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REVIEW

The effects of microRNA on the absorption, distribution, metabolism and excretion of drugs

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The importance of genetic factors (e.g. sequence variation) in the absorption, distribution, metabolism, excretion (ADME) and overall efficacy of therapeutic agents is well established. Our ability to identify, interpret and utilize these factors is the subject of much clinical investigation and therapeutic development. However, drug ADME and efficacy are also heavily influenced by epigenetic factors such as DNA/histone methylation and non-coding RNAs [especially microRNAs (miRNAs)]. Results from studies using tools, such as *in silico* miRNA target prediction, *in vitro* functional assays, nucleic acid profiling/sequencing and high-throughput proteomics, are rapidly expanding our knowledge of these factors and their effects on drug metabolism. Although these studies reveal a complex regulation of drug ADME, an increased understanding of the molecular interplay between the genome, epigenome and transcriptome has the potential to provide practically useful strategies to facilitate drug development, optimize therapeutic efficacy, circumvent adverse effects, yield novel diagnostics and ultimately become an integral component of personalized medicine.

LINKED ARTICLES

This article is part of a themed section on Epigenetics and Therapy. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2015.172.issue-11

Abbreviations

ABC, ATP-binding cassette; ABCB1/MDR1/P-gp, multidrug resistance protein 1/P-glycoprotein; ADME, absorption, distribution, metabolism, excretion; antimiR, miRNA antagonist; CYP450, cytochrome P450; DOX, doxorubicin; ESR1, oestrogen receptor alpha; ETS1, V-Ets avian erythroblastosis virus E26 oncogene homologue 1; GPX7, glutathione peroxidase 7; GSS, glutathione synthetase; HDAC, histone deacetylase; LXRA, liver X receptor α; miRNA, microRNA; mRNA, messenger RNA; ncRNA, non-coding RNA; NR1C1, PPARα; PK, pharmacokinetic; PXR, pregnane X receptor; RISC, RNA-induced silencing complex; RXR, retinoid X receptor; SLC, solute carrier; UGT, UDP-glucuronosyltransferase; UTR, untranslated region; VD receptor, vitamin D receptor

Tables of Links

TARGETS	
Enzymes[a]	**Transporters**[c]
CYP1A1	ABCA1
CYP1B1	ABCB1, MDR1/P-gp
CYP2E1	ABCC1
CYP3A4	ABCC2
DNMT1, DNA methyltransferase 1	ABCC3
DNMT3A, DNA methyltransferase 3α	ABCC4
HDAC	ABCC5
Histone methyltransferase EZH2	ABCC10
Nuclear hormone receptors[b]	ABCE1
ESR1, oestrogen receptor α, NR3A1	ABCG2
Glucocorticoid receptor, NR3C1	Cystine/glutamate exchanger, SLC7A11
LXRA, liver X receptor α, NR1H3	SERT, 5-HT transporter, SLC6A4
PPARα, NR1C1	SLC15
PXR, pregnane X receptor	vGLUT1, vesicular glutamate transporter 1, SLC17A7
RXR, retinoid receptors	

LIGANDS	
17β-oestradiol	Raloxifene
Acetaminophen, paracetamol	Tamoxifen
Cholesterol	Testosterone
Cisplatin	Topotecan
Cocaine	Vinblastine
Dexamethasone	
Dox, doxorubicin	
Fluoxetine	
Gemcitabine	
GSH, glutathione	
Halothane	
Isoflurane	
Methadone	
Mitoxantrone	

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 ([a,b,c]Alexander *et al.*, 2013a,b,c).

The proper control of absorption, distribution, metabolism and excretion (ADME) of xenobiotics is essential for living organisms to obtain energy, acquire necessary building blocks (e.g. essential amino acids) and maintain homeostasis in a complex chemical environment. Genes involved in ADME activities encode various receptor/transporters, biotransformation enzymes and accessory proteins (PharmaADME, http://pharmaadme.org/joomla/). These proteins include membrane transporters responsible for the absorption and excretion of specific molecules and enzymes to convert xenobiotics for excretion. To date, over 300 transporters and enzymes directly involved in ADME process have been described. This long list of components makes the study of ADME inherently complex, as transporters and enzymes work in concert to respond dynamically to diverse external factors. Despite the formidable complexity of the field, an understanding of ADME is critical for drug development in order to increase therapeutic efficacy and reduce adverse effects (Caldwell *et al.*, 2009; Emoto *et al.*, 2010; Bell and Wang, 2012).

It is well known that there are considerable inter-individual variations in response to drug treatment (Alomar, 2014). Besides polymorphisms within the sequence of therapeutic targets, genetic variations in ADME-related genes have been shown to affect therapeutic response through drug transportation and metabolism (Nakajima and Aoyama, 2000; Evrard and Mbatchi, 2012). However, genetic variations cannot completely explain the differences observed between individuals. Recent studies using high-throughput global molecular profiling technologies have shown that ADME activities have also been affected by a number of epigenetic factors, including DNA methylation, post-translational histone modifications and non-coding regulatory RNAs, which directly or indirectly alter the expression of ADME genes (Ivanov *et al.*, 2012). For example, microRNAs (miRNAs) are short, non-coding regulatory RNAs involved in modulating ADME-related gene expression and protein translation levels (Liu and Pan, 2014). The study of epigenetic factors on drug metabolism, pharmacoepigenetics, is a rapidly growing field and plays an important role in therapeutic efficacy by affecting the pharmacokinetic (PK) and pharmacodynamic properties of drugs. In this review, we summarize the current understanding on the involvement of miRNAs in ADME.

MicroRNA

More than 60% of human genomic DNA is transcribed into RNA, yet protein-coding genes account for only less than 3% of the genome (Bernstein *et al.*, 2012; Kellis *et al.*, 2014). Non-coding RNAs (ncRNAs) are RNAs that are not translated into proteins. Some ncRNAs, such as ribosomal RNAs and transfer RNAs, have well-established cellular roles. However, there are other classes of ncRNAs that have been recently discovered (Esteller, 2011). Among them, miRNAs are probably the best studied due to their important roles in the post-transcriptional regulation of messenger RNAs (mRNAs). miRNAs were originally discovered in the nematode *Caenorhabditis elegans* as mediators of temporal pattern formation

(Ambros, 2001; Lagos-Quintana *et al.*, 2001). These small regulatory RNAs were found to be conserved in metazoan species and have also been observed in several virus families (Pfeffer *et al.*, 2004). miRNAs are involved in a broad range of cellular activities, including proliferation, development, homeostasis, immunity, metabolism and apoptosis (Kloosterman and Plasterk, 2006; Stefani and Slack, 2008). Because of their important regulatory roles in these diverse biological processes, miRNAs display characteristic expression patterns in cells and tissues, different developmental stages and disease processes.

miRNA genes are found in diverse locations throughout the genome (Rodriguez *et al.*, 2004) and often cluster together (Lagos-Quintana *et al.*, 2001; Seitz *et al.*, 2004). Most of the sequences that encode miRNAs are transcribed by RNA polymerase II (Lee *et al.*, 2004). Many miRNAs may be transcribed on the same primary transcript (pri-miRNA). This pri-miRNA is then processed into a smaller hairpin structure (pre-miRNA) by the microprocessor complex, RNase III enzyme Drosha/DGCR8. Following nuclear export via the RanGTP-dependent double-strand RNA binding protein exportin-5, the pre-RNA is then cleaved by another RNase III enzyme, Dicer, to yield an approximately 22 nucleotide-long RNA duplex (Kim *et al.*, 2009). Unwinding by an RNA helicase allows a mature miRNA strand to be loaded onto the protein Argonaute to form the RNA-induced silencing complex (RISC). The RISC typically interacts with the 3′ untranslated region (UTR) of mRNA targets, resulting in the translational repression or degradation of the transcript. Unlike other regulatory molecules, miRNA target recognition is relatively flexible, as the miRNA sequence itself is short and the interaction between miRNA and mRNA is based upon partial sequence complementarity (Bartel, 2009). This permits a single miRNA to interact with many mRNA targets. Additionally, a single mRNA can also contain many different miRNA binding sites. It has been estimated that the majority of the human mRNAs are targeted by one or more miRNAs (Friedman *et al.*, 2009). These loose constraints governing miRNA–mRNA interactions increase the diversity of possible interactions and make miRNA-mediated regulatory networks often difficult to unravel.

At present, over 2500 human mature miRNAs have been deposited into the online repository miRBase (v20, www.mirbase.org) (Griffiths-Jones *et al.*, 2008). To decipher the interactions between miRNA and mRNA, a number of informatic tools, such as TargetScan (www.targetscan.org) (Lewis *et al.*, 2005) and miRanda (www.microrna.org) (Enright *et al.*, 2003), have been developed to predict miRNA–mRNA interactions based upon sequence complementation, binding stability and degree of sequence conservation. A typical approach to evaluate the specificity of miRNA–target interactions is the use of gene reporter assays in cell culture. A specific miRNA of interest is transfected into a cell line expressing a transgenic construct containing a reporter gene (e.g. luciferase) and the 3′-UTR region of a putative mRNA target. However, this approach relies upon overexpressed components and may ultimately have limited physiological relevance. The strongest support for *in vivo* relevance is derived from a combination of experiential methods (reviewed in Thomson *et al.*, 2011). Although thousands of miRNA–mRNA interactions have been predicted, few mRNA–miRNA interactions have been empirically validated. These validated interactions are archived in online databases, such as miRTarBase (http://mirtarbase.mbc.nctu.edu.tw/), Tarbase (http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=tarbase/index) and miRecords (http://mirecords.biolead.org/).

MicroRNAs regulate the expression of ADME phase I and II enzymes

Increasing evidence has indicated that a substantial number of transporters and drug metabolizing enzymes are regulated by miRNAs (Yu, 2007; 2009) (Table 1 and Figure 1). We collected all miRNA–ADME interactions from literature and constructed a miRNA-mediated regulatory network for ADME (Figure 1). The network contains 189 interactions among the 381 nodes, which includes 120 miRNAs and 261 ADME genes.

The biotransformation of xenobiotics is generally separated into two phases: phase I includes the addition or exposure of chemically reactive functional groups such as amine ($–NH_2$), hydroxyl (–OH), sulfhydryl (–SH) or carboxyl (–COOH) group by enzymes, in preparation for phase II, where the phase I products are further modified with water-soluble or charged chemical motif(s), converting them into water-soluble structures for excretion. Cytochrome P450 (CYP450, a class of monooxygenases) is the largest group of phase I enzymes. In humans, there are 57 functional CYP450 genes, which can be grouped into 18 different families based upon sequence similarity (Lewis, 2004). A number of miRNAs have been shown to be involved in the post-transcriptional regulation of cytochrome P450 genes (Table 1 and Figure 1). For example, the expression level of *CYP1A1* was correlated with the levels of miR-18b and miR-20b (Wang *et al.*, 2009; Glubb and Innocenti, 2011). CYP1B1 and CYP3A4 were found to be regulated by miR-27b (Tsuchiya *et al.*, 2006; Pan *et al.*, 2009a), and CYP2E1 by miR-378 (Mohri *et al.*, 2010).

