GENETICS

Contribution of cytosine desaminases of AID/APOBEC family to carcinogenesis

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Abstract

Cytosine deaminases of the AID/APOBEC family have a weighty influence on human health. These enzymes are part of the innate and humoral immunity; they participate in lipid metabolism and muscle development, protect cells from viruses and regulate retrotransposition. If the activity of AID/APOBEC deaminases is misregulated, they can become "weapons of mass destruction," causing deaminations in unprotected single-stranded DNA regions leading to genome-wide mutagenesis. Ultimately, mutations contribute to cell malignancy and rapid evolution of cancer cells, helping them to evade the organism's defense. Also, hypermutable tumor cells develop resistance to anti-cancer drugs. Here we overview current understanding of the structure, functions, and regulation of AID/APOBEC cytosine deaminases in connection to carcinogenesis.

Keywords: Cytosine deaminases AID/APOBEC, DNA damage, mutation, cancer.

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Carcinogenesis is often associated with the accumulation of a large number of new mutations in somatic cells. In one scenario, driver mutations in proto-oncogenes or tumor suppressor genes trigger uncontrolled cell proliferation, which is often accompanied by a decrease in the accuracy of replication and repair (Loeb et al., 1974; Loeb, 2001). In another, the driver mutation can by itself cause a mutator phenotype that leads to mutations in oncogenes and onset of tumorigenesis. During tumor growth, its cells accumulate additional mutations, the number of which increases after each division. Some of these mutations enhance the tumor aggressiveness and cause drug resistance of tumor cells; others are called "passenger mutations" and do not affect carcinogenesis (Stratton et al., 2009; Martincorena et al., 2015; Martincorena et al., 2017; Bailey et al., 2018).

Different tumors can differ significantly by the quantity of accrued mutations, mutation types, and their distribution along the genome, which depends on the nature of mutagenic processes operating in the specific tumor. Therefore, analysis of mutational spectra can serve as a tool to deduce what was the cause of mutations in tumors (Rogozin et al., 2003; Alexandrov et al., 2013; Rogozin et al., 2018). Recently, cytosine deaminases of the AID/APOBEC family have been implicated in etiology in many types of tumors. Enzymes of the AID/APOBEC family regularly participate in various cellular processes, from RNA editing to innate and humoral immunity, by deaminating cytosine to uracil in DNA or RNA (Conticello, 2008). Genome-wide deamination would cause a genetic catastrophe. The

activity of cytosine deaminases in the cell is strictly regulated and limited to a few mRNA molecules or selected genome loci. Aberrant regulation of deaminase activity leads to genome-wide deaminations causing catastrophic accumulation of mutations and cancer (Burns et al., 2013; Roberts and Gordenin, 2014; Rogozin et al., 2019).

Introduction to deaminases of the AID/APOBEC family

At the moment, 11 human enzymes of the AID/APOBEC family are known. They have different tissue-specific roles. All of them contain a conservative zinc-dependent cytidine-deaminase catalytic domain (CDA) (Samaranayake et al., 2006; Conticello, 2008; Salter et al., 2016) (Fig. 1). Those enzymes of this family that possess enzymatic activity catalyze a simple biochemical reaction of cytosine to uracil deamination in the single-stranded RNA or DNA (Fig. 2). The appearance of uracil in either RNA or DNA alters the coding properties of the nucleic acid molecule, and mutations appear after replication (Fig. 3, upper right corner). Also, uracil in DNA is a substrate for base excision DNA repair. During repair, apyrimidinic (AP) sites and, further, single-strand breaks/gaps can occur, which also have a mutagenic potential (Lada et al., 2007) (Fig. 3). Breaks during base excision repair are a prerequisite to the recombinogenic activity of deaminases (Di Noia and Neuberger, 2004; Poltoratsky et al., 2004). Closely spaced deaminations on opposite DNA strands may lead to double-strand breaks (Fig. 3, lower right). The catalytic activity of some deaminases or deaminase modules, APOBEC2, APOBEC4, and N-terminal domain of both APOBEC3B and APOBEC3G is not known (Fig. 2).

APOBEC1 (apolipoprotein B mRNA Editing Catalytic subunit 1) was the first identified member of the AID/APOBEC enzyme family performing deamination of cytosine in nucleic acids. In 1993, APOBEC1 was shown to be the catalytic subunit of a protein-editing complex that post-transcriptionally edits apolipoprotein B mRNA (Chen et al., 1987; Powell et al., 1987). The complete form of this apolipoprotein containing 4536 amino acids (ApoB100) is synthesized in the liver and the small intestine cells. Deamination of cytosine to uracil in position 6666 of *APOB* mRNA leads to substitution of CAA glutamine codon to UAA stop codon. When modified mRNA carrying a premature stop codon is translated, a shortened version of APOB is synthesized with a size of 48 % of the original form (ApoB48) (Teng et al., 1993; Davidson et al., 1995). Thus, in natural conditions, APOBEC1 preferably deaminates only one specific cytosine residue in the mRNA, though recently it was found that, in addition to apolipoprotein mRNA, APOBEC1 can edit 3'UTR regions of 32 different mRNAs (Rosenberg et al., 2011). It is possible, thereby for APOBEC1 to exert influence upon gene expression by microRNA and other ways. When heterologously expressed in bacteria and yeast, APOBEC1 can deaminate genomic DNA, inducing numerous substitutions in CG pairs (Harris et al., 2002; Lada et al., 2011a).

