

Review

Piracy on the molecular level: human herpesviruses manipulate cellular chemotaxis

Caleb Cornaby, Anne Tanner, Eric W. Stutz, Brian D. Poole and Bradford K. Berges

Correspondence
Bradford K. Berges
brad.berges@gmail.com

Department of Microbiology and Molecular Biology, Brigham Young University, Provo, UT 84602, USA

Cellular chemotaxis is important to tissue homeostasis and proper development. Human herpesvirus species influence cellular chemotaxis by regulating cellular chemokines and chemokine receptors. Herpesviruses also express various viral chemokines and chemokine receptors during infection. These changes to chemokine concentrations and receptor availability assist in the pathogenesis of herpesviruses and contribute to a variety of diseases and malignancies. By interfering with the positioning of host cells during herpesvirus infection, viral spread is assisted, latency can be established and the immune system is prevented from eradicating viral infection.

INTRODUCTION

Cells respond to a variety of cytokines and chemokines that allow them to migrate in different areas in the body depending on where they are needed. This process is essential for appropriate tissue maintenance, homeostasis, formation, repair and pathogen clearance (Turner *et al.*, 2014; Zhou *et al.*, 2014). Dysregulation of the delicate balance of cellular signals and/or improper positioning could impede these processes. Aside from being related to a range of diseases, viral-induced chemotaxis contributes to the epidemiology and persistence of human herpesviruses. These viruses regulate a multitude of cellular genes that direct cellular chemotaxis, thereby manipulating these genes for the benefit of the invading virus. Herpesviruses also produce various chemokines and chemokine receptors from genes in the viral genome, further affecting cellular chemotaxis. In essence, viral infection results in the piracy of cellular function as it directs cell movement in both infected and uninfected cell types.

The family *Herpesviridae* is divided into various subfamilies including *Alphaherpesvirinae*, *Betaherpesvirinae*, and *Gammapherpesvirinae* (Flint & American Society for Microbiology, 2009; Yoshida & Yamada, 2006). The nine human herpesviruses (HHVs) include herpes simplex virus type 1 (HHV-1 or HSV-1) and 2 (HHV-2 or HSV-2), varicella-zoster virus (HHV-3 or VZV), Epstein-Barr virus (HHV-4 or EBV), human cytomegalovirus (HHV-5 or hCMV), human herpesvirus 6A (HHV-6A) and 6B (HHV-6B or roseola virus), human herpesvirus 7 (HHV-7) and Kaposi's sarcoma-associated herpesvirus (HHV-8 or KSHV) (Siakallis *et al.*, 2009). All of these viral species share similar structural characteristics with a genome

composed of double-stranded DNA, an icosahedral capsid, an envelope studded with a variety of viral and host proteins, and viral tegument proteins in an amorphous layer between the capsid and envelope (Flint & American Society for Microbiology, 2009). Herpesviruses are able to remain latent in host cells for the life of the individual, during which time viral particles are undetectable but viral nucleic acids can be found, and viral gene expression is very limited. Various stimuli can cause viral reactivation, wherein viral gene expression recommences and infectious particles can be detected and shed to new hosts. Herpesviruses encode a complex assortment of proteins that manipulate cellular functions during infection in order to promote viral persistence. Human herpesviruses are an integral part of human existence, with over 90% of adults being persistently infected with one or more of these nine herpesviruses in their lifetimes. Although the incidence of serious herpesvirus-induced diseases is rare in most cases, the prevalence of infection is so high that the overall disease burden takes a toll on society.

It has been hypothesized that several herpesvirus species affect development or progression of diseases, including lymphomas, atherosclerosis, autoimmune disorders, and disruption of angiogenesis, through interference with cellular chemotaxis (Ehlin-Henriksson *et al.*, 2009; Franciotta *et al.*, 2008; Rosenkilde & Schwartz, 2004; Stern & Slobedman, 2008; Streblow *et al.*, 2001). In this review we will elaborate on the known human HHV mechanisms and pathways that influence cellular chemotaxis during viral infection. Potential benefits to herpesviruses in evolving these mechanisms will be presented as well as the resulting potential for their roles in disease development.

ALPHAHERPESVIRINAE

HSV-1, HSV-2 and VZV encompass the human pathogens of the subfamily *Alphaherpesvirinae*, typically showing lytic replication in epithelial cells and harboured as a latent infection in neuronal cells. HSV-1 is quite common in industrialized countries, with a seroprevalence of around 90% (Viejo-Borbolla *et al.*, 2012) in the adult population. Symptoms of viral infection include cold sores and redness of the skin; however, many infections are asymptomatic. HSV-1 transmittance only occurs when viral replication takes place, either during primary infection or in a reactivation event. The most common methods of transferring HSV-1 include direct skin contact and via saliva. Similar to HSV-1, HSV-2 can mask its presence from the host's immune system, demonstrating a preference to lie dormant in the sacral ganglia (HSV-1 in trigeminal ganglia) and manifest occasional lytic outbreaks, typically in the genital area. HSV-2 is one of the most common sexually transmitted diseases, with a seroprevalence of 12–20% in the USA. HSV-2 infection is of greater concern in developing countries, where seroprevalence is much higher (Weiss, 2004; Xu *et al.*, 2006). VZV primary infection results in the common childhood disease varicella (chickenpox) after which the virus establishes latency in the ganglia of a variety of neurons (Gilden *et al.*, 2014). Reactivation of the virus results in zoster (shingles) and other chronic pain diseases, which can be manifest in various places on the epithelium (Gilden *et al.*, 2014).

Until recently, not much was known about HSV and how it affects chemotaxis; however, current work has demonstrated that HSV infection has a strong influence on chemotaxis (see Table 1). Viejo-Borbolla *et al.* (2012) showed that a secreted form of viral glycoprotein G (SgG) from both HSV-1 and HSV-2 binds chemokines with high affinity. Membrane-bound glycoprotein G (gG) was shown to be necessary for chemokine-binding activity. They found that HSV SgG in both HSV-1 and HSV-2 increased chemotaxis of monocytes in infected individuals towards CXCL12 and that gG attaches to glycosaminoglycans (GAGs) at the surface of cells without negative effects on G-protein-coupled receptors (GPCRs). Another, more recent, study further investigated the mechanism by which viral SgG enhances chemotaxis. It was found that gG binds to GAGs, which induces lipid raft clustering, leading to increased CXCR4 incorporation. The conformational change causes an increase in

functional chemokine–receptor complexes at the cell surface (Martinez-Martin *et al.*, 2015). CXCL12 is the natural ligand for CXCR4 and is secreted constitutively in a variety of tissues, including the lymph nodes, bone marrow, lungs and adrenal glands (Alkhatib, 2009; Luker & Luker, 2006). It is also known that CXCR4 signalling is important in modulating the survival of neuronal cells and modulating synaptic function (Nash & Meucci, 2014). The increased functionality of CXCR4 could potentially allow infected cells to migrate to these areas *in vivo*. By migrating to areas secreting CXCL12, infected cells could come into contact with more target cells. Similar results had been observed by Bellner *et al.* (2005) when they tested the chemotactic ability of HSV-2 gG (gG-2p20). These authors found that isolated human neutrophils and monocytes followed a gradient of gG-2p20 via binding of the formyl peptide receptor (FPR) on the surface of these cells. While the chemoattractant properties have never been displayed using the full-length gG2 protein, several speculations can be made based on the findings that suggest that neutrophils and monocytes could be attracted to areas with infected cells expressing gG-2p20. This could possibly be beneficial for HSV-2 infection. Attracting a large number of phagocytic cells would increase tissue damage and activated cells, potentially enabling viral spread and propagation (Bellner *et al.*, 2005). It was shown that gG-2p20 is an FPR-activating agonist. Activation of FPR *in vivo* led to the downregulation of other chemotactic receptors. These observations suggest the possibility that the change in expression could lead to impaired clearance of HSV-2 during infection (Bellner *et al.*, 2005). In summary, a variety of studies have demonstrated the effectiveness of HSV-1 and HSV-2 in manipulating CXCR4 in infected cells.

