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Multi-faceted roles for CXC-chemokines in prostate cancer progression

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1. ABSTRACT

CXC-chemokines play an essential role in co-ordinating the function of the immune system. Increasingly, these small signaling molecules are recognized in facilitating communication between multiple cell types within the tumor microenvironment. This review will summarize the role of two members of this family, CXCL12 (stromal cell derived factor-1) and CXCL8 (interleukin-8) in promoting the disease progression of prostate cancer, the most prevalent non-cutaneous cancer in men in western society and the second leading cause of death from cancer in men. Evidence for a role of these chemokines in underpinning the development and progression of this disease is supported by examination of prostate tissue and serum samples from prostate cancer patients, from biochemical and molecular investigations conducted on cell-based models of this disease and from observation of CXC-chemokine promoted growth and systemic dissemination of human prostate tumors in *in vivo* models. The future potential of employing strategies to attenuate chemokine expression or alternatively to selectively block chemokine receptor signaling in order to effect greater long-term control or enhanced therapeutic response in this disease is also discussed.

2. INTRODUCTION

Chemokines are a superfamily of low molecular weight (8-10 kDa) chemotactic cytokines (1,2). They are both chemotactic and chemokinetic and are structurally and functionally related to growth factors. To date, more than 50 different chemokines have been identified, and are classified into four distinct groups (C, CXC, CC, and CX3C) depending on the arrangement of the conserved cysteine motif at the amino terminus. The CXC chemokine family is further classified into ELR+ and ELR- chemokines, according to the presence or absence of a conserved Glu-Leu-Arg motif in the amino terminus. The CC and CXC families represent the majority of chemokines identified to date. Chemokines exert their biological effects through interactions with specific G-protein-coupled receptors, located on the plasma membranes of target cells (2,3). There are four chemokine receptor classes and currently 20 human chemokine receptors have been identified: seven CXC receptors (CXCR1-CXCR7), 11 CC receptors (CC1-CC11), once CX3C receptor (CX3CR1) and one XCR receptor (XCR1).

Chemokines induce and regulate a wide range of biological activities. One of the most well characterized

roles of chemokines is in modulating inflammatory responses with chemokines exerting a central role in promoting tissue-specific homing of leukocytes and sub-population of T-lymphocytes to sites of infection and/or injury (1,4-6). The expression of specific chemokines, chemokine receptors, and adhesion molecules in a spatial and temporal manner determines the subgroups of leukocytes that are stimulated to migrate and their ultimate destination (4-6). Infection or injury-induced expression of chemokines generates a localized distribution of the chemokine, mediated by the oligomerization and complexing of the chemokine to glycosoaminoglycans expressed on the surface of endothelial cells. Cells expressing the cognate chemokine receptor are then drawn along the concentration gradient towards the site of infection, primarily through chemokine-promoted activation of discrete signaling pathways that promote cell polarity, induce cytoskeletal rearrangement and modulate the expression of cell-surface adhesion receptors in migrating cells.

There is an increasingly expansive literature pertaining to the expression and functional relevance of chemokines in cancer. Increased expression of numerous chemokines has been reported in human cancers, including prevalent cancers such as those of the breast, lung, gastric, pancreas and colon. Chemokines and their receptors have been shown to act at all stages of tumor development, including the neoplastic transformation of cells, the promotion of angiogenesis, in accelerating tumor growth, inducing local invasion of tumor cells and in underpinning organ-specific metastasis (7-9). In addition, it is increasingly acknowledged that chemokines play an important role in facilitating communication between cancer cells, endothelial cells and fibroblasts, as well as promoting the infiltration and activation of neutrophils and tumor-associated macrophages within the tumor microenvironment (10,11).

The focus of this review is to highlight the significance of the CXC-chemokine family in promoting the disease progression of prostate cancer. Prostate cancer is currently the most-prevalent non-cutaneous cancer in men in the Western world and is the second leading cause of male death from cancer. There is increasing evidence linking chronic inflammation with the development of prostate cancer emerging from epidemiological, histopathological and molecular pathological studies (12-15). Areas of acute or chronic inflammatory infiltrates in the prostate are extremely common and are often localized to areas of focal epithelial atrophy (16). Furthermore, the transition between atrophic epithelium and adenocarcinoma has been observed in morphological studies (17,18). The cause of the inflammation is often not clearly identified but proposed sources for its initiation include direct infection, urinary reflux and dietary factors (15,19-20). Although a direct role for chemokines in mediating the pro-inflammatory response to these stimuli remains to be established, it is conceivable that these small proteins may contribute to the initiation of prostate cancer. In this review, we will summarize the evidence presented by laboratory and clinical studies that define the emerging role for chemokine signaling in underpinning many of the clinically significant aspects of prostate cancer, including the transition to androgen-independence and the development of bony metastasis. Much of the review will be devoted to addressing the role of CXCL8 in promoting the disease progression of prostate cancer.

