HHV-8 dissemination to lymph nodes.

HHV-8 or Kaposi sarcoma-associated herpesvirus (KSHV) is primarily transmitted through saliva and initial replication of virus occurs in epithelial cells of the oropharynx. Subsequent dissemination of virus to mucosal lymphoid tissue, particularly the tonsils, targets B cells for infection, which serve as primary viral reservoirs. Infection of B cells usually results in viral latency characterised by minimal viral gene expression. In healthy immunocompetent individuals, persistence of HHV-8 is facilitated by chronic reactivation of latently infected cells. HHV-8 infection is usually asymptomatic and persistence is lifelong, however, immune dysfunction, such as caused by HIV disease, can lead to increased levels of virus reactivation and lytic replication. Cytokines can promote abnormal B cell proliferation in lymph nodes causing unicentric Castleman’s disease. Due to increased viral loads, dissemination of latently infected B cells or free virus to other lymphoid tissues can promote disease at other sites leading to the development of more severe multicentric Castleman’s disease.
Infected naive B cells bypass the germinal centre reaction.

Infection of naive B cells in lymphoid tissue leads to viral latency by default. Infected B cells are transformed and resemble plasmablasts. HHV-8 uses several membrane receptors to gain entry into susceptible cells (e.g. heparan sulfate, α3β1 integrin, DC-SIGN, xCT and ephA2) which facilitates internalisation of virus by endocytosis. Latent infection is characterised by maintenance of viral episomes in the nucleus and expression of a minimal number of viral genes which promotes long term survival of infected cells as well as escape from immune surveillance. Viral latent gene products are thought to transform naive B cells by mediating intracellular signalling events normally associated with germinal centre reactions. Infected naive B cells bypass germinal centres and localise to the marginal zone of lymphoid follicles. Infected plasmablasts are characteristically large in size and express cytoplasmic and membrane-bound immunoglobulins exclusively composed of IgM isotypes and lamda light chains.
HHV-8 latency in B cells is associated with expression of six viral proteins. The viral protein vFLIP, is thought to mediate transformation of infected B cells into plasmablasts via expression of genes under the control of the transcription factor, NF-κB. Expression of anti-apoptotic genes as well as production of B cell growth factors leads to the long term survival of latently infected B cells. A number of cell surface alterations characterise the phenotype of infected plasmablasts. A lack of CD138 (a plasma cell marker) and low/absent CD20 (a B cell marker) is evident as well as expression of the IL-6 receptor, CD19 (a B cell marker) and CD27 (a memory marker). Membrane bound immunoglobulins that are exclusively IgMλ are also hallmarks of HHV-8 infection. In normal B cell development, NF-κB drives expression of lambda light chains following unsuccessful kappa gene rearrangements. Infected plasmablasts also lack class switch recombination and somatic hypermutation due to bypassing of germinal centre reactions.
The long term survival of latently infected B cells is mediated by both anti-apoptotic and pro-growth factors. IL-6 plays a central role as a growth factor for infected B cells. HHV-8 infection promotes B cell expression of the IL-6 receptor which is composed of two protein chains, gp80 and gp130. HHV-8 produces vIL-6, a homologue cytokine of human IL-6, that signals via the gp130 chain and is independent of gp80 binding. Although vIL-6 is expressed at high levels during lytic replication, latently infected B cells express small amounts that stimulate IL-6 receptors in an autocrine and paracrine manner to provide growth signals to infected plasmablasts. Infected B cells also secrete human IL-6, due to NF-κB activation, which also binds the IL-6 receptor and promotes growth and survival of other B cells. In Castleman’s disease, an increase in the levels if human IL-6 and viral IL-6 is associated with many of the clinical symptoms of the disease.
In healthy immunocompetent hosts, HHV-8 infection is usually asymptomatic, due to restriction of virus to latently infected cells. Reactivation to replenish viral reservoirs and promote transmission to new hosts occurs periodically. When the immune system becomes dysfunctional, such as in HIV infection, immune surveillance by T cells that limits reactivation of virus is compromised. This results in increased levels of replication and new infections. Larger numbers of infected B cells in lymph node follicles can promote abnormal levels of polyclonal B cell proliferation via cytokine stimulation, particularly IL-6, resulting in lymph node enlargement (lymphadenopathy).
Polyclonal B cell proliferation associated with Castleman’s disease is mediated by increased levels of IL-6. Immune dysfunction results in increased reactivation of latent virus reservoirs which in turn increases levels of viral latent infected cells as well as lytic replication. Latently infected plasmablasts that localise to the mantle zone produce vIL-6 as well as human IL-6. Although human IL-6 is a more potent activator of the IL-6 receptor, vIL-6 is secreted at higher levels during lytic infection and can also activate endothelial cells via gp130 binding. In Castleman’s disease, increased levels of human IL-6 and often vIL-6 is detectable in plasma, as well as increased HHV-8 viral load. Increased proliferation of antibody producing plasma cells that accumulate in the interfollicular areas is also mediated by human IL-6. Activated endothelial cells produce VEGF that stimulates angiogenesis and further production of human IL-6.
Endothelial cells are an additional source of human IL-6. Infected plasmablasts and B cells that are in the lytic phase of viral replication produce vIL-6 that activates endothelial cells in lymph node capillaries. Endothelial cells do not express the full human IL-6 receptor, however, they do express gp130. They can therefore be stimulated by IL-6. vIL-6 activated endothelial cells produce vascular endothelial growth factor (VEGF) which in turn promotes angiogenesis and human IL-6 secretion by endothelial cells. Elevated systemic levels of IL-6 are associated with many of the symptoms of Castlemans’s disease, such as fever, malaise, wasting, lymphadenopathy, splenomegaly, hepatomegaly, hypoalbuminaemia, cytopaenia, polyclonal hypergammaglobulinaemia and hyponatraemia.