Review TRENDS in Molecular Medicine Vol.12 No.9

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Activation-induced deaminase: light and dark sides

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Activation-induced deaminase (AID) is required for class switch recombination (CSR) and somatic hypermutation (SHM), which are responsible for secondary diversification of antibodies in germinal centers. AID initiates these processes by deamination of cytosines on the immunoglobulin (Ig) locus, a potentially mutagenic activity. AID expression is restricted to germinal-center B cells, but the mechanisms that regulate its target specificity are not completely understood. Here, we review the most recent findings on the regulation of AID targeting and discuss how AID activity on non-Ig genes is relevant to the generation of chromosome translocations and to lymphomagenesis.

Activation-induced deaminase and antibody diversification

The immune system of vertebrates has evolved to mount adaptive responses against pathogens through the generation of a myriad of receptors for antigens of virtually unlimited diversity. During lymphocyte differentiation, T and B cells are programmed to re-arrange somatically the genes that code antigen receptors by the VDJ recombination reaction, thereby giving rise to the primary repertoire of antigen receptors. In contrast to T cells, B cells have an additional chance to diversify their antibody repertoire in germinal centers (see Glossary) after they encounter the antigen in peripheral tissues. The germinal-center reaction enables the generation of higher affinity antibodies with various functional specificities that fine-tune their response against pathogens. The two molecular mechanisms responsible for retuning the antibody repertoire are somatic hypermutation (SHM) and class switch recombination (CSR) (Figure 1). SHM involves the introduction of mutations, usually single-nucleotide substitutions, in the variable antigen-recognition portion of immunoglobulin (Ig) genes. Only those B cells in which SHM has introduced mutations that improve the affinity for their cognate antigen survive and proliferate. CSR is a region-specific recombination reaction that takes place between two switch regions of the heavy-chain Ig locus, so that the Cμ primary Ig constant region is substituted by a downstream constant region and the intervening DNA sequence is excised (Figure 1). As a result of this recombination reaction, antibodies with new effector capabilities are generated. Despite temporal and spatial overlap, CSR and SHM are distinct reactions that can take place independently of one another [1,2]. An increasing number of molecules have been associated with these two reactions, but it was not until the discovery of activation-induced deaminase (AID) by the Honjo laboratory [3] that the pieces of the puzzle started to fit to provide a clearer picture of SHM and CSR.

The identification of AID can in turn add to the understanding of B-cell lymphomagenesis. About 95% of diagnosed lymphomas are of B-cell origin, the majority of which are thought to derive from germinal-center or post-germinal-center B cells. A major hallmark of mature-B-cell lymphomas is the presence of chromosome translocations that involve the Ig locus and a proto-oncogene and that have etiological significance to disease development. The aim of this review is to provide a general view of AID function and regulation in normal physiology, focusing on some of the most recent developments in the field, and its potential contribution to the generation of malignant situations. For a more extensive perspective of AID, the reader should refer to some excellent reviews that have been recently published [4–9].

What is the function of AID?

AID was first identified as a gene selectively expressed in B cells that are activated to undergo CSR [3]. *AID* sequence has the closest homology to apolipoprotein B mRNA editing enzyme, catalytic polypeptide 1 (*APOBEC1*), an mRNA cytidine deaminase involved in lipid metabolism. Soon after its identification, AID was shown to be essential for both CSR and SHM in mice [10], and mutations in the *AID* gene were found to be associated with hyper-IgM syndrome type 2 [11,12]. Moreover, AID, when heterologously expressed in fibroblasts, is sufficient to promote CSR and SHM on transcribed substrates [13,14], implying that AID is the only B-cell-specific factor required to initiate these reactions. The actual mechanism by which AID initiates CSR and SHM has been a matter of intense debate. Because of its homology to APOBEC1, AID was first proposed to be an mRNA deaminase responsible for editing mRNA that codes for a protein, possibly an endonuclease, that would be directly or indirectly involved in SHM and CSR. However, this precursor mRNA has not yet been identified. The alternative hypothesis is that AID would deaminate cytidines directly in the variable or switch regions of the Ig locus to trigger SHM or CSR, respectively (Figure 2). As a consequence of this DNA deamination reaction, a U:G mismatch would be generated in the Ig locus that is likely to be processed through

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Available online 24 July 2006.

