Reversion mutations in patients with leukocyte adhesion deficiency type 1 leading to CD18 expression on CD3+/CD8+/CD57+ T Cells

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Somatic reversions of inherited mutations in adenosine deaminase deficiency, X-linked severe combined immunodeficiency (X-SCID), and Wiskott–Aldrich syndrome have been recognized in humans. These reversions are caused by either back mutations, with restoration of wild-type sequence, or second-site mutations, leading to compensatory changes. These mutations have been associated with milder clinical phenotypes in these primary T cell immunodeficiencies. Leukocyte adhesion deficiency type 1 (LAD-1) is an autosomal recessive immunodeficiency affecting leukocyte adhesion caused by heterogeneous mutations in the β2 integrin, CD18. These mutations prevent for mation of CD11/CD18 heterodimers and surface expression of the receptor complex. Defective or absent CD18 on leukocytes, particularly neutrophils, leads to defective adherence to the endothelium and failure to migrate to the site of infection.

Three moderately affected LAD-1 patients were studied by flow cytometry. As expected, neutrophil CD18 expression was markedly and homogeneously diminished compared to normals. However, we were surprised to find that each of these patients had a small subset of lymphocytes with normal CD18 expression (CD18+). These CD18+ lymphocytes were CD3+/CD8+/CD57+, representing potential cytotoxic T cells (CTL). CD3+/CD18+ and CD3+/CD18− lymphocytes from each patient were sorted using FACS Vantage (Becton-Dickinson) and genomic DNA was obtained. Microsatellite analysis proved patient origin of CD18+ cells in each case. Subeloning and sequencing showed heterozygous reversion mutations in patients 1 and 2, and back mutation on one of patient 3’s alleles leading to correction of his splicing defect (Table). Although the reversions in patient 1 and 2 are not to the exact wild type (wt), but to a third amino acid, they support LFA-1 expression, and the expressed LFA-1 behaves like wt.

Somatic reversions conferring CD18+ expression in these patients were detected primarily in CD3+/CD8+/CD57+ cells. This suggests that somatic revertant CD18+ CTLs may have a survival advantage in LAD-1. Whether these revertant CD18+ CTL confer advantages on the host ameliorating disease awaits ongoing functional studies. The identification of 3 cases of reversion mutations in moderate LAD-1 at one center suggests that this may be a relatively common event in this rare disease. Finally, this is the first identified series for somatic reversion in a primary phagocyte defect.

Interferon-γ receptor 1 promoter polymorphisms and susceptibility to nontuberculous mycobacterial infection

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Background: Genetic susceptibility factors have been recognized to play a critical role in otherwise healthy individuals who develop disseminated nontuberculous mycobacterial (NTM) infections. Exonic and intronic mutations in the interferon-γ receptor 1 (IFNGR1) gene are among them. In contrast, no inherited susceptibility factors have been yet associated with pulmonary nontuberculous mycobacterial (PNTM) infections.

Methods: We sequenced the IFNGR1 minimal promoter region (MPR) of 55 Caucasian patients with NTM infections, 17 disseminated and 38 pulmonary. No patients with known susceptibility factors to NTM were included. We also sequenced 86 Caucasian controls. We compared single nucleotide polymorphisms (SNPs) and inferred haplotype distributions between populations.

Findings: We identified 10 previously undescribed SNPs in the IFNGR1 MPR, two of which show strong statistical association with NTM infections in patients without other risk factors. Compared to controls, the polymorphisms −611A and −56C were significantly over-represented in patients with NTM infections (p=0.004 and 0.03, respectively), whereas polymorphism −611A was significantly over-represented in patients with PNTM infections (p=0.0001). The probability of finding...