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# APOBEC-Induced Mutagenesis in Cancer

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## Keywords

APOBEC, cytidine deaminase, cytidine deamination, mutation, mutation signature, cancer

## Abstract

The initiation, progression, and relapse of cancers often result from mutations occurring within somatic cells. Consequently, processes that elevate mutation rates accelerate carcinogenesis and hinder the development of long-lasting therapeutics. Recent sequencing of human cancer genomes has identified patterns of mutations, termed mutation signatures, many of which correspond to specific environmentally induced and endogenous mutation processes. Some of the most frequently observed mutation signatures are caused by dysregulated activity of APOBECs, which deaminate cytidines in single-stranded DNA at specific sequence motifs causing C-to-T and C-to-G substitutions. In humans, APOBEC-generated genetic heterogeneity in tumor cells contributes to carcinogenesis, metastasis, and resistance to therapeutics. Here, we review the current understanding of APOBECs' role in cancer mutagenesis and impact on disease and the biological processes that influence APOBEC mutagenic capacity.

## INTRODUCTION

Apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like (APOBEC) cytidine deaminases are a family of proteins with various normal physiological roles in adaptive immunity, innate immunity, and cholesterol production. Additionally, APOBEC dysregulation has been implicated in promoting tumorigenesis. Off-target deamination by activation-induced cytidine deaminase (AID) causes oncogenic translocations that promote B cell tumors (133). Furthermore, sequencing of human cancer genomes revealed frequent overrepresentation of C-to-T and C-to-G substitutions occurring at TC dinucleotides. These two mutation types have been ascribed to the deamination of genomic DNA by TC-specific APOBEC cytidine deaminases, are found in ~15% of all sequenced tumors, and together represent the second most abundant type of mutation in human cancer. Due to the widespread occurrence of APOBEC-induced mutations, recent efforts have focused upon understanding the molecular underpinnings of these mutations, factors that modulate their abundance, whether they can serve as prognostic markers of cancer outcomes, and if APOBECs are viable therapeutic targets.

## THE APOBEC FAMILY

The APOBEC gene family is evolutionarily conserved, with *APOBEC2* and *AID* in bony fish and *APOBEC1* and the APOBEC3 gene family evolving in mammals from gene duplication events of *AID* and subsequent divergence (40). Mice and rats have a single *APOBEC3* gene, while cats, dogs, pigs, cattle, horses, and primates have 4, 3, 2, 3, 6, and 7 *APOBEC3* genes (86, 156), respectively. Overall, humans have 11 APOBEC cytidine deaminases encoded by the following genes: *AID*, *APOBEC1*, *APOBEC2*, *APOBEC3A*, *APOBEC3B*, *APOBEC3C*, *APOBEC3D*, *APOBEC3F*, *APOBEC3G*, *APOBEC3H*, and *APOBEC4* (**Figure 1**). These APOBEC gene subfamilies have many distinct, normal physiological functions. AID, the evolutionarily founding family member, deaminates cytidines in immunoglobulin loci within lymphoid cells to induce antibody isotype switching during class switch recombination (CSR) and increases antibody–antigen affinity by somatic hypermutation (SHM). APOBEC1 is primarily known as the RNA editor responsible for a C-to-U change at nucleotide 6666 in human apolipoprotein B mRNA, which creates a stop codon and a smaller intestine-specific apoB48 protein that facilitates lipid transport to the liver, as opposed to the apoB100 protein translated from the nonedited transcript that functions in cholesterol transport (43). Additionally, APOBEC1 can function in restricting viral replication in some species (71, 132). However, in vitro APOBEC1 viral restriction does not always translate to reduced viral loads or infection (8), indicating that APOBEC1 may have limited viral restriction activity. The cellular functions of APOBEC2 and APOBEC4 are less well understood. Both APOBEC2 and APOBEC4 have cell type–specific expression, with APOBEC2 being highly expressed in cardiac and skeletal muscle (55), while APOBEC4 maintains nearly testes-specific expression (137). APOBEC2 influences the proliferation and differentiation of muscle cells, possibly through promoting cytidine demethylation (25, 119). Additionally, APOBEC2 deficiency in mice results in increased mitophagy and muscle cell damage (146). However, the mechanisms responsible for the physiological roles of APOBEC2 or APOBEC4 are unclear because cytidine deamination activity has not been reported for either. The APOBEC3 subfamily is best known for roles in viral restriction (130) and was initially described as inhibitors of retroviruses due to the ability of several APOBEC3s to inhibit HIV replication (69). Expression of APOBEC3 family members is upregulated in response to both RNA and DNA viruses and transposons via the innate immune response. APOBEC3s can act nonenzymatically and/or as deaminases to target and inhibit replication of viruses and deleterious genetic elements (130). In addition to APOBEC3

