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Zika virus infection of fetal endothelial cells: A key difference between Zika virus and other related viruses

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Although *bona fide* entry receptors for flaviviruses remain unknown, many cell surface-expressed molecules contribute to infection of these viruses as entry cofactors, including C-type lectins and the TIM and TAM family members of the phosphatidulserine (PS) receptors. Among these, we observed that TIM-family member TIM1 is efficiently used by most flaviviruses, but TAM-family member AXL is differentially used by various flaviviruses. Namely, when viruses are produced in mammalian cells, Zika virus (ZIKV), but not other flaviviruses such as dengue virus (DENV) or West Nile virus (WNV), can utilize AXL to infect cells. It remains unclear why ZIKV, but not other closely-related pathogenic flaviviruses, causes congenital defects. We show that human umbilical vein endothelial cells (HUVEC), which are fetal endothelial cells, express only AXL among the major flavivirus entry cofactors, and that ZIKV infects HUVEC and produce progeny viruses with far greater efficiency than closely-related DENV or WNV. ZIKV infection of HUVEC is primarily mediated by AXL; it is effectively inhibited by an anti-AXL antibody and AXL-KO HUVEC do not support ZIKV infection. Furthermore, ZIKV, but not DENV or WNV, can infect AXL-HEK293T in an AXL-dependent manner. Consistent with these observations, only ZIKV, but not WNV or DENV, can bind the AXL ligand Gas6. Our data suggest that the unique ability of ZIKV to infect fetuses and cause congenital malformations may derive, at least in part, from its capacity to efficiently utilize AXL and infect fetal endothelial cells in direct contact with the fetal circulation.

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