Emerging roles of chemokines in prostate cancer

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Abstract

Prostate cancer (PCa) represents the second leading cause of death among all cancer types in men in Europe and North America. Among the factors suspected to control PCa, incidence and progression, chemokines, and their receptors are now intensively studied. Chemokines are produced by tumor cells and also by the stromal microenvironment, both in the primary tumor site and in distant metastatic locations. The wide and differential distribution of chemokines and their receptors account for the pleiotropic actions of chemokines in PCa, including the modulation of growth, angiogenesis, invasion, metastasis, and hormone escape. This review will focus on the roles and the mechanisms of action and regulation of chemokines in the different steps of PCa development and will discuss the novel strategies that are currently envisioned to target chemokines in PCa.

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Introduction

Prostate cancer and chemokines

Prostate cancer (PCa) is the most commonly diagnosed cancer in males and the second leading cause of death from cancer in men. Its incidence has increased dramatically since the advent of prostate-specific antigen (PSA) screening in the early 1990s. One in six men in the US will be diagnosed with PCa in his lifetime (Jemal *et al.* 2006). Most PCas, as well as normal prostate tissue, are dependent on the presence of androgens for growth and survival. Localized PCa can be effectively treated with radical prostatectomy or radiation therapy. For more advanced cancers, androgen ablation therapy to block the function of the androgen receptor (AR), has shown beneficial effects only for hormone-responsive early-stage disease (Javidan *et al.* 2005). Cancer cells that become hormone-independent also become highly invasive, and they reach the clinical stage associated with an increased incidence of skeletal metastases as the disease progresses (Bostwick *et al.* 2004, Logothetis & Lin 2005, Taplin 2007, Devlin & Mudryj 2009). PCa shares a number of features with benign prostatic

hyperplasia (BPH) and the putative precursor of cancer, prostatic intraepithelial neoplasia. All three stages of prostate disease increase in prevalence with age and require androgens for growth and development.

So far, the factors responsible for PCa progression remain elusive. Among the mediators of carcinogenesis, the significance of chemokines in PCa progression has increased. In multicellular organisms, the interactions between individual cells are essential to ensure their correct functions in an appropriate spatial and temporal manner. In particular, cell homing requires a fine tune in embryonic development, inflammation, or immunity. Such events appear to be deregulated in the neoplastic process.

Chemokines are members of a superfamily of chemotactic cytokines (Ali & Lazennec 2007; Table 1), initially characterized because of their association with inflammatory responses, and by stimulation of leukocyte chemotaxis during inflammation (Thelen 2001, Dowsland *et al.* 2003). Chemokines constitute a large family (45 human members) of low molecular weight proteins and are mostly secretory in nature (Table 1). The chemokine family can be subdivided in four groups, based on a conserved

Table 1 The superfamily of chemokines

New nomenclature	Ligand	Receptor(s)
CXC chemokines		
CXCL1	GRO α /MGS α	CXCR2, CXCR1
CXCL2	GRO β /MGS β	CXCR2
CXCL3	GRO γ	CXCR2
CXCL4	PF4	CXCR3B
CXCL4V1		
CXCL5	ENA-78	CXCR2
CXCL6	GCP-2	CXCR1, CXCR2
CXCL7	NAP-2	CXCR2
CXCL8	IL-8	CXCR1, CXCR2
CXCL9	MIG	CXCR3, CXCR3B
CXCL10	IP-10	CXCR3, CXCR3B
CXCL11	I-TAC	CXCR3, CXCR3B, CXCR7
CXCL12	SDF-1 α/β	CXCR4, CXCR7
CXCL13	BLC, BCA-1	CXCR5
CXCL14	BRAK, Bolckine	Unknown
CXCL15	Unknown	Unknown
CXCL16		CXCR6
CXCL17	DMC	Unknown
CC chemokines		
CCL1	I-309	CCR8
CCL2	MCP-1/MCAF/TDCF	CCR2
CCL3	MIP-1 α /LD78 α	CCR1, CCR5
CCL3L1	LD78 β	
CCL3L3	LD78 β	
CCL4	MIP-1 β	CCR5
CCL4L1	AT744.2	
CCL4L2		
CCL5	RANTES	CCR1, CCR3, CCR5
CCL7	MCP-3	CCR1, CCR2, CCR3
CCL8	MCP-2	CCR1, CCR2, CCR3, CCR5
CCL11	Eotaxin	CCR3
CCL13	MCP-4	CCR1, CCR2, CCR3
CCL14	HCC-1	CCR1
CCL15	HCC-2/LKN1/MIP-1 γ	CCR1, CCR3
CCL16	HCC-4/LEC/LCC-1	CCR1, CCR2, CCR5
CCL17	TARC	CCR4
CCL18	DC-CK 1/PARC/AMAC-1	Unknown
CCL19	MIP-3 β /ELC/exodus-3	CCR7
CCL20	MIP-3 α /LARC/exodus-1	CCR6
CCL21	SLC/6CKine/SLC/exodus-2	CCR7
CCL22	MDC/STCP-1	CCR4
CCL23	MPIF/CK β 8/CK β 8-1	CCR1
CCL24	Eotaxin-2/MPIF-2	CCR3
CCL25	TECK	CCR9
CCL26	Eotaxin-3	CCR3
CCL27	CTACK/ILC	CCR10
CCL28	MEC	CCR3, CCR10

