

Oral presentation

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Activation of PPAR γ by human CMV for de novo replication impairs invasiveness of cytotrophoblast from early placenta

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Human cytomegalovirus (HCMV) contributes to pathogenic processes in immuno-suppressed individuals, in fetuses and in neonates. Infection during pregnancy is known to cause miscarriages and low-birthweight newborns and we know that in this case infection of the placenta precedes transmission to the fetus. HCMV was shown to benefit from inflammatory conditions by using the cyclooxygenase-2 (Cox-2)-dependent prostaglandin pathway for transcription of the essential immediate-early gene IE2. The fact that Cox-2 activation could serve as a source of ligand for the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR γ), which is known to play a pivotal role in controlling human trophoblast invasion, led us to hypothesize that HCMV could impair placentation through activation of PPAR γ .

By using reporter gene activation assays and confocal microscopy in the presence of specific antagonist, we provide the first evidence that PPAR γ was activated in infected cells. We demonstrated that PPAR γ antagonist dramatically impaired IE2 mRNA expression and virus production and that the major immediate-early promoter (MIEP) contained PPAR response elements (PPRE) able to bind PPAR γ , as assessed by electrophoretic mobility shift and chromatin immunoprecipitation assays. By using an *in vitro* model of primary culture of extravillous cytotrophoblasts isolated from early placentas we demonstrated that HCMV could dramatically impair cytotrophoblasts invasiveness and migration processes through activation of PPAR γ . Our data provide new clues to explain how

infection during the first trimester of pregnancy could impair implantation, placentation and therefore embryonic development.