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New Directions in the Genomics of Allogeneic Hematopoietic Stem Cell Transplantation

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ABSTRACT

Despite optimal supportive care and high-resolution HLA matching, complications such as GVHD and infection remain major barriers to the success of allogeneic HCT (allo-HCT). This has led to growing interest in the non-HLA genetic determinants of complications after allo-HCT. Most studies have examined genetic predictors of GVHD, relapse, and mortality and have focused on 3 main areas: minor histocompatibility antigen (miHAs), inflammatory mediators of GVHD, and more recently NK cell-mediated allorecognition. The genetic basis of other outcomes such as infection and drug toxicity are less well studied but are being actively investigated. High-throughput methodologies such as single nucleotide polymorphism arrays are enabling the study of hundreds of thousands of genetic markers throughout the genome and the interrogation of novel genetic variants such as copy number variations. These data offer the opportunity to better predict those at risk of complications and to identify novel targets for therapeutic intervention. This review examines the current data regarding the non-HLA genomics of allo-HCT and appraises the promises and pitfalls for integration of this new genetic information into clinical transplantation practice.

KEY WORDS

Genomics • Polymorphism • Hematopoietic • Transplantation • Cytokine • Pharmacogenomics • Tumor necrosis factor • Interleukin • Mannose-binding lectin • Natural killer cell

SPECTRUM OF COMPLICATIONS OF ALLOGENEIC HCT

Allogeneic HCT (allo-HCT) is widely used to treat a diverse range of malignant and nonmalignant diseases. The growing indications for allo-HCT and the development of reduced intensity conditioning regimens has seen the number of allogeneic transplantations continue to increase, with >15 000 performed worldwide in 2002 [1]. However, transplant-related complications remain a major obstacle [2]. The 100-d mortality rate for standard-risk patients receiving a transplant from an HLA-identical sibling is 15%-20%. Mortality is higher for patients who are older, those with significant comorbidity, those undergoing transplantation for other indications, and those receiving unrelated donor transplants. Disease relapse is the leading cause of death (30%-34% of deaths after HLA-identical sibling transplantations) [1,2], but transplant-related complications are also important. These include GVHD (15%-25%), major infection (10%-17%), and other treatment-related toxicities (35% of deaths) such as interstitial pneumonitis and hepatic veno-occlusive disease. Long-term causes of morbidity include cGVHD and infection. These complications remain significant in transplantations using reduced intensity conditioning regimens [3].

Prevention of these complications has traditionally relied on meticulous supportive care, prophylactic antimicrobials and immunosuppression, and accurate matching of donors and recipients for HLA alleles. HLA matching to minimize graft rejection and the leading cause of transplant-related morbidity, GVHD, remains a cornerstone of modern transplantation management [4]. GVHD arises from the recognition of recipient tissues as foreign by donor T cells. Three key requirements for the development of GVHD were described by Billingham in 1966 [5]. These are the presence of immunologically competent cells in the graft, the inability of the recipient to reject the transplanted cells, and the presence of antigens,

HLA antigens, in the recipient that are lacking in the graft. However, despite optimal HLA matching using high-resolution molecular techniques, aGVHD remains a major problem [6]. More than 30% of patients with chronic myeloid leukemia receiving an HLA-matched unrelated donor transplant develop severe (grades III-IV) acute GVHD [7].

If HLA disparity is central to the development of GVHD, why doesn't HLA matching prevent it? It is now appreciated that the initiation and propagation of GVHD is a multifactorial, multistep process that includes, but is not restricted to, classic HLA allorecognition [8]. GVHD is critically dependent on additional pathways including non-classic HLA allorecognition (such as by NK cells), allorecognition of miHAs, and an inflammatory milieu. The relative importance of each of these pathways is context dependent and is influenced by recipient characteristics, donor type, stem cell source, intensity of conditioning, and degree of HLA matching. Importantly, the mediators of these pathways are encoded by highly polymorphic immunoregulatory genes, and there are considerable data implicating such "non-HLA" immunogenetic polymorphisms in the risk and severity of GVHD. Further, the pathophysiology and genetic determinants influencing risk of other complications may be distinct from GVHD and less dependent on HLA.

