Immune Network
http://dx.doi.org/10.4110/in.2012.12.6.230
pISSN 1598-2629 eISSN 2092-6685

REVIEW ARTICLE

Activation-induced Cytidine Deaminase in B Cell Immunity and Cancers

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Activation-induced cytidine deaminase (AID) is an enzyme that is predominantly expressed in germinal center B cells and plays a pivotal role in immunoglobulin class switch recombination and somatic hypermutation for antibody (Ab) maturation. These two genetic processes endow Abs with protective functions against a multitude of antigens (pathogens) during humoral immune responses. In B cells, AID expression is regulated at the level of either transcriptional activation on AID gene loci or post-transcriptional suppression of AID mRNA. Furthermore, AID stabilization and targeting are determined by post-translational modifications and interactions with other cellular/nuclear factors. On the other hand, aberrant expression of AID causes B cell leukemias and lymphomas, including Burkitt's lymphoma caused by *c-myc/IgH* translocation. AID is also ectopically expressed in T cells and non-immune cells, and triggers point mutations in relevant DNA loci, resulting in tumorigenesis. Here, I review the recent literatures on the function of AID, regulation of AID expression, stability and targeting in B cells, and AID-related tumor formation.
[Immune Network 2012;12(6):230-239]

INTRODUCTION

In mammalian bone marrow during early B cell development, pro-B/pre-B cells undergo recombination activating genes (RAGs)-mediated V(D)J recombination in variable region genes of the immunoglobulin (Ig) heavy (H) chain DNA locus to obtain 'primary antibody (Ab) diversity [forming the primary B cell receptor (BCR) repertoire].' After this process, immature/mature B cells move into peripheral lymphoid organs, and antigen (Ag)/cytokine-stimulated activated B cells go through 'secondary Ab diversification' by two DNA modification processes, class switch recombination (CSR) and somatic hypermutation (SHM). CSR takes place in IgH switch (S) regions located upstream of the constant (C) region genes, while SHM occurs in variable (V) region genes. These two processes are initiated by enzyme activation-induced cytidine deaminase (AID) (1-4). AID also induces gene conversion (GCV) of V gene loci of Ig light (L) chain in chicken B cells (5,6). During these genetic events, B cells differentiate into plasma cells, which produce Abs that possess different biological activities and binding affinities against a numerous foreign Ag (pathogens) and self-Ag. AID deficiency causes significant immune deficiency with a complete lack of CSR and SHM in both mice and humans (7,8). Patients with AID deficiency display hyper-IgM syndrome and suffer from recurrent infections (8).

AID expression is strictly controlled by many factors under physiological conditions. The fine control of AID expression is quite important, because AID is a potent mutator that induces genomic instability, resulting in tumorigenesis (9). Nonetheless, aberrant expression of AID causes various B lym-

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Received on October 29, 2012. Revised on November 9, 2012. Accepted on November 13, 2012.

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Keywords: Activation-induced cytidine deaminase, B cell, Antibody, Cancer

Abbreviations: AID, activation-induced cytidine deaminase; CSR, class switch recombination; DSB, DNA double-strand break; GCV, gene conversion; IgH, immunoglobulin heavy chain; IgV, immunoglobulin variable region; S region, switch region; SHM, somatic hypermutation; 3'UTR, 3'-untranslational region phomas/leukemias and non-lymphoid solid tumors through reciprocal chromosomal translocations and mutations in tumor suppressor genes and oncogenes. Recent advances regarding B cell AID regulation, its function, and AID-mediated cancers are discussed in this review.

DISCOVERY OF AID

Over 13 years ago, Honjo and colleagues identified a novel enzyme, AID (10). They performed PCR-based subtraction using a cDNA library prepared from stimulated, class-switched CH12F3-2A mouse B lymphoma cells and screened upregulated genes to identify AID. This enzyme is homologous (34% amino acid identity) to apolipoprotein B (apoB) mRNA-editing cytidine deaminase, catalytic polypeptide 1 (APOBEC-1), but neither edits apoB mRNA nor binds to RNA targets. Honjo's group also found that AID mRNAs are specifically induced in the germinal center (GC) of secondary lymphoid tissues (10), implicating a role for AID in genetic events related to cytidine deamination in GC B cells. One year later, it was elucidated that AID is necessary for Ig CSR and SHM in both mice and humans (7,8). Further, Honjo's group demonstrated that ectopic expression of AID in non-lymphoid cells (fibroblasts) induces CSR and hypermutation in artificial DNA constructs (11,12). In addition, AID induces GCV between IgL V gene loci and pseudo-V gene segments in the chicken B cell line DT40 (5). The discovery of AID elucidated three molecular mechanisms for Ab diversity: Ig CSR, SHM, and GCV.

