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13

Beyond Pharmacogenetics

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1. Introduction

It has been observed that similar medication is subject to a considerable efficacy heterogeneity and toxicity across the human population and numerous studies, over the last 30 years, have indicated that individual genetic make-up might well be the major determinants of this variability in drug action (Nebert et al., 2008).

The intellectual foundation of the hypothesis that variation among individuals in drug response might be due to subtle genetic differences with little or no obvious phenotypes, except in response to the relevant drug, was first articulated by Arno Motulsky (Motulsky, 1957). Although the notion that certain individuals inherited a predisposition, such as to alcaptonuria or other conditions, may most likely be attributed to the British physician Archibald Garrod (Garrod, 1975). Garrod observed that parental consanguinity was more common than usual among parents of children with alcaptonuria and, with particular foresight, he developed the concept of "Chemical Individuality in Man". He proposed that drugs undergo biotransformation by specific pathways similarly to endogenous substrates and defects in such pathways, that occur with inborn metabolic errors, that could alter drug concentrations and, therefore, their effects (Meyer, 2004). It was then William Bateson (Meyer, 2004), a biologist ahead of his time, who interpreted Garrod's reports as a recessive inheritance when he popularized Mendelian genetics in Britain. Bateson discovered genetic linkage and introduced the term "genetics" at some time between 1902 and 1913.

The concept of familial clustering of unusual xenobiotic responses was reinforced during the 1940s, when a high incidence of haemolysis was observed among individuals with glucose-6-phosphate dehydrogenase deficiency when exposed to antimalarial drugs (Beutler et al., 1955a, 1955b). In the 50s, Evans et al. identified N-acetylation as a major route of isoniazid elimination (Evans et al., 1960). Although individuals varied substantially in terms of the extent to which a single dose of the drug was acetylated, less variability was observed between monozygotic twins than dizygotic twins (Roden & George Jr, 2002). This observation led to further studies that defined the clinical consequences and genetic basis underlying the fast and slow acetylator phenotypes. Shortly thereafter, Friedrich Vogel first coined the term "Pharmacogenetics", defining it as the "study of the role of genetics in drug response" (Nebert et al., 2008). More generally, the late 20th century witnessed developments in the understanding of the molecular basis of drug disposition, action and the mechanisms that determine the observed variability in drug action.

Along with the increased understanding of the molecular, cellular and genetic determinants of drug action, has come the appreciation that variants in many genes might contribute to variability in drug action.

Single Nucleotide Polymorphisms (SNPs) have been long recognized as the main source of genetic and phenotypic human variation and numerous recent studies have tried to demonstrate that SNPs make a major genetic contribution to the variability in drug effects (Evans & McLeod, 2003; Gardiner & Begg, 2006). However, the complete mapping of all human genes, arrived through the Human Genome Project, along with the advent of more powerful molecular technologies and other studies showing a poor correlation between SNPs in candidate genes and phenotypes, modifying this perception (Nebert & Vesell, 2004). Therefore, this chapter focuses on the development of Pharmacogenetics from SNPs to the new area of Genomics, or Pharmacogenomics, in an attempt to better understand and predict variations in drug response phenotypes.

2. From pharmacogenetics to pharmacogenomics

An SNP is a DNA sequence variation which occurs when a single nucleotide (A, T, C, or G) in the genome, or other shared sequences, differs between members of a biological species, or paired chromosomes in an individual. For example, a SNP might change the DNA sequence A**A**GGCTAA to A**T**GGCTAA (Fig.1).

