Differential expression of chemokine receptors and their roles in cancer imaging

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Chemokine/chemokine receptor interactions play diverse roles in cell migration and homeostasis. Emerging evidence suggests that cancer cells co-opt chemokine networks for survival, proliferation, immune evasion, and metastasis. Most of the chemokine receptors are reported to be involved in tumor progression. Given their extensive implication in cancer progression, several chemokine receptor/ligand axes are considered as potential therapeutic targets. This review provides a survey of chemokine receptor expression in cancer and evaluates the potential of chemokine receptor imaging as a tool for molecular characterization of cancer.

Keywords: molecular imaging, metastasis, chemokine receptor, chemokine, cancer

INTRODUCTION

Chemokine/chemokine receptor interactions play key roles in cell trafficking in host defense mechanisms, in organogenesis, vasculogenesis, and tissue repair. Most chemokines are secreted chemotactic cytokines of 8–12 kDa size. They can be divided into subgroups based on structural and functional characteristics. Structurally, chemokines are classified into four groups (CXC, CX3C, XC, and CC) based on the highly conserved first two of the four cysteine residues at the N-terminus (Zlotnik and Yoshie, 2000). Functionally, chemokines are classified as inflammatory or homeostatic. Inflammatory chemokines (e.g., CXCL8) are induced by inflammatory stimuli to attract polymorphonuclear leukocytes from the circulation to sites of infection or injury. Homeostatic chemokines (e.g., CXCL12), on the other hand, are constitutively expressed and regulate cell trafficking and homing during development and immune surveillance. The 48 known chemokines function by activating the 19 identified cell surface receptors that are seven-transmembrane-spanning proteins of the G-protein-coupled receptor (GPCR) superfamily. The chemokine receptor nomenclature system is based upon the chemokine subclass specificity of the receptor, whereby L (ligand) is replaced by R (receptor; Murphy et al., 2000). Although 6 of the 20 receptors are known to bind to a single ligand, several of the chemokines/receptors exhibit promiscuity and bind to more than one receptor/ligand, usually belonging to a single subclass (Zlotnik, 2006). Since the first report on the involvement of chemokine receptors in metastasis by Muller et al. (2001), significant progress has been made in deciphering their roles in cancer. More than half of the chemokine receptors are implicated in the biology of tumor growth and metastasis. A growing body of literature suggests that most chemokine receptors, as shown in Table 1, including CXCR2, CXCR3, CXCR4, CXCR7, and CCR7 play key roles in cancer cell survival, proliferation, homing, adhesion, tumor angiogenesis, and resistance to conventional and targeted therapies. Several chemokine networks are now considered potential therapeutic targets for cancer. This review focuses on the expression of several chemokine receptors for which there exists significant evidence in support of their roles in tumor biology and their possible uses as diagnostic markers.

CXCR1 AND CXCR2

CXCR1 and CXCR2 show 77% homology and considerable structural similarity but have distinct ligand-binding pharmacology (Holmes et al., 1991). CXCR1 binds to CXCL6 and CXCL8. CXCR2 binds several chemokines: CXCL1, CXCL2, CXCL3 (GROα, β, and γ), CXCL5 (ENA-78), CXCL6 (GCP2), CXCL7 (NAP2), and CXCL8 (Ahuja and Murphy, 1996; Wolf et al., 1998). In the hematopoietic system, both receptors are expressed on granulocytes, monocytes, and mast cells and on some CD8+ T cells and CD56+ natural killer (NK) cells (Chuncharapai et al., 1994). Functional effects of both the receptors are well characterized for the binding of the inflammatory ligand CXCL8 (IL8) than any other ligand (Waugh and Wilson, 2008). CXCR1 binds only CXCL8 with high affinity, whereas CXCR2 is known to bind all the ligands with high affinity (Waugh and Wilson, 2008).