FUNCTION OF AID IN B CELL HUMORAL IMMUNITY

AID as an initiator of immunoglobulin class switch recombination and somatic hypermutation processes

During humoral immune responses against Ags, B cells undergo maturation, activation, and differentiation to produce Abs. To effectively protect a multitude of Ags, Abs should mature and diverse through CSR and SHM, respectively. When mature B cells encounter Ags and are stimulated by cytokines, Ig CSR occurs as a recombination event that results in the juxtaposition of the rearranged $V_H D_H J_H$ gene upstream of a new C_H gene (13). Transcription of the corresponding unrearranged C_H genes produces germline transcripts, which are prerequisites for subsequent Ig CSR (13,14). Thus, via Ig CSR, IgM^+IgD^+ mature B cells are differentiated into class-switched B cells that can express and produce IgG, IgA, or IgE isotypes. On the other hand, SHM depends upon Ig V(D)J DNA transcription and alters the Ab repertoire via the introduction of point mutations into IgV region genes of activated B cells, thereby conferring Ab affinity maturation.

AID is a 198-amino acid protein that directly converts cytosine into uracil (U) in single-stranded target DNA of both Ig S and V regions (2,15-21). U can be processed in various ways, which leads to transition/transversion mutations in IgV region DNA during SHM or DNA double-strand breaks (DSBs) in the S region of the IgH chain gene during CSR (3,4,22). Mutations are generated either by replication over the U:G mismatch or by processing of the lesion by uracil DNA glycosylase (UNG), which leaves abasic sites (4). These abasic sites can be incised by the AP endonucleases APE1 and APE2, resulting in single-strand DNA breaks or DSBs if the abasic sites are sufficiently close on opposite strands (23,24). The mismatch repair pathway also recognizes and removes U:G mismatches, resulting in the conversion of single-strand DNA breaks to DSBs during CSR and the introduction of mutations at A:T base pairs during SHM and CSR. The abasic sites can also be replicated over by error-prone trans-lesion DNA synthesis polymerases during SHM (2). During CSR, DSBs occur at both the donor $S\mu$ and acceptor Sx regions, which are recombined by classical non-homologous end joining (NHEJ) and alternative end joining pathways (24,25). In the B cells of other animals such as birds, diversity in the IgV gene of the L chain is obtained by AID-mediated intrachromosomal GCV using upstream pseudo-$V\lambda$ gene segments as donor sequences (6,25,26).

The roles of AID in B cell tolerance and homeostasis

In addition to the roles of AID in Ig CSR, SHM, and GCV, Kelsoe's and Meffre's groups reported a role of AID in 'B cell tolerance.' They demonstrated that AID mediates central/peripheral B cell tolerance by eliminating self-reactive B cells in both mice and humans, which was proved in two studies using AID-deficient mice and human patients (27-29). On the other hand, Cogné's group recently reported that AID-driven deletion of the entire IgH chain C region gene cluster, which they termed 'locus suicide recombination,' causes expression termination of Ig at the B cell surface (30), claiming that the process is critical for B cell survival and homeostasis.

REGULATION OF AID EXPRESSION IN B CELLS

Stimuli for AID induction and transcriptional regulation

In mouse B cells, AID transcription is induced by T cell-dependent CD40 ligand (CD40L):CD40 interactions and/or T cell-independent stimuli such as the TLR4 agonist LPS (31-34). These stimuli increase AID expression mainly through NF-κB signaling (33). Immune cell (e.g., macrophages and dendritic cells)-produced cytokines [e.g., IL-4, TGF-β1, B cell-activating factor belonging to the TNF family (BAFF), and a proliferation-inducing ligand (APRIL)] also increase AID gene expression. IL-4 induces AID expression via Stat6 and protein kinase A (PKA)/CREB pathways in mouse B cells (35). BAFF stimulates B cells to express AID via the p38MAPK/CREB and JNK/AP-1 pathways after binding to BCMA (36). Our group has recently demonstrated that APRIL, but not BAFF, induces expression of the transcription factor HoxC4 via NF-κB-mediated HoxC4 gene transcription, and HoxC4 in turn binds to the AID promoter and induces AID expression in mouse B cells (37,38). In isolated human CD19$^+$ B cells, B cell agonists, CD40L with IL-4, or HLA-class II antibodies, significantly upregulate AID expression (39). Moreover, inducible nitric oxide synthase augments AID expression and potentiates Ig CSR in mouse B cells (40). In contrast, Ca^{2+} inhibits AID gene expression upon BCR activation through the Ca^{2+}/calmodulin-mediated inhibition of E2A (41), and progesterone reduces AID expression by inhibiting AID transcription (42).

