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Noncoding microRNAs: small RNAs play a big role in regulation of ADME?

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Abstract

There are considerable interindividual variations in drug absorption, distribution, metabolism and excretion (ADME) in humans, which may lead to undesired drug effects in pharmacotherapy. Some of the mechanistic causes are known, e.g., genetic polymorphism, inhibition and induction of ADME enzymes and transporters, while others such as posttranscriptional regulation of ADME genes are under active study. MicroRNAs (miRNAs) are a large group of small, noncoding RNAs that control posttranscriptional expression of target genes. More than 1000 miRNAs have been identified in the human genome, which may regulate thousands of protein-coding genes. Some miRNAs directly or indirectly control the expression of xenobiotic-metabolizing cytochrome P450 enzymes, ATP-binding cassette or solute carrier transporters and/or nuclear receptors. Consequently, intervention of miRNA epigenetic signaling may alter ADME gene expression, change the capacity of drug metabolism and transport, and influence the sensitivity of cells to xenobiotics. In addition, the expression of some ADME regulatory miRNAs is significantly changed in cells following the exposure to a given drug, and the consequent changes in ADME gene expression might result in distinct ADME properties and drug response. In this review, we summarized recent findings on the role of noncoding miRNAs in epigenetic regulation of ADME genes and discussed the potential impact on pharmacokinetics and pharmacodynamics.

Keywords

MicroRNA; Epigenetics; Gene regulation; Pharmacokinetics; Multidrug resistance; Cancer

1. Introduction

Drugs administered orally undergo a series of processes, namely absorption, distribution, metabolism and excretion (ADME). The ADME of drugs are mediated by drug-metabolizing enzymes and transporters expressed in different tissues including small intestine, liver and kidney. In particular, xenobiotic-metabolizing enzymes such as cytochrome P450 (CYP or P450) isoforms play a critical role in metabolic elimination of drugs[1], and transporters such as ATP binding cassette (ABC) and solute carrier (SLC) transporters have high impact on drug absorption, distribution and excretion[2]. The

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interactions between drugs and enzymes/transporters ultimately determine the pharmacokinetic properties and subsequently influence the pharmacodynamics (Fig. 1).

There are considerable variations in the ADME of xenobiotics in humans, which may lead to a reduced drug efficacy or an adverse drug reaction in pharmacotherapy. It is noteworthy that adverse drug reaction is one of the leading causes of morbidity and mortality, and imposes an enormous financial burden on health care[3,4]. Some of the mechanistic causes of interindividual variability in ADME are known, e.g., genetic polymorphism, induction and inhibition of drug-metabolizing enzymes and/or transporters[5,6]. For instance, genetic polymorphism of CYP2D6 is a well-known cause of the loss, reduction or enhancement of drug elimination. Thus knowing a patient's CYP2D6 genotype or phenotype would allow clinicians to practice individualized medication, i.e. to achieve a desired drug response and avoid the adverse drug events by prescribing an alternative drug or adjusting the dose[7-9]. As another example, unwanted drug effects may occur when one drug alters the exposure to a concurrent drug through the inhibition or induction of drug-metabolizing enzyme or transporter. Given the risk of adverse drug–drug interactions, one is advised to avoid concomitant use of the drugs[10]. Therefore, a mechanistic understanding of the risk of interpatient variability in ADME can help clinicians to develop appropriate approaches to prevent potential adverse drug events and achieve the desired drug efficacy.

Expression of ADME genes is tightly regulated at the transcriptional and translational levels, as well as through posttranslational modification, membrane trafficking, subcellular organization and some signal transduction pathways[11-14]. The important role of xenobiotic receptors in transcriptional regulation of ADME genes has been recognized well. Drugs can activate or deactivate a nuclear transcriptional factor to different extents and cause considerable variation in ADME (Fig. 1). Attention is drawn to the epigenetic regulation of ADME genes, including DNA methylation, histone modification and noncoding RNA (ncRNA) mediated posttranscriptional regulation[15-23]. DNA methylation is the addition of methyl group to DNA, predominantly at cytosine residues of the dinucleotide sequence CpG, mediated by the DNA methyltransferase (DNMT). Methylation of CpG islands is a known cause of gene silencing found in human diseases. Histone modifications, such as acetylation, phosphorylation and ubiquitination of histone code, are strongly associated with the *de novo* methylation of DNA underlying gene silencing. Some ADME genes are subject to DNA methylation and histone modifications, leading to an altered gene expression in cells[24-29]. In addition, there are increased studies on microRNA (miRNA) controlled posttranscriptional regulation of ADME genes (Table 1), which binds to the complementary sequences of mRNA targets and reduces gene expression. In this review, we focus on the discussion miRNA-controlled regulation of ADME genes.