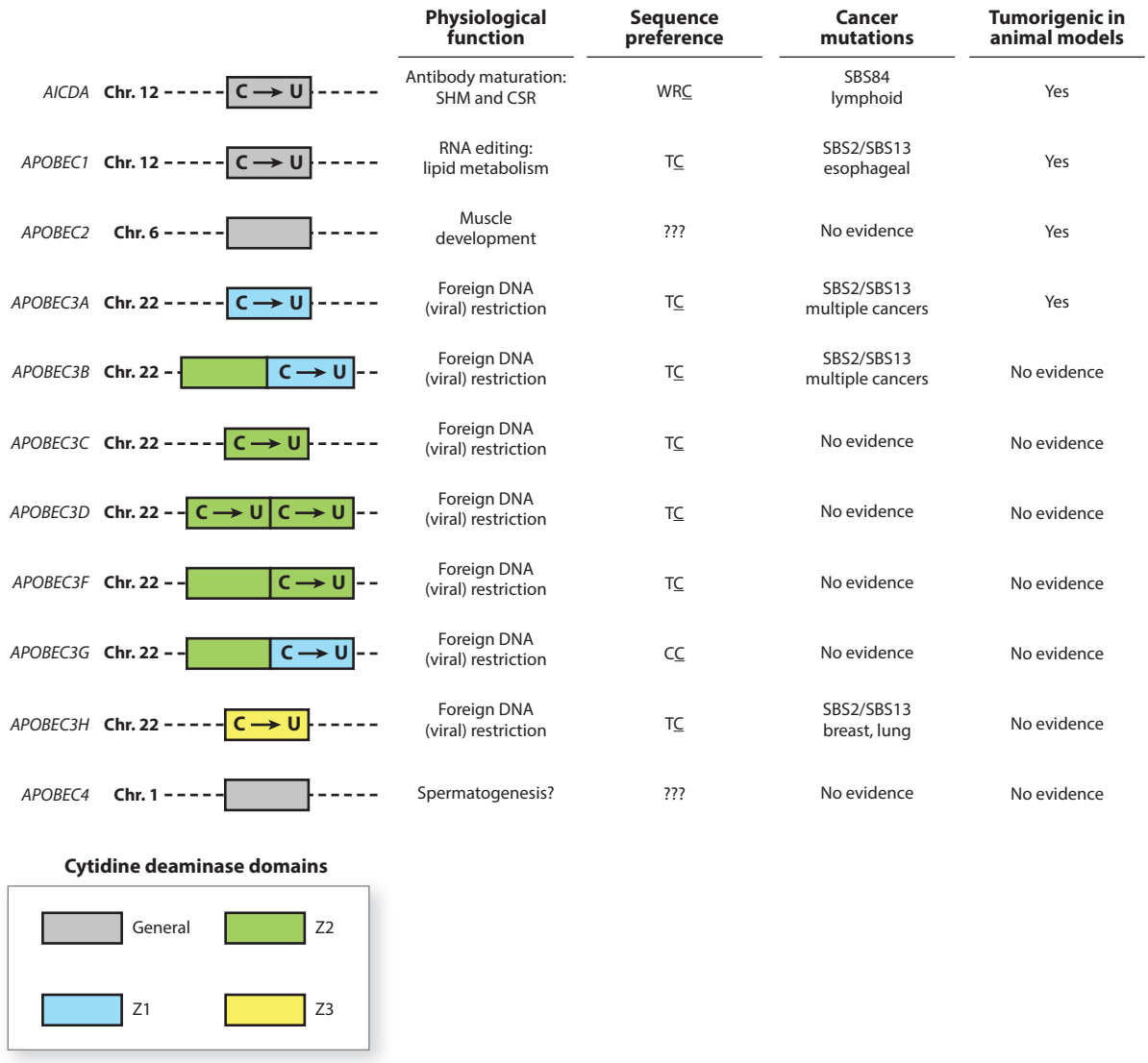


**Figure 1**

Human APOBEC genes. The CDDs of the 11 human APOBEC genes are represented as arrows and color coded by the classification for consensus sequences. Active CDDs are indicated by C → U. Known physiological functions, deamination sequence preferences, contributions to cancer mutagenesis, and ability to induce tumor formation in rodent model systems are indicated. Abbreviations: APOBEC, apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like; CDD, cytidine deaminase domain; CSR, class switch recombination; SBS, single base substitution; SHM, somatic hypermutation. Information from Reference 144.

family members playing important roles in innate immunity, their dysregulation is a major source of deleterious human genome mutations during cancer development.

## ENZYMATIC ACTIVITY

APOBEC proteins consist of either one or two cytidine deaminase domains containing the consensus amino acid motif His-X-Glu-$X_{23–28}$-Pro-Cys-$X_{2–4}$-Cys, which coordinates a required zinc

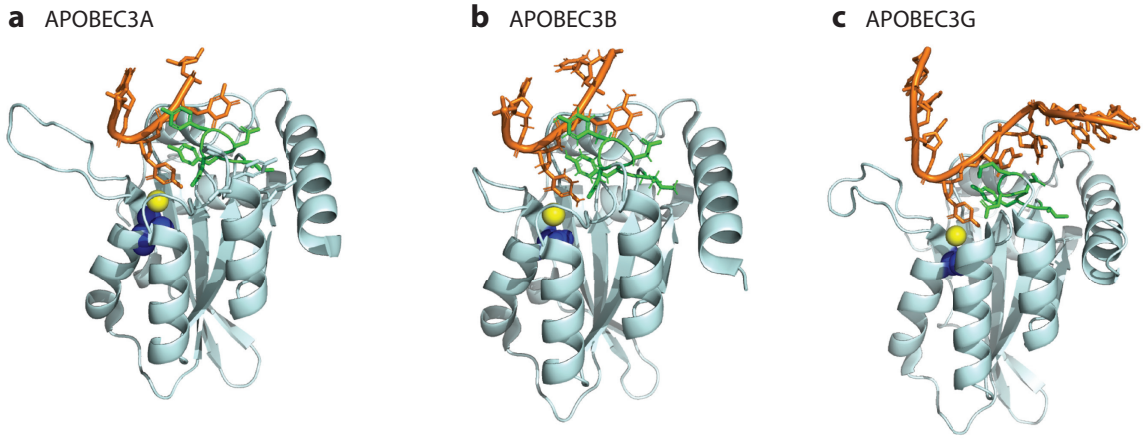


**Figure 2**

APOBECs bound to ssDNA. The structures of (*a*) APOBEC3A (PDB ID 5KEG), (*b*) APOBEC3B (PDB ID 5TD5), and (*c*) APOBEC3G (PDB ID 6BUX) (*pale cyan*) are bound to ssDNA (*orange*). The positions of catalytic glutamates are depicted as dark blue spheres. Amino acids in loop 7 responsible for sequence specificity of APOBECs are represented as green sticks. Coordinated $Zn^{2+}$ is present in yellow. Images are rendered in PyMol. Abbreviations: APOBEC, apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like; PDB ID, Protein Data Bank identification; ssDNA, single-stranded DNA.

molecule and contains the glutamate residue necessary for catalysis (13). All but two human APOBECs (APOBEC2 and APOBEC4) have been reported to convert cytidine to deoxyuridine (dU) in polynucleic acids. However, the N-terminal domains of double deaminase domain APOBECs [i.e., APOBEC3B (A3B), APOBEC3F (A3F), and APOBEC3G (A3G)] are inactive (see references in 19 and 45). Catalytic activity requires that target cytidines be in single-stranded DNA (ssDNA) (18, 24, 48) or RNA and deamination occurs in a sequence-specific manner dictated by specific amino acid residues in loop 7 of the cytidine deaminase domain (78) (**Figure 2**). Most APOBECs favor deaminating cytidines within TC dinucleotides, with CC dinucleotides being deaminated less efficiently (144). However, A3G favors CC dinucleotides, and AID targets WRC sequences (with W corresponding to A or T nucleotides) (78) (**Figure 1**). Additional amino acid residues contact the −2 nucleotide from the target cytidine, increasing the sequence context specificity of some APOBECs (152). APOBEC3A (A3A) favors YTC, while A3B prefers RTC trinucleotide sequences, where R and Y refer to purine and pyrimidine nucleotides, respectively (29). Modifications to the target cytidine (i.e., 5-methylcytosine) (73, 113) or neighboring bases (47) can also impact the efficiency of APOBEC-catalyzed deamination. APOBECs can deaminate cytidines within very small regions of ssDNA. For example, A3A can bind dinucleotides in vitro (108) and deaminate ssDNA gaps as small as four nucleotides long (20). However, when the opposite DNA strand is present within a bubble-like structure, A3A activity is reduced for ssDNA regions smaller than seven nucleotides in length (127). The ability to deaminate small ssDNA substrates presumably allows most APOBECs to deaminate cellular ssDNAs created during DNA replication, transcription, or DNA repair processes. On longer ssDNA substrates in vitro, AID and other APOBECs act processively (31, 126), deaminating multiple cytidines in a local area instead of randomly associating with independent targets. However, the processivity of APOBEC enzymes is likely reduced by ssDNA-binding proteins like replication protein A (RPA) (83) in vivo, making it unclear if processive activity contributes to the formation of APOBEC-induced mutation clusters in cancer genomes.