A few phase I enzymes have gained more attention due to their involvement in metabolizing important therapeutic agents. CYP3A4, a member of the CYP3 family predominantly expressed in liver and intestine, metabolizes more than 50% of the therapeutic drugs currently on the market (Plant and Gibson, 2003). It is also involved in the synthesis and metabolism of a number of endogenous molecules, including cholesterol, steroid hormones (e.g. testosterone), bile acids and vitamin D (Wang *et al.*, 2013c). Because of its important role in drug metabolism, changes in CYP3A4 activity (either through altered gene expression or inhibition of enzyme activity) cause a number of adverse effects associated with drug usage. CYP3A4 can be induced by ligands that bind and activate the pregnane X (PX) receptor (Lehmann *et al.*, 1998). Experimental data also indicate that the level of CYP3A4 is affected by epigenetic factors, including histone acetylation and methylation (Dannenberg and Edenberg, 2006; Kacevska *et al.*, 2012) and also miRNAs.

A recent study based upon several different miRNA target prediction programmes identified 105 miRNAs that may potentially interact with CYP3A4 mRNA (Wei *et al.*, 2014). Among the 105 miRNA candidates, 14 of them were

Table 1

List of interactions between miRNA and drug metabolism-related genes

Gene ID	Function	Interacting miRNA	References
CYP1A1	Phase I enzyme	miR-18b, -20b	Wang *et al.*, 2009; Glubb and Innocenti, 2011
CYP1B1	Phase I enzyme	miR-27b	Tsuchiya *et al.*, 2006; Chuturgoon *et al.*, 2014
CYP2A3	Phase I enzyme	miR-126*, -34	Kalscheuer *et al.*, 2008
CYP2E1	Phase I enzyme	miR-378	Mohri *et al.*, 2010; Takahashi *et al.*, 2014
CYP2J2	Phase I enzyme	Let-7b	F Chen *et al.*, 2012a
CYP3A4	Phase I enzyme	miR-27b, -577, -1, -532-3p, -627, -223, -148	Takagi *et al.*, 2008; Pan *et al.*, 2009a; Takahashi *et al.*, 2014; Wei *et al.*, 2014
CYP7A1	Phase I enzyme	miR-122a, miR-422a	Song *et al.*, 2010
CYP19A1	Phase I enzyme	miR-19b, -106a, let-7f	Shibahara *et al.*, 2012; Kumar *et al.*, 2013
CYP24A1	Phase I enzyme	miR-125b	Komagata *et al.*, 2009
GSS	Phase I enzyme	miR-125b	Tili *et al.*, 2012
GPX7	Phase I enzyme	miR-122	Akinc *et al.*, 2008
SULF1	Phase I Enzyme	miR-516a	Takei *et al.*, 2011
GSTP1	Phase II enzyme	miR-133a, -513a-3p	Zhang *et al.*, 2012; Uchida *et al.*, 2013
SULT1A1	Phase II enzyme	miR-631	Yu *et al.*, 2010
UGT1A	Phase II enzyme	miR-491-3p	Dluzen *et al.*, 2014
ABCA1	Transporter	miR-33, -33*, -758, -106b, -613, -27a, -27b, -145, -101, -135b	Ramirez *et al.*, 2011; Borel *et al.*, 2012; Kim *et al.*, 2012; Goedeke *et al.*, 2013; Kang *et al.*, 2013; Rottiers *et al.*, 2013; Zhang *et al.*, 2014; Zhao *et al.*, 2014
ABCB1/P-gp/MDR1	Transporter	miR-451, -27a, -298, -354, -7, -200c, -19a/b	Kovalchuk *et al.*, 2008; Zhu *et al.*, 2008; Pogribny *et al.*, 2010; Bitarte *et al.*, 2011; Bao *et al.*, 2012; J Chen *et al.*, 2012b; F Wang *et al.*, 2013a
ABCB11	Transporter	miR-33	Allen *et al.*, 2012
ABCC1/MRP-1	Transporter	miR-134, -326, -1291, -199a/b, -296	Guo *et al.*, 2010; Liang *et al.*, 2010; Borel *et al.*, 2012; Pan *et al.*, 2013
ABCC2	Transporter	miR-379, let-7c	Haenisch *et al.*, 2011; Zhan *et al.*, 2013
ABCC3	Transporter	miR-9*	Jeon *et al.*, 2011
ABCC4/MRP4	Transporter	miR-124a, -506, -125a/b	Borel *et al.*, 2012; Markova and Kroetz, 2014
ABCC5	Transporter	miR-128	Zhu *et al.*, 2011
ABCC6	Transporter	miR-9*	Jeon *et al.*, 2011
ABCC7/CFTR	Transporter	miR-145, -494, -1246, -509-3p	Gillen *et al.*, 2011; Ramachandran *et al.*, 2013
ABCC10	Transporter	Let-7a/e	Borel *et al.*, 2012
ABCE1	Transporter	miR-124, -203, -26a, -135b, -145	Furuta *et al.*, 2010; Borel *et al.*, 2012
ABCG1	Transporter	miR-33	Marquart *et al.*, 2010; Rayner *et al.*, 2010
ABCG2/BCRP	Transporter	miR-520h, -519c, -328, -487a, -181a	Liao *et al.*, 2008; Pan *et al.*, 2009b; To *et al.*, 2009; Wang *et al.*, 2010; Li *et al.*, 2011; Padmanabhan *et al.*, 2012; Jiao *et al.*, 2013; Ma *et al.*, 2013
SLC6A4	Transporter	miR-16, -15a	Baudry *et al.*, 2010; Tamarapu Parthasarathy *et al.*, 2012; Moya *et al.*, 2013
SLC7A5	Transporter	miR-126	Miko *et al.*, 2011
SLC7A11	Transporter	miR-27a	Drayton *et al.*, 2014
SLC15A1/PEPT1	Transporter	miR-92a	Dalmasso *et al.*, 2011b
SLC12A2	Transporter	miR-384, -494, -1246	Gillen *et al.*, 2011
SLC16A1/MCT1	Transporter	miR-124, -29a/b	KK Li *et al.*, 2009b; Pullen *et al.*, 2011
NR1I2/PX receptor	Nuclear Receptor	miR-148a	Takagi *et al.*, 2008
NR3C1/GR	Nuclear Receptor	miR-18, -124a	Vreugdenhil *et al.*, 2009
NR2B1/RXRA	Nuclear Receptor	miR-27a, -27b	Ji *et al.*, 2009; Komagata *et al.*, 2009; Mohri *et al.*, 2009
NR1I1/VD receptor	Nuclear Receptor	miR-27b, -125b	Mohri *et al.*, 2009; Pan *et al.*, 2009a
NR1C1	Nuclear Receptor	miR-10b, -506, -21, -27b	Zheng *et al.*, 2010; Kida *et al.*, 2011; Tong *et al.*, 2011; Zhou *et al.*, 2011
NR1C3	Nuclear Receptor	miR-130, -27b, -27a	Jennewein *et al.*, 2010; Kim *et al.*, 2010; Lee *et al.*, 2012
NR1C2	Nuclear Receptor	miR-15a, -199a, -214, -9	Yin *et al.*, 2010; el Azzouzi *et al.*, 2013; Thulin *et al.*, 2013
NR1H3/LXRA	Nuclear Receptor	miR-613, -206, -1	Ou *et al.*, 2011; Zhong *et al.*, 2013; Vinod *et al.*, 2014
NR2A1/HNF4A	Nuclear Receptor	miR-24, -34a	Takagi *et al.*, 2010
NR3A1	Nuclear Receptor	miR-221, -222, let-7a, miR-130a, -22, -206	Iorio *et al.*, 2005; Adams *et al.*, 2007; Zhao *et al.*, 2008; 2011b; Pandey and Picard, 2009; Xiong *et al.*, 2010; Tang *et al.*, 2011
RXRA	Modifier	miR-27a/b	Ji *et al.*, 2009

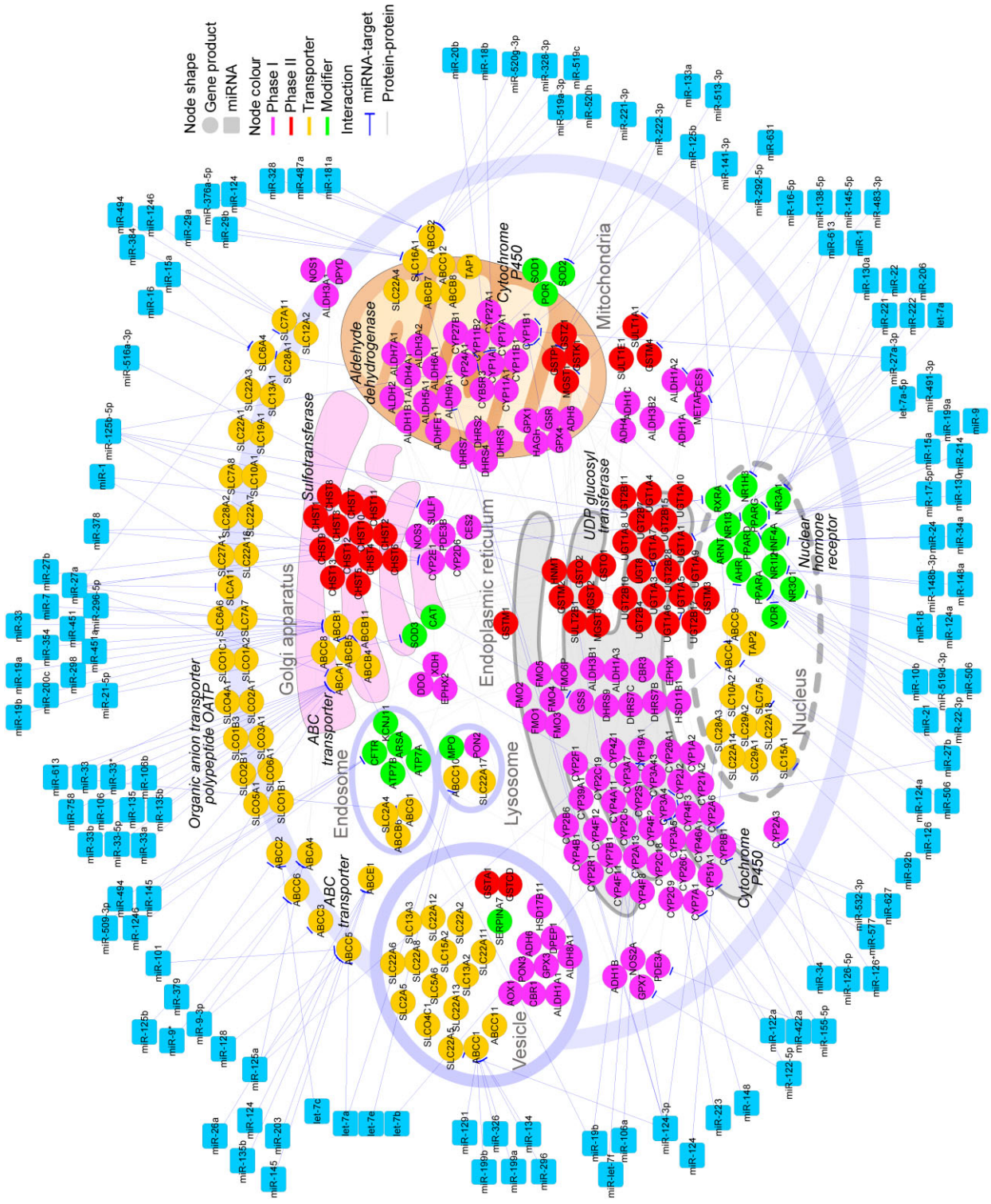

Figure 1

A hypothetical network view on the interactions between miRNA and ADME transcripts. Molecular interactions used were obtained from KEGG pathway and literature. The network contains 189 interactions between miRNA and its target genes, and 381 nodes including120 miRNAs (squares) and 261 ADME genes (circles). Different colours of circles represent different categories of ADME genes as indicated. The visualization of the network was carried our by Cytoscape.

experimentally verified to interact directly with the 3′-UTR of CYP3A4 transcript in HEK293T cells. Analysis of the miRNAs identified *in vitro* and CYP3A4 transcript and protein levels in human liver samples suggested that four of these miRNAs (miR-1, -532-3p, -577 and -627) attenuate the translation of CYP3A4 *in vivo*. Besides showing that miRNAs affect both transcript and protein levels *in vivo*, results from this study also illustrated our limited understanding of how miRNAs select their targets in cells, since only about 10% of the predicted interactions could be verified experimentally.