2. MicroRNAs in posttranscriptional gene regulation

A large portion (~98%) of human genome is comprised of non-coding DNAs, which do not code for proteins, but are proceeded to produce functional RNAs[30]. These non-coding RNAs (ncRNAs) include ribosomal RNAs, transfer RNAs, miRNAs, small nucleolar RNAs (snoRNAs) and small nuclear RNAs (snRNAs), which have critical roles in gene regulation and biological processes fundamental to physiological and pathophysiological conditions

such as diseases. Study on the function of ncRNAs is rapidly expanding towards the elucidation of their roles along with protein-coding genes in human diseases as well as development of therapeutic strategies. Among them the miRNAs, a class of small (18–25 nt in length) ncRNAs in control of posttranscriptional regulation of target genes[31-33], represent one of the most intensively studied groups of ncRNAs. Since the discovery of the first miRNA lin-4 from C. *elegans* in 1993[34], over 1000 miRNAs have been identified in human genome, which are predicted to regulate 30–60% of protein-coding genes critical for essentially all biological processes[35,36].

The biogenesis of canonical miRNAs consists of multiple steps[37]. The primary miRNA transcript (pri-miRNA) is transcribed by RNA polymerase II or III, and cleaved by the microprocessor complex Drosha-DGCR8 (Pasha) to release hairpin structured miRNA precursor (pre-miRNA) in the nucleus. Besides the Drosh-DGCR8-dependent pathway, some pre-miRNAs are generated from intronic miRNAs (Mirtrons) *via* the mRNA precursor splicing pathway. Pre-miRNA is transported from nucleus to cytoplasm by exportin-5-Ran-GTP and processed by the complex of RNase Dicer and double-stranded RNA-binding protein TRBP into a short double stranded miRNA duplex. After the duplex is unwound, the resultant guide strand mature miRNA is preferentially assembled into the RNA-induced silencing complex (RISC).

Mature miRNA incorporated in the RISC complex binds to the 3′ untranslated region (3′UTR) of target mRNAs through complementary Watson–Crick base pairings, leading to an enhanced mRNA cleavage, translational repression or dead-enylation[38]. Despite the fact that miRNA-recognition elements (MREs) are often present within the 3′UTR of target mRNAs, some sites may reside in the protein-coding regions of the target genes. The extent of gene suppression by miRNA may be related to the miRNA and mRNA levels, number of MRE sites, strength of contiguous base pairings and target site accessibility. Given the fact that a miRNA may act on multiple targets including the transcriptional factors of a given gene, knowing the miRNA signaling pathways shall help better understand miRNA regulatory mechanisms.

MicroRNAs are named using the prefix “miR” followed by a dash and a number (e.g., miR-27), according to the standard nomenclature guidelines[39,40]. Capital and lowercase “R” are used to annotate mature miRNA (e.g., miR-27) and pre-miRNA (mir-27), respectively. Another three-letter prefix is employed to identify the species of origin. For instance, *homo sapiens* miR-27 is named hsa-miR-27, and *Mus musculus* miR-27 is called mmu-miR-27. MicroRNAs with very similar sequences within a species are given the same number, with an additional lower case letters as suffixes to distinguish their difference in 1–2 nucleotides (e.g., hsa-miR-27b *versus* hsa-miR-27a). In case that the double stranded miRNA duplex is processed to two mature miRNAs, the resultant sense and antisense are denoted with −5p and −3p suffix (e.g., hsa-miR-27b-5p and hsa-miR-27b-3p), respectively. Rather, a number of early discovered miRNAs are still denoted with trivial names (e.g., let-7).

MicroRNAs play important roles in control of biological processes through posttranscriptional regulation of target genes. For instance, neuronal miR-124 has been shown to promote neuronal differentiation *via* the regulation of a complex network of

nervous system-specific alternative pre-mRNA splicing[41]. Liver-specific miR-122 regulates cholesterol and lipid metabolism by targeting those enzymes and transporters[42,43]. The evolutionarily conserved, pancreatic islet-specific miR-375 is revealed to regulate the expression of myotrophin and thus control insulin secretion[44]. In addition, a number of miRNAs have been identified as oncogenes or tumor suppressors to promote or inhibit tumor initiation, progression and metastasis[45-49]. Therefore, miRNAs constitute a group of novel pharmaceutical targets for the treatment of various human diseases.

3. MicroRNAs in control of ADME gene expression

There is also increasing evidence indicating that miRNAs are involved in posttranscriptional regulation of ADME genes[19,20], which in turn is anticipated to affect pharmacokinetics and pharmacodynamics (Fig. 1). More and more studies have demonstrated that miRNAs are able to target the 3′UTR of ADME genes, including P450 enzymes, ABC and SLC transporters, and xenobiotic receptors (Table 1). Change of ADME gene expression by miRNAs may lead to an altered capacity of drug metabolism and disposition, as well as a different response to xenobiotics.