Table 1 continued

New nomenclature	Ligand	Receptor(s)
C chemokines		
XCL1	Lymphotoctin/ATAC/SCM-1 α	XCR1
XCL2	SCM-1 β	XCR1
CX3C chemokines		
CX ₃ CL1	Fractalkine	CX3CR1

amino-terminal cysteine residues motif into CC, CXC, CX3C, and C chemokines (Table 1). There is a remarkable redundancy within chemokines, with multiple chemokines binding to the same receptor and multiple receptors binding the same chemokine (Fig. 1). Chemokines interact with G-protein-coupled receptors. These are composed of ten CCR family members, seven CXCR family members, and other receptors (XCR1, CCRL1 and 2, and CX3CR1). The chemokine system also includes three decoy receptors. These receptors bind ligands with high affinity, but do not elicit signal transduction. The D6, Duffy antigen receptor for chemokines (DARC) and CCX-CKR (ChemoCentryx, chemokine receptor), are specialized receptors for chemokine sequestration acting to regulate chemokine bioavailability and compete with active receptors (Peiper *et al.* 1995, Nibbs *et al.* 1997, Gosling *et al.* 2000). Evidence exists that a chemokine monomer is sufficient to bind and activate a chemokine receptor and induce efficient leukocyte responses (Rajaratnam *et al.* 1994, Proudfoot *et al.* 2003). Nevertheless, *in vivo* data indicate that for some chemokines, such as CCL2, CCL4, CCL5, and CXCL10, the formation of oligomers enhances leukocyte recruitment (Proudfoot *et al.* 2003, Campa-nella *et al.* 2006). At chemokine-rich sites of inflammation, it is possible that chemokines hetero-dimerize. Studies have shown that such heteromeric chemokines have considerable synergism, strongly enhancing leukocyte migration. The inflammatory chemokine CXCL8, for example, can potentiate responses induced by CCL2 and CXCL12, which act on CCR1 and CXCR4 respectively, but not with CCL21, which triggers responses through CCR7 (Gouw *et al.* 2005, 2008). In response to chemokines, chemokine receptors induce a cascade of signals, which can differ between tissues, cell types, and physiologic or pathologic conditions. In particular, a cascade of downstream signals takes place, including calcium mobilization and the activation of extracellular signal-regulated kinases 1 and 2 (ERK1 and ERK2), p38 mitogen-activated protein kinase (p38 MAPK),

Figure 1 Chemokine members and their cognate receptors.

phospholipase-C β , phosphatidylinositol 3-kinase (PI3K), RAS, the RHO family of GTPases, p21-activated kinase (PAK), and NF- κ B (Rossi & Zlotnik 2000, Richmond 2002).

Chemokines and chemokine receptors: correlation with PCa disease progression

PCa typically develops through several steps, the first being the transition from normal prostate to BPH (Bostwick *et al.* 2004). During the transitions from normal to BPH and from BPH to PCa, a number of chemokines and chemokine receptors display variations in their expression. Moreover, it is important to notice that chemokines are produced by a variety of cells, comprising cancer cells but also stromal cells such as cancer-associated fibroblasts (CAFs), endothelial cells, or infiltrating cells (macrophages, lymphocytes), which is summarized in Table 2. Most of the work on chemokines in PCa has focused on the chemokines CXCL8, CXCL12, and CCL2.

