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Major and Minor Histocompatibility Antigens to Non-Inherited Maternal Antigens (NIMA)

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1. Introduction

Immunological reactivity results from differences between the transplant host and donor for cell surface determinants known as histocompatibility antigens. Histocompatibility antigens that provoke the most severe transplant reactions are encoded by a series of genes that reside in a discrete chromosomal region termed the major histocompatibility complex (MHC) (Amos 1968). Genes of the human leukocyte antigen (HLA) system encode a complex array of histocompatibility molecules that play a central role in immune responsiveness and in determining the outcome of hematopoietic stem cell transplantation (HSCT) (Beatty, Anasetti et al. 1993; Petersdorf, Longton et al. 1995). The primary goal of histocompatibility testing for patients who are undergoing HSCT is the identification of a suitable HLA-matched donor to reduce the risk of post-transplant complications, which may result from HLA incompatibility. The extensive polymorphism of the HLA system, however, makes the selection of a comprehensively, optimally-matched donor a challenging endeavor, particularly when donors outside of the patient's immediate family are sought. If a suitable donor is not found, clinicians need to explore the possibility of permissive HLA mismatches.

Haploidentical HSCT is curative treatment for patients lacking an HLA-compatible donor or cannot wait until a suitable donor can be found (Reisner, Kapoor et al. 1981; Buckley, Schiff et al. 1999). Haploidentical HSCT is usually employed with T-cell depletion or positive selection of $CD34^+$ cells to avoid severe graft-versus-host disease (GVHD) (Aversa, Tabilio et al. 1994). However there are disadvantages, such as potential for graft failure, fatal opportunistic infections, and relapse of the treated malignancy. To deal with those problems, T-cell "replete" haploidentical HSCT have been performed by researchers in Japan (Ichinohe, Uchiyama et al. 2004). These are based on the hypothesis that long-term maternal microchimerism (MMc) is associated with acquired immunologic hyporesponsiveness to non-inherited maternal antigen (NIMA) (Andrassy, Kusaka et al. 2003; Dutta, Molitor-Dart et al. 2009). T-cell replete HSCT, without GVHD, could be accomplished by using this phenomenon of feto-maternal tolerance. Unfortunately, graft rejection and hyperacute GVHD have been reported in HSCT from NIMA-mismatched siblings, despite detecting of MMc (Okumura, Yamaguchi et al. 2007). Therefore,

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development of a predictable method for GVHD in NIMA-mismatched HSCT is needed. We have produced a novel prediction assay, using MLR-ELISPOT (mixed lymphocyte reaction; enzyme-linked immunospot) assay, for detecting reactivity to NIMA (Araki, Hirayama et al. 2010). In this review, we discuss acute GVHD in T-cell depleted and T-cell replete HSCT, the role of major and minor histocompatibility in NIMA tolerance, and prediction of acute GVHD in T-cell replete HSCT via our model assay.

2. Minor histocompatibility antigens in mouse and human

Alloantigens can be divided into major histocompatibility complex (MHC) antigen and minor histocompatibility antigen (MiHA), the former responsible for eliciting the strongest immune responses to allogeneic tissues. The MHC is referred to as the H-2 complex in mice and as the HLA complex in humans.

MHC identity of donor and host is not the sole factor determining immunological reactivity in HSCT. When transplantation is performed in an unrelated setting (MUD, matched-unrelated donor), even if MHC antigens of donor are identical to recipient, considerable transplant reactions may occur because of differences at various minor histocompatibility loci. MiHAs are capable of eliciting cellular alloimmune responses in vitro and in vivo. They are peptides derived from polymorphic proteins. Their immunogenicity arises as a result of their presentation in the context of MHC class I or II, where they are recognized by alloreactive MHC-restricted T cells. The most important immune reactions elicited by in vivo alloreactivity to MiHA are graft rejection and GVHD.

To date, human MiHAs have not been fully characterized. Some murine MiHAs have been compared with human counterparts though (see, HY antigens in Table 1). Immunological targeting of HY proteins results in a relatively high incidence of acute GVHD when male recipients receive HSCT from female donors (Stern, Passweg et al. 2006). While approximately one third of the known MiHAs are encoded in Y chromosome, many MiHAs are located on autosomal chromosomes (Table 1). Genetic linkage analysis has been used to define the genomic regions encoding the MiHAs (Akatsuka, Nishida et al. 2003; de Rijke, van Horssen-Zoetbrood et al. 2005). With these more recent advanced techniques, more human MiHAs epitopes have been identified (van Bergen, Kester et al. 2007; Kawase, Akatsuka et al. 2007; Tykodi, Fujii et al. 2008; Griffioen, van der Meijden et al. 2008; Spaapen, Lokhorst et al. 2008; Spaapen, de Kort et al. 2009; Kamei, Nannya et al. 2009; Stumpf, van der Meijden et al. 2009; Bleakley, Otterud et al. 2010; Van Bergen, Rutten et al. 2010; Sellami, Kaabi et al. 2011).

