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PRKDC mutations associated with immunodeficiency, granuloma and aire-dependent autoimmunity

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Introduction

PRKDC encodes for DNA-dependent protein kinase catalytic subunit (DNA-PKcs), a kinase that forms part of a complex (DNA-PK) crucial for DNA double-strand break (DSB) repair and V(D)J recombination. In mice, DNA-PK also interacts with the transcription factor AIRE (autoimmune regulator) to promote central T cell tolerance.

Objectives

We sought to understand the causes of an inflammatory disease with granuloma and autoimmunity, associated to decreasing T and B cell counts over time diagnosed in two unrelated patients.

Methods

Genetic, molecular, and functional analyses were performed to characterize an inflammatory disease evocative of a combined immunodeficiency.

Results

We identified *PRKDC* mutations in both patients. These patients exhibited a defect in DNA DSB repair and V(D)J recombination. Circulating T cells had a skewed cytokine response typical of Th1 and Th2 profiles. Moreover, mutated DNA-PKcs failed to promote AIRE-dependent transcription of peripheral tissue antigens *in vitro*. The latter defect correlated *in vivo*, with the production of anti-Calcium Sensing Receptor (anti-CaSR) autoantibodies, which are usually found in AIRE-deficient patients.

Conclusion

Deficiency of DNA-PKcs, a key AIRE partner, can present as an inflammatory disease with organ-specific autoantibodies and these findings highlight the essential role of DNA-PKcs in regulating autoimmune responses and maintaining AIRE-dependent tolerance in human.

Disclosure of interest

None declared.

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