nonimmune cells such as neurons are nonetheless essential for host defense against invading pathogens.

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Loss-of-Function Mutations in the IL-21 Receptor Gene Cause a Primary Immunodeficiency Syndrome

PURPOSE OF THE STUDY. This report of 2 unrelated kindreds with newly recognized mutations in the inteleukin-21 receptor gene (IL-21R) highlights the molecular basis and phenotype of a new form of immunodeficiency.

STUDY POPULATION. Two sets of kindreds were studied. The first set included a 4-year-old boy and a 10-year-old sister born from consanguineous Lebanese parents with phenotypes characterized by recurrent respiratory infections and chronic cryptosporidial gastrointestinal infection and associated chronic cholangitis, biliary fibrosis, and cirrhosis. A second unrelated set included an 8-year-old boy and a 13-year-old boy from consanguineous Columbian parents who had a phenotype similar to that of the first set, including recurrent respiratory infections, chronic cryptosporidial gastrointestinal infection, and hepatobiliary disease.

METHODS. In addition to reviewing each patient’s clinical course and basic immune evaluation, subjects underwent exome and candidate gene sequencing with directed molecular investigation into the cellular mechanism of the identified mutations.

RESULTS. All 4 patients had recurrent respiratory and gastrointestinal infections characterized by underlying B- and T-cell defects with variable natural killer cell dysfunction. Cryptosporidial infections were universal. Sequencing revealed 2 unique and unrelated homozygous recessive loss-of-function mutations in the IL-21R gene. Unlike patients with a common γ-chain deficiency, which affects several interleukin receptors, including IL-21R, the subjects in this study did not meet criteria for severe combined immunodeficiency. Patients seemed to have impaired T-cell response and memory B-cell development, thought to account for the observed increase in infections. The mechanism of cirrhosis is less clear and may be secondary to chronic infections. All patients have had grave clinical courses: 1 died of complications from liver transplant, another died of complications of hematopoietic stem cell transplant (HSCT), and the other 2 are alive but too ill to undergo HSCT.

CONCLUSIONS. This study details the phenotypes and molecular investigation of the first reported patients with IL-21R deficiency, providing insight into the role of IL-21R in immune function. The poor clinical outcome of these patients highlights the importance of early primary immunodeficiency recognition, potentially enabling HSCT before development of irreversible secondary morbidities.

REVIEWER COMMENTS. As has been the case with previously discovered primary immunodeficiencies, this small case series reveals a glimpse into a specific aspect of immune function. In this case, we have learned that the IL-21R pathway is important for T- and B-cell responses protecting from respiratory and gastrointestinal infections, especially with Cryptosporidium. The case series also imparts the critical importance of identifying primary immunodeficiency early in life so that the best opportunity for successful HSCT can be provided.


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Ribosomal Protein SA Haploinsufficiency in Humans With Isolated Congenital Asplenia

PURPOSE OF THE STUDY. To identify a potential genetic basis for isolated congenital asplenia.

STUDY POPULATION. Thirty-three patients from 23 kindreds with a history of congenital asplenia, including multiplex kindreds that suggested an autosomal dominant inheritance pattern.

METHODS. Genomic DNA was initially obtained from at least 1 member of each kindred and subjected to whole exome sequencing followed by testing of remaining subjects.

RESULTS. Eighteen (55%) of the 33 subjects from 8 of the 21 kindreds were identified with 7 different heterozygous missense mutations of the gene encoding the ribosomal protein SA (RPSA). The mutations affect highly conserved nucleotides in mammals, vertebrates, and yeast and showed complete penetrance in that all individuals carrying the mutation had isolated congenital asplenia.

CONCLUSIONS. Heterozygous mutations in RPSA underlie all isolated congenital asplenia in the multiplex families studied (but not all subjects with isolated congenital asplenia). RPSA is involved in preribosomal processing, but its role in splenic development is unknown at this time. There were no other definable defects observed in these patients. Interestingly, another mutation affecting...
different ribosomal proteins has been characterized: Diamond-Blackfan anemia is associated with haploinsufficiency in multiple different ribosomal proteins (but not RP5A) and results in bone marrow failure as well as multiple developmental defects. However, in these patients, there is no evidence of splenic abnormalities, and the current study found no evidence of hematologic abnormalities (or developmental abnormalities) in the patients harboring the RP5A mutations.

