

may be critical for PPAR α agonist-induced liver proliferation and carcinogenesis. Arsenite, which activates nuclear factor-erythroid 2-related factor 2 (Nrf2) (84), affects miRNA expression in human lymphoblastoid TH-6 cells (85), although the impact of such changes on toxicity outcomes in vivo is unknown.

Several experimental reports suggest that there may be large, differential responses in miRNA expression changes among in vitro and in vivo studies. Regulatory networks between miRNAs and targets are complex, and in vitro studies alone may be inappropriate to predict miRNA responses in vivo for these types of toxic drugs and chemicals.

Expression Profiles of miRNA in Toxicogenomics Studies

miRNA regulatory networks are complex because a single miRNA can target numerous mRNAs, often in combination with other miRNAs; thus, an understanding of miRNA roles in toxicological processes requires an overall toxicogenomics approach. Studies that employ toxicogenomics have been performed to evaluate the miRNA responses in rodent livers in order to identify potential biomarker(s) for toxicological risk assessment. A single administration of acetaminophen or carbon tetrachloride to rats has been reported to cause different miRNA expression profiles in the liver (86), specifically changes in miR-298 and miR-370 levels, which presumably target oxidative stress-related enzymes such as thioredoxin reductases. In this early work, the sample size was small, and no statistical analyses were conducted. However, significant miRNA suppression occurred as early as 6 h after exposure to the drug or chemical (3 h was not investigated in this study), which coincided with early-phase toxicity, prior to cellular necrosis. Subsequently, many studies were extensively conducted using rats or mice. For example, a significant observation from in vivo studies is that cigarette smoking causes the downregulation of many miRNAs in the lungs of both mice and rats (87), and similar results were obtained in human airway epithelial cells (88). Rats or mice were exposed to BaP or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), and their miRNA expression profiles were analyzed (see below) (89–94). If studies of miRNA expression profiles can predict effective drug-target interactions, they may also be useful in predicting environmental toxicant-target interactions and defining individual toxicant susceptibility.

Changes in miRNA Expression Affected by Environmental Pollutants and Mutagens

Dioxin toxicities range from the dysregulation of glucose and lipid metabolism, liver damage, immunosuppression, and neurobehavioral disorders to reproductive toxicity, carcinogenicity, and teratogenicity (95). In vivo, TCDD did not cause any potent hepatic miRNA expression changes in a TCDD-resistant strain of Han/Wistar rats and a TCDD-sensitive strain of Long-Evans rats (89), and similar results were obtained in mice. Moffat et al. (89) concluded that downregulation of hepatic miRNAs by TCDD is unlikely to play a significant role in TCDD toxicity in adult rodent liver. Investigations focusing on particular miRNAs have demonstrated that TCDD dysregulates the expression of miR-101a and miR-122 and that cyclooxygenase-2 (COX-2), a target of miR-101a, plays a significant role in liver damage in TCDD-exposed mice (90). COX-2, which is downstream of the AhR signaling pathway, is required for the onset of hydronephrosis in rodents. Comprehensive analyses are required to reveal why hepatic expression changes in miRNA and mRNA levels were uncorrelated and to lead to an understanding of the role of miRNA in severe TCDD-induced toxicity.

BaP (150 mg kg⁻¹ for 3 days) caused widespread changes in gene expression (in more than 400 genes investigated using DNA microarray analyses) in mice, but miRNA microarray analyses

showed almost no hepatic changes in miRNA expression (91). Similarly, chronic exposure to 50 mg kg⁻¹ and or 75 mg kg⁻¹ BaP for 28 days demonstrated significant elevation of the miR-34a expression only in the mouse liver (92). This BaP exposure triggers a DNA damage response and cell cycle effects. Thus, although miRNA expression would be coordinately regulated with the mRNA transcript, hepatic miRNA is not directly responsive to AhR agonists, such as BaP and TCDD, administered in vivo to rodents. BaP exposure does cause lung cancer; thus, miRNAs in the lung are more responsive to BaP than are those in the liver, suggesting that the organ-specific expression of miRNAs may be a possible explanation for the selective effects of BaP. Supporting these toxicological outcomes, it was reported that BaP (oral doses of 150 mg kg⁻¹ or 300 mg kg⁻¹ for 3 days) caused downregulation of miR-150, miR-241-5p, and miR-122 and upregulation of miR-34c, miR-34b-5p, and miR-29b in mouse lung (93). These miRNAs are implicated in a variety of biological processes, including immune responses, cell proliferation, and the cell cycle, which are the main pathways affected at the mRNA level. In additional experiments, miR-638 expression was increased in 68% (34 out of 50 samples) of primary human non-small-cell lung cancer tissues; this finding also suggests the possible involvement of this miRNA in BaP-induced carcinogenesis (94). Presently, miRNAs are expected to be sensitive biomarkers for evaluating environmental chemical exposure, and they may be applicable for human risk assessment.