## APOBEC-INDUCED MUTATION SIGNATURES

A role for APOBECs in causing mutations during carcinogenesis has long been suspected. The initial determination that APOBECs were DNA-editing enzymes that were found to have broad mRNA expression in various tissues combined with the discovery of AID activity in lymphoid tumors indicated that these enzymes may contribute to cancer mutagenesis (63). Subsequent analysis comparing the sequence specificity of AID, APOBEC1, and A3G to mutations in the tumor suppressor gene *APC* identified an enrichment of C mutations in TC dinucleotides, suggesting that TC-specific APOBECs could contribute to colorectal cancer mutagenesis (11). Although it was not attributed to APOBEC activity at the time, targeted sequencing of greater than 500 protein kinase genes among 25 breast cancer tumors showed a similar overrepresentation of mutations in TC dinucleotides (160). Subsequent whole-genome sequencing of 21 breast cancer tumors found frequent C-to-T and C-to-G substitutions in TC dinucleotides (114). A subset of these mutations occurred in discrete groupings within localized regions of the genome and were strand-coordinated with consecutive mutations in C bases on the top or bottom strand, which indicates they were simultaneously induced. Moreover, this phenomenon, termed kataegis, often includes switching of the strand-coordinated mutations at sites of chromosomal rearrangements, suggesting that cytidines within ssDNA intermediates generated by rearrangement-generating repair events were mutated. APOBECs were proposed as the cause of kataegis events due to their similar sequence preference and ssDNA specificity. Experimental evidence for ssDNA-specific base-damaging agents causing similar patterns of mutation clusters was provided in yeast model systems and putative APOBEC-induced kataegis events were identified in multiple myeloma, prostate, and head and neck cancers, indicating that these events occur in many cancer types (135). Multiple large-scale analyses of tumor exomes, sequenced primarily by The Cancer Genome Atlas (TCGA), found overrepresentation of TCW to TTW and TCW to TGW substitutions in many cancer genomes (3, 23, 134). These two mutation patterns, commonly referred to as APOBEC signature mutations, are classified by the Catalogue of Somatic Mutations in Cancer (COSMIC) as single base substitution signature 2 (SBS2) and SBS13 and are officially attributed to off-target APOBEC-induced cytidine deamination (2) (**Figure 3**).

Although SBS2/SBS13 mutation signatures are found in most cancer types (2) (**Figure 1**), these APOBEC signature mutations are concentrated in six specific cancer types: lung squamous cell carcinoma and adenocarcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, and bladder urothelial carcinoma (3, 23, 134). Overall, SBS2/SBS13 together are the second most common type of base substitution mutation observed in human tumors (2). Additional APOBEC-associated mutation signatures, beyond those caused by the prominent TC-specific APOBECs, also expand the extent of the APOBEC family's contribution to cancer mutagenesis. SBS84 is composed of C-to-G and C-to-T substitutions in WRC sequence contexts and occurs primarily in somatic hypermutation loci in lymphoid tumors; therefore, it is caused by AID (40). Currently, no signatures have been attributed to the deamination of genomic cytidine in CC dinucleotides that would be consistent with aberrant A3G activity.

## APOBECS CONTRIBUTING TO SBS2 AND SBS13

The identity of the specific APOBEC enzymes that cause SBS2/SBS13 mutations has been the focus of intense research. Initial work has focused on TC-specific APOBECs that can access the nucleus, which would allow for deamination of genomic DNA. As the only APOBEC solely found in the nucleus (16), A3B was the first linked to APOBEC-induced mutations (22). Overexpression of the C-terminal catalytic domain of A3B in human cell lines induces γH2AX and micronuclei

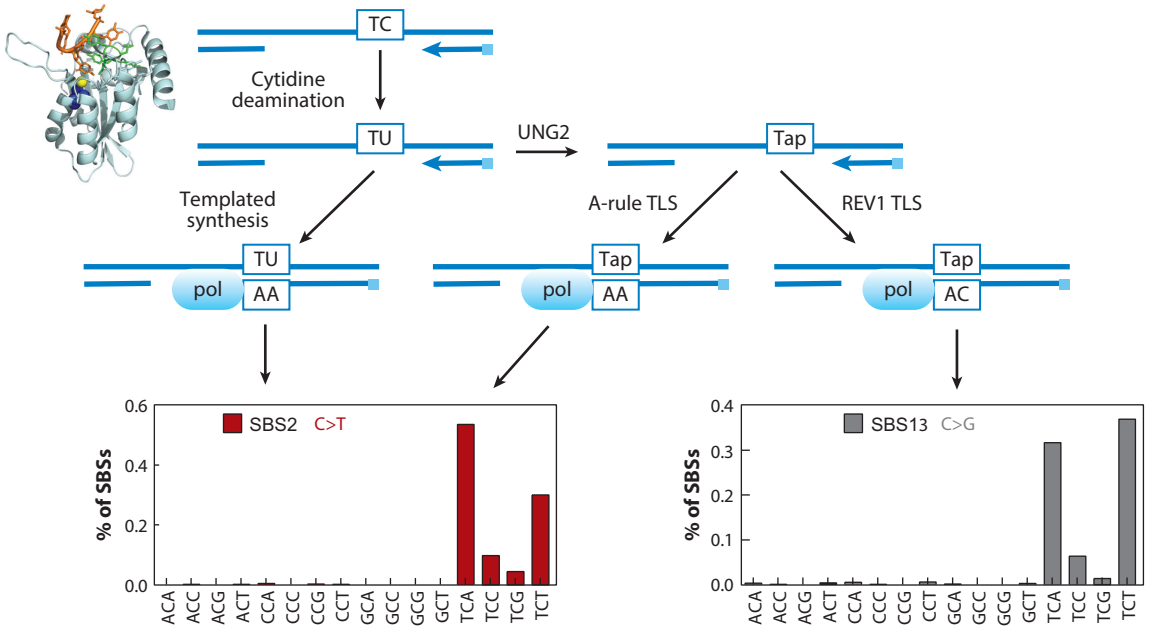


**Figure 3**

Establishment of SBS2 and SBS13 signatures. TC-specific APOBECs deaminate dC-to-dU in ssDNA. DNA synthesis using the dU as a template (*left*) results in C-to-T substitutions, which produce the SBS2 mutation signature. Alternatively, conversion of the dU to an abasic [i.e., an apurinic/apyrimidinic (AP)] site by the uracil glycosylase UNG2 stalls replicative polymerases, requiring a bypass of the abasic site by TLS. A-rule TLS (*middle*), where a polymerase inserts dA across the abasic site prior to polζ -mediated extension, also produces C-to-T substitutions, which also contributes to the SBS2 mutation signature. REV1-mediated TLS involves the insertion of a C across from the abasic site by the deoxycytidyl transferase REV1 prior to polζ -mediated extension (*right*), which produces the C-to-G substitutions that comprise signature SBS13. Abbreviations: APOBEC, apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like; polζ, polymerase ζ; SBS, single base substitution; ssDNA, single-stranded DNA; TLS, translesion synthesis. Graphs of SBS2 and SBS13 are adapted from Reference 2 (CC BY 4.0).

formation, indicators of DNA damage, which demonstrates that A3B can damage genomic DNA (22). Additionally, A3B mRNA transcript levels correlate with the SBS2/SBS13 mutation burden in human tumors (22, 23, 41, 134), and reduction of A3B expression by short hairpin RNA (shRNA) decreased genomic dU and mutation loads in several breast cancer cell lines (22). Despite these findings supporting a causative role for A3B in cancer mutagenesis, a human deletion polymorphism that results in loss of the *APOBEC3B* gene increases the risk of developing lung and breast cancers (95, 106, 170, 172). Moreover, breast cancers from carriers of this allele have greater amounts of APOBEC signature mutations (116), indicating that at least one other TC-specific APOBEC contributes to SBS2/SBS13 mutations.

