Transplant International ISSN 0934-0874

REVIEW

The influence of inherited and noninherited parental antigens on outcome after transplantation

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Keywords
HLA, inherited paternal HLA antigens, noninherited maternal HLA antigens, transplantation tolerance.

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Received: 9 January 2006
Revision requested: 1 February 2006
Accepted: 13 February 2006

doi:10.1111/j.1432-2277.2006.00304.x

Summary

Contact between the immune systems of mother and child during pregnancy has an impact on transplantation later in life. Exposure to inherited paternal human leukocyte antigens (HLA) (IPA) and the noninherited maternal HLA antigens (NIMA) can lead to either immunization or tolerization. Exposure to IPA seems to have a more immunizing effect as the mature immune system of a mother can form anti-HLA antibodies against the foreign paternal HLA molecules. On the other hand, exposure of a child to the NIMA antigens during pregnancy may lead to NIMA-specific tolerance. This review provides an overview of the current knowledge on the impact of this fetal–maternal interaction on the alloimmune response and clinical transplantation.

Introduction

Kidney transplantation is the therapy of choice for patients with end-stage renal failure. However, the number of grafts derived from cadaveric donors is not sufficient to overcome the need for donor kidneys. Furthermore, the high degree of polymorphism of the human leukocyte antigens (HLA) system makes it very difficult to find a well-matched donor [1,2]. Hence, more living-related transplantations are performed.

Graft survival is optimal when donor and recipient are HLA identical, as is the case with an HLA-identical sibling. However, in most situations, this is not possible and, therefore, also haplo-identical siblings, parents, offspring and spouses are considered as potential donors. Contact between mother and child during pregnancy can lead to either immunization or tolerization and subsequently this can have an effect on transplant outcome. A new nomenclature was proposed to assign the haplotypes of a family in which one of the siblings is a potential kidney recipient [3,4] (Fig. 1). The parents or siblings that share one haplotype with the recipient and differ for the other haplotype are potential donors. The patient inherited the IMA (inherited maternal HLA antigens) haplotype from the mother and the IPA (inherited paternal HLA antigens) from the father. When the patient is transplanted with a kidney from one of the parents or from a haplo-identical sibling, the noninherited maternal HLA antigens (NIMA) or noninherited paternal HLA antigens (NIPA) are the mismatched haplotype. This scheme can also be used in case the mother or the father is the potential kidney recipient. In case the mother is transplanted with a kidney from her offspring or from her husband the IPA is the mismatched haplotype.

Several studies have been performed to investigate the influence of noninherited and inherited parental antigens on transplantation and both immunizing (especially IPA) and tolerizing (the NIMA effect) effects have been described. This review article provides an overview of the current knowledge about inherited and noninherited parental antigens and their influence on transplantation.

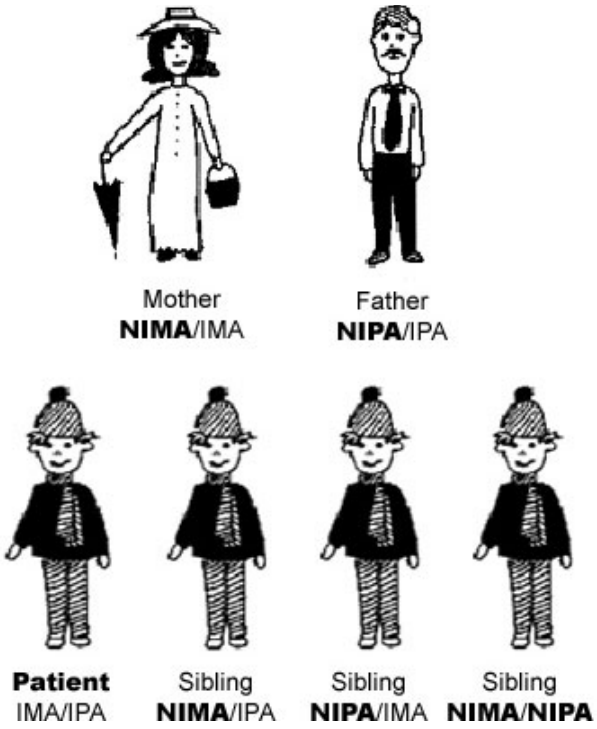


Figure 1 The NIMA nomenclature is patient-oriented; children inherit one haplotype form each of the parents. Siblings of the patient share one haplotype with the recipient and the other haplotype is the noninherited haplotype. Potential donors that are HLA identical are not illustrated. The patient inherited the IMA (inherited maternal HLA antigens) haplotype from the mother and the IPA (inherited paternal HLA antigens) from the father. When the patient is transplanted with a kidney from one of the parents or from a haplo-identical sibling, the noninherited maternal HLA antigens (NIMA) or noninherited paternal HLA antigens (NIPA) are the mismatched haplotype. In case a (multi)-parous mother is the potential kidney recipient, her child (or children) inherited HLA antigens from the father. These HLA antigens are called IPA. When the mother is transplanted with a kidney from either the offspring or the husband, the IPA is the mismatched haplotype.

Inherited paternal antigens (IPA) and influence on transplant outcome

Patients on the waiting list for kidney transplantation can be sensitized to HLA antigens through pregnancy, blood transfusion(s) and previous transplantation. The formation of antibodies directed against HLA is a major risk factor for transplant outcome.

Antibodies that are directed towards the paternal HLA antigens are found in 15–30% of women who have been pregnant [5,6]. The immunogenicity of paternal HLA antigens leading to antibody formation during pregnancy is determined by both the mismatched HLA antigens of the child and the HLA phenotype of the mother [7]. Because contact with allogeneic (paternal) HLA antigens can lead to the activation of the maternal immune system, some transplant centers have the policy of never to transplant female patients with a graft that carries HLA mismatches shared by the husband.

IPA in husband-to-wife transplantations

Several studies have investigated the influence of IPA on transplant outcome. Terasaki *et al.* showed that there was no difference in transplant survival between wife-to-husband and husband-to-wife transplantations when women had never been pregnant [8]. However, when women had previously been pregnant, graft survival was slightly lower in the husband-to-wife situation. A study by Berloco *et al.* also showed a slightly lower graft survival in husband-to-wife transplantation compared with wife-to-husband transplantation, although pregnancy was not included as a parameter in this study [9]. Furthermore, a single center study showed that the frequency of rejection episodes was similar in wife-to-husband and husband-to-wife transplantation. However, the start of the first rejection episode tended to occur earlier in husband-to-wife transplantation, while in addition steroid-resistant rejection occurred more often in husband-to-wife transplantation [10]. Pollack *et al.* showed a correlation between an unfavorable graft outcome and sharing of immunogenic mismatched HLA-A or -B antigens between cadaveric donors and husbands of previously pregnant recipients [11]. Furthermore, accelerated rejection was demonstrated especially in patients after husband-to-wife and offspring-to-mother transplantation [12]. These studies suggest that in husband-to-wife transplantation, a tendency toward inferior graft survival is seen in recipients that were previously pregnant, which might be due to immunization of females to IPA, which is not detected in the serological crossmatch before transplantation.

