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The influence of the maternal uterine immune response on placentation in human subjects

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The immunological relationship between the mammalian fetus and its mother during pregnancy has been considered similar to that between a transplanted allograft and its recipient ever since Medawar (1953) first proposed the concept of the ‘fetus as an allograft’ in the early 1950s. Based on this analogy, it has been assumed that implantation of the fetal placenta in the uterus would be controlled similarly by a maternal immune response mediated by T-cells recognizing paternally-derived alloantigens expressed by the placenta. Surprisingly, recent evidence suggests that implantation might involve predominantly a novel allogeneic recognition system based on natural killer cells rather than T-cells (Loke & King, 1995). The cellular and molecular basis of this local immune interaction between the fetal placenta and maternal uterus is now the focus of intense research interest. Since aberrant implantation can cause a variety of clinical problems, including miscarriage, intrauterine growth retardation and pre-eclampsia, an understanding of the immunological mechanism by which this process is controlled could lead to the development of regimens to improve fetal growth and development.

Placenta: Trophoblast: Natural killer cells: Immunology

An essential feature of mammalian pregnancy is the formation of a specialized organ, the placenta, which is responsible for physiological exchange between the developing fetus and its mother *in utero*. Establishment of the placenta involves a series of events known as implantation, when fetally-derived placental cells (trophoblast) invade a modified layer of maternally-derived mucosal tissue lining the pregnant uterus (decidua). Human implantation is particularly invasive compared with most other species, with placental trophoblast cells infiltrating deep into the myometrium. Since this process results in the intimate admixture of cells from a genetically-dissimilar fetus with those of the mother, the relationship between the placenta and the uterus is comparable with that between a clinically-transplanted graft and its recipient. It was assumed, therefore, that implantation would be similarly governed by the laws of classical transplantation immunology, with a maternal T-cell response to the non-self histocompatibility

antigens of the fetal placenta. Surprisingly, recent research reveals the situation to be more complex, in that implantation appears to be influenced predominantly by an unusual and perhaps unique immune system whose mechanisms have yet to be clearly defined, but which probably involves natural killer (NK) cells rather than T-cells. It is exciting to reproductive biologists as well as to immunologists that implantation could hold the key to a novel mechanism of self–non-self recognition. This process is also of great importance to obstetricians, as the underlying aetiology of several pathological conditions of pregnancy may be defective trophoblast–decidual interaction (Loke & King, 1995).

Placentation and fetal growth

An important function of the invading trophoblast is to destroy the muscular walls of the uterine spiral arteries,

Abbreviations: HLA, human leucocyte antigens; ILT, immunoglobulin-like transcripts; KAR, killer activatory receptors; KIR, killer inhibitory receptors; NK, natural killer.

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converting them into large, flaccid vessels that are no longer capable of responding to vasoactive stimuli and are capable of high conductance. This vascular transformation is essential to provide an adequate blood supply to the rapidly-growing fetus and placenta. The blood flow will be compromised if there is inadequate trophoblast invasion. This can lead to a variety of clinical pathological conditions such as miscarriage, unexplained intrauterine growth retardation, stillbirth or pre-eclampsia (Pijnenborg, 1994). At the other end of the spectrum, trophoblast over-invasion deep into the myometrium and even through to the peritoneum can occur. In this condition, placenta percreta, implantation usually occurs on areas of the uterus where the decidua is deficient, such as on a previous caesarian section scar. This illustrates that the inherently invasive proclivities of trophoblast are normally modulated by maternal decidua. Thus, implantation may be viewed as a parental tug-of-war, where the aggressive behaviour of the fetal trophoblast is constantly kept in check by the mother (Haig, 1993).