Both receptors have been shown to play important roles in tumor progression in several cancers. In melanoma, CXCR1 is ubiquitously expressed on tumor cells at all Clark levels however, high levels of CXCR2 expression were observed mostly in high-grade melanomas (Varney et al., 2006; Singh et al., 2009a). Elevated CXCR2 and CXCL8 expression are correlated with high microvessel density, tumor angiogenesis, and metastases (Varney et al., 2006). CXCL8 is also constitutively secreted predominantly by melanoma cells resulting in an autocrine stimulation of cancer cells promoting survival, proliferation, and migratory capabilities (Singh et al., 2010). In advanced prostate cancer specimens, CXCR1, CXCR2, and CXCL8 expression were found to localize...
Table 1 | Chemokine receptor expression in cancer.

| Receptor | Ligand | Adopted from Murphy et al. (2000) and Murphy (2002) | Tumor expression | Reference |
|----------|--------|--------------------------------------------------|------------------|-----------|
| CXCR1    | CXCL6, CXCL8 | Neutrophil migration; innate immunity; acute inflammation | Melanoma, prostate, breast | Varney et al. (2006), Shamaladevi et al. (2009) |
| CXCR2    | CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8 | Neutrophil migration; innate immunity; acute inflammation; angiogenesis | Melanoma, pancreatic cancer, ovarian, prostate, lung | Singh et al. (2009b,c), Ijichi et al. (2011), Keane et al. (2004) |
| CXCR3    | CXCL9, CXCL10, CXCL11 | T cell migration; adaptive immunity; Th1 inflammation | Breast, colorectal, melanoma, acute lymphocytic leukemia, B-cell chronic lymphocytic leukemia | Kawada et al. (2004, 2007), Ma et al. (2009), Kawada and Taketo (2011) |
| CXCR4    | CXCL12 | B-cell lymphopoiesis; bone marrow myelopoiesis; central nervous system and vascular development | 23 Different cancers including breast, prostate, melanoma etc. | Cabioglu et al. (2005), Salvucci et al. (2006), Scala et al. (2005), Sun et al. (2003), Wong and Korz (2008), Burger and Kipp (2006), Teicher and Fricker (2010) |
| CXCR5    | CXCL13 | B-cell trafficking; lymphoid development | Head and neck | Muller et al. (2006) |
| CXCR6    | CXCL16 | T cell migration | Prostate | Deng et al. (2010) |
| CXCR7    | CXCL12 | Cardiac development | Breast, lung, prostate | Duda et al. (2011), Miao et al. (2007), Wang et al. (2008) |
| CCR1     | CCL3, CCL5, CCL7, CCL8, CCL13, CCL14, CCL15, 16, CCL23 | T cell and monocyte migration; innate and adaptive immunity; inflammation | Colorectal, multiple myeloma | Vallet and Anderson (2011) |
| CCR2     | CCL2, CCL7, CCL8, CCL13 | T cell and monocyte migration; innate and adaptive immunity; Th1 inflammation | Multiple myeloma, prostate, Breast | Loberg et al. (2007), Lu et al. (2007), Lu and Kang (2009) |
| CCR3     | CCL5, CCL7, CCL8; CCL11, CCL13; CCL15, CCL24; CCL26 | Eosinophil, basophil, and T cell migration; allergic inflammation | Renal cell carcinoma, glioblastoma, cutaneous T-cell lymphoma (CTCL) | Johrer et al. (2005), Kleinhans et al. (2003), Kouno et al. (2004) |
| CCR4     | CCL17, CCL22 | T cell and monocyte migration; allergic inflammation | Breast, adult T-cell leukemia/lymphoma, CTCL | Ishida et al. (2003), Li et al. (2012) |
| CCR5     | CCL3, CCL4, CCL5, CCL8, CCL14 | T cell and monocyte migration; innate and adaptive immunity | Breast, prostate, glioblastoma | Kouno et al. (2004), Vaday et al. (2006) |
| CCR6     | CCL20 | Dendritic cell migration | Colorectal, pancreatic, multiple myeloma | Rubie et al. (2006, 2010) |
| CCR7     | CCL19, CCL21 | T cell and dendritic cell migration; lymphoid development; primary immune response | Breast, melanoma, NSCLC, gastric, cervical, stomach, colorectal, CLL, non-Hodgkin’s lymphoma, T cell leukemia | Cabioglu et al. (2005), Takanami (2003), Mashino et al. (2002), Ding et al. (2003), Wiley et al. (2001), Arigami et al. (2009), Kodama et al. (2007), Schimanski et al. (2005) |
| CCR8     | CCL1, CCL4, CCL17 | T cell trafficking | Kaposi sarcoma | Haque et al. (2001) |
| CCR9     | CCL25 | T cell homing to gut | Melanoma, prostate, ovarian, breast | Singh et al. (2004, 2011), Johnson-Holiday et al. (2011) |
| CCR10    | CCL26, CCL27, CCL28 | T cell homing to skin | Melanoma (immune escape) | Murakami et al. (2003) |
| CX3CR1   | CX3CL1 | T cell and NK cell trafficking and adhesion; innate and adaptive immunity; Th1 inflammation | Neuroblastoma, prostate | Rodero et al. (2008), Shulby et al. (2004) |
| XCR1     | XCL1, XCL2 | T cell trafficking | | Moser et al. (2004) |
to cytoplasm, and silencing of CXCR1 has been shown to inhibit androgen-independent prostate cancer growth (Shamaladevi et al., 2009). Similarly, CXCR2 has been shown to promote ovarian cancer through dysregulated cell cycle proteins p21 (waf1/cip1), cyclin D1, CDK6, CDK4, cyclin A, and cyclin B1, diminishing apoptosis by suppressing p53 and poly(ADP-ribose) polymerase cleavage, and enhancing angiogenesis by increasing levels of VEGF. CXCR2 expression in high-grade serous ovarian carcinoma was also found to be an independent prognostic factor of poor overall survival and of early relapse in cancer patients (Yang et al., 2010). Furthermore, CXCR1 and CXCR2 overexpression has been shown to increase cancer cell survival in response to hypoxia (Maxwell et al., 2007), and to promote tumor angiogenesis in renal cell carcinoma (Mestas et al., 2005). Not surprisingly, neutralizing antibodies and low molecular weight antagonists targeting these receptors as well as siRNA based downregulation of the receptor expression have been effective in inhibiting tumor growth and invasion in lung, ovarian, pancreatic, and melanoma tumor models (Singh et al., 2009b; Ijichi et al., 2011).

