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IFPA meeting 2016 workshop report III: Decidua-trophoblast interactions; trophoblast implantation and invasion; immunology at the maternal-fetal interface; placental inflammation

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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 2016 there were twelve themed workshops, four of which are summarized in this report. These workshops related to various aspects of placental biology but collectively covered areas of decidual-trophoblast interaction, regulation of trophoblast invasion, immune cells at the maternal-fetal interface, and placental inflammation.

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1. Decidua-trophoblast interactions

1.1. Organizer

Gendie Lash.

1.2. Speakers

Sonia DaSilva-Arnold, Christina Duzyj, Gendie Lash, Peggy Petroff.

1.3. Outline

Invasion of the uterine decidua and inner third of the myometrium by extravillous trophoblast cells (EVT) and the associated remodeling of the spiral arteries are key to the establishment of a healthy successful pregnancy. During these processes EVT interact with different decidual cell types including decidual stromal cells, uterine natural killer cells, uterine macrophages, different T cell populations, vascular smooth muscle cells, endothelial cells and myometrial cells. These interactions have the potential to alter the phenotype, and therefore function, of either interacting cell type. The aim of this workshop was to explore some of these interactions and discuss how they contribute to the establishment of a healthy pregnancy.

1.4. Summary

Peggy Petroff discussed the potential mechanisms of communication between decidual cell populations and trophoblast. Extracellular vesicles, which include exosomes and larger microvesicles, are now recognized as a conserved form of intercellular communication. From the earliest stages of development, the embryo and later, the placenta secrete copious quantities of vesicles. These vesicles are likely to influence key processes in implantation, placentation, and maternal-fetal interactions – including those between trophoblast cells and maternal immune cells. Ongoing work is defining these interactions; technological advances will play key roles in determining the nature and importance of vesicular communication between the mother and the fetus. Likely roles for extracellular vesicles include decidualization, intra-embryonic communication, and establishment of maternal tolerance to the fetus, potentially through modification of maternal antigen presenting cells.

Gendie Lash presented data on the consequences of decidual leucocyte (uterine natural killer (uNK) cell) and EVT communication. In the placental bed uNK cells are a major source of cytokines and angiogenic growth factors (AGFs) with AGF levels decreasing and cytokine levels increasing with gestational age. The factors that regulate AGF and cytokine secretion are unclear but may involve interactions between uNK cells and EVT. Co-culture of uNK cells and EVT resulted in a reduction in levels of several AGFs and cytokines. Interestingly, AGF levels were reduced under both direct and indirect co-culture conditions while cytokines were only reduced after direct contact. Local production of AGFs and cytokines in the placental bed are likely lowered when uNK cells come in direct contact with EVT, via a mechanism potentially not mediated by HLA.

Christina Duzyj discussed multinuclear trophoblast giant cells and evidence that there is ongoing terminal differentiation of EVT throughout gestation. The duration of uterine invasion by EVT has been a subject of debate. Although older literature supports the notion that invasion stops by mid-pregnancy, newer data contests this paradigm. The molecular signals that alter the invasive EVT phenotype to limit the depth of invasion to the inner third of the myometrium during pregnancy, and the eventual endpoint of EVT maturation are not understood. It was proposed that reversal of epithelial to mesenchymal EVT transition, and fusion of mononuclear interstitial EVT into multinucleated giant cells represents completion of the life course of EVT. It was suggested this fusion is a process which involves multiple stages, continues to term and is as yet poorly understood.

Sonia DaSilva-Arnold discussed how there may be a disconnection between EVT genotype and phenotype in abnormally invasive placenta. There is a need to acknowledge the role of the decidua in abnormally invasive placenta, particularly since alterations in decidual cell populations have been shown to result in abnormally invasive placentae. Specifically, there is evidence that the loss of uterine natural killer cells may contribute to trophoblast over-invasion pathologies. There is also evidence that both phenotypic and genotypic changes characteristic of epithelial-mesenchymal transition occur in the differentiation of cytotrophoblast to extravillous trophoblast.