The importance of arterial modification by trophoblast can be appreciated by pathological studies of the placental bed in cases of intrauterine growth retardation where absence of trophoblast invasion of the deeper segments of myometrial spiral arteries has been demonstrated. Recent epidemiological evidence that small size at birth is related to the development of hypertension, diabetes and coronary artery disease in later life indicates that an insult at a critical period of intrauterine development could have far reaching consequences (Barker, 1994). The relative importance of maternal nutrition *v.* correct placentation in determining normal fetal growth is much debated. However, in developed countries it would be fair to suppose that nutritional influences are likely to be of less importance than the development of a good uterine blood supply to deliver nutrients and O₂ to the growing fetus. Fundamental to this is the extent and depth of trophoblast invasion into uterine arteries in the early weeks of pregnancy.

Pre-eclampsia, or pregnancy-induced hypertension, has a very similar mechanism of induction to that of intrauterine growth retardation and also results from inadequate transformation of uterine spiral arteries by trophoblast. The difference between the two conditions is that pre-eclampsia has a superimposed maternal systemic syndrome. The symptoms are diverse, but usually include hypertension, proteinuria and oedema. These are thought to be triggered by widespread endothelial cell activation resulting from placental ischaemia inducing the liberation of some as yet unidentified factors (Wallenburg & Visser, 1994). The disease occurs predominantly in primigravidae. Other maternal factors which increase the risk of developing pre-eclampsia include a positive family history and being at the extremes of reproductive life. However, paternal factors are also important, because a multiparous woman who becomes pregnant by a new partner will have a level of risk equivalent to that of a primigravida. This points to an interaction between fetal and maternal genes, which then precipitates the onset of the disease (Cooper *et al.* 1993; Terje *et al.* 1998). Certain combinations of these genes could 'pitch' strong maternal resistance against weak trophoblast invasion, giving rise to pre-eclampsia and also to intrauterine growth retardation.

Trophoblast expression of major histocompatibility complex antigens

As the genes responsible for recognition of non-self in graft rejection are the highly polymorphic major histocompatibility complex antigens, it is obviously important to look for expression of these genes on trophoblast. Major histocompatibility complex class I antigens are expressed on the surface of most nucleated cells, and in human subjects are known as human leucocyte antigens (HLA; Janeway & Travers, 1996). At present, six HLA class I loci that have expressed protein products are recognized: three 'classical' loci (HLA-A, -B, and -C) and three 'non-classical' loci (HLA-E, -F, and -G). The three classical antigens are those normally expressed by nucleated cells. Intriguingly, the population of trophoblast cells invading the uterus (collectively known as extravillous trophoblast) are found to express at least one classical molecule (HLA-C; King *et al.* 1996) and one non-classical molecule (HLA-G; Kovats *et al.* 1990; Ellis *et al.* 1990).

Until very recently, HLA-G had commanded most attention because it is apparently only expressed in abundance by extravillous trophoblast, although this is still debated. It is accepted that HLA-G mRNA is present in a variety of cell types besides extravillous trophoblast, but the tissue distribution of the HLA-G protein is controversial. This is because of the lack of a specific antibody against HLA-G. Such an antibody has been difficult to make because of the high degree of structural similarity between the different HLA class I antigens. Some investigators have used synthetic peptides corresponding to specific amino acid sequences of HLA-G as an immunogen (McMaster *et al.* 1995). Others have immunized either HLA-A or HLA-B transgenic mice with HLA-G-transfected cells (Chumbley *et al.* 1994; Bensussan *et al.* 1995). The rationale for this strategy is that an antibody should be produced with a restricted specificity, because the recipient mice are tolerant to the common HLA epitopes and will only recognize the HLA-G-specific sequences. Using antibodies generated by both these methods, two studies have reported that HLA-G protein is expressed only by extravillous trophoblast (Chumbley *et al.* 1994; McMaster *et al.* 1995), while one study claims that even non-trophoblast elements of the placenta (e.g. chorionic villous mesenchyme and macrophages; Yang *et al.* 1996) are also stained. To date, only one study using immunohistology has surveyed a wide panel of fetal tissues, none of these expressed HLA-G protein (Chumbley *et al.* 1994). More studies of this kind with different antibodies are needed to confirm these observations. Meanwhile, the balance of evidence would seem to warrant the conclusion that abundant expression of the HLA-G protein is probably restricted to extravillous trophoblast, in spite of a more widespread pattern of tissue distribution of HLA-G mRNA.