In addition to the cancer cells, activated neutrophils express high levels of CXCR1 and CXCR2 and accumulate at the site of infection and inflammation. This neutrophil accumulation was monitored non-invasively using 99mTc labeled CXCL8 and CXCL7 proteins in different models of infection (Rennen et al., 2004). Despite the availability of a variety of monoclonal antibodies (mAbs) and small molecule structural motifs (Busch-Petersen, 2006) that can be radiolabeled, imaging studies using these agents in cancer have not yet been reported.

CXCR3

CXCR3 binds CXCL9, CXCL10, and CXCL11 with high affinity, and is expressed by the Th1 T cells, cytotoxic CD8+ T cells, Kupffer cells, endothelial cells, and activated B and NK cells (Garcia-Lopez et al., 2001). CXCR3 expression directs the migration of these cells to inflamed lymph nodes (LN) and other inflamed sites (Liu et al., 2005).

Nearly one third of melanoma (Kawada et al., 2004) and colon cancers (Kawada et al., 2007) and most of all of the breast cancer specimens tested, though to a different degree, were shown to be positive for CXCR3 (Ma et al., 2009). CXCR3 expression in breast and colon cancers and melanoma has been correlated with LN metastases, and considered an independent predictor of poor prognosis (Ma et al., 2009; Kawada and Taketo, 2011). Furthermore, colon cancer patients with tumors positive for both CXCR3 and CXCR4 had a significantly poorer prognosis than those with tumors positive only for CXCR4 or the double negatives, underscoring the importance of evaluating multiple receptors simultaneously (Kawada and Taketo, 2011). In spite of high expression on tumor cells, downregulation of CXCR3 by siRNA, or inhibition by low molecular weight agents was not shown to have an effect on breast or melanoma tumor growth but rather influenced the metastatic ability of the cancer cells to the lungs and LNs (Kawada et al., 2004). Because CXCR3 shows a notable expression on T cells associated with inflammatory conditions, such as psoriasis, rheumatoid arthritis, diabetes, inflammatory bowel disease, and multiple sclerosis, several antagonists targeting this receptor have been in clinical development (Wijtmans et al., 2008). CXCR3 expression has not yet been imaged and presents an attractive target for imaging.