1.5. Conclusions

The decidua (comprised of a complex mix of leucocytes, stromal cells, blood vessels and glandular epithelial cells) has the ability to modulate trophoblast cell phenotype and behavior. In addition, EVT are also able to modulate the phenotype and behavior of different cell types within the decidua, the best studied being the different leucocyte populations, endothelial cells and vascular smooth muscle cells. The exact mechanisms of these different interactions is not known but likely involves secreted ligands interacting with cell surface receptors, direct cell-cell interactions, as well as cellular communication via exosomes or microparticles. These complex interactions are required to facilitate invasion of the EVT to an appropriate depth as well as remodeling of the uterine spiral arteries. Any disturbances in the balance of interactions would lead to aberrant invasion and remodeling, leading to major obstetric complications such as pre-eclampsia, fetal growth restriction, late miscarriage, placenta accreta etc. This workshop highlighted some of the potential mechanisms of decidua-EVT interactions as well as the consequences of these interactions for EVT as well as some decidual cell sub-populations. It also highlighted that the majority of research to date has focused on regulation of EVT invasion and there are many other EVT traits that we know little about. The workshop stimulated lively discussion on some of these under studied areas of EVT biology.

2. Key mechanisms and novel insights into trophoblast implantation and invasion

2.1. Organizers

Martin Knöfler, Alexander Beristain.

2.2. Speakers

John Aplin, Alexander Beristain, Caroline Dunk, Jürgen Pollheimer, Michael Soares.

2.3. Outline

Trophoblast differentiation along the invasive pathway is fundamental to early implantation, placental development and establishment of the fetal-maternal interface. Multiple gene pathways and heterogeneous cellular interactions have been described

in directing and controlling trophoblast invasion. The focus of this workshop aimed to address well accepted as well as controversial paradigms central to the intrinsic control of trophoblast invasion. Novel cellular mechanisms with respect to implantation, development of an early invasive trophoblast lineage, and new insights into the versatile functions of invasive trophoblasts were discussed. The importance of key transcription factors, the cell cycle and aging as well as the role of polyploidy and ADAM proteases in differentiating extravillous trophoblast populations was a primary focus. Moreover, the role of external environmental stimuli, such as hypoxia and mechanisms regulating EVT-uterine leucocyte cross-talk were explored.

2.4. Summary

John Aplin discussed the development of the invasive trophoblast phenotype in the early stages of implantation. In early pregnancy, maternal and embryonic signals prime the receptivity of the uterine luminal epithelium (LE) before the trophectoderm (TE) of the blastocyst-stage embryo mediates attachment. It was hypothesised that receptivity requires an active maternal juxtacrine signal to initiate trophoblast differentiation. Using in vitro cell culture methods it was shown that mouse or human blastocysts or BeWo cell spheroids stably attached to confluent human endometrial epithelial Ishikawa cells, followed by breaching and trophoblast outgrowth. Day 6 human blastocysts readily attached to the Ishikawa cell layers and co-culture for 48 h demonstrated an onset of GATA3, HLAG and hCG expression. This novel model to investigate early trophoblast differentiation implicates primary syncytium as the pioneer invasive cell type in human embryo implantation, and giant cells in mouse. Interaction with the receptive epithelium initiates trophoblast differentiation and the onset of appearance of invasive behavior. These findings have clinical implications for assisted reproductive technologies as well as biological importance in understanding early placentation.

Michael Soares discussed plasticity in development of the invasive trophoblast lineage. Hemochorial placentation involves orchestrated temporal and spatial decisions governing the fate of trophoblast stem/progenitor cells. Trophoblast cell acquisition of specializations facilitating invasion and uterine spiral artery remodeling is a labile process, sensitive to the environment, and a process that is vulnerable to dysmorphogenesis in pathologic states. The rat exhibits deep intrauterine trophoblast invasion and is an experimentally tractable model for investigating mechanisms controlling trophoblast-directed changes in the uterine vasculature. Hypoxia can be used as a tool to elucidate acquisition of the invasive trophoblast phenotype. Placental adaptations to environmental challenges highlight the importance of plasticity in safeguarding a healthy pregnancy.

