Immune mediators in the placenta of hypertensive, diabetic and/or obese women

Summary

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Supervisor: Prof. Dr. Akos Heinemann
Availability: This position has been occupied.
Offered by: Medical University of Graz
Application deadline: Applications are accepted between February 05, 2018 00:00 and April 02, 2018 23:59 (Europe/Zurich)

Description

Research interests: Accumulation of leukocytes in tissues is a key feature of inflammation and a major determinant of tissue damage. Pregnancy is an immunological challenge for mother and fetus, and numerous immune cells take part in the development of the decidua. Particularly macrophages are thought to be crucial in maintaining an immune-tolerant environment in the semi-allogeneic setting of trophoblast invasion (1).

The main focus of our laboratory is to define the mechanisms that govern the trafficking of leukocytes from bone marrow, where they are generated, to the inflammatory site and their subsequent activation in tissue, where they may become harmful. Chemotactants, their receptors, and adhesion molecules both on the leukocytes and the endothelial side, play crucial roles in the multi-step process of leukocyte infiltration by facilitating leukocyte locomotion and activation, and are thus considered as promising therapeutic targets in various inflammatory conditions. Conversely, several endogenous mediators exist that down-regulate the responsiveness of leukocytes and might hence exert potent anti-inflammatory effects. When supplemented pharmaceutically, these mediators might likewise open novel therapeutic avenues. Among others we have elucidated the opposing roles of two cyclooxygenase (COX) products, prostaglandin (PG) E\textsubscript{2} and D\textsubscript{2} in leukocyte trafficking in human and animal models, and have characterized their receptors at the molecular and pharmacological level. While we have shown that its receptor EP4 is a negative regulator of eosinophil and neutrophil trafficking, and endothelial, platelet and macrophage activation (2, 3), we have also revealed a novel role for PGD\textsubscript{2} and its receptors DP1 and DP2 as potent activators of eosinophils, basophils and macrophages (4, 5).

Background: It has been suggested previously that PGE\textsubscript{2} and PGD\textsubscript{2} might play distinct roles in pathological conditions of pregnancy, but how these prostaglandins contribute to the regulation of leukocyte function in the developing decidua and, even more, how responses to PGE\textsubscript{2} and PGD\textsubscript{2} of immune cells in the placenta are altered in different gestational pathologies has not been addressed in detail. Currently we are elucidating the expression patterns and levels of enzymes involved in prostaglandin synthesis (COX isoforms, PGE and PGD synthases) and receptors for PGE\textsubscript{2} and PGD\textsubscript{2} in placental tissue.

Hypothesis: We hypothesize that an imbalance of anti-inflammatory PGE\textsubscript{2} effects and pro-inflammatory PGD\textsubscript{2} actions might contribute to complications in pregnancy, such as hypertension, preeclampsia or preterm labor. We will characterize these alterations on the cellular (e.g. endothelial cells, macrophages, innate lymphoid cells) and tissue level (i.e. placenta). The studies will provide insights in the regulation of leukocyte and endothelial function, in particular trafficking and activation, and how this process impacts on inflammation and tissue damage in the placenta.

Experimental approaches: The used methodologies comprise isolation and culturing of cells from fetal and maternal blood and placental tissues, characterization of cells by flow cytometry, quantitation and modulation of the biosynthesis of mediators and signaling molecules with RNA techniques including siRNA gene knock-down, immunoprecipitation and Western blot, and laser-scanning microscopy. The student will also be trained to characterize and quantitate specific lipid subclasses by mass spectroscopy (GC-MS, LC-MS).

Collaborations within DP-iDP:

- G. Desoye will teach the student how to isolate endothelial cells and macrophages from the placenta and/or umbilical cord, introduce them to the biology of angiogenesis and help with assays of 2-D network formation and tube formation.
- G. Marsche will supervise the studies addressing lipid metabolism of placental macrophages.
• **C. Wadsack** will provide clinically well-defined placenta samples and help the student with ex vivo placenta perfusion assays.

• In studies conducted by **M. van Poppel** the students will learn how to measure and statistically analyze cytokine plasma profiles in normal and pathological pregnancies.

**Know-how and infrastructure of the research group:** The laboratory of Akos Heinemann has a long-standing expertise in the field of leukocyte biology and pharmacology, but also in hemodynamic regulation and vascular biology. Studies are routinely carried out both with primary cells isolated from humans and cells from animal sources, complemented with cell lines for transfection/silencing experiments. The group comprises two post-doctoral fellows, three technicians and five PhD students. Various techniques are being used for a detailed analysis of leukocyte and endothelial cell function, and the group has considerable experience with in vivo models of leukocyte trafficking and inflammation. All the required equipment is available at the institute, including animal and cell culture facilities, radionuclide laboratory, flow cytometry, real-time PCR systems, fluorescence plate reader, tissue processing and fluorescence microscopy, and a microscopy system to study cell-to-cell interaction and thrombus formation under flow conditions. The group has also access to video-tracking of leukocyte locomotion and laser-scanning microscopy at the CMR.

**References:**


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4. Schuligoi, R; Sturm, E; Luschnig, P; Konya, V; Philipose, S; Sedej, M; Waldhoer, M; Peskar, BA; Heinemann, A CRTH2 and D-type prostanoid receptor antagonists as novel therapeutic agents for inflammatory diseases. Pharmacology. 2010; 85(6): 372-382.

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