IPA in offspring-to-mother transplantations

One would expect a similar difference if offspring-to-mother are compared with offspring-to-father transplantations. Studies in offspring-to-mother and offspring-to-father transplantation are less extensively performed. In 1977, Opelz and Terasaki showed that there was no difference in transplant survival of offspring grafts when the recipient was the mother or the father [13]. In 1982, Terasaki found that offspring-to-mother transplantation had a 1-year graft survival of 76% whereas the graft survival in offspring-to-father transplantation was 51%. The recipients were all nontransfused. The conclusion of this study was that there is no effect of pretransplant immunization towards IPA on graft survival. In contrast, it seems that there even is a beneficial effect [14]. HLA haplotype

sharing between mother and child during pregnancy may lead to immunomodulation as is also the case for HLA-DR-shared blood transfusions [15–17]. Finally, Mahanty *et al.* confirmed that the survival of offspring renal allografts was not different when the recipient was the mother or the father, although graft survival in multiparous women was lower than in women with a single pregnancy [18].

Taking the data of these studies together, immunization to IPA may play a role in case of husband-to-wife transplantation whereas no trend towards a worse graft survival could be observed in offspring-to-mother transplantation. A possible explanation may be that, in offspring-to-mother transplantation, sharing of HLA is present, whereas spousal donors often have more mismatches. Furthermore, it is possible that mothers become microchimeric of their child [19] facilitating graft acceptance of the child later in life.

However, one should take into consideration that in all cases a pretransplant crossmatch is performed to prevent hyperacute rejection because of donor-specific HLA alloantibodies. Transplantation is only performed when no antibodies are present, which implies a selection process in the women who finally will be transplanted.

Concerning the possible immunization towards IPA, it is important to screen and crossmatch patients before transplantation. Some women form anti-HLA antibodies after pregnancy that persist for a long period of time whereas in others the antibodies disappear. So as to detect historical sensitization, cytotoxic T lymphocytes (CTLs) specific for paternal antigens can be determined in limiting dilution assays [20]. To distinguish between high-avidity (primed) and low-avidity CTLs, CD8 monoclonal antibodies were added. In the presence of these CD8 antibodies, high-avidity CTLs are still able to react, whereas low-avidity CTLs are blocked. Strikingly, it was demonstrated that it is possible to detect primed CTLs that react with paternal antigens in both women with and without anti-HLA antibodies. Therefore, the cellular test developed to detect these primed CTL can also be helpful to detect presensitized women.

The influence of NIMA antigens

Pre- and/or postnatal exposure to NIMA is associated with a reduced HLA antibody formation against the NIMA [21] and a significantly better graft survival of kidney grafts from siblings [3,22] or from unrelated donors [23] who were mismatched for the NIMA haplotype compared with the NIPA haplotype later in life. Obviously, this led to the hypothesis that the exposure of a child to these antigens during pregnancy may lead to NIMA-specific tolerance and was the start of more research towards the influence of NIMA on renal transplant outcome.

Clinical observations

The concept of neonatal tolerance was already described in 1945 when Owen found that dizygotic bovine twins are born with a proportion of red blood cells derived from their twin [24]. Hereafter, Billingham *et al.* showed that the injection of allogeneic cells into a newborn mouse induces lifelong immunological tolerance towards the donor [25]. One year later, Owen *et al.* reported that rhesus D negative women pregnant of a rhesus D positive child are less likely to produce antibodies against rhesus if their mother was rhesus D positive [26]. The interest in the NIMA effect disappeared until the observation that highly immunized patients were less likely to form antibodies against NIMA than against NIPA (noninherited paternal HLA antigens) [21,27]. An overview of the literature regarding the NIMA effect in transplant recipients is depicted in Table 1.

The most relevant clinical finding with regard to transplantation and the NIMA effect came in 1998 when Burlingham *et al.* showed that the graft survival of NIMA haplotype mismatched sibling grafts is significantly better compared with NIPA haplotype mismatched sibling grafts (10-year graft survival of 77% and 49% respectively) [3]. Notably, the graft survival of sibling grafts expressing the NIMA haplotype is equal to HLA-identical siblings whereas the graft survival of sibling grafts expressing NIPA is similar to grafts derived from the parents. These findings were the result of a study in several transplant centers and the effect of NIMA derived from a sibling was shown in every center separately, thereby showing that the NIMA effect was strong enough to overcome differences in immune suppression. However, the effect was especially noticed when patients were not taking cyclosporine.

A study by Smits *et al.* in cadaveric kidney transplant recipients compared the survival rate of grafts with a single mismatched antigen identical to the NIMA with the survival rate of grafts in which the mismatched antigen was not identical to the NIMA [23]. They showed that recipients from donors mismatched for an HLA-A antigen that was identical to the NIMA had a significantly better survival rate compared with recipients of grafts with no mismatches. This suggests that an active process of immune regulation is involved in the NIMA effect and that HLA class I plays a role in the NIMA-specific tolerance, as is also suggested by an earlier study that showed an unresponsive state at both the cellular and the humoral level towards maternal HLA class I antigens, even during late rejection [28].

Other studies also showed an improved graft survival when NIMA haplo-identical siblings were used as bone marrow donor. van Rood *et al.* described that there was significantly less graft versus host disease and an increased

Table 1. Overview of the literature concerning the NIMA effect in patients.