MiHA	Species	Chromosome	Gene	MHC restriction	Tissue specificity	References
Y chromosome						
HY	Mouse	Y	Smcy	H-2K^k, H-2D^b	Ubiquitous	(Markiewicz et al. 1998)
HY	Mouse	Y	Uty	H-2D^b	Ubiquitous	(Greenfield et al. 1996)
HY	Mouse	Y	Dby	H-2A^b, H-2E^k	Ubiquitous	(Scott et al. 2000)
SMCY	Human	Yq11	JARID1D	HLA-A*02:01, B*07:02	Ubiquitous	(Wang et al. 1995)

MiHA	Species	Chromosome	Gene	MHC restriction	Tissue specificity	References
UTY	Human	Yq11	UTY	HLA-B8, B60	Ubiquitous	(Vogt et al. 2000)
DBY	Human	Yq11	DDX3Y	HLA-B*27:05, DRB1*15:01, DQ5	Hematopoietic	(Zorn et al. 2004)
DFFRY	Human	Yq11.2	USP9Y	HLA-A*01:01	Ubiquitous	(Pierce et al. 1999)
RPS4Y	Human	Yp11.3	RPS4Y1	HLA-B*52:01, DRB3*03:01	Ubiquitous	(Spierings et al. 2003)
TMSB4Y	Human	Yq11.221	TMSB4Y	HLA-A*33:03	Ubiquitous	(Torikai et al. 2004)
Autosomal chromosome						
H3	Mouse	2	Zfp106	$H\text{-}2D^b$	Ubiquitous	(Zuberi et al. 1998)
H4	Mouse	7	Emp3	$H\text{-}2K^b$	Ubiquitous	(Luedtke et al. 2003)
H7	Mouse	9	D9Mit182	$H\text{-}2D^b$	Ubiquitous	(Perreault et al. 1996)
H13	Mouse	2	47c1 cDNA	$H\text{-}2D^b$	Ubiquitous	(Mendoza et al. 1997)
H28	Mouse	3	NS1178	$H\text{-}2K^b$	Ubiquitous	(Malarkannan et al. 2000)
H46	Mouse	7	Il4i1	$H\text{-}2A^b$	Hematopoietic	(Sahara et al. 2003)
H47	Mouse	7	H47	$H\text{-}2D^b$	Ubiquitous	(Mendoza et al. 2001)
H60	Mouse	10	Rae1	$H\text{-}2K^b$	Hematopoietic	(Choi et al. 2001)
HA-1	Human	19p13.3	HMHA1	HLA-A*02:01, A*02:06, B60	Hematopoietic	(Mommaas et al. 2002)
HA-2	Human	7p13-p11.2	MYO1G	HLA-A*02:01	Hematopoietic	(den Haan et al. 1995)
HA-3	Human	15q24-q25	AKAP13	HLA-A*01:01	Ubiquitous	(Spierings et al. 2003)
HA-8	Human	9p24.2	KIAA0020	HLA-A*02:01	Ubiquitous	(Brickner et al. 2001)
HB-1	Human	5q31.3	HMHB1	HLA-B*44:02, B*44:03	B-cell	(Dolstra et al. 1999)
ACC-1, 2	Human	15q24.3	BCL2A1	HLA-A*24:02, B*44:03	Hematopoietic	(Akatsuka et al. 2003)
UGT2B17	Human	4q13	UGT2B17	HLA-A*02:06, A*29:02, B*44:03	Ubiquitous	(Murata et al. 2003)
LRH-1	Human	17p13.3	P2RX5	HLA-B*07:02	Hematopoietic	(de Rijke et al. 2005)
CTSH	Human	15q25.1	CTSH	HLA-A*31:01, A*33:03	Ubiquitous	(Torikai et al. 2006)
LB-ECGF1-1H	Human	2q13.33	ECGF1	HLA-B*07:02	Hematopoietic	(Slager et al. 2006)
PANE1	Human	22q13.2	CENPM	HLA-A*03:01	Hematopoietic	(Brickner et al. 2006)
SP110	Human	2q37.1	SP110	HLA-A*03:01	Hematopoietic	(Warren et al. 2006)

Table 1. Minor histocompatibility antigens in mouse and human

3. Acute GVHD in T-cell depleted or replete haploidentical transplantation

Haploidentical HSCT has made progress over the past 30 years and has become a feasible option for patients without an HLA-identical sibling donor. This is especially true for reconstitution of immunity in infants with severe combined immunodeficiency, where use of rigorously T-cell depleted marrow has been quite successful (Buckley, Schiff et al. 1999). In early trials of haploidentical HSCT, ex vivo T-cell depletion method of haploidentical bone marrow cells was an effective method reported by Reisner et al (Reisner, Kapoor et al. 1981). This procedure without immunosuppressive prophylaxis allowed durable engraftment rate about 75% with acceptable incidence of acute GVHD (36%) in patients with severe combined immunodeficiency (Buckley, Schiff et al. 1999). However, its application to haploidentical HSCT for leukemia was less encouraging due to the high incidence of graft failure (30%) and infectious complications (80%) (O'Reilly, Keever et al. 1987). In a trial from the University of Perugia, the use of T-cell depletion in combination with a high dose of stem cells overcame graft rejection as well as acute GVHD (Aversa, Tabilio et al. 1994). Improved positive selection of CD34$^+$ cells was accomplished by depletion of B cells, in addition to T cells, which resulted in a lower incidence of EBV-associated lymphoproliferative disease (LPD) (Aversa, Terenzi et al. 2005). Another method using ex vivo T-cell depletion of bone marrow cells with anti-T-cell monoclonal antibodies, followed by treatment with cyclosporine and ATG, was encouraging for the use of haploidentical marrow (Henslee-Downey, Abhyankar et al. 1997). Over 95% durable engraftment and low incidence of acute GVHD (13%) were obtained, and accompanied with an acceptable relapse rate (31%) (Mehta, Singhal et al. 2004). Although these various depletion techniques achieved benefit, to truly achieve more acceptable results, further improvement is necessary to address the high rate of malignancy relapses, acute and chronic GVHD, and otherwise, treatment-related morbidity and mortality.

