A DELETION IN THE GENE ENCODING THE CD45 ANTIGEN IN A PATIENT WITH SCID


Purpose of the Study. Defects in genes required for the development of T cells often underlie the primary immunodeficiency known as severe combined immunodeficiency (SCID). Many gene defects have been identified in SCID patients although the most common is the X-linked form of SCID that is attributable to defects in the common cytokine receptor chain. This study examined the cause of a novel type of SCID that was associated with minimal surface expression of CD45. CD45 is an abundant cell surface protein with multiple isoforms. It is a protein tyrosine phosphatase that is critical for transmembrane signal transduction.

Methods. Peripheral blood mononuclear cells from the patient were examined for expression of CD45 using standard flow cytometry techniques. The CD45 gene was sequenced using polymerase chain reaction. To confirm the role of the mutation in the defective expression of CD45, the mutant cDNA was transfected into Chinese hamster ovary cells.

Results. The patient was found to have a homozygous mutation in CD45. The 6bp deletion was located in the extracellular domain. The mutation did not affect transcript stability or translation, but protein was undetectable at the cell surface. This was true for 3 of the 8 isoforms examined and could be presumed to similarly affect all isoforms.

Conclusions. The homozygous mutation in CD45 was not found in any normal controls and was found to reproduce the defect in transfection experiments. The authors conclude that this 6bp deletion in the extracellular domain was responsible for the reduced surface expression of CD45 and the patient’s SCID.

Reviewer’s Comments. This particular patient was the first identified as being CD45-deficient in 1997, although the mutation was not identified until this manuscript. It is apparently a rare type of SCID with only 2 patients known to be CD45-deficient. This study demonstrates the importance of the 2 deleted amino acids in the surface expression of CD45 and serves as a reminder of the many types of defects that can potentially be associated with SCID.

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MUTATION IN THE CLASS II TRANS-ACTIVATOR LEADING TO A MILD IMMUNODEFICIENCY


Purpose of the Study. Major histocompatibility complex (MHC) class II deficiency or the bare lymphocyte syndrome is an autosomal recessive congenital immunodeficiency which typically is associated with a severe combined immunodeficiency (SCID)-like picture. There are 4 gene defects that can cause this disorder: class II trans-activator (CIITA), RFX, RFX5, and RFX-associated protein defects. These are all transcription factors required for the coordinate transcriptional regulation of MHC class II genes. Approximately 70 patients with MHC class II deficiency have been described and the usual course is one of unrelenting infections and death by age 4 unless a bone marrow transplant is performed. This manuscript describes 3 adult siblings who had a mild infection history and were found to have CIITA deficiency.

Methods. Monocytes, B cells, and skin dendritic/macrophage cells were stained for MHC class II expression. B cell fusions were performed to identify the complementation group (putative gene defect) and ultimately the CIITA gene was sequenced. Transfection experiments were performed to confirm the functional defect was associated with the identified mutation.

Results. A single homozygous mutation was identified in all 3 siblings. This L469P substitution in CIITA results in markedly diminished activity of the transcription factor. Importantly, the activity was not abolished.

Conclusions. This is the first CIITA mutation to result in partial activity. All other mutations have been associated with an inability to translocate to the nucleus and none have been able to stimulate transcription. The mild phenotype in these patients could be attributable to the residual activity of the mutant protein.

Reviewer’s Comments. MHC class II deficiency is characterized by severe recurrent infections, protracted diarrhea, CD4 T cell lymphopenia, immunoglobulin G (IgG) subclass and immunoglobulin A (IgA) deficiency, relative preservation of mitogen proliferative responses but absent responses to recall antigens. These 3 siblings had mild infections, aberrant functional antibodies, impaired responses to recall antigens, and CD4 T cell counts at the lower limit of normal. Two of the 3 were IgA-deficient. In all respects, their clinical presentation and laboratory findings represented a mild form of what is typically seen in MHC class II deficiency. The scientific lesson from this article is that the L469 is critical for full function of CIITA. The clinical lesson is that there are probably many patients with mutations in immunologically relevant genes with mild phenotypes that are not easily detected with currently available laboratory analyses. Only a high degree of suspicion and diligence will allow the caregiver to identify the underlying immunodeficiency.

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INTRAVENOUS GAMMA GLOBULIN THERAPY

ANTINFLAMMATORY ACTIVITY OF IVIG MEDIATED THROUGH THE INHIBITORY FC RECEPTOR


Purpose of the Study. High-dose intravenous gamma globulin (IVIG) has proven effective for the treatment of autoimmune diseases such as immune thrombocytopenia (ITP), but the mechanism for its beneficial effects have not been clearly defined. In this study, the molecular basis for the antinflammatory property of IVIG was investigated in a murine model of ITP.

Methods. ITP was induced in mice through the injection of an antiplatelet monoclonal antibody (mAb), and pretreatment with either IVIG or Fc antibody fragments (which bind to Fcy receptors on cells, but cannot bind antigens) could prevent the resulting thrombocytopenia. Through the use of specific blocking antibodies and transgenic mice, the authors tested whether IgG receptors (FcyRIIB, FcγRIIB) were involved in the protective effects of IVIG.

Results. The FcγRIIB receptor was required for protection, as demonstrated by genetic deletion or blocking with mAb. In addition, protection by IVIG was associated with the induction of FcγRIIB, which inhibits macrophage acti-
Mutation in the Class II Trans-Activator Leading to a Mild Immunodeficiency

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