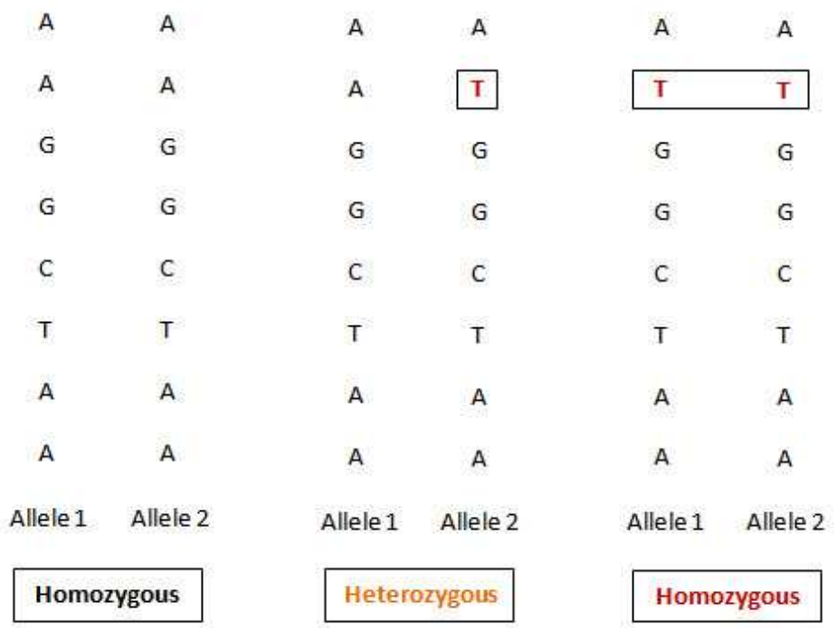


Fig. 1. Single Nucleotide Polymorphism

For a variation to be considered a SNP, it must occur in at least 1% of the population. Single Nucleotide Polymorphisms, representing about 90% of all human genetic variations, occur every 100 to 300 bases along the 3-billion-base human genome. Consequently, it has been estimated that there are at least 10 million SNPs within the human population (Kruglyak & Nickerson, 2001). They can be in coding regions (where they may be either synonymous, or

non-synonymous) or, more commonly, in non-coding regions and frequently vary according to ethnicity (Sachidanandam et al., 2001). It is in these heritable variations among individuals that the principles of Pharmacogenetics are found. However, other types of genetic variations, such as small insertions (usually <1 kb), deletions, inversions, variable numbers of tandem repeats (minisatellite), short tandem repeats (microsatellite), copy number variations (Nakamura, 2009) and combinations of these changes, can also contribute to variability in drug response, even if to a less extent than do SNPs. Therefore, the selection of a non-synonymous SNPs, or other genetic variations in coding regions, in hypothesis driven pharmacogenetic association studies, is based on their functionality, where the genetic variant leads to, or is predicted to lead to, alterations in protein function and hence drug response variability.

There are at least four examples where this approach has been correlated with significant changes in drug effects (Evans & McLeod, 2003; Gardiner & Begg, 2006). One of the best examples of SNPs relating to the outcome of therapy is the polymorphism of the gene thiopurine S-methyltransferase (*TPMT*) (Yates et al., 1997). Thiopurine S-methyltransferase is a cytosolic drug-metabolizing enzyme that catalyzes the S-methylation of 6-mercaptopurine (6-MP) and azathioprine. Weinshilboum et al. demonstrated a very clear tri-modal frequency of TPMT activity in red blood cells from 298 unrelated control adults (Weinshilboum & Sladek, 1980). One in 300 subjects lacked TPMT activity and 11% had intermediate levels. Family studies have demonstrated that the frequency distribution is due to inheritance (Weinshilboum & Sladek, 1980). While phenotypic studies have shown a clear tri-modal distribution, the genetic basis of phenotypic variation is a more complex question (Evans & Krynetsky, 2003).

To date, about seventeen variant *TPMT* alleles have been identified, although 3 variant alleles account for the majority (>95%) of persons with intermediate (1 variant allele), or low (2 variant alleles) TPMT activity (Krynetski et al., 1995; Yates et al., 1997). Subsequent clinical studies demonstrated that *TPMT* polymorphism is able to predict 6-MP toxicity and consequences of therapy (Lennard et al., 1990; Relling et al., 1999).