As an alternative to ex vivo T-cell depletion, in vivo T-cell depletion methods have been undertaken for improving relapse rates and treatment-related mortality. Lu et al. from Peking University described the transplantation of combination of G-CSF-primed bone marrow and peripheral blood with intensive immunosuppression using ATG (Lu, Dong et al. 2006). Although the cumulative incidence of grade II to IV acute GVHD was comparatively high, 40%, two-year incidences of relapses and treatment-related mortality were low, 22% and 18%, respectively. More recently, Huang et al., in the same group reported encouraging clinical outcomes in 250 patients with haploidentical HSCT. The 3-year of leukemia free survival in standard and high-risk AML was 70.7% and 55.9%, respectively, and 59.7% and 24.8% for ALL (Huang, Liu et al. 2009). In another approach, Rizzieri et al. reported that alemtuzumab was used for in vivo depletion of both recipient and donor T-cells, in order to allow for more reliable engraftment and decreased GVHD (Rizzieri, Koh et al. 2007).

Sibling-related NIMA-mismatched transplantation, as an approach to T-cell replete haploidentical HSCT, was introduced as an alternative to ex vivo or in vivo T-cell depleted haploidentical HSCT. Van Rood et al. first showed that the incidence of acute GVHD was lower in patients who received T-cell replete grafts from an NIMA-mismatched sibling than those from non-inherited paternal antigen (NIPA) -mismatched sibling (van Rood, Loberiza et al. 2002). This indicated that the presence of immunological hyporesponsiveness against

NIMA in haploidentical transplantation could be important for prevention of GVHD and other immunologic comorbidities. Ichinohe et al. also showed that T-cell replete haploidentical HSCT from NIMA-mismatched family donor was feasible in selected patients with poor-risk hematologic malignancies using standard GVHD prophylaxis (Ichinohe, Maruya et al. 2002). However, 10% of patients still experienced severe acute GVHD, and there was not a useful method to predict acute GVHD in these patients. Thus, both T-cell depleted and T-cell replete haploidentical HSCT have benefits and drawbacks (Table 2). The problems of T-cell depleted HSCT were relatively high rate of graft failure, delayed immune reconstitution resulting in infections, and relapse of malignancies (Henslee-Downey, Abhyankar et al. 1997; Guinan, Boussiotis et al. 1999; Mehta, Singhal et al. 2004; Lu, Dong et al. 2006; Huang, Liu et al. 2009). On the other hand, the problems of T-cell replete haploidentical HSCT were relatively high rates of acute GVHD and treatment-related mortality (Ichinohe, Maruya et al. 2002; van Rood, Loberiza et al. 2002; Kanda, Ichinohe et al. 2009). Therefore, if an effective method to predict GVHD is available, T-cell replete haploidentical HSCT may be feasible with relative safety; lower risk of GVHD, lower risk of infections, and lower risk of malignancy relapse.
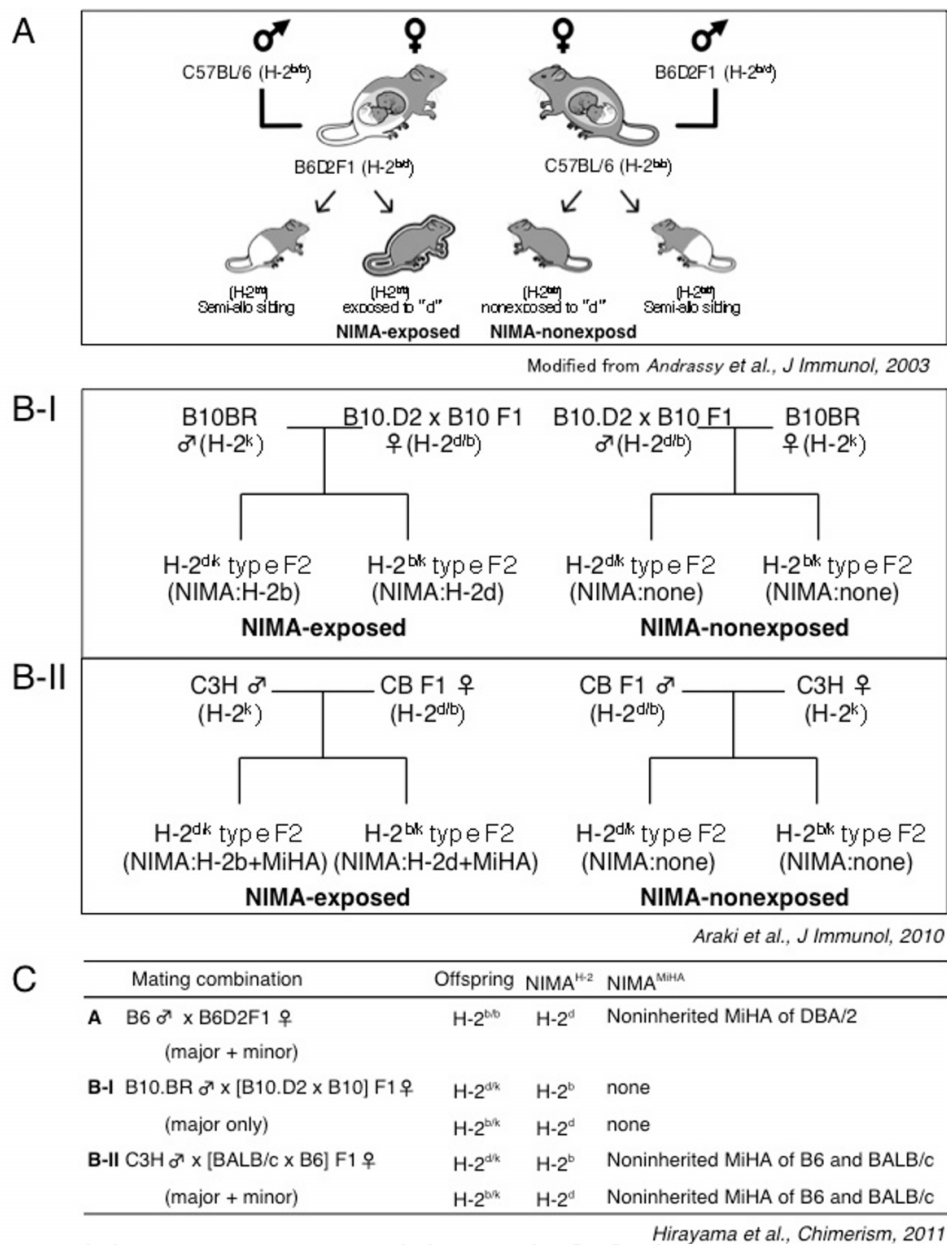
Type of HSCT	Age	Source	ATG	Acute GVHD (Grade II-IV)	Graft failure	TRM	Relapse	DFS
T-cell depleted								
(Ex vivo)	0-33	BM	+	5-8 %	3-5 %	17-47 %	11-25 %	35-38 %
(In vivo)	16-25	BM ± PB	+	13-46 %	0-13 %	22-51 %	18-31 %	18-64 %
T-cell replete								
(NIMA/ Mother)	15-28	BM or PB	-*	41-58 %	0-20 %	18-57 %	6-25 %	30-81 %
(NIPA/ Father)	17-20	BM	-*	55-63 %	13-29 %	36-45 %	Unknown	24-44 %