 1471-4914/$ – see front matter © 2006 Elsevier Ltd. All rights reserved. doi:10.1016/j.molmed.2006.07.001

Glossary

Abasic site: a sugar phosphate backbone of DNA in which a nitrogenous base has been removed.
Activation-induced deaminase (AID): the cytidine deaminase that is required for CSR and SHM, which take place in germinal-center B cells.
Chromosome translocations: chromosomal rearrangements in which part of a chromosome is detached by breakage and subsequently joined to a non-homologous chromosome.
Class switch recombination (CSR): a region-specific recombination reaction that takes place between two switch regions of the heavy chain Ig locus so that the Cμ primary Ig constant (C) region is replaced by a downstream C region and the intervening DNA sequence is excised.
c-Myc: a proto-oncogene that is often involved in chromosome translocations found in human B-cell lymphomas.
Cytidine deamination: the process by which the amino group of a cytidine base is removed causing its transformation into a uracil.
Epigenetic modifications: reversible modifications of chromatin that occur without a change in the sequence of the encoding DNA, such as DNA methylation and histone modifications.
Germinal centers: spherical masses in the center of a lymph node that contains actively proliferating B cells in which the SHM and CSR processes take place.
Non-homologous end joining (NHEJ): a DNA-repair mechanism in which two non-homologous DNA ends are repaired by ligation to one another.
P19 and p53: tumor suppressor proteins (i.e. their activity stops the formation of tumors).
Proto-oncogene: a normal cellular gene whose activation is linked to malignant transformation.
Somatic hypermutation (SHM): the process by which mutations, usually single-nucleotide substitutions, are introduced in the variable, antigen recognition portion of immunoglobulin genes.
Switch regions: highly repetitive regions that are present in the introns of the immunoglobulin heavy-chain genes that are targeted in CSR.
Uracil-N-DNA glycosylase (UNG): an enzyme that removes uracils from DNA.

uracil removal by uracil-N-DNA glycosylase (UNG) or by alternative pathways, including base-excision repair and mismatch repair, leading to CSR or SHM. Some prominent evidence supporting the DNA deamination model for AID function includes the following observations: (i) AID deaminates single-stranded DNA (ssDNA) *in vitro* and it does so with the same sequence preference that is observed in B cells [15–18]; (ii) genetic evidence shows that, in the absence of UNG, mutations at G–C pairs are biased towards transitions [19,20] and CSR is severely impaired [21]. Moreover, the mismatch repair protein MSH2 is involved in both SHM and CSR [6,7], and the combined absence of MSH2 and UNG completely abolishes CSR [22] (Figure 2); and (iii) AID has been reported to interact with switch region DNA in B cells that undergo CSR [23]. Therefore, although the RNA-versus-DNA controversy still exists [24], we consider that the experimental data available to date point to a DNA-deamination activity of AID, which is the accepted view of this review. A comprehensive review of the molecules that are downstream of DNA deamination is beyond the scope of this review [6,7], but some of them are outlined in Table 1 for clarity.

How is AID function regulated?

AID's activity has intrinsic mutagenic potential (Figure 2) and, therefore, a tight regulation is required to restrict this potential to the appropriate cell type, time and loci, and to avoid DNA lesions throughout the genome. Conceptually, two types of regulatory mechanisms can be envisioned to prevent unwanted DNA damage by AID: limiting AID availability to the appropriate cell type (i.e. germinal-center B cells) and restricting the accessibility of DNA sequences to AID function. We will briefly outline some of the evidence for these regulatory mechanisms.

