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Pre-conception Natural CMV-Specific Immunity Protects CD4+ T Cell-Depleted Rhesus Macaques from Congenital Infection after Rhesus CMV Reinfection

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Congenital CMV (cCMV) is the leading infectious disease cause of neurological defects in the newborn. While primary human CMV infection during pregnancy is associated with a 20 to 70% risk of intrauterine transmission, vertical transmission rates in CMV-seropositive women due to CMV reactivation or reinfection(s) are not well defined. Furthermore, the degree of protection conferred by natural immunity remains controversial. We recently reported on a novel nonhuman primate model of cCMV during primary infection in rhesus macaques. In this model, intravenous rhesus CMV (RhCMV) inoculation of CD4+ T lymphocyte-depleted CMV-seronegative pregnant females led to 100% placental CMV transmission and 83% fetal loss. To investigate the effect of pre-conception natural immunity on placental transmission and cCMV after CMV reinfection, five pregnant CMV-seropositive rhesus macaques were CD4+ T lymphocyte depleted at the end of the first trimester and one week later intravenously inoculated with RhCMV variants including strain UCD52 and FL-RhCMVΔRh13.1/SIVgag, a wild-type-like RhCMV clone with SIVgag inserted as an immunological marker. Following reinfection, transient, low-level RhCMV viremia was observed in 2 of 5 (40%) macaques, and a >10-fold increase in RhCMV shedding in the urine or saliva was detected in all five macaques. Amniotic fluid transmission of RhCMV was only detected in one of 5 (20%) dams after reinfection. Reinfection was also associated with a two-fold or greater boosting of circulating RhCMV-specific CD8+ T lymphocyte responses targeting the immediate early proteins. SIVgag-specific CD8+ T lymphocyte responses and shedding of SIVgag DNA in the saliva was observed in one of 3 macaques reinfected with FL-RhCMVΔRh13.1/SIVgag. The reduction in placental transmission and absence of adverse fetal sequelae after non-primary infection as opposed to primary infection indicates a protective role for preconception maternal CMV-specific CD8+ T lymphocyte and/or humoral immunity against cCMV infection in CD4+ T lymphocyte-depleted dams.

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Cytomegalovirus Infects the Developing Organ of Corti in a Mouse Model of Virally Induced Deafness.

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CMV is the most common non-genetic cause of SNHL. Pathogenesis of CMV-induced SNHL is still elusive. A key role for CMV infection and loss of spiral ganglion neurons (SGNs) has been identified in a mouse model of i.p. CMV inoculation. In turn, neither infection nor cell death were observed in the Organ of Corti (OC). This result is in contrast with pathology of infected infants. Here we investigate CMV infection in the developing OC of newborn mice and the related hearing outcomes.
Methods: Pups were inoculated i.p. with CMV (750 PFU) on the day of birth. Auditory system of newborn mice parallels that of an early 2nd trimester human fetus. CMV load and distribution in the inner ear were assessed by qPCR and histochemistry. Loss of outer and inner hair cells (OHCs, IHCs) and SGNs was investigated at multiple time-points post-infection. Whole mount technique was employed for OC analyses. Hearing was evaluated using ABR in 7 week-old mice.
Results: CMV was detected in the inner ear as early as 2 dpi, with viral load peaking at p16-21 and viral particles still measurable at p50. Of note, OHC, IHCs, and supporting cells (SCs) in the OC, as well as SGNs, showed infection. Quantitative assessment of the OC and SG identified substantial loss of OHCs and SGNs. Accordingly, infected mice displayed increased hearing thresholds at multiple frequency tone stimuli.
Conclusions: CMV inoculated i.p. in newborn mice can infect the inner ear, where HCs and SCs in the OC and SGNs show susceptibility to viral infection. This associates with progressive cell loss and substantial hearing impairment. Close similarities with CMV-induced SNHL in human infants, including hematogenous spread of CMV to the inner ear and viral involvement of the OC, support the validity of this model for preclinical investigation of CMV-related SNHL.

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