

Role of Chemokines and Chemokine Receptors in Prostate Cancer Development and Progression

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Abstract

Prostate cancer (PC) is the second leading cause of cancer deaths in men in America and Western Europe. Epidemiological studies suggest that prostate cancer incidence & increased in last few years in Asia. The causes or consequences of increasing trend of prostate cancer incidence are not completely known. Emerging evidences suggest that among the many risk factors, inflammation is the major risk factor for developing prostate cancer and its progression to metastasis. It is proposed that exposure to environmental factors such as infectious agents, dietary agents and saturated lipids leads to injury of the prostate due to chronic inflammation and regenerative risk factor lesions referred to as proliferative inflammatory atrophy (PIA). These phenomena predominantly control by a number of pro-inflammatory macromolecules such as chemokines, and their receptors. Some recent studies suggest that many of these pro-inflammatory chemokines and their receptors are the products of protooncogenes in many cancers including that of the prostate. This review focus on the current biology of chemokines and chemokine receptors in prostate cancer. An understanding of this axis may enable researchers to develop targeted strategies for prostate cancer.

Introduction

Prostate cancer (PC) represents the second leading cause of death among all cancer types in men in Europe and North America (Collin et al., 2008). Emerging evidences suggest that among the many risk factors, inflammation is a major risk factor for developing prostate cancer and its progression to metastasis (De Marzo et al., 2007). The pro-inflammatory regulators such as chemokines and their receptors network seem to play crucial functions in prostate tumorigenesis, although chemokines have been thought of primarily as leukocyte attractants. In general, the function of chemokines is to arrest leukocytes at inflamed blood vessels and to lead them to specific sites of inflammation. Due to specific function of site-specific homing for leukocytes from inflammatory sites, these mediators may play several key steps of prostate carcinogenesis including production of inflammatory cells. Chronic inflammation predisposes cells to produce dysregulated amounts of chemokines for malignant transformation and progression. The accumulating evidence also points to a direct effect of chemokines on cancer cells that express chemokine receptors. In particular, some chemokines can activate anti-apoptotic pathways in cancer cells (Singh and Lokeshwar, 2009). By either mechanism, tumor cells that secrete and/or respond to chemokines would have a selective advantage. It is extensively documented in number of studies that they contribute to a number of tumor-related processes, such as tumor cell growth, angiogenesis/angiostasis, local invasion, and metastasis in many tumor types including, prostate (Singh and Lokeshwar, 2009; Bingle et al., 2006; Papetti and Herman, 2002). Specifically, members of the chemoattractant chemokines, more popularly known as CXC chemokines, and their receptors are significant players in several of the critical steps in tumorigenesis and/or metastasis (Singh et al., 2007; Vicari and Caux, 2002; Zlotnik, 2004; Murakami et al., 2004). Many studies mentioned that they have been shown to play potentially important roles in many of the critical steps of the androgen independent and metastasis process. For example CXC chemokine CXCL-8 (IL-8) plays multiple roles in transition of androgen sensitive tumor cells to androgen insensitive, drug resistant cell in prostate cancer (Tanaka et al., 2005; Araki et

al., 2007). A recent report indicates that inhibition of IL-8 *in vitro* inhibits cell survival signaling of Akt and bcl2 in prostate cancer cells (Singh and Lokeshwar, 2009). Several other chemokines produced by primary prostate tumor cells and in distant metastasis locations are shown to play significant role in prostate tumorigenesis (Waugh et al., 2008). These wide and differential distributions of chemokines and their receptors particularly account for the pleiotropic actions of chemokines in PC, including the modulation of growth, angiogenesis, invasion, and metastasis (Vindrieux et al., 2009; Tanaka et al., 2005; Singh et al., 2007; Ben-Baruch, 2008).