CYP2E1 is involved in the metabolism of anaesthetics, such as isoflurane and halothane, organic solvents, such as ethanol and benzene, acetaminophen (paracetamol) and other compounds. Computational analysis predicted a potential miR-378 binding site within the 3′-UTR of CYP2E1 (Mohri *et al.*, 2010), the functionality of which was verified by *in vitro* reporter assays. In addition, an inverse correlation between CYP2E1 protein levels and miR-378 abundances was observed in a panel of 25 human liver specimens, providing further support for the possible significance of this interaction *in vivo* (Mohri *et al.*, 2010).

CYP1B1 is overexpressed in diverse cancers (e.g. breast, colon, lung, oesophagus, skin, lymph node, brain and testis) relative to their corresponding normal tissues (Murray *et al.*, 1997) and is known to activate various pro-carcinogens (Shimada *et al.*, 1996). In addition, CYP1B1 enhances the conversion of 17β-oestradiol into 4-hydroxyestradiol (Han and Liehr, 1994; Newbold and Liehr, 2000), a metabolite known to cause DNA damage through free radical production and which may promote the development of oestrogen-dependent cancers. Examination of the 3′-UTR of CYP1B1 transcript revealed a high-quality target site for miR-27b (Tsuchiya *et al.*, 2006), which was confirmed using luciferase reporter assays. Ablation of miR-27b targeting via an antisense oligonucleotide increased the abundance and activity of endogenous CYP1B1 in MCF-7 cells. In addition, the amount of miR-27b was inversely correlated with CYP1B1 protein level in most of the oestrogen receptor/progesterone receptor positive breast cancer samples examined (Tsuchiya *et al.*, 2006).

GSH is synthesized from glutamylcysteine and glycine by glutathione synthetase (GSS) in an ATP-dependent process (Snoke and Bloch, 1955). GSH has many cellular functions, including the scavenging of peroxides and free radical species, and the detoxification of xenobiotics (Pastore *et al.*, 2003). Overexpression of miR-125b in chronic lymphocytic leukaemia-derived cell lines reduced GSS protein abundance and led to a decrease of GSH activity (Tili *et al.*, 2012). Using a luciferase reporter assay, miR-125b was verified to directly interact with the 3′-UTR of the GSS transcript.

Glutathione peroxidase 7 (GPX7) counters oxidative stress generated from polyunsaturated fatty acid metabolism (Utomo *et al.*, 2004) and can neutralize hydrogen peroxide in the absence of glutathione (Peng *et al.*, 2012). Knockdown of GPX7 expression resulted in an increase in reactive oxygen species, DNA damage and apoptosis in oesophageal squamous epithelial cells upon exposure to bile acids *in vitro*. GPX7 level was found to be up-regulated in the livers of mice treated with antagomiR-122 (a miR-122 antagonist). This suggests a possible interaction between miR-122 and GPX7 transcript (Krutzfeldt *et al.*, 2005; Akinc *et al.*, 2008).

UDP-glucuronosyltransferases (UGTs) are responsible for the phase II processing of many endogenous (e.g. bilirubin, steroid hormones) (Bosma *et al.*, 1994; Belanger *et al.*, 2003) and exogenous (e.g. drugs, chemotherapeutics and carcinogens) compounds (recent review in Rowland *et al.*, 2013). This family of enzymes is composed of two subfamilies (UGT1A and 2B) and catalyses the addition of carbohydrate groups (e.g. glucuronide) to its substrates for excretion (Mackenzie *et al.*, 2005; Nagar and Remmel, 2006). The UGT1A family has nine alternatively spliced protein isoforms sharing a common 3′-UTR. *In silico* analysis of the UGT1A 3′-UTR identified a potential miR-491-3p target sequence (Dluzen *et al.*, 2014). Introducing a miR-491-3p mimic into HuH-7 cells reduced UGT1A1 mRNA abundance by 48% relative to non-targeting control mimics and direct interaction between miR-491-3p and UGT1A1 3′-UTR was also confirmed by reporter assays. This reduction in UGT1A1 mRNA was complemented with a significant reduction in UGTA1 enzymatic activity, as measured by the conversion of raloxifene into glucuronidated metabolites (raloxifene-6-glucuronide and -4′-glucuronide). Knockdown of the endogenous miR-491-3p level in HepG2 cells increased the abundance of these metabolites, although without reducing UGT1A1 mRNA levels (Dluzen *et al.*, 2014). An inverse correlation between miR-491-3p abundance and the quantity of UGTA3 and A6 isoforms (sharing the same 3′-UTR as UGT1A1) was also observed in samples of normal human liver (Dluzen *et al.*, 2014).

MicroRNAs regulate the expression of transporter proteins

miRNAs have also been observed to regulate two major classes of drug transporters: ATP-binding cassette (ABC) and solute carrier (SLC) proteins (Table 1 and Figure 1). As these membrane transporters facilitate the uptake and excretion of many endo- and xenobiotics, alterations in their levels may affect the PK properties of drugs.

A recent study reported that the levels of a number of ABC transporters were increased in hepatocellular carcinoma and that the increase is associated with the decrease of several miRNAs (Borel *et al.*, 2012). Using luciferase reporter assays, Borel *et al.* confirmed the interactions of some ABC transporter transcripts and miRNAs including ABCA1 (interaction with miR-101 and miR-135b), ABCC1 (miR-199a/b and miR-296), ABCC4 (miR-125a/b), ABCC5 (miR-101, -125a and let-7a), ABCC10 (let-7a/e) and ABCE1 (miR-26a, -135b and -145) (Borel *et al.*, 2012). In addition to miR-101 and miR-135b, experimental data also suggest an interaction between ABCA1 and miR-33, since administration of a locked nucleic acid miRNA antagonist (antimiR) of miR-33 into a non-human primate model resulted in functional de-repression of the ABCA1 level. This finding demonstrates the possibility of modulating the interaction between specific miRNA and mRNA using antimiR, and provides proof of principle for this antimiR-based therapeutic modality (Rottiers *et al.*, 2013).

Besides miR-199a/b and miR-296, ABCC1 transcript is also targeted by miR-326. Overexpressing miR-326 reversed the multidrug resistance phenotype, sensitizing the drug-

resistant MCF-7/VP cells to doxorubicin (DOX) (Liang *et al.*, 2010). The ABCC1 transcript was also observed to be targeted by miR-134 and the ABCC1 protein level is decreased by the increased level of miR-134 in drug-resistant H69AR cells (Guo *et al.*, 2010).

Other miRNA–ABC transporter interactions have also been reported. For example, miR-379 interacts with the 3′-UTR of ABCC2 and suppresses ABCC2 transcript level in HepG2 cells (Haenisch *et al.*, 2011). miR-298 overexpression *in vitro* down-regulated the level of ABCB1, also known as the drug transporter multidrug resistance protein 1/P-glycoprotein (MDR1/P-gp), which leads to breast cancer cell sensitivity to DOX (i.e. decreased the efflux of DOX from cells). miR-298 was found to directly interact with 3′-UTR of ABCB1 transcript (Bao *et al.*, 2011). MiR-451 and miR-27a have also been observed to suppress the expression of ABCB1 and sensitize breast cancer cells to DOX (Kovalchuk *et al.*, 2008). In a display of the complexity of miRNA–mRNA regulatory networks, overexpression of miR-19a/b has been shown to increase the abundance of the ABCB1 transcript, which is likely to be mediated through indirect interactions with other gene expression regulatory factors (Wang *et al.*, 2013a).

Cancer cells can become resistant to chemotherapy by evading miRNA-based control of ADME genes. For example, ABCG2 plays an important role in cellular transport of anti-cancer drugs, such as mitoxantrone, doxorubicin and topotecan, and has been observed to acquire a truncated 3′-UTR in drug-resistant cells relative to the parental cell line (To *et al.*, 2008). The truncated mRNA omits a miR-519c binding site, which mediates a decrease in ABCG2 expression level by miR-519c. This adaptive truncation of the 3′-UTR was later found to be present in several ABCG2-overexpressing cell lines (To *et al.*, 2009). In addition to miR-519c, other miRNAs such as miR-520h and miR-328 have also been found to interact with ABCG2 transcript. The levels of miR-520h and miR-328 are lower in cells expressing ABCG2 relative to ABCG2-negative cells (Wang *et al.*, 2010). Results from a comparative study indicated stronger inhibition of ABCG2 expression in human breast cancer cells by miR-519c and miR-328 than miR-520h (Li *et al.*, 2011).

miRNAs have also been found to affect the absorption and excretion of small molecules through SLC proteins. Folate, nucleoside and amino acid transporters all belong to the SLC transporter family and mediate the uptake of hydrophilic drugs such as gemcitabine and other nucleoside analogues (Candelaria *et al.*, 2010). These levels of membrane transporters are also regulated by miRNA. For example, the expression of SLC15 was found to inversely correlate with miR-92b, which was then demonstrated to reduce SLC15 mRNA, protein and transport activity levels in Caco2-BBE cells (Dalmasso *et al.*, 2011b). Another SLC transporter, serotonin transporter 1 (SERT1, SLC6A4), has been found to be suppressed by miR-16 (Baudry *et al.*, 2010). *In silico* target prediction identified miR-16 as a potential regulator of SLC6A4. Overexpression of miR-16 in 1C11 cells reduced the SLC6A4 level. Reduction of miR-16 by an anti-miR-16 oligonucleotide resulted in an increase of SLC6A4 level. This interaction has also been demonstrated *in vivo*: in mouse studies, administration of the selective serotonin reuptake inhibitor fluoxetine was found to increase miR-16 abundance in serotonergic raphe nuclei with a reduced SLC6A4 level (Baudry *et al.*, 2010).

miRNA profiling data identified miR-27a as down-regulated in cisplatin-resistant bladder cancer cell lines, relative to the cisplatin-sensitive lines from which they were derived (Drayton *et al.*, 2014). MiR-27a was found to directly target the cystine/glutamate exchanger – SLC7A11, which forms a heterodimer with SLC3A2 to assemble the x_c-cystine-glutamate transporter. This protein complex imports cysteine (as cystine) for the synthesis of GSH, which enables cisplatin detoxification. miR-27a expression was found to inversely correlate with SLC7A11 level in patient samples. Low miR-27a and high SLC7A11 were found to correlate with poor patient prognosis.