Research goal/methods	No. of patients	Outcome	NIMA effect	Reference
Study of the post-transplant graft function of 55 patients that received a primary maternal donor kidney transplant and influence of breast feeding	55	Improved 1 year graft function rate after maternal kidney transplantation in breastfed patients (82%) compared with nonbreastfed patients (57%)	Yes	Campbell *et al.* [57]
Determination of acceptable mismatches of patients with end-stage renal disease and PRA > 85% with CDC	26	High frequency of NIMAs among permissible mismatches 58% of patients show B-cell unresponsiveness against NIMA Note: Determined in highly immunized patients	Yes	Claas *et al.* [21]
Determination of the alloreactive response in patients with end-stage renal disease given unrelated DST prior to transplantation with MLR	47	Significant association ($P < 0.02$) between decreased MLR reactivity following DST and expression of NIMA by cells of transfusion donor Note: Patient cells *in vitro* tested: MLR	Yes	Bean *et al.* [58]
Analysis of NIMA effect in renal transplantation	5000	Paternal grafts have a higher 3-year graft survival ($P < 0.0001$) than maternal grafts	No	Opelz [31]
Analysis of maternal effect in renal transplantation	186	A better graft and patient survival (4 year, $P < 0.05$) and long term renal function in patients transplanted with a the paternal kidney compared with patients transplanted with a maternal kidney	No	Panajotopoulos *et al.* [32]
Comparison of sensitization in patients who had been exposed to NIMA or NIPA by DST and comparison of graft survival, number of rejection episodes and graft function in patients who also received a kidney graft bearing NIMA or NIPA	211	No difference in specific antibody formation, graft survival, and incidence of rejection episodes Notes: Not reported whether the number and loci of NIMA mismatches is comparable with the number and loci of NIPA mismatches Repeated exposure to same antigenic challenge Low PRA at start study	No	Pohanka *et al.* [59]
Link circulating donor cells to a functional role in human transplantation tolerance: maternal kidney transplantation after DST	1	Patient is microchimeric of NIMA expressing donor cells and this is linked to the maintenance of the tolerant state of the patient Note: Case report, no comparison with NIPA	Yes	Burlingham *et al.* [28]
Multicenter retrospective study of graft survival and rejection episodes in patients who received renal transplants from sibling donors bearing NIMA or NIPA	205	Higher graft survival in recipients of kidneys from haplo-identical siblings expressing NIMA compared with NIPA (5 year: 86 vs. 67%;10 year: 77 vs. 49%)	Yes	Burlingham *et al.* [3]
Comparison of survival rate of kidney grafts with a mismatched antigen identical to NIMA to that of grafts in which the mismatched antigen was not identical to NIMA	669	Significant better graft survival ($P = 0.02$) for HLA-A NIMA mismatched cadaveric kidney grafts compared with zero HLA-A mismatches	Yes	Smits *et al.* [23]
Comparison of outcomes of blood and marrow stem cell transplantation from maternal donors with those from paternal donors	96	At 5 years after transplantation, recipients of maternal hematopoietic cells have a higher overall survival than recipients of paternal hematopoietic cells (60% vs. 32%, $P = 0.006$) and a lower probability of nonrelapse TRM ($P = 0.008$), no difference in occurrence of severe acute GVHD and relapse of malignant diseases	Yes	Tamaki *et al.* [60]
Analysis of graft failure and GVHD after non-T-cell-depleted bone marrow transplantations from parental or haplo-identical sibling donors	269	NIMA versus NIPA haplotype mismatched sibling BMT: lower rates of acute GVHD ($P < 0.02$) mother-to-child versus father-to-child BMT: less chronic GVHD ($P < 0.02$) and lower TRM [maternal BMT ($P = 0.009$) and paternal BMT ($P = 0.03$)]	Yes	van Rood *et al.* [22]

Table 1. (contd)

Research goal/methods	No. of patients	Outcome	NIMA effect	Reference
Haplo-identical non-T-cell-depleted SCT in five patients with advanced malignancies (donors chimeric of NIMA)	5	Lack of severe GVHD in all patients (based on feto-maternal microchimerism) Note: No comparison with NIPA	Yes	Shimazaki *et al.* [29]
Determine outcome of patients with advanced hematologic malignancies who underwent HLA-2-antigen- or HLA-3-antigen incompatible non-T-cell-depleted SCT from a microchimeric NIMA mismatched donor	35	NIMA mismatch in GVH direction is associated with lower risk of severe grade III–IV acute GVHD compared with IPA ($P = 0.03$)	Yes	Ichinohe *et al.* [30]

DST, donor-specific blood transfusion; BT, blood transfusion; PRA, panel reactive antibodies; MLR, mixed lymphocyte reaction; CDC, complement dependent cytotoxicity; SCT, stem cell transplantation; GVHD, graft versus host disease; BMT, bone marrow transplantation; TRM, treatment-related mortality.

patient survival when NIMA haplo-identical siblings were used as a donor for bone marrow transplantation [22]. In contrast, this effect was not present when maternal grafts were used. Furthermore, Japanese transplant centers have successfully transplanted NIMA haplotype mismatched sibling and maternal stem cells into patients without T-cell depletion [29,30]. Patients and donors that were included in this protocol were all microchimeric for the mismatched haplotype. Chimerism may well be an important factor involved in the induction of NIMA-specific tolerance.

Maternal- versus sibling-derived grafts expressing NIMA

Because of these observations, the question is raised why the survival of grafts derived from the mother is not equal to sibling grafts expressing NIMA [3]. Besides the study by Burlingham *et al.*, several other studies also showed that maternal kidney grafts have no improved graft survival [31,32].

Several explanations can be given for this phenomenon. Of course, both when the mother is the donor and when the sibling expressing the NIMA haplotype is the donor, the mismatched haplotype is the NIMA. However, there are also differences. First, the shared haplotype with the recipient, in case the mother is the donor, is the IMA (inherited maternal antigens) haplotype, whereas the IPA haplotype is the shared haplotype in case the sibling is the donor. Furthermore, the sibling was exposed to IMA during its fetal life, whereas the mother was exposed to IPA during adult life. It is known that a proportion of single- or multiparous women develop antibodies against IPA of the child [5,20]. After transplantation it is possible that cells from the graft will recognize IPA of the recipient when the mother is the donor. However, when the sibling is the donor, the graft-derived cells will only recognize IMA that they also encountered during fetal life (and possibly during breast feeding). As it was already shown that the injection of allogeneic cells into newborn mice induces lifelong immunological tolerance towards the donor [25], one can imagine that the exposure to antigens during fetal life is a more favorable situation for the induction of tolerance than the exposure during adult life.

When the mother is the donor there is another possible disadvantage, namely that the cells derived from the mother that share the IMA haplotype are sensitized for paternal minor Histocompatibility antigens (mHa) [33].

In contrast, prenatal or perinatal recognition of mHa by the child may have a favorable effect in sibling transplantation as was suggested by the presence of mHa-specific CD8+ regulatory T cells in a tolerant kidney transplant recipient that received an HLA-identical but minor-mismatched (HA-1) kidney from her sister [34].

Furthermore, there may be an important role for chimerism [35]. Chimerism is determined as the co-existence of cells from two genetically distinct organisms in one individual. During pregnancy, there is often an exchange of cells between mother and child, which leads to feto-maternal microchimerism; the presence of fetal hematopoietic cells in the maternal blood and vice versa [19,36]. There are different ways how mother and child become chimeric: a child becomes chimeric during its fetal life that, as discussed before, is a more favorable state to become tolerant. A mother, however, becomes chimeric during adult life. Furthermore, a mother can also be chimeric of her own mother and of earlier pregnancies. All these factors may influence the immunologic responses and, therefore, may contribute to the fact that maternal grafts do not as good as sibling-derived grafts.