*More than 90% of patients were not used.
Abbreviations: ATG, anti-thymocyte globulin; TRM, treatment-related mortality; DFS, disease-free survival; BM, bone marrow; PB, peripheral blood.

Table 2. Frequency of acute GVHD in T-cell depleted and T-cell replete HSCT

4. Tolerance to non-inherited maternal antigen in murine studies

Maternal cells and fetal cells, most notably lymphocytes, are known to reciprocally traffic across the placenta during fetal development (Hall, Lingenfelter et al. 1995; Lo, Lo et al. 1996), and can result in life-long MMc in the offspring (Maloney, Smith et al. 1999). Prenatal exposure to NIMA affects the neonate's developing immune system, producing some tolerization to the non-inherited MHC components. There have been several previously reported investigations of NIMA (Burlingham, Grailer et al. 1998; Andrassy, Kusaka et al. 2003), as illustrated in Figure 1.

A

C57BL/6 (H-2$^{b/b}$) ♂   ♀   ♀   ♂ B6D2F1 (H-2$^{b/d}$)

B6D2F1 (H-2$^{b/d}$)   C57BL/6 (H-2$^{b/b}$)

(H-2$^{b/b}$) Semi-allo sibling   (H-2$^{b/b}$) exposed to "d" **NIMA-exposed**   (H-2$^{b/b}$) nonexposed to "d"   (H-2$^{b/b}$) Semi-allo sibling **NIMA-nonexposd**

Modified from Andrassy et al., J Immunol, 2003

B-I

B10BR ♂ (H-2^{k}) —— B10.D2 x B10 F1 ♀ (H-2$^{d/b}$)   B10.D2 x B10 F1 ♂ (H-2$^{d/b}$) —— B10BR ♀ (H-2^{k})

H-2^{dk} type F2 (NIMA:H-2b)   H-2^{bk} type F2 (NIMA:H-2d)   H-2^{dk} type F2 (NIMA:none)   H-2^{bk} type F2 (NIMA:none)

NIMA-exposed   **NIMA-nonexposed**

B-II

C3H ♂ (H-2^{k}) —— CB F1 ♀ (H-2$^{d/b}$)   CB F1 ♂ (H-2$^{d/b}$) —— C3H ♀ (H-2^{k})

H-2^{dk} type F2 (NIMA:H-2b+MiHA)   H-2^{bk} type F2 (NIMA:H-2d+MiHA)   H-2^{dk} type F2 (NIMA:none)   H-2^{bk} type F2 (NIMA:none)

NIMA-exposed   **NIMA-nonexposed**

Araki et al., J Immunol, 2010

C

	Mating combination	Offspring	NIMA^{H-2}	NIMA^{MiHA}
A	B6 ♂ x B6D2F1 ♀ (major + minor)	H-2$^{b/b}$	H-2^{d}	Noninherited MiHA of DBA/2
B-I	B10.BR ♂ x [B10.D2 x B10] F1 ♀ (major only)	H-2$^{d/k}$	H-2^{b}	none
		H-2$^{b/k}$	H-2^{d}	none
B-II	C3H ♂ x [BALB/c x B6] F1 ♀ (major + minor)	H-2$^{d/k}$	H-2^{b}	Noninherited MiHA of B6 and BALB/c
		H-2$^{b/k}$	H-2^{d}	Noninherited MiHA of B6 and BALB/c