Jürgen Pollheimer presented an overview of the versatile functions of invasive EVT. These include: plugging of spiral arteries, interaction with immune cells, defense against pathogens, disruption of the arterial smooth muscle layer, and invasion into arteries and glands. Furthermore, novel evidence that human EVT actively secrete factors into the maternal circulation ensuring maternal adaption to pregnancy was discussed. Data were presented showing that an EVT-specific factor is detectable in serum of pregnant women from 7 to 8 weeks of gestation. It was postulated that the EVT secretome may serve as an early predictive marker for complicated pregnancies.

Alexander Beristain discussed the role of ADAM proteases in trophoblast differentiation and how they may be involved in establishing protective mechanisms under hypoxia. Trophoblast cells differentiating along the invasive pathway regulate the expression of diverse subtypes of proteases. Invasive EVT express a specific repertoire of ADAM proteases, however the regulation and function of ADAMs in trophoblast biology is poorly understood. Global transcriptomic studies performed by various groups, supported by targeted *ex vivo* expression studies using purified subtypes of trophoblasts, have provided needed insight into their functions in early placentation. Moreover, the importance of oxygen levels has also provided insights into regulatory mechanisms controlling ADAM expression and function in invasive trophoblast subtypes, where low and high oxygen environments differentially regulate multiple subtypes of ADAM proteases.

Caroline Dunk presented recent work investigating the impact of the Y153H SNP in STOX1 transcription factor mediated effects on EVT-leucocyte interactions. It has been previously shown that the maternal decidual uNK cells and macrophages play a crucial role in the early disruption and transformation of the uterine spiral arteries. It has been hypothesised that there is a chemokine mediated communication between the EVT, vasculature and maternal leucocytes. Placental explants carrying the STOX1 Y153H mutant TF have smaller EVT outgrowths, secrete lower levels of the chemokines IL-6, IL-8, CCL-2, CXCL1, CX3CL1 and sEndoglin, while upregulating CXCL16 and Angiopoietin-2. Invasion assays showed that in comparison to wild type, Y153H STOX EVT conditioned media (Y153H CM) did not stimulate uNK invasion. Monocytes underwent apoptosis in Y153HH CM. It was also shown that Y153H mutant STOX1 expression was increased in severe early onset pre-eclamptic and preterm placenta as compared to late onset pre-eclampsia or term controls, however 60% of placentas do not carry the mutation thus it is not the only factor contributing to the pathogenesis of early onset pre-eclampsia. Preliminary data were presented showing the incidence of the GG mutation of the rs1425954 SNP in the ACVR2A promoter. This SNP is specifically enriched in early onset pre-eclamptic placentas with a small for gestational age baby, both STOX and ACVR2A SNPs were found in 7/9 of this group. In conclusion, it has been shown that EVT carrying the STOX1 mutation have an altered secretome and do not support uNK cell or monocyte invasion, and thus may contribute to the failure of uterine vascular remodeling observed in pathological placentation.

2.5. Conclusions

Complex interactions between trophoblasts and different uterine/decidual cell populations as well as environmental conditions critically regulate implantation, trophoblast invasion, and uterine vessel remodeling. An intrinsic molecular program dictates EVT/trophoblast function and differentiation, but these processes are also likely controlled by the decidual environment and its cell types. Vice versa, uterine leucocytes are affected by the EVT-specific secretome and cell-cell contacts with EVT.

3. Immunology at the maternal-fetal interface

3.1. Chairs

Margaret Petroff, Thaddeus Golos.

3.2. Speakers

Caroline Dunk, Thaddeus Golos, Ulrike Kemmerling, Gendie Lash, Leticia Reyes, Jennifer Stencel-Baerenwald.