APOBEC3H (A3H) haplotype I has been proposed to be another contributor to APOBEC-induced cancer mutagenesis. While most haplotypes of A3H are cytoplasmic, the substitutions in haplotype I impart a nuclear localization to the enzyme (92), allowing it to potentially deaminate cytidines in nuclear DNA. These mutations also reportedly limit the stability of the A3H protein (118), suggesting that the A3H haplotype I may not maintain sufficient activity to damage a nuclear genome. However, editing of viral DNA was detected in cells overexpressing A3H haplotype I (157), and markers of DNA damage in lung cancer cells expressing haplotype I have been observed (65), indicating that A3H may have sufficient activity to cause APOBEC signature mutations. Sequencing of breast cancers carrying deletions of both *APOBEC3B* alleles indicated that

APOBEC signature mutations were absent from tumors that do not have A3H haplotype I alleles (157). However, the number of tumors in this analysis may not have been sufficient to unequivocally assign the lack of the signature to the absence of a haplotype I allele. Other polymorphisms within *A3H* indicate that the protein may affect tumorigenesis. In particular, the T polymorphism of rs139293 has been associated with a higher risk of lung cancer in Chinese populations (180).

Although A3A has pancellular localization (16) but is more abundant in the cytoplasm than the nucleus (84), and A3A mRNA and protein levels are often much lower within tumor cells compared to those of other APOBECs (41, 123, 131), significant evidence indicates that A3A is the primary source of APOBEC-induced mutations in multiple tumor types. Overexpression of A3A increases γH2AX foci (85, 112), indicating that it can damage nuclear DNA. A3A mRNA levels are stabilized by the *APOBEC3A-APOBEC3B* hybrid allele (26) that occurs in the individuals carrying the germline *APOBEC3B* deletion polymorphism and is associated with increased cancer risk and APOBEC signature mutations in tumors from carriers, suggesting that elevated A3A abundance is responsible for these phenotypes. Analysis of sequence contexts for A3A- and A3B-induced mutations in yeast indicated that A3A prefers the sequences YTCA, while A3B prefers RTCA (29). Assessment of the −2-dinucleotide preference in tumors containing SBS2/SBS13 mutations indicated that YTCA was enriched over RTCA, suggesting that A3A substantially mutates many cancer genomes, while A3B-mediated mutation occurs at lower levels. Furthermore, A3A is most often the dominant source of cytidine deaminase activity in APOBEC-mutated breast cancer cell lines, including those with higher A3B expression, which is likely due to A3A's higher enzymatic activity and resistance to RNA inhibition (41). A3A mRNA abundance and cytidine deaminase activity correlate strongly with the amount of APOBEC signature mutations within a panel of breast cancer cell lines. Additionally, in multiple cancer types, A3A mRNA levels correlate more strongly with the number of SBS2/SBS13 mutations than A3B mRNA levels do. A3A's proclivity to deaminate hairpin structures and edit RNA has provided additional evidence for its role in mutating cancer genomes, as SBS2/SBS13 mutations often occur at hairpin-forming sites (21) and tumors with these mutations often bear evidence of active A3A RNA editing (74). Recent CRISPR-Cas9-mediated disruption of the *APOBEC3A* gene in several APOBEC-mutated breast cancer and lymphoid cell lines resulted in the loss of SBS2/SBS13 (125). However, the signature largely remained in *APOBEC3B*-deleted lines, indicating that A3A is the major source of APOBEC signature mutations in these cancer types.

In other cancer types, APOBECs outside of the APOBEC3 subfamily may contribute to cancer mutagenesis. In particular, APOBEC1 has been implicated in causing SBS2/SBS13 in esophageal cancer (145). Both human and rat APOBEC1 are capable of mutating bacterial DNA, the chicken DT40 cell line, and human cell lines, which result in SBS2/SBS13 mutations. Physiologically, human APOBEC1 expression is highly elevated in Barrett's esophagus, which is a precursor to esophageal adenocarcinoma that frequently contains APOBEC signature mutations, suggesting that APOBEC1 causes these mutations. However, a causative role for APOBEC1 has not been demonstrated, and A3A- or A3B-induced mutagenesis could not be excluded.

## SUBSTRATES FOR APOBEC-INDUCED MUTATION IN NUCLEAR GENOMES

APOBEC deamination of cytidine is highly favored within regions of ssDNA and is nearly undetectable on double-stranded DNA (dsDNA) (18, 24, 175). Regions of ssDNA occur transiently in cells during transcription, DNA replication, and repair processes. Mutations in tumor genomes resulting from the activity of AID and APOBEC3 family members tend to be enriched within regions corresponding to different sources of ssDNA (**Figure 4**). AID primarily targets transcription intermediates formed in immunoglobulin loci. Studies of AID on-target ssDNA

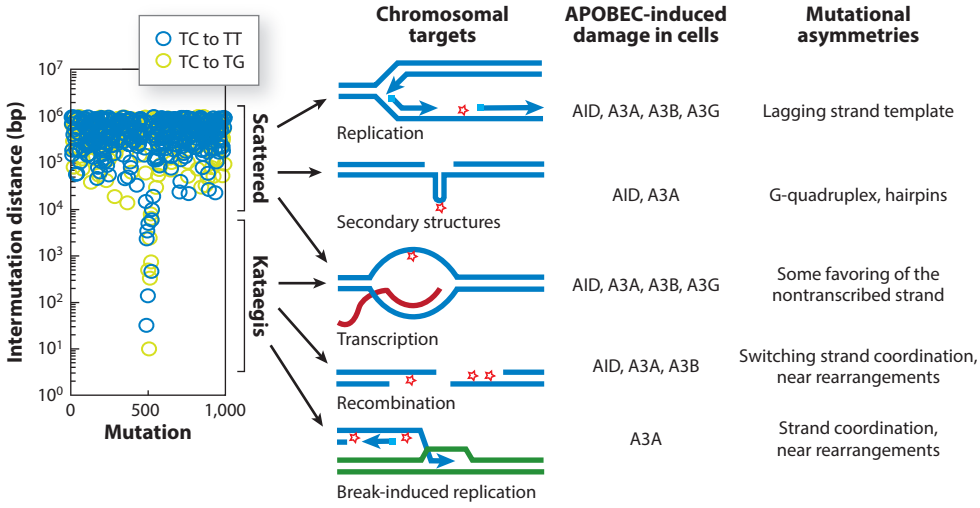


**Figure 4**

Substrates for APOBEC-induced mutations. APOBEC-induced mutations can occur scattered across genomes or in localized clusters called kataegis. Scattered mutations are associated with the deamination (*red stars*) of ssDNA formed during replication, at secondary structures, and during transcription. Kataegis is usually formed through the deamination of intermediates of the homology-directed repair of DSBs or break-induced replication. In the case of SHM, mutation clusters are associated with transcription. Multiple APOBECs induce mutation and DNA damage at these structures in cells, producing characteristic mutational asymmetries. Abbreviations: AID, activation-induced cytidine deaminase; APOBEC, apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like; A3A, APOBEC3A; A3B, APOBEC3B; A3G, APOBEC3G; bp, base pair; DSB, double-strand break; SHM, somatic hypermutation; ssDNA, single-stranded DNA. Images of chromosomal targets adapted with permission from References 66 (CC BY-NC-ND 4.0) and 67. The rainfall plot depicting kataegis and scattered mutations is adapted from Reference 114 (CC BY 3.0).

regions have identified roles for the formation of R-loops (174) and G-quadruplexes (128) as enhancers of AID activity during transcription.