3. CXC-CHEMOKINES AND CXC-CHEMOKINE RECEPTORS

Much of the literature pertaining to the role of CXC-chemokines in prostate cancer has focused on understanding the role of stromal derived factor-1α (CXCL12)-signaling or interleukin-8 (CXCL8)-signaling in prostate cancer. Until recently, CXCL12 was thought to mediate all of its biological activity through binding and activation of the CXCR4 receptor. However, this chemokine has also been identified as a cognate ligand for the recently characterized CXCR7 receptor (21). CXCL8 exerts its biological activity through two distinct receptors, CXCR1 and CXCR2. These two receptors retain significant structural identity at the nucleotide and protein sequence level but yet exhibit marked pharmacological differences with respect to the chemokines that can interact with and induce their activation. CXCR1 is markedly more selective, reportedly binding only CXCL8 and GCP-2. In contrast, the CXCR2 receptor has a broader selectivity, recognizing and being responsive to several growth-related oncogenes (CXCL1-3), ENA-78 and GCP-2 (22).

4. CXCL12, CXCR4 AND PROSTATE CANCER

Similar to their role in promoting homing of leukocytes to sites of injury and infection, chemokines have been implicated in underpinning the organ-specific metastasis of cancer (7-9). This was first demonstrated through a pathological and mechanistic study of breast cancer cell metastasis, implicating the CXCR4 receptor and CCR7 receptor in promoting systemic and lymph node metastasis of this disease, respectively (23). In these studies, pathological analysis of breast tissue established the over-expression of CXCR4 in malignant tissue relative to normal mammary epithelium while over-expression of the cognate ligand CXCL12 was detected in tissues/organs to which breast cancer frequently disseminates ie. lung, liver, bone, lymph nodes. Using the MDA-MB-231 experimental model of metastatic breast cancer, the incidence and establishment of metastatic lesions within the lungs was shown to be significantly attenuated by either systemic or orthotopic administration of a neutralizing anti-CXCR4 antibody, suggesting that CXCL12/CXCR4 interactions may not only promote the recruitment of circulating breast cancer cells to these sites but also facilitate the colonization and outgrowth of metastatic tumors.

The CXCL12/CXCR4 axis has since been shown to contribute to the biology and progression of prostate cancer. Analysis of a high-density tissue microarray constructed using tissue from over 600 patients first confirmed the over-expression of CXCR4 protein but not mRNA transcript levels in the tumor cells of localized and

metastatic prostate cancers (24). A subsequent study conducted on 35 cases of prostate cancer also identified positive CXCR4 expression in 57% of the samples analyzed, with positive expression of CXCR4 detected in three patients with confirmed lung metastasis (25). Following a further PSA-based stratification of these samples, CXCR4 expression was also determined to be elevated in those patients with pathologically-confirmed bone metastasis. High expression of CXCR4 has also been shown to correlate with metastatic disease in a further study of human prostate cancer tissue (26).

