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CXCR4: A Virus's Best Friend?

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Abstract

Viruses are dependent on their hosts for replication and dispersal in the environment; thus, the most successful viruses are those that co-evolve with their hosts. CXCR4 is a cellular chemokine receptor that plays central roles in development, hematopoiesis, and immune surveillance through signaling induced by its ligand, CXCL12. The CXCR4-CXCL12 axis has been besieged by many pathogens that employ a range of strategies to modify or exploit CXCR4 activity. While CXCR4 was identified as a critical co-factor for entry of HIV into CD4+ T cells early on, other viruses may utilize CXCR4 to gain cell entry as well. Moreover, several viruses have been found to modulate CXCR4 expression or alter its functional activity, with direct effects on cell trafficking, immune responses, cell proliferation, and cell survival. Because CXCR4 is targeted by a diverse group of viral pathogens, modification of host CXCR4 signaling activity is emerging as a common theme in virus persistence and is likely to be important for subversion of the host immune system. This review highlights major viral pathogens that use and abuse CXCR4 and explores the possible reasons why this chemokine receptor has become “a virus's best friend”.

Keywords

Chemokine receptor; CXCR4; CXCL12; GPCR; immune modulation; pathogen; stromal derived factor; SDF; trafficking; virus-host interactions

The G protein coupled receptor (GPCR) superfamily is the one of the largest groups of cell surface receptors. GPCRs are found in all eukaryotic cells, from yeast to humans. Human GPCRs are seven transmembrane proteins sometimes known as “7TM”, “serpentine”, or “heptahelical” receptors that can receive information in the form of extracellular ligands and initiate cell signaling events that induce and coordinate a vast array of physiological functions (Katritch et al., 2012; Pierce et al., 2002). GPCRs typically transmit signals into the cell through interaction with heterotrimeric G proteins. Upon ligand engagement, conformational changes in the receptor promote the exchange of GTP for bound GDP in the associated Gα subunit (Figure 1). The GTP-Gα subunit dissociates from the receptor and the

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Gβγ dimer, and then each subunit can activate specific downstream effectors and signaling pathways. There are 20 different human Gα, 6 Gβ, and 12 Gγ genes, so a large number of heterotrimers are possible (Hermans, 2003; Khan et al., 2013) and a wide range of signaling cascades can be activated (Ahmed and Angers, 2013; Boullaran and Kehrl, 2014; Zhou and Bohn, 2014), leading to various functional outcomes such as chemotaxis, adhesion, proliferation, changes in gene expression, and the determination of cell fate (Kindt, 2007; Schappi et al., 2014).

1. The human chemokine system

One important subset of the GPCR superfamily is the chemokine receptors. Chemokine receptors play a pivotal role in the cell by receiving and reacting to chemokine signals, and genes encoding these receptors have been found not only in mammals, but also in chickens, frogs and zebrafish (DeVries et al., 2006). Chemokines, or “chemotactic cytokines”, are a crucial component of the immune system. Small, soluble proteins that promote cell migration and activation by binding to their cognate GPCRs, chemokines guide the migration of immune cells throughout the body for surveillance and homeostasis. Chemokine binding generally triggers a rapid and transient release of intracellular calcium, followed by more extensive changes including cytoskeletal rearrangement and chemotaxis, or directed cell movement along chemokine concentration gradients (Charo and Ransohoff, 2006). Chemokines can be divided into four groups (C, CC, CXC, or CX3C) based on the positioning of conserved cysteine residues that form disulfide linkages stabilizing the protein structure. With 18 different human chemokine receptors and more than 50 different chemokines (Figure 2), this system represents a critical component of the immune response by providing a highly specialized mechanism for directing particular cell types to discrete locations or sites of injury or infection. Certain chemokines can bind to many different receptors; for example, CCL5, also known as RANTES, is a ligand for CCR1, CCR3, CCR4, CCR5, and HCMV US28 (Appay and Rowland-Jones, 2001; Baltus et al., 2005; Bodaghi et al., 1998). Likewise, many receptors can bind multiple chemokine ligands, as shown in Figure 2. Zlotnik et al. proposed that these promiscuous binding events may have evolved in response to viral hijacking of the chemokine system (Zlotnik et al., 2006). This is supported by the notion that the genes for chemokines and chemokine receptors are found clustered onto a few chromosomes and may have arisen from gene duplications, as ligands encoded at the same chromosomal location tend to bind the same receptor. The evolution of these chemokine clustering events has allowed the host to have flexibility and redundancy to circumvent modification and exogenous signaling implemented by viruses.

2. The CXCR4-CXCL12 signaling axis

The exploitation by pathogens of host chemokines and chemokine receptor functions is a well-documented phenomenon (Holst and Rosenkilde, 2003; Lalani and McFadden, 1999; Liston and McColl, 2003; Murphy, 2001; Sodhi et al., 2004). However, CXCR4 in particular appears to be a prime target for manipulation by a number of different viruses. The gene encoding CXCR4 is located on chromosome 2, and the gene product is a 352-amino acid protein that is expressed on a wide range of cell types, including T and B lymphocytes (Bleul et al., 1998; Bleul et al., 1997), monocytes, macrophages (Gupta et al., 1999),