Several studies suggest a functional link between chimerism and the NIMA effect. Recently, successful hematopoietic stem cell transplantations in microchimeric patients with NIMA haplotype mismatched sibling and maternal stem cells without T-cell depletion have been performed [30]. The stem cell donors used were also

microchimeric. An important issue, however, is that the degree of chimerism differs which may have an influence on the strength of the NIMA effect, as was shown in an animal model [37]. A case report described the persistence of microchimerism in a patient who was functionally tolerant of a maternal kidney allograft [28]. In this particular patient, the presence of the chimeric cells was essential to downregulate the donor-specific immune response *in vitro*. To what extent chimerism is really linked to the NIMA effect is still unclear.

A final difference between a maternal-derived graft and a sibling-derived graft is the fact that a maternal-derived graft can be seen as a second confrontation (the first confrontation was during pregnancy). In contrast, a graft derived from a NIMA haplotype mismatched sibling can be seen as a primary confrontation towards most of the antigens. The latter situation will be more advantageous for a beneficial immune response than the first situation and may also be an explanation for the differences seen in graft survival.

These clinical data that indicate that NIMA has an influence on the outcome in transplantation are based on statistical differences between groups of patients and cannot be extrapolated to an individual patient. Also the observation that only about half of the highly sensitized patients do not form antibodies against NIMA, whereas this was not the case for NIPA, clearly points out that the NIMA effect will not be present in every individual [38]. Clarification of the factors that are favorable for the NIMA effect and herewith identifying those individuals that are sensitive for NIMA is an enormous challenge. Studies aiming at these questions also will help to understand the mechanism underlying the NIMA phenomenon.

In vitro studies in healthy individuals

Another possible way to investigate the influence of NIMA are studies in healthy individuals. Table 2 depicts an overview of studies regarding the NIMA effect in healthy individuals.

A lower response towards NIMA compared with NIPA was shown when cord blood mononuclear cells (CBMC) were used as responder cells [38]. However, other groups could not confirm these results [40–42].

Already in 1990, a study on peripheral blood mononuclear cells (PBMC) of healthy individuals did not show a difference when cells were stimulated with parental cells [43]. Roelen *et al.* could not demonstrate an influence of NIMA on CTLp and HTLp frequencies when cells were stimulated with maternal or paternal cells [44]. These studies only investigated the response towards parental cells. As already described, clinical studies showed that maternal renal allografts have a poorer graft survival than NIMA haplotype mismatched grafts derived from a sibling [3,31]. Therefore, we recently investigated the response towards maternal and paternal cells and towards sibling-derived cells expressing NIMA versus NIPA separately [45]. Again, by using several cellular techniques including mixed lymphocyte reaction (MLR), Elispot analysis and fluorescence-activated cell sorter (FACS) staining, we could not demonstrate an influence of NIMA on the cellular alloimmune response in adult healthy individuals. This is in sharp contrast with clinical data supporting the NIMA effect. One of the possibilities why we were not able to show the effect could be due to the fact that the healthy individuals are not rechallenged *in vivo* with the parental HLA mismatches.

Mice experiments demonstrating an influence of NIMA

Recently, a NIMA effect was also demonstrated in mice [46,47] (Table 3 gives an overview of several studies performed in animals). Andrassy *et al.* demonstrated the NIMA effect in a mouse model in which they showed that DBA/2 (H-$2^{d/d}$) heart allografts were accepted without any additional drug or conditional treatment by >50% of the NIMA^{d}-exposed F1 backcross (H-$2^{b/b}$) recipients [46]. Additionally, graft survival was increased in NIMA^{d}-exposed F1 backcross (H-$2^{b/b}$) recipients when transplanted with a skin graft from a semiallogeneic donor and not from a fully mismatched DBA/2 (H-$2^{d/d}$) donor. This indicates that the NIMA effect is MHC restricted in case of a skin graft, which is known to be a very immunogenic model, whereas the NIMA effect seems to be not MHC restricted in case of heart allografts. Furthermore, they showed that breast feeding is necessary to elicit a NIMA effect and that microchimerism was present at different levels in fully exposed (both *in utero* and orally) NIMA mice. Importantly, the NIMA effect was not present in several other strain combinations (J. Andrassy pers. comm.), again indicating the heterogeneity in the development of NIMA-specific tolerance.

Additionally, *in vitro* experiments indicated a role especially for $CD4^{+}$ cells in the NIMA effect [46]. Indeed, the same group recently presented data in which they demonstrated an increase in $CD4^{+}$ $CD25^{+}$ latent-TGFb^{+} cells in NIMA^{d}-exposed mice (M.L. Molitor *et al.* pers. comm.). These 'regulatory' T cells were further characterized by glucocorticoid-induced tumornecrosis factor receptor family related gene (GITR) expression and IL-10 production and were shown to be responsible for a decreased humoral response and tolerance to heart allografts. However, functional studies on the immunoregulatory capacity of these cells are still lacking.

In consistence with these results, Matsuoka *et al.* showed in a mouse model of bone marrow transplantation

Table 2. Overview of the literature concerning the NIMA effect in healthy individuals.

No. of individuals or CB samples	Type of responder cells	Read out system	Stimulated with	Outcome	NIMA effect	Reference
7	PBL	CTLp, CML, MLR	PC	No difference Note: The number and loci of NIMA mismatches is not comparable with the number and loci of NIPA mismatches	No	Hadley *et al.* [43]
37	PBL	CTLp: influence of breast feeding	PC	Breast feeding can downregulate the immune response against maternal HLA antigens ($P < 0.026$) and not against paternal HLA antigens	Yes	Zhang *et al.* [61]
37	PBL	CTLp	PC	hree different CTL response patterns: 17/37 no difference towards NIMA versus NIPA, 2/37 significantly higher ($P < 0.05$) towards NIMA versus NIPA, 18/37 significantly NIMA versus NIPA Note: The number and loci of NIMA mismatches is not comparable with the number and loci of NIPA mismatches	Yes	Zhang *et al.* [62]
14	CBMC	MLR	PC	No difference	No	Harris *et al.* [40]
24	CBMC	FACS, CTLp, HTLp	PC	No difference	No	Falkenburg *et al.* [41]
35	PBL	CTLp, HTLp	PC	No difference	No	Roelen *et al.* [44]
13	CBMC	FACS, CTLp	PC	No difference in CTLp frequencies, but increase in NK-like regulatory CD3-CD8dim cells after stimulation with NIMA and increase in CTL-like CD3 + CD8bright cells after stimulation with NIPA	Yes	Moretta *et al.* [42]
28	CBMC	Standard MLR modified MLR	PC	Lower cellular response to NIMA compared with NIPA ($P = 0.045$) Note: Not always tested against both father and mother	Yes	Tsafrir *et al.* [39]
15	PBL	MLR, Elispot, FACS	PC and SC	No difference	No	van den Boogaardt *et al.* [45]

CB, cord blood; CBMC, cord blood mononuclear cells; PBL, peripheral blood lymphocytes; MLR, mixed lymphocyte reaction; CTLp, cytotoxic T-lymphocyte precursor; CML, cell mediated lysis; HTLp, helper T-cell precursor, FACS, fluorescence-activated cell sorter; PC, parental cells; SC, sibling cells.

