

Epigenetic regulation of differentially expressed Drug-metabolizing enzymes in cancer

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Running Title: Epigenetic regulation of DMEs in cancer

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Number of text pages: 47

Number of tables: 1

Number of figures: 1

Number of references: 141

Number of words in Abstract: 142

Number of words in Introduction: 629

Number of words in the Discussion: 538

Abbreviations:

ADH, alcohol dehydrogenase; ADT, androgen deprivation therapy; AhR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; BET, bromodomain-containing proteins; BERA, bioengineered RNA agent; circRNA, circular RNA; CYP450, cytochrome P450 enzyme; CTX, cyclophosphamide; DME, drug-metabolizing enzyme; DNMT, DNA methyltransferase; DOT1L, Disruptor of telomeric silencing 1-like; DPD,

dihydropyrimidine dehydrogenase; EZH2, Enhancer of zeste homolog 2; FDA, Food and Drug Administration; GST, glutathione S-transferase; HCC, hepatocellular carcinoma; HDAC, histone deacetylase; LncRNA, long non-coding RNA; MBP, Methyl-CpG binding protein; mCRPC, metastatic castration-resistant prostate cancer; NAT, N-acetyltransferase; ncRNA, non-coding RNA; NNK, 4-methylnitrosamino-1-3-pyridyl-butanone; PAH, polycyclic aromatic hydrocarbon; SAM, S-adenosyl-1-methionine; SULT, sulfotransferase; Tet, ten-eleven translocation; TSA, Trichostatin A; UGT, UDP-glucuronosyltransferase; VPA, valproic acid; 1, 25-D3, 1α , 25-dihydroxyvitamin D3; 5-FU, Fluorouracil; 5mC, 5-methylcytosine.

Abstract

Drug metabolism is a biotransformation process of drugs, catalyzed by drug-metabolizing enzymes (DMEs) including phase I DMEs and phase II DMEs. The aberrant expression of DMEs occurs in the different stages of cancer. It can contribute to the development of cancer and lead to individual variations in drug response by affecting the metabolic process of carcinogen and anticancer drugs. Apart from genetic polymorphisms, the one we know the most about, current evidence indicates that epigenetic regulation is also central to the expression of DMEs. This review summarizes differentially expressed DMEs in cancer and related epigenetic changes, including DNA methylation, histone modification, and non-coding RNAs (ncRNAs). Exploring the epigenetic regulation of differentially expressed DMEs can provide a basis for implementing individualized and rationalized medication. Meanwhile, it can promote the development of new biomarkers and targets for the diagnosis, treatment, and prognosis of cancer.

Significant statement

This review summarizes the aberrant expression of DMEs in cancer, and the related epigenetic regulation of differentially expressed DMEs. Exploring the epigenetic regulatory mechanism of DMEs in cancer can help us to understand the role of DMEs in cancer progression and chemoresistance. Also, it provides a basis for developing new biomarkers and targets for the diagnosis, treatment, and prognosis of cancer.

Introduction

With the increasing incidence and mortality every year, cancer is a major public problem worldwide and is one of the most deathful diseases for both men and women. In the United States, prostate, lung, and colorectal cancers are three major cancers in men, while the three most common cancers in women are breast, lung, and colorectal cancers (Siegel et al., 2019).

The high cancer mortality rate is due to a combination of factors including the lack of reliable biomarkers for cancer diagnosis, drug resistance, deficiency in effective targeted treatment.

Drug metabolism is a biotransformation process of drugs, which usually mediated by specific enzymes (Almazroo et al., 2017). The drug-metabolizing pathways mediated by drug-metabolizing enzymes (DMEs) are classified into phase I (functionalization) and phase II (conjugation) reactions. Phase I reactions are the redox or hydrolysis process of the drug to activate or detoxify it, which are mainly mediated by phase I DMEs, including cytochrome P450 enzymes (CYP450s), Flavin-containing monooxygenases (FMOs), alcohol dehydrogenases (ADHs), aldehyde dehydrogenases (ALDHs). CYP450s comprise 70-80% of all phase I DMEs (Nebert and Dalton, 2006). The CYP superfamily can be divided into two parts, CYP1-4 families are responsible for the biotransformation of most xenobiotic compounds, while CYP7-51 families are mainly involved in the metabolism of endogenous substances in a substrate-specific manner. Most CYP450s locate in the liver, resulting in its strong detoxification effect. The most abundantly expressed CYP450 isoforms in the liver are CYP3A4, 2C9, 2C8, 2E1, and 1A2, while CYP2A6, 2D6, 2B6, 2C19, and 3A5 are less abundant (Zanger and Schwab, 2013). CYP450s including CYP2C9, 2C19, 3A4, 3A5 are also distributed in mature intestinal epithelial cells and responsible for intestinal metabolism.

Besides, some CYP450s like CYP1A1, 1B1 mainly express extrahepatically, which are in accordance with their metabolic roles of environmental pollutants and endogenous compounds. In phase II reactions catalyzed by phase II DMEs, the products from phase I pathways conjugate with a hydrophilic endogenous compound. After conjugation, the substances are converted into water-soluble products which are easy to excrete. Most of phase II DMEs are consist of transferases, including UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), glutathione S-transferases (GSTs), N-acetyltransferases (NATs) (Almazroo et al., 2017). Phase II DMEs are mostly located in liver and kidney. UGTs are major members of Phase II DME, which mediate glucuronidation and elimination of a variety of endogenous and exogenous substances, and are considered as integral parts of detoxification enzymes in the human body (Pathania et al., 2018). GSTs catalyze the conjugation reactions of nucleophilic glutathione with various electronic xenobiotics, thus facilitating their elimination and protecting cells from oxidative stress and other stimuli (Pljesa-Ercegovac et al., 2018). The abnormal expression of DMEs may lead to changes in the metabolism of drugs or pro-carcinogens, thus causing diseases. It also brings a considerable challenge for individualized treatment by affecting the metabolic process and adverse effects. Epigenetics is the study of heritable changes in gene expression without any alternation in the DNA sequence. The main contents of epigenetics include DNA methylation, histone modification, non-coding RNAs (ncRNAs) (Ivanov et al., 2012; Zanger et al., 2014). Many factors can influence Epigenetic regulation, such as age, diet, lifestyle, environment, and disease. Accumulating evidence demonstrates that epigenetic modification changes a lot during tumorigenesis. DNA methylation and histone modification patterns of some genes, as

well as the expression of ncRNAs, are expected to be biomarkers for early detection, diagnosis, prognosis, drug disposition and clinical response of cancer (Chen et al., 2013; Xu et al., 2017; Tan et al., 2018). Reversing gene expression in cancer by changing the abnormal epigenetic modification also provides a new train of thought for the treatment of cancer (Lachenmayer et al., 2012; Liu et al., 2016). This review will give a brief summary of abnormal expression of DMEs in cancer, and epigenetic regulation of differential expression of DMEs.

Differential Expression of DMEs in cancer

CYP450s are the most abundant family of DMEs, expressing in almost all organs. CYP450s are involved in the metabolic inactivation of endogenous and exogenous compounds. In some instances, however, they also mediate the metabolic activation of many carcinogens, which increase the risk of cancer. CYP1A1 and CYP1B1 are causally implicated in activation of procarcinogens such as polycyclic aromatic hydrocarbons (PAHs); CYP2A6, CYP2A13, and CYP2E1 can metabolize nitrosamines into unstable metabolites, which can form diazonium ions; CYP2E1 is also involved in the metabolic activation of tetrachloromethane, accompanying with the production of free radicals (He and Feng, 2015). CYP3A4 participates in the metabolic activation and detoxification of hepatic carcinogen aflatoxin B1 and is tightly related to the carcinogenesis of hepatocellular carcinoma induced by aflatoxin B1 (Kamdem et al., 2006).

Emerging evidence indicates that DMEs play an essential role in the formation, prevention, metastasis, and treatment of cancer (Alzahrani and Rajendran, 2020). The high expression of

some DMEs is commonly considered as a reason for carcinogenesis, metastasis, and chemoresistance due to the increased activation of procarcinogens and inactivation of anti-cancer drugs. For instance, the high expression of CYP1A1 promotes the activation of PAH, the active metabolites covalently bond to DNA and produce DNA adducts, eventually leads to DNA damage and tumorigenesis (Moorthy et al., 2015). The overexpression of CYP2J2 in cancer cell lines brings on increased four regioisomeric epoxyeicosatrienoic acids, which promotes cancer metastasis (Jiang et al., 2007). Besides, dihydropyrimidine dehydrogenase (DPD) is pivotal to the catabolism of Fluorouracil (5-FU), so the upregulation of DPD can reduce the activity of CTX greatly (Pathania et al., 2018). The abnormal low expression of DMEs is also a risk factor for tumor initiation. Some DMEs act on carcinogen and play a detoxifying role, so the repression of them cause tumor growth. For prodrugs that require DMEs for metabolic activation, the repression of these DMEs can also cause drug resistance. Cyclophosphamide (CTX), a broad-spectrum antineoplastic prodrug, is converted to its active form by CYP2B6, 3A4 (Lindley et al., 2002). Therefore, the suppression of these CYP450s will materially affect the efficacy of CTX. The aberrant expression of DMEs occurs in several cancer types, including liver, prostate, and lung cancers. A summary of the differentially expressed DMEs and their functions is listed in Table 1.

Liver cancer

The liver is the most vital body organ for drug biotransformation and rich in DMEs. The expression and activity of DMEs can be modulated by several factors like genetic polymorphisms and disease states. It has been confirmed that the metabolism activities of

CYP isoforms are severely impaired in hepatocellular carcinoma (HCC) patients by investigating the activities of major CYPs in microsomes from normal and HCC liver tissue samples (Yan et al., 2015b).