dendritic cells (Sozzani et al., 1997), and endothelial cells (Gupta et al., 1998). The sole chemokine ligand for CXCR4 is CXCL12, which is also known as stromal cell-derived factor 1, or SDF-1 (Murdoch, 2000). CXCL12 is highly expressed by stromal cells and signaling induced through CXCR4 binding regulates cell adhesion and survival, promoting retention of hematopoietic stem cell precursors in the bone marrow. The gene encoding human CXCL12 is located on chromosome 10, which is noteworthy because the genes for all other CXC chemokines are located on chromosome 4, underscoring the unique and essential role of this ligand-receptor pair. Binding of CXCL12 to CXCR4 can activate a variety of signaling pathways that result in downstream responses such as intracellular calcium mobilization, chemotaxis, cell survival and proliferation, and changes in gene transcription, as shown in Figure 1. The specific signaling events are tissue-dependent and may differ among cell types. The CXCR4-CXCL12 axis mediates not only hematopoiesis but many other essential physiological processes, including brain development, embryogenesis, vascularization, wound healing, T-cell activation, and recruitment of memory B cells to germinal centers in secondary lymphoid organs (Bleul et al., 1998; Cronin et al., 2010; Murdoch, 2000; Zhao et al., 2010).

While it is not clear why CXCR4 is repeatedly targeted by different viruses, there are a number of intriguing possibilities. Perhaps the widespread distribution of the receptor, combined with its constitutive recycling between the cell surface and interior (Drake et al., 2006; Marchese, 2014; Zhang et al., 2004), make CXCR4 an easy access point for virus entry (see Figure 1). Indeed, CXCR4 was initially dubbed “fusin” because expression of the receptor in CD4⁺ T cells enabled T-tropic HIV-1 Env-mediated cell fusion and HIV-1 infection (Feng et al., 1996). Evolutionarily, the CXCR4-CXCL12 axis is ancient and crucial to the survival of the organism (Bleul et al., 1996; DeVries et al., 2006; Zlotnik et al., 2006). Both CXCR4 and CXCL12 are highly conserved across species, indicating that this axis may have been one of the first branches off of a primordial chemokine-receptor system, likely due to the crucial roles of this pathway in development and cell trafficking. If the evolutionary pressures implicated by the critical development roles of CXCR4-CXCL12 prevent this axis from undergoing adaptations to defend against viral exploitation, this might make CXCR4-CXCL12 a particularly attractive and sustainable target for manipulation by viruses.

The importance of controlling CXCR4 activity is underscored by the dire consequences of CXCR4 dysregulation. Interactions between CXCR4 and CXCL12 are dynamic and complex during all physiological processes, but particularly during embryogenesis, where disruption of this signaling cascade can have profoundly detrimental effects on fetal development (Busillo and Benovic, 2007; McGrath et al., 1999; Murdoch, 2000). In mice, heterozygous mutations in either the CXCR4 or CXCL12 genes can lead to severe cardiac and hematopoietic defects, while homozygous mutations are lethal (Nagasawa et al., 1996; Zou et al., 1998). Deficiencies in expression of some chemokine receptors (e.g. CCR5, discussed in section 4.1) are found in the human population with little apparent impact on human health; however, there are no documented cases of CXCR4-negative individuals. Conversely, a heterozygous genetic mutation resulting in increased CXCR4 signaling activity causes the congenital combined immunodeficiency syndrome WHIM. The mutation results in a truncation of the C-terminal intracellular domain of CXCR4 that prevents the

receptor from being internalized, consequently preventing down-regulation following stimulation with ligand (Hernandez et al., 2003). WHIM stands for Warts, Hypogammaglobulinemia (immunoglobulin deficiency), Infections, and Myelokathexis (retention of neutrophils in the bone marrow). Increased CXCR4 signaling activity in WHIM is responsible for a chronic reduction of circulating white blood cells and decreased numbers of neutrophils (neutropenia), thus limiting immune surveillance and making the individual highly susceptible to bacterial and viral infections, especially strains of human papillomavirus that cause warts on the hands and feet (Busillo and Benovic, 2007; Hernandez et al., 2003; Rajagopal et al., 2010). It remains to be seen whether the chronic up-regulation of CXCR4 in WHIM patients provides other advantages to infectious agents, such as enhanced virus entry or activation of beneficial cell signaling pathways.

Increased CXCR4 expression is also associated with metastasis of cancer cells. CXCR4 is the most common chemokine receptor found on cancer cells, reported in twenty-three different types of cancers (Hiller et al., 2011; Ok S, 2012). High CXCR4 levels in breast, prostate, and gastric cancers have been found to promote invasion and correlate with increased metastasis and poorer clinical outcomes (Ben-Baruch, 2009; Cronin et al., 2010; Hiller et al., 2011; Ok S, 2012; Popple et al., 2012; Zhao et al., 2010). CXCR4 inhibitors, initially developed for the treatment of HIV/AIDS, are now being investigated as anti-cancer therapeutics (Weitzenfeld and Ben-Baruch, 2013).

3. Exploitation by diverse pathogens

The CXCR4-CXCL12 axis has been the target of a wide range of pathogens, including RNA and DNA viruses, as well as bacteria. The CXCR4-CXCL12 axis is a target for newly emerging diseases, as well as for ancient diseases that have coevolved for millennia with the human immune system. The CXCR4-CXCL12 axis is exploited by infectious agents in several ways, as depicted in Figure 3. These include utilization of CXCR4 to gain entry into the host cell, as in the well-known example of HIV, as well as alteration of the expression or activity levels of the CXCR4-CXCL12 axis, allowing for manipulation of cell trafficking, either to promote virus dissemination or to alter immune responses. In addition, modulation of CXCR4-CXCL12 signaling can promote cell survival and proliferation, circumventing apoptosis pathways and allowing more time for production of progeny virions. Alternatively, inhibition of CXCR4 activity (or decreased expression) can reduce trafficking toward CXCL12, diminishing homing to lymphoid organs, and thus, impairing antigen presentation. Finally, some bacteria have been found to initiate CXCR4 receptor crosstalk that reduces inflammatory signaling activity of other host cell surface receptors like TLR2 (Hajishengallis et al., 2008), a strategy that has yet to be documented for viral pathogens.

