HHS Public Access

Author manuscript

Oncogene. Author manuscript; available in PMC 2023 June 16.

Published in final edited form as:

Oncogene. 2023 March ; 42(11): 785–792. doi:10.1038/s41388-023-02597-7.

CXCR7 as a novel therapeutic target for advanced prostate cancer

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Abstract

Chemokines and their cognate receptors comprise an intricate signaling network that becomes high-jacked by cancer cells for uncontrollable tumor growth and dissemination. ACKR3 (Atypical Chemokine Receptor 3), traditionally called CXCR7, is up-regulated in many cancers, including advanced prostate cancer, and represents promising targets for therapeutic intervention. Unlike typical G protein-coupled receptors such as CXCR4, CXCR7, once bound by its cognate ligand CXCL12, initiates the recruitment of β-arrestin instead of G proteins, and results in rapid internalization and degradation of CXCL12, functioning as a scavenger receptor. However, recent evidence suggests that CXCR7 may be more than a scavenger or auxiliary receptor of CXCR4 and that it may play essential roles in regulating cancer progression, some of which are independent of CXCR4 and its ligands, such as CXCL12. Constitutively active CXCR7 binds to β-arrestin. This protein complex internalizes to form a scaffold for assembling and activating various cytoplasmic kinases necessary for cell survival and tumor growth. Here we review and discuss the up-to-date knowledge on CXCR7 regulation and function and how this new understanding guides the development of CXCR7 inhibitors, focusing on prostate cancer.

INTRODUCTION

Prostate cancer (PCa) is the most common non-cutaneous cancer and the second leading cause of cancer-related deaths among males in the United States [1]. Androgen Receptor (AR) is a critical driver of PCa, most of which involve AR hyperactivity, amplification, and/or overexpression. Thus, androgen deprivation therapies constitute the mainstay treatment for advanced PCa [2]. However, the majority of patients with metastatic PCa

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AUTHOR CONTRIBUTIONS

GG and JY wrote the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

relapse, developing castration-resistant PCa (CRPC) [3]. Most CRPC tumors still require AR and can be further controlled using second-generation AR pathway inhibitors, such as enzalutamide [2]. Unfortunately, CRPC patients rapidly develop resistance to enzalutamide, often within several months of treatment [3, 4]. A significant fraction of these enzalutamide-resistant tumors have lost AR expression and acquired some forms of neuroendocrine phenotype [5]. These tumors are challenging to treat, accounting for the majority of PCa-associated deaths and urgently calling for novel therapeutic approaches [6].

Chemokines belong to a family of secreted bioactive molecules that play an essential role in maintaining homeostasis through distant cell-to-cell communication. This fine-tuned network that is comprised of chemokines and their receptors becomes hijacked in pathological conditions, such as cancer. Thus, aberrant inflammation that is ignited and maintained by pro-inflammatory factors leads to continuous tumor promotion [7]. Chemokine receptor 7 (CXCR7), officially named ACKR3 (Atypical Chemokine Receptor 3), was first described as the orphan receptor RDC1, as it is predominantly expressed in endothelial cells where it was thought to regulate cell migration and angiogenesis [8]. RDC1 was later deorphanized and renamed CXCR7 when it was found to bind with ligand CXCL12, also known as the stromal cell-derived factor (SDF1), originally reported as being a ligand of CXCR4 [9]. CXCR7 provides co-receptor function to CXCR4 in T lymphocytes to mediate human immunodeficiency virus (HIV) infection [9]. CXCR7 also plays a critical role in cardiac function. Murine global *Cxcr7* knock-out causes peri-natal lethality due to cardiac valve malformation [10]. Evidence accumulated in the last two decades that CXCR7 is de-regulated in cancer and regulates cancer progression. In particular, a consortium of pro-inflammatory cytokines and chemokines, including IL6, IL8, CXCL12, and CXCR4, create a force that drives PCa aggressiveness through increased metastasis and tumor-vascularization [11]. The interest in the therapeutic application of pro- and anti-inflammatory cytokines and chemokines for cancer control is growing [12]. In the present work, we will review the up-to-date reports on the role of CXCR7 signaling (Fig. 1) in PCa progression and potential approaches to its therapeutic targeting.