Several studies represent a series of evidence implicating that the expression of DMEs changed in HCC samples. Due to the decrease of functional hepatocytes in HCC, most of the phase I and phase II metabolizing enzymes are expressed at lower levels compared to non-cancerous liver tissues, including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP3A7, CYP4A11, NAT1, NAT2, UGT1A1, UGT1A4, UGT1A9 and UGT2B7 (Chen et al., 2014; Lu et al., 2015; Yan et al., 2015a; Yan et al., 2015b). The silence of CYP2C19 expression in hepatitis B virus-infected patients with HCC is reported to be regulated by e-box methylation of the constitutive androstane receptor (Tang et al., 2016). The dysregulation of DMEs in HCC is a pivotal reason for clinical chemotherapy failure (Ul-Islam et al., 2018). The expression of DMEs is also associated with the risk of liver cancer. CYP2E1 is related to the activation of many toxicants. The high expression of CYP2E1 is recognized as a risk factor for hepatic fibrosis (Guo et al., 2019). The research revealed that hepatic fibrotic rats with higher CYP2E1 activity develop a more severe form of HCC (Gao et al., 2018). Besides, CYP2E1 also participates in the formation of etheno-DNA adducts, which are potent carcinogens of liver cancer (Linhart et al., 2014). GSTs are detoxifying enzymes and play a predominant role in cell protection. A meta-analysis suggested that the inactivation of GSTP1 in HCC correlates with the hepatocarcinogenesis (Li et al., 2018).

Lung cancer

The lung is the main organ exposed to the inhaled chemical toxicants and carcinogens. So, the metabolizing enzymes participate in xenobiotic metabolism is essential for respiratory protection (Leclerc et al., 2010). In some instances, they can convert procarcinogens to active metabolites. These active intermediates can form DNA adducts, cause gene mutation, and eventually lead to cancer (Castell et al., 2005). The increase of CYP1A1 activity contributes to the metabolic activation and carcinogenicity of PAHs. The researchers designed a liposome-based CYP1A1 silencing nanomedicine, showing the potential for the treatment of lung cancer (Zhang et al., 2019). CYP1B1 catalyzes the activation of carcinogens N-nitrosamines like 4-methylnitrosamino-1-3-pyridyl-butanone (NNK). NNK can also induce CYP1B1 expression, thus accelerating lung cancer progression (Li et al., 2015b). GST-M2 is a detoxifying enzyme, which expressed a low level in lung cancer cells (Tang et al., 2011). The mRNA expression level of DMEs in pulmonary parenchyma, bronchial mucosa, and tumoral lung tissues were detected using a high throughput quantitative real-time RT-PCR method. It is demonstrated that ADH1B, CYP3A7, CYP4B1 show decreased mRNA levels in lung cancer (Leclerc et al., 2011).

Prostate cancer

Prostate cancer is the most common cancer that occurs in men, which is mostly androgen dependent. Androgen deprivation therapy (ADT) is still the first-line treatment of metastatic prostate cancer (Litwin and Tan, 2017). UGT2B15 and UGT2B17 are involved in androgen inactivation in prostate cells (Pâquet et al., 2012). Some studies have found that UGT2B17

deletion polymorphism is related to prostate cancer susceptibility (Karypidis et al., 2008). UGT2B15 and UGT2B17 differentially expressed during prostate cancer progression (Pâquet et al., 2012). Besides, CYPs are key inactivators of testosterone in the prostate. It was reported that decreased CYP2B6 and CYP3A4 are significantly related to the development and poor prognosis of prostate cancer (Kumagai et al., 2007; Fujimura et al., 2009). After continuous ADT, these cancers may become androgen-independent and resistant to ADT. In this process, the expression of GST-pi increases, indicating its role in the development of prostate cancer (Hokaiwado et al., 2008).

Kidney cancer

In the kidney, UGT expression is related to the clearance of many xenobiotics. A proteomic study reported that UGT1A6, UGT1A9, and UGT2B7 are the most abundant UGT subtypes in the kidney. The mRNA and protein levels of UGT1A9 and UGT2B7 are significantly down-regulated in tumor kidneys, accompanied by decreased glucuronidation capacity (Margaillan et al., 2015).

Esophageal cancer

A study revealed the potential clinical relevance between the expression of CYP2C9 and esophageal cancer. The expression of CYP2C9 in esophageal adenocarcinoma and adjacent esophageal mucosa was higher compared to esophageal squamous cell carcinoma. CYP2C9 is likely to promote esophageal cancer proliferation (Schmelzle et al., 2011).

Other hormone-induced cancers

Some DMEs are relevant to the metabolism of hormones, so the aberrant expression of these DMEs may occur in hormone-induced cancers. CYP1B1 is mainly responsible for the metabolism of estradiol, forming carcinogens 4-hydroxy estradiol. The enrichment of 4-hydroxy estradiol in breast, ovarian, and prostate is considered to be an increased risk of developing cancers (Yager, 2000). CYP1B1 is causally implicated in the carcinogenesis of breast cancer, ovarian cancer, prostate cancer, and lung cancer. CYP1B1 expression increases in estrogen-related tumors but very low in normal tissues (McFadyen et al., 1999; Carnell et al., 2004; Gajjar et al., 2012). CYP11 subfamily is responsible for steroid biosynthesis (Thomas, 2007). The down-regulation of CYP11A1 in cancers may affect the biosynthesis of steroids. Data obtained from The Cancer Gene Atlas (TCGA) database revealed CYP11A1 is significantly downregulated in 6 cancers types, including colon adenocarcinoma, renal clear cell carcinoma, hepatocellular carcinoma, lung squamous cell carcinoma, prostate adenocarcinoma and uterine corpus endometrial carcinoma (Fan et al., 2016).

Epigenetic regulation of differentially expressed DMEs in cancer

DNA methylation

DNA methylation is a dynamic process involving methylation and demethylation. DNA methyltransferase DNMT1, 3A, and 3B can transfer a methyl group to the cytosine at CpG sites to form 5-methylcytosine (5mC). Passive or active DNA demethylation can reverse DNA methylation patterns. Passive DNA demethylation is likely to be due to the reduction or inhibition of DNA methyltransferase, so the DNA methylation status cannot maintain during

DNA replication (Piccolo and Fisher, 2014). Active DNA demethylation is mainly mediated by activation-induced cytidine deaminase/ apolipoprotein B mRNA-editing enzyme complex (AID/APOBEC) or ten-eleven translocation (Tet) enzymes Tet1, Tet2, and Tet3. Methyl-CpG binding proteins (MBPs) can recognize 5-methylcytosine, which has a high affinity for 5mC. MBPs cause chromatin structure modification and remodeling by recruiting corepressor complexes such as histone deacetylase (HDAC) to methylated promoter regions, thus reducing gene expression (Clouaire and Stancheva, 2008). DNA methylation plays a critical role in gene expression and chromatin remodeling. It can repress gene expression by changing the chromatin structure directly, hindering transcription factor, or co-activator bind to the promoter region of the target gene (Moore et al., 2013).

It has been widely reported that DNA methylation is involved in the regulation of differentially expressed DMEs in tumors. In tumors, the methylation status of CpG islands (CGIs) in the gene promoter regions is closely related to the expression level of the target gene. Abnormal DNA methylation in tumors and normal tissues can be detected in body fluids such as blood and urine, indicating that DNA methylation is expected to be a biomarker for liquid biopsy, which can be used for diagnosis and monitoring of cancer. Also, the abnormal expression of DNA methyltransferase may occur in the process of cancer development, affect the expression level of DMEs, thus promoting the development of cancer. Therefore, DNA methyltransferase is a potential therapeutic target of cancer. Changing the expression of DNA methyltransferase may reverse the expression of DMEs in cancer. DNA methylation inhibitor decitabine (5-aza-2'-deoxycytidine) has been approved by the Food and Drug Administration (FDA) for the treatment of hematological malignancies (Nie et al., 2014).

Besides, considering the importance of DMEs towards personalized medicine, Genome-wide integrative analysis was used to analyze the DNA methylation and mRNA expression profiles of human tissues and hepatoma cells, which revealed that some DME genes, including *CYP1A2*, *CYP2C19*, *CYP2D6*, *GSTA4*, *GSTM5*, *GSTT1*, and *SULT1A1* are regulated by DNA methylation, potentially leading to individual differences in drug metabolism (Habano et al., 2015).

Hypomethylation Status of DME genes in cancer

DNA hypomethylation is always considered as the main reason for high-level gene expression. Some DMEs are responsible for the metabolic activation of environmental toxicants and carcinogens; their high expression can contribute to cancer progression. Meanwhile, some DMEs can metabolic inactivate anti-cancer drugs, thus causing chemoresistance (Figure 1).

CYP1A1 can activate multiple carcinogens, therefore promote cancer progression. The expression and methylation status were detected in prostate cancer cells. *CYP1A1* expression is higher in cancer cells compared to normal cells. While treated with decitabine, the expression of *CYP1A1* become much higher (Mitsui et al. 2016). In breast cancer cell line MCF-7 and T47D, estrogen receptor α can repress the expression of *CYP1A1* through recruiting DNMT3b (Marques et al. 2013).

Aberrant DNA methylation status of *CYP1B1* has been observed in several hormone-related cancer types, such as prostate cancer and breast cancer. The methylation status of *CYP1B1* was analyzed in prostate cancer tissues and benign prostatic status hyperplasia samples; the results revealed that methylation of its promoter/enhancer region was much lower in prostate

cancer, which may play a role in cancer development. It is well known that *CYP1B1* is induced by the aryl hydrocarbon receptor (AhR) and AhR nuclear translocator (ARNT) directly. When treated with DNA methyltransferase inhibitor, 5-Aza-dC, no cell line showed a significant change of the expression of AhR and ARNT, indicating that CpG methylation of *CYP1B1* promoter is key to its expression (Tokizane et al., 2005). Moreover, considering the function of metabolizing estradiol and tamoxifen, *CYP1B1* hypomethylation is perceived as a carcinogenic factor as well as predictive markers for response to tamoxifen therapy in breast cancer (Widschwendter et al., 2004).

UGT1A1 is a critical phase II metabolizing enzyme involved in the metabolic inactivation of SN38, the active metabolite of irinotecan. Irinotecan is a first-line drug for the treatment of metastatic colorectal cancer (Hahn et al., 2019). So, the hypomethylation status of *UGT1A1* may accelerate the inactivation of irinotecan to reduce the efficacy of irinotecan. Bisulfite sequencing of *UGT1A1* observed the abnormal methylation modification of specific CpG islands in UGT1A1-negative cells like HCT-116, HCT-15, and COLO-320DM, while in HT-29, HT-115 and LOVO cell lines with high expression of UGT1A1, these sites were in the hypomethylation states. Methylation of the *UGT1A1* promoter can repress its transcriptional activity completely. A combination of DNA methyltransferase inhibitor and histone deacetylase inhibitor can reverse the hypermethylation and restore the expression of UGT1A1 in UGT1A1 negative cells (Gagnon et al., 2006). Another research investigated the correlation between UGT1A1 expression and its sensitivity to irinotecan in seven colorectal cell lines. The cell lines with low UGT1A1 expression are more sensitive to irinotecan. The methylation status of *UGT1A1* can obviously affect the cytotoxicity of irinotecan (Xie et al., 2014).