HSV-2 has demonstrated the ability to manipulate chemotaxis via a host chemokine as well. A study performed by Huang *et al.* (2012) demonstrated an elevated expression of CXCL9 in the cervical mucosa of HSV-2-positive women. Further research confirmed that HSV-2 regulated the expression of CXCL9 in human cervical epithelial cells by inducing the phosphorylation and translocation of C/EBP- β to the nucleus, where it transactivates CXCL9. The known receptor for CXCL9 is CXCR3, which is expressed predominantly in non-resting T cells (Van Raemdonck *et al.*, 2015). Expression has also been observed in epithelial, endothelial, fibroblast and smooth muscle cells (SMCs) (Billottet *et al.*, 2013; Van Raemdonck

Table 1. Alphaherpesviruses change cellular receptors/chemokines

Cell type	Receptor or chemokine	Virus	Amount or functionality	References
Monocyte	CXCR4	HSV-1, HSV-2	Increase	Bellner <i>et al.</i> (2005); Viejo-Borbolla <i>et al.</i> (2012)
Neutrophil	CXCR4	HSV-1, HSV-2	Increase	Bellner <i>et al.</i> (2005)
Epithelial	CXCL9	HSV-2	Increase	Huang <i>et al.</i> (2012)

et al., 2015). This upregulation of CXCL9 was shown to result in increased migration of activated peripheral blood leukocytes (PBLs) and CD4+T lymphocytes (Huang *et al.*, 2012). Huang and associates postulate that HSV-2 is responsible for upregulating CXCL9; however, it was not shown what viral protein induced the expression or if the increase in CXCL9 expression was a cellular response to viral infection. The viral benefits for inducing migration of CD4+T cells and PBLs to sites of infection are unclear. The ability of HSV-2 to regulate CXCL9 could be investigated more in depth as this is the only study demonstrating this type of subversion in epithelial cells.

Past research has also suggested that VZV could utilize glycoproteins as chemoattractants, inducing migration of polymorphonuclear leukocytes (Ihara *et al.*, 1991). No other recent research has been conducted to determine if VZV affects chemotaxis of other infected cell types, although several studies do provide evidence for how VZV might influence cellular chemotaxis (Desloges *et al.*, 2008; Shavit *et al.*, 1999; Steain *et al.*, 2011). We now understand that HSV-1 and HSV-2 can manipulate monocytes through increasing the functionality of CXCR4 by making lipid rafts with the viral SgG protein. HSV-2 can further change the migration of cells by increasing the expression of CXCL9 in infected epithelial cells, potentially attracting CD4+T cells and PBLs to sites of infection.

BETAHERPESVIRINAE

Human cytomegalovirus (hCMV)

Also known as human herpesvirus 5, hCMV is a prominent member of the *Betaherpesvirinae* subfamily. With a seroprevalence worldwide ranging from 45 to 100%, hCMV

is a common human pathogen that is often asymptomatic in infected adults and children (Cannon *et al.*, 2010; Chen *et al.*, 1999; McGavran & Smith, 1965). hCMV has gained public scrutiny and awareness owing to further understanding of its prevalence in causing congenital infections leading to birth defects (Bialas *et al.*, 2015). In the USA it is a more common cause of birth defects than many other causes, including fetal alcohol syndrome, Down syndrome, spina bifida, HIV/AIDS, Haemophilus influenzae type B and congenital rubella syndrome (Cannon & Davis, 2005). Like other herpesviruses, hCMV is associated with various post-transplant complications and is a main viral cause of solid organ transplant and haematopoietic stem cell transplant morbidity and mortality (Ariza-Heredia *et al.*, 2014; Gandhi & Khanna, 2004). It is also known to cause severe disease in other immunocompromised individuals, such as AIDS patients. Viral shedding can occur via saliva, urine, breast milk, semen and tears. hCMV is known to infect various cell types, including epithelial cells, endothelial cells, smooth muscle cells, fibroblasts, dendritic cells and lymphocytes, the latter cell type typically remaining latently infected for the life of the host.

Using a variety of viral proteins to manipulate migration of host cells and potential target cells, hCMV uses both surface receptors and secreted chemokines (see Tables 2 and 3). Among the viral chemokines secreted by hCMV-infected cells are the products of the *UL128* and *UL146* genes. Numerous studies have been performed demonstrating how these viral gene products affect the migration of hCMV-infected cells. It has been noted that hCMV-infected monocytes demonstrate a reduced chemotactic ability owing to a downregulation of CCR1, CCR2 and CCR5 (Frascaroli *et al.*, 2006). A similar downregulation of various chemokines was observed along with an increase in migratory inhibitory factor in hCMV-infected macrophages, resulting in a lack of motility (Frascaroli *et al.*, 2009).

Table 2. Human herpesvirus-encoded chemokine receptors

Virus	Viral receptor	Result	References
hCMV	US27	Potentiates CXCR4, increases migration to various tissues	Arnolds <i>et al.</i> (2013)
	US28	Migration of infected cells to areas of inflammation	Streblov <i>et al.</i> (1999); Vomaske <i>et al.</i> (2009)
	UL33 and UL78	Prevents migration to sites of inflammation and certain tissues	Tadagaki <i>et al.</i> (2012); Tschische <i>et al.</i> (2011)
HHV-6A	U51	Prevents NK cell interaction and prevents apoptotic signals	Catusse <i>et al.</i> (2008); Fitzsimons <i>et al.</i> (2006)
HHV-6B	U12	Migrates to inflammatory and T cell-rich zones	Isegawa <i>et al.</i> (1998)
HHV-7	U51 U12	Migration of infected cells to T cell-rich and inflammatory areas	Nicholas (1996); Tadagaki <i>et al.</i> (2005)
KSHV	KSHV-GPCR	Increases cell survival	Couty <i>et al.</i> (2009); Pati <i>et al.</i> (2001); Shepard <i>et al.</i> (2001)

Table 3. Human herpesvirus-encoded chemokines

Virus	Viral chemokine	Result	References
VZV	GP I and GP II	Chemoattractant for polymorphonuclear leukocytes	Ihara <i>et al.</i> (1991)
HSV	gG2	Chemoattractant for monocytes	Bellner <i>et al.</i> (2005)
hCMV	UL146	Chemoattractant for neutrophils	Lüttichau, (2010); Penfold <i>et al.</i> (1999)
hCMV	UL128 and UL146	Attracts PBMCs and prevents monocyte migration	Frascaroli <i>et al.</i> (2006); Gao <i>et al.</i> (2013); Straschewski <i>et al.</i> (2011)
HHV-6A	U83A	Chemoattractant for T cells, monocytes and immature dendritic cells	Catusse <i>et al.</i> (2007); Dewin <i>et al.</i> (2006)
HHV-6B	U83B	Chemoattractant for monocytes	Clark <i>et al.</i> (2013); Lüttichau <i>et al.</i> (2003)
KSHV	vCCL1	Chemoattractant for monocytes	Nakano <i>et al.</i> (2003); Weber <i>et al.</i> (2001)
KSHV	vCCL2	Prevents Th1 T cell chemotaxis and attracts monocytes	Nakano <i>et al.</i> (2003); Weber <i>et al.</i> (2001)
KSHV	vCCL3	Inhibits chemotaxis of Th1 T cells and NK cells	Lüttichau <i>et al.</i> (2007)
KSHV	vIL-6	Attracts endothelial cells	Wu <i>et al.</i> (2014)

Later it was demonstrated by Frascaroli and associates that in the presence of UL128 there was a resulting downregulation of CCR1, CCR2 and CCR5 in monocytes (Straschewski *et al.*, 2011). Because of this impairment, monocytes could no longer migrate following the chemokines CCL5 and CCL2, which are ligands of the aforementioned receptors. CCL2 and CCL5 are known to be involved in the recruitment of monocytes and T cells and are secreted as pro-inflammatory cytokines in response to tissue damage or viral detection (Ansari *et al.*, 2013; Soria & Ben-Baruch, 2008). Recently, using a *UL128*-transfected cell line (CHO-UL128) to produce UL128, Gao *et al.* (2013) studied the effects of this β chemokine on cell migration. They found that UL128 acted as a chemoattractant for peripheral blood mononuclear cells (PBMCs) *in vitro* and functioned similarly to CCL3 as a chemoattractant. These results suggest that UL128 could act to prevent chemotaxis of monocytes following other gradients, such as CCL5 and CCL2, and could use a separate receptor to attract the monocytes to areas of infected cells (Gao *et al.*, 2013). This increases the cells available to be infected by hCMV, potentially furthering viral spread. The other known chemokine produced, UL146, codes for an α chemokine and viral homologue to CXCL1 (vCXCL1) (Penfold *et al.*, 1999). Two studies demonstrated that vCXCL1 could induce the chemotaxis of neutrophils *in vitro* (Lüttichau, 2010; Penfold *et al.*, 1999). Using calcium mobilization, chemotaxis and phosphatidylinositol turnover assays, it was found that vCXCL1 was a ligand for CXCR1 and CXCR2. CXCR1 and CXCR2 are both expressed on neutrophils, and it is expected that hCMV-infected endothelial cells express vCXCL1 as a chemoattractant to increase the numbers of neutrophils and assist in viral spread to other endothelial cells (Lüttichau, 2010). In a study conducted by Smith *et al.* (2004), it was observed that hCMV-infected monocytes induced

transendothelial migration *in vitro*, although the viral mechanism is unknown (Smith *et al.*, 2004).