Consequently, there has been intense interest in defining the best non-HLA genetic markers of allo-HCT outcomes and incorporating these into routine tissue typing strategies. However, the profusion of genetic markers poses formidable challenges to the development of robust predictive models. This review examines the evidence for non-HLA genetic risk factors in allo-HCT, highlights problems raised by existing studies, and discusses potential strategies to overcome these issues. In addition, newer high-throughput approaches to identify genetic risk factors are discussed.

The continuing centrality of HLA matching in allo-HCT cannot be overemphasized, and optimal HLA typing approaches continue to evolve. In particular, high-resolution HLA typing approaches may reduce the number of fully HLA-matched unrelated donors. Recent elegant studies have begun to address issues of permissible HLA mismatches and tradeoffs with other factors such as time to transplantation [9,10]. A full discussion of these issues is beyond the scope of this review, and the reader is referred elsewhere [6,11].

MINOR HISTOCOMPATIBILITY ANTIGENS AND ALLO-HCT OUTCOME

The miHAs are of interest in allo-HSCT as risk factors for allo-HCT outcome and as potential targets for immunotherapy [12-15]. The miHAs are short peptides, frequently derived from intracellular processing of proteins, that are presented on host HLA molecules and can stimulate alloreactive T cell immune responses between HLA-matched individuals. The tissue distribution of miHAs is variable, with some (eg, HA-1) expressed only by cells of hematopoietic origin, and others being ubiquitously expressed. Some miHAs are expressed by hematopoietic tumors, such as proteinase 3 in CML, and are thus potential targets of graft-versus-leukemia (GVL) responses. The genes encoding miHAs are frequently polymorphic, resulting in variation in peptide sequence that can influence intracellular processing or presentation of miHA peptide, and the stimulation of an alloreactive response if donors and recipients are disparate (mismatched) for miHA genotype.

miHA gene polymorphism may result in missense changes in the miHA peptide presented by HLA and in potential disparity in miHA genotype between donor and recipient. miHA peptides are usually only presented by a single HLA allele; eg, HA-1 is presented by HLA-A*0201. Hence, HA-1 mismatching is only relevant to the subset of transplants whose donors and recipients are HLA-A*0201 positive.

The most extensively studied miHA is HA-1, a nonapeptide encoded by the *HMHA1* (*HA-1* or *KIAA0223*) gene with 2 alleles defined by histidine ($HA\text{-}1^H$) or arginine ($HA\text{-}1^R$) at the third amino acid of the peptide. Because the $HA\text{-}1^H$ peptide binds with much greater affinity to HLA-*0201 than the $HA\text{-}1^R$ allele, transplants from $HA\text{-}1^{R/R}$ donors to $HA\text{-}1^H$ positive recipients can potentially cause GVHD, but not the reverse [16]. Numerous groups have examined HA-1 disparity as a risk factor for GVHD (Table 1). Goulmy et al [17] detected a significant association between HA-1 disparity and aGVHD in sibling myeloablative transplants, suggesting that HA-1 disparity could be used clinically as a predictor of GVHD. Subsequent studies have been conflicting, and the largest studies have concluded that the effect of HA-1 disparity is, at best, weak [18-25]. Conflicting results have also been reported for polymorphisms in the *PECAM1* gene (CD31) and allo-HCT outcome [20,23-30] (Table 1). Many of the studies are small and clinically heterogenous, and it is difficult to be conclusive about the role of miHA genetic polymorphism as a predictor of transplantation outcome. As discussed below, further studies will need to examine the role of miHA variants simultaneously with other immunogenetic and clinical variables.

Interest in miHAs as potential therapeutic targets for graft-versus-tumor responses has been driven by the observations that miHA expression is often limited to hematopoietic tumor cells [31-33], and that expansion of miHA-specific CTLs accompanies attainment of full donor lymphoid chimerism and disease remis-