The tumor suppressor p53 cascade has been extensively studied due to its important physiological role. Loss of p53 function is the most frequent genetic alteration in various types of human cancer, as the transcriptional activity of p53 is critical to its function as a tumor suppressor. Recently it was reported that p53 regulates transcriptional expression and the maturation of a group of miRNAs—in particular, the miR-34 family. Conversely, miR-34 can regulate p53 activity and function by directly repressing p53 or p53 regulators in cells (96). The p53 hot spot, located at codon 249 of exon 7, provides a molecular signature for aflatoxin exposure (97). Ingested aflatoxin B₁, which is metabolized in the liver, can bind to DNA, where it may cause a characteristic inactivation mutation of codon 249 of the p53 gene. This mutation is found in 30–60% of hepatocellular carcinomas in aflatoxin-endemic areas (98). Until now, no reports on the effect of aflatoxins on miRNA expression have been published, but it is plausible that aflatoxins could modulate p53-induced miRNAs.

Effects of Chronic Administration of Drugs or Chemicals on miRNA Expression

Chronic exposure to toxic chemicals in rodents (diet containing 420 ppm tamoxifen for 6, 12, 18, and 24 weeks) can induce alterations in miRNA expression profiles that differ from the alterations induced by acute exposure to such chemicals. For example, tamoxifen, a potent hepatocarcinogen in rats, caused significant differential expression of 33 hepatic miRNAs (20 genes upregulated; 13 genes downregulated) when administered to F344 rats for 24 weeks (99). A significant upregulation of oncogenic miRNAs—such as the miR-17-92 cluster, miR-106a, and miR-34—was observed. Numerous miRNAs, including miR-152 and miR-195, were downregulated in the livers of rats that underwent chronic treatment with tamoxifen. These miRNAs are frequently downregulated in solid tumors (100). Another study (101) demonstrated differential expression of 56 miRNAs (31 genes upregulated; 25 genes downregulated) in mice fed a diet that contained the environmental contaminant RDX (hexahydro-1,3,5-trinitro-1,3,5-triazine), at 5 mg kg⁻¹ for 28 days. Also observed were a significant upregulation of oncogenic miRNAs and a significant downregulation of tumor-suppressing miRNAs, such as let-7, the miR-17-92 cluster, miR-10b, miR-15, miR-16, miR-26, and miR-181. These findings show that chronic administration of toxic chemicals affects miRNA expression changes in the target tissues in vivo and that these effects differ from those seen with acute administration.

Involvement of miRNAs in Epigenetic Modifications

Epigenetic factors should be considered for a comprehensive understanding of environmental effects on the expression changes at the genome-wide level. There is a growing awareness that histone modification influences pre-mRNA splicing and that pre-mRNA splicing itself influences chromatin organization. In contrast, miRNA can be epigenetically regulated by DNA methylation or specific histone modification. Furthermore, miRNAs can themselves repress enzymes of DNA methylation and histone deacetylation (102). Recently, it was reported that tumor-associated aberrations in the miRNA and epigenetic machineries are widely distributed in human cancer. A meta-analysis of 45 published studies reported that 122 miRNAs were epigenetically regulated in 23 cancer types (102). Several cancer therapeutic strategies have been proposed on the basis of synthetic analogs of miRNAs; however, this field is nascent. At this time, no specific studies on the effects of drugs, chemicals, or environmental pollutants on epigenetics-related enzymes via miRNAs have been performed.