Regulating host cell chemokines can also result in chemotactic changes (see Table 4). hCMV UL144 is a viral protein that activates NF- κ B (Poole *et al.*, 2006). This leads to a cascade of multiple pathways, including induced expression of host CCL22, which acts as a chemoattractant for Th2 and regulatory T cells (Tregs). By recruiting these cells to sites of viral infection it is possible to suppress T helper and CD8+ T cells, tapering the immune response (Fielding, 2015). It has also been found that granulocyte macrophage progenitors (GMPs) latently infected with hCMV demonstrate increased expression of CCL2 (Stern & Slobedman, 2008). CCL2 is a pro-inflammatory cytokine that acts as a chemoattractant to monocytes, macrophages, dendritic cells and T cells expressing CCR2. This increase in CCL2 acts to attract CD14+ monocytes to latently infected GMPs (Stern & Slobedman, 2008). This behaviour of latently infected GMPs is likely a viral strategy employed to recruit new leukocytes to be infected; however, too little is known about *in vivo* hCMV reactivation to know if this spread and reactivation occurs before or after GMPs develop into macrophages. Further research could be done into the manipulation of hCMV-infected GMPs as there is currently just one study demonstrating this change in chemotaxis.

There are a variety of hCMV chemokine receptors shown to affect cell migration, including US27, US28, UL33 and UL78 (Fielding, 2015), all of which are homologous to human GPCRs. US27 is expressed late during lytic infection and has no known ligand (Fraile-Ramos *et al.*, 2002; Stapleton *et al.*, 2012). However, it was found to potentiate CXCR4-mediated chemotaxis, increasing the expression and amount of surface CXCR4 (Arnolds *et al.*, 2013). As previously explained, CXCR4 is a seven-membrane-

Table 4. Betaherpesviruses change cellular receptors/chemokines

Cell type	Receptor or chemokine	Virus	Amount or functionality	References
Dendritic cell	CCR7	hCMV	Decrease	Moutaftsi <i>et al.</i> (2004)
	CCR1	hCMV	Decrease	Varani <i>et al.</i> (2005)
	CCR5	hCMV	Decrease	Varani <i>et al.</i> (2005)
GMP	CCL2	hCMV	Increase	Stern & Slobedman (2008)
Monocyte	CCR1	hCMV	Decrease	Frascaroli <i>et al.</i> (2006, 2009);
	CCR2	hCMV	Decrease	Straschewski <i>et al.</i> (2011)
	CCR5	hCMV	Decrease	
	CCL22	hCMV	Increase	Poole <i>et al.</i> (2006)
T cell	CCL5	HHV-6A	Decrease/increase	Cerdan <i>et al.</i> (2001)
	CCR7	HHV-6	Increase	Hasegawa <i>et al.</i> (1994)
	CXCR4	HHV-6	Decrease	Yasukawa <i>et al.</i> (1999)
	CXCR4	HHV-7	Decrease	Yasukawa <i>et al.</i> (1999)
	CCR7	HHV-7	Increase	Hasegawa <i>et al.</i> (1994)

spanning GPCR that allows the cell to follow the chemokine gradient of its natural ligand, CXCL12, which is secreted constitutively in a variety of tissues, including the lymph nodes, thymus, bone marrow, lungs and adrenal glands (Alkhatib, 2009; Luker & Luker, 2006). The potentiation of CXCR4 resulted in increased migration to CXCL12 during *in vitro* migration assays (Arnolds *et al.*, 2013). It has been speculated that increased CXCR4 levels at appropriate times could allow hCMV-infected cells to migrate to bone marrow or lymph nodes, where there would be an increased opportunity to spread to susceptible cells (Arnolds *et al.*, 2013).

US28 was first shown to affect migration in vascular SMCs (Streblov *et al.*, 1999). It was found that US28 directed cell migration following the chemokines CCL2 and possibly CCL5. In the absence of CCL2, there was no migration of hCMV-infected SMCs (Streblov *et al.*, 1999). This would allow infected SMCs to migrate to areas of inflammation, potentially providing opportunity for viral spread to leukocytes. Later it was demonstrated that US28 acted to control migration of both infected SMCs and infected macrophages. Kledal *et al.* (1998) found that US28 also bound CX3CL1, which is a chemokine that is found on the cell surface and extracellularly in a secreted form; this work was later followed up by others (Murphy *et al.*, 2008; Vomaske *et al.*, 2009). CX3CL1 is only known to be produced by endothelial cells and results in the recruitment of inflammatory cells (Bazan *et al.*, 1997; Vomaske *et al.*, 2009). These authors found that the presence of CX3CL1 inhibited the migration of hCMV-infected SMCs, but induced the migration of hCMV-infected macrophages. It was also demonstrated that the inverse was true, in the presence of CCL5, hCMV-infected macrophages US28-mediated migration was inhibited, but hCMV-infected SMCs demonstrated normal chemotaxis, as expected (Vomaske *et al.*, 2009). This makes the viral GPCR US28 unique in that it is chemokine- and cell-type-specific.

It seems important for the virus to control cellular migration during hCMV infection. Evidence for how US28 functions was provided by Tschische *et al.* (2011), when they found that hCMV chemokine receptors heteromerize with each other. It was observed that UL33 and UL78 heteromerization resulted in silencing of US28-mediated activation of the NF- κ B pathway. Tadagaki *et al.* (2012) investigated UL33 and UL78, and found that these two GPCR homologues formed heteromers with CCR5 and CXCR4 on the surface of infected THP-1 cells. This was found to prevent cell chemotaxis facilitated by CCR5 and CXCR4 *in vitro*. CCR5 allows the cell to follow a variety of chemokines, including CCL3, CCL4 and CCL5, these being the best agonists, while CXCR4 is known to be chemoattracted to CXCL12 (Alkhatib, 2009). The majority of chemokines that act as CCR5 ligands are pro-inflammatory.

During hCMV infection the virus is able to regulate host receptors in various ways to prevent chemotaxis. It has been demonstrated that hCMV prevents CCR7 expression in monocyte-derived dendritic cells, preventing chemotaxis following CCL19 and CCL21 chemokine gradients *in vitro* (Moutaftsi *et al.*, 2004). hCMV-infected Langerhans cells also demonstrate reduced chemotaxis in response to lymphoid chemokines (Lee *et al.*, 2006). After these observations it was found by Wagner *et al.* (2008) that hCMV UL18 inhibited chemotaxis of dendritic cells *in vitro*. The extracellular UL18 is expressed late in hCMV infection and binds the leukocyte immunoglobulin-like receptor 1 molecule on the surface of dendritic cells. This results in various changes, including reduced chemotaxis, increased pro-inflammatory cytokine production, upregulation of CD83 and inhibition of CD40 (Park *et al.*, 2002; Wagner *et al.*, 2008). It was also observed that hCMV-infected dendritic cells showed downregulated chemokine expression and inhibited maturation due to vIL-10, a product of the hCMV *UL111A* gene. Dendritic cells that were able to

mature during hCMV infection showed an increase in chemotactic ability to follow the lymph node homing chemokine (Chang *et al.*, 2004). It has further been observed that chemotaxis is disrupted in infected endothelial cells. Reinhardt *et al.* (2014) demonstrated how hCMV-infected human coronary artery endothelial cell (HCAEC) chemotaxis to vascular endothelial growth factor is inhibited. HCAEC migration is important for repair post-vascular injury (Deanfield *et al.*, 2007; Waltenberger, 2007). While the observation explains how hCMV can play a role in contributing to pro-atherosclerotic phenotypes, the viral strategy for inhibiting HCAEC migration remains unknown. A further way to inhibit chemotaxis of cells is by secreting chemokine-binding proteins. hCMV-produced UL21.5 acts in this capacity by binding CCL5, acting as a chemokine sink or decoy receptor (Wang *et al.*, 2004a). This would prevent the cellular receptor from being able to bind CCL5 and follow the chemoattractant. hCMV also utilizes miR-UL148D to silence CCL5 protein synthesis in infected cells (Kim *et al.*, 2012). These studies emphasize the importance of CCL5 regulation during hCMV infection. Preventing immune cell production and detection of

CCL5 would assist in preventing the attraction of monocytes and T cells to areas of hCMV infection. While a certain number of monocytes would be beneficial for viral spread, an overabundance of monocytes and the presence of T cells could result in the impairment of viral spread.