Hypermethylation Status of DME genes in cancer

In general, DNA hypermethylation suppresses the expression of DMEs which involved in detoxification. It is causally implicated in the occurrence and development of cancer (Figure 1).

As we mentioned before, *CYP1B1* hypomethylation was observed in several hormone-related cancers. However, the hypermethylation status of the *CYP1B1* promoter can be found in colon cancer (Habano et al., 2009), bladder cancer (Putluri et al., 2011), and adolescents with acute lymphocytic leukemia (DiNardo et al. 2013), indicating a worse outcome. Metabolic profiling revealed that *CYP1B1* hypermethylation could also be found in body fluids like urine, suggesting it might be a potential biomarker for distinguishing benign bladder and bladder cancer (Putluri et al., 2011).

GSTs are significant phase II detoxification enzymes. GST-M2, a member of GST subfamily Mu-class GST, which has special clinical features. The activity of GST-M2 in human normal embryonic lung fibroblasts MRC-5 is significantly higher than in lung cancer cell line H1355. The catalytic activity of GST-M2 is closely related to DNA damage induced by carcinogens (Weng et al., 2005). The low expression of GST-M2 in lung cancer cell lines can be reversed after treatment with DNMT inhibitor decitabine. The CpG Islands on the *GST-M2* promoter is highly methylated. It is demonstrated that in lung cancer tissues, the low expression of GST-M2 is accompanied by high expression of DNMT3b, indicating a close relationship between DNA methylation and GST-M2 expression. GST-M2 expression in lung cancer cell lines can be induced after silencing DNMT3b. Consequently, the expression of GST-M2 in lung cancer cells is negatively regulated by DNA methylation. CpG hypermethylation of

GST-M2 blocks the binding of transcription factor specificity protein (Sp1) to *GST-M2* promoter, thus inhibiting the transcription of *GST-M2* (Tang et al., 2011). *GST-M2* hypermethylation is also investigated in Barrett's adenocarcinoma, pancreatic cancers (Peng et al., 2009; Tan et al., 2009).

GSTP1, the gene encoding the pi-class GST, is repressed in multiple cancer subtypes including solid tumors like prostate (Henrique and Jerónimo, 2004), breast (Fang et al., 2015), liver (Revill et al., 2013), lung cancers (Gao et al., 2009) and hematologic malignancies because of CpG islands hypermethylation in the promoter regions. The aberrant methylation status of the *GSTP1* promoter is regarded as a specific marker for prostate cancer, which can be found in at least 90% of prostate cancers (Nakayama et al., 2004). It has been reported that *GSTP1* promoter methylation may increase the incidence and recurrence of prostate cancer (Maldonado et al., 2014; Zhou et al., 2019). Besides, *GSTP1* CpG islands hypermethylation can also be detected in the urine and plasma from patients with prostate cancer. It means that *GSTP1* CpG islands hypermethylation can be used as a biomarker for the diagnosis and prognosis of prostate cancer. In a recent study, a sensitive methylation-specific polymerase chain reaction assay was applied to detect the serum-free methylated *GSTP1* DNA in patients with metastatic castration-resistant prostate cancer (mCRPC). It has demonstrated that the expression of serum free methylated *GSTP1* is closely correlated with overall survival and response to docetaxel in mCRPC (Mahon et al., 2019).

NAT1 is a phase II metabolizing enzyme that is responsible for the biotransformation of most arylamine and hydrazine substrates. Several studies have shown that NAT1 can influence the development and drug resistance of breast cancer (Rodrigues-Lima et al., 2010). The

frequency of *NAT1* methylation was significantly lower in the control group compared with the tamoxifen-resistant breast cancer group. The hypermethylation of the *NAT1* gene may affect the initiation of tamoxifen resistance in breast cancer (Kim et al., 2010).

Histone modification

Histones are the basic structural proteins of chromatin. Histone octamer consists of two copies each of histones H2A, H2B, H3 and H4, which are wrapped with 147 base pairs of DNA. Histone is a basic protein because it contains a high proportion of basic amino acids like lysine and arginine. The N terminal of histone is dissociated from the nucleosome. So, the specific amino acid residues can be modified by methylation, acetylation, phosphorylation, ubiquitination, and the like. The chromatin structure changed after modification, thus regulating the gene transcription (Luger et al., 2012). Aberrant histone modifications may lead to abnormal gene expression in cancer. Histone acetylation neutralizes its positive charge, thereby opening the chromatin structure, making it easier for transcription factors to bind to their target genes. So, histone acetylation is always regarded as a transcriptional activation signal (Haberland et al., 2009). HDACs are potential targets for cancer therapy, FDA has approved several HDAC inhibitors like Vorinostat (SAHA), Belinostat (PXD101) for the treatment of cutaneous T cell lymphoma, peripheral T-cell lymphoma. Furthermore, bromodomain-containing proteins (BETs) recognize the acetylated lysine residues of histone, which play an essential role in the process of cancer development. Thus, designing small-molecule BET inhibitors may be a promising strategy (Fu et al., 2015; Yu et al., 2015b). Histone methylation exhibits distinct functions of gene activation or repression with different

modification sites (H3K4, H3K9, H3K27, etc.) and methylation states (mono-/di-/tri-methylation) (Barski et al., 2007). Enhancer of zeste homolog 2 (EZH2) is a methyltransferase that can add methyl groups to histone H3 at lysine27 (H3K27), thus repressing gene transcription. Disruptor of telomeric silencing 1-like (DOT1L) methyltransferase is responsible for H3K79 methylation. Now the inhibitors of EZH2 and DOT1L are in clinical trials and show potent anti-cancer capacity (Mohammad et al., 2019).

Although emerging evidence suggests that these histone modifications affect the expression of DMEs in the non-tumor environment (Tang and Chen, 2015; Yan et al., 2017), the regulation of histone modification of DMEs in the tumor is lack of reporting. Considering the extensive aberrant histone modifications in cancer and their essential roles, we need to clarify the relationship between histone modification and differential expression patterns of DMEs to provide references to personalized medicine.

1 α , 25-dihydroxyvitamin D3 (1, 25-D3), the active form of vitamin D, is antiproliferative in lung adenocarcinoma. 1, 25-D3 is catabolized by CYP24A1, which overexpressed in multiple types of cancer. CYP24A1 mRNA was elevated 8- to 50- fold in lung adenocarcinoma compared to normal tissues. The overexpression of CYP24A1 is much more significant in poorly differentiated cancers, accompanied by lower survival rates (Chen et al., 2011b). In lung adenocarcinoma cells, combined treatment with DNMT inhibitor 5-Aza-dC and HDAC inhibitor Trichostatin A (TSA) increases the CYP24A1 expression and enzyme affinity to its substrate 1, 25-D3. The CHIP-qPCR assay revealed that TSA enriched H3K4me2 and H3K9ac and simultaneously decreased H3K9me2 at the *CYP24A1* promoter, thus activating the transcriptional expression of CYP24A1 (Ramnath et al., 2014). In human neuroblastoma cells,

histone deacetylase inhibitors like valproic acid (VPA) and TSA affect the expression of CYP1A1, CYP1B1, and CYP3A4 (Hřebačková et al., 2009). Another research found that inhibition of the β -catenin signaling pathway induced the CYP1A1 expression through histone H2AX phosphorylation (Kabátková et al., 2015).

Non-coding RNA

The term, non-coding RNA, refers to RNA molecules that are transcribed from genome but not translated into proteins, including microRNA (miRNA), long non-coding RNA (lncRNA) and circular RNA (circRNA) (Klingenberg et al., 2017). They can give full play to the function of gene regulation at the transcriptional and post-transcriptional levels. Mature microRNAs are single-stranded ncRNA of 22-25 nucleotides in length, which are derived from primary miRNA transcripts (pri-miRNA) (Li and Rana, 2014). The mature miRNA must assemble into the RNA-induced silencing complex to target its complementary mRNAs for translational repression or target gene degradation (Li et al., 2014). LncRNAs are transcripts longer than 200 nucleotides that have little or no protein-coding capacity, they are transcribed by RNA polymerase II, capped, spliced, and polyadenylated. LncRNA can regulate gene expression at different levels, including chromatin modification, transcription, and post-transcriptional processing (Mercer et al., 2009). Emerging evidence indicates the translation potential of lncRNAs with open reading frames, which has been overlooked over a long period (Matsumoto et al., 2017). These polypeptides encoded by lncRNAs may also play a crucial role in cancer occurrence and development, it was reported that HOXB-AS3 peptide suppresses colon cancer growth through a complex regulatory mechanism (Huang et al.,

2017). circRNAs are a novel type of RNA molecules that are different from traditional linear RNAs. They have a closed-loop structure and exist in a lot of eukaryotic transcriptomes (Qu et al., 2015). Most circRNAs are composed of exon sequences, which are conserved in different species and have regulatory potency (Memczak et al., 2013). circRNAs are not sensitive to nuclease, which makes them more stable than linear RNA owing to their closed-loop structures. Therefore, circRNAs have more potential to become biomarkers in the screening of cancer (Li et al., 2015a; Li et al., 2015c). The most common regulatory mechanism of lncRNA and circRNA is acting as the 'sponge' of miRNA, which can regulate the target gene through changing miRNA expression (Wang et al., 2010; Yu et al., 2016).

With the development of RNA-seq, Researchers have obtained the expression profiles of miRNA, lncRNA, and circRNA in different sorts of cancer and their matched paracancerous normal tissues such as liver cancer, kidney cancer, and breast cancer. They screen the ncRNAs, which are closely related to the occurrence, development, and prognosis of cancer, providing a new biomarker or target for the diagnosis or treatment of cancer (Xie et al., 2013; Li et al., 2015a; Li et al., 2015c). At present, the regulation of ncRNA on differentially expressed DMEs in the tumor is still limited in the field of miRNA. The regulation of lncRNA and circRNA needs to be further explored.

