Pharmacology & Therapeutics xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: K.-I. Inui

Significance of A-to-I RNA editing of transcripts modulating pharmacokinetics and pharmacodynamics

Masataka Nakano, Miki Nakajima *

Drug Metabolism and Toxicology, Faculty of Pharmaceutical Sciences, Kanazawa University, Kakuma-machi, Kanazawa, Japan

ARTICLE INFO

Keywords:
RNA editing
Post-transcriptional regulation
Pharmacokinetics
Pharmacodynamics

ABSTRACT

RNA editing is a post-transcriptional process that alters the nucleotide sequence of RNA transcripts to generate transcriptome diversity. Among the various types of RNA editing, adenosine-to-inosine (A-to-I) RNA editing is the most frequent type of RNA editing in mammals. Adenosine deaminases acting on RNA (ADAR) enzymes, ADAR1 and ADAR2, convert adenosines in double-stranded RNA structures into inosines by hydrolytic deamination. Inosine forms a base pair with cytidine as if it were guanosine; therefore, the conversion may affect the amino acid sequence, splicing, microRNA targeting, and miRNA maturation. It became apparent that disrupted RNA editing or abnormal ADAR expression is associated with several diseases including cancer, neurological disorders, metabolic diseases, viral infections, and autoimmune disorders. The biological significance of RNA editing in pharmacokinetics/pharmacodynamics (PK/PD)-related genes is starting to be demonstrated. The authors conducted pioneering studies to reveal that RNA editing modulates drug metabolism potencies in the human liver, as well as the response of cancer cells to chemotherapy agents. Awareness of the importance of RNA editing in drug therapy is growing. This review summarizes the current knowledge on the RNA editing that affects the expression and function of drug response-related genes. Continuing studies on the RNA editing that regulates pharmacokinetics/pharmacodynamics would provide new beneficial information for personalized medicine.

Contents

Abbreviations: ABC, ATP-binding cassette transporter; ADAR, adenosine deaminase acting on RNA; ADH, alcohol dehydrogenase; AhR, aryl hydrocarbon receptor; AKR, aldo-keto reductase; ALS, amyotrophic lateral sclerosis; AZIN1, antizyme inhibitor 1; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; A-to-I, adenosine-to-inosine; BCRP, breast cancer resistance protein; CAR, constitutive androstane receptor; CES, carboxylesterase; COMT, catechol *O*-methyltransferase; CYP, cytochrome P450; DHFR, dihydrofolate reductase; dsRNA, double-stranded RNA; ER, estrogen receptor; FMO, flavin-containing monooxygenase; FXR, farnesoid X receptor; GluR2, glutamate receptor 2; GR, glucocorticoid receptor; HCC, hepatocellular carcinoma; HNF, human hepatocyte nuclear factor; LXR, liver X receptors; miRNA, microRNA; MRP, multidrug resistance-associated protein; NR, nuclear receptor; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; OCTN, organic cation/carnitine transporter; PCA, prostate cancer antigen; PD, pharmacodynamics; PEPT, peptide transporter; P-gp, P-glycoprotein; PK, pharmacokinetics; PPAR, peroxisome proliferator-activated receptor; Pre-miRNA, precursor microRNA; Pri-miRNA, primary microRNA; PXR, pregnane X receptor; SLC, solute carrier family; SLCO, solute carrier organic anion transporter; SULT, sulfotransferase; T2DM, Type 2 diabetes mellitus; TPMT, thiopurine *S*-methyltransferase; UGT, UDP-glucuronosyltransferase; URAT, urate transporter; UTR, untranslated region; VDR, vitamin D receptor.

