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 deficiency1 or mutations in RAG1,2 MST1,3 or LCK4 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 sanguineous background, referred to the hospital at 7 years of age. He reported, the majority of patients remain genetically undetermined.

To elucidate the underlying genetic cause, we combined homogyosity mapping (Figure 1B) and exome sequencing as previously reported, with minor modifications.5 Unexpectedly, we identified a homozygous nonsense mutation located within the first exon of the Interleukin-2-inducible T-cell kinase (ITK) gene (c.C49T:p.Q17X) likely leading to nonsense-mediated decay of the corresponding gene product. The mutation was validated using capillary sequencing and showed perfect segregation under the assumption of autosomal-recessive inheritance (Figure 1C). ITK is a tyrosine kinase comprising 2 Src homology and a pleckstrin homology domain, respectively, acting downstream of the T-cell receptor complex and playing a critical role during thymic CD4+CD8+ selection.6 Itk−/− mice have reduced iNKT-cells and show an activated phenotype of peripheral CD4+ T-cells.7

All ITK-deficient patients reported to date developed EBV-associated B-cell lymphoproliferation accompanied by hepato- and splenomegaly or Hodgkin lymphoma.8-10 Decreased numbers of iNKT-cells are a hallmark feature of the disease.8-11

Surprisingly, this patient remained at sero-negative EBV status 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 mouse7 and human8-11 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,8-11 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 concordant 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 × 106 copies/mL), in line with the characteristic, marked vulnerability to EBV infection in human ITK deficiency.8-11

In conclusion, in this case we identify ITK deficiency as a novel cause of idiopathic CD4 lymphopenia. Our analysis also sheds light on the immunophenotype of ITK deficiency in the absence of EBV-associated lymphoproliferation. 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.

Nina Kathrin Serwas  
CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria

Deniz Cagdas  
Division of Immunology, Hacettepe University Ihsan Doğramaci Children’s Hospital, Ankara, Turkey

Sol A. Ban  
CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria
Contribution: N.K.P., E.S., and S.A.B. performed all experimental work; O.S., I.T., and D.C. provided clinical care of the patient, provided clinical and immunological assessment, and were involved in critical scientific discussions; K. Bienemann and A.B. were involved in scientific discussions and helped with drafting the manuscript; K. Boztug conceived this study, provided laboratory resources and planned, designed and interpreted experiments; and N.K.P. and K. Boztug wrote the first draft and the revised version of the manuscript with input from K. Bienemann and A.B. Approval was obtained from the local institutional review board. Informed consent was provided according to the Declaration of Helsinki.

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Correspondence: Kaan Boztug, CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria; e-mail: kboztug@cemm.oeaw.ac.at.

References


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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.1 Mutations or loss of p53 occur in roughly 10% of untreated MM cells and are closely associated with resistance to bortezomib and dismal prognosis.2 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.3 Deregulation of miR...
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Nina Kathrin Serwas, Deniz Cagdas, Sol A. Ban, Kirsten Bienemann, Elisabeth Salzer, Ilhan Tezcan, Arndt Borkhardt, Ozden Sanal and Kaan Boztug