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Abstract

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Grant Number: 5P01AI033484-070005
PI Name: PETERSDORF, EFFIE
PI Email:
PI Title:
Project Title: IDENTIFICATION OF PEPTIDE LIGANDS RESPONSIBLE FOR GVHD

Abstract: Clinical experience demonstrates that patients who undergo marrow transplantation from unrelated donors have a higher incidence of acute GVHD and rejection than do genotypically matched sibling transplants. Matching for the alleles of the class II genes decreases the risk of acute GVHD and improves survival. The class I genes, HLA-A, B and C, are known to be highly polymorphic and the role of matching for class I alleles is just coming into focus. We have observed a correlation between donor-recipient mismatching for HLA-C genes and increased risk of both graft rejection and cute GVHD. In our analysis of patients who experienced graft rejection, the donor and recipient mismatched HLA-C molecules encoded drastic amino acid substitutions at positions 9,99 and 156. These positions define peptide binding pockets B, D and E and are thought to influence the nature of the P2 and P3 residues of the bound peptide. Based on these clinical findings and together with available peptide data from other investigators, we hypothesize that graft rejection occurred as a result of recognition of highly dissimilar peptides by alloreactive T cells. This project will define the rules that govern peptide binding to HLA-A, B and C molecules (Specific Aim 1) and the biologically relevant peptides recognized by host-derived alloreactive cytotoxic T cell clones (Specific Aim 2). We will test the hypothesis that the peptide repertoire influences the cytotoxic T cell responses as measured by CTL-p to determine whether donor-recipient "compatibility" may be more accurately defined on the basis of biologically relevant peptide repertoires (Specific Aim 3). With the definition of the class I peptide motifs we will identify the genes that encode proteins giving rise to these peptides (Specific Aim 4). This Project will elucidate the basic immunogenetic mechanisms of peptide/MHC interactions and its influence on the alloimmune response. This information will provide the information needed to correlate alloimmune responses and MHC/peptide diversity with clinical outcome following marrow transplantation. The model proposed in this project will serve as a paradigm for the study of induction of tolerance and graft-versus-leukemia effects following transplantation from mismatched donors, and provide a biologic rationale for redefining donor suitability based on peptide/MHC motifs.

Thesaurus Terms:
MHC class I antigen, antigen presentation, bone marrow transplantation, cytotoxic T

lymphocyte, graft versus host disease, homologous transplantation, major histocompatibility complex, transplantation immunology
human genetic material tag, human tissue, polymerase chain reaction, tissue /cell culture

Institution:	FRED HUTCHINSON CANCER RESEARCH CENTER BOX 19024, 1100 FAIRVIEW AVE N SEATTLE, WA 98109
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Department:	
Project Start:	
Project End:	
ICD:	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
IRG:	

Version 2.0

Abstract

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Grant Number:	5R29CA072978-02
PI Name:	PETERSDORF, EFFIE W.
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PI Title:	
Project Title:	OPTIMIZING BMT FOR CANCER BY GENETIC MATCHING OF DONORS

Abstract: Patients with hematologic malignancies can be cured with unrelated donor (URD) marrow transplantation. Compared to transplantation from related donors, however, URD transplantation is associated with an increased risk of complications including acute and chronic graft-versus-host disease (GVHD), graft failure, and the need for prolonged immunosuppression. Recently, clinical studies have demonstrated the importance of HLA genes in influencing transplant outcome. Donor-recipient matching for the class II gene HLA-DRB1 reduces the risk of acute GVHD and improves survival, whereas mismatching for the class I genes HLA-A, B and C increases the risk of graft failure. In addition to the classical HLA genes, disparity for other genes may contribute to an increased risk of complications since HLA-A, B, C, DRB and DQB1 genotypically matched URD recipients still develop GVHD and experience graft failure. Because of the fundamental role of MHC class I and related molecules in antigen presentation and T cell recognition, HLA-E and MIC are of immediate immunological interest in the clinical transplant setting. The overall goal of this project is to determine the extent to which URD marrow transplantation can be optimized by more complete donor-recipient matching of MHC region genes. PCR-based technology will be developed to sequence HLA-E and MIC (Specific Aim l). The extent of polymorphism, the association of alleles on haplotypes and the degree of mismatching for HLA-E and-MIC alleles in URD transplant pairs will be determined (Specific Aim 2). Finally, the effect of mismatching for HLA-E and MIC alleles on the development of GVHD, graft failure and survival after marrow transplantation will be studied (Specific Aim 3). The studies proposed in this application will provide important new information concerning the biological relevance of class I region genes in the immune response and offer new approaches for improving the overall outcome of marrow transplantation.

Thesaurus Terms:
MHC class I antigen, MHC class II antigen, bone marrow transplantation, histocompatibility, histocompatibility gene, major histocompatibility complex, neoplasm /cancer transplantation
T lymphocyte, allele, antigen presentation, chemical association, genetic polymorphism,

genotype, graft versus host disease, haploidy, homologous transplantation, human mortality, immune tolerance /unresponsiveness, isoantigen, transplantation immunology
clinical research, computer assisted sequence analysis, histocompatibility typing, human subject, polymerase chain reaction

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Project Start:	01-FEB-1997
Project End:	31-JAN-2002
ICD:	NATIONAL CANCER INSTITUTE
IRG:	ET