THE LIGANDS THAT BIND TO CXCR7

SDF1 (CXCL12)

Stromal-derived factor 1 (SDF1), also known as CXCL12, is a pro-inflammatory factor that was initially discovered to drive lymphocytes and monocytes to bone marrow stroma as it engages with CXCR4 that is expressed on immune cells [13, 14]. Later, it was identified that CXCL12 also interacts with CXCR7 (Fig. 1), and this interaction is critical for immune cell chemotaxis as well [9]. The importance of CXCL12-derived signaling in cancer progression became evident through multiple independent studies that reported on the role of CXCL12 in driving bone-targeting metastases, which are common for PCa [15, 16]. Thus, PCa cells were empirically shown to respond to the CXCL12 gradient through increased transmigration through the basal membrane and endothelial cell layer derived from bone marrow [16]. CXCL12 expression is increased in metastatic PCa lesions compared to normal prostate tissues [17, 18]. Moreover, in vivo studies confirmed that CXCL12 is involved in promoting the distant metastases of PCa to the brain, bones, and lymph

nodes [19]. Finally, pre-treatment with CXCL12-specific neutralizing antibodies decreases the proliferation of bone-homing invasive PCa cells [17]. However, there is a lack of data showing if CXCL12-neutralizing antibodies are capable of blocking bone metastases of PCa in animal models.

I-TAC (CXCL11)

Besides SDF1, the chemokine receptor CXCR7 has been shown to have high-affinity binding with interferon-inducible T cell alpha chemoattractant (I-TAC), also known as CXCL11 [20]. CXCL11 is a pro-inflammatory chemokine that was first described as a cognate ligand for the CXCR3 chemokine receptor [21]. CXCL11 expression is induced in response to stimulation with pro-inflammatory factors, interferon γ, interleukin 1, and lipopolysaccharide (LPS). During inflammation, upregulated CXCL11 mediates the recruitment of T lymphocytes to the inflammation site [21, 22]. It was later discovered that CXCR7, which is highly expressed in many cancers, binds with high affinity to CXCL11 [20, 23]. However, recent studies have shown that both CXCL11 and CXCL12 are barely expressed in androgen-dependent PCa cell lines, which are positive for CXCR7 [24]. In addition, while expression of CXCR7 has been positively associated with a growth and survival advantage of PCa cells, the stimulation by CXCR7 ligands CXCL11 and CXCL12 failed to affect PCa cell proliferation [20, 24, 25], suggesting ligand-independent roles of CXCR7 in promoting PCa growth.

Macrophage migration inhibitory factor (MIF)

Macrophage migration inhibitory factor (MIF), a cytokine that is initially discovered in pituitary cells and is upregulated in response to antigen stimulation, was originally thought to be an immunomodulator that prevents immune hypersensitivity [26, 27]. It was noted that, during the immune response, antigen-activated lymphocytes release the MIF factor, which in turn arrests the chemotaxis of macrophages [27]. MIF acts as a cognate CXCR7-specific ligand as stimulation with MIF leads to receptor internalization, followed by activation of the downstream kinases that induce the chemotaxis of lymphocytes [28].

Studies have later shown that MIF is up-regulated in PCa, metastatic disease, and CRPC [29, 30], representing a promising therapeutic target for PCa. This up-regulation of MIF is mediated, at least in part, by HBP1 loss in PCa, as MIF is identified as a target of HBP1-mediated transcriptional repression [31]. Due to its immuno-regulatory function, MIF was first thought to play a role in cancer development that is limited to modulating tumor-promoting inflammation [32]. However, later MIF was proven to regulate PCa cells itself, as MIF stimulation of PC3 induces cell proliferation and dissemination. Meanwhile, the use of specific MIF-blocking antibodies reduces PCa tumor growth [33]. Treatment-induced neuroendocrine trans-differentiation of PCa cells is accompanied by the increased release of MIF factor, which was shown to be critical for NEPC cell survival and proliferation [34]. Accordingly, inhibition of MIF reduced PCa cell growth, invasive properties, and inflammatory responses [33, 35, 36]. It was recently reported that both MIF and CXCR7 are overexpressed in CRPC tumors and that the tumor-promoting effects of MIF are dependent on CXCR7 [30].