The known function of chemokines in other aspects of biology or human diseases, apart from cancer, has been detailed in several other reviews (Rossi and Zlotnik, 2000; Gerard and Rollins, 2001; Aragon-Ching et al., 2010). This review will emphasize what we believe are striking about the roles of selected chemokines in the inflammatory responses to prostate cancer initiation to metastasis process. This review will also highlight some of the similarities between the functions of chemokine receptors in physiologic homing of leukocytes and purposed roles for these receptors in prostate cancer progression and metastasis. Therefore, this review will include descriptions of possible concurrent roles in inflammation and prostate tumorigenesis. Within the space of this review, it is not possible to discuss all the available evidence regarding roles for a specific chemokine and chemokine receptors networks in details.

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Thus, a referenced summary of possible roles for some important chemokine receptors in prostate cancer is discussed. With the development of specific chemokine receptor antagonists, it may be possible to exploit the vulnerability of cancer cells by disrupting chemokine receptor-mediated signaling and directly inhibit prostate tumor growth or render tumor cells more susceptible to traditional anticancer treatment modalities. This review will focus on the roles and the mechanisms of action and regulation of chemokines in the different steps of PC development and will discuss present literature on the novel strategies that are currently envisioned to target chemokines in PC.

Prostate cancer

Adenocarcinoma of the prostate is the most common malignancy of the male genitourinary tract and is a significant health problem. The 2.4 million people living with PC, 214000 new cases per year and estimated 27000 death occurred in the United States in 2008 (Jemal et al., 2008). Localized prostate carcinomas exist in most of elderly males at the time of diagnosis, but the most of those carcinomas are asymptomatic and are medically important (Denberg et al., 2006; Giovannucci et al., 2007; Mazur and Merz, 1996; Pienta and Loberg, 2005). For this reason, the research of tumor proliferation and dissemination are even more important of this disease than of other cancers.

The most commonly used method to diagnose and evaluate prostate cancer is the PSA (Prostate Specific Antigen) test though it is far from perfect. The only test which can fully confirm the diagnosis of prostate cancer is a biopsy. The recent European Randomized Study of Screening for Prostate Cancer suggests that risks incurred by screening, diagnosis (Schroder et al., 2009; Koukourakis et al., 2009; Aus et al., 1996) and resulting treatment (Rietbergen et al., 1997; Yao and Lu-Yao, 1999; Alibhai et al., 2005; Potosky et al., 2004; Lim et al., 1995; Hamilton et al., 2001; Fowler et al., 2002) of prostate cancer are both substantial and well documented in the literature. To the extent that over diagnosis occurs with prostate-cancer screening, many of these risks occur in men in whom prostate cancer would not have been detected in their lifetime and were clinically irrelevant (Tsai et al., 2007). Treatment for prostate cancer includes surgery, radiation therapy, cryosurgery and total androgen deprivation (hormonal) therapy. Surgical removal of the prostate (also called prostatectomy) is a common treatment mainly for early stage prostate cancer. Radiotherapy is also widely used in prostate cancer treatment. However, once the tumor has spread, such local tumor removal has little impact on the overall outcome or course of disease (Jongsma et al., 2002). Thus, the disseminated tumors need innovative and systemic approaches. Early in the prostate carcinoma, such physical or chemical castration (anti-androgen) leads to regression of the tumor masses (Jin et al., 2004). However, this rarely cures prostate cancer as androgen independence develops within a year or two (Nacusi and Tindall, 2009). Thus, focus on the tumor-intrinsic events, predominantly mediated by chemokines and chemokine-receptors in androgen-independent prostate carcinomas, as novel approaches to halting the progression of this disease. In the following sections we will discuss the importance of these molecular pathways in the development and progression of PC and the therapeutic significance of the inhibition of these of pro-inflammatory signals.

