Review

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Epigenetic mechanisms of importance for drug treatment

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There are pronounced interindividual variations in drug metabolism, drug responses, and the incidence of adverse drug reactions. To a certain extent such variability can be explained by genetic factors, but epigenetic modifications, which are relatively scarcely described so far, also contribute. It is known that a novel class of drugs termed epidrugs intervene in the epigenetic control of gene expression, and many of these are now in clinical trials for disease treatment. In addition, disease prognosis and drug treatment success can be monitored using epigenetic biomarkers. Here we review these novel aspects in pharmacology and address intriguing future opportunities for gene-specific epigenetic editing.

Pharmacoepigenetics

During the last decade much information has accumulated regarding the genetic causes of differences in drug responses. This has led to the identification of many pharmacogenomic biomarkers important for individualized drug therapy, particularly in cancer treatment, that are currently in clinical use. Such biomarkers help to avoid severe complications of drug treatment, which are estimated to cost billions of dollars and cause 100,000 deaths in the USA annually. However, only 20–30% of the interindividual variations important for adverse drug reactions (ADRs) or drug efficacy can be explained by genetic factors [1–3]. Additional factors for such variability include drug–drug interactions and endocrine, environmental, and pathophysiological causes. Epigenetic control of the expression of genes encoding drug absorption, distribution, metabolism, and excretion (ADME) proteins, as well as drug target proteins, has been emphasized in recent years. Much has still to be learned about the extent and mechanisms by which epigenetic modification of gene expression contributes to short- or long-term variability in drug action. In certain cases, epigenetic modifications resulting from disease progression or drug treatment can be monitored not only in the affected tissue, but also in body fluids [4]. Such circulating DNA elements constitute a novel class of pharmacoepigenetic biomarkers amenable for use to improve and individualize drug therapy.

Drugs that interfere with the epigenetic control of gene expression are now being developed, and the potential of these so-called epidrugs (see Glossary) in the chemotherapy of cancer has already been demonstrated [5]. Apart from epidrugs, other xenobiotics may also possess epigenetic activity. For example, it was demonstrated that exposure of mice to certain drugs or drug receptor ligands during fetal life can trigger epigenetic modifications of specific genes, causing altered ADME gene expression in adult mice [6,7]. In addition, a new therapeutic concept is being developed based on the ability of transcription factors and long noncoding RNAs (lncRNAs) to target epigenetic proteins including enzymes to specific loci in the genome.

The aim of this review is to introduce readers to the novel and exciting field of pharmacoepigenetics. After a brief description of the major epigenetic mechanisms, the most recent data relevant to epigenetic regulation of ADME genes, epigenetic biomarkers of drug response, and the biological effects of epidrugs are summarized. The concept of epigenetic editing, which opens an intriguing possibility to interrogate disease-specific epigenetic signatures, is also briefly discussed.

Glossary

Bromodomains: protein domains responsible for recognition of acetylated lysine residues in histones, thus mediating the effect of histone acetylation on gene transcription.
DNA hydroxymethylation: modification of 5-methylcytosine by oxidation of the methyl group (-CH_3) to a hydroxymethyl group (-CH_2-OH), yielding 5-hydroxymethylcytosine (5hmC).
DNA methylation (DNAme): modification of cytosine residues in DNA by addition of a methyl group (-CH_3) to the fifth position of a cytosine base, yielding 5-methylcytosine (5mC).
Epidrugs: drugs that inhibit or activate disease-associated epigenetic proteins with the aim of ameliorating, curing, or preventing the disease.
Epigenetic editing: intentional overwriting of epigenetic signatures by artificial targeting of epigenetic enzymes to specific loci.
Epigenetic enzymes: epigenetic proteins belonging to the writer and eraser groups.
Epigenetic proteins: proteins that can either covalently modify DNA or histones, thus yielding epigenetic signatures (writers); or remove such epigenetic modifications (erasers); or recognize and bind to modified chromatin, thus mediating the effect of epigenetic signatures on gene transcription (readers).
Epigenetics: changes in gene function that can be inherited via cellular divisions and cannot be explained by any change in the primary sequence of nucleic acids.
Histone modification: post-translational modification of N terminus of histones (histone tail) that protrudes from the core nucleosome.
Histone-modifying enzymes: epigenetic enzymes responsible either for post-translational modification of histones or for removal of such modifications.

