such as vascular endothelial growth factor (VEGF), inflammatory cytokines [IL-6, tumor necrosis factor-alpha, interleukin-8 (IL-8)] and adipokines (adiponectin, leptin) released from adipose tissue can exert a substantial impact on the progression and outcome of many human diseases, including PC[3,16,71]. These molecules have a crucial role in obesity[73] and cell proliferation[74]. For instance, adipose tissue surrounding the prostate, i.e., periprostatic adipose tissue, is frequently invaded by prostate tumor cells, although its contribution to the tumor microenvironment is largely unknown. A recent study demonstrated that periprostatic adipose tissue produced local IL-6 at levels significantly higher than those in the circulation[67]. Other studies support a role for IL-6

production, which is up-regulated in obese patients, in PC cell migration and invasiveness[67,71].

Recently, Shariat *et al*[75] in a study of 423 preoperative and 206 postoperative blood samples from patients treated with radical prostatectomy for clinically localized PC investigated the association between sgp130 levels and PC prognosis. In the group of patients treated with radical prostatectomy, higher preoperative plasma sgp130 was significantly associated with higher pathological Gleason, extraprostatic extension, seminal vesicle invasion, lymph node metastasis and biochemical recurrence. These authors concluded that higher sgp130 plasma levels were associated with features of biologically aggressive PC. In a subset of 206 patients, postoperative sgp130 levels were 18% lower than preoperative levels. These decreased levels suggest that the higher blood levels of sgp130 are produced by tumor cells[75].

These clinical data support the biological role of the IL-6 pathway in PC, suggesting the inclusion of IL-6, sIL-6R and gp130 levels as new tumor biomarkers in PC patients[76]. Improving prediction accuracy by using more prognostic factors supports an early detection of any changes in the progression of the disease[25].

IL-6 expression in prostate cancer tissues and cell lines

The expression of IL-6 and its receptors has been investigated by several authors in benign prostate cells, PC tissues and in prostate cell lines (LNCaP, DU145, PC3). Hobisch *et al*[14] through immunohistochemical studies revealed that IL-6 expression was localized predominantly in basal cells of benign prostatic epithelium and in glandular cells of PC tissues. Another study observed that in normal prostate, IL-6 was immunolocalized in basal cells of the epithelium and gp130 was detected only in stromal cells[77]. However, Hobish *et al*[14] showed that cultured stromal cells secreted IL-6, but the rate of IL-6 was so low that there was only a minimal amount contained in the cells, and thus it may not be detectable by immunohistochemical methods. In benign prostate cells, gp130 was confined to the epithelium and stroma, and IL-6 was immunolocalized preferentially in epithelium[77]. These data are in agreement with Degeorges *et al*[78] who demonstrates that IL-6 is secreted by cultured benign prostate cells. In PC tissues, gp130 was detected in stroma and epithelium and the expression increased with Gleason Grade[77]. On the other hand, IL-6 was localized in all cell types and immunostaining increased with Gleason Grade[77]. These results are in agreement with the reported secretion of IL-6 by PC cells[79] and with increased IL-6 levels in PC patients with poor prognosis[42,48]. Palmer *et al*[80] observed that IL-6 and IL-6 receptors are expressed in PC cells. They showed that in LNCaP, DU145 and PC3 cell lines, this cytokine and its receptors are widely expressed, but not in normal prostate epithelial PZ-HPV-7 cells.

The role of the pro-inflammatory cytokine, IL-6, in PC lesions has not yet been clarified but may represent an interesting area of investigation. In order to delineate their specific functions during prostate tumor development and progression, several authors used human PC cell lines (LNCaP, DU145 and PC3)[17,81-88].

Significance of IL-6 pathway in cell growth: In vitro results

The castration-sensitive cell line, LNCaP, is one the most frequently used in PC studies. In order to improve our understanding of cellular events which may be relevant to PC patients with higher IL-6 levels, several authors treated LNCaP cells with IL-6[81,82].

