ZIKA VIRUS INFECTION OF HUMAN ENDOMETRIAL STROMAL CELLS: PROGESTERONE UPREGULATION OF VIRUS REPLICATION AND AXL CELL SURFACE EXPRESSION

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Background: In addition to mosquito bites, Zika virus (ZIKV) is transmitted among humans from mother to foetus, leading to potential severe brain malformations, and by sexual route. These observations highlight the potential importance of ZIKV infection of cells of the female reproductive tract (FRT) in both vertical and horizontal spreading of the infection.
Methods: We have investigated the potential capacity of ZIKV to infect primary human endometrial stromal cells (HESC) isolated from tissue biopsy; in addition, we attempted to infect the human endometrial cell line T-HESC stimulated or not with progesterone and cAMP for 7 days to induce its decidualization (dT-HESC). The cells were infected with either the reference African MR766 or the recent Brazilian INMI-1 strains (moi: 1). Viral expression was analyzed by indirect immunofluorescence (IIF) after staining with either anti Zika-dsRNA or anti-Zika envelope (E) mAbs. ZIKV subcellular localization was defined by fluorescence microscopy with anti-vimentin and anti-calreticulin mAbs. Infectious progeny virion production in culture supernatants was measured by a standard plaque forming assay (PFA) in Vero cells. The cell surface expression of the known ZIKV entry cofactors AXL and MER was evaluated by mAb staining and FACS analysis.
Results: Both HESC and T-HESC were productively infected with MR766 or INMI-1 resulting in ca. 80 and 8% cells positive for anti-ZIKV mAbs, respectively. However, both viral strains replicated with comparable efficiently in terms of production of infectious virions as determined by PFA. ZIKV E-protein co-localized with calreticulin in the lumen of the endoplasmic reticulum, while viral dsRNA showed a punctate staining co-localized with vimentin dense structures. Interestingly, a 2-fold increase of the % of infected cells was observed by IIF in dT-HESC vs. control T-HESC whereas the efficiency of virus replication in dT-HESC increased up to 100-fold when analyzed 144 h post-infection. The increased virus replication observed in dT-HESC was associated with the upregulation of AXL, but not of MER, on their cell surface.
Conclusions: As both primary and immortalized HESC are highly permissive to ZIKV infection and replication in vitro, particularly after their progesterone-mediated