To the editor:

Identification of ITK deficiency as a novel genetic cause of idiopathic CD4$^+$ T-cell lymphopenia

Idiopathic CD4 lymphopenia represents a heterogeneous group of combined primary immunodeficiencies with markedly reduced CD4$^+$ T-cell counts. Although several genetic etiologies including MHC class II deficiency$^1$ or mutations in RAG1,$^2$ MST1,$^3$ or LCK$^4$ have been reported, the majority of patients remain genetically undetermined.

Here we describe a 17-year-old male Turkish patient of consanguineous background, referred to the hospital at 7 years of age. He suffered from recurrent pulmonary infections causing progressive immunodefiency$^1$ or mutations in RAG1,$^2$ MST1,$^3$ or LCK$^4$ have been reported, the majority of patients remain genetically undetermined.

Until the age of 17, although PCR-based copy-number analysis indicated borderline detectable EBV virus load (1000-2000 copies/mL). As all previously reported ITK-deficient patients were analyzed when they showed EBV-induced lymphoproliferation, we here had the unique opportunity to dissect EBV-dependent and EBV-independent ITK deficiency phenotypes. Consistent with previous findings in mouse$^5$ and human$^6,11$ flow cytometry indicated an absence of iNKT-cells (Figure 1D), illustrating that the absence of iNKT-cells is a primary phenotype of ITK deficiency. Although CD4 lymphopenia has already been described in other ITK-deficient patients suffering from lymphoproliferative disease,$^6,11$ we here show that combined immunodeficiency with CD4 deficiency can be the predominant disease manifestation. Furthermore, defective T-cell proliferation has not been described in ITK-deficient patients, although it is consistent with the findings in Itk$^{-/-}$ mice. Of note, at the most recent follow-up, the patient presented with leiomyoma (not shown) and a high titer for EBV ($23 \times 10^6$ copies/mL), in line with the characteristic, marked vulnerability to EBV infection in human ITK deficiency.$^6,11$

In conclusion, in this case we identify ITK deficiency as a novel cause of idiopathic CD4$^+$ T-cell lymphopenia. Our analysis also sheds light on the immunophenotype of ITK deficiency in the absence of EBV-associated lymphoproliferative disease. Genetic assessment of patients with combined immunodeficiencies, in particular with predominant CD4 lymphopenia, should include mutational analysis of ITK even in the absence of EBV lymphoproliferation.
Figure 1. Immunological and genetic analysis. (A) The patient presented with persistently low numbers of CD4+ T-cells and elevated numbers of CD8+ T-cells throughout a period of 7 years. (B) Homozygosity mapping identified several homozygous regions. ITK (asterisk) was located inside a homozygous region on chromosome 5. (C) Identification of a homozygous nonsense mutation (c.C49T:p.Q17X) in the gene ITK. (D) The index patient shows complete absence of TCRVα24+ /TCRVβ11+ iNKT-cells.

References


To the editor:

Myeloma cell sensitivity to bortezomib is associated with Dicer1 expression

Despite considerable progress of chemotherapeutic strategies and the introduction of the proteasome inhibitor bortezomib, multiple myeloma (MM) remains an incurable disease. Mutations or loss of p53 occur in roughly 10% of untreated MM cells and are closely associated with resistance to bortezomib and dismal prognosis. Although the inhibitory effect of bortezomib is well recognized, its downstream mechanisms of cytotoxicity remain largely elusive and at times controversial.

The discovery of microRNA (miR) has revealed a new level of regulation of cell signaling and homeostasis. Deregulation of miR...
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