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The past, present and future of pharmacoepigenomics

A significant number of instances of interindividual variability in drug response, where a clear phenotypic consequence is evident in the population, have not yet been associated with variations in gene sequence. Epigenetics, along with, for example, drug interactions and disease, provides answers to some of these inconsistencies. The role of epigenetics in drug response has just started to be perceived, but its impending influence on drug metabolism and disposition promises to be important. Research in this area can provide us with novel mechanisms for this variation and also with novel biomarkers that can be useful for understanding drug response, as well as for the development of new drugs and which can, in addition, constitute predictive biomarkers for today's and tomorrow's pharmacotherapy, yielding a substantial improvement in human health.

KEYWORDS: adverse drug reactions ■ cytochrome P450 ■ drug response ■ epigenetics ■ genomics

Past

The major focus in the area of pharmaco-genomics from 2000 was to elucidate the most important polymorphic alleles and their functional consequences, partly as a consequence of the completion of the human genome sequence. Since the impact of genetic polymorphisms on drug response and efficacy was not fully known, there was no major initiative to elucidate epigenetic factors for the interindividual differences in, for example, the activity and function of drug-metabolizing enzymes and transporters. In 2000, knowledge of pharmacoepigenomics was very limited. Methylation changes in the *CYP2E1* gene in relation to birth provided an initial study from 1990. In 2004, developmental regulation of the murine *Cyp1a2* was also shown to involve methylation changes at its promoter [1]. The sex-specific expression of murine *Cyp2d9* was likewise shown to be comprised of methylation changes that were found to influence transcriptional activation [2]. During this decade the area slowly developed, and one important study revealed regulation of *CYP1A1* gene promoter methylation in response to tobacco consumption [3]. Also, initial experiments using the histone deacetylase inhibitor trichostatin and the DNA methyltransferase inhibitor 5-aza-2'-deoxycytidine revealed histone and DNA methylation processes of importance for dioxin inducible CYP1A in HeLa and MCF-7 cells [4].

Present

The steps towards some understanding of the epigenetic aspects of drug metabolism, transport and action have been discussed in our earlier review reports [5–7]. It is evident that, at present, the major genetic variants causing variable phase I and phase II dependent drug metabolism might have been identified. Despite this, there are unresolved issues regarding inter-individual differences in the metabolism of and response to several drugs, and the interindividual differences, for example, in CYP1A2 and CYP3A4 activities have not yet been elucidated. In a recent study, sex and polymorphisms in *FoxA2*, *HNF4α*, *FoxA3*, *PXR*, *ABCB1* and the *CYP3A4* promoter together explained 24.6% of the variation in hepatic CYP3A4 expression [8], leaving room for epigenetic mechanisms. A role for histone methylation in the control of murine *Cyp3a* expression has been shown in an elegant study, whereby specific histone methylation and acetylation is involved in *Cyp3a16* in the fetus switching to *Cyp3a11* in the adult mice, demonstrating the involvement of altered modifications of histone H3 [9]. Thus, DNA methylation and the numerous combinations of post-translational modifications of the histone proteins, which package the chromatin, are now implicated in influencing the expression of genes whose products are engaged in drug metabolism. In addition, the increasing

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importance of noncoding RNAs, particularly the short regulatory miRNAs, has to be emphasized and we have now seen initial studies showing their involvement in regulating the expression of drug-metabolizing genes [10,11]. Of particular interest is the regulation of the important transcription factor PXR by miR-148a, which indirectly causes an influence on CYP3A4 expression [12]. Furthermore, protein arginine methyltransferase 1 (PRMT1) has been shown to be recruited to the xenobiotic-responsive enhancer module element and to be important for the concomitant methylation of arginine 3 of histone H4, in response to the PXR agonist rifampicin [13]. Regarding drug transporters, it is evident that the ontogeny and tissue-specific expression is, to a great extent, regulated by promoter methylation [14], and that the microRNAs miR-27a and miR-451 cause overexpression of P-glycoprotein in the multidrug resistant cell lines A2780DX5 and KB-V1 [15].

Chemical entities that impinge on the epigenetic landscape, epigenetic drugs or 'epidrugs', are also gaining importance and are finding their way to the bedside [6]. Although a few of these have demonstrated efficacy against diseases, the issue of nonspecificity owing to their global effect could present unwanted consequences and could even be thought to aggravate a disorder instead of preventing it.

Future

Indeed, the area of pharmacoeugenomics has a promising future. For example, an attractive phase of epigenetics that would really be of great benefit to further understanding interindividual variation in drug response is its plasticity. Although being confronted with various environmental attacks that occasionally lead to mutations, the genetic sequence is fairly stable and incapable of responding to a rapidly changing environment. On the other hand, the epigenome has the ability to react and perform the necessary actions expected, which are anticipated to be rather immediate. Though shown to respond to environmental cues, the epigenetic message has the capacity to be passed down to daughter cells and to succeeding generations and, hence, illustrates stability [16]. While the mechanisms for such inheritance are still unclear, this has tremendous implications on the health of offspring, even in future generations. These findings could infer consequences on drug response in following generations. An important area of

research would be the epigenetic component of drug resistance and the influence of the environment on epigenetically based alterations in drug pharmacokinetics and response.

Other research themes that relate to epigenetics have not been fully introduced or established in drug-metabolism research. Transcription across the genome, for example, has recently been found to be widespread and many of these transcripts do not encode proteins [17]. The functions of these short and long nonprotein-coding RNAs are still unknown; however, it is predicted, especially for those transcribed from retrotransposed sequences, that they may play important roles in the epigenetic regulation of gene expression. The role that miRNAs carry out exemplifies this very idea and it is likely that other noncoding RNAs have similar functions as finetuners in gene regulation. This complex picture has been illustrated in cell pluripotency and differentiation [18,19]. Apparently this area is only just being considered as part of drug metabolism and action; it is likely that the issues revealed will be of great importance for the understanding of interindividual differences in drug response.

Developments in epigenetics will not be overlooked by pharmacogeneticists. Advancement in technologies that examine the epigenome, as well as those that can scrutinize specific loci, will be considered indispensable in evaluating the role of epigenetics in drug response. This will also provide the means to assess the efficacy of epigenetic drugs and investigate in great detail the impact of the environment on the epigenome in particular, and on health, in general. The implications of all of these developments to our understanding of interindividual differences in drug metabolism and action will be important. From a clinical point of view it is anticipated that a large fraction of the unknown bases for these interindividual differences can be inherent in genomic variability influencing the epigenetic factors of regulation and also in genetic polymorphisms in loci being subject to epigenetic variation. The identification of the novel molecules and genomic areas of importance can provide us with an arsenal of novel biomarkers that can be used for understanding drug response, but that are also important for the development of new drugs, as well as constituting predictive biomarkers for today's and tomorrow's pharmacotherapy, overall yielding a substantial improvement in human health.

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