By contrast, A3A- and A3B-induced mutations primarily correspond to the lagging strand template during DNA replication in model systems (66) and in sequenced tumors (62, 110, 148), although correlation of APOBEC signature mutations with higher transcription levels and modest bias for nontranscribed strands of genes suggest that transcription serves as a substrate to a lesser extent (34, 62, 110). Unlike AID, less evidence exists for mechanisms that target APOBEC3 members to chromosomal regions, and RPA binding to ssDNA inhibits APOBEC3 deamination activity rather than promotes it (20, 83). However, recent crystallographic data indicate that A3A (82, 152) bends ssDNA into a U-conformation, which results in the preferential deamination and mutation of small hairpin-forming sequences in vitro and in tumors, respectively (21, 41). Despite the presence of similar structural folds (**Figure 2**), other APOBECs (specifically A3B and A3H) lack the deamination preference for hairpins (21), suggesting that specific amino acid side chains (i.e., H29 in A3A) mediate this specificity. The conversion of inverted repeat sequences into ssDNA likely controls the formation of hairpin secondary structures, although the presence of ssDNA-binding proteins such as RPA may enhance APOBEC specificity for particular structures by binding favorably to longer ssDNA regions and blocking APOBEC activity (20). Overall, the availability of ssDNA during DNA replication is likely a major determinant of APOBEC-induced genomic mutations in tumors. In some cellular contexts, DNA damage and replication stress caused by loss of the tumor suppressor *FHIT* may increase APOBEC-generated

mutations (169). Although it has not been studied, oncogene-induced replication stress–elevated ssDNA and exhaustion of RPA (reviewed in 56) may also facilitate APOBEC-induced mutation in tumors.

Despite DNA replication being the predominant ssDNA source for APOBEC3-induced mutagenesis, APOBEC mutations are also enriched within regions coding for transfer RNAs (tRNAs) (141, 142) and at sites of DNA repair (32, 151). APOBEC3-induced mutations commonly occur as kataegis within sequenced tumors (114, 135) and model systems (51, 143, 163), within long stretches of ssDNA formed by either end resection during DNA double-strand break (DSB) repair or D-loop synthesis during break-induced replication. In addition, both normal and aberrant DNA repair pathways likely contribute to the generation of ssDNA that APOBECs can mutate. For example, elevated expression of NEIL2 can increase ssDNA during base excision repair (BER), possibly contributing to APOBEC mutagenesis in some tumors (151), and mismatch repair activity on BER substrates increases APOBEC mutagenesis, as measured using a shuttle mutation reporter in human cells (32).

## REPAIR AND TOLERANCE OF APOBEC-INDUCED DNA DAMAGE

There are multiple outcomes of APOBEC-induced deamination of cytidine bases to dU that are likely heavily modulated by multiple repair activities. When APOBEC-induced dU sites, which are indistinguishable from deoxythymidines to DNA polymerases, are not removed and serve as a template during DNA replication, it results in the insertion of deoxyadenine (dA) opposite dU (**Figure 3**). During the next round of DNA replication, the opposite dA-containing strand serves as a template, resulting in a C-to-T mutation. Removal of APOBEC-induced dUs by the uracil DNA glycosylase UNG2 in human cells creates abasic [i.e., apurinic/apyrimidinic (AP)] sites. When abasic sites are processed by glycosylase activity in the context of dsDNA, the lesion is repaired error free by completion of BER. By contrast, APOBEC/UNG2-dependent abasic sites that occur in the context of ssDNA at the replication fork are more problematic due to the lack of an opposite strand to provide the correct base, and cleavage at the abasic site by an AP endonuclease would result in a DSB. When not prevented by the activity of HMCES (109), abasic sites resulting from APOBEC activity on DNA replication–generated ssDNA can stall replicative DNA polymerases, which can increase ssDNA associated with replication and result in activation of the checkpoint protein ATR (75). The bypass of APOBEC-generated abasic sites in the context of the replication fork in human cells is poorly understood. Data from yeast model systems (67, 140, 141) and our current understanding of lesion bypass suggest that two pathways are likely employed. In yeast, recombination-dependent error-free lesion bypass reduces APOBEC-induced mutagenesis approximately five- to tenfold. Thus far, the contribution of error-free lesion bypass to the avoidance of APOBEC-induced mutagenesis has not been studied or shown experimentally in human cells. However, APOBEC mutation signature SBS13 is almost certainly driven by error-prone bypass of APOBEC-generated AP sites by translesion synthesis, which utilizes the deoxycytidyl transferase REV1 and DNA polymerase ζ (polζ) (28) (**Figure 3**). However, synthetic lethality between A3A overexpression and loss of HMCES, MAD2L2 (a subunit of human polζ) (14), or factors involved in homologous recombination (HR) indicate that similar lesion bypass pathways likely modulate APOBEC mutagenesis in human cells.

## APOBEC-INDUCED CARCINOGENESIS

Early studies into the functions of APOBECs indicated that when dysregulated, these enzymes contribute to carcinogenesis. Rat APOBEC1 expressed in mouse livers, with the goal of influencing cholesterol levels, surprisingly resulted in elevated hepatocellular carcinomas (173). Although

mRNA editing was observed in these tumors, the possible contribution of genome editing to carcinogenesis was not evaluated. Expression of AID in hepatocellular carcinoma (162) and multiple myeloma (35) mouse models also elevated tumor formation. In these cases, deleterious *Trp53* mutations and oncogenic *MYC* translocations due to aberrant AID DNA editing were established as causative mechanisms. Like APOBEC1, expression of APOBEC2 in mouse liver or lung resulted in tumorigenesis, with mRNA-edited *Eif4g2* and *PTEN* transcripts being the major molecular alterations observed (120). Efforts to evaluate the tumorigenic potential of human APOBEC3 subfamily members in mice have primarily supported a role for A3A as the primary cancer promoter. Expression of each human APOBEC3 in a TP53 knockdown liver cancer model found that only A3A elevated tumor frequency above background levels (88). Similarly, A3A expression in an $APC^{min}$ colorectal cancer mouse model increased tumor formation. In both models, A3A produced the characteristic APOBEC signature mutations, but evidence for APOBEC-generated driver mutations was not apparent (88). It remains unclear how A3A contributed to the formation of these tumors. Surprisingly, expression of A3A in mouse models of pancreatic ductal adenocarcinoma appears to drive tumorigenesis primarily by increasing chromosomal instability through an unknown mechanism independent of A3A cytidine deaminase activity (171), suggesting that noncatalytic cellular functions of various APOBECs may be important for carcinogenesis. Additional mammalian organisms (e.g., dog, horse, sheep, pig, rabbit, and elephant) also express catalytically active A3A orthologs that damage nuclear DNA when overexpressed (27, 87, 93). Whether A3A contributes to nuclear genome editing and cancer in these species remains unknown.

Despite producing many mutations across multiple human cancer types, the extent to which APOBEC-induced mutations drive carcinogenesis has been uncertain. In respect to aberrant AID activity, error-prone repair of AID-induced DSBs during CSR are known to lead to oncogenic translocations of *c-MYC* with the *IGH* locus in lymphoid cancers (35, 50, 129, 133). However, attempts to show that APOBECs produce driver mutations in several cancer types have been only marginally fruitful. Early analyses of sequenced tumors found no enrichment for APOBEC mutations in cancer driver genes (134), indicating that most APOBEC-induced mutations are not drivers of carcinogenesis. Similarly, many highly recurrent APOBEC-induced mutations occur in hairpin-forming sequences seemingly due to increased APOBEC cytidine deamination activity on these substrates (21), not selection. However, tumors with APOBEC-induced mutations also have higher instances of oncogenic *PIK3CA* mutations, which are more likely to occur at TCW sequence motifs in the p85 binding domain instead of at non-APOBEC target sequences in the kinase domain, strongly indicating that APOBECs induce these driver mutations (64). APOBEC-mutated tumors also have frequent mutations at TC dinucleotides, not within hairpin-forming sequences but in the known cancer-driver genes *TP53*, *NFE2L2*, *MUC16*, *ARID1A*, *KMT2C*, *ERBB2*, *KMT2D*, and *FGFR3* (~11.0%, 2.6%, 2.3%, 2.1%, 1.9%, 1.9%, 1.8%, and 1.6% among samples across tumor types, respectively) (21). Additional lower-frequency APOBEC mutation hotspots exist in known cancer genes, indicating the enzymes may also contribute to some cancer-specific drivers.