INTRACELLULAR SIGNALING ACTIVATED BY CXCR7

Similarly to other chemokine receptors, such as CXCR4, CXCR7 is a seven-transmembrane receptor and belongs to the G-protein coupled receptor (GPCR) family [8]. However, CXCR7 stands alone from typical chemokine receptors as it has a lower affinity to G-proteins but a higher affinity to the scaffolding protein β-arrestin 2 (ARRB2) [37] (Fig. 1). The higher affinity of CXCR7 to ARRB2 is explained by the altered DRY sequence at the transmembrane domain 3 of the receptor, which prevents G-protein recruitment, in combination with the serine-threonine enriched structure of the C-terminal domain of CXCR7 that is designed for more robust interaction with ARRB2 [38-40]. Ligand interaction with CXCR7 does not activate the typical G-alpha proteins. Instead, it induces CXCR7 phosphorylation and conformational changes, which subsequently interact with ARRB2, leading to protein complex internalization, intracellular endosomal trafficking, and final degradation of CXCL12 [37, 38]. Earlier studies have thus suggested that CXCR7 is a decoy receptor that sequesters bioactive chemokine CXCL12 from the surroundings and subjects it to lysosomal degradation. In contrast, the receptor itself cycles back to the cell membrane [23, 41, 42].

However, constitutive CXCR7 internalization and recycling back to the cell membrane were also noted in the absence of a ligand, suggesting additional CXCR7 functions beyond its being a decoy receptor [23]. It was later found that the internalized CXCR7-ARRB2 protein complex transduces intracellular signaling, which is evident through the activation of cytoplasmic protein kinases in a CXCR7-ARRB2-dependent manner [25, 37, 38]. ARRB2, as a scaffold protein, facilitates prolonged and persistent activation of cytoplasmic non-receptor protein kinases by inducing their phosphorylation and protecting them from dephosphorylation [43]. The activation of these protein kinases strongly contributes to the role of CXCR7 in regulating the oncogenic properties of cancer cells. While some studies have reported CXCR4 and CXCR7 heterodimer formation and function in conveying CXCR12-mediated signaling [44-46], such heterodimerization was not confirmed nor required for CXCR7 function in several other studies [24, 39]. In this section, we will discuss recent evidence that highlights the protein kinases that are activated by the CXCR7-ARRB2 complex to induce tumorigenesis (Fig. 1).

Mitogen-activated protein kinases (MAPK)

Mitogen-activated protein kinases (MAPK) are the most well-studied non-receptor protein kinases in the context of ARRB2-driven activation [47]. MIF has been shown to be overexpressed in many cancers, and it binds to CXCR4 and CXCR7 receptors to induce phosphorylation of MAPK and AKT and accelerate tumor growth and metastasis [48]. Further, another study showed that deletion of the carboxy terminus of CXCR7 disrupted its internalization and reduced ERK1/2 activation [38]. As of today, there are many reports suggesting that either ligand-stimulated or constitutively active CXCR7 causes increased ERK phosphorylation and activation [49, 50]. For example, we have previously shown that constitutively active CXCR7 activates the ERK pathway to drive enzalutamide-resistant PCa growth [24]. Increased expression of CXCR7 has also been shown to reactivate the ERK pathway and promotes resistance to EGFR tyrosine kinase inhibitors in aggressive

lung cancer [50]. Moreover, CXCR7 has been reported to elevate the level of ERK phosphorylation through interacting with other receptors, namely epidermal growth factor receptor (EGFR), in prostate and breast tumors [25, 51, 52]. As MAPK/ERK signaling is one of the most fundamental oncogenic pathways in cancer [53], its activation may represent a significant mechanism underlying CXCR7-mediated tumorigenesis.

AKT serine/threonine kinases

AKT, also known as Protein Kinase B, is an important pro-survival oncogene that protects tumor cells from apoptosis [54]. While CXCL12-stimulated CXCR4 is well documented to activate AKT signaling in various cancers, including PCa [55-57], CXCR7 has only been loosely connected to AKT phosphorylation [48, 58]. Several reports state that stimulation of CXCR7 with MIF factor leads to activation of both AKT and MAPK phosphorylation [30, 33, 34]. In particular, one study reported that MIF binding to CXCR7 activates the AKT signaling pathway to drive CRPC tumor growth and metastasis [30]. However, another ligand, CXCL11, was shown to bind to CXCR7 efficiently but was incapable of inducing ERK or AKT phosphorylation through CXCR7 in lymphocytes [59]. Interestingly, the study of a mouse model with prostate-specific *Pten* heterozygous deletion and *Runx2* overexpression showed concomitant increases in AKT phosphorylation and CXCR7 expression, together accelerating tumor development [60]. However, it is unclear from this study whether the increase in AKT activation is due to *Pten* loss or *Runx2/Cxcr7* up-regulation [60].