REGULATION OF IMMUNE-RELATED FACTORS BY miRNA AND THE ROLE OF miRNA IN INFLAMMATION- AND IMMUNE-MEDIATED DRUG-INDUCED LIVER INJURY

Recent studies have demonstrated that miRNAs play a crucial role in the development of immune cells and in the function of the immune system, including the differentiation and survival of immune cells, antibody production, and the inflammatory mediator release in the innate and adaptive immune responses. In fact, many studies have demonstrated the involvement of interleukins (ILs) in relation to miRNA-related diseases, such as inflammatory disorders and cancer. For example, miR-125a-5p, which was identified as a target for vascular inflammation, mediates lipid uptake and decreases the secretion of several inflammatory cytokines (e.g., IL-2, IL-6, and TNF- α) in monocyte-derived macrophages (103). The expression of miR-148a, miR-152, and miR-301 decreased in IL-6-overexpressing malignant cholangiocytes. IL-6 can increase the expression of DNA methyltransferase-1, which is a target of miR-148a and miR-152 (104). Because IL-6 signaling is mediated mainly by STAT3 (signal transducer and activator of transcription 3), the expression of STAT3 was knocked down by small interfering RNA, which decreased the IL-6-mediated expression of miR-17-92 (105). miR-21 contributes to the oncogenic potential of STAT3 in multiple myeloma cells. miR-21 induction by IL-6 was strictly STAT3 dependent through a highly conserved enhancer (106). IL-6 and STAT3 are essential cytokine and transcriptional factor molecules, respectively, for the differentiation of Th17 cells from naive T cells. This signaling pathway is essential for the inflammatory immune response as well as cancer susceptibility.

Cytokine production by dendritic cells (DCs) plays a critical role in responding to LPSs. miRNA expression analysis during the tolerized state of THP-1 cells demonstrated only miR-146a overexpression, which suggests the important role of miR-146a in LPS tolerance (107). Reduced inflammatory responses to Toll-like receptor 4 (TLR4), TLR2, and TLR5 ligands were caused by the knockdown of miR-146a, which targets IL-1 receptor-associated kinase 1 and TNF receptor-associated factor 6. This result suggests a regulatory effect of miR-146a on the signaling of these TLRs. Transfection of miR-146a into THP-1 cells mimicked LPS priming, which resulted in reduced TNF- α production, whereas transfection of the miR-146a inhibitor largely decreased LPS tolerance (108). Additionally, experiments in murine DCs demonstrated that miR-142-3p was among the most highly expressed endogenous miRNAs, whereas IL-6 was among the most highly expressed mRNAs after LPS stimulation (109). The 3' UTR of mouse IL-6 was predicted and confirmed to be a target of miR-142-3p by a luciferase reporter-gene assay and in vitro and in vivo knockdown assays. Overall, these results demonstrated that targeting

miRNAs (miR-146a and/or miR-142-3p) was a novel strategy for the treatment of endotoxin-induced adverse effects and mortality. Regarding drug-induced liver injury, halothane-induced, α -naphthylisothiocyanate-induced, and diclofenac-induced liver injuries in mice are mediated by ILs (110–112); thus, involvement of these miRNAs could be of interest.

Cytokines decrease CYP-associated drug metabolism during inflammation and infection (113), which influences susceptibility to various drugs and toxic chemicals. IL-6 decreases both the rifampicin- and phenobarbital-mediated induction of CYP2B6, CYP2C8, CYP2C9, and CYP3A4, whereas the transcriptional activities of PXR and CAR are unaffected by IL-6 (114). The generation of reactive metabolites of drugs and chemicals that are catalyzed by P450s is suggested to be a major factor in initiating drug-induced liver injury. Subsequently, the exacerbation of drug-induced liver injury is affected by increased IL expression. With respect to cytokines and drug-induced liver injury, IL-4 mediates dicloxacillin- and flutamide-induced liver injury in mice (115, 116). Th17 cell differentiation is affected by IL-6 and STAT3. IL-4, IL-5, and STAT6 are essential factors for the differentiation of Th2 cells from naive T cells. Accordingly, immune- and inflammation-mediated drug-induced liver injury might be regulated by miRNAs. We hope that the currently unreported mechanism of idiosyncratic drug-induced liver injury, in which immune- and inflammation-mediated factors are essential, will be clarified by progress in miRNA research as well as by studies of metabolic activation reactions that are catalyzed by P450s.