The lack of prevalent APOBEC-induced driver mutations among tumor samples may be partly due to the time during cancer progression at which APOBECs become dysregulated. In contrast to prostate cancers where A3B-induced mutations accumulate in a clock-like fashion beginning early in development (58), many SBS2/SBS13 mutations in lung (44) and breast (115) cancer display low allelic fraction within the primary tumors, which is consistent with the establishment of these signatures later during cancer development. Some of these subclonal mutations appear to be secondary driver mutations in lung cancers (104). Moreover, sequenced breast cancer metastases display a much higher prevalence of APOBEC signature mutations than primary tumors (5), indicating that APOBEC-induced mutation increases after cancer initiation but before metastasis, to

which the APOBECs may have contributed. In addition to creating additional driver mutations, late-onset APOBEC-induced mutagenesis could contribute to therapy resistance and/or tumor relapse by creating genetic heterogeneity within individual tumor cells. Supporting this hypothesis, xenograft mouse models featuring human estrogen receptor–positive breast cancer cells expressing an A3B-targeting shRNA are slower to regenerate tumor mass following tamoxifen treatment, while A3B-overexpressing cells have accelerated tumor regrowth (89). Similarly, treatment of human lung cancer cells with gefitinib and osimertinib chemotherapy increases both A3A expression and APOBEC signature mutations and enhances the establishment of drug-resistant clones in an A3A-dependent manner (72).

Regardless of the contribution of APOBEC-induced mutation to cancer progression and tumor relapse, the load of APOBEC signature mutations and expression of specific APOBECs in different contexts are predictive of disease prognosis. In estrogen receptor–positive (ER+) breast and ovarian cancers, higher A3B mRNA levels correlate with indicators of less favorable patient prognosis (49, 155). Correspondingly, higher levels of SBS13 predicted poor patient responses in human epidermal growth factor receptor 2-negative (HER2-), ER+ breast cancers (12), and increased SBS2/SBS13 levels are associated with poorer prognosis in multiple myeloma, possibly due to increased *MAF/MAFB* and *MYC* translocations (100, 167). This association of increased APOBEC expression or mutational signatures with poor prognosis appears to be cancer type specific. In non-small cell lung cancer (168), bladder cancer (59, 106), and clear cell ovarian cancer (149), A3B expression and/or APOBEC mutation signature abundance are predictive of better disease outcomes, which may be driven by therapies specific to these tumor types. In the case of clear cell ovarian cancer, elevated A3B activity results in increased sensitivity to platinum drugs (149), while enhanced prognosis in lung and bladder cancers may stem from increased responsiveness to immune blockage therapies (59, 168) as the higher mutation loads could elevate neoantigen production. Supporting this hypothesis, APOBEC-induced kataegis events have been found to correlate with programmed cell death ligands PD-L1 and PD-L2 expression across tumor types (17). Based upon the prognostic value of APOBEC expression and mutagenesis as well as the potential contribution of APOBECs to drug resistance and relapse, researchers are attempting to target them as cancer therapeutics. Whether specific APOBEC inhibitors can be developed and if APOBEC dysregulation is ubiquitous enough throughout a tumor to be a primary cancer therapeutic target are unknown.

## INFLUENCERS OF APOBEC-INDUCED MUTATION

### APOBEC Transcriptional Regulation

The association between elevated APOBEC mRNA abundance in tumors with APOBEC-induced mutation and genetic rearrangements in multiple cancer types indicates that transcriptional upregulation significantly contributes to APOBEC-induced mutation (23, 134). Mechanisms for transcriptional control of AID are best understood in the context of activated B cells, the immune cell type where AID is primarily, though not exclusively, expressed. The region just upstream of the transcription start site contains transcription factor–binding sites for signal transducer and activator of transcription 6 (STAT6), nuclear factor kappa B (NF-κB), homeobox C4 (HoxC4), and specificity factor proteins Sp1 and Sp3. Another region within the first intron has binding sites for B cell–specific transcription factors paired box 5 (Pax5) and E-box protein E47, which activate transcription by overcoming silencing from c-Myb, E2F, and various inhibitor of differentiation (Id) proteins. Two other regions have been shown to be critical to AID expression and are host to transcription factor–binding sites for STAT6, NF-κB, CCAAT-enhancer-binding protein (C/EBP), Smad3/Smad4, c-Myc, and basic leucine zipper transcription factor, ATF-like (BATF).

These transcription factors have been shown to regulate AID transcription upon stimulation with various activators and cytokines such as interleukin 4 (IL-4), cluster of differentiation 40 (CD40), and transforming growth factor β (TGF-β) (reviewed in 177). In nonlymphoid cells, AID can also become dysregulated, especially in the presence of prolonged inflammation, which lends itself to the theory of inflammation-associated carcinogenesis (36). Increased AID transcription has been observed in many cancer types. Pro-inflammatory cytokines, which play a critical role in inflammatory bowel disease, result in increased expression of AID in colorectal cancers (52). In gastric cells enduring chronic infection with *Helicobacter pylori*, AID transcription was upregulated in an NF-κB-dependent manner, leading to carcinogenesis (37, 99). The NF-κB pathway has also been implicated in activating AID transcription in liver (53) and bile duct (79) tumors. Also, TGF-β was shown to increase AID expression in cancer-prone hepatocytes under chronic inflammatory conditions (81).

Studying the transcriptional regulation of the *APOBEC3* genes has been more difficult, given that the seven genes are expressed at different levels in many tissues and cell types (80, 131). Within immune cells, the APOBEC3s are expressed at various levels, with A3A and A3G being prominent in cells of the myeloid lineage and $CD4^+$ T lymphocytes, respectively (131). A3A and A3G expression levels are highly dependent upon immune cell type as well as stimulation factors (42). The most characterized stimulators of APOBEC3 transcription are interferons (IFNs) in both immune and nonimmune cell types (reviewed in 42). Through IFNs, APOBEC3s can be activated via several external stimuli, such as foreign nucleic acids (e.g., plasmids) (4, 158), poly(I:C) (117, 164, 179), or IL-27 (61). Less is known about APOBEC3 transcriptional regulation in the context of cancer (**Figure 5**). Many studies of the transcriptional regulation of APOBECs in tumors have focused on A3B due to early evidence supporting its role in mutagenesis. Phorbol 12-myristate was shown to regulate A3B transcription via a noncanonical NF-κB pathway involving protein kinase C (PKC) activation in several cancer cell types and normal breast epithelial cells (91, 97). In breast cancer, A3B transcript levels have been shown to be upregulated by B-Myb via epidermal growth factor receptor (EGFR) signaling (38) and estradiol (165), linking A3B expression to normal mammary cell physiology. DNA-damaging agents have also been shown to increase A3A and A3B transcript levels in breast cancer (75, 106), via ATR-dependent transcriptional activation (75). Evidence shows that genotoxic stress contributes to A3A activation via a canonical NF-κB mechanism in conjunction with typical IFN induction from viral infection (117). Thus, activated DNA damage signaling due to inherent stress within tumors may lead to enhanced APOBEC3 expression and increased mutational burden. The DNA damage response protein p53 also regulates multiple APOBEC3 members through binding sites in the *APOBEC3* gene promoters (1, 105). *TP53* mutational status may therefore be particularly important for the establishment of A3B-mediated mutation signatures (139), as p53 normally represses A3B expression through the recruitment of the DREAM complex to the A3B promoter region (22, 124, 136). A3B expression is also modulated by the activator protein 1 (AP-1) pathway acting on an intronic enhancer within *APOBEC3B* (94).