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Basics of epigenetics

The current definition of epigenetics is changes in gene function that can be inherited via cellular divisions and cannot be explained by any change in the primary sequence of nucleic acids. In contrast to germline genetic variants, which are inherited from progenitors and are stable across lifespan, epigenetic signatures can be generated in response to various external or internal stimuli. Moreover, epigenetic regulation constitutes a means whereby an organism can 'remember' the altered gene expression pattern resulting from a stimulus (to be prepared for any eventual reoccurrence of a similar condition). To date, the conventional epigenetic mechanisms identified in mammals include DNA methylation (DNAme) and hydroxymethylation, as well as various histone modifications.

DNA methylation

The majority of CpG sites throughout the genome are fully methylated, whereas not more than 15% of them are hypomethylated and thus may be subject to variable DNAme [8]. Hypomethylated CpG sites are usually associated with CpG islands (CGIs) and their flanking regions (CGI shores). It has become evident that variable DNAme is more frequently observed at CGI shores and single CpG sites than in CGIs [9].

DNAme is known to be involved into the regulation of gene expression. Hypomethylated genomic elements are often associated with bound transcription factors (TFs), and this cytosine modification either inhibits (e.g., CREB, E2F, CTCF, Sp1, AhR) or promotes (e.g., C/EBPα) TF binding [10–12]. In addition, DNAme also regulates transcription via recruitment of methyl-CpG-binding proteins such as MBD1, MBD2, MBD4, and MeCP2 [13]. These proteins can in turn recruit additional factors such as the nucleosome remodeling deacetylase (NuRD) complex, which possesses ATP-dependent chromatin remodeling activity and contains histone deacetylases HDAC1 and HDAC2, thereby causing transcriptionally silenced chromatin (Figure 1A).

