**The role of decidual NK cells in pregnancies with impaired vascular remodelling**

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**Abstract**

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. Their involvement when it is impaired in PE/FGR pregnancies will additionally be discussed.

**Keywords**

Natural killer cell, decidua, trophoblast, spiral artery, pregnancy, pre-eclamspia

**Introduction**

Decidualisation is accompanied by substantial recruitment of maternal immune cells, with approximately 70% being natural killer (NK) cells, 20% macrophages and the remaining 10% T cells. During placentation, fetal extravillous trophoblast cells (EVT) invade into the decidua, where they encounter this enriched environment of immune cells. When EVT reach the uterine spiral arteries they actively participate in vessel remodelling which involves a loss of endothelial cells (EC) and vascular smooth muscle cells (VSMC), and matrix changes accompanied by fibrinoid deposition. The resulting high-flow, low-resistance vessel is then capable of supplying sufficient blood to the intervillous space to meet the increasing demands of the developing fetus (and placenta). There is increasing evidence indicating the importance of immune cells in regulating trophoblast invasion and spiral artery remodelling.

Insufficient spiral artery remodelling is an early characteristic of common pregnancy complications such as PE/FGR and stillbirth (Pijnenborg *et al.* 2011). FGR with or without PE affects 5–8% of human pregnancies worldwide and is a major cause of neonatal morbidity and mortality. Women who have experienced FGR or PE are twice as likely to develop cardiovascular disease compared with those having a normal pregnancy and 8 times more likely if they have both FGR and PE (Staff *et al.* 2016). Growth restricted babies also suffer life-long consequences including increased risk of both cardiovascular and metabolic diseases (Davis *et al.* 2012). There is increasing interest in the role the maternal immune system plays in the development of these conditions (Hsu and Nanan 2014).

**How can we study placental pathology in the first trimester?**

One of the greatest challenges in understanding the pathophysiology of PE and FGR remains our inability to investigate events early in pregnancy, at the time pathology is being established. Studies on term tissue, when the outcome is known, do not target the most crucial time, and so our knowledge of pathology-causing events is very limited. We have used a proxy measure of the extent of remodelling (and hence risk of PE/FGR) for our studies. Uterine artery Doppler (UtAD) Ultrasound screening of women who are undergoing surgical pregnancy termination in the first trimester (Hollis *et al.* 2001, Prefumo *et al.* 2004), can identify those who have poor spiral artery remodelling (five-fold increased risk of PE/FGR; high resistance index, hRI) compared to those with normal remodelling (low risk of PE/FGR; normal RI, nRI). We have previously reported that, in a data set of 9952 ongoing pregnancies, cases with UtAD RI >95th percentile in the first trimester had a 15% risk of PE compared with a 2.8% risk in cases with UtAD RI <95th percentile. Women with the highest degree of uterine artery resistance had a 24% chance of developing a placental complication of pregnancy (PE, FGR, or stillbirth) compared with women <95th percentile who had a 4.9% risk (Leslie *et al.* 2015). Multiple cell types can be isolated and characterised from tissue obtained at the time of termination of pregnancy; dNK cells, macrophages, T cells, stromal cells and trophoblast, and with the added information from the UtAD scans, comparisons can be made between women with an increased risk of these complications to those where remodelling is likely to be occurring normally. This has led to novel insights into the cellular and molecular events that are regulating normal and abnormal placentation (Whitley *et al.* 2007, Fraser *et al.* 2012, Wallace *et al.* 2013b, Wallace *et al.* 2014, Fraser *et al.* 2015, Wallace *et al.* 2015).