## Control of APOBEC Stability and Activity via Posttranslational Modification

Posttranslational modifications of APOBECs that modify their protein abundance or enzymatic activity may also modulate the occurrence of APOBEC-induced mutations in tumors. The best-characterized posttranslational modification of the APOBEC family is the ubiquitination and proteolytic destruction of APOBEC3 enzymes during HIV-1 infection. The HIV-encoded accessory protein, viral infectivity factor (Vif), binds the cytoplasmic APOBEC3 proteins A3D, A3F, A3G, and A3H, then complexes with an E3 ubiquitin ligase CRL5 complex, resulting in

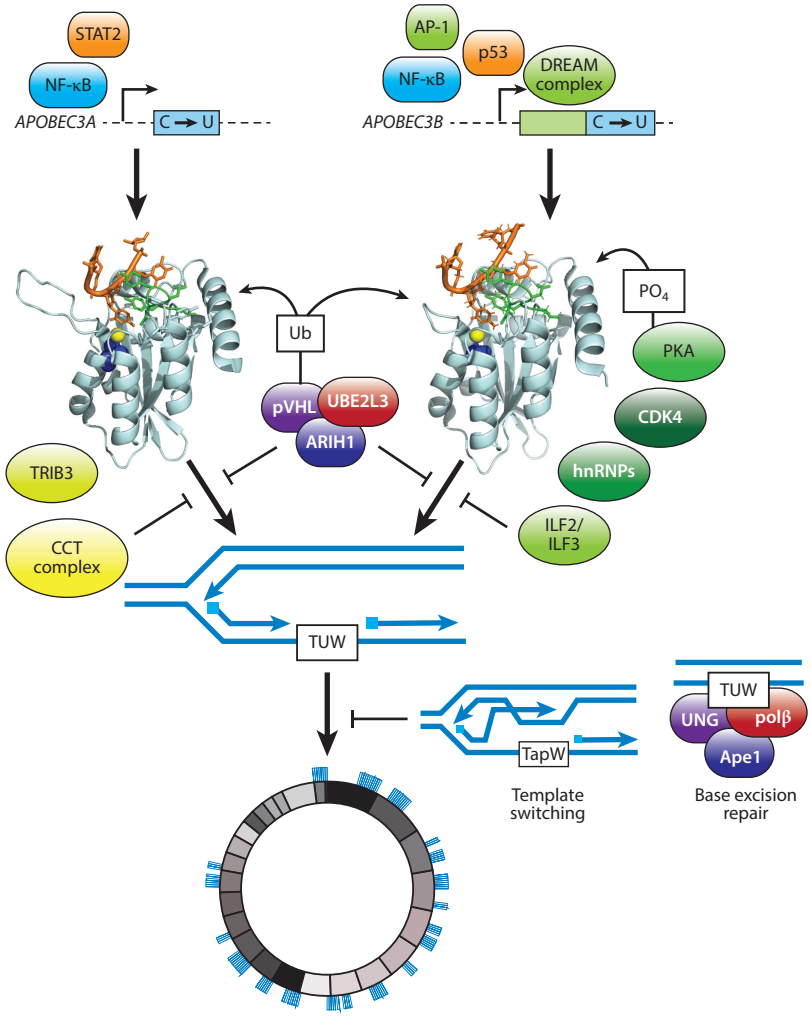


**Figure 5**

Potential modifiers of APOBEC3A and APOBEC3B activity and cancer mutagenesis. Transcriptional upregulation of APOBEC3A and APOBEC3B likely contributes to increased APOBEC-induced mutations in cancer, while identified posttranslational modifications and protein–protein interactions tend to inhibit APOBEC3A or APOBEC3B activity. Similarly, base excision repair of dU in double-stranded DNA (i.e., induced during transcription where DNA strands would be reannealed following deamination) or error-free template switching at abasic sites derived from APOBEC-induced dU during replication can prevent APOBEC signature mutations in model systems. Whether currently identified protein interactors of APOBEC3A and APOBEC3B or error-free template switching influences APOBEC-induced mutation during cancer development is currently unknown. Abbreviations: APOBEC, apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like; AP-1 activator protein 1; APE1, apurinic/apyrimidinic endonuclease 1; ARIH1, ariadne RBR E3 ubiquitin protein ligase 1; CCT, chaperonin containing TCP-1; CDK4, cyclin-dependent kinase 4; DREAM, dimerization partner, RB-like, E2F and multi-vulval class B; dU, deoxyuridine; hnRNP, heterogeneous ribonucleoprotein; ILF, interleukin enhancer-binding factor; NF-κB, nuclear factor κ B; PKA, protein kinase A; polβ, polymerase β; pVHL, von Hippel–Lindau tumor suppressor; STAT2, signal transducer and activator of transcription 2; TRIB, tribbles pseudokinase 3; Ub, ubiquitin. Images of replication forks and mutated genomes shown as a circos plot adapted with permission from References 66 (CC BY-NC-ND 4.0) and 67.

polyubiquitination and degradation by the 26S proteasome (reviewed in 54). The presence of ariadne RBR E3 ubiquitin protein ligase 2 (ARIH2) and ubiquitin-conjugating enzyme E2 L3 (UBE2L3) increases the polyubiquitination of APOBECs in the CRL5-Vif degradation pathway, and knocking out *ARIH2* decreases HIV infectivity (70), indicating that Vif-mediated APOBEC destruction requires monoubiquitination by ARIH2 and UBE2L3 followed by polyubiquitination by CRL5.

Recent characterization of A3A activity in hepatocytes indicates that UBE2L3 may also control APOBEC levels through proteasomal degradation in the absence of Vif (178) (**Figure 5**). A *UBE2L3* promoter polymorphism (rs59391722) results in higher expression of *UBE2L3* and increases susceptibility to hepatitis B infection. Overexpression of UBE2L3 in hepatitis B virus–infected human liver carcinoma cells decreased the half-life of A3A protein and increased A3A ubiquitination in vitro, suggesting that proteasomal destruction of A3A mediated the enhanced viral infection. Furthermore, A3A protein levels increased in cells following proteasome inhibitor MG132 treatment, indicating that UBE2L3-mediated A3A degradation requires proteasomal involvement. The von Hippel–Lindau tumor suppressor (pVHL) functions in coordination with the UBE2L3-ARIH1 complex for monoubiquitination and with the CRL Cullin-RING E3 ubiquitin ligase for polyubiquitination of target proteins. Overexpression of pVHL in HEK293T cells decreased protein levels of all overexpressed APOBEC3 proteins, suggesting that this pathway is conserved among APOBEC3s regardless of cellular localization (147). Currently, it is thought that pVHL acts as a substrate receptor protein by binding an APOBEC3 protein and interacting directly with the CRL complex, which polyubiquitinates the APOBEC3 and targets it for proteasomal degradation. However, whether these degradation pathways are modulated in ways that result in increased APOBEC-induced DNA damage or mutation during cancer development is unknown.