Along with NF-κB, Stat6, CREB, and HoxC4, many other transcription factors, such as E2A (E47) (43), Pax5 (44), IRF-8 (45), Sp1/3 (46), C/EBP, Smad3/4, Myb, and E2F, are known to regulate the AID gene locus to induce AID transcription (31,33,34,47). It has been shown that estrogen-estrogen receptor complexes directly bind to the AID promoter and enhance AID transcription, leading to increased AID expression (48). However, Casali's group claimed that estrogen-estrogen receptor complexes directly bind to the HoxC4 promoter, but not to the AID promoter, activating HoxC4 transcription to induce AID expression (49). The cyclooxygenase 2/prostaglandin E2 pathway also enhances AID expression in replicating B cells (50). Recently, it was demonstrated that the transcription factor BATF is directly required for the expression of both AID and germline transcripts in mouse B cells (51). In addition, transcription factors PU.1 and IRF4 induce AID expression and GCV at the Ig λ locus in chicken B cells (52).

Post-transcriptional regulation and post-translational modification of AID

MicroRNA is a small, single-stranded, non-coding RNA molecule (~22 nucleotides) that functions in the post-transcriptional regulation of target gene expression. MicroRNA binds to complementary sequences in the 3'-untranslational region (3'UTR) of target mRNA, resulting in gene silencing by translation inhibition or target mRNA degradation (53). Several studies indicate that AID expression is post-transcriptionally suppressed by microRNAs. Teng et al. (54) and Dorsett et al. (55) reported that microRNA-155 (miR-155) binds to the 3'UTR of AID and directly represses the expression and function of the AID protein. Additionally, miR-181b directly targets the AID 3'UTR and inhibits AID expression in B cells (56). In addition, miR-93 and miR-155 interact with the 3'UTR of human AID mRNA to suppress AID translation in breast cancer (MCF-7) cells (57).

In B cells, phosphorylation of AID is required for both its targeting and Ig SHM (58-60). These early reports suggest that AID phosphorylation can be used as a strategy to control AID action in a post-translational manner. Indeed, phosphorylation of threonine residue 140 of AID preferentially affects the rate of somatic mutation (61). Phosphorylation of AID on S38 (AID-S38) by PKA is required for normal CSR and SHM in mice, supporting a role for AID-S38-replication protein A (RPA) interactions in the regulation of CSR and SHM (61-63). On the other hand, phosphorylation of AID on S3 suppresses AID activity, thereby inhibiting Ig class switching and *c-myc/IgH* translocation without affecting AID levels or catalytic activity. Such phosphorylation is controlled by protein phosphatase 2 (64). Phosphorylation of AID on T27 also attenuates its intrinsic DNA deaminase activity (65).

As an example of the post-translational regulation of AID, a recent study by Li et al. showed that Fe^{2+} suppresses Ig CSR through the inhibition of AID single-stranded DNA (ssDNA) deamination activity (66).

AID-interacting proteins inside B cells and their roles in antibody diversity

It has been reported that there are many AID-interacting factors in the cytoplasm and nucleus of B cells; their functions have been previously investigated (34). Heat shock protein 90 kDa (Hsp90) specifically interacts with AID and maintains steady-state levels of functional AID via the prevention of the proteasomal degradation of AID in the cytoplasm of B cells, thereby inducing antibody diversification (67). B cell activation-induced Hsp40 DnaJa1 also interacts with AID and stabilizes cytoplasmic AID (68). Moreover, in the cytoplasm, AID stoichiometrically associates with translation elongation factor 1 alpha (eEF1α) and leads to cytosolic retention and stabilization of AID (69). Thus, three molecules (i.e., Hsp90, Hsp40 DnaJa1, and eEF1α) contribute to the stabilization and cytosolic retention of the AID protein (34).

AID shuttles between the cytoplasm and the nucleus, and contains a nuclear export sequence at its carboxyl terminus. Exportin is a protein that recognizes and binds to nuclear export sequence of 'cargo' protein (e.g., AID) in the nucleus and transports the cargo through the nuclear pore complex to the cytoplasm. It was demonstrated that the quality of AID for exportin-binding may be critical to both AID stabilization and its activity during CSR (70). And in the same vein, CSR and stabilization of AID depend on an interaction between the AID carboxyl-terminal decapeptide and factors in addition to an export receptor chromosome region maintenance 1 (Crm1)/exportin 1 (71). AID itself regulates the subcellular localization of Tet family proteins, and this event contributes to AID shuttling (72). A nuclear localization signal in AID directs AID to nucleoli, where it colocalizes with its interaction partner, the widely expressed nuclear protein CTNNBL1 (spliceosome-associated factor), and physically associates with nucleolin and nucleophosmin to control Ig CSR (73,74). According to a recent study, the transcription factor YY1 physically interacts with AID and increases nuclear AID accumulation and stability to induce CSR (75). On the other hand, REG-γ, a protein implicated in ubiquitin- and ATP-independent protein degradation, interacts with nuclear AID and modulates antibody diversification in B cells (76).