The possibility that extravillous trophoblast might express other HLA class I antigens besides HLA-G has been suspected for some time, because immunoprecipitation of labelled trophoblast proteins identifies two class I heavy chains of 45 kDa and 39 kDa associated with β_2 -microglobulin. The smaller of the two is now established to be HLA-G, but the nature of the larger heavy chain was

unclear. Evidence that this could be HLA-C was provided by recent demonstration of HLA-C mRNA from highly-purified trophoblast cells obtained by flow cytometric sorting. In addition, the expression of HLA-C protein was found with a specific monoclonal antibody (King *et al.* 1996). Thus, in the formulation of any hypothesis regarding immune recognition of extravillous trophoblast by the mother, it is necessary to consider both HLA-G and HLA-C. Furthermore, placental expression of another non-classical HLA class I molecule, HLA-E, has also been reported (Le Bouteiller & Lenfant, 1996). The pattern of mRNA expression shows that this is not restricted to tissues at the materno-fetal interface, but elucidation of the tissue pattern of HLA-E protein expression must await the development of an HLA-E specific antibody.

The functions of trophoblast HLA-G, HLA-C and HLA-E are still not known, but this area is currently the subject of intense research interest. Soon after the discovery of HLA-G one view was that such non-classical HLA class I molecules had no function but were merely vestigial molecules left behind by evolution (Parham, 1995). However, there is recent evidence that HLA-G can bind nine amino acid peptides derived from cellular proteins in an identical manner to that for classical class I HLA molecules (Lee *et al.* 1995; Diehl *et al.* 1996). The HLA-G peptides have their own specific sequence motif, suggesting that this non-classical class I molecule is potentially capable of presenting antigens to T-cells in the same way as classical class I molecules. New findings have also indicated that HLA-G might not be as monomorphic as initially thought, although the polymorphic residues were (apart from one) away from the region of the peptide-binding groove (van der Ven & Ober, 1994). Thus, there does not appear to be the same degree of selective pressure for increasing the diversity of peptides bound by HLA-G as there is for HLA-A and HLA-B, which present a diverse array of peptides to T-cells. Indeed, T-cells which recognize HLA-G and its bound peptide have yet to be detected.

The classical class I HLA-C is also somewhat unusual when compared with HLA-A and HLA-B. HLA-C has low cell surface expression and is less polymorphic than HLA-A,B, especially when positions around the peptide-binding groove are compared. These observations have raised the question of whether HLA-C is 'declining' in functional efficiency as a T-cell recognition molecule (Zemmour & Parham, 1992). HLA-E also shares the characteristics of low surface expression and minimal polymorphism. Table 1 summarizes some of the contrasting features of trophoblast HLA class I molecules compared with HLA-A and HLA-B. The overall impression is that

HLA-G, HLA-C and HLA-E might not be as important as ligands for T-cells as classical HLA molecules, HLA-A and HLA-B. It increasingly looks as if NK cells are more likely candidates for binding to trophoblast HLA class I molecules.

Leucocyte populations in the uterus

Analysis of the leucocytes in the uterus has shown that NK cells are the predominant population (Loke & King, 1995). They are also referred to as large granular lymphocytes because of the prominent granules in their cytoplasm. The total number of these cells in the uterine mucosa varies throughout the menstrual cycle. They are sparse during the proliferative phase, increase significantly throughout the secretory phase, and remain in high numbers in the decidua during the early stages of gestation. Their numbers are particularly high in *decidua basalis* at the site where trophoblast cells invade into the uterus. This temporal association with the menstrual cycle argues for a potential role of oestrogen and progesterone in the recruitment and/or proliferation of uterine NK cells. The mechanisms of action of these hormones on NK cells are however unknown. Their action is likely to be indirect because oestrogen or progesterone receptors are not expressed by uterine NK cells.