Consistent with the histo-pathological analysis of human tissue, investigations have confirmed that CXCR4 expression is absent or negligible in normal prostate epithelial cell lines but that its expression is elevated in each of the three principal cell lines exploited in laboratory-based prostate cancer research (ie. LNCaP, PC3 and DU145) Furthermore, prostate cancer cell lines have been shown to express and secrete biologically active CXCL12 (24-29). Consequently, prostate cancer cells have been exploited *in vivo* to determine the impact of CXCL12-induced/CXCR4-mediated signaling on the metastatic behaviour of these prostate cancer cells. Subcutaneous xenograft models of prostate cancer established in NOD/SCID mice have demonstrated that over-expression of CXCR4 in PC3 or 22Rv1 cells increases the tumor volume and weight, tumor invasion, blood vessel density, and the incidence of metastasis to the lymph nodes and lungs (26). A further study by the Taichman laboratory has focused more specifically in determining the role of CXCL12/CXCR4 signaling in promoting the experimental metastasis of prostate cancer to the bone (30). They observed a selective expression of CXCL12 in murine tissues closely matching the pattern of preferential metastatic spread observed in prostate cancer patients. For example, enrichment of CXCL12 expression was detected in the pelvis, tibia, femur, liver and adrenal/kidneys. Within the bone, expression of CXCL12 was selectively distributed to the metaphysis of the long bones adjacent to the growth plate with minimal expression detected within the marrow cavity. This pattern of expression is co-incident with the preferential clustering of metastatic prostate cancer lesions proximal to the growth plate, a site of high bone turnover. In subsequent experiments, they observed that neutralization of CXCL12/CXCR4 signaling using antibody or peptide-based strategies was shown to significantly reduce the skeletal metastasis burden resulting from an intracardiac injection of PC3 cells. In addition, using an intraosseous model, inhibition of CXCR4 signaling was also shown to retard the outgrowth of prostate cancer lesions within the bone. Therefore, these experimental data suggest an important role for CXCL12/CXCR4-signaling in directing the systemic spread of prostate cancer cells to the bone and the subsequent colonization of this environment.

Cell-based experiments conducted in prostate cancer cell lines have demonstrated that CXCL12/CXCR4 signaling induces cellular responses consistent with a pro-metastatic phenotype. Numerous studies have reported that administration of CXCL12 is a potent stimulant of PC3, DU145 and LNCaP cell migration and/or invasion (27,29,31,32). In addition, stimulation with CXCL12 has been reported to potentiate the adhesion of prostate cancer cells to endothelial cells (27,32,33), and extracellular matrix substrates including vitronectin, osteopontin, laminin, collagen and fibronectin (32,33). Furthermore, CXCL12 has been shown to induce the transmigration of prostate cancer cells across bone marrow endothelial monolayers (27,34), and increase the invasion of prostate cancer cells through basement membranes (27).

Molecular insights into the signaling pathways and mediators of many of these CXCL12-promoted responses in prostate cancer cells are beginning to emerge. CXCL12-signaling regulates multiple collagenolytic species within prostate cancer cells (29,31); increased MMP-9 expression has been detected in PC-3 cells while expression of MMP-1 and MMP-2 are increased in both PC3 and LNCaP cells, MMP-3 and MMP-14 are increased in PC3 cells only and MMP-10 is induced in LNCaP cells following administration of CXCL12. Synthesis and secretion of multiple collagenolytic species is likely to underpin the capacity for CXCL12/CXCR4-signaling to potentiate the tissue invasion and penetration of basement membranes by metastatic prostate cancer cells. Stimulation with CXCL12 has been reported to increase the expression of α5 and β3-integrin subunits and the expression and avidity of the αVβ3-integrin heterodimer, all of which have been shown to contribute to CXCR4-enhanced adhesion of prostate cancer cells to ECM substrates or endothelial cells (32,33). The integrin receptor αVβ3 exhibits an extremely restricted expression pattern being elevated at sites of tumour neovascularisation and in bone-metastasizing cells. The αVβ3-integrin receptor is also the major integrin receptor expressed by osteoclasts, mediating their adhesion to osteopontin, bone sialoprotein and vitronectin, each of which are major components of bone and are frequently elevated at sites of bone metastasis. In mediating adhesion to these substrates, this integrin receptor has been shown to contribute to the bone resorbing activity of osteoclasts (reviewed in (35,36)). Activation of αVβ3 has also been implicated in modulating cell signaling pathways that promote cell proliferation, cell survival, migration, and the malignancy of various cancer cells. As such the characterization of CXCR4-potentiated αVβ3 function in prostate cancer cells is likely to be of clinical relevance in regulating the adhesion, arrest and proliferation of metastatic cells within the bone microenvironment.

Interestingly, many of the *in vivo* and *in vitro* responses induced by CXCL12 signaling described for prostate cancer cells are only partially reversed by administration of an anti-CXCR4-directed intervention. While this may reflect incomplete coverage of the CXCR4 receptor using these strategies, it is also feasible that the recently characterized interaction of CXCL12 with the CXCR7 receptor may also contribute to the disease progressing and pro-metastatic activity of CXCL12. Although no studies have currently been conducted in cell-based models or patient-based samples of prostate cancer, a recent publication has reported that CXCR7-mediated signaling promotes primary tumor growth in experimental

models of breast and lung cancer and increases experimental lung metastases in immunodeficient and immunocompetent mice (21,37). CXCR7 expression was also localized by immunohistochemistry to tumor-associated blood vessels and malignant cells in lung and breast biopsy sections but was found to be absent from normal vasculature. In light of these findings future studies examining the significance of CXCR7 expression in prostate cancer tissue will be important in characterizing the receptor selectivity of CXCL12-promoted progression of prostate cancer.