PKA is specifically recruited to S regions to promote the localized phosphorylation of AID, which leads to the binding of RPA. This complex generates the high density of DNA lesions required for CSR (77). We have demonstrated that 14-3-3 directly interacts with AID and recruits AID to the 5'-AGCT-3'-rich S region, enhancing the AID-mediated DNA deamination required for CSR (78). The splicing regulator PTBP2 interacts with AID and promotes binding of AID to the S region during CSR (79). The RNA exosome, a cellular RNA-processing/degradation complex, is a long-speculated cofactor that associates with AID and targets AID deamination activity to both template and non-template strands of transcribed double-stranded DNA (dsDNA) of IgH S regions, and is required for optimal CSR (80). AID forms a complex with both KRAB domain-associated protein 1 (KAP1) and heterochromatin protein 1 (HP1), which binds to the Sμ region containing histone H3 trimethylated at lysine 9 (H3K9me3), thus providing a mechanism linking AID to epigenetic modifications and increasing the probability of cytidine deamination to effectively induce DSBs in the Sμ region as well as CSR (81). Both UNG and the mismatch repair proteins Msh2-Msh6 are important for the introduction of S region DSBs. AID binds cooperatively with UNG and Msh2-Msh6 to Ig S regions, and this depends on the AID carboxyl-terminus. Stavnezer's group demonstrated that the ability of AID to recruit UNG and Msh2-Msh6 proteins is important for DSB resolution during Ig CSR (82). Rev1 (a translesion DNA synthesis polymerase) recruits and stabilizes UNG to S regions by directly interacting with UNG, enhancing UNG glycosylation activity for Ig CSR (83). Rev1 and UNG likely contribute to a DNA-protein macromolecular complex that also includes AID, 14-3-3, the RNA exosome, and RPA, and is central to the generation and resolution of S region DSBs. DSIF complex (Spt4 and Spt5) is critical for NHEJ, which is required for CSR (84). Spt5 associates with both paused RNA polymerase II and ssDNA of the S region, and interacts with AID and recruits it to the S region. Thus, Spt5 is required for CSR (85). Spt6, a histone chaperone, regulates the histone epigenetic state of both AID target loci and the AID gene locus, and plays a critical role in both CSR and SHM (86,87). GC-associated nuclear protein (GANP) forms a complex with AID, recruiting it to both B cell nuclei and actively transcribed IgV regions to increase SHM frequency (88).

In addition, Storb's group performed a study using green fluorescent protein transgenic DT40 chicken cell lines and postulated that 'CAGGTG elements' of Ig genes are targeted by AID and required for SHM (89). Meanwhile, an Igλ regulatory element (Region A) was found to play a role in recruiting AID to the Igλ locus and is therefore important for AID-mediated GCV in chicken B cells (90,91). A splice isoform of the prototypical serine/arginine-rich (SR) protein splicing factor SRSF1 (SRSF1-3) binds preferentially to the IgV gene and makes it available for AID-induced SHM in a DT40 chicken B cell line (92).

AID-RELATED CANCERS

Aberrant expression of AID and abnormal targeting of AID activity in both B cells and non-B cells cause DSBs and DNA point mutations in Ig genes as well as in non-Ig genes, inducing tumorigenesis.

