Minor Histocompatibility antigens: from T cell recognition to peptide identification

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EDITORIAL

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PREFACE

For decades, minor histocompatibility antigens have been regarded as disturbing entities readily used to explain unwanted immune reactivities in recipients of MHC-matched bone marrow transplants Now that the nature of these antigens is being discovered, we may apply the knowledge of these disturbing entities to the benefit of human bone marrow transplantation

BACKGROUND

Bone marrow transplantation (BMT) in combination with chemoradiotherapy is used as treatment of severe aplastic anemia, leukemia, and other hematologic malignancies The ideal transplant situation is when BM donor and recipient have identical MHC antigens and are closely related Nonetheless, the results of clinical BMT reveal that the selection of MHC-identical donors is not a guarantee of avoidance of two of the major drawbacks of allogeneic BMT, i e , graft-versus-host disease (GvHD) and leukemia relapse GvHD occurs, depending on the age of recipient and the amount of T cell depletion of the graft, in 15–35% of the HLA genotypically identical donor/recipient situations [1, 2] T cell depletion of the donor marrow inoculum shows a reduction in the incidence and severity of GvHD but coincides with an increase of leukemia relapse On the one hand, mature T cells present in the donor bone marrow inoculum are essential for graft acceptance, on the other hand, they are responsible for GvHD but most probably also cause the beneficial graft-versus-leukemia (GvL) effect Several clinical studies indeed indicate a direct relationship between the GvL effect and acute and chronic GvHD [3–5] In syngeneic BMT between identical twins, in which their exists no major or minor H antigen disparity and thus no alloreactivity can be induced, relapse rates are as high as 46% [6] Recipients of autologous transplants have also a high risk of developing recurrent leukemia [7] In recipients of allogeneic BMT, the relapse rates vary from 10% to 40% [8] Thus, one may conclude that alloreactive donor T cells are probably involved in antileukemia activities Assuming that the human genome has an abundance of minor histocompatibility (mH) loci resulting in various minor histocompatibility antigen (mHag) incompatibilities between BM donor and recipient, it is tempting to state that mHags are involved in both GvH and GvL activities

mHag: THE PAST AND THE PRESENT

It is not surprising that like the MHC-encoded major H systems, the minor H antigens have important biological functions beside their role in organ and bone marrow transplantation Their latter characteristic, however, was first discovered Both types of transplantation antigens were described by Snell and coworkers [9] and distinguished from one another on the basis of their respective power in murine tumor graft rejection models [10] The role of mHag in transplantation is best analyzed in an HLA-matched situation In humans, mHag studies have predominantly been performed in the HLA-identical BMT transplantation setting The efforts of several investigators have led to the identification of a relatively small number of mHags (for review, see [11]) Until recently, mHags were T cell defined, both cytotoxic T cells (CTL) and T helper (Th) cells recognizing mHags in

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TABLE 1 Characteristics of human mHags H-Y and HA-1 to HA-5

mHag	Restriction molecules	Phenotype frequency (%)	Tissue distribution	TCR usage
H-Y	Various[a]	50	Broad[b]	Variable
HA-1	A2	69	Restricted + leukemic cells	Vβ 6 9
HA-2	A2	95	Restricted + leukemic cells	Variable
HA-3	A1	88	Broad	n t [c]
HA 4	A2	16	Broad	n t
HA 5	A2	7	Restricted + leukemic cells	n t

[a] HLA A1 A2 1, B7 and B60

[b] Expression on all hematopoietic and nonhematopoietic cell lineages

Expression restricted to the hematopoietic cell lineage

[c] n t not tested

a classical MHC restriction fashion were described [11] Whether mHags really fail to induce antibody responses has not been thoroughly investigated It is noteworthy that "autoantibodies, among which mHag-specific antibodies may be present, can readily be observed after HLA-identical BMT In sera of recipients of HLA genotypically identical BM donations, we observed broadly reactive antibodies against BM donor T and non-T cells Some of these broadly reactive sera also showed reactivity with autologous cells A correlation between the occurrence of those antibodies and acute GvHD was significant 26 of 31 patients with grades II–IV acute GvHD had cytotoxic activity versus 11 of 21 patients with grades 0–I GvHD ($p = 0\ 03$) These antibodies did not correlate significantly with chronic GvHD or with active herpesvirus infections (J W Gratama et al , unpublished observations) Specifically, the presence of an HLA-A2 restricted H-Y-specific antibody was described in the serum of a patient wherein CTLs with the same specificity were observed [12]