Hirayama et al., Chimerism, 2011

A-Left, C57BL/6 (B6) males (H-2$^{b/b}$) were mated with (B6 x DBA/2) F1 female (H-2$^{b/d}$), thus exposing the H-2$^{b/b}$ offspring in utero and via breast feeding to NIMA^{d} antigens. Right, (B6 x DBA/2) F1 males were mated with B6 female, creating H-2$^{b/b}$ backcross offspring that had not been exposed to "d" as reported by Andrassy et al. B-I-Left, B10.BR males (H-2^{k}) were mated with (B10.D2 x B10) F1 females (H-2$^{d/b}$), thus exposing the H-2$^{d/k}$ type offspring to NIMA^{b}, and H-2$^{b/k}$ type offspring to NIMA^{d} Right, (B10.D2 x B10) F1 males (H-2$^{d/b}$) were mated with B10.BR females (H-2^{k}), creating the controls; both H-2$^{d/k}$ and H-2$^{b/k}$ type offsprings that had not been exposed to b and d, respectively. These mice have B10 background, in other words, their MiHA (i.e. H-4, H-13, H-60, etc) are matched, and H-2 antigens are mismatched in both class I and II. B-II-Left, C3H males (H-2^{k}) were mated with CB (BALB/c x B6) F1 females (H-2$^{d/b}$), thus exposing the H-2$^{d/k}$ type offspring to NIMA b antigens and MiHA (NIMA$^{H-2b+MiHA}$), and H-2$^{b/k}$ type offspring to NIMA$^{H-2d+MiHA}$. Right, CB F1 males (H-2$^{d/b}$) were mated with C3H females (H-2^{k}), creating the controls; both H-2$^{d/k}$ and H-2$^{b/k}$ type offspring that had not been exposed to H-2b+MiHA and H-2d+MiHA, respectively. C, Breeding pattern were summarized in terms of major and minor histocompatibility Ags to NIMA.
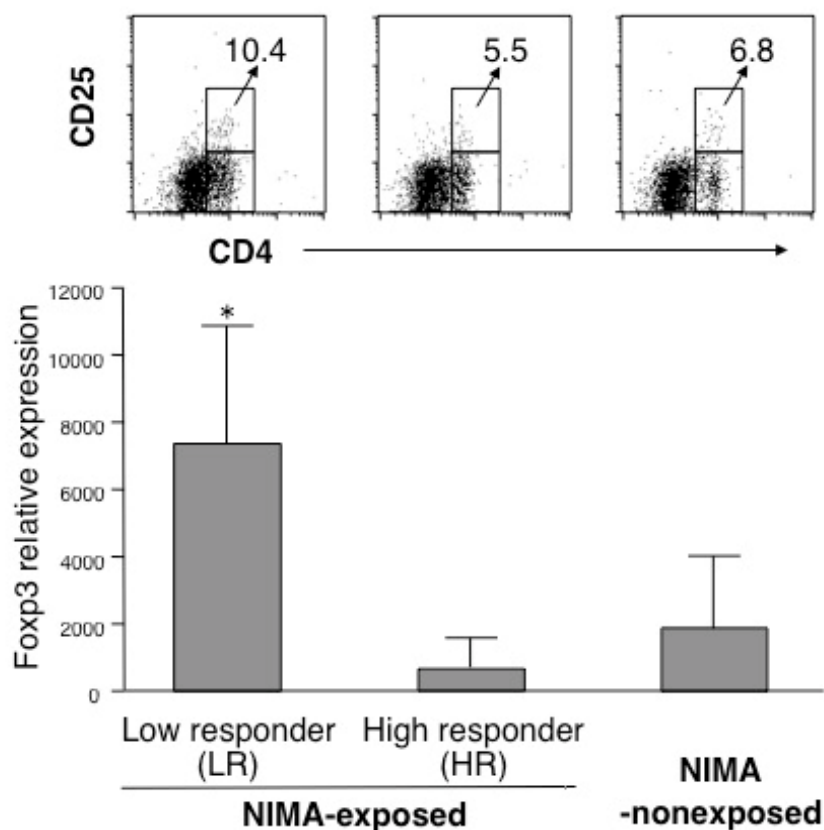
Fig. 1. Murine models for non-inherited maternal antigens.

In addition, maternal cells and MHC/HLA proteins are ingested by the baby during nursing, possibly stimulating oral tolerance (Verhasselt, Milcent et al. 2008; Aoyama, Koyama et al. 2009). The clinical benefits of developmentally acquired tolerance to NIMA were first noted by Owen et al. more than 50 years ago (Owen, Wood et al. 1954). Since then, tolerogenic effects of NIMA have been documented at both T- and B-cell levels in a variety of clinical settings (Claas, Gijbels et al. 1988; van Rood and Claas 1990; Burlingham, Grailer et al. 1998). Presence of feto-maternal tolerance was anticipated due to the presence of MMc (Andrassy, Kusaka et al. 2003), and the concept has been used in clinical studies (Ichinohe, Uchiyama et al. 2004). On the basis of this hypothesis, several transplantation centers in Japan have performed clinical trials to test the feasibility of HLA-haploidentical HSCT from a NIMA mismatched relative, without using either T-cell depletion or intensive post-transplant immunosuppression (Ichinohe, Uchiyama et al. 2004; Kanda, Ichinohe et al. 2009).

Persistent MMc is associated with antigen-specific suppression of the associated T-cell responses (van Rood, Loberiza et al. 2002). With the help of highly sensitive polymerase chain reaction (PCR)-based techniques, long-term MMc can be detected from the peripheral blood, or various tissues including liver, skin, and thyroid gland (Ichinohe, Maruya et al. 2002). Several investigators have suggested the association of long-term MMc with the development of tolerance to NIMA (Kodera, Nishida et al. 2005). Thus, successful NIMA-mismatched haploidentical HSCT have been performed confirming long-term MMc as an indication of tolerance induction, in agreement with the correlation between MMc and tolerance in mice, which has been described recently (Dutta, Molitor-Dart et al. 2009). However, in some individuals unsuccessful NIMA-mismatched haploidentical HSCT have occurred, when the concept of MMc would have predicted otherwise.