3.1. MicroRNAs regulate the expression of P450 enzymes

CYP1B1 is an extrahepatic P450 enzyme that plays an important role in procarcinogen activation. miR-27b was shown to suppress CYP1B1 protein expression in human cell lines *via* direct action on the miR-27b MRE site near the poly(A) tail[50]. Modulation of miR-27b expression/function altered CYP1B1 enzymatic activity, as indicated by the change in metabolism of various procarcinogens and 4-hydroxylation of 17β-estradiol. Interestingly, the 5′UTR of CYP1B1 was found to interact with the miR-27b MRE within the 3′UTR of CYP1B1 mRNA and almost completely block the translation of CYP1B1[51], indicating the importance of 3′UTR in CYP1B1 gene expression.

Accounting for about 7% of total hepatic P450 enzymes in human liver, CYP2E1 contributes to the metabolism of many toxicologically important chemicals (e.g., ethanol, acetone, and benzene) and therapeutic drugs (e.g., acetaminophen). CYP2E1 is readily induced by ethanol through a posttranslational regulatory mechanism[52]. The 3′UTR of human CYP2E1 was found to contain a MRE site for miR-378 [53]. Overexpression of miR-378 caused a decrease in CYP2E1 protein expression, likely through a translation inhibition mechanism. Furthermore, overexpression of miR-378 significantly reduced chlorzoxazone 6-hydroxylase activity in cells, suggesting a potential impact of miR-378 on drug metabolism.

CYP3A4 is the most abundant P450 enzyme in human liver and small intestine, and metabolizes over 50% of pharmaceutical drugs such as benzodiazepines, antivirals and steroids. It was revealed that miR-27b and mmu-miR-298 acted directly on the 3′UTR of CYP3A4 (Fig. 2A), and modulated CYP3A4 expression in human cancer cell lines following the induction with vitamin D[54]. The involvement of miRNAs in regulation of CYP3A4 might provide helpful explanation for the developmental expression of CYP3A4[55,56]. Moreover, CYP3A4 was identified as a major target for the small, non-coding vault RNA (svRNA), svRNAb, which was derived from vault RNA by a pathway different from miRNA biogenesis[57]. svRNAb was shown to down-regulate CYP3A4 3′UTR-

luciferase reporter activity. This novel finding on svRNA in regulation of CYP3A4 may not only expand the repertoire of small RNAs in gene regulation but also provide mechanistic understanding of the association between vault particles and drug resistance.

Some other P450 genes were also targeted by miRNAs (Table 1), including the regulation of CYP7A1 by miR-122a and −422a[58], CYP24A1 by miR-125b[59], and CYP2A3 by miR-126*[60]. With an increased research on miRNA-controlled epigenetic regulation of drug-metabolizing enzymes, one would expect to have an improved understanding of the significance of miRNAs in drug metabolism.

3.2. MicroRNAs regulate the expression of drug transporters

Human P-glycoprotein (P-gp/ABCB1) is expressed at high levels on the apical membrane of enterocytes, biliary surface of hepatocytes, and luminal (apical) side of kidney proximal tubule cells, and P-gp has high impact on drug absorption, distribution and excretion. Regulation of P-gp by miR-451 and −27a in human cancer cells was defined by different groups[61-64]. Following the characterization of distinct miRNA expression profiles between parental MCF-7 cells and doxorubicin (DOX)-resistant MCF-7 (MCF-7/DOX) cells, Kovalchuk et al.[61] identified a miR-451 MRE within ABCB1 3′UTR and further verified the MRE site using luciferase reporter assays. ABCB1 mRNA and protein expression was altered in cells transfected with miR-451 precursor or inhibitor. Moreover, the transfection of MCF-7/DOX cells with miR-451 precursors sensitized the cells to DOX. Meanwhile, Zhu et al.[62] found that miR-451 and −27a levels were elevated more than 2-fold in drug-resistant cancer cells than parental cells. Likewise, miRNA antagomirs or mimics changed ABCB1 expression and altered the intracellular accumulation of DOX and rhodamine 123 (RH-123). These findings demonstrate the impact of miRNAs on cellular drug disposition and chemosensitivity through epigenetic regulation of membrane transporter gene expression.