In our laboratory, we performed detailed analyses on the characteristics of a small number of mHags generated from individuals primed in vivo by mHag-mismatched bone marrow grafting or by blood transfusions [13] The results of the genetic studies and tissue expression of the male-specific mHag H-Y and of non-Y-linked mHags HA-1 to HA-5, as well as the T cell receptor (TcR) usage of some of the mHag-specific CTL clones, are summarized in Table 1 As can be seen from this table, mHags can be recognized in the context of different HLA alleles, yet HLA-A2 1 is used frequently as the mHag-presenting molecule Whether this just reflects the relatively high phenotype frequency of HLA-A2 1 (i e , 49% in the Caucasian population) or that HLA-A2 1 is optimally equipped to serve as salver for peptide presentation is unclear In view of the latter supposition, it is of interest that allelic differences exist in the interaction of MHC class I molecules with transporters associated with antigen processing [14] Among other HLA alleles, HLA-A2 shows a high affinity for TAP Indeed, TAP is required for translocation of cytosolic peptides, in addition, however, it is possible that TAP supports correct folding and loading of a subset of MHC class I molecules [14]

Phenotype frequency analyses were carried out for mHags HA-1 to HA-5 These studies revealed that some mHags, i e , HA-1, HA-2, and HA-3, appeared frequently (69–95%), whereas others, i e , HA-4 and HA-5, occurred with lesser (7–16%) frequencies in the healthy population [15] An analysis of their genetic traits demonstrated a Mendelian mode of inheritance [16] The CTL clones listed in Table 1 were also used to analyze functional expression (i e , the read-out is cell-mediated lympholysis) of the mHags on various tissues and cells [17] Differential expression was observed some, i e , H-Y, HA-3, and HA-4, are ubiquitously expressed, whereas the expression of other mHags, i e , HA-1 and HA-2, is limited to cells of the hematopoietic lineage only [17] It is important to note that mHags H-Y and HA-1 to HA-5 are expressed on clonogenic normal and leukemic precursors cells as well on myeloid and lymphoid leukemic cells isolated from the peripheral blood [18, 19] Interestingly, when analyzing the TcR usage for recognition of the HLA-A2/HA-1 ligand of 12 HLA-A2-restricted HA-1-specific CTL clones, we observed a skewed TcR repertoire usage for the recognition of mHag HA-1 in three unrelated patients [20] (Table 1) The latter results may be indicative of a dominant mHag-specific T cell response occurring during the development of GvHD after BMT

mHag: OBSTACLES IN BONE MARROW TRANSPLANTATION

Prospective Analysis

Mixed epidermal cell cultures for detecting mHag differences between HLA genotypically identical BM donors and recipients were reported by Vogelsang et al [21] and Bagot et al [22] using a skin-explant model

and a mixed epidermal cell–lymphocyte reaction, respectively Dickinson et al used the levels of cytokine production in an in vitro skin explant model as a predictor for acute GvHD before allogeneic BMT [23] Detection of mHag differences between HLA genotypically identical BM donors and recipients by limiting dilution assays has been reported by two groups of investigators The assay is based on the demonstration of the presence of pre-BMT host-reactive precursor T cells and its correlation with the occurrence of GvHD [24, 25] The readout of the T cell precursor frequency analysis is IL-2 production of the responding cell population Thus, presumably, mHag-directed activities are measured in these Th cell precursor assays It was shown that both CD4 positive and CD8 positive T cells participate in this pre-BMT anti-host response [26] Detailed analysis of the respective target structures recognized in this assay remains to be done