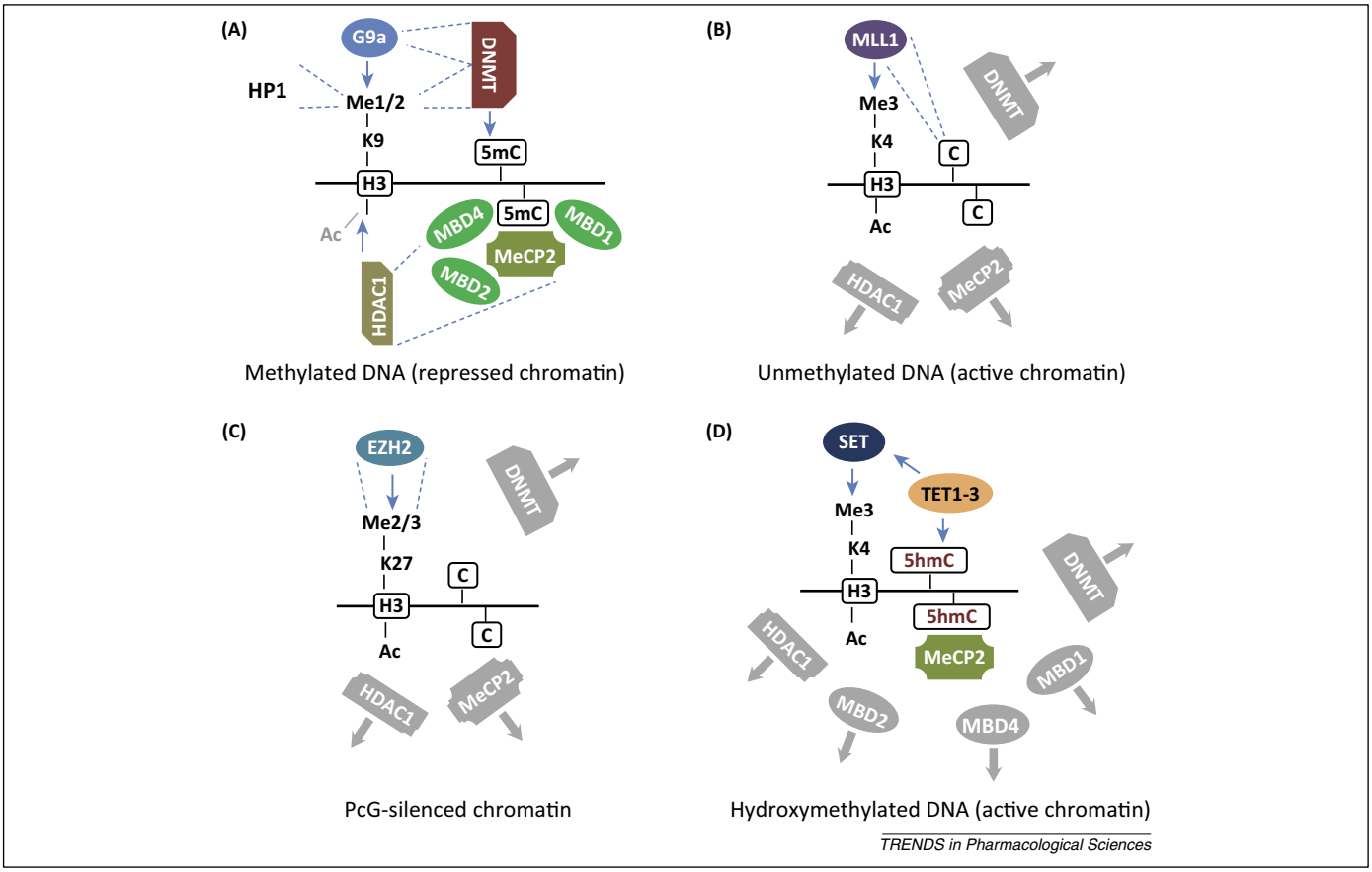

Figure 1. Crosswise interactions between epigenetic proteins and epigenetic signatures. Four major epigenetic states of chromatin are represented. **(A)** Methylated DNA (repressed chromatin). Methylated CpG sites (5-methylcytosine, 5mC) are usually present together with histone H3, which is mono- or dimethylated at Lys9 (H3K9me1/2). This co-occurrence is caused by physical interactions between DNA methyltransferases DNMT3A/B and the histone methyltransferase G9a. In addition, DNA methylation is accompanied by a hypoacetylated state of histone H3 because methyl-CpG-binding proteins (MeCP2, MBD1, MBD2, MBD4) are able to recruit histone deacetylases HDAC1 and HDAC2. Thus, 5mC, methylated H3K9, and deacetylated H3 together represent a repressive epigenetic signature. **(B)** Unmethylated DNA (active chromatin). Trimethylated histone H3 (H3K4me3) is found together with unmodified cytosine because of the binding of H3K4 methyltransferase MLL1 to unmethylated DNA and the preference of DNMT3A for unmodified H3K4. Methyl-CpG-binding proteins do not recognize unmethylated DNA and thus do not recruit histone deacetylases to H3K4me3-containing loci. Histone acetylation promotes active gene transcription. Taken together, unmethylated DNA, methylated H3K4, and acetylated H3 represent an activating epigenetic signature. **(C)** PcG-silenced chromatin. Di- and trimethylation of histone H3 at Lys27 (H3K27me2/3) is catalyzed by histone methyltransferase EZH2, which is a part of polycomb repressive complex 2 (PRC2; other components not shown). Inheritance of PcG silencing does not seem to depend on DNA methylation, but is rather achieved through self-recruitment of PRC2 to H3K27me2/3-containing loci. **(D)** Hydroxymethylated DNA (active chromatin). TET enzymes (TET1, TET2, TET3) oxidize 5mC to 5-hydroxymethylcytosine (5hmC). 5hmC can interact with MeCP2, but not with other methyl-CpG-binding proteins (MBD1, MBD2, MBD4), which thus determines the lack of HDAC1 recruitment and the acetylated state of histone H3. In addition, TET2 and TET3 proteins can activate histone methyltransferase SET1 and thus promote trimethylation of histone H3 at Lys4 (H3K4me3). These histone modifications determine transcriptionally active chromatin.

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