Analysis by immunohistochemistry of normal human prostate has revealed that CXCL8 is weakly expressed and present at the apical membrane of epithelial cells (Murphy *et al.* 2005). Concerning the transition from normal to BPH, and based on the study of cell lines, it appears that the levels of proangiogenic chemokine CXCL8 are higher in BPH compared with normal prostate, which is correlated with an increased number of myofibroblasts in the stroma of BPH (Schauer *et al.* 2008b). BPH nodules exhibit epithelial CXCL8 staining, in addition to elevated smooth muscle α -actin, reduced calponin, and altered deposition of tenascin-C relative to normal prostate zone tissue (Schauer *et al.* 2008b).

This suggests that a reactive stroma pattern is correlated with an increase in CXCL8 levels in the adjacent epithelium.

The balance of chemokines is also altered with the progression of PCa (Fig. 2). *In situ* hybridization experiments have shown that CXCL8 RNA levels increase with the Gleason score of prostate tumors (Uehara *et al.* 2005). In PCa tissues, CXCL8 staining, as well as that of CXCR1 and CXCR2, is circumferential in high-grade tumors (Murphy *et al.* 2005). The localization of CXCL8 is somewhat controversial as another study has reported that CXCL8 is expressed by the neuroendocrine cells of human PCa (Huang *et al.* 2005). This discrepancy could arise from the use of different antibodies to detect CXCL8. The same study also observed an increased expression of CXCR1 in epithelial cells of PCas compared with normal prostate. Moreover, CXCR2 is present in neuroendocrine cells (Huang *et al.* 2005). CXCL8 protein can also be detected in the serum of patients. Seric CXCL8 levels are elevated in patients with bone metastasis compared with patients with localized disease (Veltri *et al.* 1999, Lehrer *et al.* 2004).

Immunohistochemical analysis has revealed CXCL8 in benign areas adjacent to the tumor in PCa patients with recurrence compared to tissue from patients who have not recurred (Caruso *et al.* 2008). CXCL8 staining predicts recurrence with a high sensitivity and specificity (Caruso *et al.* 2008).

CXCL1, another chemokine binding to CXCR2, is lower in BPH compared with PCa, whereas the angiostatic chemokines CXCL10 and CXCL11 are more abundant in BPH compared with PCa (Ferrer *et al.* 1998, Nagpal *et al.* 2006). This is confirmed with cell lines in which CXCL1, CXCL3, CXCL5,

Table 2 Localization of chemokines and chemokine receptors

	Epithelial cells	Neuroendocrine cells	CAFs	Endothelial cells	Infiltrating cells	References
CXCL1	+					Engl (2006a), Lu (2007a)
CXCL2	+		+			Engl (2006a), Begley <i>et al.</i> (2008a)
CXCL3	+					Engl (2006a)
CXCL5	+		+			Engl (2006a), Lu (2007a), Begley <i>et al.</i> (2008a)
CXCL6	+		+			Begley <i>et al.</i> (2005), Engl (2006a)
CXCL8	+	+				Huang (2005), Murphy (2005), Schauer <i>et al.</i> (2008b)
CXCL12	+		++			Begley (2005), Berquin (2005), Begley <i>et al.</i> (2008a)
CXCL14	+					Schwartz (2005)
CCL2				+		Mazuchelli (1996), Loberg (2006), Lu (2006)
CCL20	+					Ghadjar (2008)
CX3CL1				+		Shulby (2004), Jamieson (2008)
CXCR1	+					Huang (2005)
CXCR2		+				Huang (2005)
CXCR4	+					Begley (2005)
CXCR7	+					Wang (2008)
CCR2	+					Mazuchelli (1996), Loberg (2006), Lu (2006)
CCR6	+					Ghadjar (2008)
CX3CR1	+					Shulby (2004), Jamieson (2008)

CAFs, cancer associated fibroblasts.

and CXCL6 levels are higher in more aggressive cell lines such as DU-145 and PC3 compared with LNCaP cells (Aalinkeel *et al.* 2004, Engl *et al.* 2006a, Lu *et al.* 2007a). CXCL5 levels also correlate with PCa progression and with inflammatory mediator infiltration (Begley *et al.* 2008b). In the same line, CXCL14 levels increase with Gleason score (Schwarze *et al.* 2005).