* Corresponding author at: Drug Metabolism and Toxicology, Faculty of Pharmaceutical Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan.
E-mail address: nmiki@p.kanazawa-u.ac.jp (M. Nakajima).

http://dx.doi.org/10.1016/j.pharmthera.2017.07.003
0163-7258/

Please cite this article as: Nakano, M., & Nakajima, M., Significance of A-to-I RNA editing of transcripts modulating pharmacokinetics and pharmacodynamics, *Pharmacology & Therapeutics* (2017), http://dx.doi.org/10.1016/j.pharmthera.2017.07.003

1. Introduction

Gene regulation occurs at every step in the central dogma. In addition to regulatory mechanisms that act on DNA and proteins, eukaryotic RNA transcripts are subjected to various processing, such as alternative splicing, nucleotide modification and localization. Among such regulatory mechanisms, RNA editing refers to sequence alterations, including insertion, deletion or nucleotide conversion, that offer diversity in the transcriptome. Adenosine-to-inosine (A-to-I) RNA editing is a predominant form of RNA editing in mammals (Fig. 1) (Nishikura, 2010). In 1987, an enzymatic activity that causes the unwinding of double-stranded RNA (dsRNA) was discovered in *Xenopus laevis* oocytes and embryos (Bass & Weintraub, 1987). Later, this reaction was found to be the hydrolytic deamination of adenosine to form inosine, i.e., A-to-I RNA editing, which is catalyzed by adenosine deaminase acting on RNA (ADAR) enzymes (Bass & Weintraub, 1988; Wagner, Smith, Cooperman, & Nishikura, 1989). At that time, a limited number of RNA editing sites were discovered in the coding region of mRNA by comparing the sequences of genomic DNA and cDNA using Sanger sequencing (Sommer, Köhler, Sprengel, & Seeburg, 1991). Within the past 10 years, the progress of next-generation sequencing technologies has enabled the high-throughput identification of 4.5 million A-to-I RNA editing sites, not only in the coding region but also in the non-coding region (Picardi, D'Erchia, Giudice, & Pesole, 2017). Since the base-paring property of inosine is similar to that of guanosine, the conversion of nucleotides potentially affects gene function and expression, depending on the region where the editing event occurs. For genes associated with pharmacokinetics (PK) and pharmacodynamics (PD), the roles of RNA editing have just started being studied. The purpose of this review is to outline recent findings on the role of RNA editing of PK/PD-related genes and its potential pharmacotherapeutic implications.

2. ADAR enzymes

ADAR enzymes convert the adenosines in dsRNA structures into inosines by hydrolytic deamination at the C6 position (Gerber, O'Connell, & Keller, 1997; Kim, Wang, Sanford, Zeng, & Nishikura, 1994). A highly conserved deaminase domain in the C-terminal region and dsRNA-binding domains in the N-terminal region of ADARs catalyze this reaction (Nishikura, 2016). In the ADAR family in vertebrates, there are three members, ADAR1, ADAR2, and ADAR3 (also called ADAR, ADARB1, and ADARB2, respectively) (Bass et al., 1997). The *ADAR1* gene encodes two isoforms, ADAR1 p110 (110 kDa protein) and ADAR1 p150 (150 kDa protein), using different transcription initiation sites and start codons. The former is constitutively expressed and is localized in the nucleus whereas the expression of the latter is induced by interferon and exists in both the nucleus and the cytoplasm (Desterro et al., 2003; Patterson & Samuel, 1995). ADAR2, which is also a ubiquitous form, is highly expressed in the brain and is localized in nucleus (Melcher et al., 1996b). The expression of ADAR3 is limited to the brain (Chen et al., 2000; Melcher et al., 1996b). ADAR1 (Kim et al., 1994) and ADAR2 (Melcher et al., 1996a) have A-to-I RNA editing ability whereas ADAR3 does not show editing activity (Chen et al., 2000; Herbert et al., 1997; Melcher et al., 1996b). For ADAR1 and ADAR2, homodimerization is required to exert their editing activities (Cho et al., 2003; Poulsen et al., 2006; Valente & Nishikura, 2007). Cho et al. (2003) have reported that ADAR3 is unable to homodimerize, which may account for its lack of editing activity. Although there is no strict sequence specificity for A-to-I editing, the surrounding nucleotides have some influence on recognition by ADARs. ADAR1 has a 5′ neighbor preference (A = U > C > G), but no apparent 3′ neighbor preference (Riedmann, Schopoff, Hartner, & Jantsch, 2008). The 5′ neighbor preference of ADAR2 (A ≈ U > C = G) is similar to that of ADAR1 whereas ADAR2 has a 3′ neighbor preference (U = G > C = A) (Polson & Bass, 1994). Some nucleotides are edited by either ADAR1 or ADAR2, and the others can be edited by both enzymes (Hartner et al., 2004; Lehmann & Bass, 2000).