Breast cancer resistance protein (BCRP/ABCG2) plays an important role in cellular transport of anticancer drugs (e.g., mitoxantrone, doxorubicin and topotecan). Regulation of ABCG2 at the 3′UTR by miRNAs (Fig. 2B) was studied by multiple groups[65-70]. Using luciferase reporter assay, Liao et al.[66] showed that 3′UTR of ABCG2 might be targeted by miR-520h. After defining the distinct ABCG2 mRNA expression patterns in parent S1 and drug-resistant S1MI80 cells, To et al.[68,69] found that miR-519c controlled posttranscriptional expression of ABCG2. Meanwhile, Pan et al.[67] demonstrated the regulation of ABCG2 protein expression by miR-328, after observing an inverse relationship between miR-328 and ABCG2 expression levels in drug-sensitive MCF-7 and drug-resistant MCF-7/MX100 cancer cells. Further comparative studies[65] revealed that miR-519c and −328 had stronger effects than miR-520h in regulation of ABCG2 expression in human breast cancer cells, and these ABCG2-regulatory miRNAs were down-regulated in stem-like cancer cells. Nevertheless, miR-520h was shown to target ABCG2 in PANC-1 cells and inhibit cell migration, invasion and side population[70], suggesting that miRNA-controlled regulation of ABCG2 could be cell selective.

Multidrug resistance-associated proteins (MRP/ABCC) are ubiquitously expressed in human tissues and these ABCC transporters are able to transport many endobiotics and xenobiotics. Liang et al.[71] found that miR-326 down-regulated MRP1/ABCC1 protein expression in

drug-resistant, MRP1-overexpressing MCF-7/VP cells. Consequently, overexpression of miR-326 could reverse the multidrug resistance phenotype, and sensitize the cells to DOX. Meanwhile, Guo et al.[72] showed that miR-134 inhibited ABCC1 expression, and down-regulation of ABCC1 protein expression was largely associated with the increased levels of miR-134 in H69AR cells. In addition, Haenisch et al.[73] found that miR-379 could target the 3′UTR of ABCC2 and suppress ABCC2 gene expression at the posttranscriptional level, providing a mechanistic understanding of nuclear receptor-independent induction of ABCC2 in HepG2 cells by rifampicin.

A very recent study reported by Borel et al.[74] demonstrated that a large number of ABC transporters (e.g., ABCA2, ABCB1, ABCB6, ABCC1, ABCC2, ABCC3, ABCC4, ABCC5, ABCC10, ABCC11, ABCC12 and ABCE1) were up-regulated in hepatocellular carcinoma prior to chemotherapy. Up-regulation of ABC transporters was associated with down-regulation of various miRNAs. Following computational prediction of miRNA target sites in ABC genes, a total of 13 miRNAs were shown to act on the 3′UTRs of ABCA1, ABCC1, ABCC5, ABCC10 and ABCE1 by luciferase reporter assays. These findings support the potential role of miRNAs in epigenetic regulation of ADME genes, as well as the intervention of miRNA signaling as a novel means to overcome multidrug resistance.

Besides the regulation of ABC transporters, some miRNAs were found to control the expression of SLC family transporters (Table 1). Human peptide transporter 1 (PEPT1/SLC15A1) is expressed specifically on the brush border membrane of intestinal epithelial cells, and mediates cellular uptake of various di- or tripeptides and peptidomimetic drugs such as β-lactam antibiotics. miR-92b was shown to target the 3′UTR of PEPT1, suppress PEPT1 expression at both mRNA and protein levels, and subsequently reduce PEPT1-mediated drug transport activity[75]. As another example, miR-16 was revealed to target serotonin transporter (SERT/SLC6A4)[76], the pharmacological target of selective serotonin reuptake inhibitor antidepressants. Chronic administration of fluoxetine increased miR-16 levels in serotonergic raphe nuclei and subsequently reduced SERT expression in mice, which offers a novel view on the pharmacological actions of fluoxetine.

3.3. MicroRNAs regulate the expression of nuclear receptors

MicroRNAs may regulate the expression of ADME genes not only *via* direct targeting the 3′UTRs of enzymes or transporters but also *via* "indirect" targeting the 3′UTRs of nuclear receptors (Fig. 2A) (Table 1). For instance, vitamin D receptor (VDR/NR1I1) recruits retinoid X receptor α (RXR$_\alpha$/NR2B1) to form functional heterodimer and thus controls the transcriptional expression of many critical ADME genes including CYP3A4. In addition to a direct targeting the 3′UTR of CYP3A4, miR-27b was found to regulate VDR[54] and RXR$_\alpha$[77] gene expression. The actions of miR-27b on VDR/RXR$_\alpha$ presumably enhanced its impact on CYP3A4 gene expression (Fig. 2A). Another miRNA, miR-148a, was shown to regulate the expression of pregnane X receptor (PXR/NR1I2) and subsequently influence the expression of PXR targeted ADME genes such as CYP3A4[78]. In addition, the 3′UTR of hepatocyte nuclear factor 4α (HNF4$_\alpha$/NR2A1) was targeted by a number of miRNAs[79,80]. Among them the MRE for miR-34a was demolished by the single nucleotide polymorphism

(SNP rs11574744), which might affect the regulation of ADME processes as well as the etiology of diabetes or renal cell carcinoma[80].