A large body of work has focused on CXCL12 and one of its receptors, CXCR4. The expression levels of CXCL12 and its receptor CXCR4 are higher in human PCa tissues than those of BPH tissues (Zhang *et al.* 2008). It is worth mentioning that the levels of CXCR4 found at the surface of PCa cells are relatively low, but sufficient to elicit biological responses, in particular, the adhesion of PCa cells to endothelial cells or extracellular matrix through $\alpha 5$ and $\beta 3$ integrins (Engl *et al.* 2006b). CXCR4 expression does not correlate with pathological grade, bone metastasis, or clinical response to hormonal therapy (Akashi *et al.* 2008). However, patients with a high expression of CXCR4 in tumors have a lower survival expectation than those with low expression of CXCR4 (Akashi *et al.* 2008). On the other hand, the second receptor of CXCL12, CXCR7, displays levels that correlate with tumor progression (Wang *et al.* 2008). In mice, CXCL12 is mainly seen in stromal cells and the extracellular matrix rather than in epithelial cells (Berquin *et al.* 2005).

In epithelial cells, the staining of CXCL12 is apical (Berquin *et al.* 2005). Interestingly, CXCL12 levels decrease in stromal cells and increase in epithelial cells of the prostate of PTEN-deficient mice compared with wild-type mice, whereas CXCR4 levels are up-regulated in PTEN-deficient mice compared with wild-type mice (Berquin *et al.* 2005). In addition, CXCL12 is produced by osteoblasts (Taichman *et al.* 2002).

Chemokines and their receptors are regulated through tumor progression. The more aggressive types of PCa cell lines express higher levels of CCR2 compared with less aggressive cells (Lu *et al.* 2007b). In addition, CCR2 RNA and protein levels increase in metastatic PCas compared with localized PCas (Lu *et al.* 2007b). CCR6 levels are correlated with more aggressive PCas of higher Gleason score and exhibiting higher lymph node metastasis (Ghadjar *et al.* 2008). However, CCR6 and CCL20 levels do not correlate. CXCR6 expression is high in prostate tumors, whereas its ligand CXCL16 is expressed by osteocytes (Hu *et al.* 2008).

Interestingly, chemokines and their receptors could also contribute to the variable incidence of PCa in the world. Indeed, the incidence and mortality rates of PCa are significantly higher in African-American men when compared with European-American men. A comparative microarray analysis of chemokine

Prostate

Bone

Figure 2 The network of chemokines and chemokines receptors in prostate and bone. Upper panel: prostate situation. Cancer cells express chemokines and chemokine receptors and interact with cancer-associated fibroblasts (CAFs) and endothelial cells. The production of chemokine by cancer cells and stromal cells leads to leukocyte infiltration, including macrophage recruitment. Lower panel: bone situation. Bone is a typical site of metastasis for prostate cancers. Cancer cells are attracted to the bone by chemokines produced by endothelial cells, mesenchymal stromal cells (MSCs), and osteoblasts.

expression profiles of patients with primary prostate tumors showed that CCL5, CCR7, and CXCR4 were expressed at higher levels in African–American patients compared with European–American patients (Wallace *et al.* 2008).

A number of chemokines appear to be mainly produced by stromal cells. Human prostatic CAF can

elicit malignant changes in initiated but nontumorigenic human prostatic epithelium and, in particular, CAFs are able to induce the growth of a human prostatic epithelial cell line (BPH-1; Olumi *et al.* 1999, Barclay *et al.* 2005). The analysis of the interactions of BPH cells with CAFs reveals that CAFs secrete transforming growth factor (TGF) β 1, which inhibits cellular growth

in vitro but is necessary for BPH growth *in vivo*. Indeed, TGF β 1 increases the level of CXCR4 on BPH cells. CAFs also secrete high levels of CXCL12, the ligand of CXCR4, which in turn stimulate BPH growth *in vivo* (Ao *et al.* 2007). In addition, aging prostate stromal fibroblasts secrete higher levels of CXCL12 compared with young fibroblasts isolated from the prostate of younger men (Begley *et al.* 2005). Similar observations have been reported for CXCL1, CXCL2, CXCL5, and CXCL6 (Begley *et al.* 2008a). These chemokines weakly stimulate the proliferation of stromal fibroblasts (Begley *et al.* 2008a).