Okamoto *et al*[82] found that growth of the LNCaP cell line was stimulated by the administration of IL-6, but not by their conditioned medium. Conditioned medium containing biologically active components (e.g., growth factors, cytokines) was obtained from previously cultured cells or tissues released into the media, substances that affect certain cell functions. These authors observed that DU145 and PC3 (castration-resistant) cell lines proliferate in response to stimulation with IL-6 and in response to its conditioned medium. The authors concluded that IL-6 acts as an autocrine and/or paracrine proliferative factor in PC cell lines[82]. It was demonstrated that IL-6 acts as a paracrine inducer of growth in the LNCaP cell line[17,79,82,83]. On the other hand, IL-6 functions as an autocrine growth-inducer in the DU145 and PC3 cell lines[82,84]. Chung *et al*[85] obtained similar results, finding that IL-6 acts as a growth inducer in PC3 and DU145 cell lines through an autocrine and paracrine action. However, the effect of IL-6 in LNCaP cells is still controversial. Some studies reported that IL-6 acts as an inducer of growth in this cell line[82,83,86], while others showed that IL-6 acts as an inhibitor[81,85,87]. The reason for these differences between the various studies is that IL-6 may have different functions in human PC cell line proliferation, according to their phenotypic characteristics.

Hobisch *et al*[81] generated a cell line (LNCaP-IL-6+) by exposing these cells to continuous administration of IL-6 and observed changes in their responsiveness and signal transduction. Initially, growth of LNCaP was inhibited by IL-6. After long-term treatment, the LNCaP-IL-6+ cell line began to secrete IL-6 and a higher basal proliferation rate was observed. In this situation, IL-6 induces cell growth.

Recently, there is evidence to suggest that IL-6 switches from a paracrine growth inhibitor to an autocrine growth stimulator[12,81,88]. Similar changes in responsiveness to IL-6 were observed in melanoma cells[89]. The behavior of the human prostate carcinoma LNCaP cell line may be dependent on the microenvironment of the culture system[12].

A recent study by Shariat *et al*[75] showed that sgp130 promotes PC invasiveness *in vitro*. In this study, continuous exposure of PC cells to sgp130 led to an increase in their invasiveness[75]. These authors suggest more studies are required with regard to the role of IL-6 and sgp130 in the PC biological behavior *in vitro* and *in vivo* for a better understanding of their role in this disease[75].

HORMONAL CASTRATION IN ADVANCED PROSTATE CANCER PATIENTS: ANDROGEN RECEPTOR AND IL-6 PATHWAYS

Initial treatment for organ-confined PC is usually radical prostatectomy and/or radiation therapy[90]. Although, most patients have advanced disease and are submitted to hormonal castration (HC)[90]. The initial response rate is excellent, but the majority of PC patients relapse into CRPC. CRPC is a common lethal form of PC that typically metastasizes to bone and visceral organs, frequently resulting in patient death[91,92]. Progression to metastatic disease is slow and can be accompanied by increased PSA levels[93]. The mechanisms implicated in CRPC progression are unknown. These findings suggest that CRPC progression remains the major obstacle to effective control and cure of advanced phenotype disease. Consequently, novel therapeutic strategies that target the molecular mechanism involved in CRPC are needed[94].

PC cells are androgen-dependent, in particular, testosterone is necessary for their growth and survival[91]. Thus, the blockade of testosterone initially causes a stop in PC cell growth[95]. However, not all tumor cells need testosterone for development. After HC, many tumors begin to exhibit a testosterone blockade resistance behavior. In this situation, CSPC cells undergo apoptosis and there is a selective advantage for CRPC cells with consequent proliferation[96].

The androgen receptor (AR) is an important protein involved in the normal maintenance, development and growth of prostate epithelial cells. AR is a nuclear ligand-activated transcription factor in the prostate gland and mediates the biological response of androgens with a crucial function in a molecular mechanism responsible for the transition from CSPC to CRPC progression[97-99]. The AR is expressed in the normal prostate and during various stages of prostate carcinogenesis (PIN, organ-confined tumors, metastatic tumors and before or after hormonal treatment)[100,101].

