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Review

The emerging role of RNA and DNA editing in cancer

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ABSTRACT

Nucleotide sequence modification through single base editing in animals is emerging as an important player in tumorigenesis. RNA editing especially has increased greatly during mammalian evolution and modulates diverse cellular functions presumably in a context-dependent manner. Sequence editing impacts development, including pluripotency and hematopoiesis, and multiple recent studies have shown that dysregulation of editing is associated with tumor biology. Much is yet to be learned about the role of sequence editing in human biology but this process is a critical modulator of cell regulation and may present an attractive option for therapeutic intervention in cancer in the future.

Significance: Sequence editing provides an additional regulatory layer of cancer initiation and progression that may be amenable to therapeutic design. Although editing of both RNA and DNA substrates has been known to occur for some time, the extent and implications of these modifications have been grossly underappreciated until recent genome-wide and disease-association studies were reported. This review highlights the cellular processes controlled by sequence editing, their implications in normal and cancerous states and considers potential targeted therapeutic strategies.

Contents

1. Introduction

The field of epigenetics has transformed the way we view the genome: from a once static set of nucleotides giving rise to an RNA intermediate thought to be merely a template for protein synthesis, to a highly dynamic 4-dimensional interplay of RNA, DNA and protein participants and temporal interactions that underpin cell and developmental biology. In particular, it has become evident that there is extensive RNA and DNA editing, which ostensibly provides plasticity to the system and a vehicle for environmental–epigenome interactions [1]. Two families of proteins carry out editing by deamination (Fig. 1); ADARs (Adenosine Deaminases Acting on RNA) bind to double stranded RNA

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and convert adenosine to inosine (A-to-I), which behaves as a guanosine during translation and RNA folding [2], and APOBECs (Apolipoprotein B mRNA Editing Complexes) that convert cytosine to uracil (C-to-U) in both RNA and single-stranded DNA [3,4]. At least in DNA, the methylated form of cytosine can also be deaminated to thymine (5mC-to-T) although the complete range of substrate specificity for the eleven members of the primate APOBEC protein family [including the APOBEC ortholog, activation-induced cytidine deaminase (AID)] is currently unresolved. However, the expansion of editing enzymes, from common zinc-dependent deaminase ancestors that modified tRNAs, has possibly played a significant role in animal evolution [5–7].

RNA and DNA editing pathways have likely evolved to provide context-dependent regulation of a wide variety of developmental and post-developmental processes such as retroviral control, environmentally triggered genomic and epigenomic modulation, physiological adaptation and cognition [5,8]. Intrinsic to such pervasive processes are that dysregulation thereof would lead to adverse effects. Indeed, a significant emerging consequence of abnormal editing is a strong connection to cancer biology. Associations with both solid tumors and blood cancers have been observed for multiple ADAR and APOBEC family members. For example, liver cancer has been linked to alterations in ADAR1 [9], ADAR2 [10], AID [11], APOBEC1 [12], APOBEC2 [13] and APOBEC3G [14] activities, while changes in ADAR1 [15–17], ADAR3 [18], APOBEC3B [19], APOBEC3G [20] and AID [21–23] have been implicated in blood cancers (such as leukemia and lymphoma). Moreover, recent analysis of the spectrum of mutations has implicated APOBEC-mediated editing in many cancers [24]. These studies highlight the inherent cellular susceptibilities to tumorigenesis and tumor progression in response to broad editing disruptions and uncover modulation of editing as a particularly attractive strategy for cancer therapy.

In this article, we review the rapidly accumulating evidence for the involvement of editing in cancer and coalesce what is known regarding the role of editing in normal cellular function, especially during development and differentiation, while also offering possible avenues for therapeutic intervention.

2. The enigma of RNA and DNA editing in humans

2.1. RNA editing

RNA editing was discovered almost three decades ago [25] and single base editing by ADARs has been meticulously described for a discrete number of mRNAs encoding neuroreceptors such as those for glutamate, serotonin and potassium from *Caenorhabditis elegans* to humans. The importance of such editing events is exemplified in particular by the glutamate receptor subunit GluR-2 as editing of this mRNA is essential for normal brain function and survival in mammals [26]. In these examples a specific change in RNA sequence alters the amino acid composition and property of the protein dramatically. More recently, analysis of genome-wide data has shown that ADAR-dependent A-to-I editing is far more widespread than previously understood [27–31] and affects sites in an apparently promiscuous way in many thousands of transcripts. Most of these RNAs do not code for proteins, indicating that RNA editing also modulates RNA regulatory networks. Moreover,

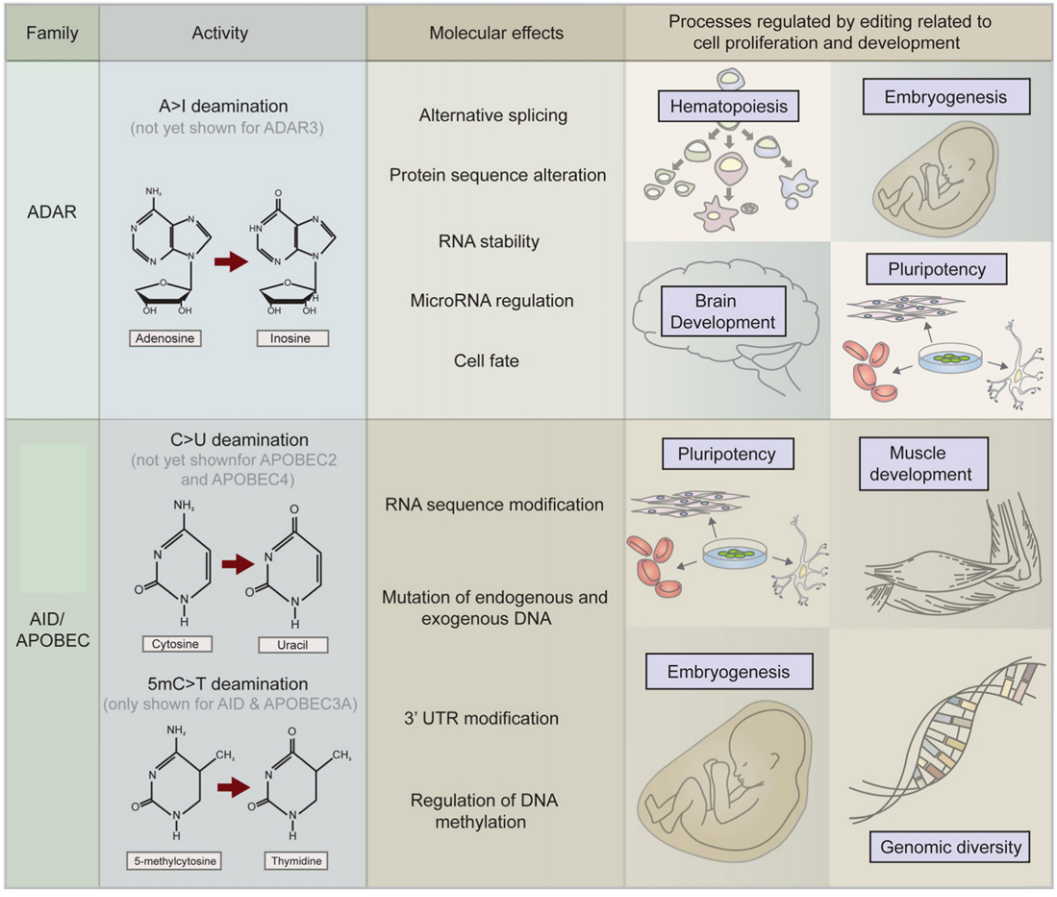

Fig. 1. Effects of RNA editing by ADAR and APOBEC enzymes. Base deamination is carried out by ADAR (A-to-I) and AID/APOBEC (C-to-U; C-to-T) protein families that result in extensive molecular effects such as ADAR: alternative splicing, protein sequence alteration, RNA stability, miRNA regulation and cell fate [2]; APOBEC: RNA sequence modification, DNA mutation, 3′ UTR modification and regulation of DNA methylation [4]. Furthermore, editing changes have widespread effects but many affect processes that are related to cell proliferation and development, e g., ADAR: hematopoiesis [53,55,63], embryogenesis [53,111], brain development [58,112] and pluripotency [54,57], APOBEC: muscle development [59], pluripotency [48,49,61], embryogenesis [60] and genomic diversity [113].

there has been an enormous increase in the extent of RNA editing in the primate lineage [32], especially in humans. ADARs also bind to and edit viral RNA, interestingly with both proviral and antiviral effects depending on the particular virus [33].