5. CXCL8, CXCR1, CXCR2 EXPRESSION IN PROSTATE CANCER

There is considerable evidence from experimental models and studies conducted on patient samples to support a role for the pro-inflammatory chemokine CXCL8 in the promotion of prostate cancer progression. Several studies have now confirmed elevated expression of this chemokine and its associated receptors in prostate cancer. Initial immunohistochemistry studies examining pro-angiogenic factor expression confirmed the expression of CXCL8 in glandular epithelial cells of prostate cancer tissue, with little or absence of staining for this chemokine detected in benign prostate hypertrophy or normal prostate epithelium (38). In addition, using immunohistochemistry, our laboratory has shown that the expression of CXCL8, CXCR1 and CXCR2 is increased in the tumor cells of prostate biopsy tissue with strong localization within epithelial cells (39). The immunoreactivity to anti-CXCL8, anti-CXCR1 and anti-CXCR2 antibodies was shown to increase with the stage of disease and demonstrated an increased cytoplasmic distribution, suggestive of an increased agonist-induced internalization of the receptors. IL-8, CXCR1 and CXCR2 immunoreactivity positively correlated with markers of cell proliferation and microvessel density. In contrast to our study (39) and that of the Kreutzer laboratory (38), Huang and colleagues have observed a differential expression of CXCL8 and its receptors between the neuroendocrine and non-neuroendocrine compartments of prostate cancer tissue (40). Their analysis of benign and malignant prostate tissue cores confirmed an increased IL-8 expression that correlated with progressive disease but suggested that this chemokine was expressed solely by neuroendocrine rather than epithelial cells. Similarly, CXCR2 expression was also only detected in the neuroendocrine cells. In contrast, CXCR1 expression was absent in neuroendocrine cells but was present in the non-neuroendocrine compartment of prostate cancer. Although, these independent studies suggest markedly different distribution pattern for this chemokine and its receptors, there is a consistent trend of increased and concurrent expression of CXCL8 and its two receptors in prostate cancer tissue, thus indicative that prostate cancer cells are subject to a continuous autocrine/paracrine stimulus. *In situ* hybridization studies have also confirmed increased mRNA transcript expression for CXCL8 in cancer cells of androgen-independent prostate cancer tissue (41). Furthermore, consistent with the characterization of increased CXCL8 expression within the cancerous prostate tissue, several studies have reported the detection and measurement of increased CXCL8 levels in the serum of patients with either localized or metastatic prostate cancer relative to control patients or patients with benign prostatic hypertrophy (42-44). In addition, CXCL8 is one of three cytokines (others include TNFalpha and IL-6) whose serum expression level is also significantly increased in patients with advanced, cachectic prostate cancer relative to non-cachetic prostate cancer patients (45). A genetic basis may also underlie the increased expression of CXCL8 in metastatic prostate cancer patients. In their analysis of IL-8 gene polymorphisms, McCarron and colleagues have reported that the incidence of a specific polymorphism that enhances promoter activity and increases CXCL8 synthesis is more prevalent in patients with metastatic prostate cancer (43).