Deaminase **AID** (Activation-induced deaminase) initiates the somatic hypermutagenesis (SHM) and class-switch recombination of immunoglobulin genes (Muramatsu et al., 1999). During SHM, uracil in the DNA template of the variable IG regions leads to C → T transitions when replicated (Fig. 3). Also, uracil-containing DNA may be repaired by the base excision repair (BER) pathway. When uracil-DNA glycosylase (UNG) cuts uracil out from DNA the intermediate product, transient AP-sites are formed. Unprocessed AP-sites block the major replicative DNA polymerases but could be bypassed in error-prone fashion by Y-family translesion DNA polymerases (Casali et al., 2006; Lada et al., 2007). In another pathway of SHM, U:G pairs are recognized by DNA mismatch repair (MMR), which generates gaps in the DNA duplex. In B cells, the gaps are oddly filled with the participation of inaccurate DNA polymerase η (Fig. 3). As a result, numerous and various point mutations appear in the variable regions of the immunoglobulin genes of activated B-lymphocytes, increasing the diversity of the antibodies (Muramatsu et al., 2000; Yoshikawa et al., 2002; Papavasiliou and Schatz, 2002; Di Noia and Neuberger, 2007). Another factor of immunoglobulins diversity, class-switch recombination, also depends on AID. Uracils, appearing on the border of constant regions of immunoglobulin heavy chain genes, are excised by BER or MMR, resulting in single- and double-stranded breaks that induce recombination leading to antibody isotype switching from IgM to IgG, IgA or IgE (Muramatsu et al., 2000; Revy et al., 2000; Okazaki et al., 2002; Stavnezer and Schrader, 2006; Di Noia and Neuberger, 2007).

After the discovery of the role of AID in immunity, it was unclear whether it deaminated either DNA or RNA (Muramatsu et al., 2000). Seminal experiments by Michael Neuberger's group unequivocally demonstrated that AID deaminates DNA (Petersen-Mahrt et al., 2002). The expression of the *AID* gene in *E. coli* cells was mutagenic, and the effect was much stronger in *ung1*$^-$ cells unable to excise uracil from DNA (Petersen-Mahrt et al., 2002; Beale et al., 2004). Purified AID deaminated single-stranded DNA *in vitro*, producing clustered mutations with a signature similar to mutations in immunoglobulin genes (Pham et al., 2003). Human deaminase AID expressed in yeast cells is mutagenic, too (Poltoratsky et al., 2004). AID increased the frequency of Can^r forward mutations almost 8-fold in the wild-type strain and 82-fold in the *ung1* mutant. The synergistic effect was observed for the frequency of reversions of nonsense mutation (that occur mainly by suppressor mutations in