The relevance of MiHA in tolerance to NIMA has not been reported. In both MHC-identical and MHC-haploidentical transplants, MiHA alloreactivities may be induced (Verdijk, Kloosterman et al. 2004). Therefore, maintaining the focus on the tolerance-induction of NIMA to MHC may have greater clinically relevance. In accord with this, we have shown differences in the NIMA tolerogenic effect in different individuals, divided into high responder (HR) or low responder (LR) categories, depending on the magnitude of the MLR of donor against recipient NIMA (Araki, Hirayama et al. 2010). The magnitude of the responses was associated with the extent of regulatory T cells (Treg) and Foxp3 expression in MHC-mismatched, MiHA-matched HSCT (Figure 2). This, with other reports, describe that Treg mediate tolerance to NIMA (Aluvihare, Kallikourdis et al. 2004; Matsuoka, Ichinohe et al. 2006). Survival rates and GVHD clinical scores of NIMA-exposed LR mice were significantly better than those of NIMA-exposed HR mice (Figure 3). Moreover, the level of MMc was correlated with the tolerogenic effect of the NIMA (Araki, Hirayama et al. 2010).
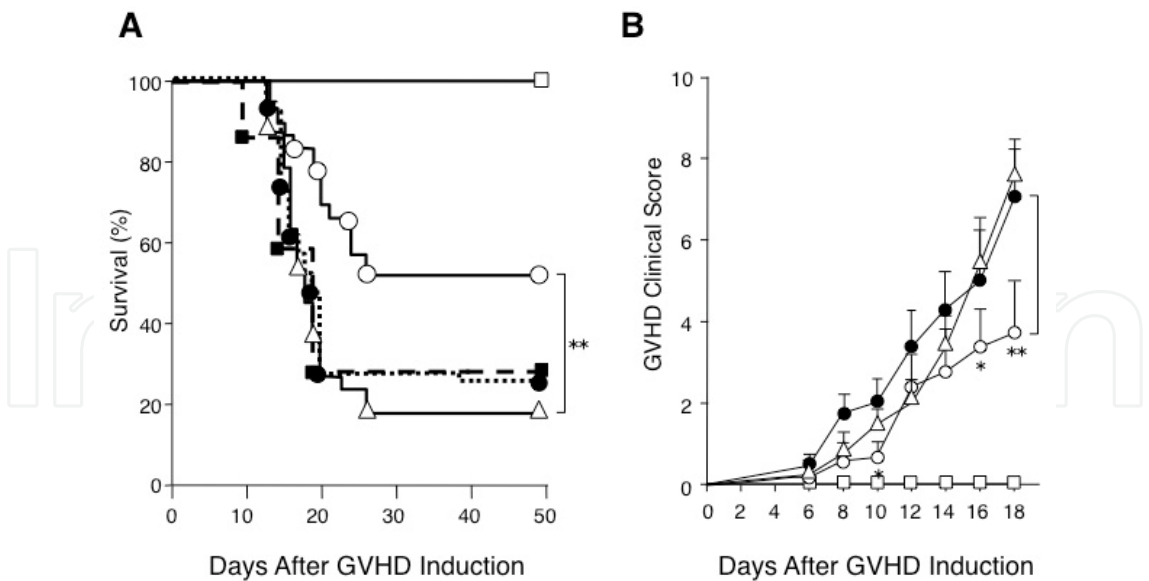
The mouse MiHA loci confers a wide range of immunogenicity, ranging from weakly to strongly immunogenic (Roopenian, Choi et al. 2002). Several studies have provided evidence that GVHD could be caused by only a limited number of mouse MiHA as described above (Choi, Yoshimura et al. 2001; Yang, Jaramillo et al. 2003; Eden, Christianson et al. 1999). The specific MiHA immunodominance was manifested on genetically varied backgrounds among B10, BALB/c, and DBA/2 strains (Sanderson and Frost 1974; Mendoza, Paz et al. 1997;

We have shown a difference of proliferative response to NIMA in NIMA-exposed and NIMA-non-exposed mice. The mice were classified into two groups by MLR, based on their reactivity to NIMA; the high responder (HR ≥ mean+1SD in NIMA-nonexposed) or the low responder (LR < mean+1SD) group (Araki, Hirayama et al. 2010). Upper, The percentage of CD4+CD25+ cells in CD4+ cell population was analyzed by flow cytometry. Lower, The relative expression of Foxp3 compared with GAPDH is presented as the mean + SE. Samples were obtained 21 days after GVHD induction from recipients injected with cells from NIMA-exposed LR, HR, and NIMA-nonexposed mice (n=5 in each group). *p<0.05.

Fig. 2. Regulatory T cells and Foxp3 expression correlated with reactivity to MHC.

Malarkannan, Horng et al. 2000). Previously, there has been no report distinguishing the reactivities of MHC and MiHA from the tolerogenic effect of NIMA. We have proposed to classify the murine models of NIMA based on major and minor histocompatibility antigens to NIMA (Hirayama and Azuma 2011) (Figure 1C). In our study, all B10 congenic mice were used as the former NIMA model, "major only" (Figure 1B-I), and those MiHA had matched entirely in this system (Araki, Hirayama et al. 2010). On the other hand, the previous model (Andrassy, Kusaka et al. 2003; Matsuoka, Ichinohe et al. 2006) (Figure 1A) and the latter our model, "major + minor" (Figure 1B-II) were mismatched at both H-2 and MiHA. Therefore, we need to consider an influence of both major and minor histocompatibility when NIMA tolerance is evaluated (Hirayama and Azuma 2011) (Figure 1C).

A, The survival of sublethally irradiated recipient B10 female mice injected with vehicle (□, n = 14), cells from NIMA-exposed LR mice (H-2$^{d/k}$, NIMA^b) (○, n = 30), HR mice (NIMA^b) (Δ, n = 33), NIMA-nonexposed mice (H-2$^{d/k}$, NIMA^{none}) (●, n = 39), and allogeneic B10.D2 mice (■, n =14). B, The GVHD clinical score was determined in recipients injected with cells from NIMA-exposed LR mice (○, n = 48), HR mice (Δ, n = 45), allogeneic mice (●, n = 47), and vehicle (□, n = 12). The degree of clinical GVHD was assessed by the scoring system that incorporates five clinical parameters: weight loss, posture, activity, fur texture, and skin integrity, grading from 0 to 2 for each parameter. A clinical index was subsequently generated by summation of the five criteria scores (maximum index=10). Data are expressed as the means + SE of individual animals. **p<0.01, *p<0.05.

Fig. 3. Two distinct reactivities to H-2 in NIMA-exposed mice resulted in differences in GVHD induction.