3.3. Outline

Immune cells at the maternal-fetal interface can serve multiple purposes. On the one hand, they play an important role in placental

development and uterine remodeling; on the other, they participate in defense against pathogens and prevent vertical transmission. Yet a third effect is the 'bystander' damage that occurs as a result of inflammation when infection or other stressors are present. In this workshop these seeming Janus-faced roles of immune and other cells, and immune-mediated processes that occur in normal pregnancy were discussed. Topics discussed included the involvement of immune cells in normal processes involved in placentation such as trophoblast invasion and spiral artery remodeling; phenotypic changes that occur in immune cells as a result of infection; and how trophoblast cells themselves respond to, and may protect against different types of infection. Furthermore, with the recent, alarming rise in transmission and teratogenic effects of Zika virus infections, two discussants illuminated novel models of primate Zika infection.

3.4. Summary

Caroline Dunk presented a global analysis of decidual immune cell populations demonstrating dynamic changes with gestation between 6 and 20 weeks, focusing in detail on uNK cell and neutrophil populations. Uterine NK cells remain constant in number (70–80%) but increasing numbers express CD314/NKG2D and Nkp80 receptors on their surface. Despite this, 2nd trimester uNK cells are less able to mount a cytotoxic response as measured by PMA-stimulated perforin release. Direct interaction with the HTR-8/SVneo trophoblast-like cell line decreased CD314 expression and uNK cell viability, while HTR-8/SVneo secreted factors decreased both IFNγ and perforin release. $CD3^{+}CD4^{+}$ T cells increase with gestation while monocytes decrease in number and differentiate to an M2c phenotype expressing both CD163 and CD206. Immature $CD209^{+}$ dendritic cells are high in the 1st trimester, numbers decrease and do not differentiate into mature $CD81^{+}$ antigen presenting cells. Recent data identifying a novel angiogenic neutrophil population similar to N2 neutrophils that is resident in 2nd trimester decidua basalis was also presented. Investigation of the decidual effect on normal healthy and pre-eclamptic peripheral blood neutrophils showed significant changes in mRNA expression of several known N1/N2 factors of which 3 can reliably distinguish pre-eclampsia from 26 week samples. It was concluded that healthy pregnancy is characterised by adaption of the decidual immune cells to a pro-angiogenic, tissue remodeling, adaptive phenotype. Resistance of the maternal immune cells to decidual differentiation may contribute to the inflammatory endothelial dysfunction and deficient uterovascular remodeling associated with pre-eclampsia.

Gendie Lash discussed the potential role of decidual macrophages in remodeling of the uterine spiral arteries. Incomplete spiral artery remodeling is associated with the pathogenesis of a number of complications of pregnancy including late miscarriage, pre-eclampsia and fetal growth restriction. Despite the importance of spiral artery remodeling in the establishment of a successful pregnancy, little is known about the molecular triggers for this complex process that appears to require the co-ordinated activity of a number of cell types including uNK cells, macrophages, EVT and vascular smooth muscle cells. Data were presented showing that decidual macrophages secrete a wide range of cytokines, angiogenic growth factors and matrix metalloproteinases. However, unlike uNK cells, they do not induce vascular smooth muscle cell morphological changes or de-differentiation. They are able to facilitate breakdown of the vascular extracellular matrix, but this is not sufficient to induce vascular smooth muscle cell separation and morphological change. Their most important role is likely in the phagocytosis of apoptotic vascular smooth muscle cells to allow their clearance from the vessel wall. It was postulated that in situations of infection or inflammation the decidual leucocytes are not able to perform their tissue remodeling roles, therefore contributing to the aetiology of complications of pregnancy.

Ulrike Kemmerling spoke about trophoblast epithelial turnover (particularly the role of caspase 8) as an innate defense mechanism against *T. Cruzi*, but not against *T. gondii*. Data were presented showing that the parasites activate different TLRs in human placental chorionic villi explants leading to differential cytokine/chemokine profiles. These data might explain, at least partially, differential susceptibility of the placenta to the infection of both parasites.

