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Molecular nature of hyper-IgM syndrome type 2

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Thomas Dorner,[Aff1]

Aff1 Charite Hospital, Berlin

Keywords

B cells, class switching, somatic hypermutation, V genes

Context

A rare human immunodeficiency disease, the hyper-IgM syndrome (HIGM), is characterized by normal or elevated serum IgM levels, a lack of detectable IgG, IgA, and IgE and a high susceptibility to bacterial infections. Whereas the molecular basis of the X-linked form (HIGM1) is mutations in the gene coding for CD40L, another HIGM syndrome (HIGM2) has been described with autosomal recessive inheritance, normal CD40L sequences and CD40L/CD40 membrane expression. The molecular nature of the intrinsic defect apparently originating in B cells in HIGM2 patients has not been identified previously.

Significant findings

This study identified 10 independent mutations in the human activation-induced cytidine deaminase (*AID*) gene in 18 patients with HIGM2 from 12 unrelated families. Almost all of these patients had high levels of IgM and very low IgG and IgA levels. Through sequencing of transcripts using V3-23 gene rearrangements, the authors found a mutational frequency of 0-0.4% in $CD19^+$ B cells and 0-0.9% in $CD27^+/CD19^+$B cells as compared to 2.6-6.3% in normal.

Strikingly, a marked follicular hyperplasia of germinal centres (GCs) was identified in these patients who typically exhibit lymphadenopathy. These GCs were about 5 to 10 times larger than GCs from controls.

Comments

This paper addresses the role of *AID*gene mutations in humans as "an experiment by nature". It supports findings using AID-/- mice that clearly demonstrate the role played by AID in activated B cells in enabling them to undergo both class switching and somatic hypermutation. The variety of different mutations points towards spontaneous mutations that lead to this syndrome.

An interesting aspect of this paper relates to the lack of GCs in HIGM1 patients, whereas HIGM2 patients develop enlarged GCs. This confirms that CD40/CD40L interaction releases an early signal for the establishment of GCs and immunoglobulin class switching, whereas AID seems to be involved in later stages of B cell differentiation. However, both pathways result in class switching and it remains to be shown why this B cell specific process is turned on by at least two independent mechanisms at distinct differentiation stages.

Methods

AID sequencing, RT-PCR, northern blot, immunohistochemical analysis of tonsil sections

References

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