Other protein kinases

CXCR7 is a membrane protein that, once bound by ARRB2, internalizes to form endosomes that are abundant in the cytoplasm. Such endosome-anchored CXCR7-ARRB2 complex works as a scaffold to interact with other proteins and assemble protein kinase complexes [24]. MAPK and AKT are the most commonly studied protein kinases in the context of CXCR7 activation. However, in principle, CXCR7-ARRB2 could interact with many other intracellular signaling kinases. In cells derived from Myc-induced PCa in mice, CXCL12 treatment was shown to rapidly activate multiple signaling pathways, including MAPK/ERK, STAT3, and NF-KB, which was attenuated by the knockdown of either CXCR4 or CXCR7 [61]. Further, in mCRPC cells, CXCL12 over-expression was shown to induce NF-kB and PKC-alpha signaling mediated by CXCR4 to induce cancer stem cell and neuroendocrine features [62]. Similarly, a separate group showed that CXCL12 increased CXCR4 expression in PC-3 cells and enhanced NF-kB-dependent transcriptional activities, increasing PC-3 cell adhesion and transendothelial migration [15]. In glioblastoma cells, the CXCL12-CXCR4 axis has also been reported to regulate AURKA activation [63]. However, both studies showed that activation of NF-kB or AURKA is dependent on the MAPK/ERK signaling, partially due to its regulation of CXCR4 expression, which subsequently affects CXCL12-CXCR4-mediated activation of the kinases. However, it is also likely that NF-kB or AURKA activation is downstream of the MAPK/ERK kinase cascade. In addition, it is unclear from these studies whether CXCR7 is involved in the regulation of the kinase activities by CXCL12-CXCR4 signaling.

Arrestins themselves serve as an important scaffolding factor for many signaling pathways. There are many previously reported ARRB1- and ARRB2-dependent kinases that are yet to be evaluated in the context of CXCR7 signaling. The c-Jun N-terminal kinase (JNK) belongs to the MAPK family, and its regulation by ARRB2 has been very well studied. Precisely, Guo et al. have shown that the C-terminus of ARRB2 binds to the N-terminal domain of JNK3, which subsequently recruits MAPK kinase 4 (MKK4) and apoptosis-signaling kinase 1 (ASK1) to the scaffold complex [64]. Later, Zhang et al. independently confirmed that ARRB2 forms an activating protein complex by bringing together MKK4 and JNK3 kinases [65]. Several recently published works shed light on the role of arrestins in the activation of oncogenic Src kinase. As such, a reconstituted GPCR-ARRB1 protein complex binds to and activates Src autophosphorylation, while ARRB1 alone fails to do so [66]. Further, utilizing structural crystallography, Perez et al. established a thorough model of ARRB2 interaction with Fgr, a Src family tyrosine kinase [67]. Wnt/β-catenin is another signaling pathway that is allosterically regulated by ARRB2, which binds to phosphorylated disheveled (Dvl) and axin, the two proteins that control β-catenin activation [68]. Taken together, these reports highlight the diversity and omnipresence of the protein kinases that are dependent on ARRB2. Nevertheless, more studies are warranted in order to identify the role of CXCR7 in the context of ARRB2-mediated molecular signaling.

CXCR7 EXPRESSION AND ONCOGENIC FUNCTIONS IN PCA

Historically, CXCL12/CXCR4 signaling axis was thought to play a pivotal role in the chemoattraction of lymphocytes to the bone marrow [9, 13]. CXCL12, expressed by osteoblasts and endothelial cells, binds to CXCR4, which is present in PCa cells, to attract them to the bone marrow. Thus, CXCL12/CXCR4 signaling has been widely evaluated as a driver for bone metastases, which are common for PCa patients [16-18]. However, the studies of CXCR7 in PCa bone metastases have been minimal thus far. There are only a handful of reports that have associated CXCR7 with distant PCa metastases [19, 30]. Instead, several studies have reported a significant role of CXCR7 in regulating tumor growth. CXCR7 expression increases following PCa progression, and as such, CXCR7 is upregulated in aggressive PCa and correlates with poor prognosis [24]. Since CXCR7 induces activation of the fundamental signaling pathways such as MAPK and AKT, it was confirmed by multiple independent groups that CXCR7 drives PCa cell proliferation and cell cycle progression in vitro and tumor growth in vivo. CXCR7 knockdown inhibits PCa cell proliferation and causes cell cycle arrest [25, 51]. CRISPR/CAS-induced frame shift of the CXCR7-encoding gene triggers cellular senescence of PCa cells [51]. The data derived from the prostate-specific *Pten*-deficient mouse model showed that prostate tumors with upregulated CXCR7 have increased AKT signaling and a more aggressive fast-growing phenotype [60]. These data unequivocally point to the vital role of CXCR7 in PCa cell proliferation and cell cycle regulation.