A, ELISPOT assay combining with MLR (MLR-ELISPOT) is a sensitive functional assay to detect alloreactivity for both major and minor histocompatibility antigens in mice. B, The IFN-γ-producing ability before GVHD induction was presented by MLR-ELISPOT. Peripheral blood mononuclear cells from NIMA-exposed LR mice (H-2$^{d/k}$, NIMA^b, n=8), HR mice (n=7), and nonexposed mice (n=6) were stimulated with B10 mice peripheral blood mononuclear cells. Data are expressed as the means + SE of individual animals. *p<0.05.

Fig. 4. Prediction of reactivity to NIMA by MLR-ELISPOT assay.

5. Reactivity to mismatched histocompatibility antgens; Tolerogenic or immunogenic?

The mechanisms by which NIMA drive the immune system toward tolerance or rejection of the allograft are still unclear. Although mismatch at MiHA can provoke severe immune responses against host cells upon transplantation (Goulmy, Schipper et al. 1996), the role of MiHA in the NIMA effects has not been described. Recently, naturally acquired tolerance and sensitization to MiHA have been reported (van Halteren, Jankowska-Gan et al. 2009). The presence of MiHA-specific Treg was shown in healthy adult women and men. In addition, it remains to be studied whether or not particular microchimeric cell types are associated with either a sensitized or a tolerized MiHA effect. Our study showed the difference of individual reactivities toward MHC, not MiHA, was critically influenced by the amount of MMc expression (Araki, Hirayama et al. 2010). The relationship between tolerogenic effect and MMc are consistent with a report of Dutta et al. They described the correlation between MMc and NIMA-specific Treg capable of suppressing both delayed type hypersensitivity and lymphoproliferative responses of effector T cells in a conventional NIMA mouse model (van Rood and Claas 1990; Andrassy, Kusaka et al. 2003). Opiela et al. described that transient exposure to low levels of NIMA alloantigens in early life may lead to long-term priming for both cytotoxic and helper T cell functions (Opiela, Levy et al. 2008). On the other hand, Aoyama et al. showed that both oral and in utero exposures to NIMA are required for the maximum induction of tolerance (Aoyama, Koyama et al. 2009). In any case, the mechanism underlying the development of tolerance versus priming to NIMA alloantigens remains to be clarified.

6. Prediction of acute GVHD in mismatched HSCT

Prediction of acute GVHD by in vitro assays prior to transplantation have not be very successful until now. In vitro detection of the frequencies of cytotoxic T-lymphocyte precursors (CTLp) and helper T-lymphocyte precursors (HTLp), in conjunction with MLR have been used as a method to detect individual reactivity to NIMA (Falkenburg, van Luxemburg-Heijs et al. 1996; Moretta, Locatelli et al. 1999; Tsafrir, Brautbar et al. 2000). Moretta et al. described that the frequency of NIMA-specific CTLp in cord blood samples were measured in order to better define the phenomenon of NIMA tolerance (Moretta, Locatelli et al. 1999). NIMA-reactive cord blood cells are detectable, but they were unable to detect differences between CTLp frequencies towards NIMA or NIPA. Falkenburg et al. investigated whether NIMA tolerance could allow transplantation over certain HLA barriers. Both CTLp and HTLp frequencies against NIPA were not statistically different than those directed against NIMA (Falkenburg, van Luxemburg-Heijs et al. 1996). Indeed, Kircher et al. showed that CTLp and HTLp frequencies were not predictive for the risk of acute GVHD in patients received allogeneic HSCT (Kircher, Niederwieser et al. 2004). Established test systems are therefore not available for the prediction of alloreactions and outcome after HSCT. Originally, it was predicted that CTLp reflects alloreactivity of class I mismatch, and HTLp reflect alloreactivity of class II mismatch. Levitsky et al. reported an evaluation of allogeneic reaction that used Treg (Levitsky, Miller et al. 2009). They generated carboxy-fluorescein diacetate succinimidyl ester-labeled CD4^{+}CD25^{high} FOXP3^{+} cells in MLR, which they called "Treg MLR". These cells had varying HLA disparities and varying reactivities to cell components. However, this method reflects only a difference related to MHC class II. Thus, the above-mentioned methods can detect MHC class I or class II

separately, but it is difficult to detect them simultaneously. Recently, we reported a novel method, MLR-ELISPOT, to overcome these difficulties, as shown in Table 3.

Assay	Target antigen	References
Frequency of CTLp	MHC class I	(Hadley et al. 1990; Falkenburg et al. 1996; Moretta et al. 1999)
Frequency of HTLp	MHC class II	(Falkenburg et al. 1996; Kircher et al. 2004)
MLR, modified MLR	MHC class II	(Tsafrir, Brautbar et al. 2000)
Treg MLR	MHC class II	(Levitsky, Miller et al. 2009)
MLR-ELISPOT for IFN-γ	MHC class I and II (MiHA)	(Araki, Hirayama et al. 2010)

Table 3. Detection assay to allogeneic antigen

Alloreactivity of NIMA-exposed mice and NIMA-nonexposed mice were evaluated by MLR, and we found quite wider range of reactivity in the former compared with the latter. This helps to indicate that feto-maternal interaction acts on both tolerance (low responder) and sensitization (high responder) (Molitor-Dart, Andrassy et al. 2008; van Halteren, Jankowska-Gan et al. 2009). The reports from Tsafrir et al. and Falkenburg et al. detected a reactivity to NIMA by MLR (Falkenburg, van Luxemburg-Heijs et al. 1996), and CTLp and HTLp (Tsafrir, Brautbar et al. 2000), respectively. Interestingly, when we scrutinized the figures in their articles, individual reactivities of NIMA-exposed group showed a wider range than the control group, and those reactivities seem to be divided into low and high reactions, although they did not discuss these observations. This was further indication that reactivity to NIMA could be detected in vitro, and the condition of feto-maternal interaction promoted either tolerance (low-responder) or sensitization (high-responder).