Peroxisome proliferator-activated receptor alpha (PPAR$_a$/NR1C1) is another important transcriptional factor that regulates the expression of genes encoding endo/xenobiotic-metabolizing enzymes. Kida et al.[81] found that miR-21 and miR-27b could target PPAR$_a$. The overexpression and inhibition of miR-21 or miR-27b in HuH-7 cells significantly decreased and increased the PPAR$_a$ protein level, respectively. Further, Tong et al.[82] showed that miR-506 was overexpressed in the hydroxycamptothecin (HCPT)-resistant human colon cancer cell line, which conferred the resistance to HCPT through the suppression of PPAR$_a$ expression. In addition, Zheng et al.[83] validated the MRE for miR-10b within the 3′UTR of PPAR$_a$, and demonstrated the modulation of PPAR$_a$ protein expression by miR-10b in steatotic L02 cells. These findings suggest that miRNAs may regulate PPAR$_a$ expression and modulate drug transport.

The liver X receptor alpha (LXR$_a$/NR1H3) is a nuclear receptor closely related to RXR and PPAR in regulation of cholesterol, lipid, bile acid, and steroid metabolism and homeostasis. hsa-miR-613 directly targeted the 3′UTR of LXR$_a$[84]. Interestingly, the activation of LXR$_a$ led to an increased expression of hsa-miR-613. The auto-regulation of LXR$_a$ was mediated through the action of sterol regulatory element binding protein (SREBP)-1c, a known LXR target gene, on the SREBP response element within the promoter of hsa-miR-613 gene. This feedback loop might be important for a tight regulation of LXR$_a$ critical for endobiotic/xenobiotic metabolism and transport.

Estrogen receptor alpha (ER$_a$/NR3A1) and glucocorticoid receptor (GR/NR3C1), known to control transcriptional regulation of some ADME genes (e.g., CYP3A4 and ABCG2), were also targeted by various miRNAs (Table 1). miR-221/222 was found to negatively regulate ER$_a$ protein expression[85]. Human breast cancer cells transfected with miR-221/222 became resistant to tamoxifen, and knockdown of miR-221/222 sensitized the cells to tamoxifen treatment, suggesting the importance of miR-221/222 in tamoxifen chemotherapy. In addition, miRNA let-7 was shown to induce cell sensitivity to tamoxifen through a negative regulation of ER$_a$ signaling in breast cancer cells[86], and miR-18, −124a and −130b were found to down-regulate GR protein expression and consequently modulate GR signaling[87,88]. While the influence of GR/ER$_a$ regulatory miRNAs on ADME gene expression has not been investigated, one may not underestimate their importance in ADME of xenobiotics.

4. Modulation of microRNA expression/maturation by small molecule drugs

The exposure to small molecule compounds such as medications, drugs of abuse, toxins or hormones may alter the expression of miRNAs in cells through *cis*- or *trans*-regulatory mechanisms (reviews[19,89]). Change in the expression or maturation of miRNAs in regulation of ADME genes would help facilitate the elimination or disposition of the drug or a concomitant agent (Fig. 3). This process presumably represents a feedback mechanism in

cellular defense against xenobiotics, while it might cause considerable variations in pharmacokinetics and dynamics.

As mentioned above, fluoxetine treatment increased miR-16 expression in mouse serotonergic raphe nuclei[76], and the activation of LXR_{α} upregulated hsa-miR-613 expression in primary human hepatocytes as well as hepatocarcinoma cells[84]. Recently, we examined the impact of 19 drugs (e.g. dexamethasone, vinblastine, bilobalide and cocaine) on the expression of ten miRNAs (e.g., miR-18a, −27b, −124a, −148a, −328, −451 and −519c) in MCF-7, Caco-2, SH-SY5Y and BE(2)-M17 cell systems[90]. Our data indicated that miRNAs were differentially expressed in human cell lines and the change in miRNA expression was dependent on multiple factors including the nature of drug, type of cells and exposure time. It was noted that dexamethasone and vinblastine, inducers of drug-metabolizing enzymes and transporters, suppressed the expression of miR-27b, −148a and −451 that were shown to down-regulate ADME genes. These observations are helpful for understanding the variable pharmacokinetics, multidrug resistance, drug–drug interactions that are independent upon nuclear receptor-mediated transcriptional regulation.