In addition, CXCR7 has also been shown to regulate angiogenesis, cell adhesion, cell invasion, and macrophage infiltration. An earlier study demonstrated that CXCR7 is a receptor of CXCL11 and CXCL12 that is expressed by many cancer cell lines as well as activated endothelial cells, inducing cell growth and adhesion [20]. Antibodies that block CXCR7 ligand MIF was shown to reduce PC-3 PCa cell growth, viability, and cell invasion

by abolishing the phosphorylation of ERK and AKT and activating apoptotic factors caspase-3/7 [33]. Further, CXCR7 depletion in PCa cells has been shown to cause reduced cell proliferation, cell cycle arrest, and hampered tumor growth and vessel formation in vivo, which is associated with decreased expression of VEGF, cyclin D1, and p-EGFR [25]. Further, CXCL12 stimulated the migration and invasion of a PCa cell line derived from the HiMyc mouse model, and these effects are abolished by the knockdown of either CXCR4 or CXCR7 [61]. In breast cancer, through gene silencing, CXCR7 was shown to control angiogenic marker expression and macrophage infiltration, thereby mediating tumorigenicity and cancer invasiveness [69]. In head and neck cancer, the CXCR7-targeting reagent did not inhibit cell cycle progression but reduced the secretion of CXCL1, an angiogenic chemokine [70]. Likewise, CXCR7 silencing suppressed the proliferation of esophageal squamous cell carcinoma and angiogenesis [71].

We and others have shown that CXCR7 is up-regulated in CRPC as compared to primary PCa [24, 30]. Moreover, CXCR7 is among the top genes that are up-regulated in PCa treated with AR pathway inhibitors such as enzalutamide. By contrast, CXCL12 and CXCR4 were unaltered. Functional assays showed that CXCR7 overexpression promotes enzalutamide resistance, which is mediated in part by MAPK/ERK and/or AKT signaling and can be abolished by ARRB2 knockdown [24, 30]. These effects are largely independent of CXCL12 and CXCR4. These data suggest that CXCR7 may be constitutively active and play more critical roles than CXCR4 in late-stage PCa, representing a promising therapeutic target.

REGULATION OF CXCR7 EXPRESSION IN PCA

CXCR7 is initially identified in endothelial cells and later found to express in fibroblasts and in a number of cancers [8, 20, 71]. The expression of the *CXCR7* gene has been shown to be regulated by multiple transcription factors. Hypermethylated In Cancer 1 (HIC1) is a transcription repressor that binds to sequence-specific DNA elements. Genome-wide expression profiling of HIC1-deficient cells identified CXCR7 as a putative target gene that is repressed by HIC1 [72]. Further analyses revealed a phylogenetically conserved HIC1-responsive element on the CXCR7 promoter, which is bound by HIC1 and its corepressor SIRT1 that inhibit CXCR7 gene transcription. HIC1 is a tumor suppressor gene that harbors 11 CpG sites within its promoter that is abundantly hypermethylated in many tumors [73]. HIC1 is thus epigenetically silenced in many cancers, including PCa, leading to the up-regulation of its target genes, such as CXCR7, that may contribute to cell proliferation and tumor growth [74]. In agreement with this, prostate-specific deletion of Hic1 in the mice results in PCa with strong metastatic behavior, which may be associated with increased expression of Slug, CXCR4, and ERK pathway activation [73].