Phase I DMEs

Abnormal miRNA expression occurs in lung cancer tissues compared with normal tissues. To clarify the functions of these miRNA, researchers established a tobacco-induced cancer rat model to investigate the relationship between miRNA and the occurrence of early lung cancer. It has been demonstrated that carcinogen could reduce the expression of miR-101,

miR-126*, miR-199, and miR-34. These miRNAs overlap with previously published reports on altered miRNA expression in human lung cancer samples, suggesting these four miRNAs may involve in lung cancer development. Treatment with NNK inhibits miR-126* but induces CYP2A3 expression, an essential enzyme to activate NNK, indicating that miR-126* has the possibility of regulating CYP2A3 (Kalscheuer et al., 2008).

The low expression level of miR-27b may contribute to the high expression of CYP1B1 in the mammary gland (Tsuchiya et al., 2006), thus cause the accumulation of 4-hydroxy estradiol, and increase the risk of breast cancer. In HCC, a report has established a negative correlation between the level of hsa-miR-128-3p, hsa-miR-143-3p and CYP2C9 expression based on *in silico* analysis and series of biochemical assays (Yu et al., 2015a).

Recently, RNA interfering (RNAi) miRNA materials are designed to interfere with the expression of DMEs. It was reported that a newly established bioengineered RNA agent (BERA), namely BERA/miR-27b-3p, can be processed into mature miR-27b-3p in human cells, thus decrease the expression and metabolic capability of CYP3A4 (Li et al., 2019b).

Phase II DMEs

In prostate cancer, miRNA is causally implicated in post-transcriptional regulation of UGTs. Androgen plays a vital role in the development of prostate cancer. UGT2B15, UGT2B17, and UGT2B28 mediate the biotransformation of androgen *in vivo*. Reporter gene assays validated that miR-376c, miR-409, and miR-494 could interact with UGT2B17, and miR-331-5p and miR-376c could bind to UGT2B15 (Margaillan et al., 2016). miR-376c can effectively repress UGT2B15 and UGT2B17 expression, accompanied by a consequent decrease in dihydrotestosterone glucuronidation. The expression of UGT2B15 and UGT2B17 are

negatively related to miR-376c expression but positively correlated to metastasis rate in advanced prostate cancer (Wijayakumara et al., 2015). miR-331-5p is also confirmed to reduce the UGT2B15 mRNA level by targeting its 3'-UTR via canonical and noncanonical pairing (Wijayakumara et al., 2018).

Furthermore, UGT2A1 is responsible for the detoxification of PAHs found in cigarette smoke, which exhibits high expression in the lung. A recent study suggested that the UGT2A1 expression level can be regulated by both miR-196a-5p and miR-196b-5p (Sutliff et al., 2019).

In breast cancer, miR-1290 is confirmed to target the 3'-UTR of NAT1 directly, which is positively correlated with the overall survival of breast cancer patients (Endo et al., 2014).

The expression of NAT10 is dysregulated in colorectal cancer, which is validated to be inhibited by miR-7616-5p (Liu et al., 2019). Published studies have identified hsa-miR-486-5p and hsa-miR-495-3p decrease the mRNA stability of phase II detoxification enzymes SULT2A1 in HepG2 human hepatocellular carcinoma cell line (Li et al., 2019a).

Summary and prospect

DMEs are implicated in the metabolic activation or inactivation of xenobiotics, which are strongly associated with the occurrence and development of cancer. During the development of cancer, the expression level of DMEs changes, thus reducing the detoxification ability of DMEs and promote cancer progression. In the treatment of cancer, the differentially expressed DMEs may influence the efficacy of anticancer drugs or cause adverse effects by affecting the metabolic process of these drugs.

Epigenetics, especially DNA methylation, plays a critical role in the regulation of differentially expressed DMEs in tumors. DNA methyltransferases are expected to be the target of antitumor drugs. Aberrant DNA methylation modifications are also promising biomarkers in liquid biopsy. A growing body of researches suggests that histone modification and ncRNA can regulate the expression of DMEs under non-tumor conditions. Histone modification and miRNA have already been proved to participate in the transcriptional regulation of differentially expressed DMEs in lung, liver, prostate, and breast cancer, and the regulatory mechanism in other cancer types needs to be further studied.

Emerging studies showed that the crosstalk among various epigenetic mechanisms is noteworthy and needs to be further explored in the regulation of DMEs. Histone modification and DNA methylation always work in concert to regulate gene expression. Methyl-CpG binding proteins recruit protein complex which contains HDACs and/or histone methyltransferases, inducing the formation of repressive chromatin circumstance (Nan et al., 1998; Fuks et al., 2003). In some instances, the administration of HDAC inhibitors like TSA and VPA reverse the hypermethylation status of certain genes (Ou et al., 2007; Gu et al., 2012). The combination of DNMT and HDAC inhibitors always lead to better efficacy, which is considered as a good strategy. Histone methylation displays closer ties with DNA methylation. S-adenosyl-l-methionine (SAM) is a universal methyl group donor, so the content of SAM in cells affects the methylation status of DNA and histone simultaneously. Furthermore, the crosstalk between DNA and histone methylation can be mediated by the interaction between DNA and histone methyltransferases (Cedar and Bergman, 2009). DNA hypermethylation status, increased repressive histone modification H3k9me2, decreased

H3K9ac and H3K4me2 modification at CYP24A1 promoter contribute to the suppression of CYP24A1 in prostate cancer. Combined treatment with DNMT inhibitor DAC and HDAC inhibitor TSA upregulated the CYP24A1 expression, accompanied by increased recruitment of Vitamin D receptor to CYP24A1 promoter (Luo et al., 2010). The interplay between miRNA and DNA methylation in gene regulation is also widely reported. The transcription and synthesis of miRNAs can be repressed by DNA methylation, and certain miRNAs can change the DNA methylation status of the gene by targeting DNMTs in return (Fuso et al., 2020). In colorectal cancer, inflammatory factor cytokine interleukin-6 was reported to promote DNMT1 nuclear translocation, and then DNMT1 causes DNA methylation of CpG islands near miR27b, thus suppressing its transcription. Due to the reduced degradation by miR27b, CYP1B1 showed a high expression level (Patel et al., 2014).

Also, further researches are required to clarify if the epigenetic regulations of DMEs contribute to the metabolism of endogenous substrates during cancer progression and its downstream impacts. To elucidate the epigenetic regulatory mechanism of DMEs in tumors can provide a basis for implementing individualized and rationalized medication, meanwhile developing new biomarkers and targets for the diagnosis, treatment, and prognosis of cancer.

Authorship contributions

Wrote or contributed to the writing of the manuscript: Wang, Yu, Jiang, Zheng, and Zeng.

References

- Almazroo OA, Miah MK, and Venkataramanan R (2017) Drug Metabolism in the Liver. *Clin Liver Dis* **21**:1-20.
- Alzahrani AM and Rajendran P (2020) The Multifarious Link between Cytochrome P450s and Cancer. *Oxid Med Cell Longev* **2020**:3028387.
- Barski A, Cuddapah S, Cui K, Roh TY, Schones DE, Wang Z, Wei G, Chepelev I, and Zhao K (2007) High-resolution profiling of histone methylations in the human genome. *Cell* **129**:823-837.
- Brodeur CM, Thibault P, Durand M, Perreault JP, and Bisailon M (2019) Dissecting the expression landscape of cytochromes P450 in hepatocellular carcinoma: towards novel molecular biomarkers. *Genes Cancer* **10**:97-108.
- Carnell DM, Smith RE, Daley FM, Barber PR, Hoskin PJ, Wilson GD, Murray GI, and Everett SA (2004) Target validation of cytochrome P450 CYP1B1 in prostate carcinoma with protein expression in associated hyperplastic and premalignant tissue. *Int J Radiat Oncol Biol Phys* **58**:500-509.
- Castell JV, Donato MT, and Gómez-Lechón MJ (2005) Metabolism and bioactivation of toxicants in the lung. The in vitro cellular approach. *Exp Toxicol Pathol* **57 Suppl 1**:189-204.
- Cedar H and Bergman Y (2009) Linking DNA methylation and histone modification: patterns and paradigms. *Nat Rev Genet* **10**:295-304.
- Chen C, Wei X, Rao X, Wu J, Yang S, Chen F, Ma D, Zhou J, Dackor RT, Zeldin DC, and Wang DW (2011a) Cytochrome P450 2J2 is highly expressed in hematologic

malignant diseases and promotes tumor cell growth. *J Pharmacol Exp Ther* **336**:344-355.

Chen G, Kim SH, King AN, Zhao L, Simpson RU, Christensen PJ, Wang Z, Thomas DG, Giordano TJ, Lin L, Brenner DE, Beer DG, and Ramnath N (2011b) CYP24A1 is an independent prognostic marker of survival in patients with lung adenocarcinoma. *Clin Cancer Res* **17**:817-826.

Chen H, Shen ZY, Xu W, Fan TY, Li J, Lu YF, Cheng ML, and Liu J (2014) Expression of P450 and nuclear receptors in normal and end-stage Chinese livers. *World J Gastroenterol* **20**:8681-8690.

Chen YW, Kao SY, Wang HJ, and Yang MH (2013) Histone modification patterns correlate with patient outcome in oral squamous cell carcinoma. *Cancer* **119**:4259-4267.

Clouaire T and Stancheva I (2008) Methyl-CpG binding proteins: specialized transcriptional repressors or structural components of chromatin? *Cell Mol Life Sci* **65**:1509-1522.

Endo Y, Yamashita H, Takahashi S, Sato S, Yoshimoto N, Asano T, Hato Y, Dong Y, Fujii Y, and Toyama T (2014) Immunohistochemical determination of the miR-1290 target arylamine N-acetyltransferase 1 (NAT1) as a prognostic biomarker in breast cancer. *BMC Cancer* **14**:990.

Fan Z, Wang Z, Chen W, Cao Z, and Li Y (2016) Association between the CYP11 family and six cancer types. *Oncol Lett* **12**:35-40.