4. Retroviruses

4.1 Human Immunodeficiency Virus (HIV)

Perhaps the best characterized example of exploitation of the CXCR4-CXCL12 axis is the use of CXCR4 as one of two obligate co-receptors for HIV entry into host cells (Berson et al., 1996; Feng et al., 1996; Horuk, 1999; Moore et al., 1997). HIV is a retrovirus and a member of the lentivirus family. HIV infection ultimately causes severe disruption of

immune responses and develops into Acquired Immune Deficiency Syndrome (AIDS), which is characterized by increased susceptibility to opportunistic infections due to loss of CD4⁺ T cell function (Cloyd and Moore, 1990; Levy, 1993). HIV enters the host cell by forming a complex between the viral envelope protein gp120 and host CD4 with either CCR5 or CXCR4; this binding initiates the activity of viral protein gp41 leading to fusion with the lipid membrane and facilitating viral entry. Once in the cell, reverse transcription occurs, generating a DNA provirus that is integrated into the host genome (Doms and Trono, 2000). While CCR5 and CXCR4 are the two most common and physiologically relevant co-receptors for HIV entry (Bleul et al., 1997; Greene and Peterlin, 2002; Moore et al., 1997), other receptors, including viral GPCR US28 from human cytomegalovirus (HCMV), can also facilitate HIV entry (Pleskoff et al., 1997). It is interesting to note that a mutation in CCR5, known as $\Delta 32$, and found in about 10% of people of European descent, conveys resistance to HIV infection (Samson et al., 1996). No such mutation has been found in CXCR4 in the population, likely due to the essential role of this receptor in development.

M-tropic variants of HIV utilize CCR5 as a co-receptor with CD4, and this co-receptor usage is characteristic of early viral isolates that infect both macrophages and T cells. CXCR4 is the co-receptor with CD4 for T-tropic strains of HIV, which infects primary T lymphocytes as well as T cell lines. The T-tropic isolates tend to be more common later in HIV infection, and dominance of these strains often coincides with immune deficiency (Bleul et al., 1997; Greene and Peterlin, 2002; Moore et al., 1997; Vicenzi et al., 2013). While the CXCR4 specific antagonist, AMD3100 (Brand name: Mozobil, generic name: plerixafor), initially showed promise as an inhibitor to T-tropic HIV infection, clinical trials showed two unexpected results (Blanco et al., 2000; De Clercq, 2009). The first was the observation of cardiac toxicity, which led to delays for the practical application of plerixafor for HIV treatment. The other observation was that treatment with plerixafor resulted in an increase in circulating white blood cells, which led to prominent use of the drug as a stem cell mobilizer in bone marrow transplants (De Clercq, 2009; Hendrix et al., 2000). Therapeutic agents that target CXCR4 may still hold promise for HIV treatment, particularly when combined with inhibitors that block CD4⁺ and/or CCR5 binding. The central role of CXCR4 in multiple disease states makes modulators of this receptor as attractive a target to the pharmaceutical industry as it has been to pathogens.

4.2 Human T-Cell Leukemia Virus Type 1 (HTLV-1)

Two rare, but serious diseases are attributed to HTLV-1 infection: Adult T cell Leukemia/Lymphoma (ATL), and HTLV-1-associated Myelopathy (HAM), or Tropical Spastic Paraparesis (TSP), a neurodegenerative disorder (Hollberg and Hafler, 1993). HTLV-1 encodes an oncoprotein, Tax1, which impacts host transcription factors, post-transcriptional regulators, signaling proteins, cell cycle associated proteins, and secretory proteins (Boxus et al., 2008). Several reports have shown that Tax1 enhances CXCR4-CXCL12 signaling, although the specific effects as well as the proposed mechanisms responsible for this potentiation have varied. One group reported that HTLV-1-infected T cells preferentially expressed CXCL12 (Arai et al., 1998). This outcome was mediated at least in part by Tax1, because expression of Tax1 in Jurkat-derived JPX-9 cells also resulted in increased CXCL12 expression. Up-regulation of CXCL12 may attract CXCR4-expressing lymphoid

cells into tissues harboring HTLV-1 infected cells, facilitating the subsequent progression of HTLV-1 associated diseases (Arai et al., 1998). There has been no recent work investigating Tax1-induced CXCL12 expression, although this seems to be an area that is ripe for future exploration.