CXCR7 belongs to the pro-inflammatory network comprised of chemokines and their receptors. As such, there is evidence that CXCR7 expression is regulated by the factors commonly involved in unfolding inflammation. Interleukin 8 (IL-8) and interleukin 6 (IL-6), pro-tumorigenic, pro-inflammatory cytokines, were shown to induce CXCR7 expression in tumor cells [25, 71]. The induction of CXCR7 gene expression by IL-6 and IL-8 signaling is driven by the activation of the NF-kB transcription factor, which was shown to bind

the CXCR7 gene promoter and induce its expression [71, 75]. Furthermore, Runt-related transcription factor 2, RUNX2, is a transaction transcription factor that is widely known to regulate bone-specific gene expression and is up-regulated in *Pten*-deficient PCa and CRPC tumors [76, 77]. RUNX2 was shown to induce CXCR7 transcription in Pten-deficient PCa tumors through direct binding to its promoter and enhancer regions [60]. CXCR7 is required for Runx2-mediated AKT phosphorylation and tumor growth in the *Pten*-deficient cells.

Recent literature suggests that CXCR7 is a direct target of AR-mediated transcriptional repression, making it a putative therapeutic target in the context of CRPC that has undergone AR pathway inhibition [24, 30, 51]. We and others have reported that AR negatively regulates CXCR7 expression through binding to AR-response elements (ARE) at an enhancer of 110 kb downstream of the gene, which likely forms a DNA loop to the promoter to suppress gene transcription. Removal of AREs by CRISPR/Cas9-mediated gene editing restored CXCR7 expression [24]. Consequently, CXCR7 expression was found up-regulated in CRPC, which have undergone systematic androgen-deprivation therapies, compared to localized, hormone-naïve PCa. CXCR7 was further induced upon the use of AR pathway inhibitors such as enzalutamide [24, 51]. The most aggressive forms of PCa, following the development of enzalutamide resistance, commonly feature the loss of AR signaling and reactivation of aberrant signaling factors that are involved in NEPC transdifferentiating [5, 78]. Whether CXCR7 expression is further induced in these late-stage NEPC tumors warrants further investigation.

THERAPEUTIC APPROACHES TO TARGET CXCR7

Despite the fact that both CXCR7 and CXCR4 share the same agonist, CXCL12, only CXCR7 has been repeatedly shown to become up-regulated in response to ADT [24, 30, 51, 79]. By contrast, an accumulated body of evidence suggests that CXCR4 can play an essential role in promoting bone-directed metastases [18, 80-82]. As such, we think that disruption of the CXCR4 signaling axis could stall bone-directed PCa cell dissemination, while CXCR7 targeting would be a promising strategy to attack advanced ADT-resistant PCa tumor growth. These findings have propelled a vigorous search for specific and efficacious inhibitors of the pathway, which will be reviewed in this section (Fig. 1).

Challenges in developing CXCR7 antagonists

As early literature demonstrated CXCR7 as a receptor for CXCL11 and CXCL12, the initial search for CXCR7 inhibitors has focused on the development of CXCR7 antagonists. The small molecule compound CCX771 was discovered and considered to be a CXCR7 antagonist since it effectively displaces CXCL12 from binding to CXCR7 [80]. It was widely utilized as a tool compound to inhibit the CXCL12-CXCR7 axis in model systems, and its therapeutic effects, either as a single treatment therapy or in combination with other drugs, were evaluated for a number of cancers. CCX771, as a single agent, inhibits the proliferation and invasiveness of human glioma cells [83]. Moreover, a limited number of preliminary studies showed that CCX771 co-treatment with AR pathway inhibitors, such as enzalutamide, exhibits combinatorial efficacy in animal models of CRPC [30]. However, despite displacing CXCL12 from the chemokine receptor, CCX771 still triggers

ARRB2 recruitment to CXCR7 and subsequent receptor internalization and activation [80]. Moreover, the structure of the CXCR7 protein predisposes its interaction with most of the exogenous and endogenous ligands to recruit ARRB2 [84, 85]. This feature makes the development of a bona fide CXCR7 antagonist a non-trivial task, and it is questionable whether CCX771 is a true CXCR7 inhibitor.