In apparent contrast to the extensive activity and impact of A-to-I RNA editing, C-to-U editing levels in RNA seem to be more modest [34]. Although this may be due to limited bioinformatic analyses, compounded by the possibility that their major targets may comprise retroviral/repeat-containing regions, which are difficult to analyze, cytosine deaminases appear to operate mostly at the DNA level (see next section). The first reported and best-studied example of C-to-U editing of RNA is the APOBEC1 mediated editing of *apoB* mRNA that introduces a premature stop codon in the transcript. This produces a shorter version of ApoB protein expressed exclusively in the small intestine where it is involved in lipid metabolism [4,35]. However, APOBEC1-mediated RNA editing has also been shown to regulate the stability of cancer-related gene mRNAs, such as neurofibromin 1, via editing of 3′ untranslated regions (3′ UTRs) [36], potentially also altering target sequences for miRNAs [37].

2.2. DNA editing

The only known type of DNA editing in mammals is deamination of cytosines carried out by AID/APOBEC proteins, either C-to-U, or if the cytosine is methylated, 5mC-to-T. AID-mediated DNA editing has been extensively studied due to its fundamental role in somatic hypermutation and diversification of immunoglobulin genes in B cells [38]. AID also introduces C-to-U mutations that result in DNA strand breaks leading to recombination events and class switching of the antibody. This process is augmented through an AID phosphorylation (Ser38)-dependent positive feedback loop [39].

APOBEC3 proteins play a vital role in innate defense against mobile genetic elements such as viruses and transposable elements in mammals [3]. For example, APOBEC3G has antiviral properties and has been shown to hypermutate the minus-strand of HIV-1 DNA during reverse transcription and inactivate the virus [40]. APOBEC3 proteins in general restrict the mobility of endogenous non-long terminal repeat (non-LTR) retroelements, such as long interspersed nuclear elements (LINEs) and short interspersed nuclear elements (SINEs) as well as LTR retrotransposons [41]. The process of APOBEC3-mediated mobility restriction of retroviral elements is beneficial for the protection of genome integrity but may further represent a domestication of this process in mammals for targeted evolution [5].

2.3. Diverse roles for editing enzymes

Sequence editing in RNA or DNA that changes the sequences of protein-coding RNA can have obvious direct functional consequences, but editing also regulates gene expression through other means. Examples include alternative splicing [42] and processing and targeting of small regulatory RNAs [43–46]. Another essential consequence of editing is the effect on RNA structure. It is becoming increasingly clear that the structure of particular non-coding RNAs, determined by precise sequence patterns, will be significant for function [47] and subtle changes in RNA sequence would, therefore, incur similar structural consequences as are found in proteins [42].

DNA editing also appears to play a role in epigenetic regulation. It has been demonstrated that AID and several other APOBEC proteins are able to deaminate 5mC-to-T, at least in vitro and several recent studies have implied a role for AID/APOBEC proteins in demethylation pathways via deamination [48–50], suggesting a function in both genetic and epigenetic remodeling of the genome.

Several editing-independent functions of ADAR and APOBEC proteins have been reported, which is not surprising given that these proteins bind to nucleic acids and have the potential to interact with multiple other cellular machineries. For example, ADAR1 forms a complex with Dicer through direct protein interactions and enhances global miRNA processing [46] while APOBEC3C restricts LINE-1 retrotransposon mobility [51] and APOBEC3G inhibits Alu element retrotransposition [52] through deaminase-independent mechanisms.

Sequence editing has evolved to diversify gene products, regulate gene expression and as a defense system to protect our genome. These roles and mutagenic nature of RNA and DNA editing, however, predispose our genome to the possibility of developmental defects and potential oncogenic outcomes through dysregulated mutagenesis. Here, we discuss what is known regarding the involvement of editing enzymes in development and then extend these observations to their emerging roles in cancer biology.

3. RNA and DNA editing enzymes in development

3.1. RNA editing in development

Several studies have demonstrated that A-to-I RNA editing has essential functions in development and these findings are uncovering mechanisms that upon dysregulation may directly impact on tumorigenesis, mainly through progenitor cell maintenance and differentiation (Fig. 1). For example, *Adar1* deletion in mice is embryologically lethal due to a failure of hematopoiesis [53]. Other studies link ADAR1 activity to adult progenitor cell maintenance [54,55] as loss of ADAR1 results in endoplasmic reticulum stress, activation of interferon signaling, altered Wnt target genes and finally, apoptosis of progenitor cells [54]. Thus, a reduction in ADAR1 activity results in a reduction of progenitor cell number, which implies that an increase in activity could lead to an oncogenic state through failure of differentiation via forced progenitor cell renewal. *Adar2* mutant mice survive to adulthood, but only if editing of the GluR2 subunit (an integral subunit of AMPA receptors that decreases calcium permeability) is restored [56]. Interestingly, this is due to ADAR2 directly influencing pluripotency and cellular differentiation during development as its activity is necessary to edit the Q/R site on the GluR2 subunit that results in calcium impermeability and ensuing neuronal differentiation [57]. This again suggests that a reduction of ADAR2 activity could lead to a cancerous state through inhibition of differentiation. Certainly, widespread and dynamic ADAR1 expression in multiple progenitor cell populations [53–55,58] and ADAR2 expression in differentiating cells [57,58] indicate essential roles for these proteins in cell fate determination. Collectively, these studies provide compelling evidence for the essential role of ADAR-mediated editing for development during both embryogenesis and in the adult and propose a potential coexistent threat of oncogenesis through a general reduction of ADAR1/2-mediated editing.

3.2. DNA editing in development

Several of the AID/APOBEC proteins also play roles in development and pluripotency. For example, *Aid* and *Apobec1* are expressed in pluripotent cells [49] and AID has been shown to be required for reprogramming toward pluripotency and during tissue regeneration, via deamination and subsequent demethylation of cytosines, and the reactivation of embryonic stem cell-specific genes such as *OCT4* and *NANOG* [48]. Global DNA demethylation is required in primordial germ cells (PGCs) for the erasure of imprints and epigenetic marks to reestablish pluripotency. This process seems to be controlled, at least in part, by AID as *Aid* deficiency in a knockout mouse model resulted in widespread hypermethylation of PGCs suggesting a global role in directing gene expression during development [50]. A recent study supports AID as a critical modulator of demethylation of genes associated with pluripotency that results in a stabilization of the pluripotent state. APOBEC2 is important for normal muscle development [59] and may promote muscle differentiation by inhibiting TGFβ signaling [60]. Apobec2a and Apobec2b are required for regeneration following injury of zebrafish retina that involves the dedifferentiation of Muller glia into

retinal progenitor cells [61]. These exciting results place AID/APOBECs at a critical juncture in the control of pluripotency and development and, opposing the general pattern observed in ADAR-mediated editing, suggests hyperactivity of AID/APOBECs may support oncogenesis.

4. RNA and DNA editing in cancer

Consistent with their roles in progenitor cell maintenance and differentiation, strong connections have been established between dysregulated editing and tumorigenesis and tumor progression (Table 1; Fig. 2). These studies and associations argue that deviations in ADAR and AID/APOBEC expression and activity, shift local or global editing equilibrium toward a potentially cancerous state.

4.1. Role of RNA editing in cancer

Direct involvement for A-to-I editing in oncogenesis has been described in human hepatocellular carcinoma (HCC) samples where antizyme inhibitor 1 (*AZIN1*) transcripts are edited in a site-specific manner by the ADAR1 p110 isoform [9]. This study shows that ADAR1 is upregulated in tumors from HCC patients and that the editing frequency of *AZIN1* mRNA also is increased. Editing causes a modification that stabilizes AZIN1 structure and increases its affinity for antizyme, a protein that normally binds and induces the degradation of the oncoproteins ornithine decarboxylase (ODC) and cyclin D1. Thus, increased RNA editing of *AZIN1* mRNA in HCC leads to increased amounts of ODC and cyclin D1, allowing cells to enter the cell cycle. The authors demonstrated, using both in vitro and in vivo models, that increasing levels of edited AZIN1 promoted enhanced protein function phenotypes resulting in increased tumorigenic potential, invasive ability and a higher incidence of tumor formation (Fig. 2A). Hyper-editing of *AZIN1* mRNA has also been reported in esophageal squamous cell carcinoma [62].

As discussed, ADAR1 activity has been shown to be essential for embryogenesis through its involvement in hematopoiesis [53,63] but a recent study indicates that it might also have a pathogenic role in chronic myeloid leukemia (CML) [15]. ADAR1 p150 isoform overexpression in cultured blood progenitor cells induces reprogramming of myeloid progenitor cells, resulting in increased hematopoietic differentiation toward the myeloid lineage, potentially through up-regulation of the transcription factor PU.1 and the generation of a mis-spliced version of *GSK3β* mRNA (Fig. 2B). The transcript encoding PU.1, *Spi1*, appears to have multiple editing sites but it is not resolved if and how RNA editing affects the expression of PU.1. The mis-spliced GSK3β fails to down-regulate β-catenin, which itself is essential for cell self-renewal. However, it has not yet been determined whether editing dependent or

Table 1
Summary of sequence editing alterations associated with oncogenic effects.