Chemokines

The chemokines represent a large group of small secreted proteins (8–11 kDa in size), which are grouped into four families (C, CC, CXC, and CX₃C) based on the spacing of key cysteine residues

near the N-terminus of these proteins. The CC and CXC families represent the bulk of known chemokines (currently 53) (Zlotnik and Yoshie, 2000). Most of the chemokines are divided between the CC and CXC classes. There are only two known C chemokines, and one known CX₃C chemokine. Several CC chemokines with six cysteines have been discovered, defining a structural subclass relative to the more numerous group of CC chemokines with four cysteines. The CXC class can also be divided into two subclasses, ELR+ and ELR-, depending on whether the tripeptide signature glu-leu-arg is found N-terminal to the first cysteine (Zlotnik and Yoshie, 2000).

Chemokines are primarily known in the regulation of the motility of hematopoietic cells (immune system cells) and their ability to stimulate directional migration of nearly all classes of leukocytes during inflammation through the activation of a group of cell surface receptors (Ruffini et al., 2007). Neutrophils, for example, migrate strongly in response to chemokines such as CXCL8 (interleukin-8) and eosinophils to CC chemokine ligand 11 (CCL11; eotaxin). Some chemokines have been expressed on specific cell types (Zlotnik and Yoshie, 2000). Many epithelial cell types and macrophages for example, produce significant levels of chemokines. These cell populations can have an immediate impact on the tumor environment. The CXC chemokines mostly ELR+ are angiogenic. These include CXCL8 (IL-8), epithelial-neutrophil activating protein (ENA-78) and growth-related genes (GRO- α , GRO- β , GRO- γ and GCP-2), and several other neutrophil activating proteins (Brat et al., 2005). The second group of CXC chemokines, which lack the ELR motif, include interferon- γ -inducible protein (IP-10), monokine induced by γ -interferon (MIG) and stromal derived factor (SDF-1) (Ogawa et al., 2002). Most of these ELR-negative CXC chemokines, have been shown to antagonize the angiogenic activities of the ELR-positive CXC chemokines as well as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) (Moore et al., 1999). It is still not clear, however, whether all of these chemokines contribute cancer related chemotaxis, or whether a specific chemokine mediates the bulk of the chemotactic activity and can be targeted for therapy. Chemokine biology is also central to the immunologic anti-tumor response through the recruitment of effector lymphocytes and the subsequent regulation of their effector function within tumor environment (Homey et al., 2002). Data from breast carcinoma studies have suggested that the specific effects mediated through chemokines could be significantly different depending on the source of ligand or receptor expression (Azenshtein et al., 2002).

Chemokine receptor

Chemokines interact with their cell-surface receptors, which are members of a large superfamily of seven-transmembrane domain, G protein-coupled receptors. The receptor nomenclature system is based on the observation that ligand selectivity of promiscuous chemokine receptors is restricted by chemokine class. Some chemokine receptors bind to multiple chemokines and vice versa, suggesting that certain redundancies exist in chemokine function. There are 18 human chemokine receptors (Zaballos et al., 1999; Homey et al., 2000; Schweickart et al., 2000; Yoshida et al., 1998) and over fifty distinct chemokines identified at present. They play very distinct role in normal cells and in cancer (Zlotnik and Yoshie, 2000). The molecular mechanism of signaling function has still not been demonstrated for Duffy, D6, CCX CKR, and CXCR7 which are all 7TM proteins that bind large subsets of chemokines (Homey et al., 2000). The ten human chemokine receptors such as CXCR1, CXCR4, CXCR5, CXCR6, CCR6, CCR8, CCR9, CCR10, XCR1 and CX₃CR1 are highly selective for one main high affinity chemokine ligand.

On the other hand, other chemokine receptors (CXCR2, CXCR3 and CXCR7) are typically highly promiscuous. For example CXCR7 is a new member of chemokine receptors, CXC family, it has been shown to bind two chemokines, CXCL12/SDF-1 and CXCL11 (Burns et al., 2006). The exact function of CXCR7 and how it is regulated in prostate and other cancers is not known.