CXCR4

CXCR4 is one of the most studied chemokine receptors. CXCR4 is a co-receptor for HIV entry, plays a pivotal role in mediating metastasis in a variety of cancers (Tamamura et al., 2006) and in autoimmune disease. To date, CXCR4 is known to bind only one endogenous ligand, CXCL12 (Zlotnik et al., 2006). CXCL12 expression is ubiquitous and it is highly secreted by stromal cells in lungs, liver, brain, bone marrow, and LNs. CXCR4 is expressed in several tissues (Gupta and Pillarisetti, 1999). The CXCR4–CXCL12 axis is also distinct from many other chemokine networks due to its role in hematopoiesis, organogenesis, and vascularization. CXCR4 or CXCL12 knock-out mice have defects in B-cell lymphopoiesis, bone marrow colonization, and cardiac septum formation resulting in late gestational lethality (Nagasawa et al., 1996; Tachibana et al., 1998).

CXCR4 is over-expressed in nearly 20 types of cancer including breast, lung, ovarian, colon, prostate, and melanoma (Balkwill, 2004). CXCR4 expression in tumor cells is markedly higher compared to many normal tissues (Cabioglu et al., 2009; Duda et al., 2011) and CXCR4 expression is regulated by many tumor-associated factors: at the transcriptional level by hypoxia, NFκB, and Yin Yang 1; at the translational level by HER-2; and at the post-translational level by E3 ubiquitin ligase and HER-2 (Luker and Luker, 2006). Elevated CXCR4 expression in tumors has been associated with an aggressive phenotype (Cabioglu et al., 2005; Kang et al., 2005; Kim et al., 2005). Overexpression of CXCR4 in primary tumors is directly correlated to increased risk for local recurrence, distant metastasis, and poor survival rates in breast, colon, and several other cancers (Cabioglu et al., 2005; Kim et al., 2005; Scala et al., 2005; Luker and Luker, 2006; Salvucci et al., 2006). In addition to primary tumors, metastases frequently exhibit increased CXCR4 expression, which may offer a new strategy for their early detection (Sun et al., 2003; Salvucci et al., 2006). The hypothesis is that CXCR4 expression enables tumor cells to home to organs expressing abundant levels of CXCL12 such as lungs, liver, brain, and bone marrow leading to establishment of metastases. Neutralizing CXCR4 chemotaxis using low molecular weight agents, peptides, antibodies, or biological agents such as siRNA, reduces the migratory capacity of cancer cells in vitro and metastatic burden in vivo in preclinical models (Li et al., 2004; Smith et al., 2004; Song and Korz, 2008).

In addition to the regular GPCR signaling-based activation of multiple downstream targets, the CXCR4–CXCL12 axis is also known to be involved in several other pathways. It can transactivate HER-2 receptor (Li et al., 2004; Luker and Luker, 2006) and mediate estrogen-independent tumorigenesis, metastasis, and resistance to endocrine therapy (Rhodes et al., 2011). Similarly, migratory effects induced by epidermal growth factor receptor and insulin-like growth factor signaling cascades in cancer cells requires CXCR4 activation (Akekawatchai et al., 2005; Phillips et al., 2005). Recent studies have also identified increased expression of CXCR4 and CXCL12 in cancer-associated fibroblasts (CAFs). CAFs play an important role in tumorogenesis and are implicated in neoplastic progression, tumor growth, angiogenesis,
and metastasis (Orimo and Weinberg, 2006). CXCL12 secreted by CAFs not only stimulates carcinoma cell growth directly through the CXCR4 receptor displayed on tumor cells but also recruits endothelial progenitor cells (EPCs) into tumors, thereby furthering angiogenesis (Kojima et al., 2010). Overall, the CXCR4–CXCL12 axis plays an active role in tumor resistance to conventional as well as targeted therapies by directly promoting cancer cell survival, invasion, and cancer stem and/or tumor-initiating cell phenotype; by recruiting myeloid bone marrow-derived cells to facilitate tumor recurrence and metastasis indirectly; by promoting angiogenesis directly or in a paracrine manner; and by providing a metastatic niche for cancer cells in the bone marrow (Duda et al., 2011).