Interestingly, Tax1 has also been shown to activate the CXCR4 promoter by forming a complex with the cellular transcription factor nuclear respiratory factor 1 (NRF1), leading to increased cell surface CXCR4 expression (Moriuchi et al., 1999). HTLV-1 infected T cell lines were also noted to exhibit an increase in CXCR4 levels (Arai et al., 1998). Moriuchi et al. suggested that the Tax1:NRF1 interaction enhanced NRF1 binding to the CXCR4 promoter, increasing receptor expression and rendering cells more likely to become infected with HIV, which might explain the accelerated progression of HIV disease observed in HTLV-1 positive HIV patients (Moriuchi et al., 1999). Another group reported that cells expressing Tax1 had increased CXCR4-mediated intracellular signaling, including increased calcium flux and augmented migration, which was attributed not to an increase in CXCR4 receptor expression, but rather to increased binding affinity between CXCL12 and CXCR4 (Twizere et al., 2007). The potentiation of CXCR4-CXCL12 by Tax1 plays such a potentially pivotal role in the pathogenesis of HTLV-1 that blocking the action of this axis with the CXCR4 antagonist plerixafor has been investigated to prevent the dissemination and ingress of leukemic cells in patients battling HTLV-1 associated ATL (Kawaguchi et al., 2009). Enhanced CXCR4-directed migration could have implications for the metastasis of not only HTLV-1 associated cancers, but any cancer in an HTLV-1 positive patient.

5. DNA Viruses

Exploitation of CXCR4 is not limited to retroviruses and has also been observed for a number of different DNA viruses. These include members of the herpesvirus, poxvirus, and papillomavirus families, which use a variety of methods for manipulation of the CXCR4-CXCL12 axis.

5.1 Herpesviruses

Members of the herpesvirus family have a large, double-stranded linear DNA genome housed in an icosahedral capsid that is surrounded by a dense protein tegument layer and a membrane envelope. In addition to a common structure, herpesviruses are characterized by the ability to establish lifelong latency in the host. The herpesviruses are descended from a common ancestor, but each virus has undergone unique co-evolution events with its host and acquired methods for manipulation of the host environment that help reduce immune clearance and favor long term virus persistence.

5.1.1 Herpes simplex virus type 1 (HSV-1)—HSV-1 is a member of the α -herpesvirus subfamily that is widespread in the population. In most people infection is asymptomatic or only mild symptoms occur, such as cold sores on the mouth or face, although these may recur with stress, sunburn, poor nutrition, or immune suppression. Investigation of the immune evasion strategies of HSV-1 that enable lifelong latency in neurons revealed that the virus can also infect dendritic cells (DC), and one consequence of that infection is down-regulation of CXCR4. Mature DC were found to have a dramatic decrease in CXCR4

expression within 8 hours post-infection, and that decrease continued for 24 hours post-infection, as determined by both Affymetrix gene chip analysis and RT-PCR (Prechtel et al., 2005). Flow cytometry revealed decreased protein levels of cell surface CXCR4 that also translated to reduced chemotaxis toward CXCL12. In contrast, recent work has shown that HSV-1 infection of epithelial tissue can induce expression of LL-37, a DC chemoattractant and activator (Ogawa et al., 2013). Although the mechanism for the down-regulation of CXCR4 during HSV-1 infection remains unknown, these findings suggest that infected DCs are less likely to migrate toward secondary lymphoid organs, at least in a CXCR4-dependent manner, to present antigen and stimulate T cell activation.

5.1.2 Epstein Barr Virus (EBV)—EBV is a γ -herpesvirus and the causative agent of infectious mononucleosis and several malignancies. EBV has also been found promote a decrease in CXCR4 upon infection, although the picture here is not entirely clear because there are conflicting reports and several studies examined the impact of individual viral proteins only, rather than virus infection, on CXCR4 expression or activity. Ehlin-Henriksson et al. found that infected B lymphocytes exhibited a decrease in surface CXCR4 at 43 and 67 hours post-infection, and this correlated with decreased migration toward CXCL12 (Ehlin-Henriksson et al., 2006). These results were in agreement with a previous study that also found decreased CXCR4 expression on EBV-transformed B cells (Nakayama et al., 2002). Virus infection was not required for this effect, as transformation with either LMP1 or EBNA2 also resulted in down-regulation of CXCR4. However, EBV-transformed B cells that gave rise to lymphomas in SCID/hu mice were actually found to have a moderate increase in CXCR4 expression (Piovan et al., 2005). CXCR4 levels were higher on the CD23⁻ subset of lymphoma cells, while the CD23⁺ subset produced high levels of CXCL12. Blocking CXCL12 with a neutralizing antibody or treatment with a CXCR4 antagonist decreased lymphoma growth in the SCID/hu mice, suggesting a role for the CXCR4-CXCL12 axis in EBV-mediated oncogenesis (Piovan et al., 2005). A recent report found that EBV LMP1 induced tyrosine sulfation of CXCR4, which correlated with increased migration toward CXCL12 and enhanced invasion of nasopharyngeal cells in a Matrigel assay (Xu et al., 2013). Notably, tyrosine sulfation is also an important post-translational modification to many chemokine receptors that enables their usage by HIV for cell entry (Farzan et al., 1999).

In addition to LMP1, EBV encodes another protein that has been documented to impact CXCR4 activity. BILF1 is a seven transmembrane receptor with homology to cellular chemokine receptors (Beisser et al., 2005; Paulsen et al., 2005), and when transfected into cells, BILF1 was found to form heterodimers with CXCR4 (Nijmeijer et al., 2010). Interaction of the viral receptor with CXCR4 impaired binding of CXCL12, resulting in reduced G protein and CREB activation (Nijmeijer et al., 2010). Formation of heteromeric complexes appears to be a widespread mechanism for regulation of CXCR4, which has been shown to form homodimers both in the absence of ligand (Babcock et al., 2003) and upon CXCL12 binding (Vila-Coro et al., 1999). CXCR4 is known to form heteromeric complexes with other cellular chemokine receptors, including CCR2 (See et al., 2011; Sohy et al., 2007) and CXCR7 (Levoye et al., 2009). Like BILF1, CXCR7 interferes with the ability of

CXCR4 to activate G proteins and trigger calcium flux in response to CXCL12 (Levoye et al., 2009; Nijmeijer et al., 2010).