6. CXCL8, ANGIOGENESIS AND PROSTATE CANCER METASTASIS

Angiogenesis is a critical and early event in the progression and metastasis of prostate cancer. CXCL8 is an ELR+, pro-angiogenic chemokine whose transcription is predominantly regulated in an AP-1 and NF-κB-dependent mechanism (46). There is an extensive literature pertaining to the pro-angiogenic activity of ELR+ CXC-chemokines and specifically that of CXCL8 which has been the subject of several past and recent reviews (47,48). Reported effects of CXCL8 administration to endothelial cells include the promotion of rapid stress fiber assembly and chemotaxis, endothelial tube formation, enhanced cell proliferation and increased activation of cell survival pathways (49-51). Several studies indicate that the CXCR2 receptor is the predominant receptor regulating endothelial cell migration and chemotaxis (49,52,53), although blockade of both CXCR1 and CXCR2 receptors has also been associated with the attenuation of neovascularization (51). Activation of the phosphotidyl-inositol-3 kinase pathway or the Erk1/2 MAPK-dependent signaling cascade has been implicated in underpinning the pro-angiogenic response to CXCL8 (49). CXCL8-induced signaling has also been shown to increase the ratio of anti-apoptotic to pro-apoptotic expression of Bcl-2 family proteins, providing a mechanistic basis to cell survival and induce the expression of matrix metalloproteinases that is consistent with the enhanced migratory potential of stimulated endothelial cells (50). Interestingly, a recent study has reported that CXCL8 signaling results in the transactivation of the vascular endothelial growth factor receptor (VEGFR) in endothelial cells, resulting in the modulation of endothelial cell permeability (54). Since this response is mediated through an intracellular, Src-dependent signaling pathway, this raises an interesting question regarding whether anti-angiogenic therapies employing antibodies directed against the ectodomain of VEGFR will be effective in cancers that exhibit elevated constitutive expression of pro-angiogenic chemokines.

Orthotopic implantation of clonal derivatives of human prostate cancer cells that exhibit differential expression of CXCL8 have confirmed that the expression of this chemokine correlates with the resultant angiogenesis, tumorigenicity and distant metastasis

observed in athymic nude mice (55,56). Clones with high CXCL8 expression gave rise to highly vascularized, rapidly growing tumors with a prevalence of lymph node metastasis. In contrast, attenuating IL-8 expression retarded tumor growth, decreased tumor vascularization and decreased the incidence of lymph node metastasis. Further studies have also highlighted that the secretion of CXCL8 by prostate cancer cells is effective in promoting the differentiation of human bone marrow mononuclear cells into osteoclast-like cells and can promote the resorption of dentine slices, suggesting an important role for this chemokine in underpinning tumor-induced osteoclastogenesis and bone resorption (57). Although bony metastasis arising from prostate cancer is more characteristic of osteoblast-mediated sclerotic bone formation, it is increasingly recognised that osteoclastic activity is essential for the initial development of tumour growth. This suggests that the metastasis of prostate cancer to the bone has an underlying osteolytic phenotype which is eventually superseded by the bone-mineralising activity of osteoblasts (58,59). Therefore, these experimental observations are consistent with the clinical observations which have revealed a correlation of (i) CXCL8 expression with angiogenesis in prostate tissue and (ii) the elevated expression of CXCL8 in patients with confirmed metastatic disease. Furthermore, the characterization that cancer cell-derived CXCL8 can assist an osteolytic-based establishment of metastatic lesions within the skeleton is consistent with the prevalence of bone metastasis in patients with advanced prostate cancer.

Consistent with the pro-angiogenic and pro-metastatic correlations characterized in patients and experimental models of the disease, cell-based investigations have confirmed that CXCL8 expression correlates with elevated MMP-9 expression and collagenolytic activity and enhances the invasive potential of prostate cancer cells through Matrigel® (55,56). In addition, CXCL8-signaling has been proposed to induce prostate cancer cell invasion of basement membranes and motility upon laminin through CXCR2-mediated modulation of β1-integrin receptor activation (60). More recently, CXCL8 signaling has been shown to utilize non-receptor tyrosine kinases including Src and focal adhesion kinase in order to underpin prostate cancer cell motility (61). However, it is evident that future research providing a more comprehensive understanding of the transcriptional, translational and post-translational signaling basis to CXCL8-promoted cell motility and cell invasion will be required in order to identify viable and effective therapeutic strategies to attenuate the disease progressing effects of this chemokine.

In addition to binding with their cognate receptor, pro-angiogenic CXC-chemokines can bind to a promiscuous, non-signaling receptor known as the Duffy antigen/receptor for chemokines (DARC). DARC is preferentially expressed on erythrocytes and endothelial cells and function primarily to clear and nullify the signaling from an over-abundance of chemokines within the environment. Experiments conducted in DARC-deficient mice have demonstrated that the absence of this receptor contributed to a reduced clearance of CXC-chemokines from the prostate tumor microcirculation leading to increased tumor vessel density and a potentiation of the rate of tumor growth (62). More recent studies also suggest that DARC inhibits angiogenesis through the promotion of senescence in vascular endothelial cells (63). Of significant interest, population studies have revealed erythrocyte expression of DARC is absent in close to 70% of African-Americans, arising as a genetic adaptation to protect against malaria infection. Consequently, it has been suggested that the capacity to leave pro-angiogenic CXC-chemokine signaling unchecked within the prostate gland may underpin the greater incidence of prostate cancer and the two-fold higher mortality rate from prostate cancer that is observed in the African-American population relative to that in Caucasian men (see ref 62 for discussion).