B cell lymphomas and leukemias

AID is required for chromosomal DSBs in *c-myc* and *IgH* loci (e.g., DNA of IgH S regions) that lead to reciprocal *c-myc/IgH* translocations, resulting in the development of B lymphomas {e.g., Burkitt's lymphomas in humans [T(8;14)] and plasmacytomas in mice [T(12;15)]} (93). Unlike AID-induced DSBs in Ig genes, genome-wide AID-dependent DSBs are not restricted to transcribed regions and frequently occur within repeated sequence elements, including CA repeats, non-CA tandem repeats, and short interspersed elements (SINEs) (94). Furthermore, Greisman et al. recently demonstrated that AID-initiated chromosomal DSBs in translocations can occur in human bone marrow pro-B cells and in mature GC B cells; additionally, WGCW motif breaks are generated at the *c-myc* locus in Burkitt’s lymphoma translocations and murine *c-myc/IgH* translocations (95). In addition, AID also produces DNA DSBs in other non-Ig genes, such as BCL6 and IRF4, which can lead to lymphoma-associated chromosomal translocations in mature B cells and result in both diffuse large B cell lymphoma (DLBCL) and multiple myeloma (96,97). In a mouse bone marrow transplantation (BMT) model, AID overexpression promotes B cell lymphomagenesis; this aberrant expression of AID in bone marrow cells induces B leukemia as well as B lymphoma in a cell lineage-dependent manner (98). Oncogenic BCR-ABL1 kinase induces aberrant AID expression in pre-B acute lymphoblastic leukemia (ALL) and B lymphoid chronic myelogenous leukemia (CML) blast crisis (99-101). The AID accelerates clonal evolution in *BCR-ABL1* ALL by enhancing genetic instability and aberrant SHM, and by negative regulation of tumor suppressor genes (102). Additionally, high expression of AID promotes chromosomal abnormalities and is associated with chronic lymphocytic leukemia (CLL) progression and CLL B cell survival (103,104). Meanwhile, AID is also expressed in $CD4^+$ T cells, which suggests that AID may have certain roles in T cell function or tumorigenesis (105). Actually, Tax oncoprotein of human T cell leukemia virus type 1 (HTLV-1) induces AID expression in human T cells through both NF-κB/Bcl-3 and CREB pathways, and aberrant AID expression might be involved in the development of adult T cell leukemia (ATL) (106).

Non-lymphoid cancers caused by AID

AID is also induced by inflammation and microbial infections in non-immune cells; this dysregulated AID expression is involved in various human cancers via its mutagenic activity. Thus, AID can play a role as a genotoxic factor. During bile duct inflammation, pro-inflammatory cytokines induce aberrant AID production and can enhance genetic susceptibility to mutagenesis, leading to cholangiocarcinogenesis (107). Likewise, pro-inflammatory cytokine mediated-aberrant AID expression in human colonic epithelial cells can lead to the generation of somatic mutations in the host genome, including the TP53 tumor suppressor gene (108). These findings provide a link between chronic inflammation and enhanced susceptibility to somatic mutations and an increased risk of cancer. Indeed, Chiba’s group performed a study using an AID transgenic mouse model to develop various organ tumors (109). In this study, Chiba’s group demonstrated that AID, a DNA mutator that plays a critical role linking inflammation to human cancers, might be involved in the generation of organ-specific genetic changes in oncogenic pathways during cancer development (109). Their subsequent study showed that the pro-inflammatory cytokine TNF-α induces strong aberrant expression of AID through NF-κB signaling pathways in human colonic epithelial cells and that AID enhances genetic instability, the accumulation of somatic mutations in the TP53 gene during chronic colonic inflammation, leading to the development of colitis-associated colon cancer (110,111). Bile acid-induced aberrant AID expression might also enhance susceptibility to genetic alterations in Barrett’s columnar-lined epithelial cells, leading to development of Barrett’s esophageal adenocarcinoma (112). In addition, the abnormal expression of AID may be involved in a subset of human lung cancers as a result of the mutation-inducing activity of AID (113). Recently, Miyazaki et al. speculated that inflammatory cytokines increase aberrant AID expression in oral squamous cells, playing an important role in the dysplasia-carcinoma sequence in the oral cavity (114). *Helicobacter pylori* infection mediates aberrant AID expression in gastric mucosal epithelial cells, which is correlated with persistent inflammation and results in the accumulation of submicroscopic deletions in various chromosomal loci in these cells (115-117). Their findings that AID, as a genotoxic factor, preferentially targets the tumor suppressor *CDKN2b-CDKN2a* locus in gastric epithelial cells suggest the significance of AID production in the development of human gastric cancer.

CONCLUDING REMARKS

AID is an essential enzyme for obtaining Ab diversity in B cells. However, in response to infections and inflammatory cytokines, aberrant expression and genome-wide targeting of AID cause genomic instability via chromosome translocations and point mutations in both B and non-B cells, thereby stimulating cancer formation. Therefore, the specific targeting for aberrant AID expression and the control of AID's off-targeting on genome could be useful strategies to prevent AID-related carcinogenesis. Future studies elucidating more precise AID functions and regulation of AID expression and targeting should lead to a more comprehensive understanding that will aid in the development of therapeutic drugs for AID-mediated diseases.

ACKNOWLEDGEMENTS

This study was supported by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science, and Technology (No. 2009-0066904).

CONFLICTS OF INTEREST

The author declares no conflict of interest.

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