5.1.3 Human Cytomegalovirus (HCMV)—HCMV is a β -herpesvirus and the leading infectious cause of congenital defects, affecting 1 in 150 children born in the United States each year (Manicklal et al., 2013). While EBV encodes one GPCR that interacts with CXCR4, HCMV encodes four GPCRs. The US27, US28, UL33 and UL78 gene products all exhibit similarity to human chemokine receptors, although only US28 has been found to signal in response to human chemokines (Billstrom et al., 1998; Slinger et al., 2010; Vomaske et al., 2009). The other three receptors, however, have all been reported to modify CXCR4 signaling activity. Tadagaki et al. used bioluminescence resonance energy transfer (BRET) to show direct interaction of UL33 and UL78 with CXCR4 and CCR5 in transfected 293T cells (Tadagaki et al., 2012). The heteromers appeared to form during biosynthesis and could be detected in the ER and Golgi. Further investigation of the impact of transfected UL33 and UL78 on endogenous CXCR4 in THP-1 cells indicated that both viral receptors decreased overall surface levels of CXCR4 by 20%, by modulating the cellular distribution and retaining the receptor in intracellular compartments. Although no change in CXCL12 binding affinity for CXCR4 was observed in the presence of UL33 or UL78, there was a marked decrease in ligand-induced intracellular inositol phosphate production, as well as intracellular calcium mobilization, when the viral receptors were present. This inhibitory effect appeared to be selective for specific signaling pathways because no change in CXCL12-induced ERK1/2 or Akt phosphorylation was noted when CXCR4 heteromerized with either UL33 or UL78. However, heteromerization with the viral receptors did block HIV infection, suggesting that CXCR4 was unable to mediate HIV entry while complexed with either UL33 or UL78 (Tadagaki et al., 2012).

In contrast to the predominantly inhibitory effects of UL33 and UL78 on CXCR4 function, the US27 receptor enhanced CXCL12 signaling in transfected cells (Arnolds et al., 2013). When US27, but not US28, was expressed in HEK293 cells that endogenously expressed CXCR4, there was greater calcium mobilization and more chemotaxis in response to CXCL12. CXCR4 expression was also up-regulated in cells that expressed US27, as determined by RT-PCR, western blotting, and immunofluorescence microscopy, although the specific mechanism for this increased gene expression remains to be determined (Arnolds et al., 2013). Because CXCL12 is highly expressed by osteoblasts in the bone marrow, one intriguing possibility is that HCMV-infected cells could be directed to travel from sites of productive infection in body tissues into the bone marrow. There, they could release virus particles that infect myeloid progenitor cells, increasing the pool of latently infected cells in the bone marrow. Conversely, when UL33 and UL78 interact with CXCR4, this would inhibit CXCR4 signaling, preventing cell movement and retaining infected cells in the body tissues, which might result in amplified local virus production. US28 has been shown to form complexes with each of the other viral receptors (Tschische et al., 2011) and could function as the switch to regulate which receptor pairings occur. When US28 interacts with UL33 and UL78, this could allow US27 and CXCR4 to form a heteromer that promotes cell movement. When US28 pairs with US27, UL33 and UL78 would be free to interact with CXCR4 and block cell movement, keeping cells at the site of infection. Tschische et al.

noted that US28:UL33 and US28:UL78 heteromers down-regulated the activation of NF- κ B compared to either US28 alone or US28:US27 heteromers (Tschische et al., 2011). The selective modulation of cell signaling pathways, along with the manipulation of cell migration patterns, could enable HCMV to create a favorable microenvironment for replication and long term persistence in the host.

To date, the effects of HCMV chemokine receptors on CXCR4 signaling were examined in transfected cells overexpressing each receptor (Arnolds et al., 2013; Tadagaki et al., 2012), as is the vast majority of work documenting GPCR heteromerization (Salanga et al., 2009; Szidonya et al., 2008). Therefore, the overall impact of virus infection on CXCR4 activity, with all four HCMV GPCRs present, remains unknown. Interestingly, there are conflicting reports describing the effect of HCMV infection on CXCR4 expression and activity. Frascaroli et al. reported that monocyte-derived macrophages (MDMs) were non-motile following infection and unable to migrate toward inflammatory chemokines (Frascaroli et al., 2009). However, CXCL12 was not among the chemokines tested, and although cell surface CXCR4 was examined, no change in the level of expression was detected. In contrast, Smith et al. found that infection of primary human monocytes promoted trans-endothelial migration and increased cell motility (Smith et al., 2004). Lecointe et al. observed that HCMV infection led to down-regulation of CXCR4 in microglial cells but not in astrocytes or MDMs, but signaling outcomes were not examined (Lecointe et al., 2002). Most recently, Warner et al. (Warner et al., 2012) reported that HCMV infection inhibited migration of cytotrophoblasts toward CXCL12. HCMV can infect a wide range of cell types, including fibroblasts, epithelial cells, endothelial cells, monocytes, and dendritic cells (Mocarski et al., 2006). A global analysis of the HCMV genome indicated that genes that are dispensable for replication in fibroblasts are actually essential for virus replication in epithelial and endothelial cells (Dunn et al., 2003). Thus, it is possible that the effects of the four HCMV GPCRs and other viral gene products on the CXCR4-CXCL12 signaling axis may differ among cell types.

