Measles virus is transmitted between humans by aerosal inhalation or contact with respiratory secretions. The main target cells are immune cells such as T and B cells, macrophages and dendritic cells that express CD150 (or SLAM) which serves as an entry receptor. CD46 expressed on most cells can also be used by some wild-type strains, but mainly vaccine strains. Measles virus infects epithelial cells using nectin-4. Endothelial cells and neurons are also infectable, but the entry receptors are unknown. It is thought that the first cells infected in the lungs are alveolar macrophages and dendritic cells that transport virus to regional lymph nodes where T and B cells become infected. Dissemination to other sites including spleen, lymphatic tissue, liver, thymus, skin and lungs follows. The characteristic skin rash is immune-mediated due to infection of dermal capillary endothelial cells and immune complex formation. Measles virus can also penetrate the brain, but is usually controlled. Infection of pulmonary epithelial cells permits transmission to other hosts.
There are three potential routes of entry of measles virus into the brain. Since the virus can infect neurons it has been proposed that access to the brain via nerve bundles in the olfactory bulb may occur. Alternatively, the virus can replicate in capillary endothelial cells and thus may infect brain capillaries and release viral particles directly into the brain parenchyma. Thirdly, infection of monocytes in peripheral blood may allow transport of virus directly across the blood-brain barrier since monocytes periodically transmigrate into the brain and differentiate into resident perivascular macrophages or microglial cells.
Since measles virus can infect and spread through neurons it is possible that the virus may access the brain parenchyma by trans-synaptic migration along the nerve bundles in the olfactory bulb. Although a unique receptor on neurons remains to be identified, it may be possible for measles virus to penetrate olfactory neurons located in the nasal epithelium. Following penetration of a neuron, measles virus can migrate along a nerve bundle via cell-to-cell spread and ultimately enter the brain parenchyma. This is thought to be mediated by microfusion events between the axon and dendrites of adjacent neurons involving viral fusion proteins (F proteins) and membrane proteins (neurokinin-1) expressed on the surface of neurons.
Bone-marrow derived monocytes are recruited to the brain where they mature into resident tissue macrophages (perivascular macrophages) or specialised brain macrophages (microglial cells). It is possible that measles virus can infect peripheral blood monocytes through the CD150 receptor. Some of these infected cells may enter the brain via the post-capillary venules (by diapedesis) and thereby transport measles virus across the blood-brain-barrier. It is unlikely that virus particles can directly penetrate the brain because of the blood-brain barrier. Tight-junctions between capillary endothelial cells and the presence of a basement membrane prevents diffusion of large molecules into the brain.
Although the receptor remains to be identified, measles virus can replicate in endothelial cells lining blood vessels. It is therefore possible that replication of measles virus in endothelial cells of brain capillaries may allow infectious virus particles to bud directly into the brain parenchyma.
Measles virus potentially gains access to the brain either via the trans-synaptic spread through nerve bundles in the olfactory bulb, release of virus from infected brain capillary endothelial cells or transmigration of infected monocytes across the blood-brain barrier. Once measles virus has penetrated the brain, primary target cells include perivascular macrophages, microglial cells and neurons. Infection of neurons does not result in budding of virus particles from the cell membrane and cell death. Virus can however spread between neurons in a cell-to-cell manner although this process takes place very slowly. Often brain complications of latent measles virus only manifest much later following primary infection.
Mouse models of measles virus infection of the brain have shown that immune control of infected neurons is dependent on IL-12, CD4+ helper T cells and IFN-γ. Infected neurons secrete chemokines (CCL5 and CXCL10) that attract T cells and antigen presenting cells (microglial cells and macrophages). Antigen presenting cells secrete IL-12 that promotes the differentiation of Th1 CD4+ helper T cells that secrete IFN-γ. Neurons express receptors for IFN-γ that induces innate anti-viral responses. Neurons do not express HLA class I receptors but expression can be induced by IFN-γ stimulation. However, CD8+ cytotoxic T cells do not kill infected neurons most likely due to the immune privilege mechanisms that protect neurons from immune damage. Usually measles virus infection of the brain is controlled, but severe encephalitis can occur where neurons are damaged by excessive activation of immune cells and pro-inflammatory cytokine production.
Acute infection with measles virus is associated with a strong Th1 cell-mediated immune response which resolves infection in the periphery. However, during acute infection and for a number of weeks following clearance of measles virus, individuals have increased susceptibility to secondary infections. This is partially due to lymphopenia that occurs during acute infection, most likely due to loss of immune cells due to infection and syncytia formation (giant cells), however cell numbers soon recover. A switch from Th1 cell-mediated responses to Th2 has been proposed as the reason for the longer lasting immunosuppression. This may be due to a lack of secretion of IL-12 by and an increase in IL-4 and TGF-β production by antigen presenting cells. Infected antigen presenting cells do not produce IL-12. Increased IL-10 secretion by Th2 CD4+ helper T cells and regulatory T cells suppresses Th1 responses and may predispose individuals to secondary infections.
It has been shown that measles virus can spread between neurons in a cell-to-cell manner, but this process occurs very slowly. Initial penetration of neurons may still depend on a specific receptor which remains to be identified. However, after infection of a neuron, virus can then spread to adjacent neurons at the synapse from the dendrite to the axon (retrograde). The transport of virus from infected neurons to adjacent uninfected neurons is thought to be mediated by microfusion events at the cell membrane where viral F proteins bind neurokinin-1 receptors expressed on neurons which facilitates membrane fusion. Viral ribonuclear protein complexes containing viral RNA accumulate at the cell membrane and can pass through to the adjacent cell. In neurons, there is incomplete assembly of virus particles at the membrane and budding of virus does not occur. This prevents antibody detection of free virus and promotes viral latency in the brain.