Several investigators have reported that evaluations of reactivity to NIMA can be assessed, but the clinical relevance remains unknown. Presence of feto-maternal tolerance was anticipated due to MMc (Andrassy, Kusaka et al. 2003), and this concept has been used in clinical studies (Ichinohe, Maruya et al. 2002). Functional importance of MMc in humans has been further studied (Carter, Cerundolo et al. 1999; Cho, Choi et al. 2006). The majority of assays used to detect donor-derived cells in a recipient's blood exploit sex-mismatch between donor and recipient or the polymorphism of the HLA-DR region of the MHC, determined with sequence specific primer PCR (SSP-PCR). SSP-PCR is commonly used for HLA typing the extent of match between donors and recipients prior to transplantation, but may not work well for detection of MMc. The sensitivity of detection of this technique can range from 0.5% to 0.01%, more than adequate for routine HLA-typing, but MMc levels may be from 0.01% to 0.001%, well below the sensitivity of the assay. Therefore, the sensitivity of SSP-PCR for HLA-DR alleles has been increased by the introduction of a nested priming of exon 2 SSP-PCR approached. Most of NIMA-mismatched haploidentical HSCT in Japan require positive MMc of the donor by using the nested SSP-PCR (Ichinohe, Maruya et al. 2002; Carter, Cerundolo et al. 1999).

Although detection of MMc was clinically used for an indication of probable tolerance to NIMA, severe acute cases of GVHD developed (Okumura, Yamaguchi et al. 2007; Kanda, Ichinohe et al. 2009). Studies indicate that NIMA allografts do better than NIPA allografts in vivo (Burlingham, Grailer et al. 1998), and in vitro T-cell responses to NIMA are significantly reduced in IL-2 and IFN-γ production assays, compared with NIPA (Andrassy,

Kusaka et al. 2003). Tsafrir et al. demonstrated this NIMA effect using umbilical cord blood mononuclear cells by a MLR assay (Tsafrir, Brautbar et al. 2000), but Hadley et al. could not detect the NIMA effect using peripheral blood mononuclear cells from healthy individuals (Hadley, Phelan et al. 1990). Thus, there is not a useful method to predict a tolerogenic effect for NIMA, although these studies may suggest that newborns are more tolerogenic to NIMA than older individuals. Recently, we demonstrated that the level of cells producing IFN-γ, but not IL-4 and IL-10, were significantly lower in NIMA-exposed group than NIMA-nonexposed group by using an MLR-ELISPOT assay in a murine model (Araki, Hirayama et al. 2010) (Figure 4). This assay should be easily applicable to humans, and is a versatile method to detect reactivities to MHC class I as well as class II. And, it may also detect reactivity to MiHA (Table 3). In other words, this assay might be useful to predict the total immunological reaction of donor T cells to recipient in mismatched HSCT.

7. Conclusions

The risk of acute GVHD might be influenced by various genetic factors HLA, MiHA, or others (Hsu, Chida et al. 2002; Lin, Storer et al. 2003). NIMA-mismatched haploidentical HSCT has been improving with sustained engraftment, lower early treatment-related mortality, and acceptable rates of GVHD. However, it has been difficult to predict severe GVHD prior to transplantation. Our recent report has addressed the issue (Araki, Hirayama et al. 2010; Hirayama and Azuma 2011). NIMA effects directed toward MHC antigen were divided into high (immunogenic) and low (tolerogenic) reactivities. Our results in mice demonstrated that there was an unevenness in the acquisition and maintenance of MMc in the offspring. Further differential inheritance of MiHA did not influence our results, i.e., the variability amongst offspring was not due to solely to differences in MiHA gene inheritance. The variability seemed intrinsic to chance events in mammalian reproduction; i.e. allogeneic pregnancy and nursing itself (Aoyama, Koyama et al. 2009; Dutta, Molitor-Dart et al. 2009). To date, T-cell replete haploidentical transplantation is performed only in the presence of detected MMc in the recipient, although individual reactivity of donor to the receipient has not been evaluated. Could the pairing result in a low-responder/tolergenic or high-responder/immunogenic situation? Therefore, our recent study is clinically relevant. T-cell replete NIMA-mismatched haploidentical transplantation could be performed more safely by using our assay to evaluate IFN-γ-producing cells of donor against NIMA as a way to further reduce graft failure, prevent transplant mortality, and prevent severe GVHD.

8. Acknowledgments

9. References

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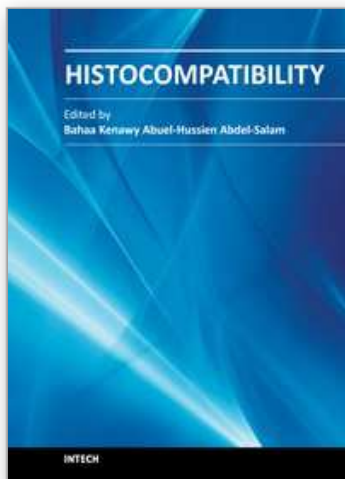
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Histocompatibility

Edited by Dr. Bahaa Abdel-Salam

This book presents some recent researches related to histocompatibility for scientists interested in this field. It includes 10 chapters, in different topics, prepared by Sundararajulu Panneerchelvam and Mohd Nor Norazmi; Giada Amodio and Silvia Gregori; Adema Ribic; Bahaa K. A. Abdel-Salam; Kai-Fu Tang; Roberto Biassoni, Irene Vanni and Elisabetta Ugolotti; Wei-Cheng Yang, Lien-Siang Chou and Jer-Ming Hu; Shatrah Othman and Rohana Yusof; Masahiro Hirayama, Eiichi Azuma and Yoshihiro Komada; Gustav Roder, Linda Geironson, Elna Follin, Camilla Thuring and Kajsa Paulsson.

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