Because miRNAs are generated from pre-miRNAs derived from the human genome or through mRNA splicing pathways, change of miRNA expression may be attributed to the actions of drugs on *cis*- or *trans*-regulatory factors of miRNA genes. For instance, estrogen was found to alter the maturation of a large number of miRNAs through the activation of ER_{α}/NR3A1[91], and GW3965 was revealed to up-regulate miR-613 through the action of SREBP-1c following the activation of LXR_{α}[84]. On the other hand, drugs may affect miRNA expression or maturation *via* targeting the proteins within miRNA processing machinery. As an example, enoxacin was found to enhance the RNA-binding protein TRBP in promoting RNA interference and miRNA processing[92,93]. Identifying how the expression of ADME regulatory miRNAs is altered by drugs and the underlying mechanisms would help understand drug actions and predict potential variation in ADME.

5. Conclusions

MicroRNAs have been recognized as critical factors in posttranscriptional regulation of target genes in humans. Many miRNAs are revealed to act on the 3′UTRs of drug-metabolizing enzymes, transporters and nuclear receptors underlying ADME processes. The same miRNA (e.g., miR-27b) may control the expression of an ADME gene (e.g., CYP3A4) *via* direct and/or indirect targeting. On the other hand, multiple miRNAs (e.g., miR-520h, −519c and −328) can regulate the expression of the same ADME gene (e.g., BCRP/ABCG2) to different extents. Change in ADME regulatory miRNA signaling, which can be driven by the drug *via* various mechanisms, may lead to an altered drug metabolism and transport, as well as variable pharmacological or toxicological responses. With the increase of studies on the relationship between miRNAs as well as other epigenetic factors and pharmacological properties, pharmacoepigenetics and pharmacoepigenomics[17,22] are expected to provide an improved understanding of interindividual variations in pharmacotherapy towards rational drug therapy.

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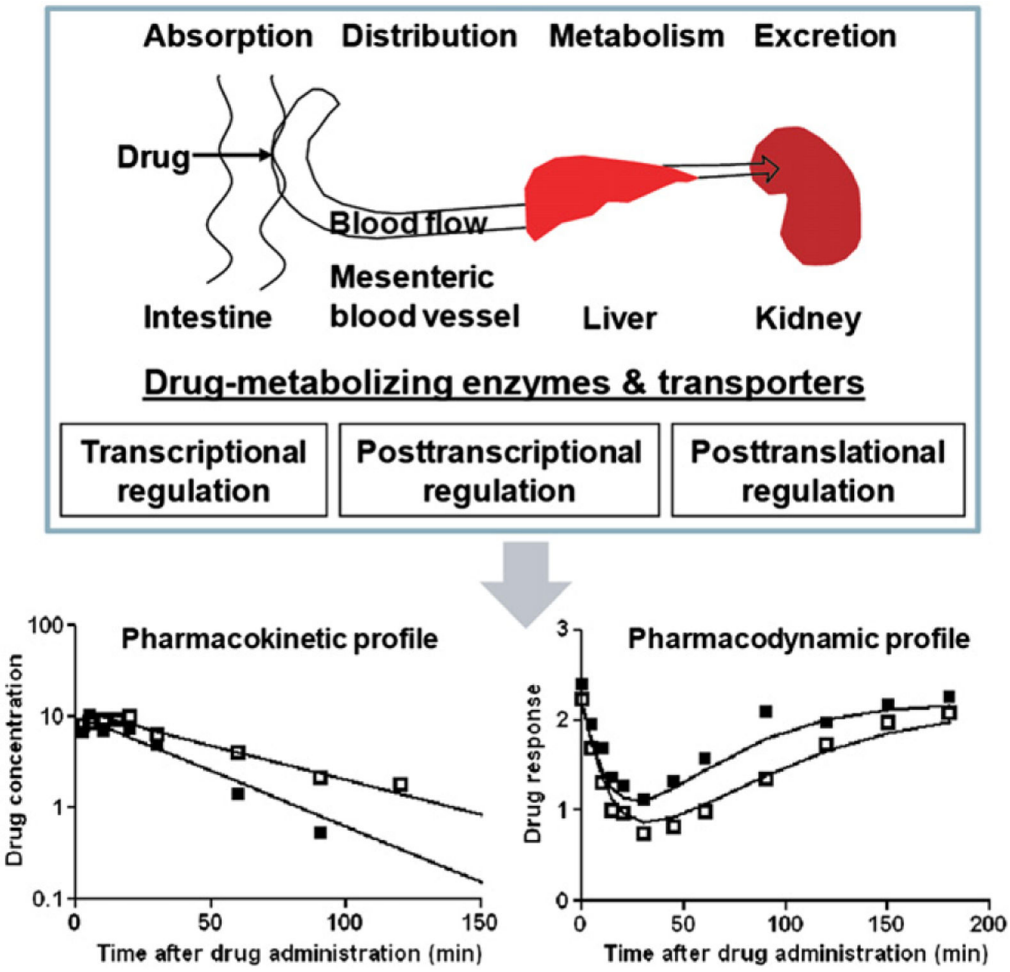

Figure 1.

