Maternal CD4+ T cell responses are critical for fetal survival following acute cytomegalovirus infection in a novel rhesus macaque model of transplacental cytomegalovirus transmission

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Introduction

Transplacental transmission of human cytomegalovirus (CMV) is the leading infectious cause of brain damage in infants worldwide, accounting for approximately 25% of all infant hearing loss. In this study, we sought to develop a nonhuman primate model of congenital CMV transmission to define the maternal immune responses that are critical to CMV transmission and fetal outcome.

Methods

To develop a nonhuman primate model of congenital CMV infection, four rhesus CMV (rhCMV)-seronegative pregnant rhesus monkeys were inoculated intravenously with rhCMV during first trimester one week after systemic administration of an anti-CD4 depleting antibody. The fetal outcome and maternal immune responses were compared to that of three rhCMV-seronegative, immune competent females infected at the same gestational time point, as well as three rhCMV-seropositive pregnant rhesus monkeys who were depleted of CD4+ T cells at the end of first trimester. Transmission outcome was determined by amniotic fluid, placental, and infant plasma and mucosal fluid rhCMV qPCR, as well as placental immunohistochemistry. Maternal rhCMV-specific T cell and antibody responses were assessed throughout acute and chronic infection.

Results:

In the CD4+ T cell-depleted group, 3 females underwent spontaneous abortion 3 weeks following rhCMV inoculation, whereas the 4th female bore a full-term infant. In contrast, all monkeys in both the immune competent, acutely rhCMV-infected group and the CD4+ T cell-depleted, chronically rhCMV-infected females carried their infants to term, indicating neither rhCMV infection nor CD4+ T cell-depletion alone resulted in high abortion rates. Congenital rhCMV infection was confirmed in the CD4+ T cell-depleted monkeys by immunohistochemical and PCR detection of rhCMV in 2 placentas and aborted fetuses, in addition to neutropenia and detectable rhCMV DNA in the saliva and urine of the surviving infant. In contrast, rhCMV transmission was only confirmed in 1 of 3 infants born to the immune competent, acutely rhCMV-infected monkeys by detection of CMV in urine at birth. While the kinetics and avidity of the CMV-binding IgG responses were similar between the immune competent and CD4+ T cell-depleted groups, the functional CMV neutralizing antibody

response was considerably delayed in the CD4+ T cell depleted group at the time of congenital CMV transmission and fetal loss.

Conclusion

Maternal CD4+ T cell responses are critical to fetal survival following primary maternal CMV infection, potentially due to their contribution to the development of CMV-neutralizing antibody responses. This nonhuman primate model for congenital CMV transmission provides an important tool for studies of maternal CMV vaccine candidates.