The AR uses di-hydrotestosterone (DHT) and testosterone as its natural ligands for phosphorylation, and the ligand-receptor complex translocates into the nucleus where it binds to a DNA sequence in the regulatory regions of AR target genes[99]. These complex interactions facilitate the activation or repression of the expression of several genes involved in the development, differentiation and proliferation of target cells. Some of these genes include *PSA* and *human glandular kallikrein 2* (*hk2*)[102].

During CRPC development, PC cells can develop alternative mechanisms which can influence their microenvironment and, consequently, their survival in an androgen-poor microenvironment[103]. Several models have been proposed to explain the development of this phenotype: hypersensitive pathways, promiscuous receptor, coactivators and corepressors, bypass pathway, PC stem cells and outlaw pathways[91,97,104-107].

In the hypersensitive pathways, the cells acquire the ability to use very low levels of androgen during HC[97]. There are three mechanisms that may or probably are involved in this pathway: (1) AR amplification, PC cells have increased expression of AR[103]. The increased AR expression allows higher ligand binding. This hypothesis is supported by results obtained with CRPC cell lines that show an increased expression of AR compared with CSCP[97]; (2) increased AR sensitivity, consequently, tumor cells are hypersensitive to the growth promoting effects of DHT[108]; and (3) increased 5-alpha-reductase activity that increases the conversion of testosterone to DHT[91].

The promiscuous pathway involves acquisition of mutations in the AR protein, consequently, the AR can be activated by nonandrogenic steroid molecules that are present in the circulation[91,97,105,106,109]. There are a large number of coactivators and corepressors involved in regulation of the AR[110]. These molecules are intermediates between the AR signaling pathway and transcriptional machinery[103]. In the bypass pathway, PC cells acquire a phenotype that allow them to survive and escape apoptosis in an androgen-depleted environment[106]. Another bypass mechanism is correlated with neuroendocrine differentiation of PC cells[106]. These cells are more represented in CRPC cells and are associated with a low rate of proliferation[106]. Neuroendocrine cells have the capacity to increase the proliferation of surrounding cells, thus progression of the PC cells occurs in a androgen-poor microenvironment[106].

The PC stem cells model showed that only a rare subset of cells is tumorigenic[111]. Collis *et al*[112] reported that a population of cells comprising 0.1% of prostate tumors (CD44+/a2h1/CD133+) without AR expression may be prostate cancer stem or progenitor cells. There is also another possible mechanism for cell survival in an androgen-poor microenvironment, where the presence of prostate cancer stem cells continually resupply the tumor cell population and are not affected by HC. These cells are capable of differentiating into androgen-dependent and -independent cells, leading to the development of a heterogeneous androgen receptor phenotype. This phenotype is typical in patients with CRPC[103,104].

Another potential hypothesis (outlaw pathway), is that during HC the AR can be activated by other nonsteroidal molecules synthesized and secreted by tumor cells, such as cytokines and growth factors [e.g., Keratinocyte Growth Factor, Epidermal Growth Factor, Insulin-like Growth Factor-1 and IL-6][113-115], leading to CRPC development and progression. Even if androgens are principally responsible for activating the AR, it is known that in the absence or presence of very low concentrations of androgens, the AR can be activated by growth factors and cytokines[113]. In prostate tumor, the microenvironment is secreting growth factors and cytokines which may directly manipulate paracrine and autocrine pathways involved in PC development and promote CRPC in patients treated with hormonal therapy[116].