Xenobiotic-metabolizing enzymes and transporters underlying drug absorption, distribution, metabolism and excretion processes are regulated at the transcriptional, posttranscriptional and posttranslational levels. Different extents of ADME gene expression may result in considerable variations in pharmacokinetics and pharmacodynamics.

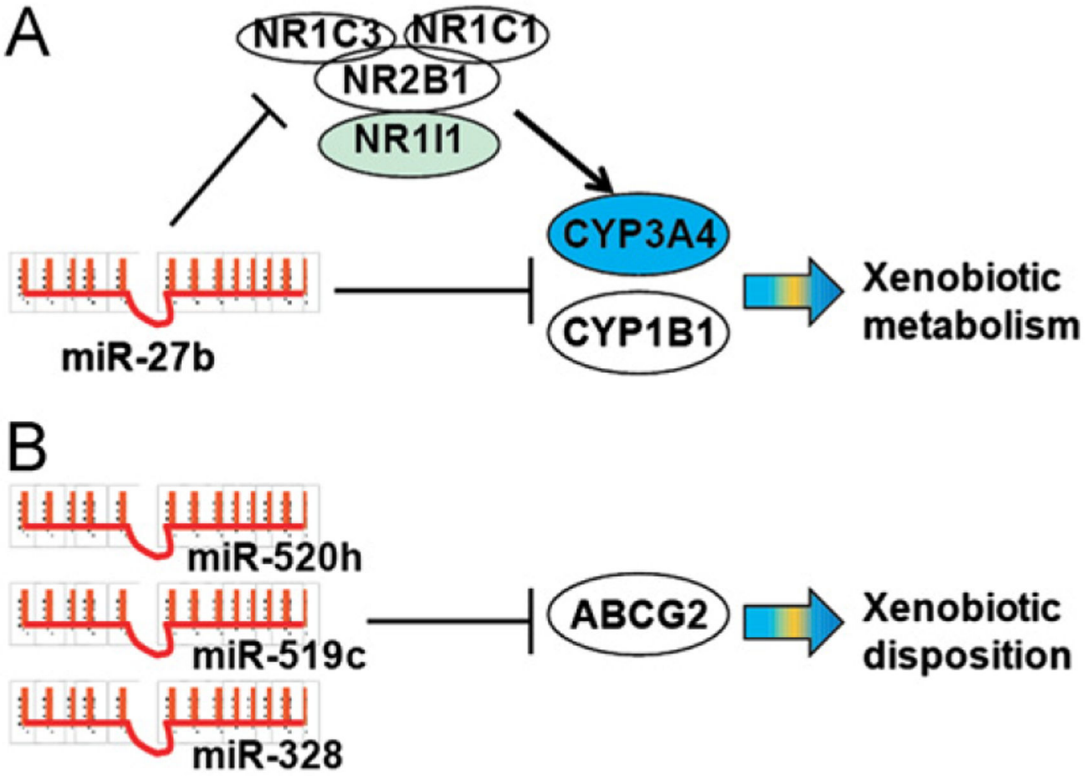

Figure 2.

(A) One microRNA (e.g., miR-27b) may regulate the expression of an ADME gene *via* direct targeting the gene (e.g., CYP3A4) and/or "indirect" targeting its regulatory factors (e.g., PPAR$_\alpha$/NR1C1, PPAR$_\gamma$/NR1C3, VDR/NR1I1 and RXR$_\alpha$/NR2B1). (B) Multiple microRNAs (e.g., miR-520h, −519c and −328) can target the same ADME gene (e.g., BCRP/ABCG2).