The CXCR4–CXCL12 axis is considered a therapeutic target for cancer and several CXCR4 inhibitors are in Phase-I trials (Wong and Korz, 2008; Duda et al., 2011). In addition to reduced metastatic burden, CXCR4 inhibition has also been shown to synergize chemotherapies in various tumor models (Redjal et al., 2006; Azab et al., 2009). As blocking the CXCR4–CXCL12 pathway becomes a viable strategy to target various solid tumors, considering the large number of normal functions that are affected by the CXCR4–CXCL12 axis, development, and evaluation of imaging agents for tracking this pathway in vivo is critical. CXCR4-based imaging agents would be beneficial to: (i) evaluate primary tumors for elevated CXCR4 expression and therapeutic intervention; (ii) screen for secondary metastatic spread to both local and distant sites; and (iii) for therapeutic monitoring.

CXCR4-based imaging agents. Antibodies, peptides, and low molecular weight agents have been used for molecular imaging of CXCR4 expression in tumors.

Monoclonal antibodies are re-gaining attention as radiopharmaceutical imaging agents. To investigate the feasibility of CXCR4-based imaging, our group radiolabeled a well-characterized monoclonal mouse anti-human CXCR4 antibody, 12G5, with $^{125}$I. 12G5 recognizes a determinant in the first and second extracellular loops of CXCR4 and its specificity to CXCR4 is well established (Baribaud et al., 2001). Single Photon Emission Computed Tomography (SPECT) imaging and biodistribution data showed clear accumulation of $[^{125}$I]12G5 in the tumors compared to isotype matched $[^{125}$I]IgG2A control antibody. Even though the highest accumulation of radioactivity was seen in the spleen and high non-specific uptake was observed due to the murine antibody background, these results establish the feasibility of using radiolabeled mAbs for imaging CXCR4 expression in tumors (Nimmagadda et al., 2009).

CXCR4 is characterized by a strong negatively charged extra-cellular surface, therefore most of the CXCR4 binding agents are highly basic and positively charged. A detailed overview of the available CXCR4 binding agents and CXCR4-based imaging agents can be found elsewhere in the literature (Mosley et al., 2009; Woodard and Nimmagadda, 2011). The majority of the CXCR4 targeted imaging agents to date have originated from the polypehemin-based peptides and cyclam-based low molecular weight agents.

The polypehemin-based peptide T140 provides the foundation for most of the peptide-based CXCR4 imaging agents. T140 is a 14-residue peptide with a disulfide bridge (T140) and a potent CXCR4 antagonist (Tamura et al., 1998). Studies have shown that four aminoacid residues, Arg2, l-3-(2-naphthyl)alanine (Nal)3, Tyr5, and Arg14, in T140 are critical for CXCR4 binding (Tamura et al., 2000). Like many unprotected peptides, T140 was found to be unstable in serum. To improve the stability, many CXCR4 selective analogs, including those with modifications at each terminus, were synthesized (Tamura et al., 2006) and labeled with various radionuclides. First within this category of peptides is Ac-TZ14011 with the carboxyl group protected via amidation for stability in vivo and a single amino group ($\theta$-Lys$^\beta$) distant from the pharmacophore allowing for conjugation of chelates. Generally, chelation of peptides reduces the affinity of the peptide for its target. $^{111}$In-DTPA conjugation to Ac-TZ14011 resulted in nearly sixfold decrease in affinity to CXCR4. Also, a 15- to 200-fold increase in uptake was observed in the liver, kidneys, and spleen (Hanaoka et al., 2006). However, reasonable accumulation observed within the tumors and radioactivity uptake values higher than the muscle or blood led to further development of these peptides as dual modality imaging agents (Kuil et al., 2011). Another amidated analog of T140, the N-terminal 4-fluorobenzoyl protected TN14003, was labeled with $^{68}$Ga using N-succinimidyl 4-($^{18}$F)fluorobenzoate or with $^{64}$Cu through conjugation with DOTA on lysine. Studies in mice harboring Chinese hamster ovarian (CHO) tumor stably expressing CXCR4 showed that CXCR4-positive tumors were distinguishable from control tumors, however, co-injection of unlabeled 4-F-TN14003 was necessary to see increased radioactivity in the CXCR4-positive tumors (Jacobson et al., 2010, 2011). Similarly, CXCL12 radiolabeled with $^{99m}$Tc or with near-infrared fluorophores demonstrate poor imaging characteristics in vivo, limiting routine use (Misra et al., 2008; Meincke et al., 2011). Demmer and colleagues, using a highly specific cyclic pentapeptide, recently reported interesting data on a peptide-based imaging agent. The $^{68}$Ga-DOTA conjugated peptide showed optimal pharmacokinetics for imaging with $^{68}$Ga, i.e., low liver uptake and faster clearance from the kidneys indicating its potential for clinical translation (Demmer et al., 2011).

