Published in final edited form as:
Transplantation. 2009 March 15; 87(5): 704–710. doi:10.1097/TP.0b013e318195c474.

IL10 AND IL10 RECEPTOR GENE VARIATION AND OUTCOMES AFTER UNRELATED AND RELATED HEMATOPOIETIC CELL TRANSPLANTATION

Li-Hui Tseng[1,3], **Barry Storer**[1], **Effie Petersdorf**[1,2], **Ming-Tseh Lin**[1,4], **Jason W. Chien**[1,2], **Bryan M. Grogan**[1], **Mari Malkki**[1], **Pei-Jer Chen**[5], **Lue P. Zhao**[1], **Paul J. Martin**[1,2], and **John A. Hansen**[1,2]

[1]The Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[2]The University of Washington, School of Medicine, Seattle, WA, USA

[5]National Taiwan University, College of Medicine, Graduate Institutes of Clinical Medicine, Taipei, Taiwan

Abstract

Background—Results of a previous study with HLA-identical siblings showed individual and synergistic associations of single nucleotide polymorphisms in the promoter region of the recipient's IL10 gene and the donor's IL10 receptor β (IL-10RB) gene with development of grades III–IV acute graft-versus-host disease (GVHD) after allogeneic hematopoietic cell transplantation (HCT).

Methods—In the current study of 936 patients who had unrelated donors, genotypes of single nucleotide polymorphisms in the IL10 gene and the IL-10RB gene were evaluated as correlates with outcomes after transplantation.

Results—We found no statistically significant associations of polymorphisms at positions −3575, −2763, −1082, and −592 of the IL10 gene or codon 238 of the IL10RB gene with severe acute GVHD, extensive chronic GVHD or non-relapse mortality after HCT. Among HLA-matched unrelated pairs, the patient's IL10/−592 genotype and donor's IL10RB/c238 genotype showed trends suggesting individual and combined associations with grades III–IV acute GVHD similar to those observed among patients with HLA-identical sibling donors.

Conclusions—Although genetic variation in IL10 pathway affects risk of acute GVHD and non-relapse mortality in HLA-identical sibling transplants, the current results indicate that genetic variation in the IL10 pathway does not significant affect these outcomes in unrelated donor transplants suggesting that the strength of the alloimmune response in the latter exceeds the anti-inflammatory activity of IL10.

Keywords

IL10; IL10 receptor; polymorphism; graft-versus-host disease; bone marrow transplantation

Address for Correspondence: Dr. John A. Hansen, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., D2-100, P.O. Box 19024, Seattle, WA 98109-1024, Telephone: 206-667-5111; fax: 206-667-5255, jhansen@fhcrc.or.
[3]current address: National Taiwan University Hospital, Department of Medical Genetics, Taipei, Taiwan
[4]current address: The Johns Hopkins University School of Medicine, Department of Pathology, Baltimore, MD, USA

Introduction

Graft-versus-host disease (GVHD) remains a major complication associated with morbidity and mortality of hematopoietic stem cell transplantation (HCT) (1). Matching for donor and recipient HLA alleles reduces risk of acute GVHD and improves outcomes after HCT (2–5). Polymorphisms in numerous non-MHC genes encoding cellular proteins that function as minor histocompatibility antigens also cause GVHD (6). Variation in other immune response genes contribute to GVHD by modulating the intensity of alloreactive T cells, inflammation and other components of the innate immune systems (7–9).

Genetic polymorphism in the promoter region of the IL10 gene has a significant impact on outcomes after HCT with HLA-identical sibling donors (10–12). In our previous study of single nucleotide polymorphism (SNP) among 993 HLA-identical sibling transplants, the presence of the IL10/−592*A allele in the patient was significantly associated with lower risks of grades III–IV acute GVHD and non-relapse mortality (NRM) (12). Results of an analysis of extended IL10 promoter region haplotypes defined by five SNPs at positions −3575, −2763, −1082, −819 and −592 showed that the −592*A allele served to identify the promoter haplotype (*T-C-A-T-A*). A subsequent study of the same population revealed the donor c238*G allele of the IL10 receptor β gene (IL10RB/c238) was associated with a reduced risk of grades III–IV acute GVHD among patients with the lower-risk IL10/−592 A/C or A/A genotypes but not among those with the high risk IL10/−592 C/C genotype. These results suggested that interactions of the patient IL10/−592 and donor IL10RB/c238 genotypes influence the risk of GVHD, supporting the hypothesis that the IL10 pathway can play an important role in controlling the severity of acute GVHD (13). In the current study, IL10 promoter and IL10RB/c238 genotypes were determined among a large cohort of patients who had HCT from unrelated donors to determine whether genetic variations in the IL10 pathway convey effects similar to those observed among patients with HLA-identical sibling donors.