Another good example of SNPs influencing therapeutic efficacy is the polymorphism of genes belonging to the superfamily of cytochrome P450 enzymes (CYP450) (Wilkinson, 2005). *CYP2D6* polymorphism is clinically important mainly due to the greater likelihood of adverse reactions (ADRs) amongst individuals, because they can be associated with poor metabolism of certain drugs, resulting in high plasma concentrations and increased likelihood of ADRs. For example, patients carrying some of the *CYP2D6* variants identified (http://www.imm.ki.se/cypalleles), have a greater risk of adverse effects from metoprolol, venlafaxine and tricyclic antidepressants, or have impaired ability to metabolically activate prodrugs like codeine and the selective oestrogen receptor modulator (SERM), tamoxifen, to form active drug metabolites (Bertilsson et al., 2002; Jin et al., 2005; Lessard et al., 1999; Mortimer et al., 1990; Sindrup & Brøsen, 1995; Stearns et al., 2003; Wuttke et al., 2002).

CYP2C19 is important in the metabolism of proton-pump inhibitors (omeprazole, lansoprazole, rabeprazole and pantoprazole), fluoxetine, sertaline and nelfinavir. Although there are several inactive genetic variants, two (*CYP2C19**2 and *CYP2C19**3) account for more than 95% of cases of poor metabolism of these drugs (Wedlund, 2000). Marked differences in the plasma levels of protein-pump inhibitors occur between genotypes and phenotypes and are reflected in drug-induced changes in gastric pH (Furuta et al., 1999).

CYP2C9 is an enzyme involved in the hydroxylation of the S form of the anti-epileptic agent phenytoin and the anticoagulant warfarin. Many *CYP2C9* variant alleles have now been reported (http://www.imm.ki.se/cypalleles) and decreased activity has been confirmed in cases with *CYP2C9*3*, by an expression system using COS cells and yeast and an *in vivo* test on healthy volunteers and patients with a known genetic polymorphism (Takahashi et al., 1998b, 2000).

Indeed, there was a 50% decrease in oral clearance capacity of (S)-warfarin in individuals with heterozygous polymorphism for *CYP2C9*3* (*CYP2C9*1/*3*), dropping to less than 10% in homozygous individuals for *CYP2C9*3* (Takahashi et al., 1998a).

These successful pharmacogenetic studies, together with the glucuronidation of an anticancer drug, irinotecan, by a member of the UDP-glucuronosyltransferase (UGT) enzyme family (Gagné et al., 2002), showing gene-drug interactions, represented a predominantly monogenic, high-penetrance trait where the functional consequence of a major gene was recognized. However, these associations were not replicated by other investigators (Hu & Ziv, 2008) and might lead to false-positive findings (Serpe et al., 2009). Indeed, even with the very strong single-gene high-penetrance disorder *TPMT*, a study correlating thiopurine related ADRs with *TPMT* genotype, noted that 78% of ADRs were not associated with *TPMT* gene polymorphism and were attributable to factors other than this drug-metabolizing enzyme (van Aken et al., 2003).

Although the presence of non-synonymous SNPs in a candidate gene may be suspected to cause variance in drug response, this cannot account for all SNPs able to cause drug response variance or susceptibility in drug response variance. Other functional SNPs implicated in variance in drug response or susceptibility variance in drug response include SNPs located in promoter, introns, splice sites and intragenic regions. Furthermore, it has been postulated that even synonymous or silent SNPs are implicated in functional consequence via hypothesized mechanisms (Kimchi-Sarfaty et al., 2007).

A more comprehensive approach is the genome-wide method (GWA) using SNP arrays (Grant & Hakonarson, 2008). With this strategy we move from studies involving the effects of single genes on drug disposition and response, to studies where the effects of several genes up to whole genome are investigated. In other words we move from Pharmacogenetics to Pharmacogenomics.

A clear advantage of this method is that it is hypothesis-free and that this may reveal unexpected SNPs related to drug response. Hence this method does not rely on current knowledge of the metabolism and mechanism of action to drug response. Recent genome-wide association studies have presented novel associations between SNPs and drug response. Studies on drug response have detected significant genome-wide associations for interferon-α, clopidogrel response and anticoagulant dose requirement (Cooper et al., 2008; Shuldiner et al., 2009; Takeuchi et al., 2009; Tanaka et al., 2009; Teichert et al., 2009). As to ADRs, significant associations have been reported for statin-induced myopathy and flucloxacillin induced liver injury (Daly et al., 2009; Link et al., 2008). Most of these studies reported novel findings and made important contributions to the field, some even with the potential to influence clinical practice.