Among agents of low molecular weight, the bicyclam AMD3100 was the first non-peptide CXCR4 inhibitor to enter clinical trials and is now used for stem cell mobilization (De Clercq, 2010). Cyclams have the ability to form strong complexes with transition metals such as copper and zinc, enabling development of a radiolabeled analog of AMD3100 and imaging of CXCR4 expression in vivo. Fortuitously, the affinity of AMD3100 increases by sevenfold when chelated to copper. Jacobson et al. and our group have investigated copper-64 radiolabeled AMD3100 (Jacobson et al., 2009; Nimmagadda et al., 2010; Weiss et al., 2012). Using subcutaneous U87 brain tumors (~20%, CXCR4+), U87 tumors stably expressing CXCR4 (~95%) (U87-stb-CXCR4) and orthotopic MDA-MB-231 (~10%) and DU4475 (~90%) breast cancer xenografts, we have demonstrated the feasibility of imaging graded levels of tumor CXCR4 expression. In these studies $^{64}$CuAMD3100-Positron Emission Tomography (PET) displayed distinct accumulation of radioactivity in the U87-stb-CXCR4 and DU4475 tumors at 90 min post-injection of the radiotracer (Nimmagadda et al., 2010). Considerable uptake was observed in the liver and lymphoid organs. Given that CXCR4 is expressed on leukocytes, monocytes and in the liver, accumulation
of radioactivity in these organs, except for the majority of the uptake in the liver, is due to CXCR4-specific binding as confirmed by blocking studies (Nimmagadda et al., 2010). Because metastases often have elevated levels of CXCR4 expression, using an experimental model of lung metastasis derived from breast cancer cells, we have also demonstrated that [64Cu]AMD3100-PET enables non-invasive in vivo visualization of metastases (Nimmagadda et al., 2010).

While [64Cu]AMD3100 shows promise as a PET imaging agent, low affinity for CXCR4 and a scaffold not flexible for the development of 18F-labeled analogs may limit clinical use. A second-generation monocyclam-based CXCR4 inhibitor, AMD3465 (Figure 1), has high affinity (41.7 ± 1.2 nM), reduced charge and is smaller in size compared to AMD3100 (Bodart et al., 2009; De Silva et al., 2011). Utilizing the aforementioned U87 and U87-stb-CXCR4 glioblastoma model, De Silva and colleagues showed that [64Cu]AMD3465-PET has the highest target selectivity reported for this class of agents (Figure 1). These results were further validated in a colon tumor model (De Silva et al., 2011). More importantly, the pyridine moiety of AMD3465 may allow structural modification for the synthesis of clinically translatable agents.

**CXCR7**

Although initially cloned as orphan receptor Receptor Dog cDNA 1 (RDC1) in 1990 (Libert et al., 1990), RDC1 was renamed CXCR7 once the binding of chemokine ligands CXCL11 and CXCL12 was characterized (Balabanian et al., 2005; Burns et al., 2006). CXCR7 binds to CXCL12 and CXCL11 with high and low affinities, respectively and plays a role in scavenging or sequestering CXCL12α (Thelen and Thelen, 2008). CXCR7 differs from other chemokine receptors in several ways. The Asp-Arg-Tyr-Leu-Ala-Ile-Val (DRY-LAIV) motif at the second intracellular loop of chemokine receptors, required for coupling a chemokine receptor to Gαi-signaling proteins, is altered in CXCR7 and its sensitivity to pertussis toxin has not been completely characterized (Thelen and Thelen, 2008). However, similar to other chemokine receptor signaling, CXCR7 stimulation by CXCL12 has been shown to induce the phosphorylation of both MAPK and Akt (Miao et al., 2007; Hartmann et al., 2008). In the hematopoietic system, CXCR7 is expressed by the neutrophils, monocytes, and B-cells. CXCR7 is required for the development of the heart, particularly cardiac valves (Sierro et al., 2007). Even though CXCR7 is poorly expressed in non-transformed tissues, increased CXCR7 expression was observed in transformed cells (Burns et al., 2006).