(BMT) that a BMT from a NIMA-exposed child to the mother led to a reduction of the morbidity and mortality of graft-versus-host disease in an antigen-specific manner [47]. In addition, an improved survival was observed. Furthermore, when $CD4^+$ $CD25^+$ regulatory T cells were depleted from the donor inoculum the tolerogenic NIMA effect disappeared. These data together with the data from Andrassy *et al.* implies an important role for $CD4^+$ regulatory T cells in establishing a NIMA effect. Matsuoka *et al.* also investigated the possibility that IPA may be able to induce tolerance in the mother. However, when a BMT from an IPA-exposed mother to the child was performed, no reduction in graft-versus-host was observed.

Besides an influence of NIMA on the cellular immune response, the humoral immune response may also be important, especially when considering the initial finding that antibody formation in highly sensitized patients occurs less often against NIMA [21]. In line with this finding, a study in mice was performed in which it was shown that NIMA influences the development of B cells [48]. Vernochet *et al.* used B lymphocytes of mice, which recognized $H\text{-}2K^k$ and $H\text{-}2K^b$ MHC class I antigens with high

Table 3. Overview of the literature concerning the MIMA effect in animal models.

Research goal/methods	Mice strain	Outcome	NIMA effect	Reference
Study of immune responses to NIMA in inbred rats after rechallenge with BT followed by MLR	RTlu/a or RTlu/1 female × PVG male offspring: RTlu/c (NIMA RT1A) and RT1u/c (NIMA RT11)	No evidence of humoral tolerance to class I NIMA and cellular tolerance to NIMA Note: No NIPA control	No	Propper *et al.* [63]
Investigation if the NIMA phenomenon can lead to inactivation via lymphocytes that are transferred from mother to child (tail skin transplantation mouse model)	BL/6 (H-$2^{b/b}$) father × B6D2F1 (H-$2^{b/d}$) mother offspring: H-$2^{b/b}$ $NIMA^{d}$-exposed mice and H-$2^{b/d}$ mice	Significant prolongation of maternal skin graft survival (both *in utero* and/or orally exposed) Correlation with the number of maternal T cells in lymph nodes ($P = 0.077$) (not correlated with B cells) Note: No NIPA control but only B6 control	Yes	Zhang and Miller [37]
Investigation of maternal antigen exposure alone on tolerance induction to a primary vascularized organ allograft in mice	BL/6 (H-$2^{b/b}$) father × B6D2F1 (H-$2^{b/d}$) mother offspring: H-$2^{b/b}$ $NIMA^{d}$-exposed mice and H-$2^{b/d}$ mice NIPA control: BL/6 (H-$2^{b/b}$) mother × B6D2F1 (H-$2^{b/d}$) father	57% of $NIMA^{d}$-exposed mice accept fully allogeneic H-$2^{d/d}$ graft ($P < 0.0004$ versus controls) Both *in utero* and oral exposure required for tolerogenic effect Possible role for chimerism Note: No NIMA effect detectable in other strain combinations	Yes	Andrassy *et al.* [46]
Investigation of the influence of maternal cells (expressing NIMA) on the development of fetal and neonatal B lymphocytes (B-cell receptor expression)	EGFP-Tg mice (B6 background) 3-83 mu/delta BcR-Tg mice (B10.D2 background)	In H-$2K^{k}$-exposed fetuses: NIMA-specific transgenic B cells (high affinity) are partially deleted during late gestation, nondeleted cells downregulate their B-cell receptor NIMA H-$2K^{b}$-exposed fetuses: transgenic B cells present an active phenotype (low affinity for NIMA)	Yes	Vernochet *et al.* [48]
Investigation of the influence of NIMA on rejection after heart transplantation in a transgenic mouse model	(CBA × CBK-Kb Tg)Fl female × CBA-BM3 3 anti-Kb TCR Tg male offspring: NIMA (Kb–) and IMA (Kb+)	NIMA mice display prolonged survival of allotransplants Reduced frequency of IFN-g and IL-2 producing cells and increase in IL-4 producing cells CD4 depletion: restoration of acute rejection Note: No NIPA control	Yes	Akiyama *et al.* [64]
Study of the impact of NIMA and IPA in BMT and investigation of the mechanism leading to tolerance in mice	BL/6 (H-$2^{b/b}$) father × B6D2F1 (H-$2^{b/d}$) mother offspring: H-$2^{b/b}$ NIMAd-exposed mice and H-$2^{b/d}$ mice	Reduced morbidity and mortality of GVHD and improved survival ($P < 0.01$ versus NIPA control) after BMT from a NIMA-exposed child to mother and not from an IPA-exposed mother to child Role for CD4 + CD25 + Treg	Yes	Matsuoka *et al.* [47]

BL/6, C57BL/6; B6D2F1, (C57BL6 × DBA2)F1; EGFP, enhanced green fluorescence protein; BMT, bone marrow transplantation; BT, blood transfusion; MLR, mixed lymphocyte reaction; Treg, regulatory T cells.

and low affinities respectively. They showed that NIMA-specific B cells with a high affinity are partially deleted during late gestation and the nondeleleted cells downregulated their B-cell receptor. In contrast, NIMA-specific B cells with a low affinity for NIMA were activated. These results indicate that patients that are highly immunized, but do not form antibodies to NIMA, may have B cells with a high affinity to NIMA resulting in tolerizing signals.

Triggering the NIMA effect: possible mechanisms

Although the mechanism that is responsible for the induction of the NIMA effect is still not clear, several assumptions have been made.

We already discussed the role of microchimerism as an important factor possibly involved in the NIMA effect [35]. However, other mechanisms have also been proposed to play a role in the induction of NIMA-specific tolerance (see also Fig. 2).