Phenotypically, decidual NK cells (CD56^{bright} CD16⁻) differ from NK cells in peripheral blood (CD56^{dim} CD16⁺). This suggests that either decidual NK cells represent a distinct subpopulation of circulating NK cells, or that they have undergone some tissue-specific differentiation. Which of these possibilities is the correct one has not yet been established. Interestingly, it has been reported that uterine NK cells share many phenotypic features with NK cells isolated from fetal liver. This indicates that NK cells with the uterine phenotype are already present very early in ontogeny, even before the appearance of T-cells (Lanier *et al.* 1992). Macrophages are also abundant at the implantation site, but these have been studied very little. However, the observation that NK cells and macrophages and not T- and B-cells comprise the major population of leucocytes in the uterus lends further support to the idea that implantation is likely to involve an innate immune system that is distinct from that seen in clinical organ transplantation, where rejection is mediated by cells of the specific immune system, T- and B-cells.

Trophoblast – natural killer cell interaction

The paucity of T-cells at the implantation site and the difficulty in demonstrating any immune reactivity of these T-cells towards invading trophoblast in human pregnancy have shifted the focus of attention towards NK cells. The accumulation of NK cells in the uterus coincident with the period of implantation, and the close anatomical relationship between these NK cells and invading trophoblast, have led to the proposal that interaction between invading trophoblast and decidual NK cells could provide the basic mechanism for allogeneic recognition of the placenta by the mother, and thus control implantation (Loke & King, 1995). The mechanisms of action of NK cells in general remain

Table 1. Characteristics of human leucocyte antigen (HLA)-C, HLA-G and HLA-E compared with HLA-A and HLA-B

HLA-C, HLA-G and HLA-E	HLA-A and HLA-B
Low surface expression	High surface expression
Few alleles	Many alleles
Polymorphism not concentrated at antigen-binding site	Polymorphism concentrated at antigen-binding site
Reactive T-cells occasionally demonstrable to HLA-C but not to HLA-G	Reactive T-cells readily demonstrable

largely undefined. However, there has been a sudden explosion of information in the past year that has increased our understanding considerably. So far, most of the information obtained is from studies on human peripheral-blood NK cells; it remains to be seen whether they are also applicable to uterine NK cells. Nevertheless, some of the principles established will provide a useful framework for consideration of decidual NK cell function.

In the context of implantation the important findings are that NK cells do express receptors capable of recognizing HLA class I molecules (Moretta & Moretta, 1997; Yokoyama, 1998). The first family of NK receptors to be found belong to the immunoglobulin superfamily, and are known as killer inhibitory receptors (KIR) because interaction with class I HLA molecules leads to the transmission of negative signals that will inhibit cytolysis or cytokine production. Subsequently, other members of the same receptor family were observed to transmit positive signals that would trigger effector functions such as killing or production of cytokines (Biassoni *et al.* 1996). These latter are known as killer activatory receptors (KAR). Both KIR and KAR are transmembrane glycoproteins and are distinguished by two distinct transmembrane and cytoplasmic domain arrangements which are responsible for either their activatory or inhibitory signalling roles. Amongst members of the KIR–KAR family there is considerable diversity in the extracellular domains which permit the receptors to discriminate between different polymorphic HLA class I molecules. Interestingly, the class I locus that might be most pertinent in influencing NK function is HLA-C (Colonna *et al.* 1993), and two subtypes of KIR–KAR that recognize all HLA-C alleles as two distinct groups have been characterized (Lanier & Phillips, 1996). The repertoire of KIR–KAR has been shown to vary between different individuals. In addition, NK cells can be found in individuals which express a particular KIR, although the individual does not possess the relevant class I ligand (Gumperz & Parham, 1995). This indicates that a mechanism for NK allogeneic recognition is in place if it should be needed (e.g. in implantation).