SNP:

single-nucleotide polymorphism

pri-miRNA: primary miRNA

pre-miRNA: precursor miRNA

miRNA-RELATED PHARMACOGENOMICS

The majority of pharmacogenomics research has focused on the role of single-nucleotide polymorphisms (SNPs). Recent large-scale studies have identified 15 million SNPs in the human genome, many of which affect gene function in promoters or in *cis*- or *trans*-regulatory elements by modifying sequences of proteins (117). Therefore, SNPs may affect activities of various enzymes and are associated with differences in drug response as well as the adverse effects of drugs and toxic chemicals. SNPs in primary miRNAs (pri-miRNAs), precursor miRNAs (pre-miRNAs), or mature miRNAs could modify various biological processes by influencing the processing or target selection of miRNAs (118, 119). SNPs in pri-miRNA or pre-miRNA are relatively rare. Only approximately 10% of human pre-miRNAs have documented SNPs, and less than 1% of miRNAs have SNPs in the functional seed sequence region (120). Although SNPs in the seed sequence region of miRNAs may be rare, these SNPs may influence the expression of hundreds of genes and related pathways. An interesting study regarding the association between SNPs in the miRNA sequence and clinical drug therapy was published by Boni et al. (121). A SNP (rs7372209) in the pri-miR-26a gene and a SNP (rs1834306) in the pri-miR-100 gene were significantly associated with the tumor response or time to progression in 61 patients with metastatic colorectal cancer who were treated with 5-fluorouracil and CPT-11 (121). This study is the first to suggest a relationship between the clinical outcome of drug therapy and SNPs in both pri-miRNAs and pre-miRNAs.

The frequency of SNPs in the MRE is low, but MRE-site polymorphisms, which affect the expression levels of relevant genes, may have a relatively higher frequency. Thus, early studies concerning miRNA in pharmacogenomics investigated SNPs in MREs on mRNAs. Many MRE-site polymorphisms are thought to be associated with phenotypes of various types of diseases because a gain of function or loss of function results in changes in the expression of target mRNAs (122). Many correlation analyses between SNPs in MREs and diseases *in vitro* or *in silico* were conducted, but only a little functional evidence has been confirmed (122). Human dihydrofolate reductase (DHFR) (123) and sulfotransferase isoform 1A1 (SULT1A1) (124) have been associated with miRNA-related polymorphisms that affect the drug response, adverse reactions, and toxicological outcomes (see below).

Approximately 20,000 MRE-site polymorphisms in miRNAs were systematically searched using Patrocles (<http://www.patrocles.org/Patrocles.htm>) and PolymiRTS (<http://compbio.uthsc.edu/miRSNP/>), databases that allow in silico predictions. However, these predictions should be carefully validated by functional studies. Recent genome-wide association studies (GWAS) performed a genome-wide scan of human variation within validated and predicted miRNA binding target sites. The genetic variants at putative miRNA binding sites are possibly functional and may contribute to phenotypic variation in drug/chemical responses and adverse reactions. From computational analyses using human whole-genome and SNP databases, 87 SNPs were identified in miRNA seed sequences, which may represent functional variants of identified GWAS SNPs (125). Furthermore, miRNAs encoding these 39 seed-site polymorphisms have been reported to be coexpressed with their predicted mRNA targets; however, functional analyses are required.

A report concerning a MRE-site polymorphism in relation to drug-metabolizing enzymes and adverse reactions has demonstrated that a C829T SNP, which occurs naturally at the MRE of miR-24 in the 3' UTR of human DHFR, causes DHFR overexpression and consequent methotrexate resistance (126). Compared with wild-type cells, cells with the mutant 3' UTR showed a twofold longer half-life of the DHFR mRNA, showed higher DHFR mRNA and DHFR protein expression levels, and were fourfold more resistant to methotrexate. In a case-control study of childhood leukemia patients, the allelic frequency of C-to-T SNPs is 14.2% in the Japanese population (123).

SULT1A1 is one of the essential enzymes in the activation or detoxification of endo- and xenobiotics as well as of dietary and environmental procarcinogens/promutagens. SULT1A1 activity showed large interindividual variability (9), which may be caused by genetic polymorphism, although the latter would not fully account for such a variation. A SNP in the 3' UTR (972C>T [rs1042157]) is significantly decreased with the SULT1A1 mRNA level ($p = 0.029$) and with enzymatic activity ($p = 0.012$) (124), demonstrating that miR-631 directly regulates SULT1A1 expression of the 3' UTR (SNP of 972C>T) in an allele-specific manner. This finding provides new information for risk assessment studies of heterocyclic amines such as *N*-hydroxyarylamines, *N*-hydroxy-heterocyclic amines, and arylhydroxamic acids.