MicroRNAs regulate the expression of nuclear receptors

Nuclear receptors play important roles in cellular responses towards environmental stimulation by activating or inactivating the expression of genes, including those that encode drug transporters and biotransformation enzymes. For instance, the retinoid X receptor (RXR) heterodimerizes with the steroid family of orphan nuclear receptors, the constitutive androstane receptor (CAR) or the pregnane X receptor (PXR) to participate in the xenobiotic-mediated transcriptional activation of CYP2B and CYP3A. This type of interaction increases the complexity of the role of miRNAs in regulating ADME activities, since miRNAs may affect the expression of ADME genes via indirect targeting the 3′-UTRs of nuclear receptors (Table 1 and Figure 1). For example, the interactions between miR-27b and miR-125b with the vitamin D (VD) receptor/RXRA alter CYP3A4 expression (Komagata *et al.*, 2009; Mohri *et al.*, 2009). The level of CYP3A4 is also affected by miR-148 through its interaction with PXRs (Takagi *et al.*, 2008).

The PPARα (NR1C1) regulates the expression of a number of ADME genes and its abundance is affected by the levels of miR-21or miR-27b (Kida *et al.*, 2011). An independent study showed that the overexpression of miR-506 also suppresses NR1C1expression, which leads to hydroxycamptothecin resistance in a colon cancer cell line (Tong *et al.*, 2011). Another miRNA-regulated nuclear receptor is liver X receptor α (LXRA/NR1H3), which is closely related to RXR and PPAR, and can be targeted by miR-613. The activation of LXRA resulted in an increased level of miR-613 (Ou *et al.*, 2011). This type of feedback loop probably plays an important part in maintaining proper ADME activity, which is critical for endo- and xenobiotic transport and metabolism.

The oestrogen receptor α (ESR1) and the glucocorticoid receptor (NR3C1) are known to affect the expression of CYP3A4 and ABCG2. MiR-221 and -222 inhibit ESR1 expression. Overexpression of miR-221/222 in a breast cancer cell line resulted in the cells becoming resistant to tamoxifen (an antagonist of the oestrogen receptor) treatment, while knocking down the level of miR-221/222 sensitized the cells (Zhao *et al.*, 2008). A similar effect was also observed with let-7b and let-7i (Y Xhao *et al.*, 2011b). The ESR1 transcript has also been observed to be targeted by miR-206, and ESR1 mRNA

Table 2

List of microRNAs affecting enzymes involved in epigenetic modifications

Gene ID	Gene description	Interacting miRNA	References
DNMT1	DNA (cytosine-5-)-methyltransferase 1	miR-126, -152, -185, -148, -140, -342	Wang *et al.*, 2011; S Zhao *et al.*, 2011a; Takata *et al.*, 2013; Azizi *et al.*, 2014; Xiang *et al.*, 2014
DNMT3A	DNA (cytosine-5-)-methyltransferase 3 alpha	miR-29b, -143, -199a, -370	Fabbri *et al.*, 2007; Garzon *et al.*, 2009; Ng *et al.*, 2009; 2014; Qi *et al.*, 2013; Chen *et al.*, 2014
DNMT3B	DNA (cytosine-5-)-methyltransferase 3 beta	miR-29, -148, -495	Fabbri *et al.*, 2007; Duursma *et al.*, 2008; Garzon *et al.*, 2009; Yang *et al.*, 2014
HDAC1	Histone deacetylase 1	miR-34, -449, -520h	Noonan *et al.*, 2009; Zhao *et al.*, 2013; Shen *et al.*, 2014
HDAC2	Histone deacetylase 2	miR-145	Noh *et al.*, 2013
HDAC4	Histone deacetylase 4	miR-1, -155, -365	Chen *et al.*, 2006; Guan *et al.*, 2011; Sandhu *et al.*, 2012
HDAC5	Histone deacetylase 5	miR-2861	H Li *et al.*, 2009a
HDAC6	Histone deacetylase 6	miR-433	Simon *et al.*, 2010
EZH2	Enhancer of zeste homologue 2	miR-26a, -26b, -101, -214, -124, -181a, -210, -424, -138	Sander *et al.*, 2008; Varambally *et al.*, 2008; Juan *et al.*, 2009; Zhang *et al.*, 2013; Overhoff *et al.*, 2014; Xie *et al.*, 2014
BMI1	B lymphoma Mo-MLV insertion region 1 homologue	miR-200c, -203 -183, -128	Godlewski *et al.*, 2008; Wellner *et al.*, 2009

abundance negatively correlates with the miR-206 level (Iorio *et al.*, 2005; Adams *et al.*, 2007). To further understand the interaction of miRNA and ESR1 transcript, Picard *et al.* performed a study on 14 miRNAs, which might be involved in ESR1expression and found that miR-22 exerted the strongest inhibition of oestrogen signalling through targeting ESR mRNA (Pandey and Picard, 2009).

Effects of epigenetic factors on miRNA expression

Even though numerous studies showed the effects of specific miRNAs on ADME-related transcripts, the levels of individual miRNA sequences are affected by intrinsic and extrinsic factors. Like other transcripts, the expression of miRNAs can be affected by epigenetic factors, such as DNA methylation. For example, rapid changes to miRNA levels have been observed upon treating cells with histone deacetylase (HDAC) inhibitors (Scott *et al.*, 2006). Alterations to miRNA promoter methylation status are associated with disease conditions. For example, the promoter of the tumour suppressor miR-125b is hyper-methylated in human breast cancer, leading to a lower level of miR-125b and the de-repression of its target transcription factor, ETS1 (V-Ets avian erythroblastosis virus E26 oncogene homologue 1) (Zhang *et al.*, 2011). In addition, the promoter of the metastasis suppressor miR-355 is also hyper-methylated in breast cancer (Png *et al.*, 2011). Hypo-methylation has also been observed to alter miRNA expression, as let-7a-3 has been found to be heavily methylated in normal human tissue, but hypo-methylated in some human lung cancers (Brueckner *et al.*, 2007).

In a display of further complexity, miRNAs can reciprocally influence epigenetic states by targeting transcripts that encode enzymes involved in DNA methylation and histone modifications (Table 2). Several HDACs have been observed by reporter assays to be regulated by different miRNAs (Scott *et al.*, 2006; H Li *et al.*, 2009a; Sato *et al.*, 2011; Wang *et al.*, 2013b). In addition, some polycomb proteins that are involved in the remodelling of chromatin structure are also regulated by miRNAs. For example, the expression of the histone methyltransferase EZH2 is repressed by miR-101 (Varambally *et al.*, 2008).

Influence of xenobiotic drugs on miRNA expression

miRNA expression also can be affected by exposure to xenobiotics. For example, the abundances of a number of miRNAs (miR-27a, -148a, -124a and miR-451) in MCF-7, Caco2, SH-SY5Y and BE(2)-M17 cell lines were affected by exposing the cells to common pharmacological agents, including dexamethasone, vinblastine, bilobalide and cocaine (Rodrigues *et al.*, 2011). As miRNAs regulate drug metabolizing enzymes and transporters, this might lead to considerable changes in the PK properties of the drug itself.

Suppression of miRNAs that control drug metabolism and disposition may explain changes in the expression of efflux transporters (Yu, 2009). For instance, the induction of CYP3A4 and ABCB1 by dexamethasone functions at least partially through the suppression of miR-27b, -451 and -148a, which may interact with CYP3A4 and ABCB1 transcripts (Rodrigues *et al.*, 2011). Vinblastine reduces the levels of miR-27a/b, -324-3p, -328, -148a and -451, which may cause the increase of ABCC1 expression in MCF-7 cells (Schrenk *et al.*, 2001), ABCB1 in LS-180 cells (Harmsen *et al.*, 2010) and CYP3A4 in HepG2 cells (Smith *et al.*, 2010). Another example

is the brain-specific miR-124a, a major regulator of neuronal identity (Conaco *et al.*, 2006; Maisel *et al.*, 2010). The abundance of this miRNA was reduced by psychoactive drugs (cocaine, methadone and fluoxetine), which might present a mechanism of neuroplasticity in response to xenobiotic agents.

Xenobiotic drugs may act on other proteins responsible for miRNA processing, leading to an altered expression of mature miRNAs (Shan *et al.*, 2008; Melo *et al.*, 2011). For example, enoxacin, a broad-spectrum antibacterial fluoroquinolone, enhanced endogenous miRNA production, including tumour suppressor miRNAs, by targeting the pre-miRNA processing protein TAR RNA-binding protein 2 (Melo *et al.*, 2011).

Host miRNA expression changes in response to the gut microbiome

The gastrointestinal tract contains a broad spectrum of microbial species that modulate the utilization of xenobiotics beyond the capability encoded in the host genome (Kau *et al.*, 2011; Haiser and Turnbaugh, 2013). Alterations to the microbiome population can influence the therapeutic efficacy of drugs (Viaud *et al.*, 2013). In addition, microbes can also contribute to dose-limiting toxicity of other agents, an undesirable effect that can be relieved by inhibition of bacterial β-glucuronidases (Wallace *et al.*, 2010).

The gut microbiome can also affect host miRNA expression, which may modulate the levels of various ADME genes and affect the ADME system. Comparison of the colon miRNA profiles of germ-free and control mice identified several dys-regulated miRNA species, including miR-128, -200C*, -342-5p, -465c-5p, -466d-3p, -466d-5p, -665 and -683 (Dalmasso *et al.*, 2011a). Using various experimental tools including luciferase assays and immunoblotting, it has been shown that the ABCC3, a cell surface transporter, is a direct target of miR-665. Microbiome inoculation down-regulated miR-665 level, which, in turn, increased the level of ABCC3 in enterocytes at both the mRNA and the protein levels (Dalmasso *et al.*, 2011a). Although the exact effects of the changes of ABCC3 level are yet to be determined, the biliary transport and excretion of organic anions are most likely to be affected . This finding demonstrates the complex interactions between gut microbiome and xenobiotic metabolism. The interaction is not just directly at chemical levels but also involves complex gene/protein networks through regulatory factors such as miRNA and other epigenetic factors.

Conclusions and future prospects

Variation between individuals in response to therapeutic agents is often attributed to the differences in host genetic factors. However, our knowledge of other contributors including epigenetic factors and microbiome dimensions is rapidly increasing. miRNA plays an important role in various physiopathological processes and substantial evidence is accumulating for its involvement in ADME. However, miRNA-mediated regulatory process is complex; although a number of computational algorithms have been developed to predict miRNA–mRNA interactions (Enright *et al.*, 2003; Lewis *et al.*, 2005), the accuracy of these predicted interactions is limited. In addition, most biological studies have been performed *in vitro* with only limited *in vivo* complementation. The precise physiologically relevant effects of miRNAs on ADME remains unclear and further study is required to generate detailed, highly substantiated empirical interaction networks to realize their diagnostic and therapeutic potential.

The recent realization of the complexity of the gut microbiome and its capacity to manipulate xenobiotics provides a new front in the study of drug metabolism and its effects on miRNA expression. Even though germ-free animal models provide some important insights on the effect of gut microbiome on host gene and miRNA expression, the host–microbiome interaction is complex and remains to be deciphered. Systems biology seeks to integrate results from different high-throughput profiling technologies to understand the dynamic changes of a biological system and predict its responses to various inputs. Using this approach to study the effects of epigenetic factors and microbiome on drug metabolism would provide a more comprehensive view on how different parts of the system interact with each other. A better understanding of factors affecting drug metabolism will be integral to personalized medicine, as it would provide guidance on drug development, increase the therapeutic efficacy, tailor specific treatment strategies for individuals and reduce adverse effects.

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Conflict of interest

The authors declare no conflict of interest.