Other chemokines are produced mainly by endothelial cells. This is the case for CCL2, which is mainly expressed by human bone marrow endothelial cells (HBME), and at a lesser extent by PCa cells (Mazzucchelli *et al.* 1996, Loberg *et al.* 2006, Lu *et al.* 2006). Human PCa cells express CX3CR1, whereas its ligand, CX3CL1, is produced by HBME and differentiated osteoblasts (Shulby *et al.* 2004). Human normal prostate epithelial cells (PrEc) weakly express CX3CR1 (Jamieson *et al.* 2008). Osteoblasts, stromal, and mesenchymal cells derived from human bone marrow aspirates express the cell-bound form of fractalkine, whereas the soluble form of the chemokine is detected in bone marrow supernatants (Jamieson *et al.* 2008), reflecting the emerging roles of mesenchymal stromal cells and chemokines in cancer (Lazennec & Jorgensen 2008).

Polymorphism of some chemokine genes is altered in PCa, which could potentially correlate with the expression levels of chemokines. A single nucleotide polymorphism of CXCL12 G801A has been reported. It appears that the genotype GA + AA is increased in PCa patients compared with healthy controls (Hirata *et al.* 2007). In addition, the genotype AA is more frequent in metastatic patients compared with non-metastatic patients (Hirata *et al.* 2007). On the other hand, no strong association between the SNPs for CXCL8-251 (A $\rightarrow$ T), CXCR1 + 860 (C $\rightarrow$ G), and CXCR2-1010 (A $\rightarrow$ G) and either the subsequent risk of PCa or individual prognostic factors among cases have been found in another study (Yang *et al.* 2006).

***In vitro* and *in vivo* effects of chemokines: growth, invasiveness, metastasis, angiogenesis, and leukocyte infiltration**

Chemokines and their cognate receptors have been shown to regulate multiple events in carcinogenesis including growth, invasion, metastasis, angiogenesis, and leukocyte infiltration. For clarity, we have classified chemokine action by subfamily.

CXC chemokines

In vitro, CXCL12 can stimulate the invasion of PCa cells, while the CXCR4 antagonist AMD3100 inhibits invasiveness (Zhang *et al.* 2008). The stimulation of invasion by CXCL12 involves in particular an induction of the matrix metalloprotease MMP-9, through an activation of PI3K and MAPK pathways (Chinni *et al.* 2006). The levels of CXCL12 in human and mouse tissues are higher in the organs, which are a site of metastasis for PCa cells (i.e. bone, liver, and kidney), compared with tissues, which rarely develop metastases following PCa (i.e. lung, tongue, and eye; Sun *et al.* 2005). CXCL12 is localized to the metaphysis of the long bones, nearest the growth plate, but not in the center of the bone marrow (Sun *et al.* 2005). In addition, CXCL12 increases the adhesion of PCa cells to an endothelial cell monolayer and to immobilized fibronectin, laminin, and collagen (Kukreja *et al.* 2005, Engl *et al.* 2006b), and to osteosarcoma cells (Taichman *et al.* 2002). This may occur through an up-regulation of α 5 and β 3 integrins (Engl *et al.* 2006b). CXCL12 also increases transendothelial migration (Taichman *et al.* 2002). CXCL12 triggers an angiogenic switch, through the up-regulation of vascular endothelial growth factor (VEGF) and CXCL8, as demonstrated by the use of siRNA against CXCR4 (Wang *et al.* 2005). Interestingly, CXCL12 down-regulates the glycolytic enzyme phosphoglycerate kinase 1, which is a negative regulator of VEGF and CXCL8 expression (Wang *et al.* 2007).

CXCL8 enhances *in vitro* growth, motility, and invasion, as well as MMP-9 and VEGF production (Reiland *et al.* 1999, Inoue *et al.* 2000, Seaton *et al.* 2008). *In vivo*, the stable transfection of CXCL8 in PCa cells stimulates tumor growth, probably through an increased angiogenesis (Inoue *et al.* 2000, Lee *et al.* 2004, Araki *et al.* 2007). Similar results have been obtained with clones of PC-3 cells expressing various amounts of CXCL8: clones producing more CXCL8 are more tumorigenic *in vivo*, lead to the development of more vascularized tumors and generate lymph node metastasis with a high incidence (Kim *et al.* 2001). On the other hand, blocking antibodies against CXCL8 can prevent prostate tumor growth in SCID mice (Moore *et al.* 1999). *In vitro* experiments have shown that CXCL8 could stimulate the differentiation of human bone marrow mononuclear cells into osteoclast-like cells. Similar effects could be obtained with PCa cell-conditioned medium. Interestingly, the effects of cancer cell-conditioned medium can be inhibited by CCL2 antibodies, which suggest that both CCL2 and CXCL8 promote osteoclastogenesis (Lu *et al.* 2007a).

