Trophoblast Dependent Secretion of Stannocalcin-1 and Interleukin-8 by Endothelial Cells and their Role as Possible Mediators of Spiral Artery Remodelling.

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Extravillous trophoblasts invade into and remodel the maternal spiral arteries (SA) replacing the endothelial cells (EC) and vascular smooth muscle cells (VSMC). The mechanism has not been completely elucidated. Using a 3D vascular spheroid model we have shown that trophoblast conditioned medium (TCM) stimulates the expression of a number of genes including interleukin 8 (IL8) and stanniocalcin-1 (STC-1). IL8 is an inflammatory cytokine that has been associated with angiogenesis while STC-1 is a widely expressed glycoprotein implicated in tumour angiogenesis. The role these two factors have in SA remodelling and how they may interact with each other has not been investigated.

OBJECTIVES

To investigate trophoblast stimulated IL8 and STC-1 secretion by endothelial cells and examine their possible role in regulating vascular smooth muscle cell function.

METHODS

The trophoblast cell line SGHPL-4 was grown in 3D culture and after 72h the TCM harvested. An angiogenic protein array was used to determine the components of the TCM. The human umbilical vein endothelial cell line SGHEC-7 was stimulated with TCM and the secretion of IL8 and STC-1 determined by ELISA. Identification of pathways activated by TCM and responsible for the increased secretion of IL8 and STC-1 were investigated using pharmacological inhibitors. The effect of recombinant IL8 and STC-1 on VSMC migration was determined by time-lapse microscopy.

RESULTS

TCM significantly stimulated the secretion of both IL8 and SCT-1 by endothelial cells (p<0.5). TCM contains a number of growth factors and cytokines including TGFβ, HGF, VEGF and IL1β. Recombinant IL1β significantly stimulated IL8 but not STC-1 secretion by endothelial cells. IL1β stimulation of IL8 secretion was significantly inhibited following inhibition of p38MAPK (p<0.001). IL8 was significantly stimulated following activation of protein kinase C (p<0.05). IL8 in combination with STC-1 stimulate VSMC migration.

CONCLUSION

TCM stimulates the secretion of IL8 and STC-1 by endothelial cells. They may act together to stimulate vascular smooth muscle cell migration; an important process in the remodelling of maternal spiral arteries.