Pharmacology & Therapeutics 143 (2014) 217–224

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

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

Associate editor: K.-I. Inui

# MicroRNAs as regulators of drug transporters, drug-metabolizing enzymes, and tight junctions: Implication for intestinal barrier function

Kenji Ikemura [a], Takuya Iwamoto [a,b], Masahiro Okuda [a,b,*]

[a] Department of Pharmacy, Mie University Hospital, Tsu, Mie 514-8507, Japan
[b] Department of Clinical Pharmacy and Biopharmaceutics, Mie University Graduate School of Medicine, Tsu, Mie 514-8507, Japan

ARTICLE INFO

Available online 11 March 2014

*Keywords:*
Intestinal barrier
Metabolizing enzymes
MicroRNA
Small intestine
Tight junction
Transporter

ABSTRACT

Drug transporters, drug-metabolizing enzymes, and tight junctions in the small intestine function as an absorption barrier and sometimes as a facilitator of orally administered drugs. The expression of these proteins often fluctuates and thereby causes individual pharmacokinetic variability. MicroRNAs (miRNAs), which are small non-coding RNAs, have recently emerged as a new class of gene regulator. MiRNAs post-transcriptionally regulate gene expression by binding to target mRNA to suppress its translation or regulate its degradation. They have been shown to be key regulators of proteins associated with pharmacokinetics. Moreover, the role of miRNAs on the expression of some proteins expressed in the small intestine has recently been clarified. In this review, we summarize current knowledge regarding the role of miRNAs in the regulation of drug transporters, drug-metabolizing enzymes, and tight junctions as well as its implication for intestinal barrier function. MiRNAs play vital roles in the differentiation, architecture, and barrier function of intestinal epithelial cells, and directly and/or indirectly regulate the expression and function of proteins associated with drug absorption in intestinal epithelial cells. Moreover, the variation of miRNA expression caused by pathological and physiological conditions as well as genetic factors should affect the expression of these proteins. Therefore, miRNAs could be significant factors affecting inter- and intra-individual variations in the pharmacokinetics and intestinal absorption of drugs. Overall, miRNAs could be promising targets for personalized pharmacotherapy or other attractive therapies through intestinal absorption of drugs.



**Contents**



## 1. Introduction

The small intestine is the primary site for the absorption of orally ingested drugs. The drugs cross the biological membranes via the transcellular or paracellular route. The transcellular pathway of transport is regulated by passive diffusion, uptake transporters, and efflux transporters, whereas tight junctions regulate the paracellular permeability

*Abbreviations:* ABC, ATP-binding cassette; BCRP, breast cancer resistance protein; CYP, cytochrome P450; I/R, ischemia–reperfusion; MCT1, monocarboxylate transporter 1; MDR1, multidrug resistance 1; miRNA, microRNA; MRP, multidrug resistance-associated protein; PEPT1, peptide transporter 1; P-gp, P-glycoprotein; PXR, pregnane X receptor; SLC, solute carrier; TJ, tight junction; UTR, untranslated region; VDR, vitamin D receptor.

* Corresponding author at: Department of Pharmacy, Mie University Hospital, 2-174 Edobashi, Tsu, Mie 514-8507, Japan. Tel.: +81 59 231 5081; fax: +81 59 232 1201.
*E-mail address:* okudam@clin.medic.mie-u.ac.jp (M. Okuda).

http://dx.doi.org/10.1016/j.pharmthera.2014.03.002
0163-7258/

in intestinal epithelial cells. Additionally, intestinal epithelial cells have the ability to metabolize orally ingested drugs via drug-metabolizing enzymes. Drug transporters, drug-metabolizing enzymes, and tight junctions in intestinal epithelial cells have been considered to play a physiological role in limiting the absorption of xenobiotics. Therefore, pharmacokinetic variability could be explained in part by marked inter- and intra-individual heterogeneity in their expressions and/or functions in the small intestine.

MicroRNAs (miRNAs), which are small non-coding RNAs, have recently emerged as a new class of gene regulator (Eulalio et al., 2008). MiRNAs post-transcriptionally regulate gene expression by binding to target mRNA to suppress its translation or regulate its degradation. McKenna et al. (2010) identified all intestinal miRNAs and showed that miRNAs play vital roles in the differentiation, cell migration, architecture, and barrier function in intestinal epithelial cells. Furthermore, they demonstrated that the expressions of drug transporters, drug-metabolizing enzymes, and tight junctions were altered in Dicer 1-deficient mice, resulting in impaired intestinal barrier function. Recently, the roles of miRNAs have received particular attention in the pharmacokinetic field (Nakajima & Yokoi, 2011), and some studies have demonstrated the importance of miRNAs in regulation of the expression of drug transporters, drug-metabolizing enzymes, and tight junctions (Ye et al., 2011; Koturbash et al., 2012). Therefore, miRNAs could be a significant factor which is responsible for the individual variation of intestinal absorption of drugs. In addition, recent studies have demonstrated that the expression patterns of intestinal miRNAs are altered in various intestinal diseases, including small bowel syndrome (Balakrishnan et al., 2012), Crohn's disease (Wu et al., 2010) and ulcerative colitis (Wu et al., 2008). The function and expression of drug transporters are known to be altered in a variety of intestinal diseases (Ikemura et al., 2009a). Thus, alteration of the expression patterns of miRNAs in the small intestine could contribute to the variations in the expression and function of drug transporters, drug-metabolizing enzymes, and tight junctions, leading to the individual differences in pharmacokinetics. This review summarizes current knowledge regarding the role of miRNAs in the regulation of drug transporters, drug-metabolizing enzymes, and tight junctions as well as its implication for intestinal barrier function.