Some studies have examined the IL-6 pathway in

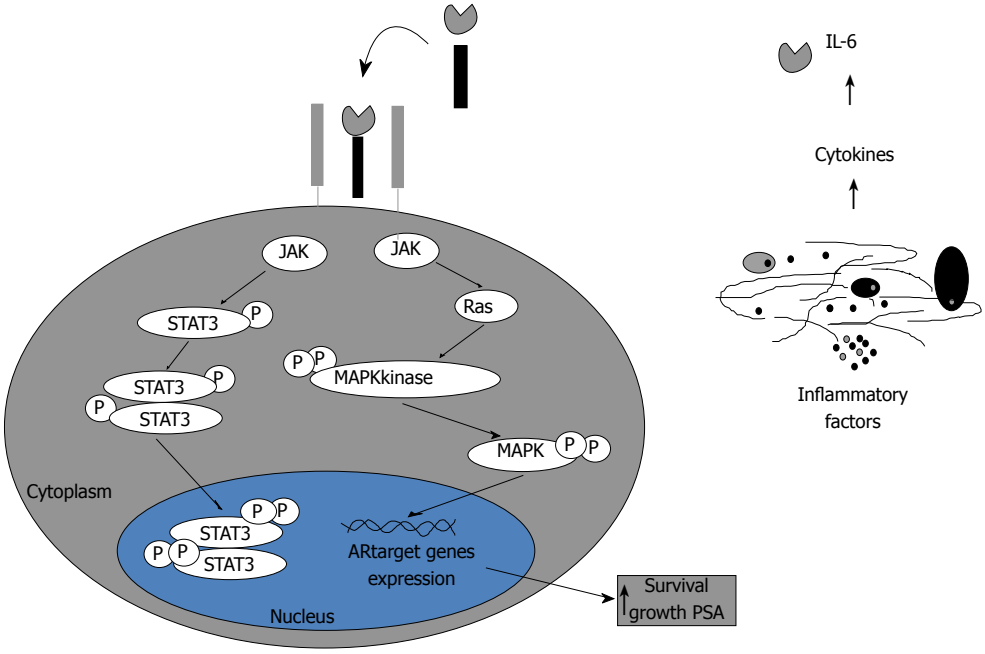

Figure 2 Hypothetical representation of AR pathway regulation by IL-6 in prostate cancer cells. IL-6: Interleukin 6; MAPK: Mitogen-activated protein kinase; STAT3: Signal transducer and activator of transcription 3; AR: Androgen receptor; PSA: Prostate-specific antigen.

CRPC progression and have revealed a possible involvement in regulation of the AR[117-119]. In the absence of androgen, IL-6 causes activation of the AR which is approximately 50% of the maximal activity induced by androgen. In low concentration conditions, androgen is potentiated by IL-6, leading to synergistic activation of the AR[93]. These observations demonstrate a cross-talk between the IL-6 pathway and AR. Due to the presence of increased IL-6 levels in patients with locally advanced or metastatic disease, the signaling pathway mediated by this cytokine could be an alternative pathway in the RCH phenotype acquisition and progression. Figure 2 shows that IL-6 activates the AR through a mechanism that is dependent on the MAPK and STAT3 signaling pathway in PC cells. This is a hypothetical representation of the AR pathway regulation by IL-6 in PC cells. The IL-6 pathway may be an alternative pathway for growth and proliferation of PC cells, under androgen deprivation conditions. IL-6 induces up-regulation of AR target gene expression such as PSA by STAT3 and MAPK signal transduction pathways. Figure 2 was adapted from[99,116].

We consider IL-6, other cytokines and growth factors as important regulators of PC growth with a significant role in the AR pathway. It has been proposed that the combined blockage of key molecules in proliferation signaling pathways (e.g., TGF, IL-6) could be one of the most promising strategies for CRPC[120]. Consequently, several authors have been investigating IL-6 activity in PC cells *in vitro* and *in vivo*. *In vitro* research on the regulation of PC cell growth and transcriptional activation of the AR by IL-6 have been focused on cell lines (LNCaP, DU145, PC3) and different results were obtained[17,82-84].

In vitro and in vivo studies on androgen receptor regulation by IL-6

The interaction between IL-6 and the AR may be more important in advanced PC patients who have elevated serum levels of IL-6 and its receptors. Several *in vitro* studies identified alternative pathways that influence or modify the activity of the AR signaling pathway in PC cells. Cross-talk between IL-6 and the AR was investigated in PC cells which transiently express the AR (DU-145) and in LNCaP cells which have a promiscuous mutated AR. Results on IL-6 induction, AR activation and tumor proliferation are contradictory. This is probably due to controversial results on the induction or stimulation effect of IL-6 on PC cell growth[121].

