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Cell and tissue tropisms of Chikungunya virus and its dissemination to the central nervous system

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Chikungunya virus (CHIKV) has been responsible for a massive outbreak in the Indian Ocean region in 2005–2006. CHIKV typically induces a benign disease characterized by fever, arthralgia, myalgia and rash. Severe cases with CHIKV-associated central nervous system (CNS) symptoms have also recently been described, notably in neonates. We have developed animal models for the mild and severe forms of the disease. Wild type (WT) mouse neonates are susceptible to CHIKV infection following intradermal inoculation, and neonatal disease severity is age-dependent. In contrast to WT adult mice, those with a partially abrogated type-I IFN pathway (IFN-α/βR$^{+/-}$ mice) develop a mild disease closely mimicking benign human Chikungunya disease. In contrast, adult mice with a totally abrogated type-I IFN pathway (IFN-α/βR$^{-/-}$ mice) develop a severe and lethal infection. In these mouse models, infection leads to viremia and CHIKV is recovered in fibroblasts from muscles, joints and skin. This cell and tissue tropism is consistent with symptoms in infected humans and confirmed by observations in patients biopsy samples. In adult IFN-α/βR$^{-/-}$ mice as well as in neonates, CHIKV infection causes a severe disease associated with high viral load in serum and peripheral tissues and dissemination to the CNS. CHIKV is not detected at the brain microvessels and parenchyma, but found in choroid plexus, ependymal and meningeal cells. In agreement with these findings, CHIKV is detected in the CSF in human patients with severe human Chikungunya disease associated with CNS symptoms. Thus, in contrast to what is observed for American encephalitic alphaviruses, CHIKV does not appear to be genuinely encephalitogenic and is associated with reversible CNS symptoms in man. This is in line with a virus that does not invade the brain parenchyma nor infect neurons. Leptomeningeal cells are, as fibroblasts, of mesenchymal origin and exhibit features similar to those of peripheral fibroblastic connective tissue capsules. Leptomeningeal cells also play an "envelope" function and form an interconnected multicellular network that acts as a regulatory interface between cerebrospinal fluid and the surface of the brain as well as between arterioles of the Virchow-Robin spaces and the surrounding brain tissue. These observations will be instrumental to understand the short- and long-term consequences of the infection of brain envelopes.