**Characterisation of dNK cells from pregnancies with impaired spiral artery remodelling**

We have shown that decidual NK cells from pregnancies with impaired remodelling have abnormalities in secreted proteins and functional interactions with other decidual cells (Fraser *et al.* 2012, Wallace *et al.* 2013b, Wallace *et al.* 2014, Fraser *et al.* 2015, Wallace *et al.* 2015). The effector functions of dNK in early pregnancy are regulated by their expression of inhibitory and activating receptors (KIR, CD94/NKG2, ILT families) which interact with trophoblast HLA Class I molecules (HLA-C/G/E). There is considerable evidence to suggest that particular combinations of highly polymorphic KIR receptors on dNK cells and HLA-C on invasive trophoblast influence pregnancy success. The frequency of maternal KIR AA genotypes in combination with a paternally derived HLA-C allele bearing a C2 epitope is increased in women with disorders of pregnancy associated with poor placentation (Hiby *et al.* 2004, Hiby *et al.* 2008, Moffett and Hiby 2009, Hiby *et al.* 2010). An alteration in the production of factors that can regulate trophoblast invasion is important in this effect (Xiong *et al.* 2013). We have demonstrated that KIR2DL/S1,3,5 and LILRB1 (ILT-2) positive dNK cells are decreased in pregnancies with a hRI and, in the case of LILRB1, that this leads to a difference in dNK cell expression of CXCL10 and TNF-(Wallace *et al.* 2015). This increased expression of TNF- and decreased expression of CXCL10 in the cells from the higher risk pregnancies could impact on their ability to regulate trophoblast migration/invasion (Wallace *et al.* 2013b).

Profiling the secretome of dNK cells suggest that they produce a range of signalling molecules that can contribute to the regulation of the trophoblast invasion/remodelling and to the overall pro- or anti-inflammatory environment (Hanna *et al.* 2006, Lash *et al.* 2006, Fraser *et al.* 2012). Extending this to our patient groups demonstrated that hRI dNK cells secrete more endostatin and angiogenin than nRI dNK cells, both of which inhibit trophoblast invasion (Wallace *et al.* 2014). Additionally secretion of the soluble IL-2 receptor (sIL-2R  subunit) was higher by the hRI dNK cells, which may be reflective of an elevated activation status in these cells.

It has been suggested that for pregnancy to be successful a state of controlled inflammation must exist (Redman and Sargent 2003) and that dysregulation of the decidua may be a key early event (Founds *et al.* 2009, Rabaglino *et al.* 2015). The overall profile of gene expression and secreted proteins produced by the immune (and other decidual) cells will be vital in determining whether there is a net pro- or anti-inflammatory balance in the tissue. It is not known whether this balance is disturbed overall in pregnancies with poor spiral artery remodelling however we have previously shown that placental tissue from the hRI versus nRI first trimester pregnancies have differential expression of genes related to immune and inflammatory responses (Leslie *et al.* 2015).

**Does immune cell regulation of placentation and vascular remodelling differ between pregnancies with normal and impaired spiral artery remodelling?**

Spiral artery remodelling is complex and involves different processes occurring in a finely orchestrated manner. Failure of one or more of these processes could result in poor remodelling. Decidual immune cells are present at the time that trophoblast invasion/vessel remodelling is taking place and are located where they could be actively regulating these processes, as well as each other (Wallace *et al.* 2012).

Trophoblast invasion of the decidua is dependent on them remaining resistant to signals detrimental to their survival. We have identified differences between our patient groups in how NK cells control trophoblast behaviour (Wallace *et al.* 2013b, Wallace *et al.* 2014, Wallace *et al.* 2015). For example, using well characterised models of trophoblast function (2D/3D culture of EVT lines (Keogh *et al.* 2007) and primary EVT explant cultures (Whitley *et al.* 2007, Wallace *et al.* 2013b)), we have shown that dNK cells from nRI pregnancies promote more trophoblast motility, chemotaxis and invasion than those from hRI pregnancies (Wallace *et al.* 2013b). Additionally, we demonstrated that dNK-induced trophoblast chemotaxis and invasion is dependent on ERK1/2 and Akt signalling, and that the dNK from the pregnancies with impaired remodelling are less able to activate these pathways (Wallace *et al.* 2013b). Although dNK have cytotoxic capacity, they do not cause trophoblast death (Kopcow *et al.* 2005), even those isolated from the hRI population (Wallace *et al.* 2013b).