The second NK cell receptor family for class I HLA molecules is known as CD94–NKG2 (Phillips *et al.* 1996; Yokoyama, 1998). These receptors are encoded by NK-associated genes located closely together as an NK complex which encodes for type II membrane glycoproteins with an external lectin-like domain (NK lectins). CD94 forms heterodimers with members of the NKG2 family (Lazetic *et al.* 1996). CD94–NKG2 has recently been found to bind to HLA-E class I molecules (Braud *et al.* 1998). The latest receptor family thought to be involved in HLA recognition by leucocytes is the immunoglobulin-like transcripts (ILT) family (Colonna *et al.* 1997, 1998). Unlike KIR and CD94–NKG2, ILT receptors are not expressed selectively by NK cells but are also found on monocytes, macrophages and B-cells. Some members of this ILT family (ILT2 and ILT4) are reported to bind to HLA class I molecules, including HLA-G (Colonna *et al.* 1997, 1998).

Thus, NK cell receptors have been described which could recognize all three trophoblast HLA class I molecules. Are these receptors expressed at the maternal–fetal interface in the uterus by decidual NK cells and other maternal leucocytes? The information on decidual leucocytes is still

sparse. The evidence so far indicates that decidual NK cells do express the same range of KIR–KAR as that described in peripheral-blood NK cells, and no new receptors have been identified (Hiby *et al.* 1997). The repertoire of KIR expressed by decidual NK cells differs in different women. Furthermore, in the same woman the repertoire of KIR expressed by decidual NK cells is different from that expressed by peripheral-blood NK cells (Verma *et al.* 1997). The mother's ability to recognize different HLA-C alleles on trophoblast, therefore, could vary, depending on the paternal HLA-C allele expressed and the repertoire of KIR specific for HLA-C alleles expressed by the mother.

CD94–NKG2 molecules are expressed strongly by virtually all decidual NK cells, and this is again in contrast to findings on peripheral-blood NK cells. We have recent evidence that CD94–NKG2 on decidual NK cells will bind strongly to HLA-E molecules (DSJ Allan, VM Braud, A King, S Verma, M McMichael and YW Loke, unpublished results). In addition, members of the ILT family are also expressed by a subpopulation of decidual NK cells and, interestingly, also by uterine macrophages. However, conclusive proof that ILT receptors can recognize HLA-G is still lacking.

To summarize, *in vivo* a potential scenario could be that decidual NK cells recognize HLA-C, HLA-G and HLA-E expressed by invading trophoblast via KIR–KAR, CD94–NKG2 and ILT receptors, resulting in a combination of positive and negative signals which regulate cytokine production and cytolysis. Decidual NK cells are known to secrete a variety of cytokines, and trophoblast cells do express receptors for many of these cytokines, so the potential for decidual NK cells influencing trophoblast growth, differentiation or migration by a paracrine network is certainly possible. In this way, a correct balance between placental invasion and maternal resistance could be achieved. The limited polymorphism exhibited by all trophoblast HLA class I molecules, together with the heterogeneity of NK cell receptor expression in different individuals, would suggest that this recognition system between maternal uterus and placenta is capable of variable outcomes in different pregnancies. It is tempting to suggest that certain combinations might prove less optimal than others, leading to poor control of trophoblast invasion and the resultant clinical conditions described earlier.

Conclusion

From the preceding discussion it is clear that the immunological mechanisms involved in human implantation are not the same as those encountered in organ transplantation in spite of superficial resemblance. Implantation appears to be influenced more by an NK cell rather than a T-cell allorecognition system. This new insight has altered our conceptual view of the immunology of implantation, and could lead to a new approach in the study of this vital stage of reproduction. Elucidation of the mechanisms by which maternal decidual leucocytes, including NK cells, control implantation is an important step towards a clearer understanding of how normal placentation is regulated and achieves the greatly increased uterine blood flow required for normal fetal growth.

