Flow-mediated modulation of villous trophoblast physiology

Summary

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Supervisor:	PD Dr. Martin Gauster
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between July 15, 2019 00:00 and September 15, 2019 23:59 (Europe/Zurich)

Description

Background:

During human gestation the placenta fulfils as a temporal villous organ a wide spread panel of pregnancy maintaining functions. Pregnancy disorders, such as severe early-onset preeclampsia and intrauterine growth restriction have been associated with defective invasion of fetal trophoblast cells into the uterine wall, involving insufficient uterine spiral artery remodelling very early in human gestation. The secondary pathologic effect of deficient uterine spiral artery conversion is that the maternal blood enters the intervillous space of the placenta at a greater velocity than normal, leading to jet-like streams surrounded by turbulences. This provokes significant aberrations in hemodynamic forces exerted on the epithelial surface of placental villi, which in turn may have serious consequences on placenta development and function. The relationship between the intensity of fluid shear stress and the biological response of the epithelial-like villous trophoblast layer, which covers placental villi, is not completely understood and merits more in-depth investigation of how placental phenotype and physiology are regulated by hemodynamic forces.

Hypothesis and objectives:

Establishment of intervillous blood flow is key for villous trophoblast phenotype and function in human first trimester of pregnancy. The hypothesis will be tested whether alterations in flow rate affects trophoblast turnover, morphology, metabolism, endocrine activity and the inflammatory response. In order to address this hypothesis, three work packages were defined, including flow culture experiments with a trophoblast cell line, primary trophoblasts and placental explants from human first trimester of pregnancy. Trophoblasts and placental explants will be cultured in recirculating culture medium at different flow rates. Thereafter, cells and explants will be subjected to biomolecular and morphological analyses, testing viability, proliferation and apoptosis as well as differentiation and syncytialization of trophoblasts in response to different flow rates. Moreover, remodelling of the cytoskeleton, apical microvilli formation and barrier function will be analysed at different flow rates. Expression of glucose transporters, lipases and lipoprotein receptors, as well as uptake and metabolic conversion of glucose and free fatty acids will be determined. Finally, placental hormone synthesis and release of proinflammatory factors will be analysed.

Methodology:

The PhD candidate will perform flow culture experiments with placental cells and tissue (explant culture). Expression analyses will be performed by qPCR, Western blot and ELISA. Moreover, the candidate will use a broad panel of histotechniques, including electron microscopy.

References:

1. Benirschke K, Kaufmann P, Baergen RN. Pathology of the Human Placenta. 2006; pp 42-49. Springer: New York, NY.
2. Roberts VHJ, Morgan TK, Bednarek P, Morita M, Burton GJ, Lo JO, Frias AE. Early first trimester uteroplacental flow and the progressive disintegration of spiral artery plugs: new insights from contrast-enhanced ultrasound and tissue histopathology. *Hum Reprod*. 2017; 32:2382-93

3. Burton GJ, Woods AW, Jauniaux E, Kingdom JC. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. *Placenta*. 2009; 30:473-82
4. Chistiakov DA, Orekhov AN, Bobryshev YV. Effects of shear stress on endothelial cells: go with the flow. *Acta Physiol (Oxf).* 2017; 219:382-408
5. Lecarpentier E, Bhatt M, Bertin GI, Deloison B, Salomon LJ, Deloron P, Fournier T, Barakat AI, Tsatsaris V. Computational Fluid Dynamic Simulations of Maternal Circulation: Wall Shear Stress in the Human Placenta and Its Biological Implications. *PLoS One*. 2016; 11:e0147262
6. Hutchinson ES, Brownbill P, Jones NW, Abrahams VM, Baker PN, Sibley CP, Crocker IP. Utero-placental haemodynamics in the pathogenesis of pre-eclampsia. *Placenta*. 2009; 30:634-41