To better enhance viral spread, hCMV uses virally encoded chemokines UL128, UL146 and vCXCL1 to attract target immune cells. The piracy of host chemokine CCL22 further assists in this process. By upregulation of CCL22 in infected monocytes, Tregs are attracted, and could assist in downregulation of an immune response to viral infection. By increasing the functionality of CXCR4, chemotaxis of virally infected cells to other tissues could be encouraged. By manipulating host chemokine receptor CCR7, hCMV can avoid migration to primary and secondary lymph tissue, evading possible detection. The dysregulation of virus-infected cell movement appears to allow hCMV the edge in evading immune detection and increase the opportunity for viral spread (see Fig. 1). Future studies investigating the function of viral chemokines and chemokine receptors could examine their effects *in vivo* utilizing

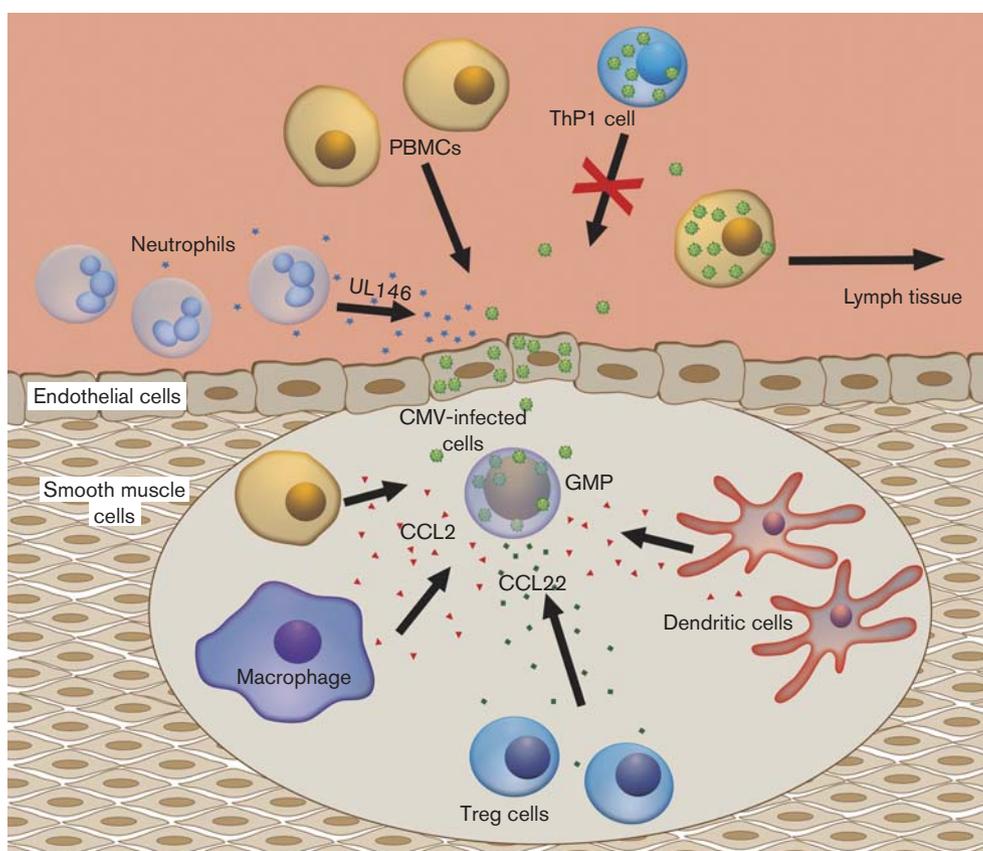


Fig. 1. Changes in cellular chemotaxis resulting from hCMV infection. hCMV uses virally encoded chemokines UL128, UL146 and vCXCL1 to attract target immune cells such as neutrophils and PBMCs. Increases in CCL2 expression further assist in attracting monocytes, macrophages and dendritic cells. Upregulation of CCL22 in infected monocytes attracts Treg cells, which can assist in downregulation of an effective immune response to viral infection. Increasing the functionality of CXCR4 allows virally infected cells to migrate to other tissues, including secondary lymphoid tissues.

animal models, as has been done with hCMV US28 (Bongers *et al.*, 2010).

Human herpesvirus 6 (HHV-6)

HHV-6, initially named human B lymphotropic virus, was first discovered in 1986 in patients with lymphoproliferative disorders (Salahuddin *et al.*, 1986). HHV-6A and HHV-6B were recognized as different variants of the same species in 1992, and in 2012 the International Committee on Taxonomy of Viruses classified them as two distinct viruses (Ablashi *et al.*, 1993; Adams & Carstens, 2012). Because classification as two distinct viruses has come relatively recently, it makes it difficult to distinguish between HHV-6A and HHV-6B in some of the early literature. The seroprevalence of HHV-6 in adults worldwide is approximately 83–100% (Hall *et al.*, 2006).

HHV-6A

HHV-6A is a betaherpesvirus that has primary tropism for CD4+T cells and can also infect CD8+T cells, natural killer (NK) cells, gamma/delta T cells, human neural stem cells, human progenitor-derived astrocytes, and oligodendrocyte progenitor cells (Ablashi *et al.*, 2014; Lusso *et al.*, 1991, 1993, 1995). It has also been shown to lytically infect B cells that have been immortalized with EBV (Ablashi *et al.*, 1989). HHV-6A can alter the expression of different cellular markers involved in cellular homing and trafficking, which causes significant disruption to immune cell function and viability. The virus has been implicated in a number of diseases including multiple sclerosis, Hashimoto's thyroiditis, and AIDS. *In vitro* studies show that HHV-6A causes upregulation of CD4 on cells that do not typically express this marker, making these cells susceptible to HIV infection and possibly contributing in the progression to AIDS (Lusso *et al.*, 1991, 2007).

HHV-6 has one functional chemokine-like protein, U83 (see Table 3). The viral chemokine U83A from HHV-6A is involved in chemoattraction and has selective specificity for receptors CCR1, CCR4, CCR5, CCR6 and CCR8. These are found on T cells, monocytes/macrophages and activated T lymphocytes (CCR1, CCR5, CCR8), skin-homing T lymphocytes (CCR4, CCR8), immature dendritic cells (CCR1, CCR6) and NK cells (CCR8) (Ablashi *et al.*, 2014; Catusse *et al.*, 2008; Dewin *et al.*, 2006). The difference in specificity of U83A (from HHV-6A) and U83B (from HHV-6B) to attract diverse cell types (see Table 3) could account for the variable tropism of the two viruses (Clark *et al.*, 2013). U83A is found in a full-length form as well as a truncated splice variant (French *et al.*, 1999). It is thought that, because of the different forms of the peptide, U83A could block both innate and adaptive immune responses, as well as attract the cells involved in these responses for further infection (Dewin *et al.*, 2006). U83A induces chemotaxis and morphological changes in cells

expressing CCR5 in a manner similar to CCL4, but with a significantly delayed internalization of CCR5 compared with CCL4. Interestingly, binding of U83A to CCR5 has been shown to inhibit CCR5 tropic HIV-1 infection (Catusse *et al.*, 2007).