In humans, all of the decidual immune cell types are located around actively remodelling vessels (Smith *et al.* 2009). There is evidence to suggest, particularly in the case of dNK cells, that they may be involved in both the initial changes (prior to the arrival of trophoblast) as well as regulating trophoblast-dependent remodelling (Smith *et al.* 2009, Hazan *et al.* 2010, Fraser *et al.* 2012, Robson *et al.* 2012, Wallace *et al.* 2012, Fraser *et al.* 2015, Lash *et al.* 2016). The structural stability of the vessel wall depends on the interaction between EC and VSMC. Dramatic changes to the architecture of the spiral artery occur as they remodel in the first trimester involving a highly co-ordinated sequence of cellular events (Whitley and Cartwright 2010).

Apoptosis of vascular cells has been implicated in spiral artery remodelling with roles for the Fas and TRAIL pathways demonstrated (Ashton *et al.* 2005, Harris *et al.* 2006, Red-Horse *et al.* 2006, Harris *et al.* 2007, Keogh *et al.* 2007, Hazan *et al.* 2010) and we and others have shown that dNK cells participate in this process (Hazan *et al.* 2010, Fraser *et al.* 2012). Importantly, dNK from the high RI group were less able to carry out this effect (Fraser *et al.* 2012). It is not yet known however whether the other immune cells present near remodelling vessels can influence vascular cell apoptosis in nRI or hRI pregnancies or if they can modulate the role played by dNK cells.

Degradation of the extracellular matrix and dedifferentiation/migration of VSMC disrupt the vessel wall and are important aspects of remodelling (Smith *et al.* 2015). Studies suggest that dNK may participate in these processes (Naruse *et al.* 2009, Hazan *et al.* 2010, Bulmer *et al.* 2012, Robson *et al.* 2012). It remains to be determined whether immune cells from nRI, but not hRI pregnancies, can lead to VSMC de-differentiation as determined by loss of contractile-related proteins including α-smooth muscle actin (α-SMA), calponin, and h-caldesmin and the adoption of a more migratory phenotype. Since there is strong evidence of the role played by trophoblast in vascular cell changes (in de-differentiation (Wallace *et al.* 2013a) and in inducing vascular cell apoptosis (Ashton *et al.* 2005, Harris *et al.* 2006, Harris *et al.* 2007, Whitley and Cartwright 2009) and migration (Bulmer *et al.* 2012, Wallace *et al.* 2013a), the effect of dNK cells in priming trophoblast in preparation for these events may add an additional level of regulation.

**What regulates the dNK cell phenotype?**

The identification of clear differences in the secretion of factors, receptor expression and functional behaviour between dNK cells isolated from pregnancies with normal versus impaired remodelling raises an important question. Since dNK cells are surrounded by a variety of cell types that could be influencing their phenotype - what cells/factors are contributing to the regulation of these differences? The possible input from stromal cells, other immune cells and trophoblast will briefly be discussed.

The number of NK cells in the endometrium increases during the mid-secretory phase of the menstrual cycle and the early stages of pregnancy. This coincides with decidualisation of the endometrium, where uterine stromal cells differentiate to specialised secretory decidual stromal cells (DSC) in the presence of progesterone. It is unclear where the dNK cells originate from; with suggestions that they infiltrate from peripheral blood (pbNK) or that they differentiate from immature endometrial NK cells. However, DSC have been implicated in both mechanisms and it is highly likely that how they recruit and educate NK cells will contribute to the differences we have observed in the dNK from women with a higher risk of pregnancy complications. DSC produce many chemokines such as CXCL8, CXCL10, and CXCL12 which are major NK cell chemoattractants (Carlino *et al.* 2008). DSC secrete TGFβ which has been shown to regulate the adoption of a dNK phenotype by pbNK cells (Keskin *et al.* 2007) and also secrete a range of other cytokines, including IL-11, IL-15 and IL-33, which can regulate the differentiation, function and secretory profile of dNK cells (Ain *et al.* 2004, Manaster *et al.* 2008, Hu *et al.* 2015, Sharma *et al.* 2016). DSC may also act by inhibiting upregulation of activating receptors in NK cells (Croxatto *et al.* 2014).