Soluble HLA

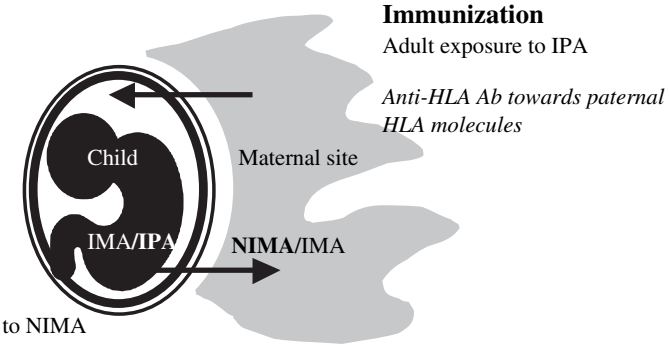
Transfer of soluble HLA from child to mother and vice versa may be important for the induction of the NIMA effect. The 39 kD soluble HLA molecule lacks a transmembrane part because of a deletion in exon 5 [49]. Because of this deletion, this soluble HLA can easily travel through the placental barrier. This molecule is absent in 16% of the population and heterozygous in 48% of the population, resulting in about 50% of the children carrying this allele. As already discussed, about half of the highly immunized patients do not form antibodies to NIMA. A study combining these parameters could reveal whether this molecule indeed plays a role in the prevention of antibody formation to NIMA.

Privileged site

Another issue is the presence of privileged sites in the human body. Privileged sites are sites where the immune system is supposed not to perform its destructive activities, for example, in the brain, the eye, and the uterus. When a graft is transplanted in such a site rejection will not occur [50]. Studies in the eye showed a specific type of immune response: the anterior chamber-associated immune deviation (ACAID) which implies that when an immune response is started, no T cells that can mediate a delayed hypersensitivity will be present and, furthermore, no antibodies that are able to fix complement will be present. So as to establish such an environment, several soluble factors are suggested to be important and especially the presence of transforming growth factor β (TGF-β) is supposed to play a central role as modulating cytokine. This cytokine can affect antigen presenting cells (APC) in such a way that they cannot give a full stimulus to T cells once arrived in the secondary lymphoid organs. These APC may be able to induce regulatory T cells that can prevent or regulate the immune response to the encountered antigens. During pregnancy, the amniotic fluid is rich in TGF-β [51], creating a suitable environment for the induction of tolerance to noninherited maternal antigens.

Immune deviation

In contrast to the concept of neonatal tolerance, i.e. the development of tolerance or nonresponsiveness towards antigens encountered by the innate immune system [24,25]), immune deviation may be an alternative mechanism involved in the NIMA effect. In murine experiments, it was demonstrated that immunization during the



Possible mechanisms:
Chimerism
Priviledged site: modulation of APC
Soluble HLA
Immune deviation
Regulatory T cells: HLA-DR sharing?

Figure 2 Exposure to IPA and NIMA during pregnancy can lead to either immunization or tolerization. Exposure to IPA seems to have a more immunizing effect as the mature immune system of a mother can form anti-HLA antibodies against the foreign paternal HLA molecules. On the other hand, exposure of a child to the NIMA antigens during pregnancy can lead to NIMA-specific tolerance.

neonatal period can lead to a protective immune response rather than to tolerance depending on the ratio of dendritic cells (DC), B cells, and T cells [52], the antigenic dose [53] and the adjuvant that is injected together with the antigen [54]. Hence, it was suggested that neonates are not immune privileged but, dependent on the type of immunization, generate Th2 or Th1 responses.

When translating the concept of immune deviation to the NIMA effect, one can suggest that the continuous exposure of the fetus towards NIMA results in both the development of a Th2-type immune response and in stimulation of T cells without a costimulatory signal by the DC, thereby inducing a tolerizing environment.

Blood transfusion effect

The immunogenetic relationship between mother and child implies sharing of one haplotype and a mismatch for the other. This is similar to the concept of the immunomodulating effect of the HLA-DR-shared allogeneic blood transfusion. Therefore, this concept can be helpful in understanding the NIMA effect. It was demonstrated that patients treated with multiple pretransplant blood transfusions had a significantly higher graft survival compared with nontransfused patients [55]. Furthermore, leukocyte-depleted transfusions were not associated with this effect, indicating that leukocytes are important for the beneficial outcome [56]. Even more interesting is that the effect is especially seen when HLA-DR sharing between blood donor and patient is present, indicating a role for HLA class II [15,16]. It is hypothesized that $CD4^+$ Tregs that recognize a foreign peptide in the context of the shared HLA-DR molecule are induced by the blood transfusion. When these cells are rechallenged with the foreign peptide that the organ donor shares with the blood transfusion donor this will lead to downregulation of the immune response towards the graft [17]. During pregnancy, HLA haplotype sharing between mother and child is present, indicating that a similar mechanism may occur; the recognition of foreign peptides in the context of shared HLA-DR. This may lead to the induction of Tregs, favoring the NIMA effect.

Conclusion

It is obvious that both NIMA and IPA have an influence on the outcome after transplantation. Exposure to IPA seems to have a more immunizing effect as the mature immune system of a mother can form anti-HLA antibodies against the foreign paternal HLA molecules (Fig. 2). This can pose an extra risk factor when a mother is the recipient of a spousal- or offspring-derived graft. Careful determination of HLA alloantibodies and sensitive cross-matches before transplantation can reduce the risk of rejection. Furthermore, detection of primed CTLs directed towards paternal antigens can help to detect presensitized women in which anti-HLA antibodies disappeared [20].

Both clinical and mouse studies clearly demonstrate a beneficial effect of NIMA. However, the mechanism involved in the NIMA effect is still not revealed, although $CD4^+$ $CD25^+$ Treg cells may play an important role [47]. Once the mechanism will be revealed this will have an enormous impact on the understanding of tolerance and thus on tolerizing strategies in transplantation, in general. Furthermore, it will provide extra opportunities for the selection of optimal donors in organ transplantation.

A multicenter study to determine the *in vitro* cellular reactivity in a large group of patients transplanted with a kidney derived from a parent and in patients transplanted with a kidney derived from a sibling may provide more information about the NIMA effect. Blood withdrawal should be performed at several time points (before and after transplantation) so as to determine the kinetics of the alloimmune response in these patients.

In conclusion, both inherited and noninherited parental antigens may affect graft survival. Further studies are necessary to determine the effect of IPA and NIMA on the alloimmune response of individual patients so as to use the presence or absence of parental HLA antigens in selecting the optimal donor for a particular patient.

Acknowledgements

We would like to thank Prof. A. Brand and Prof. Dr F. Koning for critically reading the manuscript.