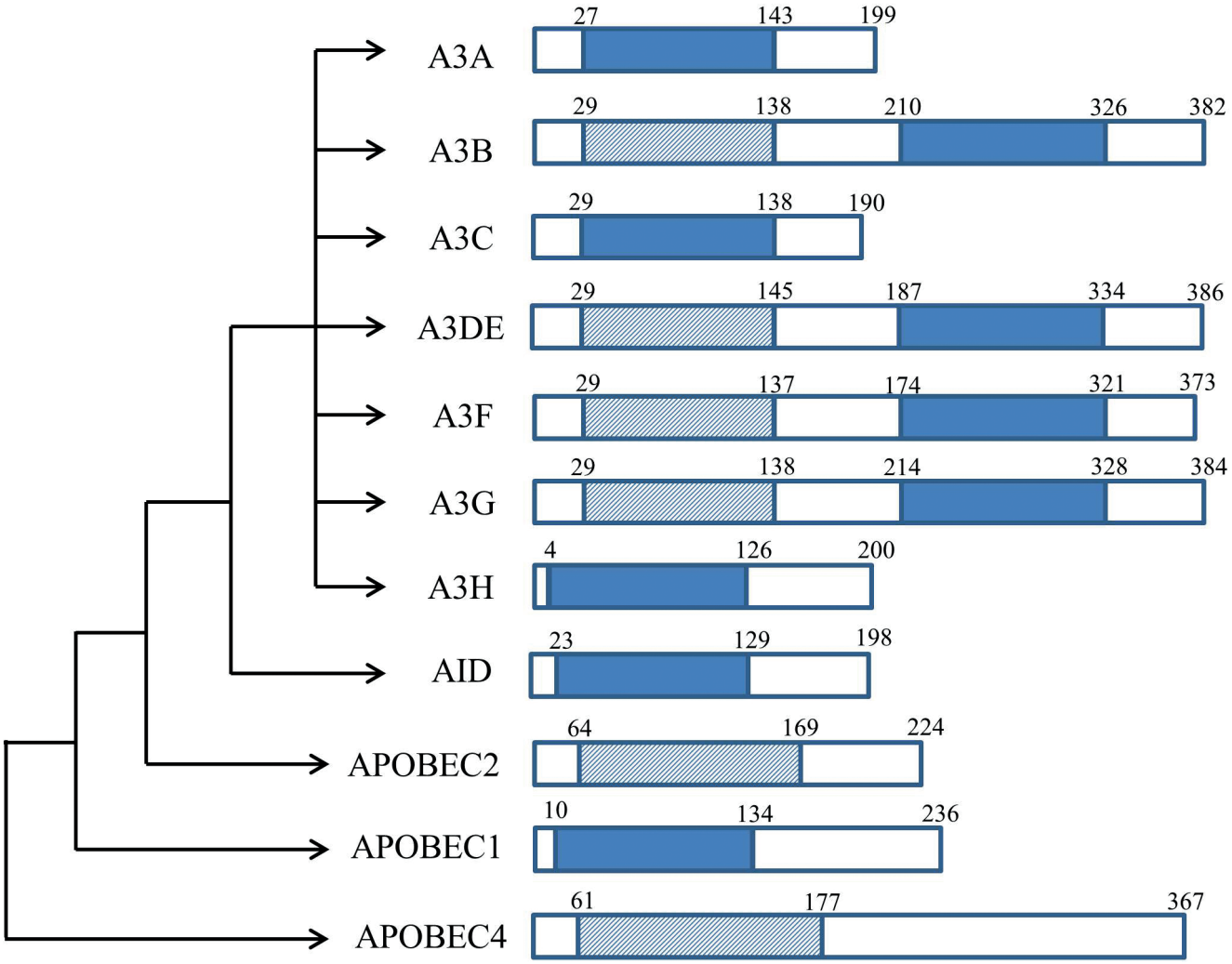

Fig. 1. Phylogenetic tree of human AID/APOBEC deaminases (Rogozin et al., 2007; Krishnan et al., 2018). Active deaminase modules are shown in solid blue, deaminase domains which have no catalytic activity are shown as cross-hatched bars. The numbers above each bar refer to amino acid positions according to (https://www.uniprot.org).

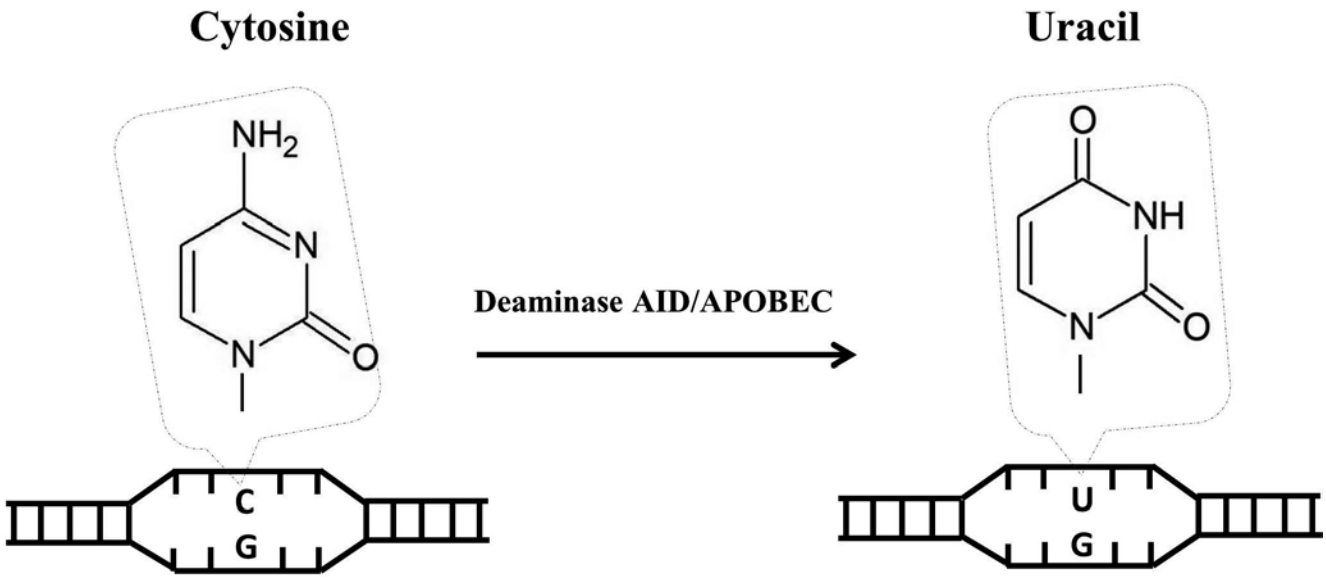

Fig. 2. Cytosine deamination performed by AID/APOBEC family deaminases on ssDNA generates U:G mispair.