5.1.4 Human Herpesvirus 6 (HHV-6)—HHV-6 is a β -herpesvirus that causes the childhood rash roseola infantum, and infection is widespread in the population with most individuals infected by age three. The predominant cell type infected by HHV-6 is CD4+ T lymphocytes, and virus reactivation is common in instances of immune suppression, particularly in patients who receive transplants and in HIV-positive individuals that progress to AIDS (Braun et al., 1997; Yamanishi, 1992). Reactivation in these immune compromised individuals leads to more serious disease, including pneumonitis, retinitis, and encephalitis. The interaction between HIV and HHV-6 has been widely studied, and CD4+ T lymphocytes can be co-infected with both viruses (Ensoli et al., 1989; Lusso et al., 1989). Although CXCR4 is one of two necessary co-factors for HIV entry in lymphocytes, Yasukawa et al. have shown that there is no such co-factor requirement for entry of either HHV-6 or the closely related HHV-7, which also infects CD4+ lymphocytes (Yasukawa et al., 1999). Treatment with anti-CXCR4 antibodies had no impact on the replication of HHV-6 or HHV-7 in culture, demonstrating that CXCR4 is not necessary for infection for these herpesviruses. However, there was a dramatic down-regulation of CXCR4, but not CCR5, surface expression following infection of CD4+ T cells with either HHV-6 or

HHV-7 (Yasukawa et al., 1999). The effect was dependent on viral gene expression, because UV-inactivated virus had no impact on CXCR4 expression. Decreased surface expression of CXCR4 was subsequently found to occur at the transcriptional level and was mediated by the activity of the repressor YY1 (Hasegawa et al., 2001). YY1 activity is regulated by binding to c-Myc, and HHV-6 infection was shown to increase the association between c-Myc and another protein partner Max. Reduced interactions between YY1 and c-Myc during infection led to increased binding of YY1 to the CXCR4 promoter resulting in a decrease in gene expression. The decrease in CXCR4 levels had functional consequences, and HHV-6 and HHV-7 infected lymphocytes exhibited reduced calcium mobilization and chemotaxis in response to CXCL12 (Hasegawa et al., 2001). Reduced surface expression of CXCR4 in HHV-6 infected cells has implications for cell trafficking and co-infection with HIV, which would be expected to be inhibited due to the limited availability of the critical entry co-factor. Indeed, replication of HIV in HHV-6 infected cells was found to be decreased compared to levels in uninfected cells (Asada et al., 1999; Carrigan et al., 1990), but the effect could not be attributed specifically to down-regulation of CXCR4. However, there are conflicting reports on the impact of HHV-6 on HIV infection, and other groups have found that CD4 is up-regulated following HHV-6 infection, increasing susceptibility to HIV, perhaps mediated through CCR5 rather than CXCR4 (Lusso et al., 1991; Lusso et al., 1995; Vignoli et al., 2000). Additional work is needed to better understand the interaction between these two pathogens and the pivotal role of CXCR4 to each virus during infection.

5.2 Poxviruses

Beyond the herpesvirus family, there are DNA viruses that utilize CXCR4 to facilitate virus entry. Myxoma virus is a member of the poxvirus family that causes disease in rabbits. While the specific cell surface receptors required for entry of poxviruses is unclear, Lalani et al found that treatment of cells with human chemokines resulted in reduced myxoma virus infection (Lalani et al., 1999). Transfection of CD4 as well as human chemokine receptors CCR1, CCR5, or CXCR4 rendered 3T3 cells permissive for myxoma virus infection, indicating that the virus could utilize diverse chemokine receptors for binding and internalization. Perhaps due to its constitutive pattern of internalization and recycling to the surface, CXCR4 may serve as a key for cellular entry of multiple different viruses.

The human poxvirus *Molluscum contagiosum* (MCV), which causes a mild skin rash, targets CXCR4 in a different way. MCV encodes two chemokine-like proteins, MC1481R1 and MC1481R2, that each interfere with chemokine signaling. While both proteins interfere with CCL3 (MIP-1 α) signaling, only MC1481R1 was found to interact directly with CXCL12 inhibiting chemokine binding to CXCR4 (Jin et al., 2011), which is intriguing because formation of oligomers is a common mechanism for regulation of chemokine activity (Proudfoot et al., 2003). The functional consequences of MC1481R1 binding to CXCL12 included reduced chemotaxis and blocking the ability of CXCL12 to inhibit Env-mediated fusion of HIV X4 strains (Jin et al., 2011). Thus, MCV-infected cells have the ability to secrete chemokine-like proteins that are likely to alter responses to CXCL12 and modulate trafficking patterns of cells expressing CXCR4.

5.3 Human Papillomaviruses (HPVs)

HPVs are a large family of small double-stranded DNA viruses which infect the dermis, genital epithelium, and the respiratory tract (Ciesielska et al., 2012; Tommasino, 2013). Over a hundred different HPV strains have been identified, and HPV is the most common sexually transmitted virus, infecting a large percentage of the human population (Houlihan et al., 2012). While many of the HPV strains are relatively benign, a number have been shown to be oncogenic and are causally associated with cervical cancers. Two of the viral strains most highly implicated in oncogenesis are HPV16 and 18 (Ciesielska et al., 2012; Howie et al., 2009; Munger and Howley, 2002).