HHV-6 has two GPCRs, U12 and U51, which encode chemokine receptors (see Table 2). U51, known to affect migration in HHV-6A infected cells, is expressed at early time points post-infection, whereas U12 is expressed late and influences chemotaxis of HHV-6B-infected cells. HHV-6A U51A has novel specificity for CCL5 and can also bind CCL2, CCL11, CCL7 and CCL13. This makes U51A unique among viral and cellular receptors in that it overlaps activity with CCR1, CCR2, CCR3 and CCR5 in the binding of CCL5 (Catusse *et al.*, 2008). There is also overlap with CCR2, CCR4, US28, UL12, D6 and Duffy in the binding of CCL2; CCR3 and E1 in the binding of CCL11; CCR1, CCR3, US28 and D6 in the binding of CCL7; and CCR2 and CCR3 in the binding of CCL13. Unlike many viral GPCRs that have constitutive signalling, U51A has been shown to perform both inducible and constitutive signalling (Catusse *et al.*, 2008; Fitzsimons *et al.*, 2006).

U51A expression has been shown to cause a reduction of CCL5 expression using the Hut78 human CD4+T lymphocyte cell line. U51A has high relative affinity for XCL1, which normally binds human receptor XCR1 found on NK cells and T lymphocytes. This binding could have a number of effects, including: preventing infected cells from interacting with NK cells; inducing chemotaxis to T lymphocytes, which could spread infection; and preventing apoptotic signals within infected cells (Cerdan *et al.*, 2001). CCL19, normally bound by human receptor CCR7, can also be bound by U51A. This could cause infected cells to migrate to the T cell-rich lymph node, promoting viral spread. HHV-6A U83A chemokine does not bind U51A. Expression of U51A ligands in the brain could also allow migration of infected cells into the central nervous system. Damaged epithelial lung cells and airway parasympathetic nerves express CCL2 and CCL11, which both bind U51A, and could promote migration of the infected cells to these areas to be transmitted to new hosts.

CCR7, which is expressed in various lymphoid tissues, is another receptor that is modulated by herpesviruses (see Table 4). HHV-6A and HHV-6B upregulate CCR7 expression in CD4+T cells (Hasegawa *et al.*, 1994). CCR7 is specific for CCL19 and CCL21 and plays roles in cell migration and proliferation (Tadagaki *et al.*, 2005). This upregulation of CCR7 could be an important aspect of HHV-6 pathogenesis as upregulation of CCR7 promotes migration of T cells and dendritic cells to the paracortex in lymph nodes (where T cell priming occurs) and the periarteriolar lymphoid sheath in the spleen, both of which are T cell-rich (Comerford *et al.*, 2013).

As mentioned previously, HHV-6A can also downregulate cellular receptors. Along with downregulation of CD46 (its entry receptor) and CD3 (Grivel *et al.*, 2003), CXCR4 is downregulated by HHV-6A in primary CD4+ T lymphocytes and the Jjhan T cell line, which affect the chemotactic response of the cells to CXCL12, the natural ligand of CXCR4 (Yasukawa *et al.*, 1999). The disruption of CXCR4/CXCL12 signalling by downregulation of CXCR4 by HHV-6A could prevent the retention of haematopoietic stem/progenitor cells (HSPCs) and more mature leukocytes in the bone marrow, allowing these cells to be mobilized and enter into circulation (Karpova & Bonig, 2015). The migration of CXCR4-expressing thymocytes out of the thymus was shown to occur in a CXCL12-dependent manner (Poznansky *et al.*, 2002; Weinreich & Hogquist, 2008); so the downregulation of CXCR4 by HHV-6A could be another way the virus prevents migration away from areas where target cells are present. Additionally, the downregulation of CXCR4 by HHV-6A could prevent homing of bone marrow-derived precursor cells to the thymus (Calderón & Boehm, 2011), possibly preventing positive and negative selection from occurring in these cells.

HHV-6 has been shown to cause modulations to CCL5 expression. This chemokine has selective chemoattractive activity on resting CD4+ memory T cells (Hasegawa *et al.*, 1994) and has been shown to be upregulated by HHV-6 in an *ex vivo* study where human tonsil blocks were infected with both HHV-6 and HIV-1. This upregulation of CCL5 was shown to suppress HIV-1 CCR5-tropic variants and possibly to stimulate replication of CXCR4-utilizing variants, which gives evidence that HHV-6 may play a role in HIV pathogenesis by promoting the switch between CCR5-tropic to CXCR4-tropic HIV-1 (Grivel *et al.*, 2001). In contrast, CCL5 expression in epithelial cells is downregulated by U51A from HHV-6A (Milne *et al.*, 2000). Epithelial cells expressing U51A also had morphological changes and exhibited increased spreading and flattening, which could increase the ability of HHV-6 to spread to uninfected cells as it is primarily spread by cell-to-cell contact (Milne *et al.*, 2000). As has been observed with other viral chemokines and chemokine receptors, their functions could be multipurpose in attracting cells to the area of infection, and also in evading the immune cells of the host so replication and latency can take place.

As described above, HHV-6A alters the expression of different cellular markers. Many of these markers are involved in cellular homing and tracking to specific areas of the body, and when altered can cause significant disruption to immune cell function and viability. Further research into HHV-6A effects on cellular trafficking could serve as a critical guide for developing new treatments to prevent these disease-causing disruptions.

HHV-6B

HHV-6B causes exanthem subitum (roseola) (Yamanishi *et al.*, 1988) and is found in approximately 95–100% of

adults worldwide. Unlike HHV-6A, HHV-6B has very little to no ability to infect CD8+ T cells, NK cells and gamma/delta T cells (Grivel *et al.*, 2003; Martin *et al.*, 2012). The cellular receptor for HHV-6B is CD134 which, like the cellular receptor for HHV-6A, CD46, is expressed on almost all human cells (Tang *et al.*, 2013), indicating that other factors are required for effective viral replication.

The HHV-6B viral chemokine U83B is specific for CCR2 and can cause chemoattraction of CCR2-expressing cells (classical and intermediate monocytes) for infection (Ablashi *et al.*, 2014; Clark *et al.*, 2013; Lüttichau *et al.*, 2003) (see Table 3). U83 from HHV-6B induced transient calcium mobilization and efficient migration in THP-1 cells (a monocyte cell line derived from monocytic leukaemia) (Zou *et al.*, 1999). U83B has been shown to have a different specificity from U83A as U83B chemoattracts CCR2-expressing monocytes, whereas U83A has a broader but still selective specificity as mentioned previously (Catusse *et al.*, 2008; Dewin *et al.*, 2006). The specificity of U83B for CCR2 appears to be due to its N-terminal region. Human chemokines can induce rapid internalization of CCR2 upon binding, whereas *in vitro* experiments show U83B does not cause CCR2 internalization. This finding is similar to the delayed internalization of CCR5 observed with U83A. CCR2 expression is induced in pro-inflammatory conditions and, interestingly, HHV-6B is associated with inflammatory diseases such as encephalitis and myocarditis (Clark *et al.*, 2013).

The HHV-6B GPCR U12 efficiently binds CCL2, CCL5 and CCL4, so it has overlapping activity with the receptors for CCL2 and CCL5 as in HHV-6A, but also has overlapping activity with the receptors for CCL4 (Balkwill, 2004; Isegawa *et al.*, 1998) (see Table 2). The exact role of chemokine receptors with these viruses is still unknown, but they could be multipurpose, in that they could have been developed for immune evasion to intercept chemokines that would otherwise be attracting immune cells to the area of infection, to attract uninfected cells that could then be infected, to induce latency, or to transition from latency to active replication.

Similar to HHV-6A, HHV-6B was shown to downregulate CXCR4 in CD4+ T lymphocytes as well as MT-4 cells. This downregulation impaired the chemotactic response of the cells to the natural ligand, CXCL12 (Yasukawa *et al.*, 1999). Similar to HHV-6A, this could induce mobilization of HSPCs into the circulation as well as prevent migration of cells out of the thymus, both of which aid in the propagation and survival of the virus.

Human herpesvirus 7 (HHV-7)

As part of the same subfamily as HHV-6A and -6B, HHV-7 shares similar characteristics, including also being a T-lymphotropic virus, although it can infect other cell types (Ablashi *et al.*, 1995; Ward, 2005). Like other human

herpesviruses, once HHV-7 is acquired, the host is infected for life. The virus is shed in saliva and spread through this route of transmission. Compared with the other human herpesviruses, much less research has been conducted on HHV-7 infection and pathogenesis. Clinically it has been associated with the development of pityriasis rosea, post-infectious myeloradiculoneuropathy, encephalopathy and other syndromes. There is some speculation on the involvement of HHV-7 in the development and progression of these diseases (Chuh *et al.*, 2004; Mihara *et al.*, 2005; van den Berg *et al.*, 1999). HHV-7 infections can have a variety of symptoms, including fever, rash, febrile respiratory problems, vomiting and diarrhoea (Clark *et al.*, 1997; van den Berg *et al.*, 1999). Infections typically occur in children and are most often asymptomatic (Ward, 2005).

