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Oral presentation

Activation of PPARγ 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 (PPARγ), 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 PPARγ.

By using reporter gene activation assays and confocal microscopy in the presence of specific antagonist, we provide the first evidence that PPARγ was activated in infected cells. We demonstrated that PPARγ 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 PPARγ, 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 PPARγ. Our data provide new clues to explain how infection during the first trimester of pregnancy could impair implantation, placentation and therefore embryonic development.