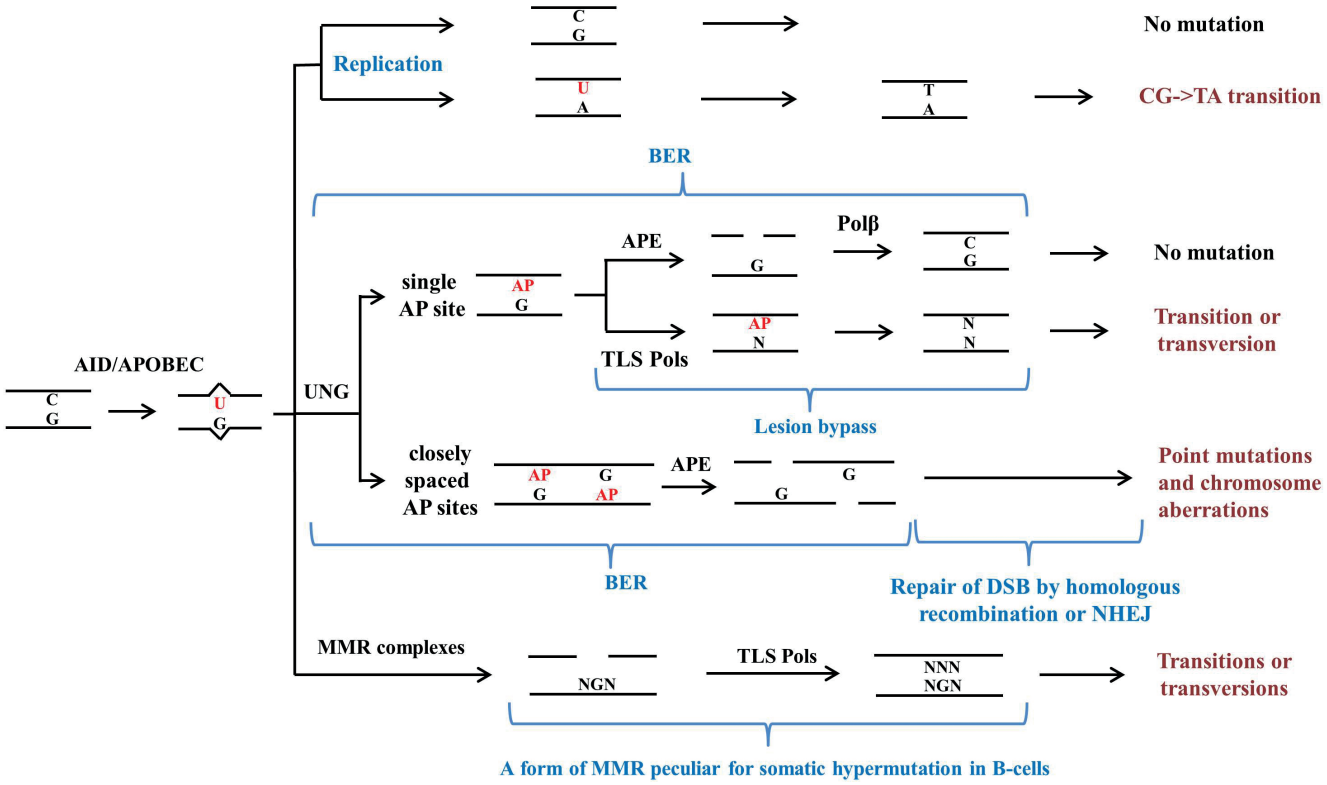

Fig. 3. Genetic consequences of cytosine deamination in DNA by AID/APOBEC. Altered DNA is shown in red; operating processes are shown in blue, enzymatic systems in black and resulting genetic alterations in maroon. U — uracil; AP — apyrimidinic site; N — any base; BER — base excision repair; MMR — mismatch repair; NHEJ — non-homologous end joining; UNG — uracil-DNA-glycosylase; APE — AP endonuclease; Pol β — DNA polymerase β; TLS Pols — translesion DNA polymerases; DSB — double-strand DNA break.

the anticodons of tRNA genes) in the *ung1* strain, with an increase up to 1290-fold over the wild-type. Sequencing of the *CAN1* gene in AID-induced Can^r mutants revealed that most mutations were transitions in GC pairs in a context similar to SHM (Mayorov et al., 2005; Rogozin and Pavlov, 2006). Genome-wide studies detected mutational clusters with a predominance of C → T transitions (Lada et al., 2012; Taylor et al., 2013).

APOBEC2 is found in the heart and skeletal muscles of mice, chickens, and humans (Liao et al., 1999; Li et al., 2014). It is necessary for the normal development of muscles and weight gain in mice (Sato et al., 2009). In the absence of APOBEC2, animals develop age-dependent myopathy (Sato et al., 2009), which was related to mitochondrial function defects (Sato et al., 2017). Heterologous expression of *APOBEC2* in yeast and bacteria did not lead to a mutator phenotype (Lada et al., 2011a), and APOBEC2 does not deaminate DNA *in vitro* (Harris et al., 2002; Lada et al., 2011a).