The major function of chemokines is to regulate leukocyte trafficking in hematopoiesis and in innate and adaptive immunity in many cell types. Other functions include angiogenic activity, apoptosis, T-cell differentiation and phagocyte activation (Kim, 2004). Inadvertent activation of chemokine receptors leads to autoimmunity by inappropriately targeting self antigens for destruction by cytotoxic T-cells and macrophages (Christopherson and Hromas, 2001). They are sub classified according to their function such as homeostatic leukocyte homing molecules (CXCR4, CXCR5, CCR7, CCR9) versus inflammatory/inducible molecules (CXCR1, CXCR2, CXCR3, CCR1-6, CX₃CR1), and substantial progress has been made, in part through the study of knock-out mice, in identifying specific phenotypes in development and disease. Phenotypes are concentrated in hematopoietic development, innate and adaptive immune responses and susceptibility to infectious agents (Cyster, 1999). Chemokine receptors preferentially expressed on important functional subsets of epithelial cells, dendritic cells, monocytes and lymphocytes have been defined in many studies (Charbonnier et al., 1999; Sallusto et al., 1998).

Chemokines and chemokine receptors in inflammation, prostate cancer development and progression

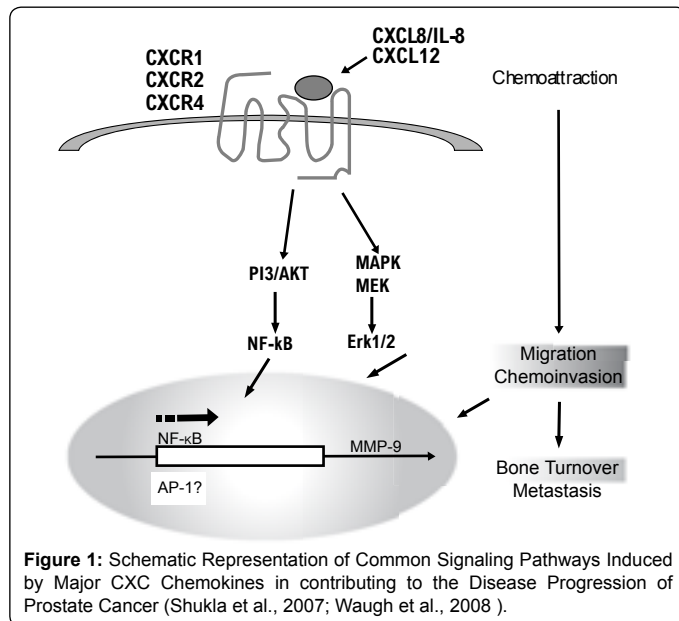
Prostate Cancer (PC) progression is a complex physiological and pathological event. Several multidisciplinary studies have been suggesting a link between chronic inflammation and PC. Several studies suggest a link between bacterial infections, inflammation and pre-deposition of pro-inflammatory proteins in the prostate gland. Such self-perpetuating mechanism can be triggered with the age of men and may increase the risk of malignancy of prostate (Yanamandra et al., 2009; Hermani et al., 2006; Xie et al., 2010). Studies have also found an increased in relative risk of PC in men with a prior history of certain sexually transmitted infections or prostatitis diseases (Sadeghi-Nejad et al., 2010; Cheng et al., 2010). Significant association between prostatitis, sexually transmitted diseases (STDs), and prostate cancer among African American, Asian American, Latino, were found in participants of the California Men's Health Study (Robert et al., 2009). Furthermore, several studies suggested genetic or germline defect or variants of several genes associated with the immunological aspects of inflammation in modulating PC risk (Vasto et al., 2008). Somatic alterations of genes are shown to be involved in defenses against inflammatory damage and in tissue recovery. Several studies showed that chronic inflammation of prostate area caused a novel putative PC precursor lesion called proliferative inflammatory atrophy, which shares some molecular traits with prostate intraepithelial neoplasia and PC (Sciarra et al., 2007). The hypothesis associating chronic inflammation and PC was tested in a number of animal models of prostate inflammation that allowed the elucidation of the mechanisms by which prostatic inflammation could lead to the initiation and progression of PC (Nelson et al., 2001; Hsing and Chokkalingam, 2006). These emerging insights into chronic inflammation in the etiology of prostate carcinogenesis hold the promise of spawning new diagnostic and therapeutic modalities for men with PC (Wagenlehner et al., 2007; Chung et al., 2005).