In LNCaP and DU-145 cell lines, IL-6 activates the AR in a ligand-independent and synergistic manner in low androgen concentrations[119]. This fact might seem paradoxical because proliferation of LNCaP was inhibited by IL-6. However, it has been suggested that IL-6 is a important molecule in the maintenance and differentiation of PC cells and this cytokine is involved in enhanced PSA mRNA regulation and in the regulation of its protein[93]. It was observed that long-term treatment with IL-6 in LNCaP cells increased expression and activity of the AR[117,119] and overexpression of IL-6 protects LNCaP cells from apoptosis induced by HC[93].

In MDA PC 2b cells (androgen-sensitive cell line), IL-6 promotes growth and this effect was dependent of the AR[76]. It is known that AR signaling is complex and there are several AR-associated proteins with a crucial role in the modulation of response in a cell type-dependent manner[122]. For this reason, IL-6 up-regulation has been investigated in PC. Additionally, authors hypoth-

esized that IL-6 may promote tumor growth through AR activation *in vivo*. In their work, MDA PC 2b cells were xenografted into nude mice. They observed that growth of MDA PC 2b xenografts in castrated animals treated with IL-6 was similar to that in non-castrated animals. In addition, tumors did not significantly grow in castrated mice and mice treated with IL-6 and bicalutamide (oral non-steroidal anti-androgen used in the treatment of PC). Bicalutamide showed an inhibitory effect on IL-6-regulated growth *in vivo*[76].

This evidence demonstrated that IL-6 has a crucial role in androgen-responsive gene expression and, consequently, is an important regulator in the growth of CRPC cells *in vitro* and *in vivo*. Another recent study evaluated the effects of IL-6 in the LNCaP cell line on phenotype changes before and after androgen deprivation[94]. *In vitro* observations indicate that the growth of LNCaP/IL-6 (IL-6-transfected LNCaP) was significantly lower than LNCaP/Co (not IL-6-transfected LNCaP) under androgen-deprivation conditions. Furthermore, LNCaP/IL-6 tumors in nude mice rapidly regressed after castration. However, LNCaP/Co tumor growth was transiently inhibited after castration and then continuously accelerated[94]. Gene microarray analyses showed that androgen deprivation resulted in the differential expression of genes involved in growth, apoptosis and carcinogenesis between LNCaP/Co and LNCaP/IL-6[94]. The principal conclusion of this study is that IL-6 produced by LNCaP may have a suppressive role on growth and a crucial function in the androgen-resistance phenotype under an androgen-poor microenvironment[94]. These and other future investigations will clarify the molecular mechanism involved in changes of phenotype in LNCaP cells that express higher IL-6 levels.

Efficient activation of the AR by IL-6 involves multiple signaling pathways such as STAT3, PI3K and MAPK. At present, little is known about these mechanisms. Some studies have used inhibitors of these signaling pathways. Inhibitors of the JAK, MAPK and PI3K signaling pathways resulted in a down-regulation of IL-6 on the AR[119]. Lin *et al*[117] showed that MAPK is important for AR activity through IL-6. These authors demonstrated that an inhibitor of MAPK abrogated IL-6 activation of the PSA promoter. In contrast, an inhibitor of the PI3K pathway had no effect on IL-6 regulation of AR activity[117]. Chen *et al*[118] also showed that JAK inhibition stopped AR activation by IL-6. This study demonstrated that the JAK-STAT pathway is implicated in AR activation by IL-6 in the LNCaP cell line. On the other hand, Zelivianski *et al*[123]. demonstrated that IL-6 up-regulated AR protein levels in low passage LNCaP cells, while in high passage LNCaP cells the opposite effect was observed.