Fang C, Wei XM, Zeng XT, Wang FB, Weng H, and Long X (2015) Aberrant GSTP1 promoter methylation is associated with increased risk and advanced stage of breast cancer: a meta-analysis of 19 case-control studies. *BMC Cancer* **15**:920.

Fu LL, Tian M, Li X, Li JJ, Huang J, Ouyang L, Zhang Y, and Liu B (2015) Inhibition of BET bromodomains as a therapeutic strategy for cancer drug discovery. *Oncotarget* **6**:5501-5516.

Fujimura T, Takahashi S, Urano T, Kumagai J, Murata T, Takayama K, Ogushi T, Horie-Inoue K, Ouchi Y, Kitamura T, Muramatsu M, Homma Y, and Inoue S (2009) Expression of cytochrome P450 3A4 and its clinical significance in human prostate cancer. *Urology* **74**:391-397.

Fuks F, Hurd PJ, Wolf D, Nan X, Bird AP, and Kouzarides T (2003) The methyl-CpG-binding protein MeCP2 links DNA methylation to histone methylation. *J Biol Chem* **278**:4035-4040.

Fuso A, Raia T, Orticello M, and Lucarelli M (2020) The complex interplay between DNA methylation and miRNAs in gene expression regulation. *Biochimie* doi: 10.1016/j.biochi.2020.1002.1006.

Gagnon JF, Bernard O, Villeneuve L, Tetu B, and Guillemette C (2006) Irinotecan inactivation is modulated by epigenetic silencing of UGT1A1 in colon cancer. *Clin Cancer Res* **12**:1850-1858.

Gajjar K, Martin-Hirsch PL, and Martin FL (2012) CYP1B1 and hormone-induced cancer. *Cancer Lett* **324**:13-30.

Gao J, Wang Z, Wang GJ, Gao N, Li J, Zhang YF, Zhou J, Zhang HX, Wen Q, Jin H, and Qiao HL (2018) From hepatofibrosis to hepatocarcinogenesis: Higher cytochrome P450 2E1 activity is a potential risk factor. *Mol Carcinog* **57**:1371-1382.

Gao P, Yang X, Xue YW, Zhang XF, Wang Y, Liu WJ, and Wu XJ (2009) Promoter

methylation of glutathione S-transferase pi1 and multidrug resistance gene 1 in bronchioloalveolar carcinoma and its correlation with DNA methyltransferase 1 expression. *Cancer* **115**:3222-3232.

Gu S, Tian Y, Chlenski A, Salwen HR, Lu Z, Raj JU, and Yang Q (2012) Valproic acid shows a potent antitumor effect with alteration of DNA methylation in neuroblastoma. *Anticancer Drugs* **23**:1054-1066.

Guo YY, Xu C, Fang Y, Wang CE, Gao N, Wen Q, and Qiao HL (2019) High CYP2E1 activity aggravates hepatofibrosis by limiting macrophage polarization towards the M2 phenotype. *Mol Carcinog* **58**:1481-1491.

Habano W, Gamo T, Sugai T, Otsuka K, Wakabayashi G, and Ozawa S (2009) CYP1B1, but not CYP1A1, is downregulated by promoter methylation in colorectal cancers. *Int J Oncol* **34**:1085-1091.

Habano W, Kawamura K, Iizuka N, Terashima J, Sugai T, and Ozawa S (2015) Analysis of DNA methylation landscape reveals the roles of DNA methylation in the regulation of drug metabolizing enzymes. *Clin Epigenetics* **7**:105.

Haberland M, Montgomery RL, and Olson EN (2009) The many roles of histone deacetylases in development and physiology: implications for disease and therapy. *Nat Rev Genet* **10**:32-42.

Hahn RZ, Antunes MV, Verza SG, Perassolo MS, Suyenaga ES, Schwartzmann G, and Linden R (2019) Pharmacokinetic and Pharmacogenetic Markers of Irinotecan Toxicity. *Curr Med Chem* **26**:2085-2107.

He X and Feng S (2015) Role of Metabolic Enzymes P450 (CYP) on Activating

Procarcinogen and their Polymorphisms on the Risk of Cancers. *Curr Drug Metab* **16**:850-863.

Henrique R and Jerónimo C (2004) Molecular detection of prostate cancer: a role for GSTP1 hypermethylation. *Eur Urol* **46**:660-669.

Ho JC, Cheung ST, Leung KL, Ng IO, and Fan ST (2004) Decreased expression of cytochrome P450 2E1 is associated with poor prognosis of hepatocellular carcinoma. *Int J Cancer* **111**:494-500.

Hokaiwado N, Takeshita F, Naiki-Ito A, Asamoto M, Ochiya T, and Shirai T (2008) Glutathione S-transferase Pi mediates proliferation of androgen-independent prostate cancer cells. *Carcinogenesis* **29**:1134-1138.

Hřebačková J, Poljaková J, Eckschlager T, Hraběta J, Procházka P, Smutný S, and Stiborová M (2009) Histone deacetylase inhibitors valproate and trichostatin A are toxic to neuroblastoma cells and modulate cytochrome P450 1A1, 1B1 and 3A4 expression in these cells. *Interdiscip Toxicol* **2**:205-210.

Hu DG, Marri S, McKinnon RA, Mackenzie PI, and Meech R (2019) Deregulation of the Genes that Are Involved in Drug Absorption, Distribution, Metabolism, and Excretion in Hepatocellular Carcinoma. *J Pharmacol Exp Ther* **368**:363-381.

Huang JZ, Chen M, Chen, Gao XC, Zhu S, Huang H, Hu M, Zhu H, and Yan GR (2017) A Peptide Encoded by a Putative lncRNA HOXB-AS3 Suppresses Colon Cancer Growth. *Mol Cell* **68**:171-184.

Imaoka S, Yoneda Y, Sugimoto T, Hiroi T, Yamamoto K, Nakatani T, and Funae Y (2000) CYP4B1 is a possible risk factor for bladder cancer in humans. *Biochem Biophys Res*

Commun **277**:776-780.

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

Jiang JG, Ning YG, Chen C, Ma D, Liu ZJ, Yang S, Zhou J, Xiao X, Zhang XA, Edin ML, Card JW, Wang J, Zeldin DC, and Wang DW (2007) Cytochrome p450 epoxygenase promotes human cancer metastasis. *Cancer Res* **67**:6665-6674.

Kabátková M, Zapletal O, Tylichová Z, Neča J, Machala M, Milcová A, Topinka J, Kozubík A, and Vondráček J (2015) Inhibition of β -catenin signalling promotes DNA damage elicited by benzo[a]pyrene in a model of human colon cancer cells via CYP1 deregulation. *Mutagenesis* **30**:565-576.

Kalscheuer S, Zhang X, Zeng Y, and 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.

Kamdem LK, Meineke I, Gödtel-Armbrust U, Brockmüller J, and Wojnowski L (2006) Dominant contribution of P450 3A4 to the hepatic carcinogenic activation of aflatoxin B1. *Chem Res Toxicol* **19**:577-586.

Kanwal R, Pandey M, Bhaskaran N, MacLennan GT, Fu P, Ponsky LE, and Gupta S (2014) Protection against oxidative DNA damage and stress in human prostate by glutathione S-transferase P1. *Mol Carcinog* **53**:8-18.

Karypidis AH, Olsson M, Andersson SO, Rane A, and Ekström L (2008) Deletion polymorphism of the UGT2B17 gene is associated with increased risk for prostate

cancer and correlated to gene expression in the prostate. *Pharmacogenomics J* **8**:147-151.

Kim SJ, Kang HS, Jung SY, Min SY, Lee S, Kim SW, Kwon Y, Lee KS, Shin KH, and Ro J (2010) Methylation patterns of genes coding for drug-metabolizing enzymes in tamoxifen-resistant breast cancer tissues. *J Mol Med (Berl)* **88**:1123-1131.

Klingenberg M, Matsuda A, Diederichs S, and Patel T (2017) Non-coding RNA in hepatocellular carcinoma: Mechanisms, biomarkers and therapeutic targets. *J Hepatol* **67**:603-618.

Kumagai J, Fujimura T, Takahashi S, Urano T, Ogushi T, Horie-Inoue K, Ouchi Y, Kitamura T, Muramatsu M, Blumberg B, and Inoue S (2007) Cytochrome P450 2B6 is a growth-inhibitory and prognostic factor for prostate cancer. *Prostate* **67**:1029-1037.

Lachenmayer A, Toffanin S, Cabellos L, Alsinet C, Hoshida Y, Villanueva A, Minguez B, Tsai HW, Ward SC, Thung S, Friedman SL, and Llovet JM (2012) Combination therapy for hepatocellular carcinoma: additive preclinical efficacy of the HDAC inhibitor panobinostat with sorafenib. *J Hepatol* **56**:1343-1350.

Leclerc J, Courcot-Ngoubo Ngangue E, Cauffiez C, Allorge D, Pottier N, Lafitte JJ, Debaert M, Jaillard S, Broly F, and Lo-Guidice JM (2011) Xenobiotic metabolism and disposition in human lung: transcript profiling in non-tumoral and tumoral tissues. *Biochimie* **93**:1012-1027.

Leclerc J, Tournel G, Courcot-Ngoubo Ngangue E, Pottier N, Lafitte JJ, Jaillard S, Mensier E, Lhermitte M, Broly F, and Lo-Guidice JM (2010) Profiling gene expression of whole cytochrome P450 superfamily in human bronchial and peripheral lung tissues:

Differential expression in non-small cell lung cancers. *Biochimie* **92**:292-306.

