The role of minor histocompatibility antigens in GVHD and rejection: a mini-review

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The success of HLA genotypically identical bone marrow grafting is still hampered by graft-versus-host disease (GVHD) and rejection of the graft. One of the causes of the latter complications could be attributed to minor histocompatibility (mH) antigen disparities between the HLA identical siblings (1).
In this mini-review we will share our current knowledge on the possible impacts of human mH antigen disparities between HLA identical donor and recipient on the outcome of bone marrow transplantation.

mH Antigens and Graft Rejection

With regard to the possible influence of mH antigens on bone marrow graft rejection, expression of mH antigens on haematopoietic stem cells (HPC) might be relevant in presensitized patients receiving a mH antigen positive T cell depleted marrow graft. For that purpose, the expression of the male specific antigen H-Y, the first mH antigen known to play a role in HLA identical but sex mismatched bone marrow exchange (2), was studied for its expression on HPC. It became clear that indeed H-Y is expressed on CFU-GEMM, CFU-GM and BFU-E (3). Experiments carried out to study the expression of other (non sex-linked) mH antigens (designated HA-1 to HA-5, see below) demonstrated differential expression of the latter antigens, namely only HA-3 appeared to be expressed on HPC (4).
We recently described a case study favoring the supposition that expression of mH antigens on HPC might negatively influence engraftment (5). The occurrence of a graft rejection in a female bone marrow transplant recipient of a T lymphocyte depleted graft from her phenotypically HLA identical father was analyzed in detail. Despite very intensive conditioning regimens, residual recipient's derived cytotoxic T lymphocytes (CTL) directed against mH antigens expressed on peripheral blood lymphocytes and on donor haematopoietic progenitor cells remained and may be responsible for this graft failure (5).

mH Antigens and GVHD

The aetiology of GVHD presumes that immunocompetent donor T cells are reacting against the host tissues. Although the precise nature of the composition of the effector cells mediating the host attack is still unknown, one may conclude from the experimental animal data that both the $Lyt2^+$ and the $L_3T_4^+$ T cell subsets cause GVHD to mH antigen differences (6-10; for detailed information see elsewhere in this volume: Korngold et al.). Likewise in man, reports on CD8 depleted marrow grafting (11-13) indicated a prime role for the latter subset in the pathogenesis of GVHD. Nonetheless, these studies also pointed to a role of the CD4 T cell subset in the acute phase of GVHD.
Our in vitro studies indeed demonstrate anti-host T cell reactivities in patients' blood samples taken after HLA identical bone marrow transplantation. Anti-host CTLs were always observed in patients suffering from chronic GVHD, whereas anti-host proliferative T cells (Th) were mainly found in patients with acute GVHD (14,15). Both CTL and proliferative T cell activities are directed against non-MHC or mH antigens for which the HLA identical patient and donor differed. Likewise, Tsoi et al. (16) and Irlé et al. (17) demonstrated the presence of mH antigen specific proliferative T cells in patients suffering from GVHD. Subsequently, by the use of selective depleted T cell subsets we showed that the anti-host Th cell responses are mediated by CD4+ve class II (HLA-DR and -DP) restricted T cells (18); the anti-host CTL responses have the CD8 phenotype and recognize the mH antigens in the context of class I (HLA-A or -B) molecules (1, and unpublished observations).

mH Antigens HA-1 to HA-5; Immunogenetics and Clonal Analysis

Five out of 21 anti-host cytotoxic effector cell populations were previously analyzed. These five cytotoxic T cell lines were derived from five different patients. They recognized mH antigens designated as HA-1, -2, -3, -4 and -5 in a classical MHC restricted fashion, whereby HA-1, -2, -4 and -5 use HLA-A2 as restriction molecule and mH antigen HA-3 appeared to be recognized in association with HLA-A1 (1). We recently generated CTL clones specific for these five non sex-linked mH antigens. With the usage

of the latter CTL clones, immunogenetic studies were carried out to determine the mH antigen gene frequencies and to make an inventory in each of the five patients of mH antigen HA-1, -2, -3, -4 and -5 specific anti-host CTL responses after BMT. With regard to the latter, we acquired from each of three CTL lines (anti HA-1, anti HA-4, anti HA-5 which were derived from 3 different patients) one clone specific for the mH antigen HA-1. This observation favors the existence of immunodominant mH antigens (manuscript submitted for publication). Performance of population (N=100) genetic analysis revealed that some appeared most frequent (72-90%) whereas other mH antigens occurred with lesser frequencies (8-16%) in the healthy population (manuscript submitted for publication).

mH Antigen Typing is not limited by MHC Restriction

Evidently, absence of the required MHC class I restricting antigen hampers adequate genetic analysis. Likewise, prospective typing of patients and their potential donors using our T cell clones specific for mH antigens is limited to those individuals carrying the required HLA molecule. In search of solving the latter deficit, we have used electroporation to introduce cloned HLA genes into the cells of interest. From our recent studies we may conclude that gene transfection has proven to be a reliable technique for adequate mH antigen recognition and consequently circumvents the deficit of required HLA molecules in mH antigen typing (manuscript submitted for publication).

Differential mH Antigen Expression in the Skin

Finally, we would like to briefly touch upon one of the affected organs during GVHD after bone marrow grafting, namely the skin. Following histopathological studies, it becomes clear that dermal and epidermal infiltration by CD8+ cells correlate with the severity of GVHD (19-22) whereby keratinocytes appeared to be a target for the GVHD attack (23). Following phenotypic and functional in vitro analysis however, CD4 T cells appeared to be clearly present as well among the skin infiltrating cells (24-26). The antigenic target structures involved could be tissue specific antigens on epithelial but not on lymphoid cells like in the studies of Tsoi et al. (27). On the other hand, they could be mH antigenic structures possessing a broad tissue distribution. Therefore, we aimed at investigating the expression of mH antigens on keratinocytes (K) by studying their susceptibility to lysis by our MHC restricted H-Y and mH antigen HA-1 to -5 specific CTLs. Hence, a modified ^{51}Cr release was developed wherein cultured human K could be used as target cells (28). Next, the expression of the minor H antigen H-Y on male HLA-A2+ve K was explored. From our experiments it became clear that male HLA-A2-ve K are susceptible to lysis by HLA-A2 restricted H-Y specific CTLs; the specific recognition is clearly enhanced by IFNγ treatment of K (29). With regard to the other mH antigens HA-1 to HA-5, our recent studies revealed expression of the mH antigen HA-3 on human K (30, and manuscript in preparation).

To get insight into the mH antigen as target structure for GVHD as well their local function, we currently investigate the expression of mH antigens on different tissues. It is noteworthy that the H-Y specific MHC restricted cytotoxic T cell clones, originally derived from and selected for its reactivity against peripheral blood lymphocytes (1), react so far with "Y peptide(s)/MHC class I complexes" expressed on male cells derived from a series of different tissues (unpublished observations).

Acknowledgments

The authors would like to thank Els Blokland, Jos Pool, and Astrid Bakker for their technical expertise and Mrs. Annemarie Suter for typing the manuscript. This work was supported in part by grants from the Dutch Foundation for Medical and Health Research (Medigon), the J.A. Cohen Institute for Radiopathology and Radiation Protection (IRS), and the Macropa Foundation.

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