7. CXCL8-SIGNALING IN ANDROGEN-INDEPENDENCE AND CHEMORESISTANCE

During the initial phase of prostate cancer, the growth of the tumor is primarily regulated by increased androgen signaling. Testosterone, the major circulating androgen, is converted by 5-α-reducatase to dihydroxy-testosterone (DHT) within the prostate cancer cell. DHT has increased avidity in binding to and inducing dimerization-mediated transcriptional activity of the androgen receptor (AR), resulting in an altered gene expression profile that favors cell cycle progression and ultimately growth of the tumor. Although targeted strategies to deplete androgen synthesis or androgen signaling are initially effective in controlling the disease, many of these patients will ultimately relapse and experience an androgen-independent progressive disease. A more detailed discussion of androgen signaling and the proposed mechanisms underpinning the development of androgen-independent disease have been expertly reviewed elsewhere (64,65). However, ligand-independent activation of the AR is acknowledged as one of the principal pathways by which growth factors and cytokines may contribute to the promotion of an androgen-independent growth of prostate cancer cells. Several published studies have already alluded to a role for CXCL8 signaling in promoting androgen-independent growth of prostate cancer cells since CXCL8-promoted proliferation was inhibited in the presence of AR blockade and through demonstration that CXCL8 signaling potentiates AR transcriptional activity in luciferase assays (61,66). Observations from our own laboratory have also identified a mechanism by which CXCL8 signaling potentiates not only the transcriptional activation of the AR but also increases the expression of this steroid hormone receptor in prostate cancer cells (Seaton and Waugh, unpublished data). Consequently, we and others have confirmed that the inhibition of CXCL8-signaling in prostate cancer cells renders them more sensitive to the growth-inhibitory effects of anti-androgen therapeutic agents, including the AR antagonist, bicalutamide.

Treatment options for patients that initially fail to respond or ultimately relapse on androgen ablation therapy are extremely limited given the intrinsic resistance of

castration-refractory prostate cancer to conventional chemotherapy agents. Within the past five years, trials combining glucocorticoids with docetaxel have reported modest survival benefits for a cohort of prostate cancer patients (67). Therefore, despite the breakthrough that these trial results herald in the use of chemotherapy in advanced prostate cancer, identifying mechanisms that further increase the sensitivity of prostate cancer cells to docetaxel-based therapy or indeed a wider spectrum of chemotherapy agents is essential to increasing the survival and prognosis of patients.

Hypoxia is prevalent within prostate cancer and is a significant risk factor in this disease. Hypoxic cancer cells are frequently more resistant to chemotherapy-induced cell death. Our laboratory has recently confirmed that transcription of the CXCL8 gene and significantly that of its receptors CXCR1 and CXCR2 is induced in hypoxic prostate cancer cells (68). The increased synthesis and secretion of this chemokine coupled with increased expression of its signaling competent receptors suggests that hypoxic prostate cancer cells are subject to an increased autocrine/paracrine signaling stimulus. Further published and unpublished studies from our laboratory have demonstrated that CXCL8 signaling is coupled to the activation of several cell survival pathways. For example, we have shown that addition of CXCL8 to androgen-independent prostate cancer cells induces activation of the phospatidyl-inositol-3-kinase (PI3K)/Akt and mTOR pathways (69). Further unpublished observations have also characterized that CXCL8 signaling induces the transcriptional activity of NF-κB and HIF-1, regulating the expression of multiple anti-apoptotic genes and genes that regulate the survival and metabolic conditioning of prostate cancer cells during oxygen and nutrient deprivation (Wilson, Maxwell and Waugh, unpublished observations) Significantly, we have shown that the induction of CXCL8 signaling under hypoxic culture conditions contributes to the diminished sensitivity of PC3 cells to etoposide (68). Therefore, targeting CXCL8 signaling or components of its downstream effector genes is a viable option to restore the sensitivity of cancer cells within the hypoxic regions of tumors to chemotherapy drugs.