References

Adams BD, Furneaux H, White BA (2007). The micro-ribonucleic acid (miRNA) miR-206 targets the human estrogen receptor-alpha (ERalpha) and represses ERalpha messenger RNA and protein expression in breast cancer cell lines. Mol Endocrinol 21: 1132–1147.

Akinc A, Zumbuehl A, Goldberg M, Leshchiner ES, Busini V, Hossain N *et al*. (2008). A combinatorial library of lipid-like materials for delivery of RNAi therapeutics. Nat Biotechnol 26: 561–569.

Alexander SPH, Benson HE, Faccenda E, Pawson AJ, Sharman JL Spedding M *et al* (2013a). The Concise Guide to PHARMACOLOGY 2013/14: Enzymes. Br J Pharmacol 170: 1797–1867.

Alexander SPH, Benson HE, Faccenda E, Pawson AJ, Sharman JL Spedding M *et al* (2013b). The Concise Guide to PHARMACOLOGY 2013/14: Nuclear Hormone Receptors. Br J Pharmacol 170, 1652–1675

Alexander SPH, Benson HE, Faccenda E, Pawson AJ, Sharman JL Spedding M *et al* (2013c). The Concise Guide to PHARMACOLOGY 2013/14: Transporters. Br J Pharmacol 170: 1706-1796.

Allen RM, Marquart TJ, Albert CJ, Suchy FJ, Wang DQ, Ananthanarayanan M *et al*. (2012). miR-33 controls the expression of biliary transporters, and mediates statin- and diet-induced hepatotoxicity. EMBO Mol Med 4: 882–895.

Alomar MJ (2014). Factors affecting the development of adverse drug reactions (Review article). Saudi Pharm J 22: 83–94.

Ambros V (2001). microRNAs: tiny regulators with great potential. Cell 107: 823–826.

Azizi M, Teimoori-Toolabi L, Arzanani MK, Azadmanesh K, Fard-Esfahani P, Zeinali S (2014). MicroRNA-148b and microRNA-152 reactivate tumor suppressor genes through suppression of DNA methyltransferase-1 gene in pancreatic cancer cell lines. Cancer Biol Ther 15: 419–427.

el Azzouzi H, Leptidis S, Dirkx E, Hoeks J, van Bree B, Brand K *et al*. (2013). The hypoxia-inducible microRNA cluster miR-199a~214 targets myocardial PPARδ and impairs mitochondrial fatty acid oxidation. Cell Metab 18: 341–354.

Bao L, Haque A, Jackson K, Hazari S, Moroz K, Jetly R *et al*. (2011). Increased expression of P-glycoprotein is associated with doxorubicin chemoresistance in the metastatic 4T1 breast cancer model. Am J Pathol 178: 838–852.

Bao L, Hazari S, Mehra S, Kaushal D, Moroz K, Dash S (2012). Increased expression of P-glycoprotein and doxorubicin chemoresistance of metastatic breast cancer is regulated by miR-298. Am J Pathol 180: 2490–2503.

Bartel DP (2009). MicroRNAs: target recognition and regulatory functions. Cell 136: 215–233.

Baudry A, Mouillet-Richard S, Schneider B, Launay JM, Kellermann O (2010). miR-16 targets the serotonin transporter: a new facet for adaptive responses to antidepressants. Science 329: 1537–1541.

Belanger A, Pelletier G, Labrie F, Barbier O, Chouinard S (2003). Inactivation of androgens by UDP-glucuronosyltransferase enzymes in humans. Trends Endocrinol Metab 14: 473–479.

Bell LC, Wang J (2012). Probe ADME and test hypotheses: a PATH beyond clearance *in vitro–in vivo* correlations in early drug discovery. Expert Opin Drug Metab Toxicol 8: 1131–1155.

Bernstein BE, Birney E, Dunham I, Green ED, Gunter C, Snyder M (2012). An integrated encyclopedia of DNA elements in the human genome. Nature 489: 57–74.

Bitarte N, Bandres E, Boni V, Zarate R, Rodriguez J, Gonzalez-Huarriz M *et al*. (2011). MicroRNA-451 is involved in the self-renewal, tumorigenicity, and chemoresistance of colorectal cancer stem cells. Stem Cells 29: 1661–1671.

Borel F, Han R, Visser A, Petry H, van Deventer SJ, Jansen PL *et al*. (2012). Adenosine triphosphate-binding cassette transporter genes up-regulation in untreated hepatocellular carcinoma is mediated by cellular microRNAs. Hepatology 55: 821–832.

Bosma PJ, Seppen J, Goldhoorn B, Bakker C, Oude Elferink RP, Chowdhury JR *et al*. (1994). Bilirubin UDP-glucuronosyltransferase 1 is the only relevant bilirubin glucuronidating isoform in man. J Biol Chem 269: 17960–17964.

Brueckner B, Stresemann C, Kuner R, Mund C, Musch T, Meister M *et al*. (2007). The human let-7a-3 locus contains an epigenetically regulated microRNA gene with oncogenic function. Cancer Res 67: 1419–1423.

Caldwell GW, Yan Z, Tang W, Dasgupta M, Hasting B (2009). ADME optimization and toxicity assessment in early- and late-phase drug discovery. Curr Top Med Chem 9: 965–980.

Candelaria M, de la Cruz-Hernandez E, Perez-Cardenas E, Trejo-Becerril C, Gutierrez-Hernandez O, Duenas-Gonzalez A (2010). Pharmacogenetics and pharmacoepigenetics of gemcitabine. Med Oncol 27: 1133–1143.

Chen BF, Gu S, Suen YK, Li L, Chan WY (2014). microRNA-199a-3p, DNMT3A, and aberrant DNA methylation in testicular cancer. Epigenetics 9: 119–128.

Chen F, Chen C, Yang S, Gong W, Wang Y, Cianflone K *et al*. (2012a). Let-7b inhibits human cancer phenotype by targeting cytochrome P450 epoxygenase 2J2. PLoS ONE 7: e39197.

Chen J, Tian W, Cai H, He H, Deng Y (2012b). Down-regulation of microRNA-200c is associated with drug resistance in human breast cancer. Med Oncol 29: 2527–2534.

Chen JF, Mandel EM, Thomson JM, Wu Q, Callis TE, Hammond SM *et al*. (2006). The role of microRNA-1 and microRNA-133 in skeletal muscle proliferation and differentiation. Nat Genet 38: 228–233.

Chuturgoon AA, Phulukdaree A, Moodley D (2014). Fumonisin B(1) modulates expression of human cytochrome P450 1b1 in human hepatoma (Hepg2) cells by repressing Mir-27b. Toxicol Lett 227: 50–55.

Conaco C, Otto S, Han JJ, Mandel G (2006). Reciprocal actions of REST and a microRNA promote neuronal identity. Proc Natl Acad Sci U S A 103: 2422–2427.

Dalmasso G, Nguyen HT, Yan Y, Laroui H, Charania MA, Ayyadurai S *et al*. (2011a). Microbiota modulate host gene expression via microRNAs. PLoS ONE 6: e19293.

Dalmasso G, Nguyen HT, Yan Y, Laroui H, Charania MA, Obertone TS *et al*. (2011b). MicroRNA-92b regulates expression of the oligopeptide transporter PepT1 in intestinal epithelial cells. Am J Physiol Gastrointest Liver Physiol 300: G52–G59.

Dannenberg LO, Edenberg HJ (2006). Epigenetics of gene expression in human hepatoma cells: expression profiling the response to inhibition of DNA methylation and histone deacetylation. BMC Genomics 7: 181.

Dluzen DF, Sun D, Salzberg AC, Jones N, Bushey RT, Robertson GP *et al*. (2014). Regulation of UDP-glucuronosyltransferase 1A1 expression and activity by microRNA 491-3p. J Pharmacol Exp Ther 348: 465–477.

Drayton RM, Peter S, Myers K, Miah S, Dudziec E, Bryant HE *et al*. (2014). MicroRNA-99a and 100 mediated upregulation of FOXA1 in bladder cancer. Oncotarget 5: 6375–6386.

Duursma AM, Kedde M, Schrier M, le Sage C, Agami R (2008). miR-148 targets human DNMT3b protein coding region. RNA 14: 872–877.

Emoto C, Murayama N, Rostami-Hodjegan A, Yamazaki H (2010). Methodologies for investigating drug metabolism at the early drug discovery stage: prediction of hepatic drug clearance and P450 contribution. Curr Drug Metab 11: 678–685.

Enright AJ, John B, Gaul U, Tuschl T, Sander C, Marks DS (2003). MicroRNA targets in Drosophila. Genome Biol 5: R1.

Esteller M (2011). Non-coding RNAs in human disease. Nat Rev Genet 12: 861–874.

Evrard A, Mbatchi L (2012). Genetic polymorphisms of drug metabolizing enzymes and transporters: the long way from bench to bedside. Curr Top Med Chem 12: 1720–1729.

Fabbri M, Garzon R, Cimmino A, Liu Z, Zanesi N, Callegari E *et al.* (2007). MicroRNA-29 family reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B. Proc Natl Acad Sci U S A 104: 15805–15810.

Friedman RC, Farh KK, Burge CB, Bartel DP (2009). Most mammalian mRNAs are conserved targets of microRNAs. Genome Res 19: 92–105.

Furuta M, Kozaki KI, Tanaka S, Arii S, Imoto I, Inazawa J (2010). miR-124 and miR-203 are epigenetically silenced tumor-suppressive microRNAs in hepatocellular carcinoma. Carcinogenesis 31: 766–776.

Garzon R, Liu S, Fabbri M, Liu Z, Heaphy CE, Callegari E *et al.* (2009). MicroRNA-29b induces global DNA hypomethylation and tumor suppressor gene reexpression in acute myeloid leukemia by targeting directly DNMT3A and 3B and indirectly DNMT1. Blood 113: 6411–6418.

Gillen AE, Gosalia N, Leir SH, Harris A (2011). MicroRNA regulation of expression of the cystic fibrosis transmembrane conductance regulator gene. Biochem J 438: 25–32.

Glubb DM, Innocenti F (2011). Mechanisms of genetic regulation in gene expression: examples from drug metabolizing enzymes and transporters. Wiley Interdiscip Rev Syst Biol Med 3: 299–313.

Godlewski J, Nowicki MO, Bronisz A, Williams S, Otsuki A, Nuovo G *et al.* (2008). Targeting of the Bmi-1 oncogene/stem cell renewal factor by microRNA-128 inhibits glioma proliferation and self-renewal. Cancer Res 68: 9125–9130.

Goedeke L, Vales-Lara FM, Fenstermaker M, Cirera-Salinas D, Chamorro-Jorganes A, Ramirez CM *et al.* (2013). A regulatory role for microRNA 33* in controlling lipid metabolism gene expression. Mol Cell Biol 33: 2339–2352.

Griffiths-Jones S, Saini HK, van Dongen S, Enright AJ (2008). miRBase: tools for microRNA genomics. Nucleic Acids Res 36 (Database issue): D154–D158.

Guan YJ, Yang X, Wei L, Chen Q (2011). MiR-365: a mechanosensitive microRNA stimulates chondrocyte differentiation through targeting histone deacetylase 4. FASEB J 25: 4457–4466.

Guo L, Liu Y, Bai Y, Sun Y, Xiao F, Guo Y (2010). Gene expression profiling of drug-resistant small cell lung cancer cells by combining microRNA and cDNA expression analysis. Eur J Cancer 46: 1692–1702.

