HHV-8, also known as Kaposi sarcoma-associated herpesvirus (KSHV), is a gamma herpesvirus primarily transmitted through saliva. The virus initially replicates in epithelial cells of the oropharynx and subsequently targets B cells which is a primary viral reservoir. Infection of B cells usually results in viral latency characterised by minimal viral gene expression. Hence these cells are not readily detectable by immune surveillance. Trafficking of infected B cells to lymphoid tissues allows additional B cells to be infected when the lytic replication cycle is triggered. Latently infected B cells can disseminate to other parts of the body via the blood. HHV-8 also has the ability to infect endothelial cells potentially causing a malignancy to develop. Lytic infection of B cells in the oropharynx may promote infection of epithelial cells and shedding of virus into saliva for potential transmission to other hosts. Latently infected B cells remain undetected in the body for long periods of time and the virus is therefore present lifelong. HHV-8 infection is usually asymptomatic when the immune system is intact.
HHV-8 can use a variety of receptors to gain entry into target cells that are primarily B cells but also epithelial and endothelial cells. The majority of B cells are latently infected and contain episomal copies of viral DNA in the nucleus which expresses a minimal number of viral genes needed to maintain the viral episomes and prevent activation of the lytic cycle. The lytic cycle is activated by external events such as immune activation of the B cell via BCR stimulation or interaction with CD4+ helper T cells. Latent viral proteins inhibit the activation of the B cell, however, periodic reactivation of infected B cells does occur to promote transmission to other hosts. Additional genes transcribed during lytic replication also interfere with anti-viral immunity involving both innate and adaptive responses.
A common manifestation of HHV-8 infection, when the immune system is compromised, is the development of malignant lesions in the skin, although involvement of mucosal or visceral sites are also possible. It is thought that these lesions develop when vascular endothelial cells in skin capillaries become infected with HHV-8. This may occur by direct infection of capillary endothelial cells or via recruitment of circulating infected endothelial progenitor cells to the vasculature. In immunocompetent individuals, HHV-8 infection is usually asymptomatic, since virus replication is controlled. The virus escapes detection by existing in latent form, however, if HIV infection occurs or immunosuppressive therapy is introduced, reactivation of latent virus is increased leading to increased infection of endothelial cells.
Infection of endothelial cells leads to their transformation and proliferation. Invasion of the subendothelial cell layer, such as the dermis of the skin, occurs. Proliferation is mainly driven by cytokine stimulation of latently infected cells in a paracrine manner. Viral cytokines such as vIL-6, a homologue molecule of human IL-6, stimulates the production of VEGF. Viral IL-6, produced by latent and lytically infected cells, is able to stimulate the gp130 chain of the IL-6 receptor and results in modulation of gene transcription. The viral GPCR, a constitutively active homologue of the IL-8 receptor, is expressed in lytically infected cells and also alters intracellular signaling pathways to promote cell transformation and cytokine production. The secretion of VEGF is a primary driver of endothelial cell proliferation via the VEGF receptor. Most of the proliferating cells are latently infected with HHV-8 and develop into characteristic spindle cells.
The formation of a Kaposi sarcoma lesion is due to the increased proliferation of latently infected spindle cells. This is driven by low levels of HHV-8 lytic replication in some cells resulting in the production of cytokines, particularly VEGF and vIL-6. VEGF promotes additional angiogenesis that supplies oxygen and nutrients to the tumour cells. Increased vascularisation and trapping of extravasated red cells in spaces between the spindle cells leads to the characteristic red colour of the lesions. Infiltration of immune cells such as T cells, plasma cells and macrophages, is also a consequence of chemokine release from lytic infected cells. Viral chemokines that are homologues of human CCL1,-2 and -3 contribute to the chemotaxis of immune cells to the site of the lesion.
Kaposi sarcoma lesions develop in the skin at late stages of HHV-8 reactivation following a failing of the immune system to control virus replication. Dissemination of virus produced by increased lytic replication promotes the development of additional lesions which may also be due to increased infection of circulating endothelial stem cells. Malignancies can also develop at mucosal sites or in other organs. Spindle cells do not appear to metastasise to other sites, rather new lesions develop following free virus infections of endothelial cells or recruitment of infected endothelial cells to the vasculature.