References

1. Marsh SG, Albert ED, Bodmer WF, *et al.* Nomenclature for factors of the HLA system, 2004. *Tissue Antigens* 2005; **65**: 301.
2. Tiercy JM. Molecular basis of HLA polymorphism: implications in clinical transplantation. *Transpl Immunol* 2002; **9**: 173.
3. Burlingham WJ, Grailer AP, Heisey DM, *et al.* The effect of tolerance to noninherited maternal HLA antigens on the survival of renal transplants from sibling donors. *N Engl J Med* 1998; **339**: 1657.
4. van Rood JJ, Claas FHJ. Both self and non-inherited maternal HLA antigens influence the immune response. *Immunol Today* 2000; **21**: 269.
5. Suciu-Foca N, Reed E, Rohowsky C, Kung P, King DW. Anti-idiotypic antibodies to anti-HLA receptors induced by pregnancy. *Proc Natl Acad Sci USA* 1983; **80**: 830.
6. van Rood JJ, Eernisse JG, van Leeuwen A. Leucocyte antibodies in sera from pregnant women. *Nature* 1958; **181**: 1735.

7. Dankers MK, Roelen DL, Korfage N, *et al.* Differential immunogenicity of paternal HLA Class I antigens in pregnant women. *Hum Immunol* 2003; **64**: 600.
8. Terasaki PI, Cecka JM, Gjertson DW, Takemoto S. High survival rates of kidney transplants from spousal and living unrelated donors. *N Engl J Med* 1995; **333**: 333.
9. Berloco P, Pretagostini R, Poli L, *et al.* Living kidney transplantation between spouses: results in 100 cases. *Transpl Int* 1994; **7** (Suppl. 1): S314.
10. Foss A, Leivestad T, Brekke IB, *et al.* Unrelated living donors in 141 kidney transplantations: a one-center study. *Transplantation* 1998; **66**: 49.
11. Pollack MS, Trimarchi HM, Riley DJ, Casperson PR, Manyari LE, Suki WN. Shared cadaver donor-husband HLA class I mismatches as a risk factor for renal graft rejection in previously pregnant women. *Hum Immunol* 1999; **60**: 1150.
12. Rosenberg JC, Jones B, Oh H. Accelerated rejection following offspring-to-mother and husband-to-wife transplants. *Clin Transplant* 2004; **18**: 729.
13. Opelz G, Terasaki PI. Studies on the strength of HLA antigens in related donor kidney transplants. *Transplantation* 1977; **24**: 106.
14. Terasaki PI, Perdue S, Mickey MR, Sasaki N. Offspring to mother kidney transplants. An example of donor-specific immunized transplants. *Transplantation* 1982; **33**: 450.
15. Lagaaij EL, Hennemann IP, Ruigrok M, *et al.* Effect of one-HLA-DR-antigen-matched and completely HLA-DR-mismatched blood transfusions on survival of heart and kidney allografts. *N Engl J Med* 1989; **321**: 701.
16. Lazda VA, Pollak R, Mozes MF, Barber PL, Jonasson O. Evidence that HLA class II disparity is required for the induction of renal allograft enhancement by donor-specific blood transfusions in man. *Transplantation* 1990; **49**: 1084.
17. Waanders MM, Roelen DL, Brand A, Claas FHJ. The putative mechanism of the immunomodulating effect of HLA-DR shared allogeneic blood transfusions on the alloimmune response. *Transfus Med Rev* 2005; **19**: 281.
18. Mahanty HD, Cherikh WS, Chang GJ, Baxter-Lowe LA, Roberts JP. Influence of pretransplant pregnancy on survival of renal allografts from living donors. *Transplantation* 2001; **72**: 228.
19. Evans PC, Lambert N, Maloney S, Furst DE, Moore JM, Nelson JL. Long-term fetal microchimerism in peripheral blood mononuclear cell subsets in healthy women and women with scleroderma. *Blood* 1999; **93**: 2033.
20. van Kampen CA, Versteeg-van der Voort Maarschalk MF, Langerak-Langerak J, van Beelen E, Roelen DL, Claas FHJ. Pregnancy can induce long-persisting primed CTLs specific for inherited paternal HLA antigens. *Hum Immunol* 2001; **62**: 201.
21. Claas FHJ, Gijbels YF, van der Velden-de Munck JJ, van Rood JJ. Induction of B cell unresponsiveness to noninherited maternal HLA antigens during fetal life. *Science* 1988; **241**: 1815.
22. van Rood JJ, Loberiza FR, Zhang MJ, *et al.* Effect of tolerance to noninherited maternal antigens on the occurrence of graft-versus-host disease after bone marrow transplantation from a parent or an HLA-haploidentical sibling. *Blood* 2002; **99**: 1572.
23. Smits JMA, Claas FHJ, van Houwelingen HC, Persijn GG. Do noninherited maternal antigens (NIMA) enhance renal graft survival? *Transplant International* 1998; **11**: 82.
24. Owen RD. Immunogenetic consequences of vascular anastomoses between bovine twins. *Science* 1945; **102**: 400.
25. Billingham RE, Brent L, Medawar PB. 'Actively acquired tolerance' of foreign cells. 1953. *Transplantation* 2003; **76**: 1409.
26. Owen RD, Wood HR, Foord AG, Sturgeon P, Baldwin LG. Evidence for actively acquired tolerance to Rh antigens. *Proc Natl Acad Sci USA* 1954; **40**: 420.
27. Claas FHJ, Gijbels YF, van Veen A, *et al.* Selection of cross-match negative HLA-A and/or -B mismatched donors for highly sensitized patients. *Transplant Proc* 1989; **21**: 665.
28. Burlingham WJ, Grailer AP, Fechner JH, *et al.* Microchimerism linked to cytotoxic T-lymphocyte functional unresponsiveness (clonal anergy) in a tolerant renal-transplant recipient. *Transplantation* 1995; **59**: 1147.
29. Shimazaki C, Ochiai N, Uchida R, *et al.* Non-T-cell-depleted HLA haploidentical stem cell transplantation in advanced hematologic malignancies based on the feto-maternal microchimerism. *Blood* 2003; **101**: 3334.
30. Ichinohe T, Uchiyama T, Shimazaki C, *et al.* Feasibility of HLA-haploidentical hematopoietic stem cell transplantation between noninherited maternal antigen (NIMA)-mismatched family members linked with long-term feto-maternal microchimerism. *Blood* 2004; **104**: 3821.
31. Opelz G. Analysis of the 'NIMA effect' in renal transplantation. Collaborative Transplant Study. *Clin Transpl* 1990: 63.
32. Panajotopoulos N, Ianhez LE, Neumann J, Sabbaga E, Kalil J. Immunological tolerance in human transplantation. The possible existence of a maternal effect. *Transplantation* 1990; **50**: 443.
33. Verdijk RM, Kloosterman A, Pool J, *et al.* Pregnancy induces minor histocompatibility antigen-specific cytotoxic T cells: implications for stem cell transplantation and immunotherapy. *Blood* 2004; **103**: 1961.
34. Cai J, Lee J, Jankowska-Gan E, *et al.* Minor H antigen HA-1-specific regulator and effector CD8+ T cells, and HA-1 microchimerism, in allograft tolerance. *J Exp Med* 2004; **199**: 1017.
35. Ichinohe T, Teshima T, Matsuoka K, Maruya E, Saji H. Fetal-maternal microchimerism: impact on hematopoietic stem cell transplantation. *Curr Opin Immunol* 2005; **17**: 546.

