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Chapter 1 : Decidua: Cartwright, J E - www.nxgvision.com

Hypoxia and Placental Remodelling. Judith E Cartwright. Rosemary J Keogh since the pathophysiology involves placental hypoxia leading to ineffective spiral artery remodeling in the first.

The role of decidual NK cells in pregnancies with impaired vascular remodelling. The pathologies of the dangerous pregnancy complications pre-eclampsia PE and fetal growth restriction FGR are established in the first trimester of human pregnancy yet we know little of how this happens. Finely tuned interactions between maternal and placental cells are essential for pregnancy to progress without complications; however, the precise nature of this cross-talk and how it can go wrong are crucial questions that remain to be answered. This review summarises recent studies examining the role played by natural killer cells in regulating normal placentation and remodelling. During pregnancy, maternal uterine spiral arteries SAs are remodelled from minimal-flow, high-resistance vessels into larger diameter vessels with low resistance and high flow. Fetal extravillous trophoblasts EVT have important roles in this process. Decidual natural killer cells dNK cells are the major maternal immune component of the decidua and accumulate around SAs before trophoblast invasion. A role for dNK cells in vessel remodelling is beginning to be elucidated. This review examines the overlapping and dissimilar mechanisms used by EVT and dNK cells in this process and how this may mirror another example of tissue remodelling, namely cancer development. Additional papers discussing cancer development are also included. Both interact with vascular cells lining the SA, as well as with each other, to promote transformation of the SA. EVT differentiation has previously been likened to the epithelial-mesenchymal transition in cancer cells, and we discuss how dNK-EVT interactions at the maternal-fetal interface can also be compared with the roles of immune cells in cancer. The investigation of pregnancy as a multicellular system involving both fetal and maternal components, as well as comparisons to similar examples of tissue remodelling, will further identify the key mechanisms in SA remodelling that are required for a successful pregnancy. In the first 20 weeks of pregnancy a number of important changes take place in the maternal uterine vasculature. Vascular endothelial and smooth muscle cells are lost from the spiral arteries and are replaced by fetal trophoblast cells. The resulting increase in blood flow to the intervillous space ensures that the fetus receives the nutrients and respiratory gases required for growth. Failure of the vessels to remodel sufficiently is a common feature of pregnancy pathologies such as early pregnancy loss, intrauterine growth restriction and pre-eclampsia. Although there is evidence to suggest that some vascular changes occur prior to trophoblast invasion, it is clear that in the absence of trophoblast invasion the remodelling of the spiral arteries is reduced. The cellular and molecular mechanisms by which trophoblasts influence vessel structure have been little studied. Trophoblasts synthesize and release a plethora of cytokines and growth factors including members of the tumour necrosis factor family such as tumour necrosis factor alpha, Fas-ligand and tumour necrosis factor-related apoptosis-inducing ligand. Recent studies suggest that these factors may be important in regulating the remodelling process by inducing both endothelial cell and vascular smooth muscle cell apoptosis. Decidual NK dNK cells are present during uterine spiral artery remodelling, an event that is crucial for successful placentation and the provision of an adequate blood supply to the developing fetus. Spiral artery remodelling is impaired in the pregnancy complication pre-eclampsia. Although dNK cells are known to play active roles at the maternal-fetal interface, little is known about their effect on endothelial integrity, an important component of vessel stability. We present a study in which we have modelled dNK-endothelium interactions, using first-trimester dNK cells isolated from both normal pregnancies and those with impaired spiral artery remodelling. We have established a functional role for dNK cells in the disruption of endothelial structures and have suggested how impairment of this process may be contributing to the reduced vessel remodelling in pregnancies with a high uterine artery resistance index. These findings have implications for our understanding of the pathology of pre-eclampsia and other pregnancy disorders where remodelling is impaired. Transformation of the uterine spiral arteries SAs during pregnancy is

