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How Does the Maternal Immune System Contribute to the Development of Pre-eclampsia?

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Abstract

An immunological aura has hovered over the study of pre-eclampsia for many years but there has still been little progress in explaining the various 'immune' phenomena associated with this elusive disease. When considering the *primary* defect of placentation that leads to pre-eclampsia the focus should be on the intermingling of the invasive placental trophoblast cells with maternal leukocytes in the uterine wall. The MHC status of trophoblast cells is a crucial factor to be considered, as these molecules can act as ligands for uterine immune cells, including T cells, NK cells and myelomonocytic cells. Extravillous trophoblast cells express an unusual combination of HLA-C, HLA-G and HLA-E molecules and only one of these HLA molecules, HLA-C, shows any appreciable polymorphism. In humans, uNK cells express an array of receptors, some of which are known to bind to the HLA class I molecules expressed by extravillous trophoblast cells. HLA-C is the dominant ligand for killer immunoglobulin-like receptors (KIR) expressed by uterine NK cells that may deliver an inhibitory or activating signal. KIR haplotypes comprise two groups, A and B; these differ principally by having additional activating receptors in the B haplotype. In any pregnancy, the maternal KIR genotype could be AA (no activating KIR) or AB/BB (presence of between one and five activating KIRs). The HLA-C ligands for KIR on trophoblast cells may belong to two groups, C1 and C2 that are defined by a dimorphism at position 80 of the α1 domain. This maternal–fetal immunological interaction, occurring at the site of placentation, therefore involves two polymorphic gene systems, maternal KIRs and fetal HLA-C molecules. Uterine NK-cell function is thus likely to vary in each pregnancy. In pre-eclamptic pregnancies we have found that some KIR/HLA-C combinations appear unfavourable to trophoblast-cell invasion due to the overall signals that the NK cell receives. The academic excitement of this work is the realisation that this is a novel form of allorecognition based on NK cells that operates entirely differently from self/non-self discrimination used by T cells.

Keywords: Pre-eclampsia; NK cell; Trophoblast; Killer immunoglobulin-like receptor; HLA-C

1. Immune phenomena in pre-eclampsia

Although pre-eclampsia remains a 'disease of theories', two observations about this disease have stood the test of time. Firstly, it is generally agreed that the primary pathogenesis of the condition in most cases is inadequate transformation of the spiral arteries by extravillous trophoblast cells (EVT) [1]. Secondly, the view that some sort of 'immune maladaptation' is responsible for the development of the disease is widely held [2,3]. How can these two observations be reconciled?

The initial reports from Robertson, Pijnenborg and colleagues that trophoblast invasion was defective in pre-eclampsia have been confirmed in numerous studies and are now supported by Doppler ultrasound studies of maternal uterine blood flow [4,5]. Many mechanisms have been proposed to explain what controls the degree of infiltration of trophoblast. The immune cells of the mother are good candidates because these are the cells in an individual that are capable of discriminating between foreign fetal trophoblast cells and 'self' maternal cells. When thinking about the regulation of placentation this means that it is the immune cells in the uterus that

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are important to consider. As the trophoblast cells migrate through the decidua they contact leukocytes that are predominantly components of the innate immune system, natural killer (NK) cells and macrophages [6]. How can the immune phenomena associated with pre-eclampsia be connected with the local uterine immune response?

Traditionally, immune responses have been characterised by the features of memory and specificity. Pre-eclampsia is mainly a disease of primiparous women and subsequent pregnancies seem to be at low risk [7–9]. This has been considered akin to a 'vaccination' by the placenta so that after a first exposure the mother is protected. The protective effect of the first pregnancy has been interpreted as similar to immunological memory but, importantly, this is only seen if the first pregnancy is normal. In contrast, if the first pregnancy is complicated by pre-eclampsia then subsequent pregnancies are still at considerable risk [10,11]. Therefore, the pre-eclamptic placenta seems not to exert the same protective effect, an observation that is more difficult to explain in terms of immunological memory.

The concept of immunological specificity in pre-eclampsia refers to the disease being partner specific. Whether this occurs or not is a subject of continual debate because of additional confounding factors such as a long birth interval [8,12]. Recent reports suggest that as the years accumulate after a first pregnancy then the risk does fall in women who have not had pre-eclampsia irrespective of the partner. However, there are many other studies that have shown that if the first pregnancy is normal then the risk does increase in subsequent pregnancies if there is a change of partner. Conversely, if a primipara has pre-eclampsia, then the risk falls with a change of partner [13,14]. A further observation that might have an immunological explanation is that in pregnancies resulting after oocyte donation the risk of pre-eclampsia is increased up to 30% [15]. In this situation, in immunological terms, the fetus is entirely 'non-self' and completely lacks the recipient mother's 'self'.