Further unpublished data from our laboratory also confirms that CXCL8 signaling may be induced in prostate cancer cells in response to the administration of chemotherapeutic agents. In certain circumstances, the potentiation of CXCL8 signaling leads to significant decreases in the sensitivity of prostate cancer cells to specific drugs eg. oxaliplatin or TRAIL (Wilson and Waugh, unpublished data). Docetaxel, the taxane currently used in treating progressive, metastatic prostate cancer also potentiated the transcription of CXCL8 in androgen-independent prostate cancer cells but inhibiting endogenous and drug-induced CXCL8 signaling did not alter the sensitivity of these cells to docetaxel. In contrast, another published study has reported that the overexpression of CXCL8 in clones derived from an androgen-independent prostate cancer cell line did correlate with a two-fold decrease in the cytotoxicity of docetaxel (66). The clinical significance of constitutive, hypoxia-induced or indeed chemotherapy-induced CXCL8 signaling in reinforcing the intrinsic chemoresistance of prostate cancer cells remains to be established in relevant, *in vivo*-based clinical models of this disease.

8. CONCLUSION: CXCL8 AND CXCL12 SIGNALING AS THERAPEUTIC TARGETS IN PROSTATE CANCER

As in breast cancer, CXCL12/CXCR4 signaling is firmly established in promoting the proliferation, survival and metastasis of prostate cancer. CXCL8-signaling seems no less important in regard to promoting the progression of this disease given its multiple functions (Figure 1). We and others have shown that CXCL8 signaling potentiates the proliferation of androgen-dependent and androgen-independent prostate cancer cells, confers the development of an androgen-independent state, and modulates the invasion and adhesion of these cells, consistent with the observed promotion of metastasis in orthotopic models of prostate cancer in mice. We have also shown that the induction of CXCL8 signaling potentiates the activation of cell survival pathways and decreases the sensitivity of prostate cancer cells to many chemotherapy agents, suggesting a role in the evasion of apoptosis. Furthermore, the secretion of CXC-chemokines from cancer cells will impact on multiple other cell types within the immediate microenvironment of the tumor. We have already alluded to the pro-angiogenic effects of CXCL8 on the endothelial cells of the vascular system that have been extensively characterized by several laboratories. In addition, the secretion of CXCL8 will act to drive neutrophil and macrophage recruitment to tumor sites. Instead of promoting an immune-based eradication of the tumor, evidence is growing to suggest that the CXC-chemokine-mediated promotion of a TH2 immune response may actually favor tumor promotion and indeed progression to a more aggressive disease. Within the bone microenvironment, tumor-derived CXCL8 is further reported to influence osteoclast-activation, suggesting a role of this chemokine in assisting the initial lytic phase of bone colonization by infiltrating prostate cancer cells. In this regard, the pathology of CXCL8, CXCR1 and CXCR2 over-expression in progressive prostate cancer and our understanding of this chemokine in underpinning multiple "Hallmarks of Cancer" (70), is supportive of this chemokine being further investigated as a potential therapeutic target. Such strategies may include the exploitation of thalidomide, glucocorticoids and/or emerging anti-inflammatory chemopreventative agents such as curcumin that have been shown to deplete the transcription of CXCL8 in cell-based assays and *in vivo* models (71-74). Alternatively, as already developed to inhibit CXCL12-induced CXCR4 signaling, a range of small molecules or antibody-based therapeutics targeting CXCL8 or its receptors may permit direct perturbation of CXCL8 signaling in tumors. The availability of such agents will permit the conduct of further pre-clinical experiments that can address the most appropriate strategy (antibody versus small molecule) to target chemokines within the tumor microenvironment. In addition, receptor-targeted strategies will need to consider the aspect of chemokine