Editing enzyme	Cancer	Indication
ADAR	Brain	Reduced editing of GluR in malignant gliomas [93]
	Brain	Reduced editing promotes glioma cell invasion [94]
	Brain	Reduced editing promotes glioma cell migration and invasion [64]
	Leukemia	Disease-associated alternative splicing of PTPN6 caused by RNA hyper-editing [95]
	Bladder	Reduced editing levels in tumors [96]
ADAR1	Leukemia	ADAR1 deletion eliminated leukemic cells [17]
	Leukemia	High ADAR1 p110 isoform in pediatric leukemia [16]
	Leukemia	Increased ADAR1 expression and editing in leukemia progenitor cells [15]
	Breast	Increased ADAR1 expression and editing in tumors [97]
	Liver	Increased ADAR1-dependent editing of AZIN1 RNA in tumors [9]
	Melanoma	Reduced ADAR1 levels in metastatic melanomas, ADAR1 is regulated by miR-17 and miRNA-432 that are over expressed in cancer cells [98]
	Esophageal	Over expression in tumors and hyper-editing of FLNB and AZIN1 RNA [62]
ADAR2	Brain	ADAR2 overexpression inhibits astrocytoma growth in vitro and in vivo [99]
	Various	ADAR2 upregulated in various carcinomas and cancer cell lines [100]
	Lung	Low levels of ADAR2 mRNA in lung cancer cell lines [101]
	Astrocytoma	Loss of ADAR2-mediated editing in high-grade astrocytoma [102]
ADAR3	Leukemia	ADAR3 is mutated in acute myeloid leukemia [18]
ADAR1/2	Brain	Reduced editing of GLI1 mRNA in tumors [66]
	Prostate	Upregulation of ADAR1/ADAR2, altered editing of androgen receptor mRNA [103]
	Liver	Disrupted ADAR expression and editing balance in hepatocellular carcinoma [10]
ADAR1/2/3	Brain	Decreased editing of GluR transcripts in astrocytomas [104]
	Various	Hypo-editing in tumors, increase in ADAR1/2 decreased proliferation in GBM [68]
AID	Liver	AID induced mutation in Trp53 induces cancer in mouse model [11]
	T-cell lymphoma	AID overexpression induces oncogenesis in mouse model [22]
	B-cell lymphoma	AID-mediated mutations contribute to B cell lymphoma [23]
	Gastric	AID-mediated mutations in CDKN2a/b contribute to gastric cancer [83]
	Leukemia/lymphoma	AID overexpression induced B cell leukemia/lymphoma [21]
APOBEC1	Liver	APOBEC1-mediated editing of NAT1 mRNA in liver tumors [12]
	Testicular	APOBEC1 deficiency results in testicular germ cell tumor susceptibility [84]
	Neurofibromatosis	Increased APOBEC1 editing of NF1 mRNA in neurofibromatosis [76]
	Intestinal adenoma	APOBEC1 stabilizes Cox-2 in adenoma formation [105]
	General	*Apobec1* mRNA expression is regulated by p53 [106]
APOBEC2	Liver/lung	APOBEC2 overexpression results in mutations in tumor suppressor genes and cancer [13]
APOBEC3A	General	APOBEC3A overexpression leads to DNA damage [107]
	General	APOBEC3A activity induces DNA breaks and activates DNA damage response [108]
APOBEC3B	Breast	APOBEC3B upregulated in breast cancer cell lines; increased C to T mutations [79]
	Lymphoma	APOBEC3B upregulated in lymphoma cell lines; increased C to T mutations [19]
	General	APOBEC3B may be responsible for mutagenesis patterns in multiple cancers [81]
APOBEC3A/B	Breast	Overexpression of APOBEC3A and B mimic mutation patterns observed in breast cancer [109]
APOBEC3G	Lymphoma	APOBEC3G is a prosurvival, DNA repair enzyme in lymphoma [20]
	Colorectal/liver	APOBEC3G promotes liver metastasis in a mouse model of colorectal cancer [14]
APOBEC	Breast	Hypothesized APOBEC-mediated somatic mutations in breast cancer [78]
	General	Increased APOBEC3 mutator activity may influence cancer development [110]
	General	APOBEC-mediated mutagenesis is pervasive and correlates with APOBEC mRNA levels [80]
	General	APOBEC signatures are observed in multiple cancer types [24]

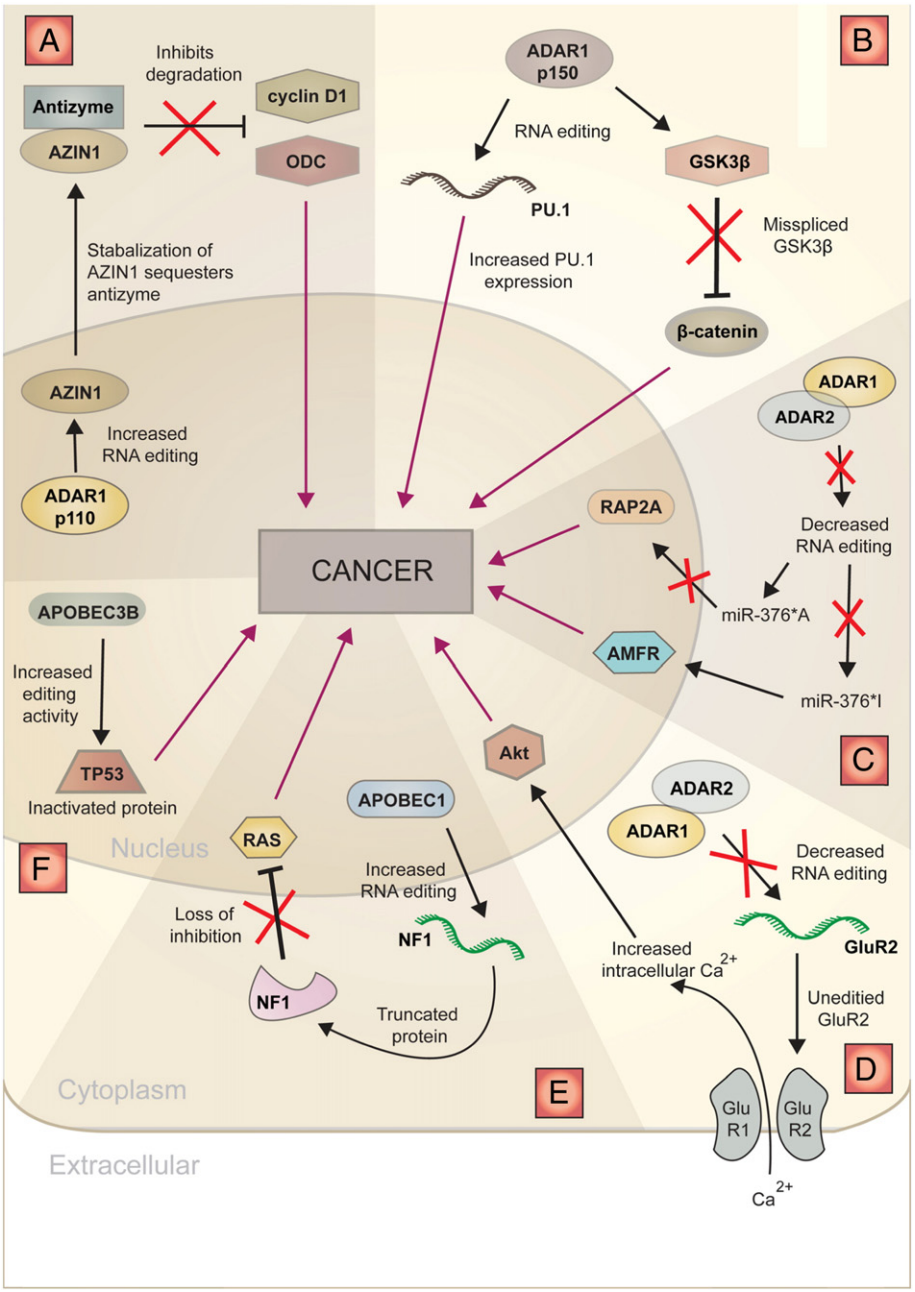

Fig. 2. Mechanisms of dysregulated editing leading to a cancerous state. (A) Elevated ADAR p110 levels increase the editing frequency of *AZIN1* transcripts. This leads to a stabilization of AZIN1 and sequestration of antizyme that inhibits the degradation of oncoproteins ODC and cyclin D1 [9]. (B) Increased levels of ADAR1 p150 produce an up-regulation of the transcription factor PU.1 as well as the generation of a mis-spliced version of GSKβ that is unable to down-regulate β-catenin [15]. (C) A loss of RNA editing of miR-376a* results in an increase in un-edited miR-376a*A (that downregulates RAP2A) and a decrease in edited miR-376a*I (that increases AMFR due to a loss of miRNA suppressor activity), which combine to increase migration and invasion [64]. (D) AMPA receptors containing the un-edited form of GluR2 are more permeable to Ca^{2+} resulting in increased levels of intracellular Ca^{2+} that activate the Akt pathway [65]. (E) Increased APOBEC1 levels correlate with hyper-editing of the tumor suppressor NF1 mRNA. Editing produces a truncated version of NF1 that fails to inhibit the oncogenic RAS pathway [76]. (F) Overexpression of APOBEC3B is associated with mutation and inactivation of the tumor suppressor gene *TP53* [79].

independent mechanisms are responsible for the altered splicing pattern of *GSK3β* mRNA seen in the myeloid progenitor cells. These effects in chronic myeloid leukemia progression are most likely due to interferon-responsive ADAR1 p150 activity since this isoform is up-regulated in CML patient samples while ADAR2 and ADAR3 expression levels are very low in these cells. Furthermore, up-regulation of ADAR1 p150 correlated with BCR/ABL (oncogenic gene fusion protein) amplification and increased A-to-I editing in CML patient samples. Similarly, Steinman et al. revealed that ADAR1 is required for the survival of leukemia cells [17]. BCR/ABL-positive marrow cells, in which ADAR1 was conditionally deleted, were transplanted into mice to induce the development of leukemia and loss of ADAR1 in this model led to clearance of CML in marrow and peripheral blood.