Mice genetically lacking either ADAR1 or ADAR2 were generated. It has been reported that the ADAR1-null mouse dies with numerous tissue failures at the embryogenesis stages (E11.5–12.5) (Wang et al., 2004), and the ADAR2-null mouse dies with epileptic seizures at postnatal day 20 (Higuchi et al., 2000), suggesting that ADAR proteins are indispensable for life.

3. Functional significance of A-to-I RNA editing of coding genes and miRNAs

Following the conversion of adenosine into inosine, the nucleotide is interpreted as a guanosine, leading to a series of functional consequences depending on the site of A-to-I editing (Fig. 2) (Zipeto, Jiang, Melese, & Jamieson, 2015). Editing in the coding region of pre-mRNA may change the genetic code, resulting in a change in the amino acid sequence. Editing in the intron may affect splicing by generating or deleting alternative splice sites. The editing events within the 3′-untranslated region (3′-UTR) have the potential to create or destroy the binding site of microRNAs (miRNAs) (Borchert et al., 2009; Deffit & Hundley, 2016; Farajollahi & Maas, 2010).

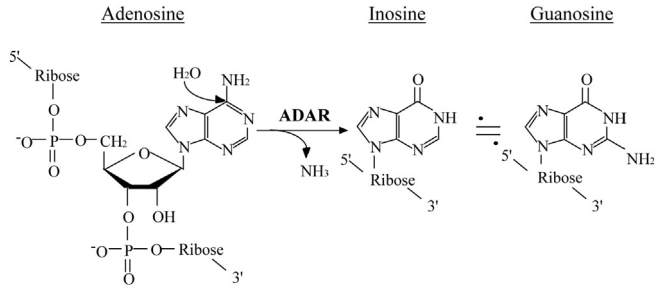

Fig. 1. A-to-I RNA editing, which refers to the deamination of adenosine to inosine in the RNA molecule. Adenosine deaminase acting on RNA (ADAR) enzymes convert adenosine to inosine by hydrolytic deamination. Inosine is recognized by the cellular machinery as if it were guanosine.

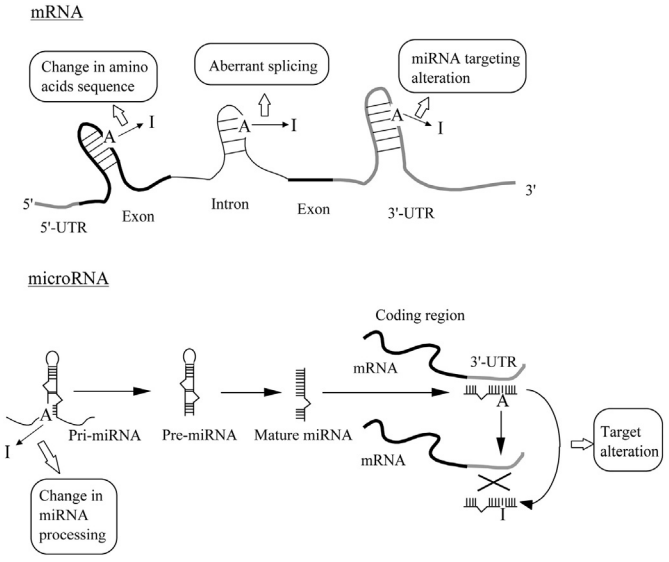

Fig. 2. Functional significance of A-to-I RNA editing. A-to-I editing occurs in double-stranded RNA structure. Editing in the coding region of pre-mRNA may change the amino acid sequence. Editing in the intron may affect splicing by generating or deleting alternative splice sites. The editing events within the 3′-untranslated region (3′-UTR) have the potential to create or destroy the binding site of miRNAs. The A-to-I change in a miRNA transcript can alter its processing, thereby affecting miRNA expression. A-to-I editing of the miRNA seed sequence could change its target selection or binding efficiency.

Please cite this article as: Nakano, M., & Nakajima, M., Significance of A-to-I RNA editing of transcripts modulating pharmacokinetics and pharmacodynamics, *Pharmacology & Therapeutics* (2017), http://dx.doi.org/10.1016/j.pharmthera.2017.07.003