critical to support the developing fetus, and is impaired in some pregnancy disorders, including preeclampsia. Decidual natural killer dNK cells play a role in SA remodeling, although their interactions with fetal trophoblast remain unclear. A uterine artery Doppler resistance index RI in the first trimester of pregnancy can be used as a proxy measure of the extent of SA remodeling; we have used this technique to characterize dNK cells from pregnancies with normal normal RI and impaired high RI SA remodeling, which display least and highest risk of developing preeclampsia, respectively. We examined the impact of dNK cell secreted factors on trophoblast motility, chemoattraction, and signaling pathways to determine the contribution of dNK cells to SA transformation. We demonstrated that the chemoattraction of the trophoblast by dNK cells is impaired in pregnancies with high RI, as is the ability to induce trophoblast outgrowth from placental villous explants. Therefore, by characterizing pregnancies using uterine artery Doppler RI before dNK cell isolation, we have identified that impaired dNK-trophoblast interactions may lead to poor placentation. These findings have implications for pregnancy pathological conditions, such as preeclampsia. During the first trimester of human pregnancy, fetally-derived extravillous trophoblast EVT invade into the uterine decidua and remodel the uterine spiral arteries to ensure that sufficient blood reaches the maternal-fetal interface. Decidual macrophages have been implicated in the regulation of decidual remodelling, and aberrant activation of these immune cells is associated with pre-eclampsia. The monocytic cell line THP-1 was activated to induce a classically- or alternatively-activated macrophage phenotype and the conditioned media was used to treat the EVT cell line SGHPL-4 in order to determine the effect of macrophage polarisation on trophoblast behaviour in-vitro. Macrophages can regulate trophoblast functions that are critical during decidual remodelling in early pregnancy. Importantly, there is differential regulation of trophoblast function in response to the polarisation state of these cells. Our studies indicate that the balance between a pro- and anti-inflammatory environment is important in regulating the cellular interactions at the maternal-fetal interface and that disturbances in this balance likely contribute to pregnancy disorders associated with poor trophoblast invasion and vessel remodelling. During pregnancy, a specialized type of NK cell accumulates in the lining of the uterus decidua and interacts with semiallogeneic fetal trophoblast cells. Here, we have used uterine artery Doppler RI in the first trimester of pregnancy as a proxy measure of the extent of transformation of the spiral arteries to identify pregnancies with a high RI, indicative of impaired spiral artery remodeling. We have used flow cytometry to examine dNK cells isolated from these pregnancies compared with those from pregnancies with a normal RI. These results indicate that dNK cells from high RI pregnancies may display altered interactions with trophoblast via decreased expression of HLA-binding cell-surface receptors, impacting on successful transformation of the uterus for pregnancy. Decidual natural killer dNK cells have been shown to both promote and inhibit trophoblast behavior important for decidual remodeling in pregnancy and have a distinct phenotype compared to peripheral blood NK cells. We investigated whether different levels of oxygen tension, mimicking the physiological conditions of the decidua in early pregnancy, altered cell surface receptor expression and activity of dNK cells and their interactions with trophoblast. Cell surface receptor expression was examined by flow cytometry, and the effects of secreted factors in conditioned medium CM on the trophoblast cell line SGHPL-4 were assessed in vitro. This study demonstrates dNK cell phenotype and secreted factors are modulated by oxygen tension, which induces changes in trophoblast invasion and endovascular-like differentiation. Alterations in dNK cell surface receptor expression and secreted factors at different oxygen tensions may represent regulation of function within the decidua during the first trimester of pregnancy.

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[et al.] Role of reactive oxygen species in chronic hypoxia-induced pulmonary hypertension and vascular remodeling / Eva Nozik-Grayck and Kurt R. Stenmark Hypoxia and placental remodeling / Judith E. Cartwright.

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Chapter 3 : - NLM Catalog Result

Ashton SV, Whitley GS, Dash PR, Wareing M, Crocker IP, Baker PN, and Cartwright JE. Uterine spiral artery remodeling involves endothelial apoptosis induced by extravillous trophoblasts through Fas/FasL interactions.

Chapter 4 : Publications Authored by Judith E Cartwright | PubFacts

Hypoxia-induced VaScular reModelinG and Hy- Hypoxia and Placental Remodeling Judith E. Cartwright, Rosemary J. Keogh, and Martha C. Tissot van Patot.

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