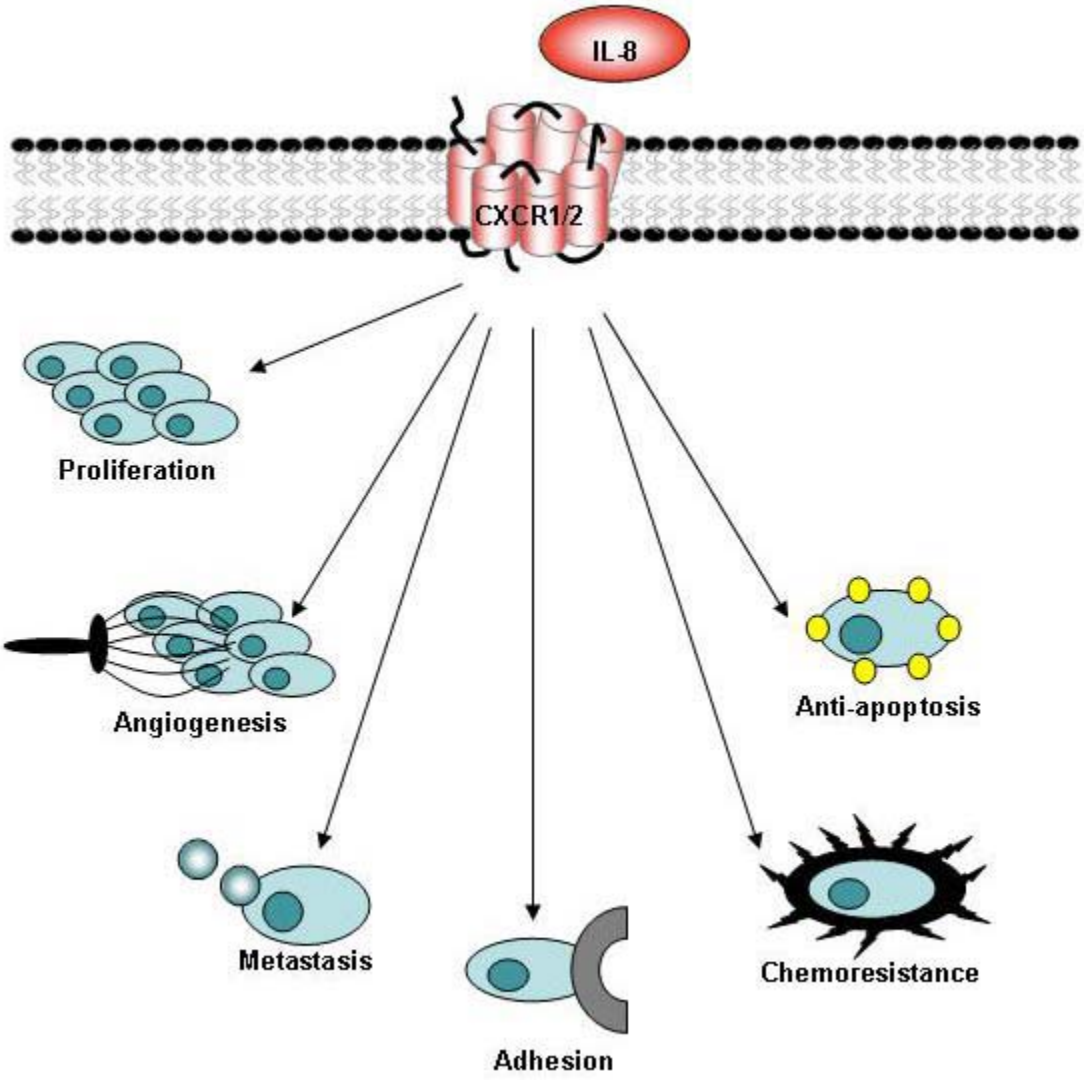

Figure 1. Schematic representation of CXCL8-induced functions contributing to the disease progression of prostate cancer.

signaling redundancy in order to inhibit all of the disease promoting effects of CXCL12 and CXCL8 ie. are dual CXCR4/CXCR7 or CXCR1/CXCR2 inhibitors more effective than agents that simply inhibit the activation of a single receptor. Finally, in light of our emerging knowledge regarding chemokine signaling in underpinning resistance to therapeutic agents, further pre-clinical experiments should identify the chemotherapy agents that should be administered in conjunction with CXC-chemokine inhibitors in order to derive the greatest clinical benefit.

In conclusion, constitutive synthesis of CXCL8 and CXCL12 has been characterized within the tumor cells of prostate cancer tissue. The resultant secretion of these chemokines modulates cancer cell, endothelial cell, stromal cell and inflammatory cell function within the tumor microenvironment. Important roles for CXC-chemokines in promoting tumor growth, angiogenesis and metastasis have been established. Emerging studies also suggest that the induction of chemokines plays an important role in modulating the response of the tumor to therapeutic interventions.

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Note Added in Proof: During the proof reading process, a manuscript detailing elevated CXCR7 expression in aggressive prostate cancer tissue has been reported. Signaling through the CXCR7 receptor has been reported to confer a survival advantage and to increase cell adhesion and cell invasion properties of prostate cancer cells. Wang et al., J. Biol. Chem 2007; Dec 5, epub ahead of print.

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