ZIKA VIRUS INFECTS CYTOTROPHOBLASTS AND HOFBAUER CELLS IN CHORIONIC VILLI FROM FIRST-TRIMESTER HUMAN PLACENTAS AND DOWNREGULATES CELLULAR MARKERS

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Zika virus (ZIKV), a member of the Flavivirus family is responsible for the recent pandemic in the Americas. Women infected during pregnancy have prolonged viremia and an increased risk of transmitting virus to the fetus, which can lead to devastating birth defects. Intrauterine growth restriction, a placental defect, is often found in cases of congenital ZIKV infection. How ZIKV disseminates from maternal blood to the placenta and reaches the fetus is unknown. We recently reported that ZIKV infects numerous human primary cell types and chorionic villus explants from early gestation human placentas, expressing ZIKV E and NS3 proteins and producing infectious progeny virrions, suggesting two distinct routes of placental transmission. Here, we compared infection in villus explants from human placentas at different stages of development in the first trimester. Consistent patterns of ZIKV proteins were detected in proliferating cytotrophoblasts that reduced expression of Ki67, a proliferation marker. A subset of cytotrophoblasts that went on to populate distal cell columns and anchoring villi produced infectious progeny. Hofbauer cells, or fetal macrophages, in the villus core that bordered proximal cell columns were also infected and downregulated the macrophage markers CD163 and LYVE1. In contrast, in floating villi with intact syncytiotrophoblasts perfused by virus inoculum, Hofbauer cells were rarely infected except near small foci of proliferating cytotrophoblasts. In summary, we identified sites most vulnerable to ZIKV infection ex vivo and suggest that maternal virus infects the placenta in the intervillous blood space and undermines development in early gestation.

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