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REVIEW

Epigenetic regulation of drug metabolism and transport

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Abstract The drug metabolism is a biochemical process on modification of pharmaceutical substances through specialized enzymatic systems. Changes in the expression of drug-metabolizing enzyme genes can affect drug metabolism. Recently, epigenetic regulation of drug-metabolizing enzyme genes has emerged as an important mechanism. Epigenetic regulation refers to heritable factors of genomic modifications that do not involve changes in DNA sequence. Examples of such modifications include DNA methylation, histone modifications, and non-coding RNAs. This review examines the widespread effect of epigenetic regulations on genes involved in drug metabolism, and also suggests a network perspective of epigenetic regulation. The epigenetic mechanisms have important clinical implications and may provide insights into effective drug development and improve safety of drug therapy.

Abbreviations: CAR, constitutive androstane receptor; DNMTs, DNA methyltransferases; H3K4me1, histone 3 lysine 4 monomethylation; H3K4me2, histone 3 lysine 4 dimethylation; H3K4me3, histone 3 lysine 4 trimethylation; H3K9me2, histone 3 lysine 9 dimethylation; H3K9me3, histone 3 lysine 9 trimethylation; H3K27me3, histone 3 lysine 27 trimethylation; H3K36me3, histone 3 lysine 36 trimethylation; HATs, histone acetyltransferases; HDAC, histone deacetylases; lncRNAs, long non-coding RNAs; miRNAs, microRNAs; ncRNAs, non-coding RNAs; P450s, cytochrome P450s; SULTs, sulfotransferases; TSS, transcription start sites; UGTs, UDP-glucuronosyltransferases; UTR, untranslated region

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1. Introduction

Drug metabolism is the biotransformation process of pharmaceutical substances or xenobiotics, usually conducted by specialized enzymatic systems. Drug metabolism is divided into three phases. Phase-I contains the modification reactions of oxidation, reduction, and hydrolysis. Typical examples of phase-I enzymes include cytochrome P450s (P450s), flavin monooxygenases (FMOs), alcohol dehydrogenases (ADHs), aldehyde dehydrogenases (ALDHs), cytochrome P450 oxidoreductase (POR), aldo-keto reductase (AKR), quinone oxidoreductase (NQO), dihydropyrimidine dehydrogenase (DPYD), carboxylesterase (CES), paraoxonase (PON), and epoxide hydrolase (EPHX). Phase-II consists of conjugation reactions usually catalyzed by transferase enzymes, such as UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), glutathione S-transferases (GSTs), N-acetyltransferases (NATs), thiopurine methyltransferase (TPMT), catechol-O-methyl transferase (COMT). Phase-III is the uptake and excretion process of drugs and their metabolites through transporters. In a coordinated fashion to transport endogenous and exogenous substances into and out of cells, transporters can be divided into two groups: uptake and efflux transporters. Major drug transporters include solute carrier transporters (SLCs) and ATP-binding cassette transporters (ABCs). The function of enzymes and transporters involved in the three phases determines the duration and intensity of a drug's effect.

Factors influencing the expression and function of drug-metabolizing enzymes and transporters are critical to the metabolic process and therapeutic outcome of a drug. It is well known that genetic variations of enzymes and transporters can lead to altered drug response. Many genetic polymorphisms in genes encoding drug-metabolizing enzymes and transporters have been identified[1,2], which can be translated into clinical differences. However, the large interindividual variations in drug response can only be partly explained by genetic factors. For most cases, only 10%–30% of phenotype variations can be explained by genetic polymorphisms in genes encoding drug-metabolizing enzymes and transporters[3]. The genetic information can be differentially expressed in one individual over time and space, and even monozygotic twins do not always show the same phenotype, so epigenetic factors are now considered as an important part of the molecular control for gene expression[4]. In this review, the general concept of epigenetics will be briefly introduced, and its regulation on genes encoding proteins involved in drug metabolism and transport will be overviewed. We will also examine the epigenetic mechanisms as a regulatory network and discuss the implications of epigenetic research on pharmacotherapy.

2. Property of epigenetics

Epigenetics studies heritable changes in gene expression that are not caused by alterations in DNA sequences. Epigenetic regulation leads to relatively stable changes that are potentially affected by many other factors, such as age, diet, life style, disease and environment. Several mechanisms of epigenetic regulation have been extensively studied, including DNA methylation, histone modifications, and non-coding RNAs, each of which can change gene expression without altering the underlying DNA sequences.

2.1. DNA methylation

DNA methylation usually refers to the addition of a methyl group to the cytosine pyrimidine ring at the 5 position in a CpG dinucleotide context. Status of DNA methylation on a CpG site is maintained by DNA methyltransferases (DNMTs) and demethylases and can be inherited through cell divisions. DNA methylation is necessary for proper gene regulation, chromosomal stability, and parental imprinting[5]. It plays an important role in long-term silencing of transcription and in heterochromatin formation. One way DNA methylation can silence transcription is that it directly alters chromatin structure and prohibits the binding of transcription factors or co-activators to their targeted sites containing this modification, and therefore decreases the gene expression. DNA methylation may also recruit methyl binding proteins (MBPs) that interact with co-repressors and lead to an inactive chromatin status[6,7].

2.2. Histone modifications

Histone proteins in the nucleosome, surrounded by 146 bp DNA, play a dominant role in the regulation of gene expression. Several covalent modifications on the N-termini of histone proteins have been discovered, many of which contain distinct regulatory functions and are transmissible through cell divisions[8]. Histone modifications can be divided into those that correlate with activation or repression of gene expression. Histone H3 acetylation is an important epigenetic modification regarding the ability for genes to be transcribed. Acetylation has the most potential to unfold chromatin, because it neutralizes the basic charge of the lysine residual and loosens the interaction between histone and DNA. Acetylation is generally associated with activation of transcription. Several histone acetyltransferases (HATs) have been identified as transcription co-activators. In contrast, histone deacetylation is generally associated with repression of transcription. Histone deacetylases (HDACs) have been identified as transcriptional co-repressors[9].

Methylation of histone by methyltransferases can lead to different effects on gene transcription, depending on which residual is methylated and the level of methylation (mono-, di-, tri-methylation) occurs[10]. By analyzing the chromatin landmark and transcription initiation at most promoters in human ES cells, three classes of genes with various histone methylations have been identified[11]. The majority of actively transcribed genes have H3K4me2/3-modified nucleosomes around the transcription start sites (TSS), and H3K36me3 along the gene-coding regions after TSSs. Certain genes do not have H3K4me2/3-modified nucleosomes around their TSS; some of them are enriched with H3K27me3 along the genes. A ChIP-on-chip study demonstrates that H3K27me3 forms broad local enrichments over silent genes and intergenic regions on gene-rich regions on mouse chromosomes[12]. Vast data have confirmed that H3K4me3 and H3K4me2 are related to initiation of gene transcription, H3K36me3 is correlated to elongation of gene transcription, whereas H3K27me3 is associated with suppression of gene transcription[10,13–18]. Although both H3K4me3 and H3K4me2 are associated with activation of transcription initiation, H3K4me3 is enriched more frequently around TSSs of genes, whereas H3K4me2 is found in a broader range of promoters, enhancers, and long-range regulatory elements. H3K4me2 sites also have a higher degree than H3K4me3 to associate with tissue-specific gene regulation[13]. Interestingly, the co-occurrence between histone acetylation of H3K9/H3K14 and methylation of H3K4 is very high for actively transcribed genes[13,19]. One of the reasons may be that the complex of general transcription factors is selectively