Macrophages have extraordinary plasticity in their phenotype. Decidual macrophages are generally considered to have a phenotype similar to that of an alternatively-activated macrophage, with expression of genes associated with tissue remodelling and immune modulation. However they also express some genes associated with classically-activated, immune effector macrophages, demonstrating their potential to mount an effective inflammatory response (Gustafsson *et al.* 2008, Houser *et al.* 2011). Decidual macrophages are located in close proximity to dNK cells, in the vicinity of the spiral arteries (Reister *et al.* 1999). Both cell types are present in advance of the invasive trophoblast (King *et al.* 1998), (Smith *et al.* 2009) and while trophoblast are actively remodelling, and are capable of producing an abundance of secreted factors that are likely to exert effects on the other (Lash *et al.* 2016). There is evidence to suggest that decidual macrophages can regulate how dNK cells interact with trophoblast, partly through macrophage production of TGF- (Co *et al.* 2013). In addition decidual macrophages have been shown to regulate dNK cell production of cytotoxic mediators such as perforin, TRAIL and FasL (Laskarin *et al.* 2012), which may be relevant to the ability of dNK to regulate vascular cell apoptosis during the remodelling process (Fraser *et al.* 2012).

T cell subsets in the decidua differ considerably from those in the circulation, with approximately 35% CD4+ and 65% CD8+. An example of a subset that may be particularly important in promoting implantation and immune tolerance are the regulatory T cells (Tregs, CD4+CD25+). The decidua in the first trimester contains many CD4+CD25brightFoxP3+ T cells (Tilburgs *et al.* 2008) and a lower number of Tregs has been associated with PE (Quinn *et al.* 2011). Further complexity has been added to the immune regulatory networks by description of subgroups of innate lymphoid cells (ILCs), other than NK cells, which can contribute regulating the environment at the maternal-fetal interface (Doisne *et al.* 2015). It will be interesting to determine if the T cell and ILC populations differ between the hRI and nRI first trimester tissue and to determine whether this has any functional consequence on interactions with neighbouring cells, such as the dNK cells.

The crosstalk between trophoblast and dNK cells is extensive (Wallace *et al.* 2012). Engagement of specific receptors on dNK cells when they interact with trophoblast has important functional consequences in terms of cytokine and angiogenic factor secretion as well as regulating cytotoxic potential (El Costa *et al.* 2009). It is known that trophoblasts can induce changes in dNK receptors (Zhang *et al.* 2015) for example, the expression of cell surface inhibitory receptors by dNK can be influenced by maternal HLA-C expressed on trophoblast (Sharkey *et al.* 2015). Recent studies also suggest that there can be transfer of HLA-G from trophoblast to dNK thus regulating them in a dynamic and localised manner (Tilburgs *et al.* 2015). It is also interesting to note that in our previous studies we have identified inherent differences in the behaviour of trophoblast cells from pregnancies with impaired spiral artery remodelling (Whitley *et al.* 2007), which highlights the importance of profiling multiple cell types from the same pregnancy.

**Conclusions**

We have demonstrated that dNK cells behave differently at a cellular and molecular level in the first trimester in pregnancies at higher risk of PE/FGR compared to those where spiral artery remodelling is occurring normally. By combining this information with what we know about other cell types in these pregnancies we are starting to develop an integrated picture of the overall events occurring at the maternal-fetal interface. It is only when we increase our understanding of first trimester placental and decidual biology from the same patient that we will be able to establish biological networks, modelling both healthy and pathological pregnancies. Ultimately such understanding will help diagnosis and clinical management.

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