References

- Barker DJB (1994) *Mothers, Babies, and Disease in Later Life*. London: BMJ Publishing Group.
- Bensussan A, Mansur I-G & Mallet V (1995) Detection of membrane-bound HLA-G translated products with a specific monoclonal antibody. *Proceedings of the National Academy of Sciences USA* **92**, 10292–10296.
- Biaassoni R, Cantoni C, Falco M, Verdiani S, Bottino C, Vitale M, Conte R, Poggi A, Moretta A & Moretta L (1996) The human leukocyte antigen (HLA)-C-specific 'activatory' or 'inhibitory' natural killer cell receptors display highly homologous extracellular domains but differ in their transmembrane and intracytoplasmic portions. *Journal of Experimental Medicine* **183**, 645–650.
- Braud VM, Allan DSJ, O'Callaghan CA, Soderstrom K, D'Andrea A, Ogg GS, Lazetic S, Young NT, Bell JI, Phillips JH, Lanier LL & McMichael AJ (1998) HLA-E binds to natural killer cell receptors CD94/NKG2A, B and C. *Nature* **391**, 795–799.
- Chumbley G, King A, Gardner L, Howlett S, Holmes N & Loke YW (1994) Generation of an antibody to HLA-G in transgenic mice and demonstration of the tissue reactivity of this antibody. *Journal of Reproductive Immunology* **27**, 173–186.
- Colonna M, Borsellino G, Galco M, Ferrara GB & Strominger JL (1993) HLA-C is the inhibitory ligand that determines dominant resistance to lysis by NK1- and NK2-specific natural killer cells. *Proceedings of the National Academy of Sciences USA* **90**, 12000–12004.
- Colonna M, Navarro F, Bellón T, Llano M, Garcia P, Samaridis J, Angman L, Cella M & López-Botet M (1997) A common inhibitory receptor for major histocompatibility complex class I molecules on human lymphoid and myelomonocytic cells. *Journal of Experimental Medicine* **186**, 1809–1818.
- Colonna M, Samaridis J, Cella M, Allen RL, O'Callaghan CA, Dunbar R, Ogg GS, Cerundolo V & Rolink A (1998) Human myelomonocytic cells express an inhibitory receptor for classical and nonclassical MHC class I molecules. *Journal of Immunology* **160**, 3096–3100.
- Cooper DW, Brennecke SP & Wilton AM (1993) Genetics of pre-eclampsia. *Hypertension in Pregnancy* **12**, 1–23.
- Diehl M, Münz C, Keilholz W, Stevanovic S, Holmes N, Loke YW & Rammensee HG (1996) Non-classical HLA-G molecules are classical peptide presenters. *Current Biology* **6**, 305–314.
- Ellis SA, Palmer MS & McMichael J (1990) Human trophoblast and the choriocarcinoma cell line BeWo express a truncated HLA class I molecule. *Journal of Immunology* **144**, 731–735.
- Gumperz JE & Parham P (1995) The enigma of the natural killer cell. *Nature* **378**, 245–248.
- Haig D (1993) Genetic conflicts in human pregnancy. *Quarterly Review of Biology* **68**, 495–532.
- Hiby SE, King A, Sharkey AM & Loke YW (1997) Human uterine NK cells have a similar repertoire of Killer Inhibitory and Activatory receptors to those found in blood, as demonstrated by RT-PCR and sequencing. *Molecular Immunology* **34**, 419–430.
- Janeway CA & Travers P (1996) *Immunobiology: The Immune System in Health and Disease*. London: Current Biology Ltd.
- King A, Boocock C, Sharkey A, Gardner L, Beretta A, Siccardi AG & Loke YW (1996) Evidence for the expression of HLA-C class I mRNA and protein by human first trimester trophoblast. *Journal of Immunology* **156**, 2068–2076.
- Kovats S, Main EK, Librach C, Stubblebine M, Fisher SJ & DeMars R (1990) A class I antigen, HLA-G, expressed in human trophoblasts. *Science* **248**, 220–223.