Materials and Methods

Study populations

The study population consisted of patients who had HCT from unrelated donors at the Fred Hutchinson Cancer Research Center between 1985 and 2002 (Table 1). Among approximately 1600 unrelated HCT cases, 936 had DNA samples retrieved from patients, donors or both patients and donors for genotyping. All patients were prepared with myeloablative conditioning regimens, and more than 90% received methotrexate and cyclosporine after HCT. Indications for HCT included acute lymphoblastic leukemia (n=130), acute myelogenous leukemia (n=174), chronic myelogenous leukemia (n=538), other hematopoietic malignancies (n=12), and non-malignant disorders including myelodysplastic syndrome (n=82).

Histocompatibility testing and donor selection criteria have been described previously (14). High resolution sequencing method was used to type the alleles of exons 2 and 3 of the class I HLA-A, -B and –C genes. A combination of genotyping with high resolution sequence specific oligonucleotide probes (SSOP) followed, when necessary, by sequencing of exon 2 was used to assess matching of the class II DRB1 and DQB1 genes. Patient and unrelated donor were classified as HLA-matched if they had the same HLA-A, B, C and DRB1 alleles. Mismatching was defined as the presence of a donor antigen or allele not shared by the recipient or the presence of a recipient antigen or allele not shared by the donor. Among the 818 cases with DQ typing data available, 423 were either fully matched (n=387) or mismatched for only a single HLA-DQ antigen or allele (n=36). For purposes of the current analysis, these 423 cases were defined as the HLA-matched group. All patients and donors

gave written informed consent according to protocols approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Genotyping of SNPs

Genotypes of SNPs at −3575 (rs1800890), −2763 (rs6693899), −1082 (rs1800896) and −592 (rs1800872) of the IL10 gene and c238 (rs2834167) of the IL10RB gene were determined by polymerase chain reaction/restriction fragment length polymorphism as described previously (12–13). Complete genotyping for the four IL10 SNPs was performed for 692 patients and 697 donors. An additional 204 donors were genotyped for IL10/−592 and IL10/−1082 with the use of the Illumina Beadarray™ platform (15–16). All 901 donor samples were tested for IL10RB/c238 genotype, and results were informative in all but 2 samples.

Analysis of Clinical Outcomes

The data were analyzed in February 2008 with a median follow-up of the surviving patients at 121 months (5–251 months). Genotypes were correlated with the incidence rates of severe (grades III–IV) acute GVHD, extensive chronic GVHD and non-relapse mortality (NRM) by using proportional hazards regression models and multivariate analysis with adjustment for patient age at transplant (continuous), donor-recipient sex mismatch, use of total body irradiation in the conditioning regimen, disease risk group, and source of stem cells (bone marrow vs. peripheral blood) as described previously (12–13). Transplant year (continuous) was included in the multivariable analysis because of increased sensitivity for diagnosing gut GVHD after 1991 and use of prophylactic fluconazole and ganciclovir as a standard of post-transplant care since 1992. HLA match status was not included in the multivariable analysis, but instead a separate subset analysis was performed to evaluate the potential effect of HLA-mismatch. An analysis of HLA-DP, a recently discovered risk factor for acute GVHD (17), was not included since there was no significant difference in the distribution of HLA-DP mismatches among the 3 IL10 and IL10RB genotypes. Acute and chronic GHVD were diagnosed and graded according to standard criteria (18–19). NRM was defined as death before recurrent malignancy. The cumulative incidence of acute GVHD, chronic GVHD and NRM were estimated according to the methods of Andersen et al. (20). Death was considered as a competing risk for analysis of acute and chronic GVHD, and recurrent malignancy was considered as a competing risk for analysis of chronic GVHD and NRM. Follow-up was censored at the time of a competing event.

All P values are two-sided and derived from likelihood ratio statistics from the proportional hazards regression models. Tests for trend were carried out by assigning the ordinal values 1, 2, and 3 to the genotypes M/M, M/m, and m/m, respectively and testing the association of the resulting variable with outcome. “M” represents the more frequent (major) allele, and “m” represents the less frequent (minor) allele in the studied population.

Results

Genotype and transplant outcomes among overall study population

The cumulative incidence of grades III–IV acute GVHD at day 100 after unrelated HCT was 37%, compared to 19% after HCT from HLA-identical siblings (Table 1). The cumulative incidence of NRM at 5 years after unrelated HCT was 39%, compared to 25% after HCT from HLA-identical siblings. No statistically significant associations were observed between the IL10 patient or donor genotypes or the IL10RB donor genotype and the risks of grades II–IV acute GVHD (data not shown), grades III–IV acute GVHD, extensive chronic GVHD or NRM after unrelated HCT (Table 2). The cumulative incidence rates of grades III–IV acute GVHD at day 100 were 36%, 39% and 33% with patient IL10/−592 C/C, A/C and A/

A genotypes, respectively (trend hazard ratio: 1.0; trend P = 0.77), and 38%, 35% and 39% with donor IL10RB/c238 A/A, A/G and G/G genotypes, respectively (trend hazard ratio: 0.9; trend P = 0.51).