- Levesque E, Labriet A, Hovington H, Allain EP, Melo-Garcia L, Rouleau M, Brisson H, Turcotte V, Caron P, Villeneuve L, Leclercq M, Droit A, Audet-Walsh E, Simonyan D, Fradet Y, Lacombe L, and Guillemette C (2020) Alternative promoters control UGT2B17-dependent androgen catabolism in prostate cancer and its influence on progression. *Br J Cancer* **122**:1068-1076.
- Li D, Knox B, Chen S, Wu L, Tolleson WH, Liu Z, Yu D, Guo L, Tong W, and Ning B (2019a) MicroRNAs hsa-miR-495-3p and hsa-miR-486-5p suppress basal and rifampicin-induced expression of human sulfotransferase 2A1 (SULT2A1) by facilitating mRNA degradation. *Biochem Pharmacol* **169**:113617.
- Li J, Tan S, Kooger R, Zhang C, and Zhang Y (2014) MicroRNAs as novel biological targets for detection and regulation. *Chem Soc Rev* **43**:506-517.
- Li J, Yang J, Zhou P, Le Y, Zhou C, Wang S, Xu D, Lin HK, and Gong Z (2015a) Circular RNAs in cancer: novel insights into origins, properties, functions and implications. *Am J Cancer Res* **5**:472-480.
- Li MY, Liu Y, Liu LZ, Kong AW, Zhao Z, Wu B, Long X, Wu J, Ng CS, Wan IY, Du J, Mok TS, Underwood MJ, and Chen GG (2015b) Estrogen receptor alpha promotes smoking-carcinogen-induced lung carcinogenesis via cytochrome P450 1B1. *J Mol Med (Berl)* **93**:1221-1233.
- Li P, Chen S, Chen H, Mo X, Li T, Shao Y, Xiao B, and Guo J (2015c) Using circular RNA as a novel type of biomarker in the screening of gastric cancer. *Clin Chim Acta* **444**:132-136.

Li X, Tian Y, Tu MJ, Ho PY, Batra N, and Yu AM (2019b) Bioengineered miR-27b-3p and miR-328-3p modulate drug metabolism and disposition via the regulation of target ADME gene expression. *Acta Pharm Sin B* **9**:639-647.

Li Y, Cai Y, Chen H, and Mao L (2018) Clinical significance and association of GSTP1 hypermethylation with hepatocellular carcinoma: A meta-analysis. *J Cancer Res Ther* **14**:S486-S489.

Li Z and Rana TM (2014) Therapeutic targeting of microRNAs: current status and future challenges. *Nat Rev Drug Discov* **13**:622-638.

Lindley C, Hamilton G, McCune JS, Faucette S, Shord SS, Hawke RL, Wang H, Gilbert D, Jolley S, Yan B, and LeCluyse EL (2002) The effect of cyclophosphamide with and without dexamethasone on cytochrome P450 3A4 and 2B6 in human hepatocytes. *Drug Metab Dispos* **30**:814-822.

Linhart K, Bartsch H, and Seitz HK (2014) The role of reactive oxygen species (ROS) and cytochrome P-450 2E1 in the generation of carcinogenic etheno-DNA adducts. *Redox Biol* **3**:56-62.

Litwin MS and Tan HJ (2017) The Diagnosis and Treatment of Prostate Cancer: A Review. *JAMA* **317**:2532-2542.

Liu F, Luo LM, Wei YG, Li B, Wang WT, Wen TF, Yang JY, Xu MQ, and Yan LN (2015) Polymorphisms of the CYP1B1 gene and hepatocellular carcinoma risk in a Chinese population. *Gene* **564**:14-20.

Liu Y, Zheng X, Yu Q, Wang H, Tan F, Zhu Q, Yuan L, Jiang H, Yu L, and Zeng S (2016) Epigenetic activation of the drug transporter OCT2 sensitizes renal cell carcinoma to

oxaliplatin. *Sci Transl Med* **8**:348ra397.

Liu Z, Liu X, Li Y, Ren P, Zhang C, Wang L, Du X, and Xing B (2019) miR-6716-5p promotes metastasis of colorectal cancer through downregulating NAT10 expression.

Cancer Manag Res **11**:5317-5332.

Lu L, Zhou J, Shi J, Peng XJ, Qi XX, Wang Y, Li FY, Zhou FY, Liu L, and Liu ZQ (2015)

Drug-Metabolizing Activity, Protein and Gene Expression of UDP-Glucuronosyltransferases Are Significantly Altered in Hepatocellular Carcinoma Patients. *PLoS ONE* **10**:e0127524.

Luger K, Dechassa ML, and Tremethick DJ (2012) New insights into nucleosome and chromatin structure: an ordered state or a disordered affair? *Nat Rev Mol Cell Biol*

13:436-447.

Luo W, Karpf AR, Deeb KK, Muindi JR, Morrison CD, Johnson CS, and Trump DL (2010)

Epigenetic regulation of vitamin D 24-hydroxylase/CYP24A1 in human prostate cancer. *Cancer Res* **70**:5953-5962.

Mahon KL, Qu W, Lin HM, Spielman C, Cain D, Jacobs C, Stockler MR, Higano CS, de

Bono JS, Chi KN, Clark SJ, and Horvath LG (2019) Serum Free Methylated Glutathione S-transferase 1 DNA Levels, Survival, and Response to Docetaxel in

Metastatic, Castration-resistant Prostate Cancer: Post Hoc Analyses of Data from a Phase 3 Trial. *Eur Urol* **76**:306-312.

Maldonado L, Brait M, Loyo M, Sullenberger L, Wang K, Peskoe SB, Rosenbaum E, Howard

R, Toubaji A, Albadine R, Netto GJ, Hoque MO, Platz EA, and Sidransky D (2014)

GSTP1 promoter methylation is associated with recurrence in early stage prostate

cancer. *J Urol* **192**:1542-1548.

Margaillan G, Lévesque É, and Guillemette C (2016) Epigenetic regulation of steroid inactivating UDP-glucuronosyltransferases by microRNAs in prostate cancer. *J Steroid Biochem Mol Biol* **155**:85-93.

Margaillan G, Rouleau M, Fallon JK, Caron P, Villeneuve L, Turcotte V, Smith PC, Joy MS, and Guillemette C (2015) Quantitative profiling of human renal UDP-glucuronosyltransferases and glucuronidation activity: a comparison of normal and tumoral kidney tissues. *Drug Metab Dispos* **43**:611-619.

Matsumoto A, Pasut A, Matsumoto M, Yamashita R, Fung J, Monteleone E, Saghatelian A, Nakayama KI, Clohessy JG, and Pandolfi PP (2017) mTORC1 and muscle regeneration are regulated by the LINC00961-encoded SPAR polypeptide. *Nature* **541**:228-232.

McFadyen MC, Breeman S, Payne S, Stirk C, Miller ID, Melvin WT, and Murray GI (1999) Immunohistochemical localization of cytochrome P450 CYP1B1 in breast cancer with monoclonal antibodies specific for CYP1B1. *J Histochem Cytochem* **47**:1457-1464.

Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, Maier L, Mackowiak SD, Gregersen LH, Munschauer M, Loewer A, Ziebold U, Landthaler M, Kocks C, le Noble F, and Rajewsky N (2013) Circular RNAs are a large class of animal RNAs with regulatory potency. *Nature* **495**:333-338.

Mercer TR, Dinger ME, and Mattick JS (2009) Long non-coding RNAs: insights into functions. *Nat Rev Genet* **10**:155-159.

- Mitsui Y, Chang I, Kato T, Hashimoto Y, Yamamura S, Fukuhara S, Wong DK, Shiina M, Imai-Sumida M, Majid S, Saini S, Shiina H, Nakajima K, Deng G, Dahiya R, and Tanaka Y (2016) Functional role and tobacco smoking effects on methylation of CYP1A1 gene in prostate cancer. *Oncotarget* **7**:49107-49121.
- Mohammad HP, Barbash O, and Creasy CL (2019) Targeting epigenetic modifications in cancer therapy: erasing the roadmap to cancer. *Nat Med* **25**:403-418.
- Moore LD, Le T, and Fan G (2013) DNA methylation and its basic function. *Neuropsychopharmacology* **38**:23-38.
- Moorthy B, Chu C, and Carlin DJ (2015) Polycyclic aromatic hydrocarbons: from metabolism to lung cancer. *Toxicol Sci* **145**:5-15.
- Mutka SC, Green LH, Verderber EL, Richards JP, Looker DL, Chlipala EA, and Rosenthal GJ (2012) ADH IB expression, but not ADH III, is decreased in human lung cancer. *PLoS One* **7**:e52995.
- Nakayama M, Gonzalgo ML, Yegnasubramanian S, Lin X, De Marzo AM, and Nelson WG (2004) GSTP1 CpG island hypermethylation as a molecular biomarker for prostate cancer. *J Cell Biochem* **91**:540-552.
- Nan X, Ng HH, Johnson CA, Laherty CD, Turner BM, Eisenman RN, and Bird A (1998) Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. *Nature* **393**:386-389.
- Nebert DW and Dalton TP (2006) The role of cytochrome P450 enzymes in endogenous signalling pathways and environmental carcinogenesis. *Nat Rev Cancer* **6**:947-960.
- Nie J, Liu L, Li X, and Han W (2014) Decitabine, a new star in epigenetic therapy: the

clinical application and biological mechanism in solid tumors. *Cancer Lett* **354**:12-20.

Ou JN, Torrisani J, Unterberger A, Provencal N, Shikimi K, Karimi M, Ekstrom TJ, and Szyf M (2007) Histone deacetylase inhibitor Trichostatin A induces global and gene-specific DNA demethylation in human cancer cell lines. *Biochem Pharmacol* **73**:1297-1307.

Pâquet S, Fazli L, Grosse L, Verreault M, Têtu B, Rennie PS, Bélanger A, and Barbier O (2012) Differential expression of the androgen-conjugating UGT2B15 and UGT2B17 enzymes in prostate tumor cells during cancer progression. *J Clin Endocrinol Metab* **97**:E428-432.

Pastina I, Giovannetti E, Chioni A, Sissung TM, Crea F, Orlandini C, Price DK, Cianci C, Figg WD, Ricci S, and Danesi R (2010) Cytochrome 450 1B1 (CYP1B1) polymorphisms associated with response to docetaxel in Castration-Resistant Prostate Cancer (CRPC) patients. *BMC Cancer* **10**:511.

Patel SA, Bhambra U, Charalambous MP, David RM, Edwards RJ, Lightfoot T, Boobis AR, and Gooderham NJ (2014) Interleukin-6 mediated upregulation of CYP1B1 and CYP2E1 in colorectal cancer involves DNA methylation, miR27b and STAT3. *Br J Cancer* **111**:2287-2296.

Pathania S, Bhatia R, Baldi A, Singh R, and Rawal RK (2018) Drug metabolizing enzymes and their inhibitors' role in cancer resistance. *Biomed Pharmacother* **105**:53-65.