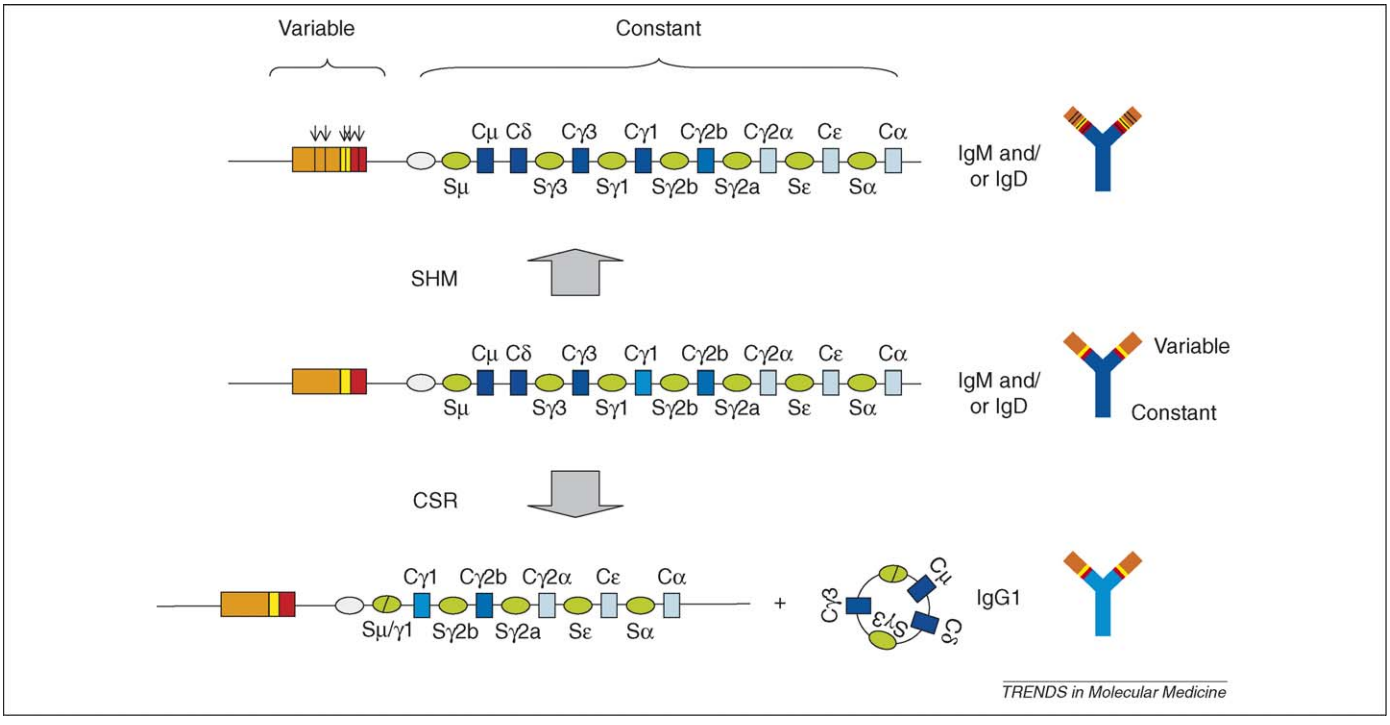

Figure 1. Generation of the secondary antibody repertoire by SHM and CSR. Two molecular mechanisms are responsible for the secondary diversification of antibodies in germinal centers. SHM alters the antigen-binding region of the antibody by introducing nucleotide substitutions (depicted as arrows) in the rearranged variable region of the Ig genes, thereby enabling the generation of antibodies with higher affinity for antigen. CSR is a region-specific recombination reaction that exchanges the primary Cμ constant region with a downstream constant region (blue boxes), giving rise to antibodies with new effector functions. The recombination takes place between the switch regions (green ovals) preceding the corresponding constant regions and results in the excision of the intervening DNA sequence. The figure illustrates recombination from Sμ to Sγ1. Molecules on the right side of the figure represent IG proteins encoded by the Ig genes shown on the left.

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