The previous examples link hyper-editing to cancer. Hypo-editing, possibly through the reduction of both ADAR1 and ADAR2, of a specific miRNA, miR-376a*, promotes glioblastoma cell invasion in orthotopic glioma models in mice [64]. The editing frequency of miR-376* was also almost completely abolished in tumor samples from patients with glioblastoma, the most aggressive form of glioma. Unedited miR-376a*, but not edited miR-376a*, was shown to downregulate RAP2A (suppressor of glioblastoma cell invasion) in human glioma cell lines through direct binding to miRNA binding sites in the 3′ UTR of *RAP2A* mRNA. In

addition, the unedited miRNA failed to target and suppress autocrine motility factor receptor (AMFR), the receptor for the tumor motility-stimulating protein AMF, normally down-regulated via binding to the 3′ UTR of *AMFR* mRNA by the edited form of miR-376*. Decreased levels of RAP2A promoted glioma invasiveness in invasion assays while up-regulated AMFR seemed more significant for increased glioma migration (Fig. 2C). This study elegantly illustrates how RNA editing (which modifies only one base pair of a small RNA) can alter target specificity that results in contrasting cellular effects of the edited and unedited forms of a miRNA.

A decrease in RNA editing activity has additionally been demonstrated to activate pathways that result in an increase in tumor susceptibility. For example, enhanced susceptibility to glioblastoma proliferation and invasion was observed upon Akt pathway activation caused by reduced RNA editing of the AMPA receptor component GluR2 (Fig. 2D) [65]. Furthermore, knockdown of either ADAR1 or ADAR2 in neuroblastoma cell-lines results in hypo-edited GLI1, a transcription factor in the Hedgehog signaling pathway, increasing its transcriptional activity and supporting increased cellular proliferation [66]. The activation of the Hedgehog signaling pathway may potentially underlie some of the widespread GLI1-dependent oncogenic effects [67].

Apart from the clear connections to cancer via sequence alteration, regulation of pluripotency and cellular differentiation, and the expression of tumor suppressors and oncogenes, RNA editing may also be involved in tumorigenesis through additional pathways. There is evidence that hypo-editing of Alu elements correlates with multiple tumors, for example brain, prostate, lung, kidney, and testis [68], possibly through interference of gene regulatory functions, such as protection against retrotransposition targeting tumor suppressors [e.g. suppression of tumorigenicity 18 (ST18) and mutated in colorectal cancers (MCC)] [68,69]. Additionally, chronic inflammation related to viral infection is known to be tumorigenic, perhaps in part due to inflammation-mediated up-regulation of ADAR1 and RNA editing [70] and this may have been co-opted by viruses to dampen the normal antiviral response [71]. Finally, RNA editing of non-coding RNAs remains largely unexplored with the exception of miRNAs. It is well established that a number of miRNAs can affect tumorigenesis [72] and that editing of miRNAs can alter their target spectra [73]. Editing of other classes of non-coding RNA that are involved in cell differentiation, such as long non-coding RNAs [74], is also likely to contribute to the control of cell growth and cell fate.

Intriguingly, A-to-I RNA editing has been shown to regulate adaption to physical environments, such as temperature in octopus [75]. It is therefore possible to suspect that other environmental factors like food, chemicals or stress could potentially influence editing in other organisms. Environmental factors undoubtedly play a role in cancer initiation and development, and alterations to the editing balance may be part of the equation, although this still needs to be investigated.

There are studies linking C-to-U RNA editing to cancer. APOBEC1 has been implicated in peripheral nerve-sheath tumors in people with neurofibromatosis 1 through the increased APOBEC1-mediated RNA editing of neurofibromin 1 (NF1) mRNA [76]. Editing introduces a stop codon that produces the translation of a truncated version of neurofibromin protein resulting in loss of its tumor suppressor activity and the activation of the oncogenic RAS pathway (Fig. 2E). Interestingly, transgenic overexpression of APOBEC1 in rabbit and mouse livers resulted in liver dysplasia and HCC through excessive editing of hepatic mRNAs such as tyrosine kinase [77]. This reveals APOBEC1, and related editing patterns, as potentially oncogenic. Furthermore, hyper-editing of the novel APOBEC1 target 1 (NAT1) mRNA that encodes a tumor suppressor gene is linked to liver cancer [12]. APOBEC1-mediated editing of the 3′ end of full length *NAT1* mRNA creates stop codons and truncated protein products leading to the loss of translational repression usually provided by NAT1.

4.2. Role of DNA editing in cancer

Deamination of methylated C-to-T, carried out by AID/APOBEC activity, is a common mutagenic process in the human genome that suggests a potential link to cancer. Indeed, overexpression of APOBEC enzymes, in particular APOBEC3, has been associated with cancer and APOBECs have been proposed to cause mutations in a number of oncogenes and tumor suppressor genes (Table 1; Fig. 2F). A recent study of 21 breast cancers revealed a phenomenon of localized hypermutation, almost exclusively C-to-T transitions at TpC dinucleotides, that appear to co-localize with somatic rearrangements [78], implicating APOBEC activity. It was subsequently demonstrated in primary breast tumors that APOBEC3B expression and activity correlated with observed APOBEC-mediated somatic mutations [79]. Overexpression of APOBEC3B in vitro was associated with increased mutability and inactivation of the tumor suppressor *TP53*, widespread DNA damage and delayed cell cycle arrest followed by cell death. In support of a more general role for APOBEC3B in cancer, Roberts et al. showed that APOBEC3B is likely the major candidate for inducing APOBEC mutation patterns observed in bladder, cervical, breast, head and neck, and lung cancers [80], while a separate study from Burns et al., reinforced the robust link of APOBEC3B activity to the same cancer types [81]. Most recently, an analysis of almost 5 million somatic substitutions from over 7000 sequenced cancer genomes revealed that mutational signatures characterized by C-to-T mutations are present in the majority of cancer types, and are especially prominent in bladder and breast cancer [24]. Two of these signatures can clearly be linked to AID/APOBEC activity based on the sequence context of the mutation, but it is also possible that AID/APOBEC proteins are involved in other signatures through demethylation of 5mC-to-T.

AID is critical for the correct functioning of the vertebrate immune system and is primarily expressed in activated B cells where it has been shown to drive the onset of germinal center lymphoma by inducing chromosomal translocations [23]. Moreover, AID is expressed in other cell types and tissues, such as breast and ovary [82] and gastric epithelial cells [83], where it may be responsible for oncogenic hypermutation and translocation.

Interestingly, a deficiency in APOBEC1 expression seems to be involved in altered susceptibility to testicular germ cell tumors (TGCTs) in both a conventional and a transgenerational manner, the latter persisting in the absence of the causative ancestral allele [84]. APOBEC1 deficiency in mice increased TGCT risk in only the paternal germ lineage whereas it was protective for males when inherited from the maternal lineage. These effects may be mediated via *Apobec1* interactions with other TGCT modifier genes *TP53*, *Eif2s2* and *Deadend 1* [84].

5. Therapeutic intervention

Rapidly accumulating data linking dysregulated sequence editing to cancer suggests that therapeutic modulation of this process would be a promising area for the treatment of many cancers. In support of this prospect, downregulation of ADAR1 has been shown to be effective in tumor regression in a mouse model of chronic myelogenous leukemia [17]. As ADAR1 is upregulated in multiple tumor types (Table 1), and has functions in progenitor cell maintenance [15,55], a targeted anti-ADAR1 therapeutic may provide a broadly beneficial cancer drug. However, care must be taken to tease out the underlying pathways as ADAR1 isoforms are differentially regulated in cancers [9,15]. Many cancers bear the signatures of APOBEC induced mutations [80,81] and inhibitors of APOBECs (in particular APOBEC3B) could be a promising strategy to prevent accumulation of mutations. Theoretically, introducing point mutations in editing enzymes would help to reduce hyper-editing [85] and in the future could be introduced by zinc finger nucleases specific to editing enzymes [86]. These, or similar strategies, would have broad therapeutic potential and could also be used to further understand the function of specific editing sites.

Editing enzyme levels could be used as prognostic markers for early detection of cancer and to determine post-therapeutic outcomes. Elevated APOBEC3B levels would potentially represent a promising biomarker for certain cancers like breast cancer [79] and low levels of ADAR1 have been associated with high risk of childhood lymphoma [16]. However, as discussed above, hyper-editing [9,15] and hypo-editing [64,87] can result in cancerous states depending on the type of cancer and the genes edited. This argues for a more targeted technique as opposed to a general approach, which may lead to multiple off-site effects due to the widespread activity of editing enzymes. Next generation drug delivery systems will greatly enhance the potential for a targeted approach, such as using nanoparticles [88] and exosomes [89].

A potentially exciting strategy is to target the mRNA expression of the editing enzymes, and specific hypo- or hyper-edited RNAs (or DNA) that are responsible for the disease phenotype, using RNA-based technologies. Approaches currently being explored are RNA interference (RNAi), antisense oligonucleotides (ASOs) and steric-blocking oligonucleotides (reviewed in [90]). Oligonucleotides are attractive therapeutic candidates as they can be extensively chemically modified and are consequently excellent substrates for drug design parameters such as target specificity and stability. As proof of concept, locked nucleic acid (LNA) oligonucleotides have recently been used to block specific A-to-I RNA editing [91]. Here, the binding register of a snoRNA (HBII-52) in an intron of the *5HT2C* receptor gene and the K/R site in the human *NEIL1* pre-mRNA, a ubiquitously expressed and abundant base excision glycosylase, were successfully targeted in vitro. Recent advances in structural determination of editing sites [92] may uncover useful strategies for therapeutic design of artificial editing substrates that exploit endogenous editing activity.

6. Conclusions

The field of single base sequence editing has experienced a major transformation as whole genome sequencing has revealed pervasive editing throughout the transcriptome. As a consequence, sequence editing is emerging as a widespread phenomenon that controls many key developmental and functional aspects of cellular processes. Notably, RNA editing has dramatically increased in mammals, especially in the brains of primates and humans, and mainly in repetitive sequences of the genome whose recent expansion closely parallels mammalian complexity [5]. This newly evolved layer of regulatory control possibly provides a substrate for environmentally induced adaptation during development and in the adult, and rapid evolution of higher-order cognitive abilities. However, any disturbances in this finely tuned system would have a range of cellular consequences, including vulnerabilities to cell fate and proliferative disturbances.

The link between sequence editing and cancer is strengthening. Especially important in this regard are the differences in the expression of editing enzymes and activity in pluripotency and cellular differentiation. The prevailing hypothesis, with supporting data accumulating rapidly, is that dysregulated editing may provide susceptibilities for tumorigenesis and tumor progression. Therefore, targeted (either mRNA- or tumor-specific targets) therapeutics, as opposed to altering global editing levels through manipulation of protein levels, would be of great value to the cancer field due to editing imbalances observed in tumorigenesis and tumor progression and recent observations linking ADAR1 down-regulation to the regression of tumor growth [17]. Drug discovery relies heavily on suitable druggable targets and a deep understanding of their endogenous molecular pathways is necessary to ascertain disease specificity and potential side effects. Thus, the immediate challenge is gaining a comprehensive understanding of the functional consequences and the underlying mechanisms controlling the regulation of sequence editing and roles that this activity plays in normal and abnormal cellular behavior to inform future therapeutic and diagnostic development for targeting aberrant RNA and DNA editing in cancers.

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References

[1] J.S. Mattick, RNA as the substrate for epigenome–environment interactions: RNA guidance of epigenetic processes and the expansion of RNA editing in animals underpins development, phenotypic plasticity, learning, and cognition, Bioessays 32 (2010) 548–552.
[2] Y.A. Savva, L.E. Rieder, R.A. Reenan, The ADAR protein family, Genome Biol. 13 (2012) 252.
[3] A. Koito, T. Ikeda, Apolipoprotein B mRNA-editing, catalytic polypeptide cytidine deaminases and retroviral restriction, Wiley Interdiscip. Rev. RNA 3 (2012) 529–541.
[4] H.C. Smith, R.P. Bennett, A. Kizilyer, W.M. McDougall, K.M. Prohaska, Functions and regulation of the APOBEC family of proteins, Semin. Cell Dev. Biol. 23 (2012) 258–268.
[5] G. Barry, J.S. Mattick, The role of regulatory RNA in cognitive evolution, Trends Cogn. Sci. 16 (2012) 497–503.
[6] S.G. Conticello, The AID/APOBEC family of nucleic acid mutators, Genome Biol. 9 (2008) 229.
[7] Y. Jin, W. Zhang, Q. Li, Origins and evolution of ADAR-mediated RNA editing, IUBMB Life 61 (2009) 572–578.
[8] J.S. Mattick, M.F. Mehler, RNA editing, DNA recoding and the evolution of human cognition, Trends Neurosci. 31 (2008) 227–233.
[9] L. Chen, Y. Li, C.H. Lin, T.H. Chan, R.K. Chow, Y. Song, M. Liu, Y.F. Yuan, L. Fu, K.L. Kong, et al., Recoding RNA editing of AZIN1 predisposes to hepatocellular carcinoma, Nat. Med. 19 (2013) 209–216.
[10] T.H. Chan, C.H. Lin, L. Qi, J. Fei, Y. Li, K.J. Yong, M. Liu, Y. Song, R.K. Chow, V.H. Ng, et al., A disrupted RNA editing balance mediated by ADARs (Adenosine Deaminases that act on RNA) in human hepatocellular carcinoma, Gut (2013), http://dx.doi.org/10.1136/gutjnl-2012-304037.
[11] A. Takai, T. Toyoshima, M. Uemura, Y. Kitawaki, H. Marusawa, H. Hiai, S. Yamada, I. M. Okazaki, T. Honjo, T. Chiba, et al., A novel mouse model of hepatocarcinogenesis triggered by AID causing deleterious p53 mutations, Oncogene 28 (2009) 469–478.
[12] S. Yamanaka, K.S. Poksay, K.S. Arnold, T.L. Innerarity, A novel translational repressor mRNA is edited extensively in livers containing tumors caused by the transgene expression of the apoB mRNA-editing enzyme, Genes Dev. 11 (1997) 321–333.
[13] S. Okuyama, H. Marusawa, T. Matsumoto, Y. Ueda, Y. Matsumoto, Y. Endo, A. Takai, T. Chiba, Excessive activity of apolipoprotein B mRNA editing enzyme catalytic polypeptide 2 (APOBEC2) contributes to liver and lung tumorigenesis, Int. J. Cancer 130 (2012) 1294–1301.
[14] Q. Ding, C.J. Chang, X. Xie, W. Xia, J.Y. Yang, S.C. Wang, Y. Wang, J. Xia, L. Chen, C. Cai, et al., APOBEC3G promotes liver metastasis in an orthotopic mouse model of colorectal cancer and predicts human hepatic metastasis, J. Clin. Invest. 121 (2011) 4526–4536.
[15] Q. Jiang, L.A. Crews, C.L. Barrett, H.J. Chun, A.C. Court, J.M. Isquith, M.A. Zipeto, D.J. Goff, M. Minden, A. Sadarangani, et al., ADAR1 promotes malignant progenitor reprogramming in chronic myeloid leukemia, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 1041–1046.
[16] C.H. Ma, J.H. Chong, Y. Guo, H.M. Zeng, S.Y. Liu, L.L. Xu, J. Wei, Y.M. Lin, X.F. Zhu, G.G. Zheng, Abnormal expression of ADAR1 isoforms in Chinese pediatric acute leukemias, Biochem. Biophys. Res. Commun. 406 (2011) 245–251.
[17] R.A. Steinman, Q. Yang, M. Gasparetto, L.J. Robinson, X. Liu, D.E. Lenzner, J. Hou, C. Smith, Q. Wang, Deletion of the RNA-editing enzyme ADAR1 causes regression of established chronic myelogenous leukemia in mice, Int. J. Cancer 132 (2013) 1741–1750.
[18] J. Zhang, C.G. Mullighan, R.C. Harvey, G. Wu, X. Chen, M. Edmonson, K.H. Buetow, W.L. Carroll, I.M. Chen, M. Devidas, et al., Key pathways are frequently mutated in high-risk childhood acute lymphoblastic leukemia: a report from the Children's Oncology Group, Blood 118 (2011) 3080–3087.
[19] M. Shinohara, K. Io, K. Shindo, M. Matsui, T. Sakamoto, K. Tada, M. Kobayashi, N. Kadowaki, A. Takaori-Kondo, APOBEC3B can impair genomic stability by inducing base substitutions in genomic DNA in human cells, Sci. Rep. 2 (2012) 806.
[20] R. Nowarski, O.I. Wilner, O. Cheshin, O.D. Shahar, E. Kenig, L. Baraz, E. Britan-Rosich, A. Nagler, R.S. Harris, M. Goldberg, et al., APOBEC3G enhances lymphoma cell radioresistance by promoting cytidine deaminase-dependent DNA repair, Blood 120 (2012) 366–375.
[21] Y. Komeno, J. Kitaura, N. Watanabe-Okochi, N. Kato, T. Oki, F. Nakahara, Y. Harada, H. Harada, R. Shinkura, H. Nagaoka, et al., AID-induced T-lymphoma or B-leukemia/lymphoma in a mouse BMT model, Leukemia 24 (2010) 1018–1024.
[22] I.M. Okazaki, H. Hiai, N. Kakazu, S. Yamada, M. Muramatsu, K. Kinoshita, T. Honjo, Constitutive expression of AID leads to tumorigenesis, J. Exp. Med. 197 (2003) 1173–1181.
[23] L. Pasqualucci, G. Bhagat, M. Jankovic, M. Compagno, P. Smith, M. Muramatsu, T. Honjo, H.C. Morse III, M.C. Nussenzweig, R. Dalla-Favera, AID is required for germinal center-derived lymphomagenesis, Nat. Genet. 40 (2008) 108–112.
[24] L.B. Alexandrov, S. Nik-Zainal, D.C. Wedge, S.A. Aparicio, S. Behjati, A.V. Biankin, G. R. Bignell, N. Bolli, A. Borg, A.L. Borresen-Dale, et al., Signatures of mutational processes in human cancer, Nature 500 (2013) 415–421.

[25] R. Benne, J. Van den Burg, J.P. Brakenhoff, P. Sloof, J.H. Van Boom, M.C. Tromp, Major transcript of the frameshifted coxII gene from trypanosome mitochondria contains four nucleotides that are not encoded in the DNA, Cell 46 (1986) 819–826.
[26] P.H. Seeburg, A-to-I editing: new and old sites, functions and speculations, Neuron 35 (2002) 17–20.
[27] L. Bazak, A. Haviv, M. Barak, J. Jacob-Hirsch, P. Deng, R. Zhang, F.J. Isaacs, G. Rechavi, J.B. Li, E. Eisenberg, et al., A-to-I RNA editing occurs at over a hundred million genomic sites, located in a majority of human genes, Genome Res. 24 (2013) 365–376.
[28] B.E. Wulff, M. Sakurai, K. Nishikura, Elucidating the inosinome: global approaches to adenosine-to-inosine RNA editing, Nat. Rev. Genet. 12 (2011) 81–85.
[29] J.B. Li, E.Y. Levanon, J.K. Yoon, J. Aach, B. Xie, E. Leproust, K. Zhang, Y. Gao, G.M. Church, Genome-wide identification of human RNA editing sites by parallel DNA capturing and sequencing, Science 324 (2009) 1210–1213.
[30] B.R. Graveley, A.N. Brooks, J.W. Carlson, M.O. Duff, J.M. Landolin, L. Yang, C.G. Artieri, M.J. van Baren, N. Boley, B.W. Booth, et al., The developmental transcriptome of *Drosophila melanogaster*, Nature 471 (2011) 473–479.
[31] I.X. Wang, E. So, J.L. Devlin, Y. Zhao, M. Wu, V.G. Cheung, ADAR regulates RNA editing, transcript stability, and gene expression, Cell Rep. 5 (2013) 849–860.
[32] N. Paz-Yaacov, E.Y. Levanon, E. Nevo, Y. Kinar, A. Harmelin, J. Jacob-Hirsch, N. Amariglio, E. Eisenberg, G. Rechavi, Adenosine-to-inosine RNA editing shapes transcriptome diversity in primates, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 12174–12179.
[33] C.E. Samuel, Adenosine deaminases acting on RNA (ADARs) are both antiviral and proviral, Virology 411 (2011) 180–193.
[34] B.R. Rosenberg, C.E. Hamilton, M.M. Mwangi, S. Dewell, F.N. Papavasiliou, Transcriptome-wide sequencing reveals numerous APOBEC1 mRNA-editing targets in transcript 3′ UTRs, Nat. Struct. Mol. Biol. 18 (2011) 230–236.
[35] L.M. Powell, S.C. Wallis, R.J. Pease, Y.H. Edwards, T.J. Knott, J. Scott, A novel form of tissue-specific RNA processing produces apolipoprotein-B48 in intestine, Cell 50 (1987) 831–840.
[36] V. Blanc, N.O. Davidson, APOBEC-1-mediated RNA editing, Wiley Interdiscip. Rev. Syst. Biol. Med. 2 (2010) 594–602.
[37] G. Chai, N. Liu, J. Ma, H. Li, J.L. Oblinger, A.K. Prahalad, M. Gong, L.S. Chang, M. Wallace, D. Muir, et al., MicroRNA-10b regulates tumorigenesis in neurofibromatosis type 1, Cancer Sci. 101 (2010) 1997–2004.
[38] C. Keim, D. Kazadi, G. Rothschild, U. Basu, Regulation of AID, the B-cell genome mutator, Genes Dev. 27 (2013) 1–17.
[39] B.Q. Vuong, K. Herrick-Reynolds, B. Vaidyanathan, J.N. Pucella, A.J. Ucher, N.M. Donghia, X. Gu, L. Nicolas, U. Nowak, N. Rahman, et al., A DNA break- and phosphorylation-dependent positive feedback loop promotes immunoglobulin class-switch recombination, Nat. Immunol. 14 (2013) 1183–1189.
[40] R.S. Harris, K.N. Bishop, A.M. Sheehy, H.M. Craig, S.K. Petersen-Mahrt, I.N. Watt, M. S. Neuberger, M.H. Malim, DNA deamination mediates innate immunity to retroviral infection, Cell 113 (2003) 803–809.
[41] A. Koito, T. Ikeda, Intrinsic immunity against retrotransposons by APOBEC cytidine deaminases, Front. Microbiol. 4 (2013).
[42] L.E. Rieder, R.A. Reenan, The intricate relationship between RNA structure, editing, and splicing, Semin. Cell Dev. Biol. 23 (2012) 281–288.
[43] M.J. Blow, R.J. Grocock, S. van Dongen, A.J. Enright, E. Dicks, P.A. Futreal, R. Wooster, M.R. Stratton, RNA editing of human microRNAs, Genome Biol. 7 (2006) R27.
[44] Y. Kawahara, B. Zinshteyn, P. Sethupathy, H. Iizasa, A.G. Hatzigeorgiou, K. Nishikura, Redirection of silencing targets by adenosine-to-inosine editing of miRNAs, Science 315 (2007) 1137–1140.
[45] G. Meister, M. Landthaler, Y. Dorsett, T. Tuschl, Sequence-specific inhibition of microRNA- and siRNA-induced RNA silencing, RNA 10 (2004) 544–550.
[46] H. Ota, M. Sakurai, R. Gupta, L. Valente, B.E. Wulff, K. Ariyoshi, H. Iizasa, R.V. Davuluri, K. Nishikura, ADAR1 forms a complex with dicer to promote MicroRNA processing and RNA-induced gene silencing, Cell 153 (2013) 575–589.
[47] M.A. Smith, T. Gesell, P.F. Stadler, J.S. Mattick, Widespread purifying selection on RNA structure in mammals, Nucleic Acids Res. 41 (2013) 8220–8236.
[48] N. Bhutani, J.J. Brady, M. Damian, A. Sacco, S.Y. Corbel, H.M. Blau, Reprogramming towards pluripotency requires AID-dependent DNA demethylation, Nature 463 (2010) 1042–1047.
[49] H.D. Morgan, W. Dean, H.A. Coker, W. Reik, S.K. Petersen-Mahrt, Activation-induced cytidine deaminase deaminates 5-methylcytosine in DNA and is expressed in pluripotent tissues: implications for epigenetic reprogramming, J. Biol. Chem. 279 (2004) 52353–52360.
[50] C. Popp, W. Dean, S. Feng, S.J. Cokus, S. Andrews, M. Pellegrini, S.E. Jacobsen, W. Reik, Genome-wide erasure of DNA methylation in mouse primordial germ cells is affected by AID deficiency, Nature 463 (2010) 1101–1105.
[51] A.V. Horn, S. Klawitter, U. Held, A. Berger, A.A. Jaguva Vasudevan, A. Bock, H. Hofmann, K.M. Hanschmann, J.H. Trosemeier, E. Flory, et al., Human LINE-1 restriction by APOBEC3C is deaminase independent and mediated by an ORF1p interaction that affects LINE reverse transcriptase activity, Nucleic Acids Res. 42 (2014) 396–416.
[52] A.E. Hulme, H.P. Bogerd, B.R. Cullen, J.V. Moran, Selective inhibition of Alu retrotransposition by APOBEC3G, Gene 390 (2007) 199–205.
[53] Q. Wang, J. Khillan, P. Gadue, K. Nishikura, Requirement of the RNA editing deaminase ADAR1 gene for embryonic erythropoiesis, Science 290 (2000) 1765–1768.
[54] W. Qiu, X. Wang, M. Buchanan, K. He, R. Sharma, L. Zhang, Q. Wang, J. Yu, ADAR1 is essential for intestinal homeostasis and stem cell maintenance, Cell Death Dis. 4 (2013) e599.
[55] R. XuFeng, M.J. Boyer, H. Shen, Y. Li, H. Yu, Y. Gao, Q. Yang, Q. Wang, T. Cheng, ADAR1 is required for hematopoietic progenitor cell survival via RNA editing, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 17763–17768.
[56] M. Higuchi, S. Maas, F.N. Single, J. Hartner, A. Rozov, N. Burnashev, D. Feldmeyer, R. Sprengel, P.H. Seeburg, Point mutation in an AMPA receptor gene rescues lethality in mice deficient in the RNA-editing enzyme ADAR2, Nature 406 (2000) 78–81.
[57] N.P. Whitney, H. Peng, N.B. Erdmann, C. Tian, D.T. Monaghan, J.C. Zheng, Calcium-permeable AMPA receptors containing Q/R-unedited GluR2 direct human neural progenitor cell differentiation to neurons, FASEB J. 22 (2008) 2888–2900.
[58] M.M. Jacobs, R.L. Fogg, R.B. Emeson, G.D. Stanwood, ADAR1 and ADAR2 expression and editing activity during forebrain development, Dev. Neurosci. 31 (2009) 223–237.
[59] Y. Sato, H.C. Probst, R. Tatsumi, Y. Ikeuchi, M.S. Neuberger, C. Rada, Deficiency in APOBEC2 leads to a shift in muscle fiber type, diminished body mass, and myopathy, J. Biol. Chem. 285 (2010) 7111–7118.
[60] A. Vonica, A. Rosa, B.L. Arduini, A.H. Brivanlou, APOBEC2, a selective inhibitor of TGFbeta signaling, regulates left–right axis specification during early embryogenesis, Dev. Biol. 350 (2011) 13–23.
[61] C. Powell, F. Elsaeidi, D. Goldman, Injury-dependent Muller glia and ganglion cell reprogramming during tissue regeneration requires Apobec2a and Apobec2b, J. Neurosci. 32 (2012) 1096–1109.
[62] Y.-R. Qin, J.-J. Qiao, T.H.M. Chan, Y.-H. Zhu, F.-F. Li, H. Liu, J. Fei, Y. Li, X.-Y. Guan, L. Chen, Adenosine-to-inosine RNA editing mediated by ADARs in esophageal squamous cell carcinoma, Cancer Res. 74 (2013) 840–851.
[63] J.C. Hartner, C.R. Walkley, J. Lu, S.H. Orkin, ADAR1 is essential for the maintenance of hematopoiesis and suppression of interferon signaling, Nat. Immunol. 10 (2009) 109–115.
[64] Y. Choudhury, F.C. Tay, D.H. Lam, E. Sandanaraj, C. Tang, B.T. Ang, S. Wang, Attenuated adenosine-to-inosine editing of microRNA-376a* promotes invasiveness of glioblastoma cells, J. Clin. Invest. 122 (2012) 4059–4076.
[65] S. Ishiuchi, Y. Yoshida, K. Sugawara, M. Aihara, T. Ohtani, T. Watanabe, N. Saito, K. Tsuzuki, H. Okado, A. Miwa, et al., Ca^{2+}-permeable AMPA receptors regulate growth of human glioblastoma via Akt activation, J. Neurosci. 27 (2007) 7987–8001.
[66] T. Shimokawa, M.F. Rahman, U. Tostar, E. Sonkoly, M. Stahle, A. Pivarcsi, R. Palaniswamy, P.G. Zaphiropoulos, RNA editing of the GLI1 transcription factor modulates the output of Hedgehog signaling, RNA Biol. 10 (2013) 321–333.
[67] H. Zhu, H.W. Lo, The human glioma-associated oncogene homolog 1 (GLI1) family of transcription factors in gene regulation and diseases, Curr. Genomics 11 (2010) 238–245.
[68] N. Paz, E.Y. Levanon, N. Amariglio, A.B. Heimberger, Z. Ram, S. Constantini, Z.S. Barbash, K. Adamsky, M. Safran, A. Hirschberg, et al., Altered adenosine-to-inosine RNA editing in human cancer, Genome Res. 17 (2007) 1586–1595.
[69] R. Shukla, K.R. Upton, M. Munoz-Lopez, D.J. Gerhardt, M.E. Fisher, T. Nguyen, P.M. Brennan, J.K. Baillie, A. Collino, S. Ghisletti, et al., Endogenous retrotransposition activates oncogenic pathways in hepatocellular carcinoma, Cell 153 (2013) 101–111.
[70] J.H. Yang, X. Luo, Y. Nie, Y. Su, Q. Zhao, K. Kabir, D. Zhang, R. Rabinovici, Widespread inosine-containing mRNA in lymphocytes regulated by ADAR1 in response to inflammation, Immunology 109 (2003) 15–23.
[71] D. Dominissini, S. Moshitch-Moshkovitz, N. Amariglio, G. Rechavi, Adenosine-to-inosine RNA editing meets cancer, Carcinogenesis 32 (2011) 1569–1577.
[72] C.M. Croce, Causes and consequences of microRNA dysregulation in cancer, Nat. Rev. Genet. 10 (2009) 704–714.
[73] G.M. Borchert, B.L. Gilmore, R.M. Spengler, Y. Xing, W. Lanier, D. Bhattacharya, B.L. Davidson, Adenosine deamination in human transcripts generates novel microRNA binding sites, Hum. Mol. Genet. 18 (2009) 4801–4807.
[74] M. Guttman, J. Donaghey, B.W. Carey, M. Garber, J.K. Grenier, G. Munson, G. Young, A.B. Lucas, R. Ach, L. Bruhn, et al., lincRNAs act in the circuitry controlling pluripotency and differentiation, Nature 477 (2011) 295–300.
[75] S. Garrett, J.J. Rosenthal, RNA editing underlies temperature adaptation in K+ channels from polar octopuses, Science 335 (2012) 848–851.
[76] D. Mukhopadhyay, S. Anant, R.M. Lee, S. Kennedy, D. Viskochil, N.O. Davidson, C → U editing of neurofibromatosis 1 mRNA occurs in tumors that express both the type II transcript and apobec-1, the catalytic subunit of the apolipoprotein B mRNA-editing enzyme, Am. J. Hum. Genet. 70 (2002) 38–50.
[77] S. Yamanaka, M.E. Balestra, L.D. Ferrell, J. Fan, K.S. Arnold, S. Taylor, J.M. Taylor, T.L. Innerarity, Apolipoprotein B mRNA-editing protein induces hepatocellular carcinoma and dysplasia in transgenic animals, Proc. Natl. Acad. Sci. U. S. A. 92 (1995) 8483–8487.
[78] S. Nik-Zainal, B. Alexandrov Ludmil, C. Wedge David, P. Van Loo, D. Greenman Christopher, K. Raine, D. Jones, J. Hinton, J. Marshall, A. Stebbings Lucy, et al., Mutational processes molding the genomes of 21 breast cancers, Cell 149 (2012) 979–993.
[79] M.B. Burns, L. Lackey, M.A. Carpenter, A. Rathore, A.M. Land, B. Leonard, E.W. Refsland, D. Kotandeniya, N. Tretyakova, J.B. Nikas, et al., APOBEC3B is an enzymatic source of mutation in breast cancer, Nature 494 (2013) 366–370.
[80] S.A. Roberts, M.S. Lawrence, L.J. Klimczak, S.A. Grimm, D. Fargo, P. Stojanov, A. Kiezun, G.V. Kryukov, S.L. Carter, G. Saksena, et al., An APOBEC cytidine deaminase mutagenesis pattern is widespread in human cancers, Nat. Genet. 45 (2013) 970–976.
[81] M.B. Burns, N.A. Temiz, R.S. Harris, Evidence for APOBEC3B mutagenesis in multiple human cancers, Nat. Genet. 45 (2013) 977–983.
[82] S. Pauklin, I.V. Sernandez, G. Bachmann, A.R. Ramiro, S.K. Petersen-Mahrt, Estrogen directly activates AID transcription and function, J. Exp. Med. 206 (2009) 99–111.