Retrospective Analysis

Two recent retrospective analyses were reported describing the influence of mHags on the development of acute GvHD after transplantation of bone marrow from HLA-identical siblings One report concerned our own analysis of the influence of mHag HA-1, -2, -4, and -5 mismatches between HLA-identical BM donor/recipient pairs (i e , BM donor mHag negative and BM recipient mHag positive) on the occurrence of acute GvHD of grade II or more The results can be summarized as follows a mismatch for HA-1 and/or HA-2, -4, -5 was significantly associated with GvHD (p = 0 006) The main effect of the significant association with the development of GvHD appeared to be caused by an HA-1 mismatch, because a single HA-1 mismatch between donor and recipient reached a p value of 0 02 [27] The latter association is seemingly in contradiction with the absence of functional expression of mHag HA-1 on GvH target tissue such as keratinocytes [17] (Table 1) However, HA-1 is clearly expressed on the professional antigen-presenting cells (APC), i e , dendritic cells (DC) and Langerhans cells (LC) [28] The latter bone marrow-derived APC are most potent in inducing alloreactive T cell responses [29, 30] The conditioning regime prior to BMT will eliminate most of recipient's hematopoietic cells, yet residual recipient cells including DC can be present Host LC can persist for a long time after BMT [31] So far, there exists little information on the details of the mechanism(s) of GvH pathogenesis It is plausible that the antigen presentation by the professional APCs accounts for the primary induction of allo, i e , mHag, directed T cell activity and that subsequent local production of inflammatory cytokines plays an important role in tissue destruction Without doubt, cytokines do play a significant role in the development of GvHD [32]

Besides cytokines, soluble factors such as soluble HLA (sHLA) also possibly participate in the regulation of (allo) immune responses Enhanced levels of sHLA, possibly as a consequence of the increased cytokine production, are reported in GvHD patients [33, 34] On the other hand, sHLA has the capacity to downregulate T cell responses [35] Zavazava and Kronke showed that sHLA-treated Fas-expressing T cells upregulate CD95-L and subsequently undergo apoptosis [35]

The other retrospective study on the influence of mismatched mHag on the development of acute GvHD after HLA-identical BMT was reported by Behar et al [36] This study dealt with allelic differences between donor and recipient for the polymorphic adhesion molecule CD31 CD31 mismatches between BM donor and recipient are associated with an increased risk of severe GvHD disease of grade III or IV (p = 0 004) The platelet–endothelial cell adhesion molecule 1 (CD31) has broad expression it is constitutively expressed on vascular endothelial cells, bone marrow stem cells, platelets, and leukocytes [36] Interestingly, anti-CD31 monoclonal antibodies seemed to recognize the allelic forms differentially No CD31-specific T cell responses were reported, which separates this transplantation antigen from the classical ones described in humans and rodents earlier

Summarizing, these retrospective analyses demonstrate, for the first time in humans, the putative influence of mHag differences on the outcome of bone marrow transplants It is clear that these studies need confirmation in larger groups of patients as well as by other laboratories Nonetheless, incorporation of typing for these mHags for BM donor selection in those cases where more than one HLA-matched BM donor is available seems justified

DO mHags PLAY A ROLE IN GRAFT-VERSUS-LEUKEMIA REACTIVITY?

In humans, evidence of an antileukemic effect associated with allogeneic BMT is mainly based on clinical data Regarding the in vitro immune studies on the GvH/GvL mechanisms after BMT, it has been shown that alloreactive donor T cells are responsible for GvHD and that donor CTLs may eliminate leukemic cells by reacting with alloantigens or tumor-specific antigens or both [37] Besides donor-derived T cells reactive for ligands (like mHags) that are shared by host PBLs and leukemic cells [38–40], anti-host CTL responses that are specific for either PHA blasts or leukemic cells have also been observed in vitro [41–46] Some reports argue that GvH and GvL activities can be dissected, whereas nonseparable effector cells that exhibit both activities also exist

TABLE 2 Identification of human mHags

Restriction molecule	mHag	Peptide (no of amino acids)	Origin
HLA A2 1	HA 2	YIGEVLVSV (9 AA)	Nonfilamentous class I myosin, involved in cell locomotion and organelle transport
HLA B7	H Y	SPSVDKARAEL (11 AA)	SMCY, transcription factor for spermatogenesis?
HLA A2 1	H Y	FIDSYICQV (9 AA)	SMCY

[42] MHC unrestricted mechanisms may also operate to eliminate leukemic cells [47–50]