Anti-CXCR7 antibodies

As an alternative to small molecule inhibitors, potent antagonists for receptor proteins can be developed using the platform of specific monoclonal antibodies. Antibodies have fewer off-target effects due to their higher specificity to target peptides/proteins. There has been some success in the development of antibody-based molecules that target CXCL12-binding chemokine receptors. Utilizing a platform of antibodies derived from a single variable domain (VHH) of heavy chain antibodies found in the Camelidae family, also known as nanobodies, reflecting their relatively small protein size (12–15 kDa), several anti-CXCR7 nanobodies were developed. Further, they were shown to successfully displace CXCL12 from the chemokine receptor and prevent ARRB2 recruitment [70]. CXCR7-targeting nanobody therapy was shown to decrease tumor growth and vascularization in a patient-derived xenograft model of head and neck cancers. More recently, another research group reported on a successful attempt to create chimeric anti-CXCR7 antibodies called X7Ab, which were based on the mouse-derived single-chain antibody merged with an Fc fragment derived from human immunoglobulin G1 [86]. X7Ab effectively inhibits CXCL12-induced ARRB2 recruitment to CXCR7. In addition, the combination of X7Ab with temozolomide slows glioblastoma growth in a syngeneic model. Interestingly, X7Ab treatment triggers the activation of natural killer cells, which mediate the innate anti-tumor immune response. Therefore, it may be exciting and beneficial to evaluate the combination of CXCR7-targeted therapy with immune therapy in suppressing cancer.

Small molecule inhibitors of CXCR7

Most recent efforts focus on the development of small molecule inhibitors that could specifically disrupt CXCR7 and ARRB2 interaction. High-throughput screening discovered that diphenylacetamides could effectively reduce ARRB2 recruitment to CXCR7. However, the bioavailability of the compound in animals is low, which limits further investigation of the compound *in vivo* using animal models [87]. Notably, another group reported that high-throughput pre-screening combined with several rounds of structural optimizations rendered a highly specific CXCR7 antagonist, called ACT-1004–1239, that is capable of disrupting ligand-induced ARRB2 recruitment [88]. The compound performed exceptionally well in clinical evaluation showing good tolerability. A first-in-human study assessed the absorption, distribution, metabolism, and excretion (ADME) parameters of ACT-1004–1239 on six healthy male volunteers. The compound showed a clearance half-life of 36 h [89]. In a separate study, CXCL12 plasma level in healthy volunteers was assessed as a biomarker for CXCR7-targeting by ACT-1004–1239. Administration of a single 200 mg dose of the compound doubled the plasma level of CXCL12 within 24 h, which returned to baseline within 144 h post-dosing. These preliminary data show great promise and importance for further evaluation of ACT-1004–1239 therapeutic efficacy on preclinical models of CRPC.

CONCLUSION

In summary, CXCL12 was initially identified as a ligand of CXCR4 that inhibits the infection of lymphocytes by certain lymphocytetropic HIV-1 strains [14], and CXCR7 was considered as a co-receptor for this process [9]. Early literature on CXCR7 has focused on its role as a decoy receptor that sequesters CXCL12 in the cellular microenvironment and regulates the CXCL12-CXCR4 pathway [23, 41, 42] and some studies have also reported the CXCR4-CXCR7 heterodimers in mediating downstream signaling CXCR12-mediated signaling [44-46]. Major advances have been made in the last decade, identifying a critical function of CXCR7 in tumorigenesis, which is independent of CXCR4 or even CXCL12. CXCR7 was found to be up-regulated in many cancers, including CRPC and enzalutamide-resistant PCa, without accompanying increases in CXCR4 or CXCL12 [24]. However, whether CXCR7 is further up-regulated in the late-stage NEPC and how it functions and interacts with the tumor microenvironment warrants future investigation. Albeit responsive to CXCL12 stimulation, CXCR7 was reported to be constitutively active, recruiting ARRB2 and activating downstream kinases, such as MAPK/ERK [24, 49, 50]. These major breakthroughs have revolutionized the field of CXCR7 inhibitor development. Earlier attempts focused on searching for CXCR7 antagonists that compete with CXCL12/11, which has proven challenging as CXCR7 has a high affinity with these ligands. Moreover, CXCR7 is far easier to be activated by something that it binds than to be de-activated [84, 85]. In fact, compounds initially thought of as CXCR7 antagonist, such as CCX771, was later found to increase CXCR7 downstream signaling. Recent efforts in the development of CXCR7 inhibitors have thus shifted to screening for compounds that might inhibit ARRB2 recruitment by CXCR7 [89]. Such efforts have already yielded several promising drugs, such as ACT-1004–1239. Future investigations should focus on fine-tuning such compounds to further improve bioavailability and reduce toxicity, examining the efficacy of lead compounds for inhibiting cancer using preclinical models, and evaluating their performance in clinical trials.

ACKNOWLEDGEMENTS

This work was supported in part by the Prostate Cancer Foundation 2017CHAL2008 (to JY), the U.S. National Institutes of Health R01CA172384 (to JY), the Northwestern Prostate SPORE P50CA180995 (to JY), and the NIH/NCI training grant T32CA009560 (to GG).