REVIEWER COMMENTS. The importance of this study is that many of these cases developed invasive bacterial infection early in childhood, most often involving Streptococcus pneumoniae (61%) with a high mortality rate (45%) (Mahaoudi N, et al. J Pediatr. 2011;158[1]:142–148, 148.e1). Thus, isolated congenital asplenia has overlapping features with recently defined TLR defects (eg, MyD88, IRAK4 deficiency) in that both are associated with childhood invasive bacterial infections that have a high mortality rate. Consequently, any child with invasive bacterial infection should be evaluated for absence of a spleen (presence of Howell-Jolly bodies, directed imaging studies) as well as studied for other congenital immune defects associated with this clinical presentation. In view of the autosomal dominant transmission of some cases of isolated congenital asplenia, family members of an affected patient should also be evaluated for possible asplenia.

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HIV AND INFECTIOUS DISEASES

Chronic Progressive HIV-1 Infection Is Associated With Elevated Levels of Myeloid-Derived Suppressor Cells


PURPOSE OF THE STUDY. Myeloid-derived suppressor cells (MDSC) consist of a heterogeneous population of progenitor cells and immature myeloid cells that are potent suppressors of T-cell function in many tumor models. The purpose of this study was to evaluate the possibility that MDSC play a role in HIV-induced immunosuppression.

STUDY POPULATION. Ninety-seven patients participated in this study: 16 healthy controls; 20 HIV-infected individuals with suppressed viral loads; 49 HIV-infected treatment-naive individuals; 2 individuals with hepatitis C co-infection; 4 HIV-infected individuals failing to respond to treatment; and 8 individuals with lung cancer as positive controls.

METHODS. Flow cytometry analysis was performed on freshly isolated peripheral blood mononuclear cells. MDSC were defined as CD11b+CD14–CD33+CD15+. CD4+CD25+, FoxP3+ regulatory T cells were also analyzed. Mixed lymphocyte reactions and proliferation assays were used to measure suppressor function.

RESULTS. Subjects with progressive or chronic uncontrolled HIV infection had significantly higher levels of MDSC than healthy controls. Subjects with lung cancer, as expected, had elevated MDSC. In HIV-infected individuals, percent MDSC correlated positively with elevated viral load (>50 000/mL) and low CD4 count (<250/mm3). In addition, effective antiretroviral therapy was associated with normalization of MDSC number; individuals with elevated MDSC before antiviral therapy had significant reductions in MDSC after initiation of therapy. MDSC number was correlated with generation of CD4+CD25+FoxP3+ regulatory T cells. Finally, MDSC directly impaired the proliferative capacity of T cells of healthy donors and HIV controllers.

CONCLUSIONS. Uncontrolled HIV infection is associated with elevated levels of MDSC. These cells potentially contribute to the impaired T-cell responses characteristic of progressive HIV disease.

REVIEWER COMMENTS. The variety of hematopoietic cells seems endless, and as new cell types are defined, they routinely seem to be affected by HIV infection. MDSC are a case in point. The relevance of these cells in tumor biology has recently been better defined. It has long been known that chronic inflammation creates a tumor-inducing environment. It is now speculated that infiltrating MDSC inhibits effective immunologic control of evolving malignant cells. The current study suggests that MDSC may contribute to the immunopathogenesis of HIV. Are these cells contributing to the immunologic suppression associated with HIV, or are they a regulatory response to HIV-associated persistent immune activation? As described in an accompanying Editorial Comment (Macatangay BJ, et al. AIDS. 2012;26[12]:1567–1569), dampening the effects of MDSC could be important in purging latent HIV reservoirs in approaches aimed at curing HIV disease. However, understanding the immunoregulatory networks involved in HIV pathogenesis is likely critical for the design of effective HIV immune-based therapies.

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Vaccine-Induced Plasma IgA Specific for the C1 Region of the HIV-1 Envelope Blocks Binding and Effector Function of IgG


PURPOSE OF THE STUDY. A recently completed Phase III vaccine trial demonstrated a 32% estimated efficacy. An
# Ribosomal Protein SA Haploinsufficiency in Humans With Isolated Congenital Asplenia

Thomas A. Fleisher

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