HHV-7 has been shown to influence migration in human cells in a variety of ways (see Tables 1 and 4). Yasukawa *et al.* (1999) showed that it downregulated transcription and surface expression of CXCR4 in CD4+T cells. As described before, CXCR4 is the receptor for CXCL12, which is secreted by various cells in the lymph nodes, bone marrow, etc. With CXCR4 assistance, T cells can follow a CXCL12 gradient to sites of inflammation (Domanska *et al.*, 2013). After infection with HHV-7, Yasukawa *et al.* (1999) tested the migration and intracellular levels of Ca²⁺ of CD4+T cells. It was found that infected cells demonstrated less migration following the CXCL12 gradient and decreased levels of intracellular Ca²⁺ compared with the mock-infected cells used as controls. It is currently unknown what viral factor(s) contribute to the downregulation of CXCR4. It has been demonstrated that lower levels of CXCR4 in HHV-7-positive T lymphocytes prevent infection by CXCR5-tropic HIV-1 (Yasukawa *et al.*, 1999). Future research could explore how HHV-7 manipulates CXCR4 in infected cells and further confirm the findings of Yasukawa *et al.* (1999), as theirs is the only study investigating this change in chemotaxis.

While CXCR4 is a cellular GPCR that is influenced post-viral infection, HHV-7 has two known viral chemokine receptors, products of the U12 and U51 genes. These genes were identified as GPCR homologues and later Tadagaki *et al.* investigated the functionality of the protein products of these genes (Nicholas, 1996; Tadagaki *et al.*, 2005). They verified that these proteins do accumulate on the surface of the cell. Further, they verified that they could act as functional chemokine signal receptors. Cells expressing U12 and U51 expressed heightened levels of intracellular Ca²⁺ after appropriate signalling through the U12 and U51 GPCRs. Testing the chemotactic effect of the expression of these proteins in the Jurkat T cell line using microchannel migration techniques, it was found that cells expressing U12 migrated effectively following a gradient of CCL19 and CCL21. This would make U12 a viral homologue of the cellular GPCR CCR7, as it also responds to both CCL19 and CCL21. Both of these chemokines are strongly expressed in the T cell zone of secondary lymphoid

tissues and are important in lymphocyte homing and migration (Nomura *et al.*, 2001). It has also been observed that CCR7 expression is upregulated during HHV-7 infection (Hasegawa *et al.*, 1994). While the strategy behind the manipulation of cellular chemotaxis following these ligand chemokines is still unclear, it could be speculated that migration to such areas could be beneficial for HHV-7 transmission as T cells are preferential targets of infection. Tadagaki *et al.* (2005) also speculated that expression of these viral proteins could aid in immune evasion and viral replication. Further research in murine L1.2 cells showed that U12 and U51 products could respond to CCL22 and CCL19, respectively (Tadagaki *et al.*, 2007). Gene products U12 and U51 could act with CCR4 and CCR7, respectively, to direct migration in this cell line in response to CCL22 and CCL19 (Luther *et al.*, 2002). If this were to hold true in human cells infected with HHV-7, then infected cells would be expected to migrate more to areas of inflammation, as CCL22 is a pro-inflammatory chemokine secreted by a wide variety of cells, and areas of high T cell density as CCL19 is constitutively expressed by stromal cells in the T cell zone (Luther *et al.*, 2002). These areas would be attractive locations for the viral spread of HHV-7.

GAMMAHERPESVIRINAE

Epstein–Barr virus (EBV)

The main cause of viral mononucleosis, EBV infects nasopharyngeal epithelial cells and B lymphocytes (Balfour *et al.*, 2005; Cohen, 2000). Viral spread is mainly accomplished through shedding in saliva (Balfour *et al.*, 2005). EBV gains access to appropriate host cells by using viral gp350 to bind CD21 (a type 2 complement receptor) on the cell surface; the viral envelope then fuses with the cell membrane, releasing the viral capsid and associated tegument proteins into the cytoplasm (Toussiroit & Roudier, 2008). The virus uses major histocompatibility complex class II molecules as cofactors when infecting B lymphocytes (Li *et al.*, 1997). During its latent infection of host B cells, EBV expresses one of four possible latency programmes, depending on cellular development and conditions (Young & Rickinson, 2004). It is likely that reactivation *in vivo* of latent virus is due to the differentiation of infected memory B lymphocytes (Amon & Farrell, 2005; Hochberg *et al.*, 2004b). EBV is associated with a variety of malignancies owing to its ability to regulate cell proliferation, including Burkitt's lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma, gastric carcinoma, and post-transplant lymphoproliferative disorder (Hochberg *et al.*, 2004a; Kutok & Wang, 2006; Shibata & Weiss, 1992; Young & Rickinson, 2004).

During infection of B cells, EBV controls the expression of various endogenous chemokines and chemokine receptors (see Table 5). One such manipulated receptor that is shown to affect migration is CXCR4. As previously described it is

Table 5. Gammaherpesvirus changes cellular receptors/chemokines

Cell type	Receptor or chemokine	Virus	Amount or functionality	References
B cell	CXCR4	EBV	Decrease	Ehlin-Henriksson <i>et al.</i> (2006, 2009);
	CCR7	EBV	Decrease/increase	Nakayama <i>et al.</i> (2002)
	CCR6	EBV	Increase	Nakayama <i>et al.</i> (2002)
	CCR10	EBV	Increase	
	CXCR5	EBV	Decrease	Ehlin-Henriksson <i>et al.</i> (2009); Nakayama <i>et al.</i> (2002)
	EBI2	EBV	Increase	Birkenbach <i>et al.</i> (1993); Kelly <i>et al.</i> (2011)
Endothelial	CXCL8	KSHV	Increase	Wang <i>et al.</i> (2004b)
	CCL2	KSHV	Increase	Pati <i>et al.</i> (2001); Xu & Ganem (2007)
	CCL5	KSHV	Increase	
	CXCL7	KSHV	Increase	
	CXCL16	KSHV	Increase	

the receptor for CXCL12, which is secreted by various cells in a number of organs, including the lymph nodes, lungs, liver, kidneys, heart and bone marrow (Teicher & Fricker, 2010). Ehlin-Henriksson *et al.* (2006) demonstrated that tonsillar B cells infected with EBV showed reduced expression of CXCR4 (Ehlin-Henriksson *et al.*, 2006). Assays of chemotactic migration further showed that infected tonsillar B cells had decreased ability to migrate towards CXCL12. This decreased expression and the subsequent lack of chemotaxis was demonstrated in EBV-immortalized B cells as well (Nakayama *et al.*, 2002). The inability to follow the CXCL12 gradient would prevent infected B cells from migrating to tissues expressing only this chemokine. CCR7 is another host receptor that is virally regulated during EBV infection. In a later study by Ehlin-Henriksson *et al.* (2009), it was found that CCR7 is down-regulated in tonsillar B cells post-infection. This change in expression led to decreased migration following the natural chemokine ligand CCL21. CCL21 is produced by stromal cells in primary and secondary lymphoid tissues and lymphatic endothelial cells in the peripheral tissue (Comerford *et al.*, 2013). It is critical for directing the formation of secondary lymphoid tissues such as spleen, Peyer's patches, and lymph nodes (Ohl *et al.*, 2003). It has also been surmised that CCR7 ligands are influential in tertiary lymphoid organs (Comerford *et al.*, 2013). Immortalized B lymphoblast cell lines (LCLs) have been shown to have an increased expression of CCR7 compared with uninfected cells. This upregulation resulted in increased migration following a CCL21 gradient in assays of chemotaxis (Nakayama *et al.*, 2002). While these results may seem to be paradoxical, it is possible that the difference in expression could be a result of a different latency programme or stage of viral infection. Ehlin-Henriksson *et al.* (2009) used harvested tonsillar B cells and measured CCR7 expression and cellular migration 7 days post-infection. In contrast, LCLs are a result of EBV immortalization of B lymphocytes, the process taking several weeks to establish the cell line and expressing a type III latency programme (Young & Rickinson, 2004). The difference in expression could be a result of either the

length of infection or the latency programme employed by the virus post-infection.