IL10/IL10RB genotype and acute GVHD in HLA-matched unrelated transplants

To determine whether HLA mismatching in this cohort of unrelated HCT recipients might confound detection of an association between IL10 and IL10RB genotypes and severe acute GVHD, we examined the effect of IL10 and IL10RB variation in the HLA-matched subset (n = 423). In this analysis, we found trends similar to those observed among patients with HLA-identical sibling donors (Table 3). The trend hazard ratio was 0.8 (trend P = 0.23) for association of the IL10/−592*A allele in the patient with a lower incidence of grades III–IV acute GVHD. Likewise, the trend hazard ratio was 0.8 (trend P = 0.15) for association of the IL10RB/c238*G allele in the donor with a lower incidence of grades III–IV GVHD. A significant association with grades III–IV acute GVHD was observed for the IL10/−1082 genotype of the donor (trend hazard ratio: 1.3; trend P=0.02). The cumulative incidences of grades III–IV acute GVHD at day 100 were 25%, 39%, and 40% for patients with donor IL10/−1082*A/A, A/G, and G/G genotypes, respectively (Table 3).

Combined analysis of patient IL10/−592 genotypes and donor IL10RB/c238 genotypes

In the previous report among 953 HLA-identical sibling transplants (13), the patients were stratified into 9 groups according to the IL10/−592 genotype of the patient and the IL10RB/c238 genotype of the donor to examine the combined effect of IL10 and IL10RB SNPs on severe acute GVHD. As reported previously (13), a beneficial effect of the IL10RB*G allele in the donor was observed only among patients with the IL10/−592* A/A and A/C genotypes, but not among patients with IL10/−592 C/C genotype. The trend hazard ratios for the IL10RB/c238* G allele were 0.6 and 0.7 among HLA-matched unrelated transplant patients with IL10/−529 A/C and A/A genotype, respectively and 0.5 and 0.4 among HLA-identical sibling transplant patients with IL10/−529 A/C and A/A genotype, respectively (Table 4).

Discussion

Polymorphisms in the promoter region of the IL10 gene have been associated with GVHD and NRM after HCT from an HLA-identical sibling donor (10–12). In previous reports, we have shown the IL10/−592*A allele and the IL10RB/c238*G alelle were significantly associated with lower risk of severe acute GVHD (trend hazard ratio: 0,7 and 0.7, respectively). In unrelated HCT, the presence of IL10R2-G-C-C or the absence of IL10R3-G-C-C haplotype, defined by a microsatellite (IL10R) and 3 SNPs (−1082, −819 and −592), was associated with a higher risk of NRM in a cohort of 132 patients (21), and the presence of alleles 12, 14 or 15 of IL-10G (or IL10/−1064) microsatellite polymorphism was associated with a higher risk for NRM among a cohort of 131 patients (22). However, significant association of IL10 gene polymorphism with GVHD after unrelated HCT has not been reported. In the current study of unrelated HCT, statistically significant associations of the patient IL10/−592 or donor IL10RB/c238 genotypes with severe acute GVHD were not detected, unlike results previously reported in our study of HCT with HLA-identical sibling donors (12–13). Among HLA-matched unrelated pairs, however, the patient's IL10/−592 genotype and donor's IL10RB/c238 genotype showed trends suggesting individual and combined associations with grades III–IV acute GVHD similar to those observed among patients with HLA-identical sibling donors.

IL10 downregulates immune response and may facilitate the induction of tolerance after allogeneic transplantation (23–26). Holler et al. and Baker et al., have shown that higher

IL10 production after ex-vivo stimulation of recipient's cells before transplantation is associated with reduced risks of acute GVHD and non-relapse mortality (27–28). However, elevated serum IL10 concentration after transplantation has been associated with increased risks of acute GVHD and non-relapse mortality (29–30). ihThe administration of exogenous IL10 in murine allogeneic transplantation models also has inconsistent effect (31–33). Conflicting results have been reported regarding the genetic controls of IL10 production (34–37). Previous studies have reported that IL10 G-C-C haplotype (defined by −1082, −819 and −592) is associated with higher IL10 production in vitro. The association of IL10/−1082*G allele, IL10/−592*C allele, or G-C-C haplotype in patients with a higher risk of acute GVHD and autologous GVHD (11–13,38) have lead to the assumption that IL10 may promote alloimmune response (38). Results from other studies, however, have shown an association of the G-C-C haplotype with lower IL10 production in vitro (36–37).