The **APOBEC3** (A3) human deaminase subfamily includes seven proteins: A3A, A3B, A3C, A3DE, A3F, A3G, and A3H, possessing one deaminase module (A3A, A3C, A3H) or two modules (A3B, A3DE, A3F, A3G), (Fig. 1). The genes encoding these proteins are located on chromosome 22 in tandem (Jarmuz et al., 2002). APOBEC3 deaminases protect cells from exogenous and endogenous retroelements by inducing hypermutagenesis in the viral genome. A3B, A3DE, A3F, A3G, and A3H inhibit the replication and infectivity of HIV-1 (Doehle et al., 2005; Chaipan et al., 2013). A3G has been shown to inhibit HIV-1/Δvif infectivity through the degradation or hypermutagenesis of the viral minus-strand DNA (Sheehy et al., 2002; Harris et al., 2003). A3B, A3F, and A3G prevent infection with the hepatitis B virus by introducing numerous CG → TA transitions into the virus DNA (Suspene et al., 2005; Bonvin et al., 2006). A3A, A3B, A3DE, and A3H inhibit the Alu retrotransposition (Bogerd et al., 2006; Orecchini et al., 2018). A3A, A3C, and A3H deaminate papillomavirus DNA (Vartanian et al., 2008). A3A inhibits replication of the adeno-associated virus (AAV), a member of the parvovirus family (Chen et al., 2006). A3A, which has one deaminase module, can inhibit replication of both wild-type AAV and the autonomous parvovirus minute virus of mice (MVM) by a DNA deamination-independent mechanism (Narvaiza et al., 2009). Perhaps deaminase binds to viral RNA and sterically inhibits further elongation of reverse transcription (Bishop et al., 2008). In this relation, APOBEC1, all APOBEC3 proteins and another member of this family, deaminase AID, inhibit hu-

man LINE-1 retrotransposition, and can do it through a deamination-independent manner (Bogerd et al., 2006; Muckenfuss et al., 2006; Stenglein and Harris, 2006; Kinomoto et al., 2007; Schumann, 2007; Pak et al., 2011; Orecchini et al., 2018).

Although the single cytidine-deaminase domain of A3A has significant homology with the C-terminal domain of A3G (~ 65 %) and A3B (~ 90 %), A3A has no antiviral activity against HIV-1 (Goila-Gaur et al., 2007; Caval et al., 2014). Endogenous A3A is a predominantly cytoplasmic protein and is not expected to be genotoxic (Land et al., 2013), but when upregulated, it causes DNA damage (Suspène et al., 2017). Under conditions of overexpression, A3A becomes genotoxic (Land et al., 2013) and can enter the nucleus (Chen et al., 2006). Studies have shown that A3A induction activates severe DNA damage response (DDR) in a deaminase-dependent manner. Ectopic expression of A3A in U2OS osteosarcoma cells caused an accumulation of phosphorylated histone γ-H2AX, which is a marker of double-stranded DNA breaks (Chowdhury et al., 2005; Landry et al., 2011). At the same time, phosphorylated forms of replication protein A (RPA), activation of ATM protein kinase, and cell cycle arrest in the early S phase were observed in response to DNA damage (Shiloh, 2003; Jackson and Bartek, 2009; Landry et al., 2011). While a mutant A3A gene encoding a protein without deaminase activity was expressed, a cascade of events of the response to DNA damage was not triggered. In HEK293 cells, overexpression of A3A was also cytotoxic (Burns et al., 2013). Recently, it was shown that, besides DNA, A3A could deaminate transcripts of 3078 genes at more than 4200 sites and change the amino acid sequence of 1110 proteins (Sharma et al., 2015; Sharma et al., 2017). Those include genes associated with breast cancer, hematologic neoplasms, amyotrophic lateral sclerosis, Alzheimer disease, and primary pulmonary hypertension (Sharma et al., 2017). A3A expression is mutagenic in yeast cells (Taylor et al., 2013; Hoopes et al., 2016). Heterologous expression of the two-domain A3B is also mutagenic in *E. coli* and yeast (Bogerd et al., 2006; Taylor et al., 2013). The N-terminal deaminase module of A3B does not possess the catalytic activity and is not mutagenic, but enhances both the deaminase activity of the C-terminal domain and binding to the substrate single-stranded DNA (Bogerd et al., 2006; Fu et al., 2015). Heterologous expression of A3C and A3G is mutagenic in *E. coli* and yeast (Harris et al., 2002; Schumacher et al., 2005; Lada et al., 2011a; Taylor et al., 2013).

APOBEC4 deaminase was found bioinformatically by analyzing protein sequence databases and is present in mammals, chickens, and frogs (Rogozin et al., 2005). It weakly interacts with single-stranded DNA, does not exhibit deaminase activity *in vitro*, and enhances the replication of HIV-1 (Marino et al., 2016). No mutator phenotypes were detected in yeast and bacteria expressing APOBEC4 (Lada et al., 2011a).

