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Placental endothelial dysfunction in preeclampsia - The role of the ion channel Piezo1 and its fine-tuning by fatty acids

Summary

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Supervisors:	Prof. Dr. Christian Wadsack Dr. Hanna Allerkamp
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between August 03, 2022 00:00 and September 20, 2022 23:59 (Europe/Zurich)

Description

Background:

Preeclampsia (PE) is a hypertensive pregnancy disorder and a leading cause for maternal and perinatal death. Pathophysiologically, PE is thought to be evoked by impaired placental adaptation of the uterine blood vessels to pregnancy, which creates oxidative stress in the placenta, leading to the release of antiangiogenic and pro-inflammatory factors into the maternal circulation. While placental endothelial dysfunction is well described in PE, the underlying mechanisms still remain poorly understood and treatment options are limited (1).

Piezo1 is a mechanosensitive, Ca^{2+} permeable ion channel recently identified in the membrane of endothelial cells (2). It is involved in important vascular functions such as mediating vasodilation via nitric oxide, maintenance of the endothelial barrier, and vascular remodelling (3-5), all of which can be impaired in PE placentae. Furthermore, Piezo1 seems to play a role in adaptation of the utero-placental arteries to pregnancy (6), which were shown to change their reactivity to shear stress and flow (7).

Because Piezo1 is embedded in the phospholipid bilayer of the cell membrane, the composition of those lipids can fine-tune its function. It was shown that different fatty acids can be incorporated into the cell membrane and subsequently change Piezo1 mechanical response (8). During pregnancy, the maternal lipid metabolism adapts to the special metabolic needs. In PE, it was already shown that the concentration of various fatty acids in the maternal serum is altered (9). Furthermore, our lab already demonstrated that both, fatty acid availability and placental metabolism, determine fatty acid availability in the fetal circulation (10). However, the involvement of Piezo1 in placental endothelial function and possible regulating mechanisms via fatty acids in PE have not been investigated yet.

Hypothesis and Objectives:

We hypothesise that Piezo1 is a key player interlinking the placental lipid environment with endothelial function in normal and PE pregnancies. We aim to investigate the influence of the fatty acid profiles in normal and PE human pregnancies as well as the placental fatty acid transfer on placental endothelial cells. Subsequently, we aim to link these findings to Piezo1 regulated endothelial function. We expect that differences in fatty acid profiles will change endothelial cell membrane characteristics and thereby alter Piezo1 response in PE.

Methodology:

Placental tissue from normal and PE pregnancies will be collected at term after delivery. Lipid profiles will be characterized by lipidomics in a) maternal blood, b) cord blood, and c) the membrane fraction of isolated primary placental endothelial cells. These cells are isolated and collected on an ongoing basis and well established in our lab. To investigate fatty acid transfer of candidate targets shown to influence Piezo1 regulation, *ex vivo* placental perfusion of normal and PE term placentae will be conducted. This technique allows investigation of placental fatty acid transfer, uptake and metabolism and has already been established in normal placentae in our lab (10).

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Results will be used to inform subsequent *in vitro* assays using primary placental endothelial cells to investigate a) membrane properties (e.g. bending stiffness by atomic force microscopy), b) fatty acid influence on mechanically mediated Piezo1 regulation (e.g. calcium influx and channel activity by microfluidics and patch-clamping) and c) Piezo1 downstream functions (e.g. angiogenesis, nitric oxide production, and endothelial barrier integrity). Fatty acid and Piezo1 influence on placental chorionic artery reactivity will be investigated by myography.

Overall, this will provide a comprehensive characterization of the involvement of Piezo1 in placental endothelial dysfunction in PE and its fine-tuning via fatty acids. The general role of Piezo1 in the placental endothelium and other possible regulatory mechanisms are currently investigated in an ongoing project in our group, so that both projects will complement each other and thereby help to identify new treatment possibilities for PE in the future.

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