Haenisch S, Laechelt S, Bruckmueller H, Werk A, Noack A, Bruhn O *et al.* (2011). Down-regulation of ATP-binding cassette C2 protein expression in HepG2 cells after rifampicin treatment is mediated by microRNA-379. Mol Pharmacol 80: 314–320.

Haiser HJ, Turnbaugh PJ (2013). Developing a metagenomic view of xenobiotic metabolism. Pharmacol Res 69: 21–31.

Han X, Liehr JG (1994). DNA single-strand breaks in kidneys of Syrian hamsters treated with steroidal estrogens: hormone-induced free radical damage preceding renal malignancy. Carcinogenesis 15: 997–1000.

Harmsen S, Meijerman I, Febus CL, Maas-Bakker RF, Beijnen JH, Schellens JH (2010). PXR-mediated induction of P-glycoprotein by anticancer drugs in a human colon adenocarcinoma-derived cell line. Cancer Chemother Pharmacol 66: 765–771.

Iorio MV, Ferracin M, Liu CG, Veronese A, Spizzo R, Sabbioni S *et al.* (2005). MicroRNA gene expression deregulation in human breast cancer. Cancer Res 65: 7065–7070.

Ivanov M, Kacevska M, Ingelman-Sundberg M (2012). Epigenomics and interindividual differences in drug response. Clin Pharmacol Ther 92: 727–736.

Jennewein C, von Knethen A, Schmid T, Brune B (2010). MicroRNA-27b contributes to lipopolysaccharide-mediated peroxisome proliferator-activated receptor gamma (PPARgamma) mRNA destabilization. J Biol Chem 285: 11846–11853.

Jeon HM, Sohn YW, Oh SY, Kim SH, Beck S, Kim S *et al.* (2011). ID4 imparts chemoresistance and cancer stemness to glioma cells by derepressing miR-9*-mediated suppression of SOX2. Cancer Res 71: 3410–3421.

Ji J, Zhang J, Huang G, Qian J, Wang X, Mei S (2009). Over-expressed microRNA-27a and 27b influence fat accumulation and cell proliferation during rat hepatic stellate cell activation. FEBS Lett 583: 759–766.

Jiao X, Zhao L, Ma M, Bai X, He M, Yan Y *et al.* (2013). MiR-181a enhances drug sensitivity in mitoxantone-resistant breast cancer cells by targeting breast cancer resistance protein (BCRP/ABCG2). Breast Cancer Res Treat 139: 717–730.

Juan AH, Kumar RM, Marx JG, Young RA, Sartorelli V (2009). Mir-214-dependent regulation of the polycomb protein Ezh2 in skeletal muscle and embryonic stem cells. Mol Cell 36: 61–74.

Kacevska M, Ivanov M, Wyss A, Kasela S, Milani L, Rane A *et al.* (2012). DNA methylation dynamics in the hepatic CYP3A4 gene promoter. Biochimie 94: 2338–2344.

Kalscheuer S, Zhang X, Zeng Y, Upadhyaya P (2008). Differential expression of microRNAs in early-stage neoplastic transformation in the lungs of F344 rats chronically treated with the tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Carcinogenesis 29: 2394–2399.

Kang MH, Zhang LH, Wijesekara N, de Haan W, Butland S, Bhattacharjee A *et al.* (2013). Regulation of ABCA1 protein expression and function in hepatic and pancreatic islet cells by miR-145. Arterioscler Thromb Vasc Biol 33: 2724–2732.

Kau AL, Ahern PP, Griffin NW, Goodman AL, Gordon JI (2011). Human nutrition, the gut microbiome and the immune system. Nature 474: 327–336.

Kellis M, Wold B, Snyder MP, Bernstein BE, Kundaje A, Marinov GK *et al.* (2014). Defining functional DNA elements in the human genome. Proc Natl Acad Sci U S A 111: 6131–6138.

Kida K, Nakajima M, Mohri T, Oda Y, Takagi S, Fukami T *et al.* (2011). PPARα is regulated by miR-21 and miR-27b in human liver. Pharm Res 28: 2467–2476.

Kim J, Yoon H, Ramirez CM, Lee SM, Hoe HS, Fernandez-Hernando C (2012). MiR-106b impairs cholesterol efflux and increases Aβ levels by repressing ABCA1 expression. Exp Neurol 235: 476–483.

Kim SY, Kim AY, Lee HW, Son YH, Lee GY, Lee JW *et al.* (2010). miR-27a is a negative regulator of adipocyte differentiation via suppressing PPARgamma expression. Biochem Biophys Res Commun 392: 323–328.

Kim VN, Han J, Siomi MC (2009). Biogenesis of small RNAs in animals. Nature reviews 10: 126–139.

Kloosterman WP, Plasterk RH (2006). The diverse functions of microRNAs in animal development and disease. Dev Cell 11: 441–450.

Komagata S, Nakajima M, Takagi S, Mohri T, Taniya T, Yokoi T (2009). Human CYP24 catalyzing the inactivation of calcitriol is post-transcriptionally regulated by miR-125b. Mol Pharmacol 76: 702–709.

Kovalchuk O, Filkowski J, Meservy J, Ilnytskyy Y, Tryndyak VP, Chekhun VF *et al.* (2008). Involvement of microRNA-451 in resistance of the MCF-7 breast cancer cells to chemotherapeutic drug doxorubicin. Mol Cancer Ther 7: 2152–2159.

Krutzfeldt J, Rajewsky N, Braich R, Rajeev KG, Tuschl T, Manoharan M *et al.* (2005). Silencing of microRNAs *in vivo* with 'antagomirs'. Nature 438: 685–689.

Kumar P, Luo Y, Tudela C, Alexander JM, Mendelson CR (2013). The c-Myc-regulated microRNA-17~92 (miR-17~92) and miR-106a~363 clusters target hCYP19A1 and hGCM1 to inhibit human trophoblast differentiation. Mol Cell Biol 33: 1782–1796.

Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T (2001). Identification of novel genes coding for small expressed RNAs. Science 294: 853–858.

Lee JJ, Drakaki A, Iliopoulos D, Struhl K (2012). MiR-27b targets PPARγ to inhibit growth, tumor progression and the inflammatory response in neuroblastoma cells. Oncogene 31: 3818–3825.

Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH *et al.* (2004). MicroRNA genes are transcribed by RNA polymerase II. EMBO J 23: 4051–4060.

Lehmann JM, McKee DD, Watson MA, Willson TM, Moore JT, Kliewer SA (1998). The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions. J Clin Invest 102: 1016–1023.

Lewis BP, Burge CB, Bartel DP (2005). Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell 120: 15–20.

Lewis DF (2004). 57 varieties: the human cytochromes P450. Pharmacogenomics 5: 305–318.

Li H, Xie H, Liu W, Hu R, Huang B, Tan YF *et al.* (2009a). A novel microRNA targeting HDAC5 regulates osteoblast differentiation in mice and contributes to primary osteoporosis in humans. J Clin Invest 119: 3666–3677.

Li KK, Pang JC, Ching AK, Wong CK, Kong X, Wang Y *et al.* (2009b). miR-124 is frequently down-regulated in medulloblastoma and is a negative regulator of SLC16A1. Hum Pathol 40: 1234–1243.

Li X, Pan YZ, Seigel GM, Hu ZH, Huang M, Yu AM (2011). Breast cancer resistance protein BCRP/ABCG2 regulatory microRNAs (hsa-miR-328, -519c and -520h) and their differential expression in stem-like ABCG2+ cancer cells. Biochem Pharmacol 81: 783–792.

Liang Z, Wu H, Xia J, Li Y, Zhang Y, Huang K *et al.* (2010). Involvement of miR-326 in chemotherapy resistance of breast cancer through modulating expression of multidrug resistance-associated protein 1. Biochem Pharmacol 79: 817–824.

Liao R, Sun J, Zhang L, Lou G, Chen M, Zhou D *et al.* (2008). MicroRNAs play a role in the development of human hematopoietic stem cells. J Cell Biochem 104: 805–817.

Liu N, Pan T (2014). RNA epigenetics. Transl Res doi: 10.1016/j.trsl.2014.04.003; [Epub ahead of print].

Ma MT, He M, Wang Y, Jiao XY, Zhao L, Bai XF *et al.* (2013). MiR-487a resensitizes mitoxantrone (MX)-resistant breast cancer cells (MCF-7/MX) to MX by targeting breast cancer resistance protein (BCRP/ABCG2). Cancer Lett 339: 107–115.

Mackenzie PI, Bock KW, Burchell B, Guillemette C, Ikushiro S, Iyanagi T *et al.* (2005). Nomenclature update for the mammalian UDP glycosyltransferase (UGT) gene superfamily. Pharmacogenet Genomics 15: 677–685.

Maisel M, Habisch HJ, Royer L, Herr A, Milosevic J, Hermann A *et al.* (2010). Genome-wide expression profiling and functional network analysis upon neuroectodermal conversion of human mesenchymal stem cells suggest HIF-1 and miR-124a as important regulators. Exp Cell Res 316: 2760–2778.

Markova SM, Kroetz DL (2014). ABCC4 is regulated by microRNA-124a and microRNA-506. Biochem Pharmacol 87: 515–522.

Marquart TJ, Allen RM, Ory DS, Baldan A (2010). miR-33 links SREBP-2 induction to repression of sterol transporters. Proc Natl Acad Sci U S A 107: 12228–12232.

Melo S, Villanueva A, Moutinho C, Davalos V, Spizzo R, Ivan C *et al.* (2011). Small molecule enoxacin is a cancer-specific growth inhibitor that acts by enhancing TAR RNA-binding protein 2-mediated microRNA processing. Proc Natl Acad Sci U S A 108: 4394–4399.

Miko E, Margitai Z, Czimmerer Z, Varkonyi I, Dezso B, Lanyi A *et al.* (2011). miR-126 inhibits proliferation of small cell lung cancer cells by targeting SLC7A5. FEBS Lett 585: 1191–1196.

Mohri T, Nakajima M, Takagi S, Komagata S, Yokoi T (2009). MicroRNA regulates human vitamin D receptor. Int J Cancer 125: 1328–1333.

Mohri T, Nakajima M, Fukami T, Takamiya M, Aoki Y, Yokoi T (2010). Human CYP2E1 is regulated by miR-378. Biochem Pharmacol 79: 1045–1052.

Moya PR, Wendland JR, Salemme J, Fried RL, Murphy DL (2013). miR-15a and miR-16 regulate serotonin transporter expression in human placental and rat brain raphe cells. Int J Neuropsychopharmacol 16: 621–629.

Murray GI, Taylor MC, McFadyen MC, McKay JA, Greenlee WF, Burke MD *et al.* (1997). Tumor-specific expression of cytochrome P450 CYP1B1. Cancer Res 57: 3026–3031.

Nagar S, Remmel RP (2006). Uridine diphosphoglucuronosyltransferase pharmacogenetics and cancer. Oncogene 25: 1659–1672.

Nakajima T, Aoyama T (2000). Polymorphism of drug-metabolizing enzymes in relation to individual susceptibility to industrial chemicals. Ind Health 38: 143–152.

Newbold RR, Liehr JG (2000). Induction of uterine adenocarcinoma in CD-1 mice by catechol estrogens. Cancer Res 60: 235–237.

Ng EK, Tsang WP, Ng SS, Jin HC, Yu J, Li JJ *et al.* (2009). MicroRNA-143 targets DNA methyltransferases 3A in colorectal cancer. Br J Cancer 101: 699–706.