Deamination and mutagenesis by AID/APOBECs

All currently known human AID/APOBECs are structurally similar to each other, but their functions are very different. After the breakthrough discovery of deaminases, especially AID, the urgent problem was to understand how they realize their catalytic potential in targeted genome compartments, in specific cells and tissues. Purified AID needs RNase treatment to exert deamination activity on single-stranded DNA (Bransteitter et al., 2003); RNA attenuates A3B activity (Xiao et al., 2017), suggesting a role of RNA bound to deaminases in the regulation of their activity. AID deaminations in single-stranded DNA *in vitro* lead to clustered mutations in defined DNA sequence contexts (Pham et al., 2003) by intertwined scanning and catalysis (Mak et al., 2013). Transcription has an essential role in AID activity because it constantly generates ssDNA (Pham et al., 2003). AID causes multiple clustered mutations under transcriptional pausing and stalling (Canugovi et al., 2009). Transcription is not the only source of unprotected ssDNA, and mutations attributed to APOBECs are detected in parity on both transcribed and non-transcribed DNA strands in human tumors (Kazanov et al., 2015). Yeast cells expressing human AID have revealed deamination on both DNA strands with more efficient uracil repair in the transcribed DNA strand (Mayorov et al., 2005). Genome-wide studies of APOBEC-induced mutations in yeast firmly established the connection of deamination with transcription (Taylor et al., 2014; Lada et al., 2015; Saini et al., 2017). DNA may be transiently exposed to APOBEC deaminases during replication (Green et al., 2016). Lagging DNA strand replication involves more complicated transactions, thus leaving unprotected ssDNA more frequently. Not surprisingly, a third of mutations attributed to APOBECs are inferred to occur during DNA replication on the lagging strand in cancer cells (Seplyarskiy et al., 2016). APOBEC-dependent deamination preferentially occurs in the lagging strand in yeast (Hoopes et al., 2016) and *E. coli* (Bhagwat et al., 2016). One additional source of ssDNA substrates for deaminases is homologous recombination (Poltoratsky et al., 2010; Taylor et al., 2013).

Double-stranded DNA is resistant to deaminase action. Transcription, replication, and repair provide transient single-stranded regions that can be deaminated. Single-strand DNA binding proteins (e.g., RPA) attenuate the ability of APOBECs to work on ssDNA (Pham et al., 2008; Lada et al., 2011b). Accessibility of ssDNA to RPA versus competing APOBECs determines the extent of mutagenic action of deaminases. The sites/situations

where the balance is shifted to APOBECs are one of the factors for the appearance of hypermutated regions in cells. The mutations caused by deaminases are found in the regions of the chromosomes that contain a large number of genes and are transcribed early (Kazanov et al., 2015).

Footprints of deaminases in DNA

Studies in microbial models and analysis of cancer genomes allowed identification of specific deaminase imprints in DNA termed "AID/APOBEC mutational signatures." A mutational signature is a specific combination of base substitutions and other mutations in a defined sequence context (Rogozin and Pavlov, 2003). By studying the mutational signatures in cancer cells, it is possible to deduce with some probability the strength and duration of the action of the mutagenic factor (Nik-Zainal et al., 2012). About 30 signatures of various mutational processes have now been identified in cancer genomes, two of them (no. 2 and no. 13) belong to the APOBEC family deaminases, (Nik-Zainal et al., 2012; Alexandrov et al., 2013; Alexandrov and Stratton, 2014). APOBEC mutational signatures were found in more than half of human cancers (Alexandrov et al., 2013). The remnants of APOBECs deaminations, C → T transitions and C → G transversions in the preferred 5'-TC (A/T)-3' motifs that can be caused by A3A and A3B, were found in 3.8 % of multiple myeloma cases, along with translocations occurring in the vicinity of the preferred AID 5'-WRC-3' motifs. Patients with an increased number of such mutations had a poor prognosis (Walker et al., 2015).

The study of 1020 cell lines of various types of cancer from the COSMIC (Catalog of Somatic Mutations in Cancer) somatic mutation database has revealed APOBEC mutational signatures in more than 100 cell lines (Jarvis et al., 2018). In 5 % of skin cancer cell lines, 19 % of lung cancer, and 48 % of breast cancer, mutations were found that might have been induced by APOBEC deaminases. There was a strong positive correlation between the abundance of APOBEC signatures in breast cancer cell lines with overall base substitution mutation loads (Jarvis et al., 2018). Bladder cancer analysis by TCGA (The Cancer Genome Atlas) revealed the APOBEC mutational signature in 84 % of bladder cancer samples. The expression of both A3A and A3B in bladder cancer samples correlated with overall mutation load in bladder cancer (Glaser et al, 2018). Mutations in the DNA damage response genes (*TP53, ATR, BRCA2)* and chromatin regulatory genes (*ARID1A, MLL, MLL3)* were substantially enriched in the bladder cancer samples with the APOBEC signature (Glaser et al., 2018).

In 2012, another interesting hallmark of deaminase action was discovered by the international team of researchers of the Wellcome Trust Sanger Institute in the analysis of the genomes of breast cancer samples. Among multiple scattered mutations, clusters of closely spaced mutations were found. The phenomenon was named kataegis, from Greek "thunderstorm." The majority of mutations were CG → TA transitions; therefore it was suggested that APOBEC deaminases are connected to kataegis (Nik-Zainal et al., 2012). Almost at the same time, C- or G-coordinated mutation clusters (multiple changes of either "C" or "G" in continuous DNA strand) were detected in genomes of multiple myeloma, prostate, and head and neck cancer (Roberts et al., 2012) and were linked to APOBEC activity, because of frequently occurring mutations in TCW (W=A or T) motifs characteristic to several APOBEC deaminases (Roberts et al., 2012). Expression of model deaminase genes *PmCDA1* and *AID* in yeast resulted in kataegis, too, confirming a link between the activity of deaminases and kataegis (Lada et al., 2012; Lada et al., 2013). A3A and A3B mutation specificity in yeast was similar to mutations found in some breast cancers; kataegistic clusters depended on DSBs (Taylor et al., 2013). Kataegis is defined as the proximity of six or more mutations with an average intermutation distance less than one kb in the same DNA strand (Nik-Zainal and Morganella, 2017). Mechanistically, kataegis might be explained by the appearance of continuous single-stranded regions during transcription or repair of double-stranded DNA breaks or break-induced replication (Sakofsky et al., 2014). Kataegis is often observed in junction regions of chromosomal rearrangements in human tumor cells. Typically, the APOBEC signature consists of C → T transitions in the characteristic motifs and C → G transversions, which result from the operation of translesion polymerases on the damaged strand with an AP site (Taylor et al., 2013; Hoopes et al., 2017). The similarity in specificity and distribution of mutations induced by deaminases in model systems and found in tumors indicate that AID/APOBEC deaminases play a significant role in cancer origin and development.