The IL10 receptor complex is composed of 2 subunits, IL10 receptor α (IL10RA) and IL10RB. IL10RB functions as an accessory subunit for signaling when IL10 binds to IL10RA (39). The substitution of nucleotide A by nucleotide G at position cDNA 238 results in an amino acid change at codon 47 of Lys by Glu (K47E) and is located at the first extracellular FnIII domain repeat of IL10RB (13,40). Frodsham et al. have shown that the IL-10RB/c238*G allele is associated with higher mRNA production, higher surface expression of IL10RB, and greater IL10-mediated inhibition of LPS-induced TNFα production (41), suggesting that the IL10/c238*G allele in the donor may allow for a higher level of IL10 signal transduction and thereby increase the immune suppressive activity of the IL10 pathway. The synergistic effect of IL10/−592*A allele in patients and IL10RB/c238*G allele in donors on the reduction of GVHD incidence indicates the IL10 pathway is regulated by functional polymorphisms that result in variable IL10 production by recipients and variable signal transduction through the IL10 receptor on the donors cells.

The incidence and severity of acute GVHD is greater in unrelated donor compared to HLA-identical HCT. However, the relative risks of grades III–IV acute GVHD were only 1.2 to 1.4 and 1.4 to 1.9 for the mismatch of HLA-A, B, C and DRB1 among two large cohorts of unrelated transplant performed under the auspices of the National Marrow Donor Program (NMDP) in the United States (n= 1874) and Japan (n=1298), respectively (3,5), and was 2.0 for mismatch of both class I and class II antigens among patients who had HCT at our center (42). The recent retrospective study of high resolution HLA-typing from NMDP also demonstrated that the relative risk for any single HLA-A,B, C or DRB1 mismatch was 1.5 (43). The more intense allo-immune reaction elicited by mismatching for HLA and minor histocompatibility antigens in unrelated HCT may diminish the relative effects of other individual risk factors for severe GVHD. Although a weak association of a higher risk of severe acute GVHD with IL10/−1082*G allele of donors was observed among both HLA-identical sibling transplants (HR=1.2) and HLA-matched unrelated transplants (HR= 1.3), the decreased risk of grades III–IV acute GVHD associated with the IL10/−592*A allele among patients with HLA-identical sibling donors (HR=0.8) was not observed among those with HLA-matched unrelated donors (HR=1.0) (Table 3). Further studies with larger HLA-matched unrelated transplant populations will be necessary in order to elucidate the potential weak effects of donor's IL10 promoter genotype on the development of severe acute GVHD.

Our current results do not exclude the possibility that the IL10/−592*A allele of the patient and IL-10RB/c238*G allele of the donor have individual and combined effects that reduce the risk of severe acute GVHD after unrelated HCT. The magnitude of these individual effects relative to the higher overall incidence of acute GVHD after unrelated HCT appears to be smaller than observed after HCT with HLA-matched sibling donors. Our results suggest that efforts to detect associations between genetic risk factors and acute GVHD are

likely to be more productive in studies of HCT with HLA-identical sibling donors than in studies with unrelated donors.

Acknowledgments

The authors thank Craig Nisperos for technical assistance and Susan Lennox for manuscript preparation.

This work has been supported by grants AI33484, AI49213, CA18029, CA15704, CA18221, HL088201 and HL87690 from the National Institutes of Health, USA; and grants NSC94-2314-B-002-271, IBMS-CRC93-T02 and NSC 95-2314-B-002-101, Taiwan.

Abbreviation

GVHD	graft-versus-host disease
HCT	hematopoietic cell transplantation
HR	hazard ratio
IL10	interleukin 10
IL10RB	interleukin 10 receptor β
NRM	non-relapse mortality
SNP	single nucleotide polymorphism