CXCR7 expression on breast, lung, and prostate cancer cells positively correlates with their proliferation, vascularization, and metastatic potential (Miao et al., 2007). CXCR7 is highly expressed on tumor-associated vasculature and not on normal endothelium suggesting a role in tumor angiogenesis (Miao et al., 2007; Mazzinghi et al., 2008). Blockade of CXCR7 signaling using low molecular weight agents, antibodies or siRNA results in smaller tumors and reduced metastatic dissemination in preclinical models (Miao et al., 2007). CXCR7 expression is also regulated by CXCR4 suggesting that combined blockade of CXCR4 and CXCR7 may have synergistic therapeutic effects. Imaging agents specific for CXCR7 have not been reported even though CXCL12 labeled with a near-infrared fluorophore has been used recently for in vivo imaging (Meincke et al., 2011). The availability of mAbs and low molecular weight agents present an opportunity for imaging this important target.

**CCR7**

Of the CC family receptors only CCR7, due to its pivotal role in directing LN metastasis, will be discussed in this review. CCR7 binds two ligands, CCL21 and CCL19, which are secreted in LNs. CCR7 is highly expressed by naïve T cells and dendritic cells and is required for homing these cells to the LNs for initiating an adaptive immune response (Forster et al., 2008). CCR7 is also one of the well-characterized receptors with respect to its role in the formation of secondary lymphoid structures (Muller et al., 2003).

CCR7 has been shown to be over-expressed in several cancers including breast, non-small cell lung cancer, esophageal, gastric, and chronic lymphocytic leukemia (Holmes et al., 1991; Muller et al., 2001; Mashino et al., 2002; Ding et al., 2003; Takanami, 2003; Zlotnik, 2006). CCR7 expression correlates with decreased survival of patients with colorectal cancer (Gunter et al., 2005). Unlike CXCR4, CCR7 expression on tumor cells mostly correlates with LN metastasis. Given the role of CCR7 in directing the lymphocytes to the LNs, this observation suggests the possible

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**FIGURE 1** (A) Structure of [64Cu]AMD3465; (B) Surface CXCR4 expression in U87 and U87-stb-CXCR4 cells by flow cytometry; (C) PET/CT imaging of CXCR4 expression in subcutaneous brain tumor xenografts with [64Cu]AMD3465 (De Silva et al., 2011); (D) Tumor-to-muscle, tumor-to-blood, and tumor-to-tumor ratios from biodistribution studies of [64Cu]AMD3465 in subcutaneous brain tumor xenografts.
Clinical implications and future challenges

Since the implication of CXCR4 in the metastatic cascade, considerable progress has been made in establishing the role of various chemokine receptors in tumor biology. The direct involvement of chemokine receptor/ligand networks in tumor development, progression, and immune evasion suggests a potential role for chemokine network based therapeutic agents as adjuvants to existing therapies. Even though several chemokine targeted agents are in use, redundancy in chemokine signaling suggests that receptor-targeted strategies that eliminate redundant functions of chemokine signaling may have a greater effect than agents that solely target the effects of chemokines. Conveniently, many inhibitors of chemokine receptors are also in development for other diseases, such as multiple sclerosis or rheumatoid arthritis, which could be translated to oncology. Because chemokine receptors/ligands are expressed on multiple cancer cell types, effects of the inhibition of these networks should have broad therapeutic application. The broader tissue expression of the receptors also calls for a continuous evaluation of receptor dynamics within the tumor microenvironment, which offers exciting opportunities as well as challenges to the imaging community. Availability of inhibitors and chemical scaffolds for almost all chemokine receptors provides a solid ground to focus on the development of suitable imaging agents. Even though receptor expression, such as those of CXCR4 and CCR7, is well characterized, there is great need to characterize expression of other chemokine receptors in tumors methodically. Another challenge in translating these imaging agents to the clinic is the possibility of low receptor density on tumor cells that may be lower than the sensitivity of detection of some of the imaging modalities. This is compounded by the fact that significantly higher expression of the target on immune cells may act as “sink” for the imaging agent. Some of these concerns could be evaluated in biologically relevant preclinical models. As chemokine receptor blocking agents move into the clinic for targeted cancer therapy, availability of respective imaging agents will not only improve accuracy and precision of the molecular characterization of cancer but also that of other diseases.

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