The role of AID/APOBECs in the etiology of cancer

Discovery of deaminases led to a prediction that lack of control over deaminases in the cell might lead to genome-wide mutagenesis and cancer (Neuberger et al., 2003). The hypothesis quickly found experimental support from studies with model systems discussed above and evidence from analysis of human cancers; this led to the tremendous expansion of a number of publications on the roles of various deaminases in carcinogenesis (Rogozin et al., 2018).

Hepatic dysplasia and hepatocellular carcinoma were observed in transgenic mice and rabbits with constitutive expression of **APOBEC1** (Yamanaka et al., 1995). With the constitutive expression of **APOBEC2** in transgenic

mice, liver and lung cancer developed, and changes in the RNA nucleotide sequence of some oncogenes were also found (Okuyama et al., 2011). Transgenic mice with constitutive expression of **AID** developed malignant T-cell lymphomas, and micro-adenomas/adenocarcinomas in the lung, hepatocellular carcinomas, gastric cancer; in parallel, point mutations in T-cell receptors, *MYC, KRAS, TP53* genes were frequently observed (Okazaki et al., 2003; Morisawa et al., 2008). Aberrant activity of AID can trigger double-stranded DNA breaks not only in immunoglobulin genes but in other susceptible genomic regions, which leads to chromosomal translocations between immunoglobulin genes and other genes. During such events, proto-oncogenes translocate to cis-regulatory transcriptional elements and strong immunoglobulin enhancers that cause unregulated constitutive expression of the translocated gene (Ramiro et al., 2004; Robbiani et al., 2009; Nussenzweig and Nussenzweig, 2010). Such rearrangements are the hallmark of lymphomas (Okazaki et al., 2007). AID is implicated in the hypermutagenesis of oncogenes controlling proliferation and apoptosis—*MYC, PIM1, JUND,* and *BCL2*—and B cell development and activation genes—*PAX5, CD79b, AICDA, IRF8, BACH2,* and *NFKB*—as well as promoters and super-enhancers regulating the cell cycle and apoptosis (Gaidano et al., 1997; Qian et al., 2014). Studies have shown that there are over a hundred of such genes (Casellas et al., 2016). Normally, AID activity is restricted to the activated B-lymphocytes and some tissues, but in most lymphomas, the expression of this deaminase is constant (Okazaki et al., 2007).

Analysis of the expression level of various deaminases in breast cancer has revealed that 38–70 % of tissue samples and cell lines have an increase in the expression of APOBEC3B, but not other deaminases of this family. These cell lines have twice as many mutations as those that express low levels of A3B expression and an increase of C → T transitions. Knockdown of A3B caused a decrease in the total number of transitions (Burns et al., 2013). Therefore, it was concluded that A3B is the leading source of mutations in breast cancer. Further studies of 19 types of cancer according to The Cancer Genome Atlas (TCGA) revealed an elevated A3B level in head and neck, bladder, cervix, and lung cancers, also with C → T predominance in the context of 5'-TC-3', which is characteristic of APOBEC3 deaminases (Burns et al., 2013). In some types of cancer, these mutations reached 68 % of all mutations (Roberts et al., 2013). In the case of estrogen-positive breast cancer, expression of A3B is associated with poor prognosis during treatment. A3B regulates the estrogen receptor, enhances tumor growth and confers resistance to treatment with tamoxifen (Periyasamy et al., 2015; Law et al., 2016).

Some experimental evidence, however, argues against the overwhelming dominance of A3B in cancer etiology. It turned out the human genome has the common deletion polymorphism on chromosome 22 in the APOBEC3 subfamily gene locus (Kidd et al., 2007). Carriers of the deletion allele lack a 29.5 kb fragment between the fifth exon of A3A and the eighth exon of A3B, and cells produce a transcript containing the 3'-untranslated region (3'-UTR) from A3B and the coding part identical to the A3A gene. The main difference between the 3'-UTR of the two genes is that the A3A 3'-UTR contains Alu-repeat (Kidd et al., 2007). The deletion is rare in Europe (9 %) and Africa (0.9 %), more common in Asia (36.9 %) and America (57.7 %), and almost ubiquitous in Oceania (92.9 %) (Kidd et al., 2007). Contrary to the expectations, breast cancer rates are comparable in all these regions. Also, the polymorphism is more common in European and Chinese women with breast cancer, than in healthy ones (Xuan et al., 2013). The total number of mutations in the genomes of breast cancer cells is increased in cells with deletion polymorphism (Nik-Zainal et al., 2014). The A3A-UTR_{A3B} chimeric transcript expressed in HEK293T cells increases both the chimeric A3A mRNA level yielding 10–20-fold and the deaminase activity A3A in comparison to A3A-UTR_{A3A}. Therefore, it was concluded that the expression level of A3A is regulated by the 3'-UTR region. The chimeric protein also caused more damage and double-stranded breaks than the naturally occurring A3A, which explained the association of deletion polymorphism with a large number of mutations in cancer cells (Caval et al., 2014). It became apparent that A3B is not the only factor in mutagenesis conferred by deaminases in cancer.

