Research Number: 3000006122
Title: Prenatal Determinants of Congenital Human Cytomegalovirus Disease: Correlation of ex vivo Modeling with Prenatal Clinical Samples
Principal Investigator: Prof. Dana Wolf
Institute: Hadassah Hebrew University Medical Center
Year (Start): 2010 Year (End): 2012

Background: Human cytomegalovirus (HCMV) is the leading cause of congenital infection, associated with severe birth defects and intrauterine growth retardation. The mechanism of HCMV transmission via the maternal-fetal interface is largely unknown, and there are no animal models for HCMV. The initial stages of infection are believed to occur in the maternal decidua.

Research Hypothesis: Infection of ex vivo decidual organ cultures with low-passage clinical strains will reliably model early events in the maternal-fetal interface during intrauterine transmission.

Aims: Characterize viral and tissue determinants of HCMV transmission and pathogenesis in the maternal-fetal interface; Specific aims:

Establish ex vivo model of HCMV transmission in the maternal-fetal interface.
Study the kinetics of HCMV infection in the novel ex vivo decidual organ culture model
Evaluate the effect of new antiviral agents in the decidual milieu

Methods: We have established and employed a novel human decidual organ culture, using both clinically- and laboratory-derived HCMV strains.

Results: Viral spread in the tissue was demonstrated by progression of infected-cell foci with a 1.3 to 2-log increase in HCMV DNA and RNA between 2-9 days post infection, expression of immediate-early and late proteins, appearance of typical histopathological features of natural infection, and a dose-dependent inhibition of infection by ganciclovir and acyclovir. HCMV infected a wide-range of cells in the decidua, including invasive cytotrophoblasts, macrophages, endothelial, decidual, and dendritic cells. Cell-to-cell viral spread was revealed by focal extension of infected-cell clusters, inability to recover infectious extracellular virus, and high relative proportions (88-93%) of cell-associated viral DNA. Intriguingly, neutralizing HCMV hyperimmune globulins exhibited inhibitory activity on viral spread in the decidua even when added at 24 hrs post infection—providing a mechanistic basis for their clinical use in prenatal prevention.

Conclusions: The ex-vivo infected decidual cultures present a unique insight into patterns of viral tropism and spread, defining initial stages of congenital HCMV transmission, and can serve to evaluate the effect of new antiviral interventions within the maternal-fetal interface milieu.

Key words: Congenital HCMV infection,; Maternal-fetal transmission; Placenta; Maternal decidua
Publications associated with the project:
