Review

Cancer Research

RNA Editome Imbalance in Hepatocellular Carcinoma

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Abstract

Adenosine-to-inosine conversion (A-to-I editing), a posttranscriptional modification on RNA, contributes to extensive transcriptome diversity. A-to-I editing is a hydrolytic deamination process, catalyzed by adenosine deAminase acting on double-stranded RNA (ADAR) family of enzymes. ADARs are essential for normal mammalian development, and disturbance in RNA editing has been implicated in various pathologic disorders, including cancer. Thanks to next-generation sequencing, rich databases of transcriptome evolution for cancer development at the resolution of single nucleotide have been generated. Extensive bioinformatic analysis revealed a complex picture of RNA editing change during transformation. Cancer displayed global hypoediting of *Alu*-repetitive elements with gene-specific editing pattern. In particular, hepatocellular carcinoma editome is severely disrupted and characterized by hyper- and hypoediting of different genes, such as hyperedited *AZIN1* (antizyme inhibitor 1) and *FLNB* (filamin B, β) and hypoedited *COPA* (coatomer protein complex, subunit α). In hepatocellular carcinoma, not only the recoding editing in exons, but also the editing in noncoding regions (e.g., *Alu*-repetitive elements and microRNA) displays such complex editing pattern with site-specific editing trend. In this review, we will discuss current research progress on the involvement of abnormal A-to-I editing in cancer development, more specifically on hepatocellular carcinoma. *Cancer Res; 74(5); 1301–6. ©2014 AACR.*

Introduction

Hepatocellular carcinoma represents the fifth most common type of all cancer for men and the seventh for women worldwide (1). It also has a high mortality rate of 0.93, which ranks hepatocellular carcinoma as the third leading cause of death from cancer worldwide (2). The demoralizing outcome of hepatocellular carcinoma is mainly due to late manifestation of large tumor, rendering early curative intent treatment infeasible. The late symptom onset is a result of a multistep transformation process that usually takes 10 to 30 years. In addition to the bleak fact that hepatocellular carcinoma is asymptomatic in early stage, the available treatment options for intermediate-advanced stage patients are also disappointing. The extreme low response rate to chemotherapy makes its effects negligible; and the only available small-molecular inhibitor against multikinases (sorafenib) can only prolong the survival of patients with hepatocellular carcinoma for 3 months (3). All these facts put more novel and effective therapeutic interventions in urgent needs, therefore extensive efforts have been devoted to identify new druggable molecular targets. Previous studies have focused much attention on revealing DNA mutations and gene expression change. However, at least 20% hepatocellular carcinomas fail to be identified to harbor driver DNA mutations, suggesting that other driver events could be responsible for hepatocellular carcinoma initiation and progression. Recently, RNA editing has entered the limelight in cancer and refutes the conception that DNA dictates nucleotides in RNA. RNA editing is defined as chemical modifications on RNA transcript after synthesis by RNA polymerases. In this review, we will focus on the most prevalent type of RNA editing in human, adenosine-to-inosine conversion (A-to-I editing). Although more comprehensive information about A-to-I editing is available in another review by Nishikura (4), we will here give a brief overview of this process and then focus in more depth on A-to-I editing's involvement in cancer development, and more specifically in hepatocellular carcinoma.

Adenosine-to-Inosine Editing

RNA editing was originally discovered in trypanosome mitochondria where four extra nucleotides not encoded by the gene were found in *coxII* transcript to restore the reading frame of the encoded protein (5). Since then, different types of RNA editing of various RNA molecules (e.g., mRNA, tRNA, and rRNA) have been documented across multiple species. As one of the most well-characterized type of RNA editing, A-to-I editing was initially discovered as an RNA duplex unwinding activity in *Xenopus* embryos (6, 7). It was later elucidated as a hydrolytic deamination process catalyzed by a family of enzymes known as ADAR, abbreviation for adenosine deAminase acting on double-stranded RNA (dsRNA; ref. 8). As suggested by the name, dsRNA secondary structure is necessary for A-to-I editing and it affects both the frequency and distribution of editing across genome. The frequency of editing

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is largely determined by the length and perfectness of dsRNA. Although short (or long but imperfect) dsRNA exhibits site-selective editing at certain adenosine only, long perfect dsRNA (>100 bp) tends to be more promiscuously hyperedited with up to 50% of adenosine converted to inosine (9). As for genome-wide distribution of A-to-I editing, it was initially thought to be rare events limited to coding exons. However, next-generation sequencing has revealed that A-to-I editing is abundant and majority of A-to-I editing locates in noncoding regions, mainly introns and untranslated regions (UTRs; Fig. 1). The overrepresentation of A-to-I editing in noncoding regions is probably caused by high incidence of dsRNA formation by the embedded repetitive elements, for example, *Alu* elements (10). Furthermore, editing in noncoding regions tends to be promiscuous hyperediting, compared with site-selective editing found in coding regions.

ADARs

ADARs, the catalyzer of A-to-I editing, are highly conserved in vertebrates with three *ADAR* genes in human. All three ADAR members share a common modular structure, with N-terminal two to three repeats of dsRNA-binding domain and C-terminal catalytic deaminase domain; however, different isoforms exist. In particular, ADAR1 has two major isoforms transcribed from alternative promoters, and initiated from different start codon due to alternative splicing (11). ADAR1-150 kDa longer form is synthesized from an IFN-inducible promoter and shuttles

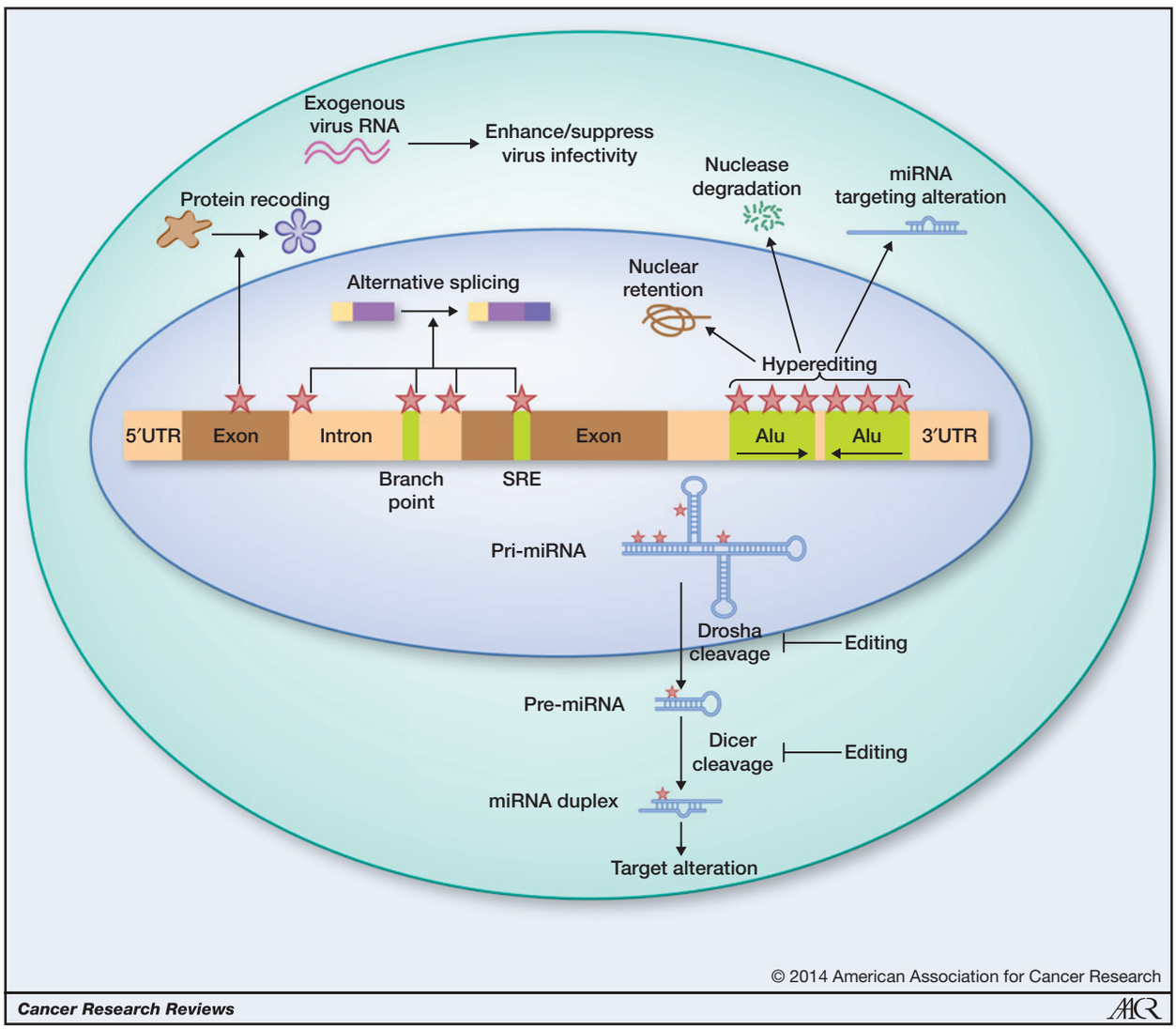

Figure 1. Genome-wide distribution of A-to-I editing and its consequences. Site-selective recoding editing in coding regions can change protein amino acid sequence and hence, potentially protein functions. Editing that involves splicing motif alteration (creation or elimination) or happens in SREs can affect alternative splicing or splicing efficiency. Hyperediting of 3′UTR due to the higher chance of dsRNA formation between the embedded repetitive elements, such as *Alu*, can result in target mRNA nuclear retention, degradation by inosine-specific nucleases, or alteration of miRNA-mediated silencing. Editing can also target endogenous stem-loop structures (e.g., those present along miRNA biogenesis pathway), as well as exogenous dsRNA (e.g., virus genome).

between nucleus and cytoplasm; in contrast, the truncated ADAR1-110 kDa form is transcribed from a constitutively active promoter and predominately localizes in nucleus (12). ADAR1 and ADAR2 are editing competent, and ubiquitously expressed in multiple human tissues; however, no editing activity or substrate has been discovered for ADAR3 and its expression is restricted to brain (13–15). In this case, it is worth mentioning that ADARs function as homodimer. ADAR1 and ADAR2 can form both homodimer and heterodimer, but ADAR3 only exists as monomer, which might explain its incompetence in editing (16).

ADARs play important roles during normal development as reflected by different transgenic animal models, as wells as human diseases associated with dysfunctional A-to-I editing. In *Caenorhabditis elegans*, homozygous deletion of both *CeADR1* and *CeADR2* revealed their importance to normal vulva development and chemotaxis (17). In *Drosophila*, deletion of *dADAR* led to severe deficits of behavior control in adults, like temperature-sensitive paralysis and locomotor uncoordination (18). In mouse, homozygous deletion of *Adar2* resulted in a seizure prone phenotype and early lethality after birth (between P0 and P20; ref. 19). In contrast with the viable phenotype of $Adar2^{-/-}$ mouse, $Adar1^{-/-}$ mouse was embryonic lethal (died between E11.5 and E12.5), mainly due to defective hematopoiesis and liver disintegration (20, 21). In human, RNA editing is also a tightly regulated process, disturbance in RNA editing have been associated with many diseases, including cancer, which will be discussed in following session. Significantly different editing site preference of serotonin 2C receptor (5-HT2cR) was observed in prefrontal cortex of depressed suicidal victims, and failure of editing at the Q/R site of glutamate receptor subunit B (GluR-B) was suggested contributing to neuronal death in patients with sporadic amyotrophic lateral sclerosis (22, 23). Furthermore, loss-of-function mutation in ADAR1 was linked to an inherited autosomal dominant disease, dyschromatosis symmetrica hereditaria (DSH; ref. 24). All these examples emphasize the critical physiologic functions carried by fine-tuned A-to-I editing.

Decoding of A-to-I Editing

How is A-to-I editing interpreted by different cellular machineries? When A-to-I editing was first discovered, it was identified as an RNA duplex unwinding activity because of the I:U mismatch (6). From the view of base-paring property, A-to-I editing equals to structural change, either increasing or decreasing the stability of targeted dsRNA by targeting A:C mismatch or A:U base pair, respectively.

From the view of biologic significance, the meaning of A-to-I editing depends on its location (Fig. 1). Site-selective editing in coding region has the potential to recode protein as inosine is recognized as guanosine by translational machinery, the prototypical examples of this category are recoding editing of GluR-B and 5-HT2cR (25, 26). Similarly, alternative canonical splicing sites (5′-GU-branch point-AG-3′) can also be created or destroyed because splicing machinery also recognizes inosine as guanosine. One such well-known case is the negative autoregulation of ADAR2 by self-editing, which creates a 3′ proximal splicing acceptor site and leads to frame shift in ADAR2 (27). Although editing of canonical splicing motif is rare, editing of splicing regulatory elements (SRE) in exons is more abundant (28). Instead of creating or destroying alternatively spliced isoforms, editing of SREs can affect splicing efficiency.

For 3′UTR, which consists of vast majority of editing, understanding the role of hyperediting in this region is still in its infancy, albeit hyperediting has been associated with regulation of transcript stability and location. Hyperediting in 3′UTR can affect transcript stability through alteration of microRNA (miRNA)-targeting sites because inosine preferentially base pairs with cytosine. Alternatively, hyperediting in 3′UTR can recruit inosine-specific nucleases and subsequently leads to the edited target degradation. Both human endonuclease V and Tudor staphylococcal nuclease have been demonstrated to interact with hyperedited dsRNAs and promote its cleavage (29, 30). As for the location of hyperedited RNA, nuclear retention of edited RNAs has been reported by a $P54^{nrb}$ containing tri–protein complex (31). However, more recent studies suggested that hyperediting in 3′UTR did not affect transcript stability, subcellular location, or translatability of edited RNAs (32). Therefore, the nuclear retention mechanism might be a gene-specific phenomenon. Considering different observations from various studies, as wells as the enormous transcript diversity generated by hyperediting in 3′UTR, understanding of editing in this region still demands intensive efforts.

Finally, editing in endogenous stem-loop structure of primary miRNA is also decoded by different cellular machineries along miRNA biogenesis and function pathway. Editing outside of miRNA seed sequence was shown to suppress efficient Drosha and Dicer processing, which is necessary for miRNA maturation (33). On the other hand, editing inside of miRNA seed sequence can redirect miRNA silencing targets (34). Therefore, in complement to editing of 3′UTR harboring miRNA-binding site, editing of miRNA itself is another gate to affect transcript stability.

A-to-I Editing and Cancer Development

Cancer, like other diseases, has also been associated with disturbance of A-to-I editing. However, cancer incidence was not reported to change in either ADAR transgenic mouse models or in humans suffering DSH. Therefore, editing is unlikely an early initiation hit along the transformation slope (19–21, 24). Nonetheless, editing deregulation has been associated with tumor progression in many different types of cancers. Hence, it should be considered as a driver event for cancer development. However, editing deregulation cannot be simply categorized as a tumor-suppressive or oncogenic process because the ultimate effects of A-to-I editing deregulation depend on the actual edited targets. Furthermore, comprehensive analysis of available editing database revealed a complex cancer editing picture: tumors are characterized by global hypoediting in repetitive elements accompanied with gene-specific editing pattern along transformation, that is, there is a

lack of joint editing trend for different genes in cancer (35). Therefore, effects of editing disturbance on cancer development should be addressed on a gene-specific level. For more information about A-to-I editing and cancer development, you can refer to review by Dominissini and colleagues (36).

Several genes with altered editing frequency in different tumors have been identified. Underediting of *GluR-B* in human glioblastoma multiforme without apparent differential expression of ADAR2 was first documented by Maas and colleagues (37). Subsequently, underediting GluR-B was shown to increase Ca^{2+} permeability of a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type GluR, and in turn, facilitated tumor cell migration and proliferation (38). Similarly, bladder cancer-associated protein (BLCAP) was shown to be underedited in primary bladder cancer, but the physiologic importance of edited *BLCAP* remains unexplored (39). In opposite to the underediting of *GluR-B* and *BLCAP*, hyperediting of filamin B, β (*FLNB*) and antizyme inhibitor 1 (*AZIN1*) was identified in esophageal squamous cell carcinoma (ESCC). More importantly, edited AZIN1 conferred gain-of-function phenotype associated with aggressive tumor behavior of ESCC (unpublished data). Finally, in hematologic malignancies, abnormal A-to-I editing of hematopoietic cell phosphatase (*PTPN6*) gene was associated to acute myelogenous leukemia (AML). The novel editing of *PTPN6* IVS3 putative branch point in AML led to intron3 retention and predicted nonsense translation of *PTPN6* (40). In short, different cancers show distinct editing patterns of relevant genes, and there is an association between disturbed editing and cancer development. However, the biologic significance of an edited gene on transformation is important to be demonstrated before drawing a causal relationship between editing and cancer.

What brings the editing disturbance during cancer development? One possible cause is the expression change of editing enzymes, ADARs. As the regulatory machineries controlling ADAR activity remain largely unknown, most studies have focused on investigating the expression change of ADARs. For instance, both adult and pediatric gliobalstomas were characterized by underediting of ADAR2-specific target GluR-B at Q/R site; however, both tumors did not show change of ADAR2 mRNA level. Nonetheless ADAR2 activity (as evaluated by the extent of self-editing of ADAR2) was shown to be decreased (37). To understand this, one should bear in mind that ADARs function as homodimer (16). Overexpression of one ADAR member can affect the editing frequency of the other member's specific target given that nonfunctional heterodimer between ADAR members can form. Indeed both ADAR1 and ADAR3 mRNA showed increased expression in brain tumor and forced expression of ADAR1 inhibited editing frequency of ADAR2-specific site (41). This might explain the incongruent change between ADAR2 mRNA and its target editing frequency. In other tumors, differential expression of ADARs could be more directly responsible for disturbed editing balance of their respective targets. For instance, hepatocellular carcinoma was reported to have increased expression of ADAR1 but decreased expression of ADAR2 at both mRNA and protein levels (42). The differential expression change of ADAR1 and ADAR2 was responsible for hyperediting of *AZIN1* and hypoediting of coatomer protein complex, subunit-α (*COPA*), respectively. Hence, different tumors seem to have differential expression pattern of ADARs. To resolve the dilemma of incongruent expression of ADARs across different tumors, an imbalanced ADAR expression model was proposed as a general phenomenon observed for cancer (36). However, other than ADAR expression, editing can be affected by multiple factors, including environmental stimuli. Therefore, with more research on regulatory machineries governing ADAR editing activity in future, we hope the underlying cause of editing disturbance in cancer could be better understood.

Editome Imbalance in Hepatocellular Carcinoma

Even though a few concrete examples have suggested the involvement of editing deregulation in several types of cancers, none aberrant editing has been recognized in hepatocellular carcinoma until our group first reported the increased recoding editing in *AZIN1* (43). However, hepatocellular carcinoma cannot be simply regarded as a hyperedited cancer type. More recent large-cohort hepatocellular carcinoma editome study revealed hepatocellular carcinoma displayed a severely disrupted editome balance characterized by gene-specific editing pattern (42). The newly identified abnormal recoding editing is hyperediting of *FLNB* and hypoediting of *COPA*. Similar to other cancers, there is a lack of joint editing trend for different genes in hepatocellular carcinoma. This is probably caused by the substrate specificity of different ADAR members that displayed opposite expression changes in hepatocellular carcinoma (increased ADAR1 and decreased ADAR2). As established from both studies, *AZIN1* is specifically edited by ADAR1, whereas *COPA* can only be edited by ADAR2, and *FLNB* is a common target of ADAR1 and ADAR2 (42, 43). Not only did the recoding editing show opposite editing trend, but also the editing in *Alu*-repetitive elements of different genes had the same pattern. Therefore, hepatocellular carcinoma is best summarized as an editome imbalanced cancer.

As mentioned earlier, the biologic significance of an edited gene on transformation is important to be illustrated to claim the association of editing disturbance and cancer. For hepatocellular carcinoma, the first evidence about involvement of editing in carcinogenesis was established from *AZIN1* recoding editing; however, evidence for *FLNB* and *COPA* is still lacking. Recoding editing of *AZIN1* replaces a genetically encoded serine by glycine at position 376, causing a conformational change of AZIN1 and thereby increasing its affinity to antizyme. By doing so, edited AZIN1 spares ornithine decarboxylase and cyclin D1 from antizyme-mediated degradation, thus promotes hepatocellular carcinoma cell proliferation (43). Given the oncogenic role of the edited AZIN1, edited AZIN1 could be a promising drug target for future therapeutic development against hepatocellular carcinoma.

Similar to recoding editing, editing in noncoding regions of different genes also shows inconsistent change in hepatocellular carcinoma. Editing of miRNAs in either normal adult liver tissue or hepatocellular carcinoma has been reported [e.g., miRNA (miR)-151, miR-197, and miR99a]. Furthermore, decreased editing of miR-376a and increased editing of

miR-376c were demonstrated for hepatocellular carcinoma (44). However, the study was performed with deep sequencing of combined cDNA from 18 patients instead of paired cDNA from individual patient. Therefore, whether there is a joint trend for the editing frequency of either miRNAs among the patients with hepatocellular carcinoma awaits further investigation.

Specifically for hepatocellular carcinoma, it is also worth discussing the intricate relationship between RNA editing and virus infection, as 60% to 90% of hepatocellular carcinoma are caused by hepatitis B/C virus (HBV/HCV) infection and subsequent chronic inflammation (45). However, it is difficult to categorize editing simply as antiviral or proviral mechanism. In support of antiviral functions, IFN-inducible ADAR1-150 kDa is able to directly edit HCV replicon RNA and inhibit virus replication (46). Furthermore, as an indirect antiviral mechanism, ADAR1 is critical for both embryonic and adult hematopoiesis, an essential system for maturation of all immune system cells (20, 21, 47). On the other hand, editing activity of ADARs can be harnessed by some viruses (e.g., HIV) to stimulate their replication, making ADAR1 as a proviral factor (48). The proviral effects of ADARs can be either dependent or independent of editing activity. ADAR1 has been shown able to inhibit the dsRNA-activated protein kinase, an important effecter of antiviral immunity by general inhibition of translation initiation, independent of editing activity (49). Moreover, ADAR1 can also directly edit virus RNA (e.g., HIV), and the editing activity is associated with enhanced virus infectivity (48). Whether ADAR1 also plays similar proviral roles in hepatocellular carcinoma still awaits further investigation. In combination, ADAR1 might be the pertinent factor contributing to persistent virus infection in different virus-induced cancers, given the dilemma situation generated by ADAR1 through manipulations on both host immune system and virus genome.

Conclusion and Future Perspectives

A-to-I RNA editing, as a posttranscriptional regulator generating extensive transcript diversity, is vital for normal mammalian development. It has also been implicated in normal functions of multiple human organs, with majority of studies focused on nervous system. Being a tightly regulated process, disturbance of normal editome balance is associated with various pathologic conditions, including cancer. Hepatocellular carcinoma is characterized as a cancer with imbalanced editome and gene-specific editing pattern in both coding and noncoding regions. Editome imbalance opens another field for more novel drug discovery and development. Therapy development can center two major components of A-to-I editing, the upstream catalyzer (ADAR enzymes) and the downstream function executer (edited targets). ADAR expression imbalance can be restored by overexpression or downregulation of the abnormally expressed members. However, given the substrate promiscuity of ADARs, this strategy might lead to unpredictable outcome. Importantly, substrate-specific inhibition of editing is recently proposed to be feasible by a helix-threading peptide target (50). This will provoke more creative strategy development to restore editing balance in gene-specific manner.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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