Peng DF, Razvi M, Chen H, Washington K, Roessner A, Schneider-Stock R, and El-Rifai W (2009) DNA hypermethylation regulates the expression of members of the Mu-class

glutathione S-transferases and glutathione peroxidases in Barrett's adenocarcinoma.

Gut **58**:5-15.

Piccolo FM and Fisher AG (2014) Getting rid of DNA methylation. *Trends Cell Biol*

24:136-143.

Pljesa-Ercegovac M, Savic-Radojevic A, Matic M, Coric V, Djukic T, Radic T, and Simic T

(2018) Glutathione Transferases: Potential Targets to Overcome Chemoresistance in Solid Tumors. *Int J Mol Sci* **19**:3785.

Putluri N, Shojaie A, Vasu VT, Vareed SK, Nalluri S, Putluri V, Thangjam GS, Panzitt K,

Tallman CT, Butler C, Sana TR, Fischer SM, Sica G, Brat DJ, Shi H, Palapattu GS,

Lotan Y, Weizer AZ, Terris MK, Shariat SF, Michailidis G, and Sreekumar A (2011)

Metabolomic profiling reveals potential markers and bioprocesses altered in bladder cancer progression. *Cancer Res* **71**:7376-7386.

Qu S, Yang X, Li X, Wang J, Gao Y, Shang R, Sun W, Dou K, and Li H (2015) Circular RNA:

A new star of noncoding RNAs. *Cancer Lett* **365**:141-148.

Ramnath N, Nadal E, Jeon CK, Sandoval J, Colacino J, Rozek LS, Christensen PJ, Esteller M,

Beer DG, and Kim SH (2014) Epigenetic regulation of vitamin D metabolism in

human lung adenocarcinoma. *J Thorac Oncol* **9**:473-482.

Revill K, Wang T, Lachenmayer A, Kojima K, Harrington A, Li J, Hoshida Y, Llovet JM, and

Powers S (2013) Genome-wide methylation analysis and epigenetic unmasking

identify tumor suppressor genes in hepatocellular carcinoma. *Gastroenterology*

145:1424-1435. e1425.

Rodrigues-Lima F, Dairou J, Busi F, and Dupret JM (2010) Human arylamine

N-acetyltransferase 1: a drug-metabolizing enzyme and a drug target? *Curr Drug Targets* **11**:759-766.

Sawers L, Ferguson M, Ihrig B, Young H, Chakravarty P, Wolf C, and Smith G (2014) Glutathione S-transferase P1 (GSTP1) directly influences platinum drug chemosensitivity in ovarian tumour cell lines. *Br J Cancer* **111**:1150-1158.

Schmelzle M, Dizdar L, Matthaei H, Baldus SE, Wolters J, Lindenlauf N, Bruns I, Cadeddu RP, Kröpil F, Topp SA, Schulte am Esch J, Eisenberger CF, Knoefel WT, and Stoecklein NH (2011) Esophageal cancer proliferation is mediated by cytochrome P450 2C9 (CYP2C9). *Prostaglandins Other Lipid Mediat* **94**:25-33.

Schnekenburger M, Karius T, and Diederich M (2014) Regulation of epigenetic traits of the glutathione S-transferase P1 gene: from detoxification toward cancer prevention and diagnosis. *Front Pharmacol* **5**:170.

Siegel RL, Miller KD, and Jemal A (2019) Cancer statistics, 2019. *CA Cancer J Clin* **69**:7-34.

Slattery ML, Samowitz W, Ma K, Murtaugh M, Sweeney C, Levin TR, and Neuhausen S (2004) CYP1A1, cigarette smoking, and colon and rectal cancer. *Am J Epidemiol* **160**:842-852.

Sohn OS, Fiala ES, Requeijo SP, Weisburger JH, and Gonzalez FJ (2001) Differential effects of CYP2E1 status on the metabolic activation of the colon carcinogens azoxymethane and methylazoxymethanol. *Cancer Res* **61**:8435-8440.

Su WH, Chao CC, Yeh SH, Chen DS, Chen PJ, and Jou YS (2006) OncoDB.HCC: an integrated oncogenomic database of hepatocellular carcinoma revealed aberrant cancer target genes and loci. *Nucleic Acids Res* **35**:D727-D731.

- Sutliff AK, Watson CJW, Chen G, and Lazarus P (2019) Regulation of UGT2A1 by miR-196a-5p and miR-196b-5p. *J Pharmacol Exp Ther* **369**:234-243.
- Tan AC, Jimeno A, Lin SH, Wheelhouse J, Chan F, Solomon A, Rajeshkumar NV, Rubio-Viqueira B, and Hidalgo M (2009) Characterizing DNA methylation patterns in pancreatic cancer genome. *Mol Oncol* **3**:425-438.
- Tan SK, Pastori C, Penas C, Komotar RJ, Ivan ME, Wahlestedt C, and Ayad NG (2018) Serum long noncoding RNA HOTAIR as a novel diagnostic and prognostic biomarker in glioblastoma multiforme. *Mol Cancer* **17**:74.
- Tang SC, Wu MF, Wong RH, Liu YF, Tang LC, Lai CH, Hsu CP, and Ko JL (2011) Epigenetic mechanisms for silencing glutathione S-transferase m2 expression by hypermethylated specificity protein 1 binding in lung cancer. *Cancer* **117**:3209-3221.
- Tang X and Chen S (2015) Epigenetic Regulation of Cytochrome P450 Enzymes and Clinical Implication. *Curr Drug Metab* **16**:86-96.
- Tang X, Ge L, Chen Z, Kong S, Liu W, Xu Y, Zeng S, and Chen S (2016) Methylation of the Constitutive Androstane Receptor Is Involved in the Suppression of CYP2C19 in Hepatitis B Virus-Associated Hepatocellular Carcinoma. *Drug Metab Dispos* **44**:1643-1652.
- Tchou JC, Lin X, Freije D, Isaacs WB, Brooks JD, Rashid A, De Marzo AM, Kanai Y, Hirohashi S, and Nelson WG (2000) GSTP1 CpG island DNA hypermethylation in hepatocellular carcinomas. *Int J Oncol* **16**:663-676.
- Thomas JH (2007) Rapid birth-death evolution specific to xenobiotic cytochrome P450 genes in vertebrates. *PLoS Genet* **3**:e67.

- Tokizane T, Shiina H, Igawa M, Enokida H, Urakami S, Kawakami T, Ogishima T, Okino ST, Li LC, Tanaka Y, Nonomura N, Okuyama A, and Dahiya R (2005) Cytochrome P450 1B1 is overexpressed and regulated by hypomethylation in prostate cancer. *Clin Cancer Res* **11**:5793-5801.
- Ul-Islam S, Ahmed MB, Shehzad A, Ul-Islam M, and Lee YS (2018) Failure of Chemotherapy in Hepatocellular Carcinoma Due to Impaired and Dysregulated Primary Liver Drug Metabolizing Enzymes and Drug Transport Proteins: What to Do? *Curr Drug Metab* **19**:819-829.
- Wang J, Liu X, Wu H, Ni P, Gu Z, Qiao Y, Chen N, Sun F, and Fan Q (2010) CREB up-regulates long non-coding RNA, HULC expression through interaction with microRNA-372 in liver cancer. *Nucleic Acids Res* **38**:5366-5383.
- Weinberg OK, Marquez-Garban DC, Fishbein MC, Goodglick L, Garban HJ, Dubinett SM, and Pietras RJ (2005) Aromatase inhibitors in human lung cancer therapy. *Cancer Res* **65**:11287-11291.
- Weng MW, Hsiao YM, Chiou HL, Yang SF, Hsieh YS, Cheng YW, Yang CH, and Ko JL (2005) Alleviation of benzo[a]pyrene-diolepoxide-DNA damage in human lung carcinoma by glutathione S-transferase M2. *DNA Repair (Amst)* **4**:493-502.
- Widschwendter M, Siegmund KD, Müller HM, Fiegl H, Marth C, Müller-Holzner E, Jones PA, and Laird PW (2004) Association of breast cancer DNA methylation profiles with hormone receptor status and response to tamoxifen. **64**:3807.
- Wijayakumara DD, Hu DG, Meech R, McKinnon RA, and Mackenzie PI (2015) Regulation of Human UGT2B15 and UGT2B17 by miR-376c in Prostate Cancer Cell Lines. *J*

Pharmacol Exp Ther **354**:417-425.

Wijayakumara DD, Mackenzie PI, McKinnon RA, Hu DG, and Meech R (2018) Regulation of UDP-Glucuronosyltransferase 2B15 by miR-331-5p in Prostate Cancer Cells Involves Canonical and Noncanonical Target Sites. *J Pharmacol Exp Ther* **365**:48-59.

Xie FW, Peng YH, Wang WW, Chen X, Chen X, Li J, Yu ZY, and Ouyang XN (2014) Influence of UGT1A1 gene methylation level in colorectal cancer cells on the sensitivity of the chemotherapy drug CPT-11. *Biomed Pharmacother* **68**:825-831.

Xie H, Ma H, and Zhou D (2013) Plasma HULC as a promising novel biomarker for the detection of hepatocellular carcinoma. *Biomed Res Int* **2013**:136106.

Xu RH, Wei W, Krawczyk M, Wang W, Luo H, Flagg K, Yi S, Shi W, Quan Q, Li K, Zheng L, Zhang H, Caughey BA, Zhao Q, Hou J, Zhang R, Xu Y, Cai H, Li G, Hou R, Zhong Z, Lin D, Fu X, Zhu J, Duan Y, Yu M, Ying B, Zhang W, Wang J, Zhang E, Zhang C, Li O, Guo R, Carter H, Zhu JK, Hao X, and Zhang K (2017) Circulating tumour DNA methylation markers for diagnosis and prognosis of hepatocellular carcinoma. *Nat Mater* **16**:1155-1161.

Yager JD (2000) Endogenous estrogens as carcinogens through metabolic activation. *J Natl Cancer Inst Monographs* **2000**:67-73.

Yan L, Wang Y, Liu J, Nie Y, Zhong XB, Kan Q, and Zhang L (2017) Alterations of Histone Modifications Contribute to Pregnane X Receptor-Mediated Induction of CYP3A4 by Rifampicin. *Mol Pharmacol* **92**:113-123.