- Lanier LL, Chang C, Spits H & Phillips JD (1992) Expression of cytoplasmic CD3ε proteins activated human adult natural killer (NK) cells and CD3γ,δ,ε complexes in fetal NK cells. *Journal of Immunology* **149**, 1876–1880.
- Lanier LL & Phillips JH (1996) Inhibitory MHC class I receptors on NK cells and T cells. *Immunology Today* **17**, 86–91.
- Lazetic S, Chang C, Houchins JP, Lanier LL & Phillips JH (1996) Human natural killer cell receptors involved in MHC class I recognition are disulfide-linked heterodimers of CD94 and NKG2 subunits. *Journal of Immunology* **157**, 4741–4745.
- Le Bouteiller P & Lenfant F (1996) Antigen-presenting function(s) of the non-classical HLA-E, -F and -G class I molecules: the beginning of a story. *Research in Immunology* **147**, 301–313.
- Lee N, Malacko AR, Ishitani A, Chen MC, Bajorath J, Marquardt H & Geraghty DE (1995) The membrane-bound and soluble forms of HLA-G bind identical sets of endogenous peptides but differ with respect to TAP association. *Immunity* **3**, 591–600.
- Loke YW & King A (1995) *Human Implantation: Cell Biology and Immunology*. Cambridge: Cambridge University Press.
- McMaster MT, Librach CL, Zhou Y, Lim KH, Janatpour MJ, DeMars R, Kovats S, Damsky C & Fisher SJ (1995) Human placental HLA-G expression is restricted to differentiated cytotrophoblasts. *Journal of Immunology* **154**, 3771–3778.
- Medawar PB (1953) Some immunological and endocrinological problems raised by the evolution of viviparity in vertebrates. *Proceedings of the Society for Experimental Biology*, pp. 320–338. New York: Academic Press.
- Moretta A & Moretta L (1997) HLA class I specific inhibitory receptors. *Current Opinion in Immunology* **9**, 694–701.
- Parham P (1995) Antigen presentation by class I major histocompatibility complex molecules: a context for thinking about HLA-G. *American Journal of Reproductive Immunology* **34**, 10–19.
- Phillips JH, Chang CW, Mattson J, Gumperz JE, Parham P & Lanier LL (1996) CD94 and a novel associated protein (94AP) form a NK cell receptor involved in the recognition of HLA-A, HLA-B, and HLA-C allotypes. *Immunity* **5**, 163–172.
- Pijnenborg R (1994) Trophoblast invasion. *Reproductive Medicine Review* **3**, 53–73.
- Terje R, Rasmussen S, Brunborg H, Gjessing HK, Lie-Nielsen E & Irgens LM (1998) Fetal and maternal contributions to risk of pre-eclampsia: population based study. *British Medical Journal* **316**, 1343–1347.
- van der Ven K & Ober C (1994) HLA-G polymorphisms in African Americans. *Journal of Immunology* **153**, 5628–5633.
- Verma S, King A & Loke YW (1997) Expression of killer-cell inhibitory receptors (KIR) on human uterine NK cells. *European Journal of Immunology* **27**, 979–983.
- Wallenburg HCS & Visser W (1994) Pregnancy-induced hypertensive disorders. *Current Opinion in Obstetrics and Gynaecology* **6**, 19–29.
- Yang Y, Chu W, Geraghty DE & Hunt JS (1996) Expression of HLA-G in human mononuclear phagocytes and selective induction by IFN-γ. *Journal of Immunology* **156**, 4224–4231.
- Yokoyama WM (1998) HLA class I specificity for natural killer cell receptor CD94NKG2A: two for one in more ways than one. *Proceedings of the National Academy of Sciences USA* **95**, 4791–4794.
- Zemmour J & Parham P (1992) Distinctive polymorphism at the HLA-C locus: implications for the expression of HLA-C. *Journal of Experimental Medicine* **176**, 937–950.