References

1. Ferrara JLM, Deeg HJ. Graft-versus-host disease. N Engl J Med 1991;324:667. [PubMed: 1994250]
2. Beatty PG, Clift RA, Mickelson EM, et al. Marrow transplantation from related donors other than HLA-identical siblings. N Engl J Med 1985;313:765. [PubMed: 3897863]
3. Flomenberg N, Baxter-Lowe LA, Confer D, et al. Impact of HLA class I and class II high-resolution matching on outcomes of unrelated donor bone marrow transplantation: HLA-C mismatching is associated with a strong adverse effect on transplantation outcome. Blood 2004;104:1923. [PubMed: 15191952]
4. Petersdorf EW. HLA matching in allogeneic stem cell transplantation. Curr Opin Hematol 2004;11:386. [PubMed: 15548992]
5. Morishima Y, Sasazuki T, Inoko H, et al. The clinical significance of human leukocyte antigen (HLA) allele compatibility in patients receiving a marrow transplant from serologically HLA-A, HLA-B, and HLA-DR matched unrelated donors. Blood 2002;99:4200. [PubMed: 12010826]
6. Perreault C, Decary F, Brochu S, Gyger M, Belanger R, Roy D. Minor histocompatibility antigens. Blood 1990;76:1269. [PubMed: 2207305]
7. Krenger W, Hill GR, Ferrara JLM. Cytokine cascades in acute graft-versus-host disease. Transplantation 1997;64:553. [PubMed: 9293864]
8. Dickinson AM, Middleton PG, Rocha V, Gluckman E, Holler E. Eurobank members. Genetic polymorphisms predicting the outcome of bone marrow transplants. Br J Haematol 2004;127:479. [PubMed: 15566351]
9. Mullally A, Ritz J. Beyond HLA: the significance of genomic variation for allogeneic hematopoietic stem cell transplantation. Blood 2007;109:1355. [PubMed: 17008540]
10. Cavet J, Middleton PG, Segall M, Noreen H, Davies SM, Dickinson AM. Recipient tumor necrosis factor-alpha and interleukin-10 gene polymorphisms associate with early mortality and acute graft-versus-host disease severity in HLA-matched sibling bone marrow transplants. Blood 1999;94:3941. [PubMed: 10572111]
11. Socie G, Loiseau P, Tamouza R, et al. Both genetic and clinical factors predict the development of graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Transplantation 2001;72:699. [PubMed: 11544434]

12. Lin MT, Storer B, Martin PJ, et al. Relation of an interleukin-10 promoter polymorphism to graft-versus-host disease and survival after hematopoietic-cell transplantation. N Engl J Med 2003;349:2201. [PubMed: 14657427]
13. Lin MT, Storer B, Martin PJ, et al. Genetic variation in the IL-10 pathway modulates severity of acute graft-versus-host disease following hematopoietic cell transplantation. Synergism between IL-10 genotype of patient and IL-10 receptor β genotype of donor. Blood 2005;106:3995. [PubMed: 16109775]
14. Petersdorf EW, Anasetti C, Martin PJ, et al. Limits of HLA mismatching in unrelated hematopoietic cell transplantation. Blood 2004;104:2976. [PubMed: 15251989]
15. Fan JB, Oliphant A, Shen R, et al. Highly parallel SNP genotyping. Cold Spring Harbor Symp.Quant.Biol 2003;68:69. [PubMed: 15338605]
16. Chien JW, Zhao LP, Hansen JA, Fan WH, Parimon T, Clark JG. Genetic variation in bactericidal/permeability-increasing protein influences the risk of developing rapid airflow decline after hematopoietic cell transplantation. Blood 2006;107:2200. [PubMed: 16304058]
17. Shaw BE, Gooley T, Malkki M, Madrigal JA, Begovich AB, Horowitz MM, Gratwohl A, Ringdén O, Marsh SG, Petersdorf EW. The importance of HLA-DPB1 in unrelated donor hematopoietic cell transplantation. Blood 2007;15:4560. [PubMed: 17726164]
18. Przepiorka D, Weisdorf D, Martin P, et al. Consensus conference on acute GVHD grading. Bone Marrow Transplant 1995;15:825. [PubMed: 7581076]
19. Sullivan KM, Agura E, Anasetti C, et al. Chronic graft-versus-host disease and other late complication of bone marrow transplantation. Semin Hematol 1991;28:250. [PubMed: 1887253]
20. Anderson, PK.; Borgan, O.; Gill, RD.; Keiding, N. Statistical models based on counting processes. Springer-Verlag; 1993.
21. Keen LJ, Defor TE, Bidwell JL, Davies SM, Bradley GA, Hows JM. Interleukin-10 and tumor necrosis factor alpha region haplotypes predict transplant-related mortality after unrelated donor stem cell transplantation. Blood 2004;103:3599. [PubMed: 14701704]
22. Bettens F, Passweg J, Gratwohl A, et al. Association of TNFd and IL-10 polymorphisms with mortality in unrelated hematopoietic stem cell transplantation. Transplantation 2006;81:1261. [PubMed: 16699452]
23. Fiorentino DF, Zlotnik A, Mosmann TR, Howard M, O'Garra A. IL-10 inhibits cytokine production by activated macrophages. J Immunol 1991;147:3815. [PubMed: 1940369]
24. Groux H, Bigler M, de Vries JE, Roncarolo MG. Interleukin-10 induces a long-term antigen-specific anergic state in human CD4+ T cells. J Exp Med 1996;184:19. [PubMed: 8691133]
25. Taylor PA, Lees CJ, Blazar B. The infusion of ex vivo activated and expanded $CD4^+CD25^+$ immune regulatory cells inhibits grafted-versus-host disease lethality. Blood 2002;99:3493. [PubMed: 11986199]
26. Hoffmann P, Ermann J, Edinger M, Fathman CG, Strober S. Donor type $CD4^+CD25^+$ regulatory T cells suppress lethal acute graft-versus-host disease after allogeneic bone marrow transplantation. J Exp Med 2002;196:389. [PubMed: 12163567]
27. Holler E, Roncarolo MG, Hintermeier-Knabe R, et al. Prognostic significance of increased IL-10 production in patients prior to allogeneic bone marrow transplantation. Bone Marrow Transplant 2000;25:237. [PubMed: 10673693]
28. Baker KS, Roncarolo MG, Peters C, Bigler M, DeFor T, Blazar BR. High spontaneous IL-10 production in unrelated bone marrow transplant recipients is associated with fewer transplant-related complications and early deaths. Bone Marrow Transplant 1999;23:1123. [PubMed: 10382951]
29. Hempel L, Korholz D, Nussbaum P, Bonig H, Burdach S, Zintl F. High interleukin-10 serum levels are associated with fatal outcome in patients after bone marrow transplantation. Bone Marrow Transplant 1997;20:365. [PubMed: 9339750]
30. Takatsuka H, Takemoto Y, Okamoto T, et al. Predicting the severity of graft-versus-host disease from interleukin-10 levels after bone marrow transplantation. Bone Marrow Transplant 1999;24:1005. [PubMed: 10556960]