HPV16 and 18 express the viral oncogenes E6 and E7. E6 and E7 have been found to enhance cell proliferation and migration, and this activity is mediated in part through inactivation of host tumor suppressors p53 and Rb, as well as through the activation of telomerase (Munger and Howley, 2002). In HPV16/18-infected cells, E6 and E7 enhance CXCR4 and CXCL12 expression and activity, leading to increased CXCR4-mediated migration, survival, and proliferation (Amine et al., 2009; Chow et al., 2010). Chow et al. reported an increase in CXCL12, CXCR4, and CXCR7 expression in HPV16/18-immortalized keratinocytes, as well as heightened PI3K/Akt activation induced by CXCL12 signaling through CXCR7 (Chow et al., 2010). CXCR7 has been identified as a second receptor for CXCL12, although the role of CXCR7 in CXCL12 signaling remains unclear (Balabanian et al., 2005; Burns et al., 2006). Amine et al. showed the E6 and E7 oncoproteins enhanced the signaling outcomes of the CXCR4-CXCL12 axis in HPV-positive tumor cells, increasing the metastatic potential of these cells (Amine et al., 2009). They further demonstrated that silencing of E6 or E7 via gene knock-down or with drug treatment led to reduced CXCL12-directed migration and an overall decrease in CXCR4 expression. The specific mechanism responsible for the up-regulation of CXCL12 and CXCR4 remains unclear; however, one possibility is that E6 and E7 may stabilize CXCR4 following a CXCL12-induced signaling event, thus reducing receptor degradation (Chow et al., 2010). They also detected a significant amount of CXCL12 bound to the cell surface via glycosaminoglycans, resulting in increased availability of ligand to bind the receptor and initiate a signaling cascade, versus ligand being secreted into the extracellular milieu (Chow et al., 2010).

While the mechanism driving the potentiation of the CXCR4-CXCL12 axis by HPV oncoproteins remains unclear, the benefits conferred to the virus are obvious. Enhanced signaling in infected keratinocytes could promote the proliferation and migration of nearby keratinocytes, facilitating virus entry into adjacent cells, promoting cell proliferation and viral gene expression. The enhanced metastatic activity conferred by E6 and E7 expression in HPV-positive tumor cells could aid in virus dissemination and maintenance. The implications to the host could be devastating, as increased expression and activity of the CXCR4-CXCL12 axis could promote the proliferation and survival of transformed HPV positive cells and increase the metastatic potential of HPV-positive cervical cancers. However, targeting E6 and E7 with the antiviral drug cidofovir can dampen CXCR4 expression and CXCL12-directed cell invasion (Amine et al., 2009). A greater understanding of the role of CXCR4-CXCL12 in cervical cancers could also enable the use

of plerixafor and other drugs to mitigate enhanced CXCR4 activity in these cells. In addition, HPV infection has been shown to increase the risk of HIV infection (Houlihan et al., 2012). While the mechanism responsible for increased susceptibility to HIV may be multifaceted, understanding the role of CXCR4 could promote the use of the CXCR4 antagonists in HPV/HIV-positive patients, both to mitigate HIV entry into cells, as well as dampen CXCR4-mediated metastasis of HPV transformed cells. Moreover, an increased risk of HIV infection in HPV-positive individuals could serve as an additional motivation behind efforts to broaden the use of the HPV vaccine.

6. Other Pathogens

Chikungunya virus (CHIKV) is an alphavirus in the *Togaviridae* family. CHIKV is an insect-borne virus that is transmitted to humans by several species of mosquitos including *Aedes aegypti* (Schwartz and Albert, 2010). While the molecular mechanisms underlying CHIKV pathogenesis remain elusive, it was recently reported that infection resulted in strong induction of CXCR4 (Saxena et al., 2013). Both human dermal fibroblasts and 293T cells were found to have a dramatic up-regulation of CXCR4 within 12 hours of infection and the increased levels were sustained for 24 hours post-infection. These results have led to speculation that CXCR4 may act as a receptor for virus entry; however, this has not yet been demonstrated and many viral entry receptors are down-regulated upon infection to limit superinfection by a related virus. Another possibility is that upregulation of CXCR4 by CHIKV promotes a cell trafficking pattern that is more beneficial to the virus.

Although this review has focused on manipulation of CXCR4 by viruses, it is worth noting that bacterial pathogens have also exploited this receptor as an effective way to modify the host immune environment. *Porphyromonas gingivalis* is Gram negative anaerobe associated with periodontitis (Pihlstrom et al., 2005). One critical virulence factor for *P. gingivalis* is the fimbriae that not only mediate adhesion, but also inhibit inflammatory immune responses. The fimbriae protein complex (Pg-fimbriae) was found to bind directly to CXCR4 and activate a cAMP-dependent PKA response (Hajishengallis et al., 2008). In addition, the Pg-fimbriae induced cross-talk between CXCR4 and TLR2 that suppressed TLR2-mediated NF- κ B activation, diminishing the inflammatory immune response, and promoting bacterial survival and virulence *in vivo*. Blocking CXCR4 with plerixafor treatment led to increased bacterial clearance. Thus, *P. gingivalis* has developed a novel method for impairing the innate TLR2 pathway through manipulation of CXCR4 that enables the pathogen to persist and avoid immune clearance (Hajishengallis et al., 2008).