Since it has been estimated that the human genome contains more than 10 million SNPs, comprehensive genome-wide SNP pharmacogenomic association studies would require too

many SNPs. Various strategies may be adopted to overcome these challenges: one could be to improve high-throughput sequencing technologies capable of sequencing a full human genome in the most cost-effective way, another to combine the candidate gene approach with the genome wide SNP association studies strategy (Kooloos et al., 2009), or to apply genome-wide haplotype pharmacogenomic association studies (Srinivasan et al., 2009).

Haplotypes are a combination of alleles at different markers along the same chromosome that are inherited as a unit. Unlike a genotype, the identity of a single polymorphic location on both chromosomal alleles, a haplotype is the specific combination of nucleotides present at all of the polymorphic locations within a single chromosomal allele. All the genetic variations in a population, or species, can be described as the sum of all haplotypes present among the individuals of that population, or species. Nucleotide differences between these haplotypes are responsible for heterozygous genotypes and provide information useful in ascertaining the identity and/or structure of a haplotype. Consequently, haplotyping nucleotide polymorphisms requires two steps: firstly, the identification of the polymorphisms and, secondly, the determination of which polymorphisms are allelic to one another (Fig.2).

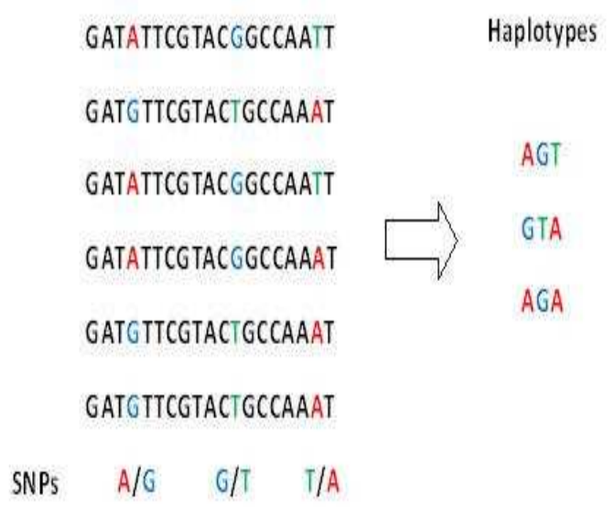


Fig. 2. Haplotypes: a set of closely linked genetic markers (SNPs) present on one chromosome which tend to be inherited together

Although the primary tool used in pharmacogenetic association studies has traditionally been the genotyping of SNPs, recent evidence indicates that determining haplotypes may be more informative than genotyping single variants (Evans & McLeod, 2003). Indeed, in this context, a study evaluated whether the response to inhaled β_2-agonist therapy for asthma was best predicted by individual non-synonymous SNPs, or 13 SNPs within the β_2-adrenoceptor gene (*ADRB2*) (Drysdale et al., 2000). It reported that these 13 SNPs were organized into only 12 of the possible 8,192 SNP haplotype combinations. Although haplotype analyses did define a patient group with a significantly superior response to β_2-agonist therapy, only 5/12 appeared with more than a 10% frequency in the multiethnic cohort studies. Therefore, there has been a great deal of interest in defining the haplotype

structure of the human genome (e.g. the human ''HapMap'' project). The HapMap project (The International HapMap Project, 2003) focuses on SNPs that are relatively common among human populations; assessing these SNPs at an appropriate density (i.e. number and position across the human genome) will provide new insights into the polymorphic nature of the human genome.