[83] Y. Matsumoto, H. Marusawa, K. Kinoshita, Y. Niwa, Y. Sakai, T. Chiba, Up-regulation of activation-induced cytidine deaminase causes genetic aberrations at the CDKN2b–CDKN2a in gastric cancer, Gastroenterology 139 (2010) 1984–1994.
[84] V.R. Nelson, J.D. Heaney, P.J. Tesar, N.O. Davidson, J.H. Nadeau, Transgenerational epigenetic effects of the Apobec1 cytidine deaminase deficiency on testicular germ cell tumor susceptibility and embryonic viability, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) E2766–E2773.
[85] Z. Chen, T.L. Eggerman, A.V. Bocharov, I.N. Baranova, T.G. Vishnyakova, G. Csako, A. P. Patterson, Hypermutation induced by APOBEC-1 overexpression can be eliminated, RNA 16 (2010) 1040–1052.
[86] L. Li, L. Krymskaya, J. Wang, J. Henley, A. Rao, L.F. Cao, C.A. Tran, M. Torres-Coronado, A. Gardner, N. Gonzalez, et al., Genomic editing of the HIV-1 coreceptor CCR5 in adult hematopoietic stem and progenitor cells using zinc finger nucleases, Mol. Ther. 21 (2013) 1259–1269.
[87] M. Cheung, J.R. Testa, Diverse mechanisms of AKT pathway activation in human malignancy, Curr. Cancer Drug Targets 13 (2013) 234–244.
[88] C. Chakraborty, S. Pal, G.P. Doss, Z.H. Wen, C.S. Lin, Nanoparticles as 'smart' pharmaceutical delivery, Front. Biosci. (Landmark Ed.) 18 (2013) 1030–1050.
[89] S. El-Andaloussi, Y. Lee, S. Lakhal-Littleton, J. Li, Y. Seow, C. Gardiner, L. Alvarez-Erviti, I.L. Sargent, M.J. Wood, Exosome-mediated delivery of siRNA in vitro and in vivo, Nat. Protoc. 7 (2012) 2112–2126.
[90] R. Kole, A.R. Krainer, S. Altman, RNA therapeutics: beyond RNA interference and antisense oligonucleotides, Nat. Rev. Drug Discov. 11 (2012) 125–140.
[91] R.A. Mizrahi, N.T. Schirle, P.A. Beal, Potent and selective inhibition of A-to-I RNA editing with 2′-O-methyl/locked nucleic acid-containing antisense oligoribonucleotides, ACS Chem. Biol. 8 (2013) 832–839.
[92] L.E. Rieder, C.J. Staber, B. Hoopengardner, R.A. Reenan, Tertiary structural elements determine the extent and specificity of messenger RNA editing, Nat. Commun. 4 (2013) 2232.
[93] S. Maas, S. Patt, M. Schrey, A. Rich, Underediting of glutamate receptor GluR-B mRNA in malignant gliomas, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 14687–14692.
[94] S. Ishiuchi, K. Tsuzuki, Y. Yoshida, N. Yamada, N. Hagimura, H. Okado, A. Miwa, H. Kurihara, Y. Nakazato, M. Tamura, et al., Blockage of Ca(2+)-permeable AMPA receptors suppresses migration and induces apoptosis in human glioblastoma cells, Nat. Med. 8 (2002) 971–978.
[95] A. Beghini, C.B. Ripamonti, P. Peterlongo, G. Roversi, R. Cairoli, E. Morra, L. Larizza, RNA hyperediting and alternative splicing of hematopoietic cell phosphatase (PTPN6) gene in acute myeloid leukemia, Hum. Mol. Genet. 9 (2000) 2297–2304.
[96] F. Galeano, A. Leroy, C. Rossetti, I. Gromova, P. Gautier, L.P. Keegan, L. Massimi, C. Di Rocco, M.A. O'Connell, A. Gallo, Human BLCAP transcript: new editing events in normal and cancerous tissues, Int. J. Cancer 127 (2010) 127–137.
[97] S.P. Shah, R.D. Morin, J. Khattra, L. Prentice, T. Pugh, A. Burleigh, A. Delaney, K. Gelmon, R. Guliany, J. Senz, et al., Mutational evolution in a lobular breast tumour profiled at single nucleotide resolution, Nature 461 (2009) 809–813.
[98] Y. Nemlich, E. Greenberg, R. Ortenberg, M.J. Besser, I. Barshack, J. Jacob-Hirsch, E. Jacoby, E. Eyal, L. Rivkin, V.G. Prieto, et al., MicroRNA-mediated loss of ADAR1 in metastatic melanoma promotes tumor growth, J. Clin. Invest. 123 (2013) 2703–2718.
[99] F. Galeano, C. Rossetti, S. Tomaselli, L. Cifaldi, M. Lezzerini, M. Pezzullo, R. Boldrini, L. Massimi, C.M. Di Rocco, F. Locatelli, et al., ADAR2-editing activity inhibits glioblastoma growth through the modulation of the CDC14B/Skp2/p21/p27 axis, Oncogene 32 (2013) 998–1009.
[100] J.M. Flanagan, J.M. Funes, S. Henderson, L. Wild, N. Carey, C. Boshoff, Genomics screen in transformed stem cells reveals RNASEH2A, PPAP2C, and ADARB1 as putative anticancer drug targets, Mol. Cancer Ther. 8 (2009) 249–260.
[101] I. Valles, M.J. Pajares, V. Segura, E. Guruceaga, J. Gomez-Roman, D. Blanco, A. Tamura, L.M. Montuenga, R. Pio, Identification of novel deregulated RNA metabolism-related genes in non-small cell lung cancer, PLoS One 7 (2012) e42086.
[102] S. Tomaselli, F. Galeano, L. Massimi, C. Di Rocco, L. Lauriola, A. Mastronuzzi, F. Locatelli, A. Gallo, ADAR2 editing activity in newly diagnosed versus relapsed pediatric high-grade astrocytomas, BMC Cancer 13 (2013) 255.
[103] H.D. Martinez, R.J. Jasavala, I. Hinkson, L.D. Fitzgerald, J.S. Trimmer, H.J. Kung, M.E. Wright, RNA editing of androgen receptor gene transcripts in prostate cancer cells, J. Biol. Chem. 283 (2008) 29938–29949.
[104] C. Cenci, R. Barzotti, F. Galeano, S. Corbelli, R. Rota, L. Massimi, C. Di Rocco, M.A. O'Connell, A. Gallo, Down-regulation of RNA editing in pediatric astrocytomas: ADAR2 editing activity inhibits cell migration and proliferation, J. Biol. Chem. 283 (2008) 7251–7260.
[105] V. Blanc, J.O. Henderson, R.D. Newberry, Y. Xie, S.J. Cho, E.P. Newberry, S. Kennedy, D.C. Rubin, H.L. Wang, J. Luo, et al., Deletion of the AU-rich RNA binding protein Apobec-1 reduces intestinal tumor burden in Apc(min) mice, Cancer Res. 67 (2007) 8565–8573.
[106] O. Ashur-Fabian, A. Har-Zahav, A. Shaish, H. Wiener Amram, O. Margalit, O. Weizer-Stern, D. Dominissini, D. Harats, N. Amariglio, G. Rechavi, apoB and apobec1, two genes key to lipid metabolism, are transcriptionally regulated by p53, Cell Cycle 9 (2010) 3761–3770.
[107] M.D. Stenglein, M.B. Burns, M. Li, J. Lengyel, R.S. Harris, APOBEC3 proteins mediate the clearance of foreign DNA from human cells, Nat. Struct. Mol. Biol. 17 (2010) 222–229.
[108] S. Landry, I. Narvaiza, D.C. Linfesty, M.D. Weitzman, APOBEC3A can activate the DNA damage response and cause cell-cycle arrest, EMBO Rep. 12 (2011) 444–450.
[109] B.J. Taylor, S. Nik-Zainal, Y.L. Wu, L.A. Stebbings, K. Raine, P.J. Campbell, C. Rada, M. R. Stratton, M.S. Neuberger, DNA deaminases induce break-associated mutation showers with implication of APOBEC3B and 3A in breast cancer kataegis, Elife 2 (2013) e00534.
[110] J.P. Vartanian, D. Guetard, M. Henry, S. Wain-Hobson, Evidence for editing of human papillomavirus DNA by APOBEC3 in benign and precancerous lesions, Science 320 (2008) 230–233.
[111] J.C. Hartner, C. Schmittwolf, A. Kispert, A.M. Muller, M. Higuchi, P.H. Seeburg, Liver disintegration in the mouse embryo caused by deficiency in the RNA-editing enzyme ADAR1, J. Biol. Chem. 279 (2004) 4894–4902.
[112] H. Wahlstedt, C. Daniel, M. Enstero, M. Ohman, Large-scale mRNA sequencing determines global regulation of RNA editing during brain development, Genome Res. 19 (2009) 978–986.
[113] R. Chahwan, S.N. Wontakal, S. Roa, Crosstalk between genetic and epigenetic information through cytosine deamination, Trends Genet. 26 (2010) 443–448.