Identification of MHC II-restricted minor histocompatibility antigens after HLA-identical stem-cell transplantation.

BACKGROUND: After allogeneic hematopoietic stem-cell transplantation (HSCT), donor-derived T cells may elicit graft-versus-host disease (GVHD) and graft-versus-tumor (GVT) responses. The main targets of GVHD and GVT responses after human leukocyte antigen (HLA)-identical HSCT are minor histocompatibility antigens (mHAgS), that is, polymorphic gene products in which recipient and donor differ. Thus, for increasing beneficial GVT and decreasing life-threatening GVHD responses, knowledge of the relevant mHAgS is required. Here, we sought to identify mHAgS recognized by CD4 T cells using a novel serologic approach. METHODS: To identify candidate mHAgS recognized by CD4 T cells, a cDNA expression library from peripheral blood mononuclear cells of a patient with ?-thalassemia major was screened with serum taken at different time points after HLA-identical HSCT. RESULTS: Immune responses against 18 antigens were identified with serum taken 100 days posttransplantation, when the patients had recovered from acute GVHD II. Except for one, no humoral responses against these antigens were detected 25 days or 1 year after transplantation. Sequence comparison of these antigens between recipient and donor revealed three polymorphisms of which two were contained within epitopes predicted to bind to HLA-DR molecules of the
patient. Using cytokine secretion and capture assays, T cells specific for the polymorphic antigens of the recipient, but not the donor, were isolated from peripheral blood monocyte cells after HSCT.

CONCLUSIONS: The serologic approach described here facilitates the rapid identification of mHAgs recognized by CD4 T cells. Furthermore, the correlation of humoral and cellular immune responses with acute GVHD implies a role of these antigens in GVHD pathology.