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Is there a role for exosomes in foetoplacental endothelial dysfunction in gestational diabetes mellitus?

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ABSTRACT

Gestational diabetes mellitus (GDM) is a disease of pregnancy associated with endothelial dysfunction in the foetoplacental vasculature. Foetoplacental endothelial dysfunction is characterized by changes in the L-arginine–adenosine signalling pathway and inflammation. The mechanisms involved in these alterations are suggested to be hyperglycaemia, hyperinsulinemia, and oxidative stress. These conditions increase the release of exosomes, nanovesicles that are generated from diverse cell types, including endothelial cells. Since exosomes can modulate vascular function, they may play an important role in foetoplacental endothelial dysfunction seen in GDM pregnancies. In this review, we summarized current knowledge on the potential role of exosomes in foetoplacental endothelial dysfunction seen in this disease of pregnancy.

1. Introduction

Gestational diabetes mellitus (GDM) is a disease characterized by maternal glucose intolerance first appearing or diagnosed during pregnancy. It is associated with maternal hyperglycaemia, and foetal hyperglycaemia and hyperinsulinemia [1]. Mothers diagnosed with GDM and children born to GDM pregnancies have a higher risk for developing metabolic syndrome, type 2 diabetes mellitus, or cardiovascular disease in later life [2,3]. GDM is associated with endothelial cell activation and dysfunction in both the microvasculature and macrovasculature of the placenta (i.e., foetoplacental vasculature) [4,5]. Endothelial cell activation is characterized by a proinflammatory, procoagulant state of the endothelial cells lining the lumen of blood vessels and is associated with increased expression of adhesion molecules [6–10], such as intracellular adhesion molecule type 1 (ICAM-1) as reported in GDM [11,12]. Also, a functional disassociation between the synthesis and bioavailability of nitric oxide (NO), a key vasodilator in the foetoplacental vasculature, is reported in this disease [5]. Endothelial activation is seen in early stages of vascular diseases such as atherosclerosis [13]. Thus, involvement of endothelial activation in the pathophysiology of foetoplacental endothelial dysfunction in GDM pregnancy is likely. Along with hyperglycaemia, inflammation, and oxidative stress in GDM-associated endothelial dysfunction, we here focus on the involvement of endothelial-derived exosomes in endothelial dysfunction and activation in the foetoplacental vasculature in GDM pregnancies.

2. Foetoplacental endothelial (dys)function in healthy pregnancy and GDM

The placenta is the organ responsible for maternal-foetal

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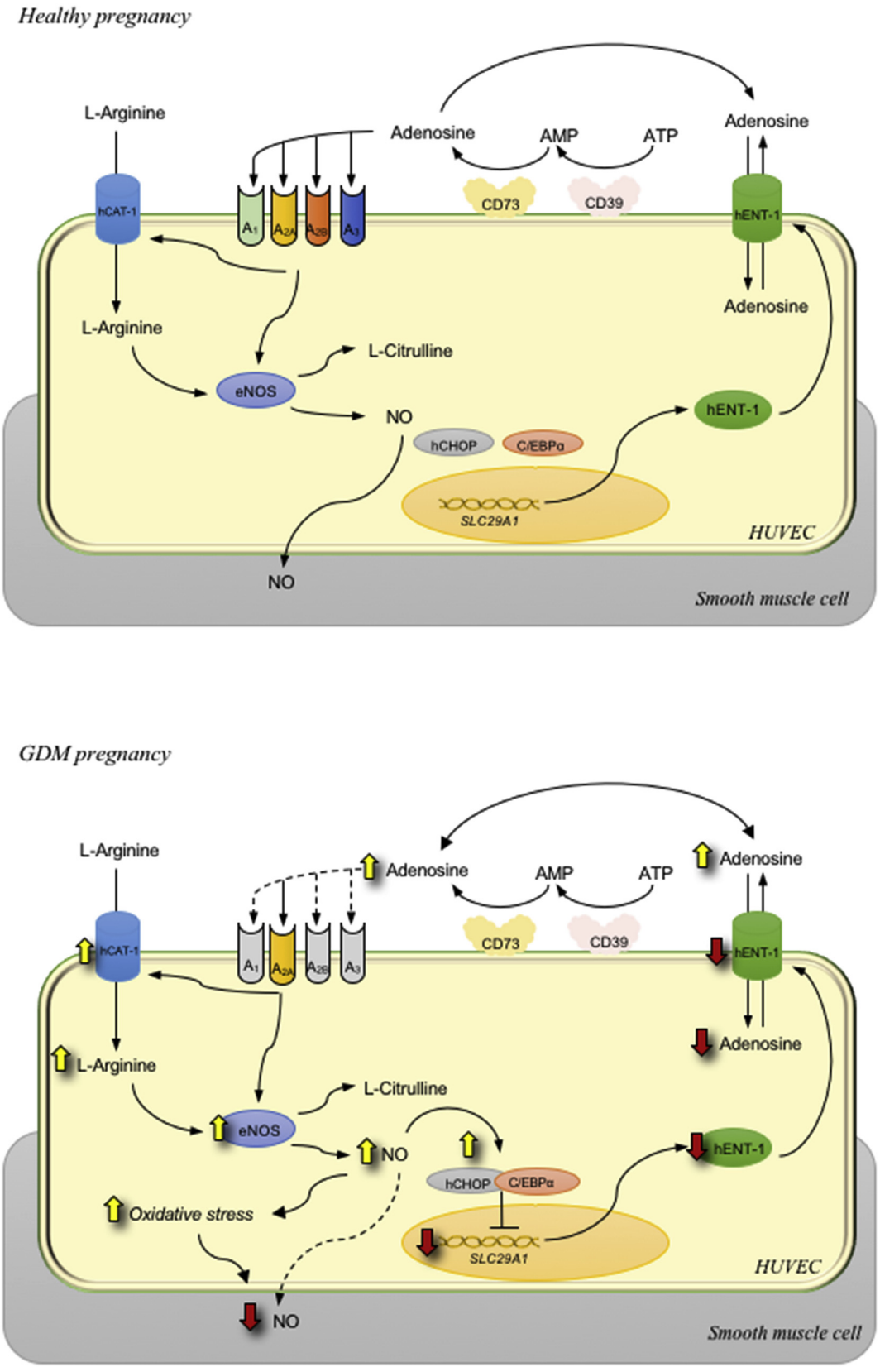

Fig. 1. Adenosine/L-Arginine/Nitric Oxide (ALANO) signalling pathway in HUVECs from normal and gestational diabetes mellitus pregnancies. A, In HUVECs from normal pregnancies (healthy pregnancy), transport of L-arginine is mainly mediated by the human cationic amino acid transporter 1 (hCAT-1). L-Arginine is used by the endothelial nitric oxide synthase (eNOS) for the generation of L-citrulline and nitric oxide (NO), which reaches the vascular smooth cells to cause vasodilation. hCAT-1 and eNOS activity is modulated by extracellular adenosine through the activation of A_1, A_{2A}, A_{2B}, and A_3 adenosine receptors. Adenosine is generated from ATP/ADP catabolism via the CD39/CD73 axis, and its extracellular concentration is kept in physiological ranges by its transport into the cell mediated by the human equilibrative nucleoside transporter 1 (hENT1). The physiological