UGT2 families are important enzymes that are involved in the metabolism of multiple endobiotics and xenobiotics. Sun et al. (128) identified a SNP, c.1761T>C (rs3100), in 3' UTR of the UGT2B15 isoform; this SNP affects the expression of the UGT2B15 mRNA in HepG2, MCF-7, and Caco-2 cell lines. The location of the SNP may create or diminish an unknown miRNA binding site. Another SNP, C3435T, in exon 26 of the MDR1 gene, caused no amino acid change and was associated with the significantly lower duodenal expression of MDR1 and thereby the increased plasma concentrations of digoxin after oral administration (129). Because the full miRNA profile is unlikely to be known, an unknown miRNA binding site may be created or diminished by the SNP. Further experimental evidence is required.

In the near future, drug responses or susceptibility to xenobiotic toxicity will be predicted by large-scale GWAS and follow-up functional experiments. Data indicating which miRNAs are relevant in various phenotypic outcomes will be gathered. This new class of miRNA-related polymorphisms may contribute to the interindividual variability in adverse drug responses and toxicant-induced adverse events.

CIRCULATING miRNA IN BODY FLUIDS AS POTENTIAL TOXICOLOGICAL BIOMARKERS

The presence of stable circulating miRNAs in serum and their potential as cancer markers was first reported by Lawrie et al. (130), and, subsequently, circulating miRNAs have been extensively

studied mainly for the diagnosis and prognosis of cancer diseases, especially at an early stage (131). However, these early studies have been limited by their lack of constant standards in quantification and by inconsistencies in methodologies. The first study of a plasma miRNA profile in liver injury was conducted by Wang et al. (132). The authors reported that acetaminophen increased the levels of miR-122 and miR-192 in mouse plasma in a dose-dependent and exposure-duration-dependent manner that paralleled that of alanine aminotransferase (ALT) and caused histopathological changes in the liver. Subsequently, increased plasma concentrations of miR-122, miR-133a, and miR-124 were reported to correspond to injuries in liver, muscle, and brain tissues, respectively, as each of these is the abundant and specific miRNA in each organ (133). The miR-122 plasma concentration increased more quickly and dramatically than did the aminotransferase activities in the blood samples of liver-injured mice, reflecting the extent of hepatocellular injury (134). This change was more specific for viral-, alcohol-, and chemical-induced liver injury than for other organ damage and was a more stable and reliable biomarker (134). The plasma miRNA profiles in the rat liver injury model could be useful in identifying specific and sensitive biomarkers for differentiating pathogenesis of acute and chronic liver injury, as well as hepatocellular injury, cholestasis, steatosis, steatohepatitis, and fibrosis (135).

These lines of data suggest that plasma miRNAs may be superior noninvasive human biomarkers in distinguishing the different types of liver injury compared with conventional biomarkers, such as ALT and alkaline phosphatase (ALP), although detailed evaluations remain to be performed. Plasma miRNAs might be used to determine the types of liver injury in order to decide on the appropriate therapy, or they might be used to clinically evaluate the progress of liver function recovery following liver injury. Urinary miRNA profiles could diagnose liver injury induced by hepatotoxicants (acetaminophen or carbon tetrachloride) in rats (136). Discerning miRNA-related associations with disease development (137) and conducting comparative miRNA expression profile studies across models will be important for a comprehensive understanding of the physiological implications of miRNA changes. Moreover, can circulating miRNAs affect other signaling pathways? Nevertheless, circulating miRNAs in biological fluids have great potential in toxicological studies, e.g., as a novel, informative, and noninvasive method for extrapolating animal toxicity data to humans.

CONCLUSIONS

The importance of understanding the critical role of miRNAs, their involvement with drug-metabolizing enzymes and nuclear receptors, and implications for toxicological studies is recognized. Increasing interest in miRNA research creates new areas in toxicology: the effects of physiological conditions such as alcohol, diet, smoking, stress, supplements, hormones, medication, or diseases on miRNA expression; the effects of inter- and intraindividual differences in miRNA expression on drug response or susceptibility to xenobiotic toxicants; the effects of miRNA and/or target mRNA genetic polymorphisms on drug response, pharmacokinetics, and pharmacodynamics; and the identification of new noninvasive biomarkers to extrapolate animal-derived toxicology data to humans. miRNAs will contribute to the comprehensive understanding of drug- or chemical-induced toxicity, which will facilitate drug development and clinical pharmacotherapy.

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