## 2. Biogenesis and regulatory mechanisms of microRNAs

Currently, more than 2578, 1908, and 728 miRNAs in human, mouse, and rat, respectively, have been identified (miRbase Release 20, http://www.mirbase.org/). It is estimated that miRNAs regulate the expression of more than 30% of all human genes (Berezikov et al., 2005). Fig. 1 shows the biogenesis and function of miRNAs. Canonical miRNAs are transcribed from genes as long primary transcripts (pri-miRNAs) that form as a stem loop structure by RNA polymerase II. In the nucleus, pri-miRNAs are processed into 70–100-nucleotide-long hairpin pre-miRNAs by the Drosha–DGCR8 complex. On the other hand, non-canonical intronic small RNAs produced from spliced introns and debranching (called mirtrons) bypass the Drosha-processing step, but are processed into pre-miRNAs by the spliceosome. These pre-miRNAs are then exported from the nucleus to the cytoplasm by Exportin-5, which is a member of the nuclear receptor family. Following export from the nucleus, pre-miRNAs are then further processed by the cytoplasmic RNAase III, Dicer, releasing a 22-nucleotide RNA duplex as mature miRNA. The mature miRNAs are incorporated into the RNA-induced silencing complex and guided to their mRNA targets through interactions with members of the argonaute family, such as Ago1–4. MiRNAs post-transcriptionally regulate gene expression by binding to the 3′-untranslated region (UTR) of target mRNA (Kim, 2005; Filipowicz et al., 2008). There is increasing evidence suggesting that miRNAs play critical roles in many key biological processes, such as cell growth, tissue differentiation, cell proliferation, embryonic development, and apoptosis (Esquela-Kerscher & Slack, 2006). Therefore,

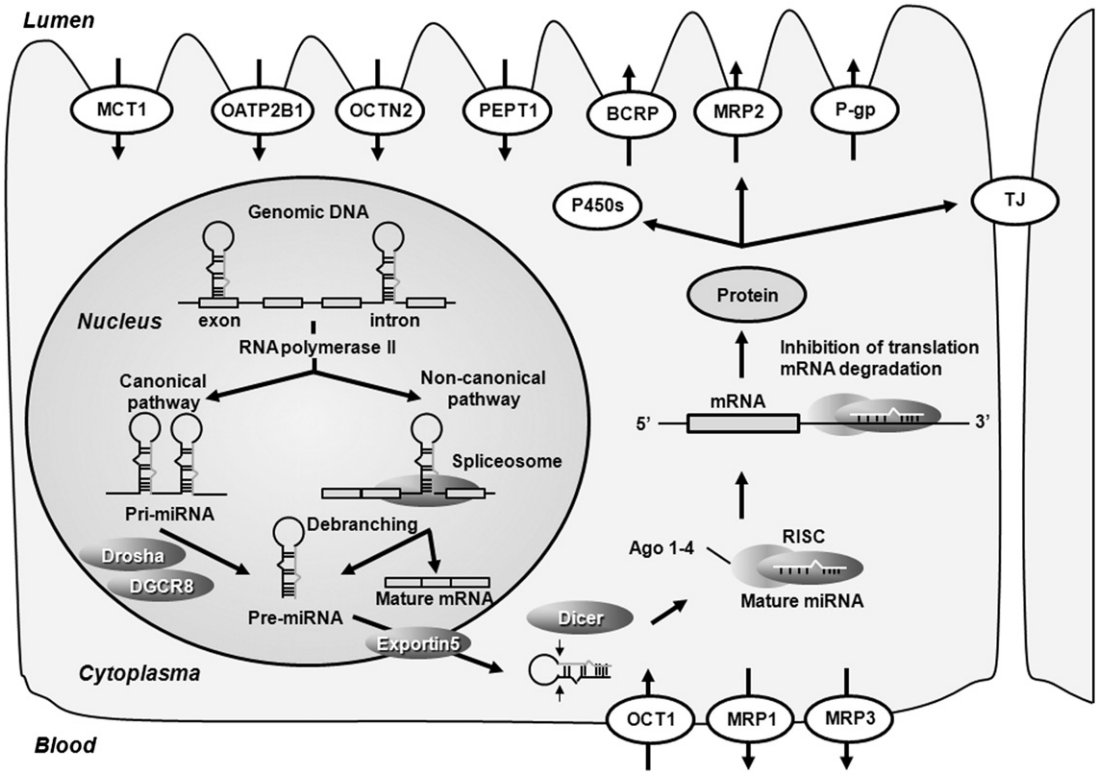


**Fig. 1.** Biogenesis and function of miRNAs. Ago1–4, argonaute family RNA-binding protein 1–4; BCRP, breast cancer resistance protein; MCT1, monocarboxylate transporter 1; MRP1, multidrug resistance-associated protein 1; MRP2, multidrug resistance-associated protein 2; MRP3, multidrug resistance-associated protein 3; OATP2B1, organic anion transporting polypeptide 2B1; OCT1, organic cation transporter 1; OCTN2, organic cation/carnitine transporter 2; PEPT1, peptide transporter 1; P450s, cytochrome P450; RISC, RNA-induced silencing complex; TJ, tight junction.