Yan T, Gao S, Peng X, Shi J, Xie C, Li Q, Lu L, Wang Y, Zhou F, Liu Z, and Hu M (2015a) Significantly decreased and more variable expression of major CYPs and UGTs in

liver microsomes prepared from HBV-positive human hepatocellular carcinoma and matched pericarcinomatous tissues determined using an isotope label-free UPLC-MS/MS method. *Pharm Res* **32**:1141-1157.

Yan T, Lu L, Xie C, Chen J, Peng X, Zhu L, Wang Y, Li Q, Shi J, Zhou F, Hu M, and Liu Z (2015b) Severely Impaired and Dysregulated Cytochrome P450 Expression and Activities in Hepatocellular Carcinoma: Implications for Personalized Treatment in Patients. *Mol Cancer Ther* **14**:2874-2886.

Yu D, Green B, Marrone A, Guo Y, Kadlubar S, Lin D, Fuscoe J, Pogribny I, and Ning B (2015a) Suppression of CYP2C9 by microRNA hsa-miR-128-3p in human liver cells and association with hepatocellular carcinoma. *Sci Rep* **5**:8534.

Yu L, Gong X, Sun L, Zhou Q, Lu B, and Zhu L (2016) The Circular RNA Cdr1as Act as an Oncogene in Hepatocellular Carcinoma through Targeting miR-7 Expression. *PLoS ONE* **11**:e0158347.

Yu L, Wang Z, Zhang Z, Ren X, Lu X, and Ding K (2015b) Small-molecule BET inhibitors in clinical and preclinical development and their therapeutic potential. *Curr Top Med Chem* **15**:776-794.

Yu MW, Pai CI, Yang SY, Hsiao TJ, Chang HC, Lin SM, Liaw YF, Chen PJ, and Chen CJ (2000) Role of N-acetyltransferase polymorphisms in hepatitis B related hepatocellular carcinoma: impact of smoking on risk. *Gut* **47**:703-709.

Yu W, Chai H, Li Y, Zhao H, Xie X, Zheng H, Wang C, Wang X, Yang G, Cai X, Falck JR, and Yang J (2012) Increased expression of CYP4Z1 promotes tumor angiogenesis and growth in human breast cancer. *Toxicol Appl Pharmacol* **264**:73-83.

Zanger UM, Klein K, Thomas M, Rieger JK, Tremmel R, Kandel BA, Klein M, and Magdy T (2014) Genetics, epigenetics, and regulation of drug-metabolizing cytochrome p450 enzymes. *Clin Pharmacol Ther* **95**:258-261.

Zanger UM and Schwab M (2013) Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther* **138**:103-141.

Zhang M, Wang Q, Wan KW, Ahmed W, Phoenix DA, Zhang Z, Elrayess MA, Elhissi A, and Sun X (2019) Liposome mediated-CYP1A1 gene silencing nanomedicine prepared using lipid film-coated proliposomes as a potential treatment strategy of lung cancer. *Int J Pharm* **566**:185-193.

Zhou X, Jiao D, Dou M, Chen J, Li Z, Li Y, Liu J, and Han X (2019) Association of glutathione-S-transferase p1 gene promoter methylation and the incidence of prostate cancer: a systematic review and meta-analysis. *J Cancer Res Clin Oncol* **145**:1939-1948.

Footnotes

This work was supported by the National Natural Science Foundation of China [81702801];
the National Key R&D Program of China [2017YFE0102200]; Leading Talent of "Ten
Thousand Plan"- National High-Level Talents Special Support Plan.

Figure Legends

Figure 1. The methylation status of DME genes contributes to cancer progression and chemoresistance. White dots represent cytosine, Black dots represent 5-methyl cytosine.

Table 1. List of differentially expressed DMEs during carcinogenesis and their functions

Cancer type	Variation trend	Functional classification	DMEs	Roles in cancer	Reference	
Liver cancer	Upregulation	Increased activation of procarcinogens	CYP1B1	CYP1B1 increases the HCC risk and associated with the activation of procarcinogens.	(Su et al., 2006; Liu et al., 2015)	
	Downregulation	Potential impact on drug efficacy and toxicity	CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5	They are responsible for the metabolism of various drugs. Due to the decrease of functional hepatocytes, their expressions are down-regulated, which may reduce drug efficacy and increase drug toxicity.	(Chen et al., 2014; Yan et al., 2015a; Hu et al., 2019)	
		Potential biomarkers in cancer		CYP2E1	CYP2E1 activity decreases during hepatocarcinogenesis, the specific mechanism remains unknown.	(Ho et al., 2004)
				CYP11A1	The loss of CYP11A1 contributes to abnormal steroid synthesis.	(Fan et al., 2016)

		Decreased inactivation of carcinogens	CYP26A1	CYP26A1 participates in the inactivation of retinoic acid which may promote HCC progression.	(Brodeur et al., 2019)
			NAT1, NAT2	They are responsible for the biotransformation of most arylamine and hydrazine substrates.	(Yu et al., 2000; Hu et al., 2019)
			UGT1A1, UGT1A4, UGT1A9, UGT2B7	These UGTs detoxify endogenous and environmental carcinogens through glucuronidation reaction.	(Lu et al., 2015; Yan et al., 2015b)
			GSTP1	GSTP1 is a detoxifying enzyme that protects cells from various stimuli like hypoxia and oxidative stress.	(Tchou et al., 2000; Li et al., 2018)
Lung cancer	Upregulation	Catabolism of anti-proliferation compound	CYP24A1	CYP24A1 catabolizes the antiproliferation compound 1, 25-D3.	(Chen et al., 2011b)

	Increased activation of procarcinogens	CYP1A1, CYP1B1	They catalyze the activation of carcinogens related to tobacco use like NNK and PAHs.	(Li et al., 2015b; Zhang et al., 2019)	
		CYP19A1	CYP19A1 is an estrogen synthesis enzyme that can promote the steroidal growth-stimulatory pathway.	(Weinberg et al., 2005)	
	Downregulation	Potential biomarkers in cancer	ADH1B	ADH1B is indispensable in the metabolism of fatty acids, retinoid, ethanol which are associated with lung cancer.	(Mutka et al., 2012)
			CYP3A7, CYP4B1	The specific role is not clear.	(Leclerc et al., 2011)
			CYP11A1	The loss of CYP11A1 contributes to abnormal steroid synthesis.	(Fan et al., 2016)
	Decreased inactivation of carcinogens	GST-M2	GST-M2 is a detoxifying enzyme that can protect lung cells from DNA damage.	(Tang et al., 2011)	

Prostate cancer	Upregulation	Increased activation of procarcinogens	CYP1A1	CYP1A1 mediates the metabolic activation of pro-carcinogens PAHs.	(Mitsui et al., 2016)
		Elimination of anti-cancer drugs	CYP1B1	CYP1B1 metabolizes estradiol to carcinogen 4-hydroxy estradiol and is related to the resistance to docetaxel.	(Pastina et al., 2010)
		Potential biomarkers in cancer	UGT2B17	UGT2B17 is responsible for the elimination of the inactive metabolites androstane- α -diol and androsterone. It's also associated with metastasis.	(Pâquet et al., 2012; Levesque et al., 2020)
	Downregulation	Decreased inactivation of carcinogens	CYP3A4, CYP2B6	They are key inactivators of testosterone which are significantly related to the development of prostate cancer.	(Kumagai et al., 2007; Fujimura et al., 2009)
			GSTP1	The loss of GSTP1 leads to an increase of intracellular ROS and DNA damage, promotes the occurrence of cancer.	(Hokaiwado et al., 2008; Kanwal et al., 2014)

			UGT2B15	UGT2B15 is a negatively regulated target gene in CRPC, inactivating the active androgen dihydrotestosterone in prostate cells.	(Pâquet et al., 2012)
		Potential biomarkers in cancer	CYP11A1	The loss of CYP11A1 contributes to abnormal steroid synthesis.	(Fan et al., 2016)
Breast cancer	Upregulation	Increased activation of procarcinogens	CYP1B1	CYP1B1 metabolizes estradiol to carcinogen 4-hydroxy estradiol, resulting in DNA adducts.	(Gajjar et al., 2012)
		Promote tumor growth	CYP4Z1	CYP4Z1 is a fatty acid hydroxylase that promotes angiogenesis and the development of breast cancer.	(Yu et al., 2012)
	Downregulation	Decreased inactivation of carcinogens	GSTP1	GSTP1 detoxifies carcinogens and cytotoxic drugs.	(Schnekenburger et al., 2014)
Kidney cancer	Downregulation	Potential impact on drug efficacy and toxicity	UGT1A9, UGT2B7	UGT1A9 and UGT2B7 are responsible for the clearance of drugs such as propofol and sorafenib in the kidney.	(Margaillan et al., 2015)

Esophageal cancer	Upregulation	Promote tumor growth	CYP2C9	CYP2C9 promotes the proliferation of early esophageal cancer.	(Schmelzle et al., 2011)
Ovarian cancer	Upregulation	Increased activation of procarcinogens	CYP1B1	CYP1B1 metabolizes estradiol to carcinogen 4-hydroxy estradiol.	(Gajjar et al., 2012)
		Elimination of anti-cancer drugs	GSTP1	GSTP1 is closely related to the chemoresistance of platinum drugs.	(Sawers et al., 2014)
Colorectal cancer	Upregulation	Increased activation of procarcinogens	CYP1A1	CYP1A1 participates in the metabolic activation of PAHs in tobacco and increases the risk of colorectal cancer.	(Slattery et al., 2004)
			CYP2E1	CYP2E1 is involved in the metabolic activation of potent carcinogens azoxymethane and methylazoxymethanol.	(Sohn et al., 2001)
Bladder cancer	Upregulation	Increased activation of procarcinogens	CYP4B1	CYP4B1 metabolic activates the carcinogen 2-aminofluorene.	(Imaoka et al., 2000)

	Downregulation	Potential biomarkers in cancer	CYP1A1, CYP1B1	Metabolomic profiling revealed their deficiency in bladder cancer, with specific mechanism remains unknown.	(Putluri et al., 2011)
Hematologic malignancy	Upregulation	Increased activation of procarcinogens	CYP2J2	CYP2J2 converts arachidonic acid to carcinogen epoxyeicosatrienoic acids and promotes cancer growth.	(Chen et al., 2011a)

