ANTIANGIOGENIC EFFECT OF SOLUBLE VEGFR-1 IN PLACENTAL ANGIOGENESIS

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Differential splicing of the flt-1 mRNA generates soluble variant of VEGF receptor-1(sVEGFR-1/sFlt-1). The action of vascular endothelial growth factor (VEGF) is antagonised by sVEGFR-1. This soluble receptor regulates the level of free VEGF which is critical in ensuring physiological angiogenesis. In this study, we tested the hypothesis that placental angiogenesis is tightly modulated by the release of sVEGFR-1 and its expression is upregulated by hypoxia. Immunolocalisation studies showed progressively intense staining for sVEGFR-1 and VEGF in the trophoblast of placental villous explants throughout gestation. Endothelial cell migration studies using a modified Boyden\'s chamber showed a significant increase in cell migration in response to VEGF which was significantly attenuated in the presence of exogenous sVEGFR-1.

Furthermore, stimulation of endothelial cells with VEGF led to adose-dependent increase in the release of sVEGFR-1 as determined by ELISA. Exposure of normal placental villous explants to hypoxia (1% pO2) increased trophoblast expression of sVEGFR-1 when compared with tissue normoxia (5% pO2). In addition, conditioned media from hypoxia treated placental villous explants induced a significant increase in endothelial cell migration which was significantly reduced in presence of sVEGFR-1. This study demonstrates that sVEGFR-1 may regulate placental angiogenesis by controlling the bioavailability of free and active VEGF.

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