As common SNPs are phylogenetically older than rare SNPs, they have arisen from recombination events of ancestral haplotypes (Wall & Pritchard, 2003). Therefore, focusing on these common SNPs will allow for the reconstruction of these ancestral haplotypes, tracing human evolutionary history. More importantly, the use of common SNPs to map the human haplotype structure will identify the haplotypes that make up the majority (perhaps up to 90%) of human variations and will be the most informative source for GWA pharmacogenomic studies. Recent evidence suggests that genotyping just 6 to 8 ''haplotype tag'' SNPs per 10–100 kb of genomic DNA may provide enough information to determine an individual's haplotype for that region (Gabriel et al., 2002; Wall & Pritchard, 2003). This suggests that genotyping these haplotype tag SNPs will be the method of choice for the haplotyping of individual patients for common variations in genome-wide haplotype pharmacogenomic association studies. According to these new strategies, there is an ever increasing use of genome-wide association studies in the field of Pharmacogenomics, with several studies appearing between 2010 and 2011 (Daly, 2010). However, it has become apparent that there may be allelic epigenetic modifications at some genes that cause these alleles to exhibit different expression patterns (Fournier et al., 2002). Indeed, in the future it may be important to refine our concept of haplotypes and, therefore, GWA, beyond DNA sequence variations, to include other information, such as allelic epigenetic factors, which are inherited through mitosis and meiosis with the DNA itself and serve to extend the information content of the human genome (Jenuwein & Allis, 2001).

3. Pharmacoepigenetics and pharmacoepigenomics

Epigenetics is usually defined as the study of mitotically heritable changes in gene expression that are not attributable to nucleic acid sequence alterations. Therefore epigenetics refers to the regulation of various genomic functions controlled by stable, but potentially reversible changes in DNA methylation and chromatin structure (Henikoff & Matzke, 1997). Epigenomics refers to the study of epigenetics on a genome-wide basis (Peedicayil, 2008).

There are two major mechanisms of epigenetic regulation, methylation of cytosines in the DNA sequence and modification of the histone proteins that the DNA is wrapped around. The coordination of both mechanisms results in dramatic changes in the remodelling of chromatin and altered gene transcription (Flanagan & Petronis, 2005). One of the most recent important observations is the increasing evidence that epigenetic factors play an important role in the etiopathogenesis of human diseases and the discovery that epigenetic risk factors open new opportunities for diagnostic, prognostic and therapeutic approaches in human biology. Indeed, epigenetic factors contribute to numerous genomic functions, from the regulation of gene activity to genome stability and segregation of chromosomes, such as: genomic imprinting, X chromosome inactivation and suppression of parasitic DNA elements (Urnov & Wolffe, 2001). Moreover, epigenetic variation across individuals is much richer in comparison to DNA sequence variation and identical DNA sequences in unrelated

individuals exhibit significant epigenetic variation. Therefore, such epigenetic differences may have an impact on gene expression that translates into differential density of receptors, or varied numbers of molecules of an enzyme, factors that might contribute to the pharmacokinetic and pharmacodynamic drug variability. The main goals of Pharmacoepigenomics and Pharmacoepigenetics are to predict drug response and/or adverse reactions, based on the epigenetic individuality of an organism.

3.1 The effect of methylation/deacetylation on drug response

There are almost 300 genes involved in the absorption, distribution, metabolism, and excretion (ADME) of pharmaceutical compounds in humans. It has been demonstrated that DNA methylation, or histone modifications, potentially participate in the regulation of almost 60 human ADME genes (Kacevska et al., 2011). A correlation between the epigenetic state of the gene and a possible influence on drug therapy outcome has been experimentally established only for a few ADME genes. Nevertheless, there is credible evidence that epigenetic factors influence ADME gene expression, which, in turn, leads to changes in the metabolism and distribution of drugs. For example, about 30% of the lungs of heavy smokers and 70% of light smokers' lungs have a CYP1A1 expression, with complete, or partial methylation of the *CYP1A1* gene (Anttila et al., 2003). An increase in the methylation level was observed as early as 1-7 days after individuals had stopped smoking, possibly explaining the smoking-related increase in CYPA1A expression (Anttila et al., 2003). Moreover, hypomethylation at sites coinciding with the transcription activator binding sites, such as Arnt and Sp1, leads to overexpression of CYP1B1 in prostate cancer and correlates to the progression of malignancy (Tokizane et al., 2005).