Prostate tumorigenesis occurs through several steps, the first

being the transition from normal prostate to PIN in many cases (Yanamandra et al., 2009; Hermani et al., 2006), but not all BPH diseases establish cancer in later stage. During the transitions from normal to PIN and from PIN to PC, a number of chemokines and chemokine receptors display variations in their expression. It is most important to notice that chemokines are produced by a variety of cells such as tumor-associated fibroblasts, endothelial cells, or tumor infiltrating cells such as macrophages and or lymphocytes have selected advantage of progression of prostate disease. Many studies have been suggested that chemokines CXCL8, CXCL12, and CCL2 level increased with the progression of prostate PC. Expression of IL-8 is low levels in normal human prostate at the apical membrane of epithelial cells (Murphy et al., 2005). The levels of proangiogenic chemokine IL-8 is higher in PIN compared with normal prostate tissue and cell lines represent the PIN and stroma tissue of PIN. This suggests that a reactive stroma pattern is correlated with an increase in CXCL8 levels in the adjacent epithelium.

It is suggested that many CXC chemokines are involved in prostate tumor invasion and metastasis. This is very important mechanism of prostate tumor progression. The ability to break matrix barriers causes the vast majority of morbidity and mortality from prostate cancer due to metastasis to vital organs such as bone, liver and lymph nodes. Histological analyses in *de-novo* human tumor specimens and animal tumor models showed that cancer cells invading into adjacent healthy tissues or breaching a basement membrane to access a vessel for dissemination. Cell motility and invasion is tightly controlled by growth factors and cytokines during organogenesis, inflammation and wound healing, while it appears to become dysregulated during tumorigenesis. This lack of control and direction results in invasion. Prostate cancer cells that becomes hormone-independent become highly invasive with an increased incidence of skeletal/bone metastases as the disease progresses (Gladson and Welch, 2008; Bostwick et al., 2004; Logothetis and Lin, 2005). PC 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 PC progression remain elusive. Among the mediators of carcinogenesis, the significance of chemokines in PC 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. In the PC context and other cancer, chemokines play diverse effects and some of them deriving from their ability to induce cell migration and angiogenesis. The ability of chemokines to enhance the motility of leukocytes, endothelial cells, and by tumor cells is a key factor in determining the cancer establishment and progression. On the other hand, some chemokines may inhibit angiogenesis and angiostatic effects.

The expression level of chemokines is also altered with the progression of PC. *In situ* hybridization experiments have shown that CXCL8 RNA and its receptors CXCR1 and CXCR2 levels increase with the Gleason score (Grade) of prostate tumors (Gladson and Welch, 2008). The localization of CXCL8 is somewhat controversial as another study has reported that CXCL8 is expressed by the neuroendocrine cells of PC. 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 PC



as compared with normal prostate. Moreover, CXCR2 is present in neuroendocrine cells. CXCL8 protein is also detected in the serum of PC patients. Serum CXCL8 levels are elevated in patients with bone metastasis compared with patients with localized disease (Waugh et al., 2008).

Several studies have shown that tumor progression depends on expression of chemokines and related receptors. It is mediated through several survival factors such as PI3k/AKT pathways. Some chemokine receptors are shown to involve in NF-kB mediated pathways in many cancers including, that of prostate. These survival factors are constitutively activated. The more aggressive tumors and PC cell lines express higher levels of CXCR1, CXCR2, CXCR4 than less aggressive cells. In addition, CXCR4 RNA and protein levels increased in metastatic PC compared with localized PC (Taichman et al., 2002) CXCR1 levels are correlated with more aggressive PC of higher Gleason score and exhibiting higher lymph node metastasis (Uehara et al., 2005). However, CXCR2 and CXCR7 levels correlate high in prostate tumors, whereas its ligand CXCL12 expressed in low in many high grade of tumors (Murphy et al., 2005). The literature pertaining to the role of CXC-chemokines in prostate cancer have focused on understanding the role of IL-8 or CXCL12 signaling in prostate cancer and activation of these survival factors. The summary of review to highlight the significance of this CXC-chemokine family mediated common signaling pathways in promoting the disease progression of PC is illustrated in Figure 1.