31. Smith SR, Terminelli C, Pennline KJ, Kenworthy-Bott L, Donkin J, Calzetta A. Inhibitory effects of recombinant human interleukin 10 on disease manifestation in a P→F_1 model of acute graft versus host disease. Transplantation 1995;59:890. [PubMed: 7701586]
32. Blazar BR, Taylor PA, Smith S, Vallera DA. Interleukin-10 administration decreases survival in murine recipients of major histocompatibility complex disparate donor bone marrow grafts. Blood 1995;85:842. [PubMed: 7833486]
33. Blazar BR, Taylor PA, Panoskaltsis-Mortari A, et al. Interleukin-10 dose-dependent regulation of $CD4^+$ and $CD8^+$ T cell-mediated graft-versus-host disease. Transplantation 1998;66:1220. [PubMed: 9825821]
34. Turner DM, Williams DM, Sankaran D, Lazarus M, Sinnott PJ, Hutchinson IV. An investigation of polymorphism in the interleukin-10 gene promoter. Eur J Immunogenet 1997;24:1. [PubMed: 9043871]
35. Crawley E, Kay R, Sillibourne J, Patel P, Hutchinson I, Woo P. Polymorphic haplotypes of the interleukin-10 5' flanking region determine variable interleukin-10 transcription and are associated with particular phenotypes of juvenile rheumatoid arthritis. Arthritis Rheum 1999;42:1101. [PubMed: 10366102]
36. Keijsers V, Verweij CL, Westendorp RGJ, Breedveld FC, Huizinga TWJ. IL-10 polymorphisms in relation to production and rheumatoid arthritis. Arthritis Rheum 1997;40 suppl. 9:S179.
37. Gibson AW, Edberg JC, Wu J, Westendorp RG, Huizinga TW, Kimberly RP. Novel single nucleotide polymorphisms in the distal IL-10 promoter affect IL-10 production and enhance the risk of systemic lupus erythematosus. J Immunol 2001;166:3915. [PubMed: 11238636]
38. Miura Y, Thoburn CJ, Bright EC, Chen W, Nakao S, Hess AD. Cytokine and chemokine profiles in autologous graft-versus-host disease (GVHD): interleukin 10 and interferon gamma may be critical mediators for the development of autologous GVHD. Blood 2002;100:2650. [PubMed: 12239181]
39. Pestka S, Krause CD, Sarkar D, Walter MR, Shi Y, Fisher PB. Interleukin-10 and related cytokines and receptors. Annu Rev Immunol 2004;22:929. [PubMed: 15032600]
40. Josephson K, Logsdon NJ, Walter MR. Crystal structure of the IL-10/IL-10R1 complex reveals a shared receptor binding site. Immunity 2001;15:35. [PubMed: 11485736]
41. Frodsham AJ, Zhang L, Dumpis U, et al. Class II cytokine receptor gene cluster is a major locus for hepatitis B persistence. Proc Natl Acad Sci USA 2006;103:9148. [PubMed: 16757563]
42. Petersdorf EW, Gooley TA, Anasetti C, et al. Optimizing outcome after unrelated marrow transplantation by comprehensive matching of HLA class I and II alleles in the donor and recipient. Blood 1998;92:3515. [PubMed: 9808542]
43. Lee SJ, Klein J, Haagenson M, Baxter-Lowe LA, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. Blood 2007;110:4576. [PubMed: 17785583]

Table 1

Characteristics of patients with unrelated donors and HLA-identical sibling donors (12)