Ng EK, Li R, Shin VY, Siu JM, Ma ES, Kwong A (2014). MicroRNA-143 is downregulated in breast cancer and regulates DNA methyltransferases 3A in breast cancer cells. Tumour Biol 35: 2591–2598.

Noh JH, Chang YG, Kim MG, Jung KH, Kim JK, Bae HJ *et al.* (2013). MiR-145 functions as a tumor suppressor by directly targeting histone deacetylase 2 in liver cancer. Cancer Lett 335: 455–462.

Noonan EJ, Place RF, Pookot D, Basak S, Whitson JM, Hirata H *et al.* (2009). miR-449a targets HDAC-1 and induces growth arrest in prostate cancer. Oncogene 28: 1714–1724.

Ou Z, Wada T, Gramignoli R, Li S, Strom SC, Huang M *et al.* (2011). MicroRNA hsa-miR-613 targets the human LXRα gene and mediates a feedback loop of LXRα autoregulation. Mol Endocrinol 25: 584–596.

Overhoff MG, Garbe JC, Koh J, Stampfer MR, Beach DH, Bishop CL (2014). Cellular senescence mediated by p16INK4A-coupled miRNA pathways. Nucleic Acids Res 42: 1606–1618.

Padmanabhan R, Chen KG, Gillet JP, Handley M, Mallon BS, Hamilton RS *et al.* (2012). Regulation and expression of the ATP-binding cassette transporter ABCG2 in human embryonic stem cells. Stem Cells 30: 2175–2187.

Pan YZ, Gao W, Yu AM (2009a). MicroRNAs regulate CYP3A4 expression via direct and indirect targeting. Drug Metab Dispos 37: 2112–2117.

Pan YZ, Morris ME, Yu AM (2009b). MicroRNA-328 negatively regulates the expression of breast cancer resistance protein (BCRP/ABCG2) in human cancer cells. Mol Pharmacol 75: 1374–1379.

Pan YZ, Zhou A, Hu Z, Yu AM (2013). Small nucleolar RNA-derived microRNA hsa-miR-1291 modulates cellular drug disposition through direct targeting of ABC transporter ABCC1. Drug Metab Dispos 41: 1744–1751.

Pandey DP, Picard D (2009). miR-22 inhibits estrogen signaling by directly targeting the estrogen receptor alpha mRNA. Mol Cell Biol 29: 3783–3790.

Pastore A, Federici G, Bertini E, Piemonte F (2003). Analysis of glutathione: implication in redox and detoxification. Clin Chim Acta 333: 19–39.

Pawson AJ, Sharman JL, Benson HE, Faccenda E, Alexander SP, Buneman OP *et al.*; NC-IUPHAR (2014). The IUPHAR/BPS Guide to PHARMACOLOGY: an expert-driven knowledge base of drug targets and their ligands. Nucleic Acids Res 42 (Database Issue): D1098–1106.

Peng D, Belkhiri A, Hu T, Chaturvedi R, Asim M, Wilson KT *et al.* (2012). Glutathione peroxidase 7 protects against oxidative DNA damage in oesophageal cells. Gut 61: 1250–1260.

Pfeffer S, Zavolan M, Grasser FA, Chien M, Russo JJ, Ju J *et al.* (2004). Identification of virus-encoded microRNAs. Science 304: 734–736.

Plant NJ, Gibson GG (2003). Evaluation of the toxicological relevance of CYP3A4 induction. Curr Opin Drug Discov Devel 6: 50–56.

Png KJ, Yoshida M, Zhang XH, Shu W, Lee H, Rimner A *et al.* (2011). MicroRNA-335 inhibits tumor reinitiation and is silenced through genetic and epigenetic mechanisms in human breast cancer. Genes Dev 25: 226–231.

Pogribny IP, Filkowski JN, Tryndyak VP, Golubov A, Shpyleva SI, Kovalchuk O (2010). Alterations of microRNAs and their targets are associated with acquired resistance of MCF-7 breast cancer cells to cisplatin. Int J Cancer 127: 1785–1794.

Pullen TJ, da Silva Xavier G, Kelsey G, Rutter GA (2011). miR-29a and miR-29b contribute to pancreatic beta-cell-specific silencing of monocarboxylate transporter 1 (Mct1). Mol Cell Biol 31: 3182–3194.

Qi L, Hongjuan H, Ning G, Zhengbin H, Yanjiang X, Tiebo Z *et al.* (2013). miR-370 is stage-specifically expressed during mouse embryonic development and regulates Dnmt3a. FEBS Lett 587: 775–781.

Ramachandran S, Karp PH, Osterhaus SR, Jiang P, Wohlford-Lenane C, Lennox KA *et al.* (2013). Post-transcriptional regulation of cystic fibrosis transmembrane conductance regulator expression and function by microRNAs. Am J Respir Cell Mol Biol 49: 544–551.

Ramirez CM, Davalos A, Goedeke L, Salerno AG, Warrier N, Cirera-Salinas D *et al.* (2011). MicroRNA-758 regulates cholesterol efflux through posttranscriptional repression of ATP-binding cassette transporter A1. Arterioscler Thromb Vasc Biol 31: 2707–2714.

Rayner KJ, Suarez Y, Davalos A, Parathath S, Fitzgerald ML, Tamehiro N *et al.* (2010). MiR-33 contributes to the regulation of cholesterol homeostasis. Science 328: 1570–1573.

Rodrigues AC, Li X, Radecki L, Pan YZ, Winter JC, Huang M *et al.* (2011). MicroRNA expression is differentially altered by xenobiotic drugs in different human cell lines. Biopharm Drug Dispos 32: 355–367.

Rodriguez A, Griffiths-Jones S, Ashurst JL, Bradley A (2004). Identification of mammalian microRNA host genes and transcription units. Genome Res 14 (10A): 1902–1910.

Rottiers V, Obad S, Petri A, McGarrah R, Lindholm MW, Black JC *et al.* (2013). Pharmacological inhibition of a microRNA family in nonhuman primates by a seed-targeting 8-mer antimiR. Sci Transl Med 5: 212ra162.

Rowland A, Miners JO, Mackenzie PI (2013). The UDP-glucuronosyltransferases: their role in drug metabolism and detoxification. Int J Biochem Cell Biol 45: 1121–1132.

Sander S, Bullinger L, Klapproth K, Fiedler K, Kestler HA, Barth TF *et al.* (2008). MYC stimulates EZH2 expression by repression of its negative regulator miR-26a. Blood 112: 4202–4212.

Sandhu SK, Volinia S, Costinean S, Galasso M, Neinast R, Santhanam R *et al.* (2012). miR-155 targets histone deacetylase 4 (HDAC4) and impairs transcriptional activity of B-cell lymphoma 6 (BCL6) in the Emu-miR-155 transgenic mouse model. Proc Natl Acad Sci U S A 109: 20047–20052.

Sato F, Tsuchiya S, Meltzer SJ, Shimizu K (2011). MicroRNAs and epigenetics. FEBS J 278: 1598–1609.

Schrenk D, Baus PR, Ermel N, Klein C, Vorderstemann B, Kauffmann HM (2001). Up-regulation of transporters of the MRP family by drugs and toxins. Toxicol Lett 120: 51–57.

Scott GK, Mattie MD, Berger CE, Benz SC, Benz CC (2006). Rapid alteration of microRNA levels by histone deacetylase inhibition. Cancer Res 66: 1277–1281.

Seitz H, Royo H, Bortolin ML, Lin SP, Ferguson-Smith AC, Cavaille J (2004). A large imprinted microRNA gene cluster at the mouse Dlk1-Gtl2 domain. Genome Res 14: 1741–1748.

Shan G, Li Y, Zhang J, Li W, Szulwach KE, Duan R *et al.* (2008). A small molecule enhances RNA interference and promotes microRNA processing. Nat Biotechnol 26: 933–940.

Shen Q, Yao Q, Sun J, Feng L, Lu H, Ma Y *et al.* (2014). Downregulation of histone deacetylase 1 by microRNA-520h contributes to the chemotherapeutic effect of doxorubicin. FEBS Lett 588: 184–191.

Shibahara Y, Miki Y, Onodera Y, Hata S, Chan MS, Yiu CC *et al.* (2012). Aromatase inhibitor treatment of breast cancer cells increases the expression of let-7f, a microRNA targeting CYP19A1. J Pathol 227: 357–366.

Shimada T, Hayes CL, Yamazaki H, Amin S, Hecht SS, Guengerich FP *et al.* (1996). Activation of chemically diverse procarcinogens by human cytochrome P-450 1B1. Cancer Res 56: 2979–2984.

Simon D, Laloo B, Barillot M, Barnetche T, Blanchard C, Rooryck C *et al.* (2010). A mutation in the 3′-UTR of the HDAC6 gene

abolishing the post-transcriptional regulation mediated by hsa-miR-433 is linked to a new form of dominant X-linked chondrodysplasia. Hum Mol Genet 19: 2015–2027.

Smith NF, Mani S, Schuetz EG, Yasuda K, Sissung TM, Bates SE *et al.* (2010). Induction of CYP3A4 by vinblastine: role of the nuclear receptor NR1I2. Ann Pharmacother 44: 1709–1717.

Snoke JE, Bloch K (1955). Studies on the mechanism of action of glutathione synthetase. J Biol Chem 213: 825–835.

Song KH, Li T, Owsley E, Chiang JY (2010). A putative role of micro RNA in regulation of cholesterol 7alpha-hydroxylase expression in human hepatocytes. J Lipid Res 51: 2223–2233.

Stefani G, Slack FJ (2008). Small non-coding RNAs in animal development. Nature reviews 9: 219–230.

Takagi S, Nakajima M, Mohri T, Yokoi T (2008). Post-transcriptional regulation of human pregnane X receptor by micro-RNA affects the expression of cytochrome P450 3A4. J Biol Chem 283: 9674–9680.

Takagi S, Nakajima M, Kida K, Yamaura Y, Fukami T, Yokoi T (2010). MicroRNAs regulate human hepatocyte nuclear factor 4alpha, modulating the expression of metabolic enzymes and cell cycle. J Biol Chem 285: 4415–4422.

Takahashi K, Oda Y, Toyoda Y, Fukami T, Yokoi T, Nakajima M (2014). Regulation of cytochrome b5 expression by miR-223 in human liver: effects on cytochrome P450 activities. Pharm Res 31: 780–794.

Takata A, Otsuka M, Yoshikawa T, Kishikawa T, Hikiba Y, Obi S *et al.* (2013). MicroRNA-140 acts as a liver tumor suppressor by controlling NF-κB activity by directly targeting DNA methyltransferase 1 (Dnmt1) expression. Hepatology 57: 162–170.

Takei Y, Takigahira M, Mihara K, Tarumi Y, Yanagihara K (2011). The metastasis-associated microRNA miR-516a-3p is a novel therapeutic target for inhibiting peritoneal dissemination of human scirrhous gastric cancer. Cancer Res 71: 1442–1453.

Tamarapu Parthasarathy P, Galam L, Huynh B, Yunus A, Abuelenen T, Castillo A *et al.* (2012). MicroRNA 16 modulates epithelial sodium channel in human alveolar epithelial cells. Biochem Biophys Res Commun 426: 203–208.

Tang L, Pu Y, Wong DK, Liu T, Tang H, Xiang T *et al.* (2011). The hepatitis B virus-associated estrogen receptor alpha (ERalpha) was regulated by microRNA-130a in HepG2.2.15 human hepatocellular carcinoma cells. Acta Biochim Biophys Sin (Shanghai) 43: 640–646.

