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Identification of a B cell activation specific enzyme

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Keywords

B cells, class switching, somatic hypermutation, V genes

Context

Although recombination of V genes is well characterized, other fundamental processes further diversifying the Ig repertoire, such as class switching and in particular somatic hypermutation still remain enigmatic. Notably, these two types of genetic alteration in the immune system take place in a highly specialized microenvironment called the germinal center resulting in the generation of high-affinity antibodies for a given antigen during affinity maturation. However, the involved enzymes or enzymatic complexes are not identified to date. Previously, cDNA subtraction between stimulated and nonstimulated CH12F3-2 cells identified a novel member of the RNA editing cytidine deaminase family, activation-induced cytidine deaminase (AID) which was specifically expressed in germinal center B cells (see Additional information).

Significant findings

This study demonstrates that induced overexpression of AID in CH12F3-2 cells enhanced class switching from IgM to IgA without any other stimulation. Moreover, AID deficiency in a TT2 ES cell line was able to block class switching in B cells. In addition, somatic hypermutation was also found to be dramatically reduced in AID-/- B cells after immunization.

The study could provide evidence that AID is involved in class switching by using three independent transfectants under an inducible tetracycline promoter. This was confirmed by measuring serum levels of IgM, IgG, and IgA in AID-/- mice at 10 weeks of age and immunizing AID-/- chimera.

Notably, AID-/- IgM^+ B cells developed normally and were found to be activated more strongly after antigenic stimulation than AID+/- IgM^+B cells, although AID-deficient B cells had a defect in class switching.

After immunization with nucleoprotein (NP)-conjugated chicken Î³-globulin, no anti-NP IgG1 was produced by AID-/- chimera; AID-/- Î¼ chains contained 10 times fewer mutations than AID+/- Î¼ chain in particular mutations in CDR 1 and CDR 2 were lacking.

Comments

The results of this study indicate that AID-/- B cells are defective in class switching and somatic hypermutation, indicating that both molecular processes depend on a common molecular mechanism involving AID. However, the authors did not report on the nature of the mutations in comparison to other known data. Since the possibility cannot be excluded that replication is involved in hypermutation, the detailed mechanisms and enzymatic complexes involved need to be identified.

Methods

AID-deficient (-/-) mice, flow cytometry, immunohistochemical analyses, immunization with NP-conjugated chicken gammaglobulin.

Additional information

Muramatsu M, Sankaranand VS, Anant S, Sugai M, Kinoshita K, Davidson NO, Honjo T: **Specific expression of activation-induced cytidine deaminase (AID), a novel member of the RNA-editing deaminase family in germinal center B cells.** *J Biol Chem* 1999, **274**:18470-18476 (PubMed abstract).

References

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