Other chemokines with the ability to bind to CXCR2 might be involved in PCa. Indeed, CXCL1 is also able to stimulate *in vitro* invasion and *in vivo* growth of PCa cells (Moore *et al.* 1999, Inoue *et al.* 2000). Mouse CXCL1 plays a role in prostate hyperplasia. Indeed, transgenic mice expressing keratinocyte-derived chemokine (KC) display prostate hyperplasia with increased acini diameter and higher Ki67 staining (Schauer *et al.* 2008a). In the same line, CXCL5 (which also binds CXCR2) is able to stimulate the growth of PCa cell lines *in vitro* (Begley *et al.* 2008b). Similarly, in athymic mice, overexpression of CXCL8 in human PrEc implanted subcutaneously leads to hyperplasia, but no change of apoptotic index (Schauer *et al.* 2008a). However, the increase in Ki67 staining of PrEc is not observed with the single injection of PrEc, but only when PrEc–CXCL8 are coinjected with prostate stromal cells (Schauer *et al.* 2008a).

CCL chemokines

CCL2 is able to stimulate PCa cell migration and proliferation *in vitro* (Loberg *et al.* 2006, Lu *et al.* 2006). Neutralization of CCL2 with antibodies inhibits tumor growth in a xenograft model using VCaP cells (Loberg *et al.* 2007). In addition, inhibition of CCL2 leads to a reduction of macrophage infiltration in the tumor (Loberg *et al.* 2007). Interestingly, the coinjection of U937 promonocytic cells with PC3 cells increases tumor growth and angiogenesis, probably through an increased expression of CCL2 (Craig *et al.* 2008).

CCL5 and its receptor CCR5 are expressed by PCa cell lines (Vaday *et al.* 2006). CCL5 stimulates both the proliferation and invasion of PCa cells *in vitro* (Vaday *et al.* 2006).

CX3CL1

The adhesion of PCa cells to bone marrow endothelial cells and their migration toward human osteoblast are reduced in flow conditions by neutralizing antibodies against CX3CL1 (Shulby *et al.* 2004).

Receptors

The roles of CXCR2 and CXCR3 in carcinogenesis have been investigated in the model of TRAMP mice. These mice, which express SV40 T antigen under the control of probasin promoter, develop spontaneous prostate tumors (Gingrich & Greenberg 1996). The breeding of TRAMP mice with CXCR2 KO mice leads to the development of smaller and less vascularized tumors in TRAMP/CXCR2(–/–) mice compared with TRAMP/CXCR2(+ / +) mice (Shen *et al.* 2006a). On the other hand, the same type of

experiments with TRAMP and CXCR3 KO mice showed that CXCR3 was enhancing tumor development and vascularization (Shen *et al.* 2006a), suggesting that CXCR2 and CXCR3 have opposite roles on PCa development in mice.

In the same line, the role of the DARC, which is a decoy receptor for a number of ELR + CXC chemokines, has been investigated (Szabo *et al.* 1995). DARC is mainly expressed by erythrocytes and endothelial cells. *In vitro*, erythrocytes from wild-type mice but not from DARC-deficient mice are able to clear CXCL1 and CXCL8 produced by PCa cells (Shen *et al.* 2006b). Cross-breeding of DARC KO mice with TRAMP mice leads to an increase in tumor growth and vascularization compared with TRAMP mice (Shen *et al.* 2006b). In addition, KC and MIP-2 levels are elevated in the tumor of TRAMP/DARC–/– mice (Shen *et al.* 2006b). This mechanism could account at least in part for the higher incidence of PCa in the African–American population, which frequently displays a lack of DARC expression on erythrocytes.

Concerning CXCL12 receptors, *in vivo*, the neutralization of CXCR4 with antibodies reduces the development of bone metastasis, following intracardiac injection of the cells (Sun *et al.* 2005). In addition, the growth of PCa cells directly injected in the tibia is reduced by the i.p. injection of CXCR4 antibodies (Sun *et al.* 2005).