Characteristic	Unrelated transplant Number (%)	Sibling transplant Number (%)
HLA compatibility, n (%)		
Matched [a]	423 (45)	993 (100)
mismatched	395 (42)	0
unknown	118 (13)	0
Age, median years (range)	35 (<1 – 59)	38 (<1–67)
Transplant year, n (%)		
1985–1991	159 (17)	391 (39)
1992–2002	777 (83)	602 (61)
Gender match (patient/donor), n (%)		
Male/Male	329 (35)	332 (33)
Male/Female	202 (22)	250 (25)
Female/Male	234 (25)	189 (19)
Female/Female	171 (18)	222 (22)
Total body irradiation, n (%)		
yes	858 (92)	537 (54)
no	78 (8)	456 (46)
Disease group, n (%) [b]		
non-malignant disease	82 (9)	170 (17)
low risk malignancy	546 (58)	497 (50)
high risk malignancy	308 (33)	326 (33)
Source of stem cells, n (%)		
bone marrow	905 (97)	848 (85)
peripheral blood	31 (3)	145 (15)
Outcomes, cumulative incidence		
Grades II–IV acute GVHD (day 100)	86%	56%
Grades III–IV acute GVHD (day 100)	37%	19%
Clinical extensive chronic GVHD (5 years)	52%	43%
Non-relapse mortality (5 years)	39%	25%

[a] patient and donor matched for HLA-A, B, C and DRB1

[b] non-malignant disease: aplastic anemia, immune deficiency disorder, lymphoproliferative disease, myelodysplastic syndrome and paroxysmal nocturnal hematuria; low risk malignancy: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) or non-Hodgkin lymphoma (NHL) in remission and chronic myelogenous leukemia (CML) in chronic phase; high risk malignancy: ALL, AML, chronic lymphocytic leukemia, NHL in relapse, CML beyond chronic phase, multiple myeloma and Hodgkin's disease.

Table 2

Outcomes after unrelated hematopoietic cell transplantation, according to IL10 promoter region and IL10RB/c238 genotypes

		Grades III–IV acute GVHD [a]			Extensive chronic GVHD			Non-relapse mortality		
Gene/SNP	**Genotype (n)[b]**	**Incidence[c]**	**Trend hazard ratio[d]**	**Trend P value**	**Incidence[c]**	**Trend hazard ratio[d]**	**Trend P value**	**Incidence[c]**	**Trend hazard ratio[d]**	**Trend P value**
Patients (n=692)										
	C/C (402)	36%			52%			37%		
IL10/−592	A/C (235)	39%	1.0	0.72	54%	1.0	0.92	40%	1.2	0.09
	A/A (55)	33%	(0.9–1.3)		47%	(0.9–1.2)		44%	(1.0–1.4)	
	A/A (200)	36%			51%			39%		
IL10/−1082	A/G (338)	37%	1.0	0.60	51%	1.1	0.53	39%	1.0	0.70
	G/G (154)	38%	(0.9–1.2)		55%	(0.9–1.2)		39%	(0.8–1.1)	
	C/C (313)	40%			51%			41%		
IL10/−2763	A/C (299)	33%	0.9	0.49	51%	1.0	0.61	37%	0.9	0.08
	A/A (80)	40%	(0.8–1.1)		59%	(0.9–1.2)		34%	(0.7–1.0)	
	T/T (291)	39%			49%			42%		
IL10/−3575	A/T (301)	35%	0.9	0.37	55%	1.0	0.96	35%	0.9	0.19
	A/A (100)	36%	(0.8–1.1)		49%	(0.9–1.2)		39%	(0.7–1.1)	
Donors (n=901)										
	C/C (505)	35%			52%			37%		
IL10/−592	A/C (350)	39%	1.1	0.24	53%	1.1	0.33	42%	1.1	0.11
	A/A (46)	46%	(0.9–1.3)		46%	(0.9–1.3)		39%	(1,0–1.4)	
	A/A (256)	36%			53%			41%		
IL10/−1082	A/G (433)	40%	1.0	0.97	52%	1.0	0.44	38%	0.9	0.34
	G/G (212)	34%	(0.9–1.2)		51%	(0.8–1.1)		37%	(0.8–1.1)	
	C/C (285)	35%			49%			39%		
IL10/−2763	A/C (305)	39%	1.1	0.55	54%	1.0	0.69	36%	1.0	0.66
	A/A (107)	35%	(0.9–1.3)		55%	(0.9–1.2)		37%	(0.8–1.1)	
	T/T (267)	36%			48%			39%		
IL10/−3575	A/T (328)	38%	1.0	0.94	55%	1.1	0.53	36%	1.0	0.99
	A/A (102)	33%	0.8–1.2)		52%	(0.9–1.2)		40%	(0.8–1.2)	

Transplantation. Author manuscript; available in PMC 2011 January 11.