In that same study of LCLs, it was found that they expressed increased amounts of CCR6 and CCR10, the natural ligands of which are CCL20 and CCL28, respectively. Migration assays confirmed that this change resulted in increased chemotaxis towards CCL20 and CCL28 chemokine gradients (Nakayama *et al.*, 2002). CCL20 is an inflammatory chemokine involved in the recruitment of dendritic cells, CD4+ T lymphocytes and B lymphocytes (Zhao *et al.*, 2014). CCL28 is secreted by epithelial cells that line the mucosa and is used to recruit IgA⁺ plasma cells (Vazquez *et al.*, 2015; Wilson & Butcher, 2004). CCL28 expression is highest in the salivary glands (Liu *et al.*, 2012). It would be in the best interest of EBV to regulate these receptors, allowing the virus to migrate to mucosal tissues, such as the salivary gland, for effective viral spread. Chemotaxis to sites of inflammation could result in viral reactivation and increased targets for further infection. A final cellular receptor that is downregulated during infection, effecting a change in chemotaxis, is CXCR5. The inability to migrate owing to lowered levels of CXCR5 was observed in LCLs and infected tonsillar B cells (Ehlin-Henriksson *et al.*, 2009; Nakayama *et al.*, 2002). CXCR5 allows B cells to migrate in response to CXCL13 (Carlsen *et al.*, 2004). CXCL13 is an important chemokine for secondary lymphoid tissue development, and the main cells responsible for secretion of CXCL13 are follicular dendritic cells (Cyster *et al.*, 2000; Legler *et al.*, 1998). It is expressed in vascular tissue, Peyer's patches, and inflamed lymphoid tissue (Ebisuno *et al.*, 2003; Mazzucchelli *et al.*, 1999; Okada *et al.*, 2002; Shi *et al.*, 2001). A recent study of murine B lymphocyte positioning in CXCR5-negative mice demonstrated that CXCR5 is important for the retention of B cells in Peyer's patches (Schmidt & Zillikens, 2013). While avoiding tissue types expressing CXCL13 could be beneficial for the virus, possibly assisting in immune avoidance, the exact reason for regulating CXCR5 is still unclear. Another receptor thought to be

influenced by EBV is EBV-induced gene 2 (*EBI2*). Infected B cells display a heightened expression of *EBI2* (Birkenbach *et al.*, 1993; Kelly *et al.*, 2011). While it remains unknown how EBV manipulates *EBI2* expression in B lymphocytes, it has been observed that *EBI2*⁺ cells migrate following a 7α -OHC gradient (Liu *et al.*, 2011). 7α -OHC is the natural ligand of *EBI2* and is expressed by stromal cells of secondary lymph tissue, assisting in directed migration during cell chemotaxis in these areas (Gatto & Brink, 2013; Hanne-douche *et al.*, 2011). Exaggerated expression of *EBI2* by EBV could result in migration to the outer follicular zone in secondary lymph tissue, preventing migration toward T cell zones and germinal centres (Cyster, 2010).

The viral regulation of host lymphocytes extends to controlling various chemokines produced during infection, resulting in a change in the chemotaxis of uninfected cells. EBNA-3C, a viral product essential in establishing latency and immortalization of B cells, acts to regulate two host-produced chemokines, CXCL10 and CXCL11 (McClellan *et al.*, 2012). EBNA-3C has been found to interact with both transcriptional co-repressors and co-activators (Cotter & Robertson, 2000; Radkov *et al.*, 1999; Touitou *et al.*, 2001). Using the EBV-negative BJAB cell line, McClellan *et al.* (2012) showed that expression of EBNA-3C reduces expression of these two chemokines. The result is decreased migration of CXCR3⁺ cells (McClellan *et al.*, 2012). Cells that express and migrate in response to CXCL10 and CXCL11 via CXCR3 include various T lymphocytes, including CD8⁺T cells. CXCL10 and CXCL11 are typically expressed to attract Th1 cells in response to infection. EBV has also demonstrated the ability to influence the expression of chemokines via microRNAs (miRNAs). miR-BHRF1-3, an EBV-produced miRNA, has the ability to silence CXCL11 protein synthesis (Xia *et al.*, 2008). Downregulation of these chemokines suggests that immune avoidance could be a reason behind viral manipulation. Repression of CXCL11 would prevent attraction of cytotoxic T cells that might recognize virally infected B lymphocytes.

The chemokine receptor CXCR4 is a popular target for manipulation, and EBV, like other herpesviruses, uses it to prevent cell migration to certain tissue areas, probably to avoid immune detection. To achieve this same purpose, EBV also downregulates CCR7. During infection, the virus increases the host chemokine CCR6, allowing infected cells to more readily migrate to areas of inflammation. CCR10 function is also pirated, allowing infected cells to migrate toward epithelial cells, such as mucosal epithelial cells. This is likely vital for the spread of EBV. Reduction in expression of CXCL10 and CXCL11 could help in immune avoidance by suppressing the ability to attract T lymphocytes via these chemokines (see Fig. 2).

Kaposi's sarcoma herpesvirus (KSHV)

KSHV, also known as human herpesvirus 8 (HHV-8), is named after Moritz Kaposi, who originally described a

unique skin lesion in the 1870s. The discovery of the association of herpesviral DNA sequences in Kaposi's sarcoma (KS) did not occur until 1994 (Chang *et al.*, 1994; Ganem, 2010). KS presents as tumours most often found in the dermis but can also be found in lungs, liver and intestines (Moore & Chang, 2003). KSHV is also linked to primary effusion lymphoma and multicentric Castleman's disease (Avey *et al.*, 2015; Cesarman *et al.*, 1995; Soulier *et al.*, 1995).

KSHV encodes three secreted chemokines; vCCL1 (ORF K6 or vMIP-I/MIP-1a), vCCL2 (ORF K4 or vMIP-II/MIP-1b) and vCCL3 (ORF K4.1 or vMIP-III/BCK), which activate CCR8, CCR3 and CCR4, respectively (see Table 3). This set of chemokines antagonizes the recruitment of Th1 and NK cells. This redirects the immune response from a Th1-like response towards a Th2 profile. vCCL2 has also been shown to prevent CCL5-mediated chemotaxis of Th1-like lymphocytes (Moore & Chang, 2003; Stebbing *et al.*, 2003; Weber *et al.*, 2001). The receptor XCR1, which normally binds the ligand XCL1 and is involved in T-cell recruitment, is selectively activated by vCCL3 but is also blocked by vCCL2. The opposing function and differing time of expression of the two viral chemokines could indicate the importance of the regulation of the XCR1 receptor in KSHV infection and pathogenesis. Neutrophils have high levels of XCR1, and vCCL3 chemoattracts these cells, which may indicate that neutrophils play a role in viral spread (Lüttichau *et al.*, 2007). vCCL1 and vCCL2 expression were also shown to induce migration of monocytes. This could play a role in the process of tumour development in KS as circulating monocytes could be recruited to KSHV-infected cells, thus propagating the infection (Nakano *et al.*, 2003).

KSHV encodes a GPCR (vGPCR or ORF74) that is homologous to CXCR2 and has a high level of constitutive activity (Arvanitakis *et al.*, 1997; Cesarman *et al.*, 1996; Hensbergen *et al.*, 2004; Pati *et al.*, 2001) (see Table 2). Constitutive expression of ORF74 in microvascular lung endothelial cells inhibits migration and increases cell survival. This inhibitory effect on migration can be reversed by endogenous chemokines CXCL10 and CXCL12. These act as inverse agonists of ORF74, as seen in an *in vitro* wound closure assay, where CXCL10 increased migration of ORF74-expressing cells. Limiting migration of infected cells may aid in immune evasion and KSHV survival. Constitutive expression of ORF74 has also been shown to attract uninfected endothelial cells, which could then be infected and propagate the infection (Couty *et al.*, 2009).