Recent research in prostate carcinoma has focused on the role of sIL-6R. The trans-signaling pathway mediated by complex IL-6/sIL-6R seems to have an important role in the pathophysiology of certain inflammatory, nervous system and cardiovascular diseases and some cancer types[34]. The IL-6/sIL-6R complex can have an antiapoptotic role and is therefore considered a possible cause of certain cancers such as colon cancer and melanoma[26,34,52,124-127]. To the best of our knowledge, the classical and trans-signaling pathways in specific PC events are not well known. Furthermore, sIL-6R showed a stronger association with disease progression than IL-6[54], suggesting a role of complex IL-6/sIL-6R in the spread of metastases. Santer *et al*[54] conducted a study with the principal aim of determining the effect of complex IL-6/sIL-6R on PC cell proliferation and in metastasis formation. These authors focused their studies on sIL-6R, because it is the first element in the IL-6 signaling pathway. They found that activation of sIL-6R resulted in increased PC cell motility and migration[54]. Thereby, it is believed that sIL-6R may be important in the metastastic process through down-regulation of the tumor suppressor, maspin, by sIL-6R. In contrast, the IL-6 trans-signaling pathway reduces PC cell proliferation[54].

It was suggested that targeting sIL-6R may be an alternative method of improving anti-IL-6 therapies used in PC treatment[54]. Understanding how the IL-6 pathway affects cellular events in the PC cell microenvironment and its interaction with the AR pathway will allow the development of preventive and therapeutic strategies for PC patients in the future.

IL-6 TARGETING

The importance of the IL-6/IL-6R pathway in the regulation of PC cells and the potential involvement of this signaling pathway in androgen-resistant growth of PC cells makes it a good candidate for targeted therapy. In this perspective, the use of IL-6-neutralization antibodies, antisense oligonucleotides and antagonists should be the subject of study[88]. The principal goal is to identify new therapies to target tumor cells and/or microenvironment and consequently increase the chances of survival for PC patients with aggressive phenotypes and those who develop resistance to hormonal therapy.

It has been reported that IL-6R blockade by IL-6R antagonists might reduce tumor cell growth and consequently disease progression[128]. The IL-6/IL-6R signaling pathway involves numerous proteins and a large number of phosphorylation cascade pathways. Downstream molecules of these proteins and pathways may be crucial targets for specific therapies. For example, inhibition of STAT3 suppresses PC progression[129] and reduces STAT3 target gene expression, such as VEGF, Bcl-X and cyclin D1 and leads to apoptosis[130].

Other investigations are involved in the study of the chimeric monoclonal anti-IL-6 antibody, siltuximab (CNT0 328). Steiner *et al*[131] showed that tumor growth in nude mice inoculated with LNCaP-IL-6+ cells after CNTO 328 treatment was reduced. Other studies obtained analogous results when PC3 and LuCaP 35 xenografts were treated with CNTO 328[132,133]. Another study reported that CNT0 328 can inhibit PC cell growth *in vitro* and improve survival by reducing the level of ca-

Table 1 Summary of several studies on IL-6, sIL-6R and sgp130 levels in prostate cancer patients and targeted therapies for the IL-6 signaling pathway

	Ref.	Conclusions
Prognostic implications	[15,16]	L-6 level is a significant prognostic factor for PC. A significantly shorter survival in PC patients was associated with elevated IL-6 levels, serum PSA levels and aggressive disease
	[48,57-60]	The serum levels of IL-6 were significantly higher in PC patients with metastatic disease
	[48,62-66]	The levels of IL-6, sIL-6R and TGF-β1 predicted biochemical recurrence after surgery or radical prostatectomy
	[75]	In patients treated with radical prostatectomy higher preoperative plasma sgp130 was significantly associated with higher pathological Gleason, extraprostatic extension, seminal vesicle invasion, lymph node metastasis and biochemical recurrence. The postoperative sgp130 levels were 18% lower than preoperative levels
Therapeutic implications	[131-133]	These studies involved the chimeric monoclonal anti-IL-6 antibody, siltuximab (CNT0 328) It was shown that tumor growth in nude mice inoculated with LNCaP-IL-6+ cells after CNTO 328 treatment was reduced. Analogous results were obtained when PC3 and LuCaP 35 xenografts were treated with CNTO 328
	[135]	The administration of siltuximab in a group of patients who had already received docetaxel therapy had no clinical efficacy
	[136]	PC cells can develop resistance to docetaxel and STAT1 is increasingly expressed in docetaxel-resistant PC cells
	[84]	The treatment of the PC3 cell line with Sant7 inhibits cell growth more efficiently than other anti-IL-6 antibodies
	[134]	CNT0 328 can inhibit PC cell growth *in vitro* and improve survival by reducing the level of cachexia in an animal model of PC
	[133]	In mice, CNT0 328 inhibited the conversion of CSPC into more aggressive disease
	[137]	STAT3 and MAPK activity is suppressed in patients taking siltuximab, which may inhibit IL-6-mediated drug resistance