36. Maloney S, Smith A, Furst DE, *et al.* Microchimerism of maternal origin persists into adult life. *J Clin Invest* 1999; **104**: 41.
37. Zhang L, Miller RG. The correlation of prolonged survival of maternal skin grafts with the presence of naturally transferred maternal T cells. *Transplantation* 1993; **56**: 918.
38. van Rood JJ, Claas FHJ. The influence of allogeneic cells on the human T and B cell repertoire. *Science* 1990; **248**: 1388.
39. Tsafrir A, Brautbar C, Nagler A, Elchalal U, Miller K, Bishara A. Alloreactivity of umbilical cord blood mononuclear cells: specific hyporesponse to noninherited maternal antigens. *Hum Immunol* 2000; **61**: 548.
40. Harris DT, Schumacher MJ, Locascio J, Booth A, Bard J, Boyse EA. Immunoreactivity of umbilical cord blood and post-partum maternal peripheral blood with regard to HLA-haploidentical transplantation. *Bone Marrow Transplant* 1994; **14**: 63.
41. Falkenburg JH, Luxemburg-Heijs SA, Lim FT, Kanhai HH, Willemze R. Umbilical cord blood contains normal frequencies of cytotoxic T-lymphocyte precursors (ctlp) and helper T-lymphocyte precursors against noninherited maternal antigens and noninherited paternal antigens. *Ann Hematol* 1996; **72**: 260.
42. Moretta A, Locatelli F, Mingrat G, *et al.* Characterisation of CTL directed towards non-inherited maternal alloantigens in human cord blood. *Bone Marrow Transplant* 1999; **24**: 1161.
43. Hadley GA, Phelan D, Duffy BF, Mohanakumar T. Lack of T-cell tolerance of noninherited maternal HLA antigens in normal humans. *Hum Immunol* 1990; **28**: 373.
44. Roelen DL, van Bree FP, van Beelen E, van Rood JJ, Claas FHJ. No evidence of an influence of the noninherited maternal HLA antigens on the alloreactive T cell repertoire in healthy individuals. *Transplantation* 1995; **59**: 1728.
45. van den Boogaardt DEM, van Miert PPMC, Koekkoek KM, *et al.* No in vitro evidence for a decreased alloreactivity towards noninherited maternal HLA antigens in healthy individuals. *Hum Immunol* 2006; in press.
46. Andrassy J, Kusaka S, Jankowska-Gan E, *et al.* Tolerance to noninherited maternal MHC antigens in mice. *J Immunol* 2003; **171**: 5554.
47. Matsuoka K, Ichinohe T, Hashimoto D, Asakura S, Tanimoto M, Teshima T. Fetal tolerance to maternal antigens improves the outcome of allogeneic bone marrow transplantation by a CD4+CD25+ T-cell-dependent mechanism. *Blood* 2006; **107**: 404.
48. Vernochet C, Caucheteux SM, Gendron MC, Wantyghem J, Kanellopoulos-Langevin C. Affinity-dependent alterations of mouse B cell development by noninherited maternal antigen. *Biol Reprod* 2005; **72**: 460.
49. Kubens BS, Passler M, Grossewilde H. Segregation study of the soluble 39-Kd HLA class-I heavy-chain. *Hum Immunol* 1994; **40**: 247.
50. Streilein JW, Masli S, Takeuchi M, Kezuka T. The eye's view of antigen presentation. *Hum Immunol* 2002; **63**: 435.
51. Wilbanks GA, Streilein JW. Fluids from immune privileged sites endow macrophages with the capacity to induce antigen-specific immune deviation via a mechanism involving transforming growth factor-beta. *Eur J Immunol* 1992; **22**: 1031.
52. Ridge JP, Ephraim JF, Matzinger P. Neonatal tolerance revisited: turning on newborn T cells with dendritic cells. *Science* 1996; **271**: 1723.
53. Sarzotti M, Robbins DS, Hoffman PM. Induction of protective CTL responses in newborn mice by a murine retrovirus. *Science* 1996; **271**: 1726.
54. Forsthuber T, Hualin YC, Lehmann PV. Induction of Th1 and Th2 immunity in neonatal mice. *Science* 1996; **271**: 1728.
55. Opelz G, Sengar DP, Mickey MR, Terasaki PI. Effect of blood transfusions on subsequent kidney transplants. *Transplant Proc* 1973; **5**: 253.
56. Persijn GG, Cohen B, Lansbergen Q, van Rood JJ. Retrospective and prospective studies on the effect of blood transfusions in renal transplantation in The Netherlands. *Transplantation* 1979; **28**: 396.
57. Campbell DA Jr, Lorber MI, Sweeton JC, Turcotte JG, Niederhuber JE, Beer AE. Breast feeding and maternal-donor renal allografts. Possibly the original donor-specific transfusion. *Transplantation* 1984; **37**: 340.
58. Bean MA, Mickelson E, Yanagida J, Ishioka S, Brannen GE, Hansen JA. Suppressed antidonor MLC responses in renal transplant candidates conditioned with donor-specific transfusions that carry the recipient's noninherited maternal HLA haplotype. *Transplantation* 1990; **49**: 382.
59. Pohanka E, Cohen N, Colombe BW, Lou C, Salvatierra O Jr, Garovoy MR. Non-inherited maternal HLA antigens and protection against sensitisation. *Lancet* 1990; **336**: 1025.
60. Tamaki S, Ichinohe T, Matsuo K, Hamajima N, Hirabayashi N, Dohy H. Superior survival of blood and marrow stem cell recipients given maternal grafts over recipients given paternal grafts. *Bone Marrow Transplant* 2001; **28**: 375.
61. Zhang L, van Bree S, van Rood JJ, Claas FH. Influence of breast feeding on the cytotoxic T cell allorepertoire in man. *Transplantation* 1991; **52**: 914.
62. Zhang L, van Rood JJ, Claas FH. The T-cell repertoire is not dictated by self antigens alone. *Res Immunol* 1991; **142**: 441.
63. Propper DJ, Woo J, Stewart KN, Catto GR, Power DA. Immune responses to noninherited maternal RT1A antigens in inbred rats. *Transplantation* 1991; **52**: 331.
64. Akiyama Y, Caucheteux SM, Iwamoto Y, Guimezanes A, Kanellopoulos-Langevin C, Benichou G. Effects of noninherited maternal antigens on allotransplant rejection in a transgenic mouse model. *Transplant Proc* 2005; **37**: 1940.