Leticia Reyes discussed links between periodontal disease and adverse outcomes of pregnancy. *Porphyromonas gingivalis* (Pg), a keystone species of periodontal disease, has been implicated in preterm delivery. The presence of Pg within the placental villous mesenchyme is linked to shorter gestational age in pregnancies with histologic chorioamnionitis, chorioamnionitis with funisitis, pre-eclampsia and pre-eclampsia with HELLP-syndrome. Since Pg subverts host antimicrobial defenses, it was postulated that infection of the placental stroma perturbs the activation state of fetal macrophages. The co-localization of macrophage markers was measured: anti-inflammatory CD163 and pro-inflammatory CD68 in preterm specimens matched by gestational age and complication. It was that found Pg positive placentas had decreased CD68+/CD163 ratios suggesting a shift towards an anti-inflammatory profile.

Jennifer Stencel-Baerenwald discussed Zika virus (ZIKV) as a neuroteratogenic pathogen and the need for animal models that can be used to test vaccines and antiviral drugs. Data were presented demonstrating vertical transmission of ZIKV in a non-human primate model of infection using *M. nemestrina*. Viral load was detected in fetal organs including the brain and placenta. Moreover, periventricular lesions and white matter hypoplasia were observed in the fetal brain using serial magnetic resonance imaging. Collectively, these findings enhance our understanding of transplacental ZIKV trafficking and provide the basis for a novel ZIKV model for therapeutic intervention.

Thaddeus Golos continued the discussion on Zika virus. Maternal infection with Zika virus has been correlated in Brazil with fetal microcephaly, however questions remain regarding maternal susceptibility, rates of fetal infection, and risk factors such as co-infection. A rhesus macaque model has been developed demonstrating consistent susceptibility to Zika but rapid (within 10 days) clearance in nonpregnant individuals. As seen in pregnant women, prolonged maternal viremia (up to 10 weeks) was observed in pregnant monkeys, and only sporadic fetal viral RNA was detected within individual pregnancies; however all pregnancies had detectable viral burden and fetal inflammatory pathology; thus 100% maternal-fetal transmission was noted. The macaque model will allow investigation of maternal and environmental factors influencing transmission to the fetus, and development of strategies to interrupt fetal infection.

3.5. Conclusions

Immune cells and trophoblast cells have dual roles in pregnancy, which include both establishment of normal placentation and protection when the maternal-fetal interface is threatened with infection. Macrophages and uterine NK cells are understood now to play distinct molecular roles in placentation, which may be perturbed in the setting of infection-induced inflammation and in defective placental developmental processes such as that in pre-eclampsia. Ongoing work continues to identify novel cell types that may be entirely unique to the maternal fetal interface, and it will be particularly important to identify the roles these cells play in

normal and abnormal pregnancy. Finally, the rapid response of the biomedical research community in development of new, highly relevant models of clinical infection is critical for our ability to respond to future emerging pathogens that endanger maternal and fetal health.

4. Inflammation – what is it and how does it affect the placenta

4.1. Chairs

Murray Mitchell, Kent Thornburg.

4.2. Speakers

Murray Mitchell, David Olson, Pepper Schedin, Kent Thornburg.

4.3. Outline

Inflammation or mediators of inflammation play important roles in many physiological and pathological mechanisms in reproductive biology. The relationships between pathogen-driven inflammation versus non-infectious inflammation or more simply, 'hot' versus 'cold' inflammation are complex. The different intracellular pathways that are activated in chronic versus acute processes are important and not understood even though they should result in different approaches to therapy. This workshop was designed to discuss these two types of inflammation and how they apply to the human placenta with the hope that the field can develop a more appropriate nomenclature for describing the inflammatory processes.