Recently, donor lymphocyte transfusions (DLTs) as treatment for relapsed leukemia appeared successful at least for patients with CML (as reviewed in [51]) DLT together with IFNα induced remissions in relapsed CML patients after allogeneic BMT [8, 52, 53] Little is known about the mechanism(s) of the DLT-induced remission in relapsed patients after BMT The therapeutic efficacy of DLT in leukemia relapse after BMT is most probably based on alloreactivity in the GvH direction, because this donor leucocyte therapy is associated with a significant occurrence of marrow aplasia and GvHD [54] It is likely that post-DLT, donor-derived anti-mHag-specific CTLs potentiate a potent GvL effect As stated earlier, in vitro studies with our mHag-specific CTL clones provide an explanation for the GvL effect mHag-specific CTL clones were shown to specifically lyse freshly isolated myeloid and lymphoid leukemia cells [19] and are capable of fully inhibiting the growth of mHag-positive clonogenic myeloid leukemia precursor cells [18]

mHags: FROM T CELL RECOGNITION TO PEPTIDE IDENTIFICATION

Our mHag-specific T cell clones were indispensable for the biochemical identification of the mHag peptides The biochemical isolation procedure, i e , affinity chromatography combined with microcapillary reversed-phase high-performance liquid chromatography (HPLC) coupled with electrospray ionization mass spectrometry [55], was successfully used for the identification of mHag peptides A series of mHag peptides is presently known, the HLA-A2 1-restricted HA-2 and the HLA-B7-restricted H-Y were the first ones described [56, 57] (Table 2) In addition, the amino acid composition of the HLA-A2 1-restricted HA-1 (manuscript in preparation) and the HLA-A2-restricted H-Y T cell epitopes have been determined [58] As expected, mHags are naturally processed peptides from intracellular proteins that associate with MHC products [59] In addition, these peptides are derived from genes with important biological function [60, 61] (Table 2) To support the latter notion, we investigated whether the mHags are evolutionarily conserved between human and nonhuman primates Indeed, the human HA-2 and H-Y peptides can be recognized on the cell surface of nonhuman primate cells, transfected with human class I genes, by our human HA-2- and H-Y-specific class I restricted CTL clones Furthermore, mHag peptides can be eluted from HLA-A2 1 molecules expressed on the transfected nonhuman primate cells This implies that the mHag peptides have been conserved for at least 35 million years [62] Moreover, concurrent with the identification of the human H-Y peptide, a murine H-Y peptide was characterized [63] and appeared to be derived from the same evolutionarily conserved SMCY protein

mHags. USEFUL TOOLS IN BONE MARROW TRANSPLANTATION

The putative clinical potentiality of mHags is presently based on in vitro results of functional and clinical studies performed in the past Bearing this yet-restricted information in mind, some areas of clinical application are worth mentioning The utility for diagnosis in BM donor selection is self-evident We are currently identifying the mH genes so that mH typing on the molecular level can be performed The pronounced immunogenic behavior of mHag HA-1 on GvHD is, together with the recently obtained amino acid composition, the basis for immunomodulation of GvHD Designing mHag peptide analogues that function as MHC or T cell receptor antagonists might interfere with the harmful anti-host mHag-directed T cell reactivities post-HLA-identical BMT Our nonhuman primate study shows the possibility of using transgenic chimpanzees or rhesus monkeys as a model for studying BMT-related reactivities such as GvHD An animal model is also required for studying the potential application of mHags with broad tissue distribution, such as H-Y and HA-3, in induction of tolerance in mHag-negative BM donors to prevent GvHD and in mHag-negative BM recipients to prevent rejection Achieving tolerance prior to transplantation

would decrease the necessity for using pharmacological immunosuppression

Most promising is immunotherapy for leukemia using CTLs specific for mHag peptide for the treatment of refractory, residual, or relapsed leukemia The mHags with restricted tissue distribution (e g , HA-1 and HA-2) are candidates for adoptive immunotherapy of leukemia Upon transfusion, either pre-BMT as part of the conditioning regimen or post-BMT as adjuvant therapy, the mHag peptide-specific CTLs will eliminate the patient's leukemia cells and, if of patient origin, also the patient's hematopoietic cells, but will spare the patient's nonhematopoietic cells If necessary, subsequent donor BMT will restore the patient's hematopoietic system The ideal situation is to generate mHag peptide CTLs ex vivo from mHag-negative BM donors for mHag-positive patients A universal option would be to generate "prefab" mHag peptide-specific CTLs by the use of mHag-negative healthy blood donors with common HLA-homozygous haplotypes Transduction of these CTLs with a suicide gene makes elimination of the CTL possible in case adverse effects occur Future research should also focus on the possibility of mHag donor immunization of mHag-negative BM donors prior to BMT to mHag-positive high-risk relapse recipients

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