ORF74 has been shown to activate the transcriptional activators NF- κ B and activator protein 1 (AP-1), leading to the downstream production of signals including IL-6, IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF) and CCL5 (Pati *et al.*, 2001; Schwarz & Murphy, 2001; Shepard *et al.*, 2001). Elevated levels of CXCL8 are observed in KS patients and can activate KSHV-infected cell growth and induce chemotaxis (Wang

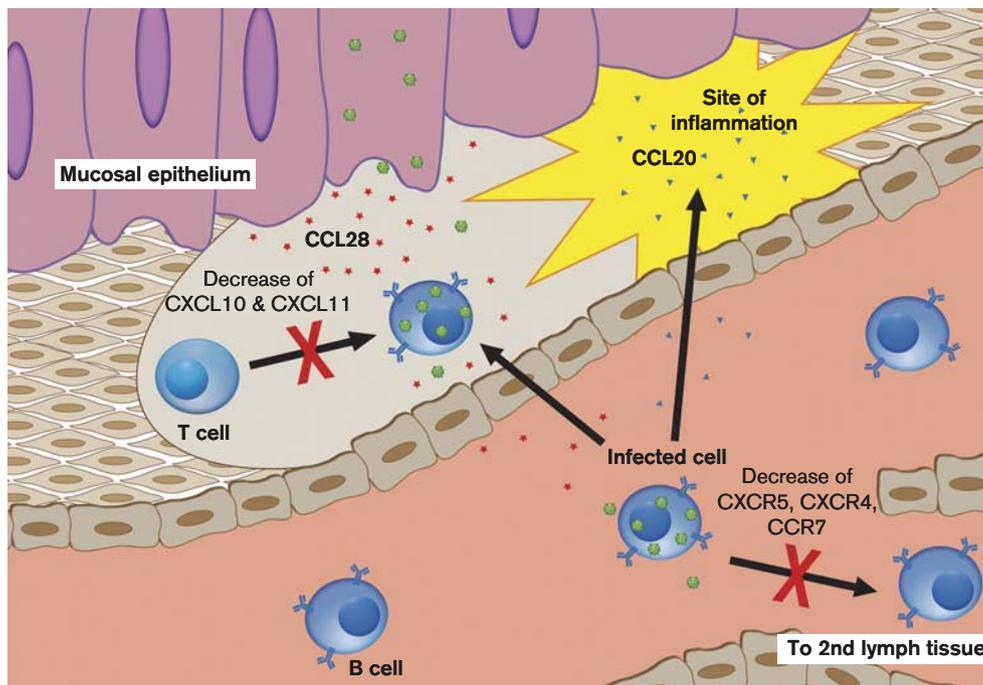


Fig. 2. Changes in cellular chemotaxis resulting from EBV infection. EBV decreases expression of cellular CXCR4 and CCR7 to prevent migration to certain tissue areas, probably to avoid immune detection. Increases in host chemokine CCR6 allow infected cells to migrate to areas of inflammation. CCR10 function is also pirated, allowing infected cells to migrate toward epithelial cells, such as mucosal epithelial cells. Downregulation of CXCL10 and CXCL11 could help in immune avoidance by suppressing the ability of infected cells to attract T lymphocytes.

et al., 2004b). CXCR1 and CXCR2, receptors that bind CXCL8, have been found to be expressed in KS lesions. CXCR4 has also been found to be expressed on cells in these lesions, which is important as this receptor acts as a co-receptor for CXCR4-tropic strains of HIV (Masood *et al.*, 2001; Pati *et al.*, 2001; Wang *et al.*, 2004b). These combined effects of ORF74 could stimulate the proliferation, migration and chemotaxis of endothelial cells in KS.

KSHV encodes a homologue of IL-6, vIL-6, that has been shown to promote migration of endothelial cells in both autocrine and paracrine fashions. Inhibition of this migration can be specifically inhibited by a DNA methyltransferase 1 (DNMT1) inhibitor, suggesting that the mechanism of vIL-6 is dependent on enhancing expression of DNMT1. As the control of DNA methylation is crucial for gene expression and other cellular processes, disruption of methylation could be a mechanism for KS tumorigenesis (Wu *et al.*, 2014).

There are a number of different cellular chemotactic proteins shown to be upregulated by KSHV, including: CCL2, CXCL7, CCL5, GM-CSF, CXCL16 and angiogenin (Xu & Ganem, 2007) (see Table 5). Some of these, such as CCL5 and GM-CSF, likely increase migration of endothelial cells toward KSHV-GPCR-expressing KS cells

(Bussolino *et al.*, 1989; Pati *et al.*, 2001). In contrast, CXCL16 appears to play an indirect role in tumour growth and expansion through migration of activated T cells (Xu & Ganem, 2007). KSHV also causes downregulation of certain genes. The KSHV miRNA miR-K12-10a downregulates the cytokine receptor TNF-like weak inducer of apoptosis (TWEAK) receptor. This inhibits the pro-inflammatory response and also provides protection from TWEAK-induced apoptosis (Abend *et al.*, 2010).

Latency-associated nuclear antigen 1 (LANA-1; encoded by ORF73), a latently expressed gene, has been shown to hinder neutrophil chemotaxis, which interferes with recruitment of neutrophils to infected areas and could be a way in which latent KSHV survives host-induced acute inflammation. Neutrophil recruitment is restored in LANA-1 knockdowns, although not to the level of uninfected cells, indicating that KSHV has other mechanisms to repress neutrophil recruitment (Li *et al.*, 2011).

As seen with other herpesviruses, KSHV can induce or inhibit cellular migration, according to what is most beneficial for viral infection at the given stage. It not only interferes with cellular marker expression, it also induces increased production of specific chemokines and cytokines, which leads to other issues in cellular function and trafficking.

CONCLUDING REMARKS

With exposure to human herpesviruses being very common, it is important to understand how these infectious human pathogens influence infected and uninfected cell types. The viruses of the subfamily *Alphaherpesvirinae* use gG to increase the functionality of CXCR4, leading to increased chemotaxis to a variety of tissues while being able to manipulate cellular chemokines, such as CXCL9, to attract PBLs. Viruses of the subfamily *Betaherpesvirinae*, also capable of producing and manipulating chemokine and chemokine receptors, influence a variety of cells during infection. hCMV inhibits migration in infected monocytes and potentially attracts monocytes, PBMCs, macrophages, dendritic cells and regulatory T cells to sites of infection. Similarly, through its ability to attract target cells, HHV-6 is able to induce chemotaxis of T lymphocytes, monocytes, immature dendritic cells, and NK cells to areas of infected cells using viral U83. T cells infected with HHV-6 are further manipulated, as viral and cellular GPCRs allow cells to migrate to sites of inflammation and areas rich in T cells. Also manipulating T cells, HHV-7 prevents infected T lymphocytes from migrating to various organs and tissues by downregulating CXCR4. However, it too potentially encourages migration to inflammatory sites and locations high in T cells by inducing cells to follow chemokine gradients of CCR7, CCL21, CCL22 and CCL19.

Further masters of cellular piracy, viruses of the subfamily *Gammaherpesvirinae* also influence cellular chemotaxis to avoid immune detection and spread viral infection throughout the host until latency can be established. To prevent newly infected cells from potentially migrating to lymph tissue and other organs, EBV reduces expression of CXCR4, CCR7 and CXCR5. By downregulating the chemokines CXCL10 and CXCL11, EBV could prevent infected cells from attracting cytotoxic T cells. To regulate chemotaxis of cells during infection, KSHV regulates the attraction or avoidance of neutrophils and monocytes by viral chemokines vCCL1, 2 and 3. KSHV would be able to induce the chemotaxis of uninfected endothelial cells by upregulating various cellular chemokines and activating the NF- κ B pathway, enabling viral spread.

Though our current understanding of how human herpesviruses affect host cell migration during infection is rather expansive, there still remain various areas for future research opportunities. In this review we have elaborated on the cells potentially affected by virally encoded and virally induced chemokines and chemokine receptors. However, the full range of cells affected by these chemokines remains to be tested and investigated further. Several virally regulated cell chemokine receptors suspected of influencing viral spread and immune avoidance are in need of confirmatory scientific inquiry. Several human herpesviruses have not been studied extensively for effects on cellular chemotaxis, such as the viruses of the subfamily *Alphaherpesvirinae* and HHV-7. These areas leave a variety of opportunities for future research that could contribute

to our understanding of how these viruses lead to disease pathogenesis and progression.

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