2. Immunology of placentation: NK cell receptors and trophoblast ligands

Both parents have a genetic contribution to pre-eclampsia but it is clear that the mother's contribution is greater than the father's [16,17]. No particular genes have been identified as yet and the possibility that some could be immune system genes is still open. Certain ethnic groups have a particularly high incidence of the disease, notably Afro-Caribbeans and African Americans. Furthermore, there is an increased incidence when there is racial dissimilarity between the parents [18,19]. The obvious gene system that shows considerable ethnic variation is the major histocompatibility complex (MHC), but there have not been any convincing associations of any particular MHC genes or of phenomena such as MHC sharing between parents to indicate that the MHC is of importance in the development of the syndrome.

How can all these observations be viewed in the context of the maternal immune response to the invading trophoblast? Previous attempts to explain how the immune system functions in normal and abnormal pregnancies have generally centred on the necessity for maternal T-cell immunomodulation as set out by Medawar [20]. The problems with using this old paradigm are two: Firstly, T cells are a minor component of lymphocytes at the placental bed; it is NK cells that make up to 70% of decidual leukocytes. Secondly, EVT does not display any major T-cell ligands, specifically HLA class II and HLA-A and HLA-B class I molecules [6]. Instead, the invading trophoblast cells express an unusual and unique combination of three class I molecules, HLA-G, HLA-E and HLA-C. Of these only HLA-C shows any appreciable polymorphism and will therefore vary depending on the father's contribution. Furthermore, HLA-C is the dominant ligand for NK cells, making it an attractive candidate for a trophoblast molecule that is recognised by uterine NK cells. The receptors that bind to different groups of HLA-C allotypes are known as killer immunoglobulin-like receptors (KIR) [21,22]. Like the MHC, this family of genes also shows extreme genomic variation both in the number of individual KIR genes an individual possesses together with allelic polymorphism at each KIR locus. Thus, there is a receptor-ligand system, KIR in the mother and HLA-C in the fetal trophoblast, where both elements show polymorphism. It is possible that certain combinations of particular KIR with HLA-C ligands may not allow optimal trophoblast invasion and these would be associated with pre-eclampsia.

We therefore compared the KIR and HLA-C genotypes in women with pre-eclampsia and those who had normal pregnancies [23]. HLA-C allotypes can be discriminated by KIR as two groups that differ at position 80 of the α1 domain, HLA-C1^{asn80} and HLA-C2^{lys80} (Fig. 1). Both groups can be recognised by KIR that are either inhibitory or activating, so that the balance of signals the NK cells receives will vary depending on the combination of KIR available for a particular HLA-C ligand. KIR genotypes can be simply divided into two haplotypes, A and B. The A haplotype has only inhibitory

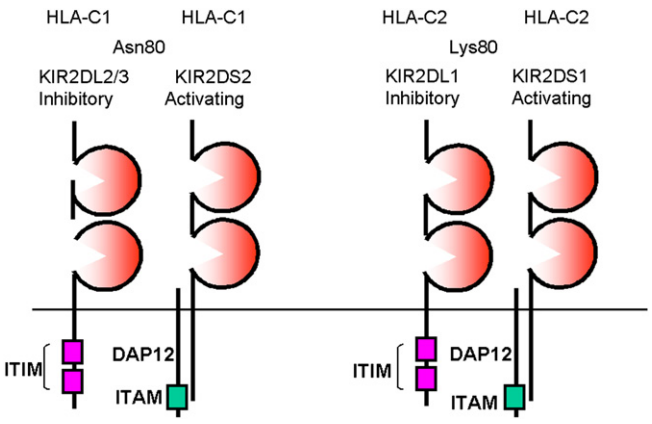

Fig. 1. KIR receptors and their HLA-C ligands. Both HLA-C1 and HLA-C2 groups have corresponding inhibitory and activating KIR receptors. Inhibitory receptors signal through intra-cellular ITIM motifs and activating receptors on association with the adaptor molecule DAP-12 which has ITAM motifs.