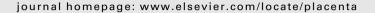


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# IFPA Meeting 2013 Workshop Report III: Maternal placental immunological interactions, novel determinants of trophoblast cell fate, dual *ex vivo* perfusion of the human placenta



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#### ABSTRACT

Workshops are an important part of the IFPA annual meeting as they allow for discussion of specialised topics. At IFPA meeting 2013 there were twelve themed workshops, three of which are summarized in this report. These workshops related to various aspects of placental biology but collectively covered areas of placental function, cell turnover and immunology: 1) immunology; 2) novel determinants of placental cell fate; 3) dual perfusion of human placental tissue.

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### 1. Maternal placental immunological interactions: advances in the field

**Chairs**: Caroline Dunk and Michelle Letarte **Speakers**: Mohamed Abumaree, Christian Castillo, Anne Croy, Caroline Dunk, Sylvie Girard, Alison Wallace, Cristian Zenerino

#### 1.1. Outline

This workshop aimed to discuss some of the latest findings and techniques that have contributed to our expanding knowledge of the interactions between the maternal decidual leukocytes and fetal trophoblast and their effects.

#### 1.2. Summary

Caroline Dunk discussed the dynamic changes in decidual leukocyte populations across gestation. The uterine natural killer (uNK) cells are known to play important roles in spiral artery angiogenesis, trophoblast invasion and vascular remodeling. However little is known about the signaling pathways regulating these effects. It has recently been shown that activation of the Sphingosine S1P pathway via S1PR5 on uNK cells can downregulate vascular endothelial cell growth factor (VEGF) expression and decrease uNK cell mediated trophoblast migration and *in vitro* angiogenesis. In the second trimester S1PR5 expression levels are decreased in uNK cells. It has been further shown that the second trimester decidua is an immune tolerant environment characterized by uNK cells incapable of mounting a cytotoxic response, M2 macrophages, and the appearance of a novel N2 angiogenic neutrophil population.

Anne Croy addressed the heterogeneity of uNK cell activation pathways. During mesometrial decidualization in mice, a transient population of uNK cells is established and expands until midpregnancy. Initially these cells enhance mesometrial angiogenesis, new vessel pruning and uterine lumen closure and thereby the rate of conceptus development and growth. Uterine NK cells then participate in induction of endothelial tip cells and in initiation of spiral arterial remodeling. Uterine NK cell surface receptors that recognize MHC ligands and those that recognize other ligands are both independently essential in these processes and play different roles in regulation of uNK cell-produced VEGF.

Alison Wallace presented a study investigating uNK cells in pregnancies with poor spiral artery remodeling. Uterine artery Doppler resistance index (RI) in the first trimester of pregnancy can be used as a proxy measure of the extent of remodeling of the uterine spiral arteries. Using this technique uNK cells were isolated from pregnancies with normal (normal RI) or impaired spiral artery remodeling (high RI). Their receptor expression phenotype and contribution to trophoblast chemotaxis and invasion were determined. High RI uNK cells displayed decreased expression of the receptors ILT2 and KIR2DL1/S1, and were less able to chemoattract trophoblast and induce extravillous trophoblast outgrowth from explants. This may contribute to poor placentation in high RI pregnancies.

Christian Castillo discussed how *Trypanosoma cruzi* (*T. cruzi*) induces cellular proliferation and differentiation in the trophoblast. The congenital transmission rate of *T. cruzi* is low, suggesting the

existence of local placental antiparasitic mechanisms; of which epithelial turnover of trophoblast may be one. In order to determine whether the parasite is able to induce cellular proliferation and differentiation in the trophoblast, BeWo cells and chorionic villi explants were incubated in the presence and absence of *T. cruzi* and respective positive controls. *T. cruzi* induced a significant increase of BrdU incorporation into DNA, in the number of mitosis, nucleolar organizer regions, expression and secretion of hCG. It was concluded that *T. cruzi* may increase trophoblast cell turnover.

Mohamed Abumaree discussed modulation of macrophage differentiation from inflammatory M1 to anti-inflammatory M2 macrophages by placental cells. During pregnancy the mother must adapt her immune response to foreign paternal antigens, possibly by signals given by the pregnancy to the mother's immune cells. Such tolerogenic signals may include the interaction between immune cells and trophoblast debris which are shed from the placenta into the maternal blood during normal pregnancy. It was shown that trophoblast debris can shift macrophage differentiation from the inflammatory M1 into an anti-inflammatory M2 phenotype. This result suggests a new immunosuppressive property of trophoblast debris that may be employed to protect the fetal allograft from the maternal immune system in normal pregnancy.

Sylvie Gerard addressed how inflammation may be a cause of placental dysfunction in high-risk pregnancies. The mechanism underlying the association between inflammation during human pregnancy and developmental abnormalities in the fetus were discussed. Evidence was provided of a distinct inflammatory profile in placenta from human high-risk pregnancies associated with reduced fetal movements. Using an *in vitro* model of human term placental explants a direct modulation of placental function by inflammatory cytokines was shown. These data give new insights into the mechanisms linking prenatal inflammation, placental dysfunction and altered fetal development and give possible therapeutic targets aimed to protect the placenta and subsequently the developing fetus.

Cristian Zenerino presented evidence on the anti-inflammatory effect of low molecular weight heparin (LMWH) being mediated by placental high mobility group box 1 (HMGB1) modulation. LMWH has been widely used for treating pre-eclampsia since several trials described its anti-inflammatory effect, although its mechanisms of action on the placental tissue are still unclear. HMGB1 is a transcription factor with extracellular cytokine-like functions able to induce pro-inflammatory molecules. LMWH binds to HMGB1 in vitro, thus changing its structural conformation and inhibiting its activity. It was investigated whether anti-inflammatory LMWH activity is mediated by HMGB1 modulation. Higher levels of HMGB1 were found in pre-eclamptic placenta compared to controls. In addition, decreased HMGB1, TNF-α and IL-6 gene expression and increased HMGB1 protein was found in LMWH-treated villous explants. These data suggest that LMWH could exert its antiinflammatory effect on the placental tissue by changing HMGB1 structural conformation thus impairing its function.

#### 1.3. Conclusions

The immune system is increasingly recognized as an integral part of a successful pregnancy. Transient inflammation is essential for any immune response and also for normal placental function; however sustained inflammation is associated with pregnancy

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