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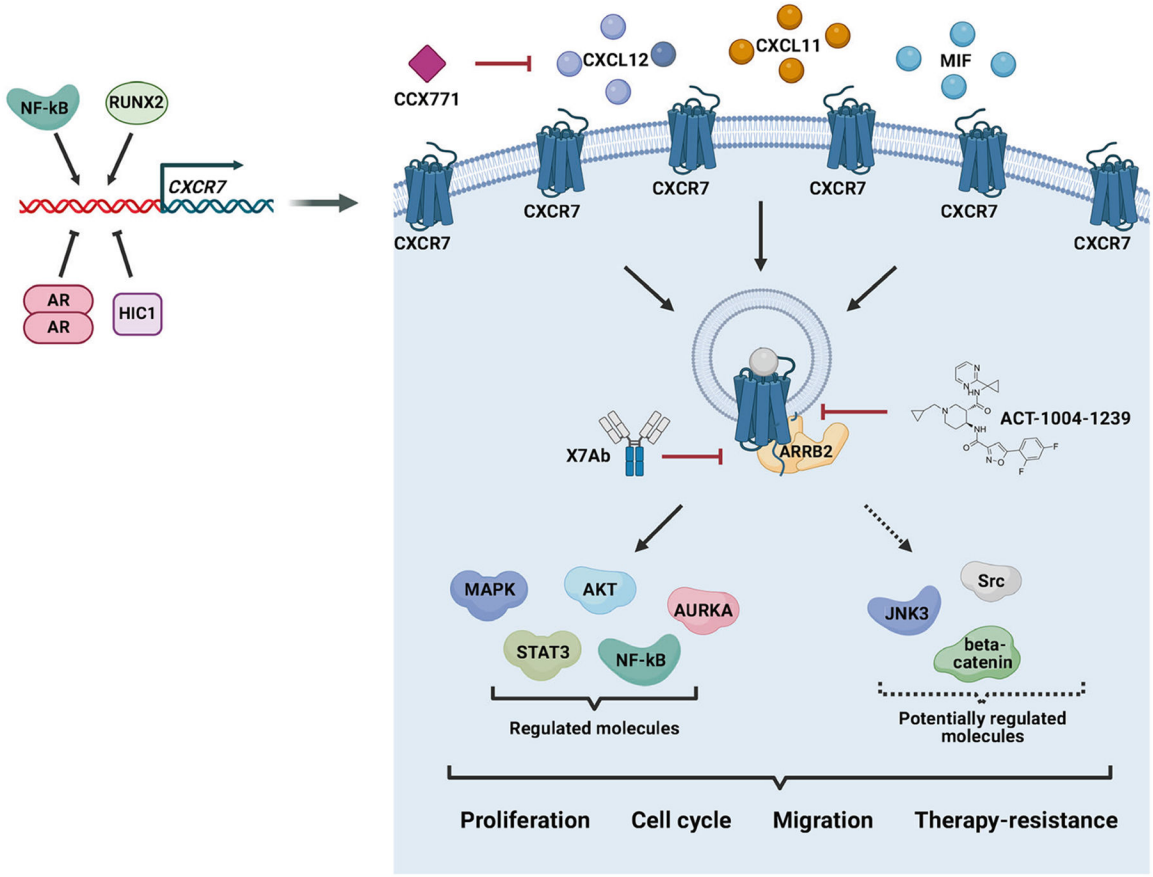

Fig. 1. A schematic representation of CXCR7 regulation, function, and therapeutic targeting.

CXCR7 is frequently upregulated in aggressive cancers, including therapy-resistant neuroendocrine prostate cancer, partially due to the loss of AR and/or HIC1, an oncosupressor, concomitantly with the increased activity of NF-kB and RUNX2. The upregulated CXCR7 transmits downstream signaling through ARRB2 recruitment either in response to ligand binding or in a ligand-independent fashion. Internalized CXCR7-ARRB2 complex forms a scaffold that assembles and activates cytoplasmic kinases, which mediate cancer cell survival, proliferation, and therapy evasion. Antagonists (e.g., CCX771), recombinant antibodies (e.g., X7Ab), and small molecule inhibitors (e.g., ACT-1004–1239) have been developed, aiming to inhibit CXCR7 activation and/or disrupt ARRB2 recruitment and block subsequent signal transduction. Image created with BioRender.