Abstract

The human hemochorial placenta is a structure formed by the invasion of cytotrophoblasts into the uterus. Previous studies from our laboratory have demonstrated a role for heparan sulfate proteoglycans (HSPGs) and their binding proteins in interactions between human trophoblastic and uterine cell lines in vitro. In this study, expression of both mRNA and protein of a novel, cell surface, heparin/heparan sulfate interacting protein (HIP), by human trophoblastic cell lines-i.e., JAR, JEG, and BeWo-and by human cytotrophoblast was examined throughout gestation. Immunohistochemistry of the human fetal-maternal interface demonstrated abundant HIP expression in cytotrophoblast cells, with lesser staining in syncytiotrophoblast and little or no staining in surrounding stromal or decidual cells. Staining with antibodies to the basement membrane HSPG, perlecan, demonstrated a pattern of staining complementary to that of HIP. Cytotrophoblasts in the uterine stroma, not affiliated with attached villi, displayed a less intense deposition of perlecan. In vitro binding studies of 125I-perlecan to a 17-amino acid synthetic peptide sequence of HIP, which has a high affinity and specificity for heparin/heparan sulfate, indicates that perlecan binds to the HIP peptide with high affinity (KDapp = 0.6 nM) and in a heparin-inhibitable manner. Furthermore, HIP antibodies inhibited by 61-88% in vitro invasion by trophoblasts in assays using primary cultures of normal human cytotrophoblasts. Consistent with this was the observation that immunohistochemically detectable HIP expression was greatly reduced in pre-eclamptic cytotrophoblasts, a condition in which trophoblast invasion is abnormally shallow. It is suggested that HIP potentiates human cytotrophoblast interactions with HSPGs, in vivo, and facilitates trophoblast invasion processes.