Human umbilical vein endothelium-derived exosomes play a role in foetoplacental endothelial dysfunction in gestational diabetes mellitus

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Abstract

Gestational diabetes mellitus (GDM) characterizes by foetoplacental endothelial dysfunction. Human umbilical vein endothelial cells (HUVECs) from women with GDM show increased L-arginine transport via the human cationic amino acid transporter 1 (hCAT-1). Moreover, expression of endothelial nitric oxide synthase (eNOS) and nitric oxide synthesis are increased. Exosomes are increased in maternal plasma from GDM. We evaluated the role of foetoplacental endothelial exosomes on endothelial dysfunction in GDM. Exosomes were isolated from HUVECs from normal (ExN) and GDM (ExGDM) pregnancies. HUVECs were exposed (8 h) to ExN or ExGDM and used for wound recovery assay (up to 8 h), L-arginine transport, hCAT-1 and eNOS expression and activity, reactive oxygen species (ROS) generation, and 44 and 42 kDa mitogen activated protein kinases (p44/42mapk) and protein kinase B/Akt (Akt) activation. Wound recovery was slower in GDM compared with normal pregnancies and was recovered by ExN. However, ExGDM delayed wound recovery in cells from normal pregnancies. GDM-increased L-arginine transport, hCAT-1 and eNOS expression and activity, and p44/42mapk activation were blocked by ExN, but ExGDM increased these parameters and ROS generation, and reduced eNOS phosphorylation at threonine495 in cells from normal pregnancies. Inhibition of p44/42mapk, but not Akt reversed GDM-increased L-arginine uptake. In conclusion foetoplacental endothelial-released exosomes play a role in the maintenance of a GDM phenotype in HUVECs. It is suggested that ExN and ExGDM cargo are different with differential effects in cells from normal or GDM pregnancies. This phenomenon could contribute to the understanding of mechanisms behind foetoplacental endothelial dysfunction in GDM pregnancies.

Keywords

Exosomes; Diabetes; Endothelium; Arginine; Nitric oxide; Umbilical vein