APOBEC function is also commonly regulated by posttranslational phosphorylation. cAMP-dependent protein kinase A (PKA) phosphorylates AID within an RXXS/T consensus site at residue serine 38 (S38) (reviewed in 177), which serves to mediate AID–RPA interactions, promoting efficient CSR and possibly increasing oncogenic *MYC/IGH* translocations (111). AID S38A can deaminate DNA within Ig S-regions in vitro and associate with Ig S-regions in stimulated B cells while failing to recruit RPA to these regions (166). This suggests that either RPA's role in CSR occurs postdeamination, potentially in the recruitment of repair factors, or RPA enhances CSR. Interestingly, AID S38 phosphorylation has also been observed in unstimulated 3T3 fibroblasts and HEK293T cells (101), suggesting that PKA may regulate AID in contexts beyond CSR and SHM in B cells. AID S38G has been reported to maintain CSR function in B cells (7), calling into question the exact role of S38 phosphorylation in this process. Serine 3 (S3), threonine 27 (T27), threonine 140 (T140), and tyrosine 184 (Y184) have been identified as additional AID phosphorylation sites in splenic B cells. Isolated studies have shown that S3 phosphorylation suppresses CSR and Myc/IgH translocations in stimulated B cells, suppresses hypermutation in 3T3 fibroblasts (57), and promotes nuclear stability of AID (90). Phosphorylation of T27 augments AID interactions with RPA in HEK293T cells and CSR activity in knock-in mice, although this may be due to the interdependence of T27 and S38 phosphorylation (9). AID T27A S38A double mutants reportedly lack the ability to initiate CSR in stimulated B cells (121). T140 phosphorylation appears to be catalyzed by PKC, suggesting an alternative pathway for AID regulation rather than via S38 and T27 phosphorylation. AID T140A knock-in mice have impaired CSR and SHM, suggesting that T140 plays an important additional role in AID regulation (102). The identification of T140 phosphorylation in 3T3 fibroblasts suggests that, similar to S38 phosphorylation, T140 phosphorylation is not unique to B cells and may have effects beyond CSR and SHM.

PKA also phosphorylates A3G at threonine 32 (T32) (154) and threonine 218 (T218) (46) as well as A3B at threonine 214 (T214) (98) (**Figure 5**). A3G T32 phosphorylation desensitizes A3G to HIV-1 Vif (77, 176), resulting in decreased proteasome-mediated degradation (96, 150, 161) and higher cellular and virion A3G abundance. However, phosphomimetic A3G T32E maintains wild-type deaminase activity in vitro and normal cellular localization (46). By contrast, phosphorylation of A3G T218 and A3B T214 occurs in the C-terminal catalytic domains and decreases deaminase activity (46, 98). A3B T214D (and T214E) mutants also lack cellular foreign DNA-editing activity while preserving nuclear localization. This is consistent with the proposed role for T214 in stabilizing the position of cytosine favorable for deamination (152, 153). Molecular dynamics simulations further support this role and predict that T214 phosphorylation impairs the binding of substrate by excluding the target cytosine from A3B's active site via electrostatic repulsion. Interestingly, A3B phosphomimetic mutants still retain antiretroviral activity and LINE-1 retrotransposon restriction (98), which reportedly does not depend on the catalytic activity of A3B (159) and A3A (15). Characterizing the regulation of A3B and other APOBEC3 family members by PKA in the context of tumors and additional pathways for posttranslational APOBEC regulation is needed to better understand the importance of APOBEC modifications in cancer mutagenesis.

## Other APOBEC-Interacting Proteins

Beyond proteins that chemically modify APOBECs, other protein–protein interactions modulate the activity of these enzymes. In SHM, AID-mediated recruitment of RPA stabilizes ssDNA formed on the nontemplate strand during transcription of Ig variable (V) regions, allowing AID to more efficiently deaminate these regions (30, 101). Additional interactions with RNA pol II, associated Spt5 and Spt6, and 14-3-3 proteins further promote nontranscribed strand deamination (177). AID deamination of the template strand also occurs and is dependent on recruitment by AID of the RNA exosome complex to S regions of Ig loci (10). AID off-target mutations in hematological cancers are enriched in transcribed genes and may similarly be targeted by noncoding RNAs and the exosome (122). However, whether similar factors control the access of AID to transcription-associated ssDNA in gastric tumors (99) and other tumor types (138) is unknown. During CSR, inhibiting AID interactions with RPA impairs both recombination and recruitment of RPA to these regions in vivo. AID interaction with the spliceosome-associated factor CTNNBL1 has also been identified as important for SHM and gene conversions (39). While the mechanism by which this interaction affects AID activity has not been fully elucidated, studies suggest that CTNNBL1 is involved in regulating AID nuclear translocation and subnuclear localization (68).

More recently, interacting proteins for A3B and A3A have been identified (**Figure 5**). A3B interacts specifically with cyclin-dependent kinase 4 (CDK4), which impairs normal CDK4-dependent nuclear import of cyclin D1, likely by nuclear sequestering of A3B-bound CDK4 or competitive binding of CDK4 (103). This interaction disrupts cell proliferation and may promote both A3B antiviral activity and cancer mutagenesis by stalling cells in G1/S phase. The DExD/H-box helicase 9 (DHX9) suppresses A3B antihepatitis B (HBV) activity by impairing the binding of A3B to HBV pregenomic DNA (pgDNA) (33). A3B has also been shown to interact in cells with multiple heterogeneous ribonucleoproteins (hnRNPs) (76, 107) and interleukin enhancer-binding factor 2 (ILF2) and ILF3 (76). Interactions with hnRNP A1 or ILF2 result in attenuation of in vitro A3B deaminase activity (76), suggesting a possible regulatory role in cells. A3A directly binds to the chaperonin-containing TCP-1 (CCT) complex (60), and depletion of this complex increases APOBEC-induced DNA damage, suggesting that the CCT complex limits A3A access to genomic DNA. A3A has also been shown to interact with the nuclear protein TRIB3, which

reduces steady-state A3A levels in a proteasome-independent manner, thus decreasing APOBEC-induced mutations and DSBs (6).

## CONCLUSIONS

Although there has been much progress in characterizing both the molecular underpinnings and the consequences of APOBEC-induced mutagenesis in cancer, many mysteries remain, especially for tumors mutated by APOBEC3 family members. For solid tumors unassociated with viral infections, events that trigger APOBEC expression are unclear. Although elevation of A3A, A3B, or A3H-haplotype I transcription in tumor cells versus normal somatic cells is likely required for APOBEC-driven mutagenesis, it does not always appear to be sufficient in every tumor, as there are many tumors with high A3B and A3A expression without increased SBS2/SBS13 mutations. Almost certainly, posttranslational modifications, protein–protein interactions, targeted degradation, cellular localization, DNA repair processes, and ssDNA availability affect the extent of APOBEC-induced mutagenesis differentially in distinct cancer types and tumors and among individual cells. In addition, the recent finding that A3A is likely the primary driver of APOBEC mutagenesis in many tumors has created new interest in the mechanisms responsible for elevated A3A activity in tumor cells. Finally, several studies have shown that targeting repair activities that respond to APOBEC activity may be a promising therapeutic option. However, the practical application of these pursuits will likely rely on how homogeneous and consistent APOBEC activity is within the tumor cell population.

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