Knockdown of CXCR7, the second receptor of CXCL12, in PC-3 or LNCap C4-2 cells slightly reduces cell growth *in vitro* (Wang *et al.* 2008). On the other hand, overexpression of CXCR7 in the same cells enhances their proliferation (Wang *et al.* 2008). Moreover, CXCR7 can prevent apoptosis and increase *in vitro* invasion (Wang *et al.* 2008). *In vivo*, CXCR7 silencing strongly reduced the tumor growth of C4-2B cells (Wang *et al.* 2008).

Do chemokines modulate hormone escape?

Hormone-refractory PCas are of particular concern for clinicians as they exhibit a higher aggressiveness and lack of efficient treatment (Taplin 2007, Devlin & Mudryj 2009). Several groups have begun to investigate whether chemokines could be involved in this phenomenon. To date, the only chemokine identified in such phenomenon is CXCL8, but conflicting results have been published. Indeed, the stable transfection of CXCL8 cDNA in AR-positive PCa cells reduces their dependence to androgens and reduces the growth inhibition observed in the presence of anti-androgens as bicalutamide, through CXCR1 (Araki *et al.* 2007).

On the other hand, Seaton *et al.* (2008) reported that CXCL8 could enhance the proliferation of cancer cells, but this could not be observed in the presence of bicalutamide. Another difference with the study from Araki was that CXCL8 action occurred through CXCR2 (Seaton *et al.* 2008). CXCL8 action on AR activity is also controversial. CXCL8 reduces AR and PSA levels of LNCaP and LAPC4 cells according to Araki *et al.* (2007), but Seaton *et al.* (2008) showed that CXCL8 not only increases AR and PSA RNA and protein levels in LNCaP and 22Rv1 cells, but also increases AR activity. This finding was also confirmed by Lee *et al.* (2004) who showed that CXCL8 activates the AR and confers androgen-independent growth to PCa cells. CXCL8 increases the recruitment of AR to PSA promoter in LNCaP cells (Lee *et al.* 2004). CXCL8 also increased the survival of PCa cells treated with the drug docetaxel (Araki *et al.* 2007).

Mechanisms of control of expression of chemokines and chemokine receptors

So far, the signals and the mechanism of regulation of chemokines in PCa remain poorly studied. Most studies have analyzed the effects of nuclear receptors such as AR and vitamin D₃ receptor (VDR) on chemokine expression.

CXCL8 is a target of VDR in PCa cells. Addition of 1 α ,25-dihydroxyvitamin D₃ (VD₃) down-regulates CXCL8 levels, through NF- κ B inhibition, by blocking p65 nuclear translocation (Bao *et al.* 2006). Recently, the role of RelB and the alternative NF- κ B pathway leading to overexpression of IL-8 in PCa have been demonstrated (Xu *et al.* 2009).

Similarly, Penna *et al.* (2008) reported that the VDR agonist elocalcitol inhibits CXCL8 production induced by inflammatory cytokines in BPH and CXCL8-induced proliferation of these cells.

CX3CL1 is the target of another nuclear receptor, AR. The androgen dihydrotestosterone increases the cleavage of CX3CL1 from the plasma membrane of bone, but does not cleave the cell-bound form of CX3CL1 from HBME (Jamieson *et al.* 2008). The extravasation of PCa cells expressing CX3CR1 could be enhanced by androgens, through free fractalkine. The ability of cancer cells to adhere to the bone marrow endothelium would be unaltered (Jamieson *et al.* 2008).

The reintroduction of AR in the AR-negative DU-145 PCa cell lines leads to a down-regulation of CXCR4 and CCR1 RNA levels and the modified cell lines became unresponsive in terms of *in vitro* invasion to CXCL12 and CCL3, the respective ligands of CXCR4 and CCR1 (Akashi *et al.* 2006).

Conclusion

Chemokines and their receptors show differential expression along with PCa progression. It is interesting to note that numerous chemokines are involved in these different steps, even though most of the current work has explored only a small part of the chemokine superfamily. Based on the fact that chemokines are expressed by different types of cells, not only in the prostate but also in distant organs, targets of metastasis, this draws a fine network of interactions between these factors. Both the stromal and epithelial compartments are involved in terms of chemokine production. Chemokines affect not only angiogenesis but also other processes such as proliferation, hormone-escape, and leukocyte infiltration. Chemokines and their receptors constitute not only novel markers of PCa but also possible targets for future therapies.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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