PC: Prostate cancer; CSPC: Castration-sensitive prostate cancer; TGF-β1: Transforming growth factor-beta1; IL-6: Interleukin-6; sIL-6R: Soluble interleukin-6 receptor; STAT3: Signal transducer and activator of transcription 3; MAPK: Mitogen-activated protein kinase.

chexia in an animal model of PC[134]. In addition, CNT0 328 has been shown in mice to inhibit the conversion of CSPC into more aggressive disease, bone metastasis, and difficult to treat CRCP[133].

In a clinical trial, it was shown that the administration of siltuximab in a group of patients who had already received docetaxel therapy had biological, but not clinical efficacy[135]. PC cells can develop resistance to docetaxel, and Patterson *et al*[136] reported that STAT1 is increasingly expressed in docetaxel-resistant PC cells. The high heterogeneity of prostate tumors can explain this resistance to docetaxel in PC cells[11]. Recent studies indicate that STAT3 and MAPK activity is suppressed in patients taking siltuximab, which may inhibit IL-6-mediated drug resistance[137]. However, in a study that involved patients with CRPC, where the disease had progressed beyond docetaxel therapy, siltuximab had a minimal clinical effect, despite positive biological IL-6 inhibition[135].

Lou *et al*[83] reported that targeting IL-6 may have multiple advantages in patients that receive limited therapeutic and survival benefit from conventional therapies. In a previous study, Borsellino *et al*[84] found that treatment of the PC3 cell line with Sant7, a modified interleukin-6 which binds with high affinity to IL-6R but does not bind with gp130, inhibits cell growth more efficiently than other anti-IL-6 antibodies.

We believe that the development and availability of IL-6 inhibitors is fundamental for the treatment of IL-6-dependent cancers, where the IL-6 signaling pathway is deregulated. This review demonstrates the role of IL-6 and the levels of its receptors as prognostic factors in PC patients. These deregulated levels could be important in anti-IL-6 therapy development. Table 1 presents a summary of several studies on IL-6, sIL-6R and sgp130 levels in PC patients and targeted therapies for the IL-6 signaling pathway. However, more studies and appropriate clinical trials are needed to determine the effectiveness of anti-IL-6 therapies in cancer patients.

CONCLUSION

The information presented in this review suggests that the IL-6 signaling pathway plays an important role in PC development/progression, and IL-6 is able to maintain tumor growth through the AR pathway in androgen-deprived conditions. Further studies are suggested to assess the functionality of the IL-6/sIL-6R complex in PC. Understanding how IL-6 affects cellular events in the PC cell microenvironment and its interaction with the AR pathway will allow the development of preventive and therapeutic strategies for PC patients in the future. However, it is also important to study and characterize other signaling pathways involved in CRPC progression and the cross-talk among them, allowing the design of new and more adequate targeted therapies. Additionally, diverse studies reported that serum and plasma levels of IL-6 and sIL-6R are increased in patients with aggressive disease and a poor prognosis, suggesting the inclusion of IL-6 and the levels of its receptors as putative new tumor biomarkers. In addition, changes in serum IL-6 levels could help direct additional treatment strategies in the future, however, clinical studies are needed to assess this potential.

In conclusion, IL-6 is a good candidate for the development of targeted therapies in PC, but more studies and appropriate clinical trials need to be carried out to ascertain the effectiveness of anti-IL-6 therapies in PC patients.

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