Some studies have suggested that chemokines and their receptors could also contribute to the higher incidence of PC in African-American men when compared to European-American men. A comparative microarray analysis of chemokine 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). Genetic polymorphism of some chemokine genes is altered in PC, 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 PC 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 (Hendrix et al., 2000). In the light of growing evidence of chemokines involvement in all stages of prostate cancer progression, manipulation of their signaling pathway may have therapeutic benefit. Several antagonist including AMD 3100 and T22 of CXCL12 are tested but are unlikely to be effective owing to pharmacokinetic problems (Hendrix et al., 2004; Civenni and Sommer, 2009). Apart from metastasis, increasing evidence suggests that chemokines are implicated in neoplastic cell transformation. Chemokines regulate proliferation and migration of various types of normal stem and progenitor cells, including precursor cells of neuroectodermal origin. Based on this it is conceivable that the established role of chemokines in cancer cell proliferation and organ-specific metastasis might also be associated with stem cell-like cells present in the tumor. Such cancer stem cells represent a small subpopulation of tumor cells that are thought to initiate and sustain tumor formation (Burger et al., 1999). The IL-8 and CXCL1 have been demonstrated to continually stimulate certain cells expressing the CXCR1 and CXCR2 by autocrine and paracrine mechanism and leading to malignant and oncogenic transformation (Waugh et al., 2008). Clinical observations and mouse models have shown that inflammation can be pro-tumorigenic CXCL16 and CXCR6 arising in an inflammatory milieu and mediate pro-tumorigenic effects of inflammation through direct effects on cancer cell growth and by inducing the migration and proliferation of tumor-associated leukocytes (Darash-Yahana et al., 2009). The multi-faceted roles of chemokine and chemokine receptors in PC are outlined in Table 1.

Conclusion Remarks

Chemokines and chemokine-receptors seem to be important factors not only play a significant role in normal cell physiology but also regulate as they in many tumor related mechanisms such as increase in cell survival and migration associated with metastasis of several cancers including prostate. Leukocyte infiltration is a cardinal feature of inflammation and important in progression of prostate cancer. This mechanism of up-regulation not only autocrine and paracrine mechanism of tumor cells secreted chemokines to promote tumorigenesis but also they responsible for eliciting local accumulation of inflammatory cells that appear to play a same role in the formation of peri- and intra-tumoural infiltrates. Chronic inflammation predisposes and secretion of tumor related chemokines (CXC) are likely to be important factors in prostate cancer formation and progression. In part, chemokines may be a consequence of its ability to attract mononuclear cells to cancer sites, where they provide growth or angiogenic factors that enhance cancer development. However, accumulating evidence also points to a direct effect of chemokines on cancer cells that express chemokine receptors. In

- ❖ Chemokines and chemokine receptors axis can promote oncogenic and cellular transformation.
- ❖ They act as autocrine growth factors and increase clonal proliferation and tumor angiogenesis mediated by chemokine receptors.
- ❖ They induce production of matrix metalloproteinases in malignant cells, thereby enhancing local invasive potential and metastasis.
- ❖ Targeting chemokines and chemokine receptors in cancer-related inflammation and underlying mechanisms of chemokine action in PC facilitate the development of novel therapies in the future.

Table 1: Overview of Chemokines and Chemokine Receptors in Prostate Cancer.

chemokine receptors. In particular, some chemokines can activate anti-apoptotic pathways in these cells. By either mechanism, tumor cells that secrete and/or respond to chemokines would have a selective advantage of host systems to promote tumorigenesis.

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