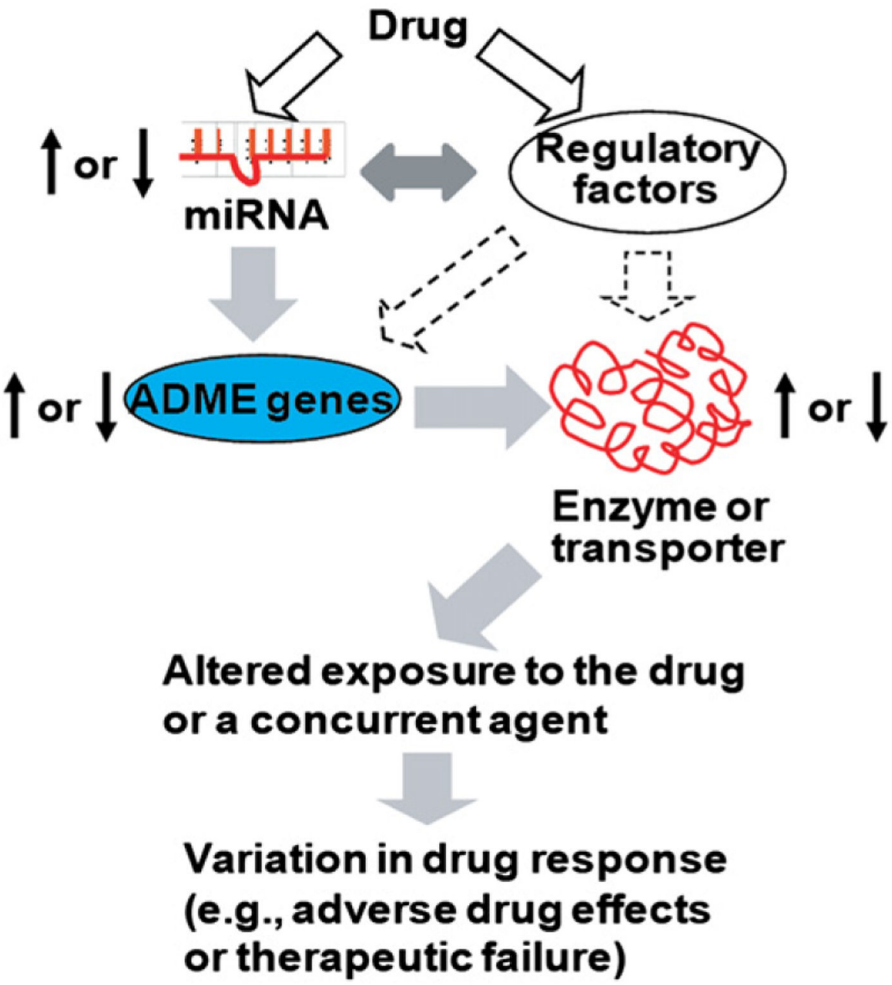

Figure 3.

Change in the expression/maturation of ADME gene regulatory miRNAs by a drug may alter the expression of drug-metabolizing enzymes and/or transporters, resulting in a variable drug exposure and drug response.

Table 1

Drug-metabolizing enzymes, transporters and nuclear receptors shown to be targeted by miRNAs.

Name		MicroRNA	Reference
Enzymes	CYP1B1	miR-27b	50
	CYP2A3	miR-126*, miR-34	60
	CYP2E1	miR-378	53
	CYP3A4	miR-27b, mmu-miR-298	54
		svRNAb	57
	CYP7A1	miR-122a, miR-422a	58
	CYP24A1	miR-125b	59
Transporters	ABCB1/P-gp	miR-451	61,63
		miR-27a and miR-451	62,64
	ABCG2/BCRP	miR-520h	65,66,70
		miR-519c	65,68,69
		miR-328	65,67
	ABCA1	miR-101, miR-135	74
		miR-33a, miR-33b	94-96
		miR-758	97
		miR-106b	98
	ABCC1	miR-134	72
		miR-326	71
		miR-199a, miR-199b, miR-296	74
	ABCC2	miR-379	73
	ABCC3	mmu-miR-665	99
		miR-9*	100
	ABCC4	miR-125a, miR-125b	74
	ABCC5	miR-101, miR-125a, Let-7a	74
		miR-128	101
	ABCC6	miR-9*	100
	ABCC7	hsa-miR-145, hsa-miR-494	102
	ABCC10	Let-7a, Let-7e	74

Name		MicroRNA	Reference
	ABCE1	miR-26a, miR-135b, miR-145	74
	SLC6A4	miR-16	76
	SLC15A1	miR-92b	75
	SLC12A2	hsa-miR-384, hsa-miR-494 and hsa-miR-1246	102
	SLC16A1	miR-124	103
Nuclear receptors	NR1I2/PXR	miR-148a	78
	NR3C1/GR	miR-18 and miR-124a	87
		miR-130b	88
	NR2B1/RXR$_{\alpha}$	miR-27a/b	77
	NR1I1/VDR	miR-27b and mmu-miR-298	54
		miR-125b	104
	NR1C1/PPAR$_{\alpha}$	miR-10b	83
		miR-506	82
		miR-21	81,105
		miR-27b	81
	NR1C3/PPAR$_{\gamma}$	miR-130	106
		miR-27b	107,108
		miR-27a	109
	NR1C2/PPAR$_{\beta}$	miR-15a	110
	NR1H3/LXR$_{\alpha}$	miR-613	84
	NR2A1/HNF4$_{\alpha}$	miR-24, miR-34a	79,80
	NR3A1/ER$_{\alpha}$	miR-221, miR-222	85,111
		Let-7	86
		miR-130a	112
		miR-22	113