APOBEC3A can be more cytotoxic and genotoxic than APOBEC3B (Caval et al., 2015). In yeast cells, it was possible to establish a difference in the preferred deamination motifs, YTCA for A3A and RTCA for A3B (Y = pyrimidine, R = purine), and thereby determine what proportion of tumors possess A3A versus A3B signatures (Chan and Gordenin, 2015). It is uniformly agreed that A3A overexpression can cause double-stranded DNA breaks and apoptosis, but there is controversy in the case of A3B (Landry et al., 2011; Burns et al., 2013; Taylor et al., 2013; Caval et al., 2014). The study of the relative roles of A3A and A3B in cancer needs further thorough investigation.

Factors affecting the activity of AID/APOBEC deaminases

The normal expression of AID/APOBECs is tissue-specific in humans (Conticello, 2008; Salter et al., 2016). We know that the heterologous expression of deaminase genes in bacterial and yeast cells leads to an increase in the frequency of mutations (Harris et al., 2002; Lada et al., 2011a). High levels of deaminases are potentially harmful, though the correlation between deaminase lev-

els and actual deamination is complicated (Siriwardena et al., 2018) and the activity of deaminases in human cells is under tight control. When the deaminase activity regulation is compromised, the enzymes deaminate cytosine in nonspecific loci of the genome, which leads to an increase in the frequency of mutagenesis and malignant transformation of tissues (Yoshikawa et al., 2002; Ramiro et al., 2004; Robbiani et al., 2009; Roberts et al., 2013). The search for factors affecting deaminase activity might help identify new risk factors and methods for the prevention and treatment of cancer.

Both bacterial lipopolysaccharides and human papillomavirus-like particles induce AID expression in murine B cells (Okazaki et al., 2007). Epstein-Barr virus and hepatitis C virus induce AID expression in B-lineage cells (Okazaki et al., 2007). Chronic inflammation on the background of cancer or virus infection leads to the release of cytokines TGFβ, TNFα, IL-4, IL-13, which initiate the expression of *AID* and cause the subsequent mutation of the tumor suppressor *TP53* and other genes and solid tumor development (Kumar et al., 2014; Choudhary et al., 2017). Studies show that in chronic inflammation and hypoxia, the risk of developing cancer is increased due to an elevated level of A3A and the subsequent enhancement of RNA editing by this protein, since the expression of A3A and A3B is stimulated by interferons (Bonvin et al., 2006; Sharma et al., 2017). Increasing the amount of these proteins is one of the stages in the development of the immune response to infection with viruses. Infection of breast and bladder cancer cell lines with Sendai virus led to a strong induction of A3A, but more moderate induction of A3B, possibly because of the initially high expression of A3B deaminase in cancer cells (Middlebrooks et al., 2016).

Cancer cells multiply faster than normal with fervent replication. Therefore, the number of mutations in tumors increases with time (Hanahan and Weinberg, 2011). Permanent divisions deplete protein complexes that ensure the stable progression of the replication fork. Many oncogenes induce replication stress, defined as the impediment of replication, which also contributes to the accumulation of mutations. The number of sites with unprotected ssDNA increases, creating favorable conditions for APOBEC mutagenesis (Cescon and Haibe-Kains, 2016; Hoopes et al., 2016). Anti-cancer drugs camptothecin, gemcitabine, hydroxyurea, and the DNA polymerase inhibitor α-aphidicolin also induce replication stress. The stress increases the activity of deaminases A3A and A3B (Kanu et al., 2016).

It has been suggested that the regulation of the expression of A3A and A3B may also occur at the post-transcriptional level using miRNA. The 3'-UTR A3A is 674 bp long. Hundreds of potential microRNA binding sites were found in the 3'-UTR of A3A. In the 3'-UTR of A3B with a length of 356 bp 82 potential microRNA binding sites were predicted. It is possible that the repression of A3A by miRNA will be tighter than A3B or chimeric A3A-UTR$_{A3B}$ (Cao and Wu, 2017). Also, four kinds of miRNA bind to target sites in the AID 3'-UTR and reduce the amount of the protein (Zan and Casali, 2013). Modulation of APOBEC gene expression by miRNA might be a perspective method of modulation of deaminase activity in cancer.

There is no doubt that deaminases of the AID/APOBEC family contribute significantly to tumor origins and progression. We expect that many puzzles and mysteries related to cancer/deaminases connection that surfaced during the first two decades of research in the field will be subject to intense future studies.

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