4.4. Summary

Kent Thornburg introduced the concepts of 'hot' and 'cold' inflammation. According to the *Britannica Encyclopedia Pathology*, the definition of inflammation is the response to tissue damage that "… consists of changes in blood flow, an increase in permeability of blood vessels, and the migration of fluid, proteins, and white blood cells (leucocytes) from the circulation to the site of tissue damage." This is the classical scenario of so-called "hot-inflammation." However, it is becoming increasingly clear that another form of inflammation can occur with many of the same cell signaling events and gene expression patterns as in hot inflammation but without leucocyte infiltration and fluid extravasation. This has become known as "cold inflammation" or "metinflammation"; this condition may become a chronic state that harms tissues through increasing levels of oxidative stress and detrimental cytokines.

Murray Mitchell discussed how inflammation or mediators of inflammation play important roles in many physiological and pathological mechanisms including: asthma, diabetes, heart diseases, obesity, certain cancers, depression, dementia and rheumatoid arthritis. "Inflammation" during pregnancy is thought to result in increased risk of disorders including childhood leukemia. The relationships between pathogen-driven inflammation versus non-infectious inflammation are complex. Nature has utilised inflammatory mediators, notably cytokines, in physiological mechanisms as well as in acute responses to stimuli. Hence sterile inflammation, cold inflammation and metinflammation are physiological mechanisms, for example used for parturition.

David Olson discussed the great confusion regarding naturally occurring inflammatory events and infection in birth at term and preterm. There is confusion over the roles of inflammation vis-à-vis infection (chorioamnionitis) in the ontogeny of birth at term and especially at preterm. This can lead to an over-diagnosis of chorioamnionitis and an unnecessary number of cesarean sections with their associated risks. Both the non-infectious inflammatory processes (termed 'cold' or 'sterile' inflammation) and infectious processes (termed 'hot' inflammation) involved with preterm birth were discussed. In addition, the adverse effects of infection upon the fetus were described. Methods used to diagnose and define histologic chorioamnionitis and infectious chorioamnionitis were also discussed and new tools for mitigating the effects of infection considered.

Pepper Schedin discussed inflammation at epithelial cell barriers. The immune system, once thought to be an independent monitor of tissue injury and initiator of tissue repair, is increasingly appreciated for its integrated roles in normal tissue biology. For example, the study of mucosal biology, or how an organ exposed to the outside environment is protected from foreign antigens, has identified immune cell functions that shed light on basic epithelial cell decisions including proliferation, differentiation, death, and immune avoidance. Thus it is not surprising that dysregulated immune function contributes to numerous epithelial pathologies ranging from solid cancers to premature births. At this point in time, a wealth of knowledge has been obtained regarding the complex, and at times seemingly disparate roles of hot (Th1-skewed) and cold (Th2 and/or Th17 skewed) inflammation in mucosal biology and cancer. Cross fertilization between these fields is poised to significantly advance our understanding of placental biology and positively impact human pregnancies. However, because the immune system is intimately involved in numerous aspects of placental biology, that path forward will have its share of surprises, unbiased high quality data will be of the essence. As a potential new practitioner of immune biology, it will be necessary to understand the inherent yin yang of the immune system, which is always under balance and counter balance influences in an effort to maximally ward off external threats while minimizing damage to self. The key to moving forward is to embrace the complexity of immune data without preconceived ideas as to what immune cells or functions constitute a 'good' or 'bad' immune milieu within the placenta.

4.5. Conclusions

With vigorous audience participation, there was agreement that 1) hot and cold inflammation are important processes in normal and pathological pregnancies and that 2) there is a need for better terminology in defining inflammation in the placenta. The many apparent roles of the immune system in pregnancy have not been well defined. Thus, there is an urgent need for research to clarify roles of hot and cold inflammatory processes in placentation and in placental function as pregnancy progresses. The group suggested that a working group be formed to develop a white paper on the topic.

Conflict of interest statement

None of the authors have any conflict of interest to declare.