		Grades III–IV acute GVHD [a]			Extensive chronic GVHD			Non-relapse mortality		
Gene/SNP	**Genotype (n)[b]**	**Incidence[c]**	**Trend hazard ratio[d]**	**Trend P value**	**Incidence[c]**	**Trend hazard ratio[d]**	**Trend P value**	**Incidence[c]**	**Trend hazard ratio[d]**	**Trend P value**
	A/A (455)	38%			55%			37%		
IL10RB/c238	A/G (364)	35%	0.9	0.51	48%	0.9	0.27	43%	1.1	0.53
	G/G (80)	39%	(0.8–1.1)		49%	(0.8–1.1)		34%	(0.9–1.2)	

[a] Grading of acute GVHD was not available for 16 patients.

[b] Genotyping of IL10/−2763 and IL10/−3575 was performed in 697 donors, and genotyping of IL10RB/c238 was not informative in 2 donor samples.

[c] Cumulative incidence of grade III–IV acute GVHD, extensive chronic GVHD and non-relapse mortality at day 100, 5 years and 5 years, respectively.

[d] 95% confidence intervals were indicated in the parentheses.

Table 3

Grades III – IV acute GVHD, according to IL10 and IL10RB/c238 genotypes among HLA-matched unrelated transplants

	HLA-matched unrelated transplant (n = 423) [a]			
Gene/SNP	**Genotype, (N) [b]**	**Incidence [c]**	**Trend hazard ratio [d]**	**Trend P value**
Patients				
IL10/−592	C/C (196)	36%		
	A/C (111)	35%	0.8	0.23
	A/A (25)	24%	(0.6–1.1)	
IL10/−1082	A/A (90)	33%		
	A/G (163)	35%	1.1	0.48
	G/G (79)	37%	(0.8–1.4)	
IL10RB/c238	A/A (0)			
	A/G (0)	ND	ND	ND
	G/G (0)			
Donors				
IL10/−592	C/C (223)	35%		
	A/C (157)	35%	1.0	0.83
	A/A (17)	41%	(0.7–1.3)	
IL10/−1082	A/A (110)	25%		
	A/G (205)	39%	1.3	0.02
	G/G (82)	40%	(1.0–1.7)	
IL10RB/c238	A/A (203)	38%		
	A/G (152)	32%	0.8	0.15
	G/G (38)	34%	(0.6–1.1)	

[a] matched for HLA-A, B, C and DRB1 alleles. Genotypes were determined among 332 patients and 397 donors respectively. ND: not done.

[b] The numbers in the parenthesis indicates number of unrelated transplants.

[c] cumulative incidence of grades III–IV acute GVHD at day 100.

[d] 95% confidence intervals were indicated in the parentheses.

Table 4

Grades III – IV acute GVHD, according to combined patient IL10/−592 and donor IL10RB/c238 genotypes, comparing results with unrelated versus related recipients

Genotype		Overall unrelated transplant (n=639)[a]			HLA-matched unrelated transplant (n=311)[a]			HLA-identical sibling transplant (n=953)[b]		
Patient IL10/−592	Donor IL10RB	Incidence of GVHD [c]	Trend hazard ratiod	Trend P valued	Incidence of GVHD [c]	Trend hazard ratio[d]	Trend P value[d]	Incidence of GVHD [c]	Trend hazard ratio[d]	Trend P value[d]
C/C	A/A	37% (189)			37% (97)			22% (292)		
	A/G	34% (154)	1.0	0.82	36% (72)	1.0	0.87	22% (183)	1.0	0.81
	G/G	47% (30)	(0.8–1.3)		38% (16)	(0.7–1.4)		24% (29)	(0.8–1.4)	
A/C	A/A	40% (105)			40% (48)			22% (190)		
	A/G	37% (97)	0.9	0.46	28% (46)	0.6	0.09	11% (141)	0.5	0.004
	G/G	31% (16)	(0.6–1.3)		30% (10)	(0.3–1.1)		8% (37)	(0.3–0.8)	
A/A	A/A	35% (23)			33% (9)			15% (33)		
	A/G	12% (17)	1.1	0.83	0% (8)	0.7	0.74	9% (32)	0.4	0.07
	G/G	63% (8)	(0.5–2.6)		40% (5)	(0.1–4.2)		0% (16)	(0.1–1.2)	

[a] Among the 655 patients with paired patient/donor samples available, 320 pairs were matched for HLA-A, B, C and DRB1 alleles. Grading of acute GVHD was not available for 16 patients.

[b] results from a cohort of 953 recipients with HLA-identical sibling donors (12–13).

[c] cumulative incidence of grades III–IV acute GVHD at day 100. Numbers of cases are indicated in parentheses.

[d] The trend hazard ratios and trend P values were analyzed within each stratum of patients IL10/−592 genotype. 95% confidence intervals were indicated in the parentheses.