Thomson DW, Bracken CP, Goodall GJ (2011). Experimental strategies for microRNA target identification. Nucleic Acids Res 39: 6845–6853.

Thulin P, Wei T, Werngren O, Cheung L, Fisher RM, Grander D *et al.* (2013). MicroRNA-9 regulates the expression of peroxisome proliferator-activated receptor δ in human monocytes during the inflammatory response. Int J Mol Med 31: 1003–1010.

Tili E, Michaille JJ, Luo Z, Volinia S, Rassenti LZ, Kipps TJ *et al.* (2012). The down-regulation of miR-125b in chronic lymphocytic leukemias leads to metabolic adaptation of cells to a transformed state. Blood 120: 2631–2638.

To KK, Zhan Z, Litman T, Bates SE (2008). Regulation of ABCG2 expression at the 3′ untranslated region of its mRNA through modulation of transcript stability and protein translation by a putative microRNA in the S1 colon cancer cell line. Mol Cell Biol 28: 5147–5161.

To KK, Robey RW, Knutsen T, Zhan Z, Ried T, Bates SE (2009). Escape from hsa-miR-519c enables drug-resistant cells to maintain high expression of ABCG2. Mol Cancer Ther 8: 2959–2968.

Tong JL, Zhang CP, Nie F, Xu XT, Zhu MM, Xiao SD *et al.* (2011). MicroRNA 506 regulates expression of PPAR alpha in hydroxycamptothecin-resistant human colon cancer cells. FEBS Lett 585: 3560–3568.

Tsuchiya Y, Nakajima M, Takagi S, Taniya T, Yokoi T (2006). MicroRNA regulates the expression of human cytochrome P450 1B1. Cancer Res 66: 9090–9098.

Uchida Y, Chiyomaru T, Enokida H, Kawakami K, Tatarano S, Kawahara K *et al.* (2013). MiR-133a induces apoptosis through direct regulation of GSTP1 in bladder cancer cell lines. Urol Oncol 31: 115–123.

Utomo A, Jiang X, Furuta S, Yun J, Levin DS, Wang YC *et al.* (2004). Identification of a novel putative non-selenocysteine containing phospholipid hydroperoxide glutathione peroxidase (NPGPx) essential for alleviating oxidative stress generated from polyunsaturated fatty acids in breast cancer cells. J Biol Chem 279: 43522–43529.

Varambally S, Cao Q, Mani RS, Shankar S, Wang X, Ateeq B *et al.* (2008). Genomic loss of microRNA-101 leads to overexpression of histone methyltransferase EZH2 in cancer. Science 322: 1695–1699.

Viaud S, Saccheri F, Mignot G, Yamazaki T, Daillere R, Hannani D *et al.* (2013). The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Science 342: 971–976.

Vinod M, Chennamsetty I, Colin S, Belloy L, De Paoli F, Schaider H *et al.* (2014). miR-206 controls LXRα expression and promotes LXR-mediated cholesterol efflux in macrophages. Biochim Biophys Acta 1841: 827–835.

Vreugdenhil E, Verissimo CS, Mariman R, Kamphorst JT, Barbosa JS, Zweers T *et al.* (2009). MicroRNA 18 and 124a down-regulate the glucocorticoid receptor: implications for glucocorticoid responsiveness in the brain. Endocrinology 150: 2220–2228.

Wallace BD, Wang H, Lane KT, Scott JE, Orans J, Koo JS *et al.* (2010). Alleviating cancer drug toxicity by inhibiting a bacterial enzyme. Science 330: 831–835.

Wang F, Xue X, Wei J, An Y, Yao J, Cai H *et al.* (2010). hsa-miR-520h downregulates ABCG2 in pancreatic cancer cells to inhibit migration, invasion, and side populations. Br J Cancer 103: 567–574.

Wang F, Li T, Zhang B, Li H, Wu Q, Yang L *et al.* (2013a). MicroRNA-19a/b regulates multidrug resistance in human gastric cancer cells by targeting PTEN. Biochem Biophys Res Commun 434: 688–694.

Wang H, Wu J, Meng X, Ying X, Zuo Y, Liu R *et al.* (2011). MicroRNA-342 inhibits colorectal cancer cell proliferation and invasion by directly targeting DNA methyltransferase 1. Carcinogenesis 32: 1033–1042.

Wang JH, Shih KS, Wu YW, Wang AW, Yang CR (2013b). Histone deacetylase inhibitors increase microRNA-146a expression and enhance negative regulation of interleukin-1beta signaling in osteoarthritis fibroblast-like synoviocytes. Osteoarthritis Cartilage 21: 1987–1996.

Wang L, Oberg AL, Asmann YW, Sicotte H, McDonnell SK, Riska SM *et al.* (2009). Genome-wide transcriptional profiling reveals microRNA-correlated genes and biological processes in human lymphoblastoid cell lines. PLoS ONE 4: e5878.

Wang Z, Schuetz EG, Xu Y, Thummel KE (2013c). Interplay between vitamin D and the drug metabolizing enzyme CYP3A4. J Steroid Biochem Mol Biol 136: 54–58.

Wei Z, Jiang S, Zhang Y, Wang X, Peng X, Meng C *et al.* (2014). The effect of microRNAs in the regulation of human CYP3A4: a systematic study using a mathematical model. Sci Rep 4: 4283.

Wellner U, Schubert J, Burk UC, Schmalhofer O, Zhu F, Sonntag A *et al*. (2009). The EMT-activator ZEB1 promotes tumorigenicity by repressing stemness-inhibiting microRNAs. Nat Cell Biol 11: 1487–1495.

Xiang Y, Ma N, Wang D, Zhang Y, Zhou J, Wu G *et al*. (2014). MiR-152 and miR-185 co-contribute to ovarian cancer cells cisplatin sensitivity by targeting DNMT1 directly: a novel epigenetic therapy independent of decitabine. Oncogene 33: 378–386.

Xie L, Zhang Z, Tan Z, He R, Zeng X, Xie Y *et al*. (2014). microRNA-124 inhibits proliferation and induces apoptosis by directly repressing EZH2 in gastric cancer. Mol Cell Biochem 392: 153–159.

Xiong J, Yu D, Wei N, Fu H, Cai T, Huang Y *et al*. (2010). An estrogen receptor alpha suppressor, microRNA-22, is downregulated in estrogen receptor alpha-positive human breast cancer cell lines and clinical samples. FEBS J 277: 1684–1694.

Yang D, Wang G, Zhu S, Liu Q, Wei T, Leng Y *et al*. (2014). MiR-495 suppresses mesendoderm differentiation of mouse embryonic stem cells via the direct targeting of Dnmt3a. Stem Cell Res 12: 550–561.

Yin KJ, Deng Z, Hamblin M, Xiang Y, Huang H, Zhang J *et al*. (2010). Peroxisome proliferator-activated receptor delta regulation of miR-15a in ischemia-induced cerebral vascular endothelial injury. J Neurosci 30: 6398–6408.

Yu AM (2007). Small interfering RNA in drug metabolism and transport. Curr Drug Metab 8: 700–708.

Yu AM (2009). Role of microRNAs in the regulation of drug metabolism and disposition. Expert Opin Drug Metab Toxicol 5: 1513–1528.

Yu X, Dhakal IB, Beggs M, Edavana VK, Williams S, Zhang X *et al*. (2010). Functional genetic variants in the 3′-untranslated region of sulfotransferase isoform 1A1 (SULT1A1) and their effect on enzymatic activity. Toxicol Sci 118: 391–403.

Zhan M, Qu Q, Wang G, Zhou H (2013). Let-7c sensitizes acquired cisplatin-resistant A549 cells by targeting ABCC2 and Bcl-XL. Pharmazie 68: 955–961.

Zhang H, Zhao M, Lv Z, Zhang X, Qin X, Wang H *et al*. (2013). MiR-138 inhibits tumor growth through repression of EZH2 in non-small cell lung cancer. Cell Physiol Biochem 31: 56–65.

Zhang M, Wu JF, Chen WJ, Tang SL, Mo ZC, Tang YY *et al*. (2014). MicroRNA-27a/b regulates cellular cholesterol efflux, influx and esterification/hydrolysis in THP-1 macrophages. Atherosclerosis 234: 54–64.

Zhang X, Zhu J, Xing R, Tie Y, Fu H, Zheng X *et al*. (2012). miR-513a-3p sensitizes human lung adenocarcinoma cells to chemotherapy by targeting GSTP1. Lung Cancer 77: 488–494.

Zhang Y, Yan LX, Wu QN, Du ZM, Chen J, Liao DZ *et al*. (2011). miR-125b is methylated and functions as a tumor suppressor by regulating the ETS1 proto-oncogene in human invasive breast cancer. Cancer Res 71: 3552–3562.

Zhao J, Lammers P, Torrance CJ, Bader AG (2013). TP53-independent function of miR-34a via HDAC1 and p21(CIP1/WAF1.). Mol Ther 21: 1678–1686.

Zhao JJ, Lin J, Yang H, Kong W, He L, Ma X *et al*. (2008). MicroRNA-221/222 negatively regulates estrogen receptor alpha and is associated with tamoxifen resistance in breast cancer. J Biol Chem 283: 31079–31086.

Zhao R, Feng J, He G (2014). miR-613 regulates cholesterol efflux by targeting LXRα and ABCA1 in PPARγ activated THP-1 macrophages. Biochem Biophys Res Commun 448: 329–334.

Zhao S, Wang Y, Liang Y, Zhao M, Long H, Ding S *et al*. (2011a). MicroRNA-126 regulates DNA methylation in CD4+ T cells and contributes to systemic lupus erythematosus by targeting DNA methyltransferase 1. Arthritis Rheum 63: 1376–1386.

Zhao Y, Deng C, Lu W, Xiao J, Ma D, Guo M *et al*. (2011b). let-7 microRNAs induce tamoxifen sensitivity by downregulation of estrogen receptor alpha signaling in breast cancer. Mol Med 17: 1233–1241.

Zheng L, Lv GC, Sheng J, Yang YD (2010). Effect of miRNA-10b in regulating cellular steatosis level by targeting PPAR-alpha expression, a novel mechanism for the pathogenesis of NAFLD. J Gastroenterol Hepatol 25: 156–163.

Zhong D, Zhang Y, Zeng YJ, Gao M, Wu GZ, Hu CJ *et al*. (2013). MicroRNA-613 represses lipogenesis in HepG2 cells by downregulating LXRα. Lipids Health Dis 12: 32.

Zhou J, Wang KC, Wu W, Subramaniam S, Shyy JY, Chiu JJ *et al*. (2011). MicroRNA-21 targets peroxisome proliferators-activated receptor-alpha in an autoregulatory loop to modulate flow-induced endothelial inflammation. Proc Natl Acad Sci U S A 108: 10355–10360.

Zhu H, Wu H, Liu X, Evans BR, Medina DJ, Liu CG *et al*. (2008). Role of microRNA miR-27a and miR-451 in the regulation of MDR1/P-glycoprotein expression in human cancer cells. Biochem Pharmacol 76: 582–588.

Zhu Y, Yu F, Jiao Y, Feng J, Tang W, Yao H *et al*. (2011). Reduced miR-128 in breast tumor-initiating cells induces chemotherapeutic resistance via Bmi-1 and ABCC5. Clin Cancer Res 17: 7105–7115.