7. Concluding Remarks

Pathogens have evolved many mechanisms for evasion and manipulation of the host immune system. This review has focused on viral modification of human chemokine receptor CXCR4 and its ligand CXCL12. CXCR4 is of great interest because of its many roles in normal human physiology, as well as the fact that it has been, and continues to be, the target of many different pathogens that exploit the signaling of this receptor in a myriad of ways. CXCR4's endogenous expression in many tissues, its roles in development and hematopoiesis, as well as its role in immune cell trafficking, make it a very attractive target

for pathogens that utilize the receptor for everything from navigating their way into the cell, to enhancing cell survival and proliferation, to choreographing the dissemination and trafficking of infected cells. While the high functionality of the CXCR4-CXCL12 axis certainly contributes to its appeal as a target for viruses, we propose that there could be another reason it has been utilized over and over again. The CXCR4-CXCL12 receptor ligand pair arose early in vertebrate evolution, and due to its crucial roles in development, has been highly conserved across species and throughout human evolution. While other chemokines and chemokine receptors have been able to evolve alternate signaling pathways to counteract or override viral hijacking, the CXCR4-CXCL12 axis has not had this flexibility. This, coupled with its many roles that can be modulated to benefit pathogens, has made it not only an attractive target, but a sustainable one.

Although CXCL12 is the only known chemokine ligand for CXCR4, recent evidence has shown that ubiquitin can also bind and signal through CXCR4 (Saini et al., 2010a; Saini et al., 2010b). Ubiquitin is one of the most highly conserved proteins in all eukaryotes, and it plays a major role in regulation of protein activity, including targeting them for proteasome degradation and also triggering immune responses to pathogens. Manipulation of the host ubiquitin system by viruses has been well-documented (Gustin et al., 2011; Viswanathan et al., 2010). It remains to be seen how viral modulation of the ubiquitin pathway might alter CXCR4 signaling and vice-versa, but it is clear that the intersection of the CXCR4 and ubiquitin pathways as major targets of exploitation by pathogens will need to be explored.

Due to its ubiquity, stability, or many important physiological functions, the CXCR4-CXCL12 axis has been targeted by numerous pathogens. For the very same reasons it invites pathogen manipulations, this axis has also become an important target for biomedical interventions. A deeper understanding of how and why CXCR4 has become “a virus’s best friend” will most certainly inform and enhance treatment and prevention strategies for a number of human diseases of global importance.

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Highlights

- The human chemokine system, its origins, and exploitation by viral pathogens are discussed.
- CXCR4 is likely a common target because it is highly conserved and critical for development.
- We discuss the implications of CXCR4 dysregulation by pathogens like HIV and herpesviruses.

Figure 1. The CXCR4-CXCL12 signaling axis

CXCL12 binds to the N-terminal domain of CXCR4 at the cell surface, triggering a conformational change that activates the associated heterotrimeric G protein. The G protein subunits dissociate into the GTP-bound G α subunit and the G $\beta\gamma$ dimer, and each subunit can activate various signaling cascades, such as mitogen activated protein kinases (MAPKs) or adenylyl cyclase, which produces the second messenger cAMP. Other signaling pathways involve activation of phospholipase C (PLC), leading to calcium mobilization (Ca²⁺) and activation of protein kinase C (PKC) or phosphoinositide 3-kinase (PI3K), leading to activation of the pro-survival effector Akt (also known as protein kinase B). The CXCR4-CXCL12 signaling cascade can take various routes, but ultimately leads to cell proliferation, migration, and/or survival. After ligand binding, the receptor is internalized (far right) in vesicles that pinch off from the plasma membrane; receptors are later recycled back to the cell surface.

Figure 2. Chemokine receptors and cognate ligands

This schematic represents human and viral chemokine receptors, with non-signaling chemokine receptors indicated with a red X. Chemokine receptors are grouped by the class of chemokine they bind and depicted as seven-transmembrane structures spanning the outer rim of the circle, as they might be shown spanning the plasma membrane of a cell. Chemokines, designated by the bubbles placed outside the large circle, are grouped based on structural differences in the cysteine residues in the N-terminus and designated with an L for ligand. There are four classes of chemokines: CCL (green), CXCL (blue), XCL (red), and CX3CL (purple). Viral chemokine receptors are labeled in red and placed in the category with human cellular ligands that they have been reported to bind. KSHV ORF74 and Herpesvirus saimiri ECRF3 both bind CXCL chemokines, while HCMV US28, HHV-6 U12, HHV-7 U12, and Equine herpesvirus E1 bind CC chemokines. HCMV US28 also binds to CX3CR1.

Figure 3. Mechanisms of viral exploitation of CXCR4

Three panels depict virus-infected cells inside an organ (white oval with red virus inside), with one larger cell showing CXCR4 signaling in detail. Arrows indicate direction of expected cell traffic relative to the cells in the central organ shown. **A.** Some viruses, like HIV, utilize CXCR4 as a receptor or co-receptor to gain entry into the cell, exploiting host machinery to express viral genes and proteins. **B.** Potentiation of CXCR4-CXCL12 signaling can have a number of outcomes, including increased cell survival, proliferation, and chemotaxis. This can result in a greater number of infected cells, dissemination of infected cells, and/or homing of cells to lymphoid organs where they may serve as a reservoir of latency. **C.** Decreased CXCR4-CXCL12 expression and signaling can allow the virus to direct cells toward other chemokine signals or prevent virus-infected cells from entering the lymphoid organs to reduce the likelihood that they present antigen and elicit an antiviral immune response.