Similarly, CYP1A2, an enzyme abundant in the liver, is involved in the metabolism of many drugs (Zhou et al., 2010). Known SNPs account only partially for the wide interindividual differences observed for CYP1A2 (Jiang et al., 2006). Therefore, it has been implied that an epigenetic component in CYP1A2 regulation is responsible for the variability in CYP1A2 expression and the methylation status of a CpG island in exon 2, consisting of 17 CpG dinucleotides, has been shown to correlate with interindividual differences in CYP1A2 mRNA levels (Ghotbi et al., 2009). It has also been demonstrated that the methylation status of even a single CpG located far upstream from the transcriptional start site (−2579 bp) could contribute to differential CYP1A2 expression. Such interindividual variations might affect the pharmacokinetic and pharmacodynamic metabolization of the drug through CYP1A2, potentially failing the drug treatment or leading to ADRs. Among the members of the CYP2 family, the *CYP2A6*, *CYP2C9*, *CYP2D6*, *CYP2J2*, *CYP2R1*, *CYP2S1* and *CYP2W1* genes contain putative important CpG islands, suggesting a potential role for DNA methylation in their regulation (Ingelman-Sundberg et al., 2007).

As to phase II drug metabolism, glutathione-S-transferase genes, it has been shown that the extent of promoter methylation is dependent on the haplotype of the glutathione-S-transferase P1 (*GSTP1*) gene in breast cancer patients (Rønneberg et al., 2008). Moreover, hypermethylation of *GSTP1* is a common molecular alteration in human prostate cancer (Woodson et al., 2008). Irinotecan is a first-line treatment for metastatic colorectal cancer. Its active metabolite is inactivated through glucuronidation mediated by the UGT1A1 enzyme. The level of UGT1A1 expression is highly variable among primary colon tumours, thereby

contributing to their differential sensitivity to irinotecan treatment. UGT1A1 expression in colon tumours correlates with the methylation of its promoter and the outcome of cancer chemotherapy (Gagnon et al., 2006).

The *SLC19A1* gene encodes the reduced folate carrier. This enzyme is responsible for cellular uptake of reduced folates and of antifolate drugs, including methotrexate, the most effective drug against primary central nervous system lymphoma. The level of reduced folate carrier differs significantly among lymphoma samples and is associated with methylation of the *SLC19A1* promoter. It has been hypothesized that an increase in SLC19A1 methylation can contribute to methotrexate resistance in tumour cells (Ferreri et al., 2004).

The promoter of the *ABCB1* gene that encodes the P-gp transporter is found hypomethylated in cancer cell lines, manifesting a multidrug-resistance phenotype compared to drug-sensitive cell lines (Baker & El-Osta, 2004). These differences in methylation are also associated with histone modifications. Such epigenetic mechanisms have been shown to be responsible for the increased tolerance shown by certain types of cancer cells to anticancer drugs, such as doxorubicin, paclitaxel and vincristine. Hypomethylation of *ABCB1* can also be induced by exposure of drug-sensitive cells to chemotherapeutic drugs (Baker et al., 2005). Once established, this epigenetic mark can then stably perpetuate through mitotic divisions of cells, manifesting as acquired multidrug resistance.

In addition to these ADME genes, epigenetic influence has also been documented for the α-1 adrenergic receptors (α1-ARs). The three subtypes of α1-AR (α_{1a}AR, α_{1b}AR, and α_{1d}AR) display tissue-specific expression patterns and undergo subtype switching in response to many pathological stimuli. Basal expression of the α_{1d}AR (*ADRA1D*) subtype is dependent on the binding of Sp1 in the two proximal promoter GC boxes of the gene and this binding was shown to be dependent on the methylation status of the promoter region (Michelotti et al., 2007). The expression of the chemokine receptor CXCR4, involved in leukocyte trafficking, seems to be epigenetically regulated, as reported in human pancreatic cancer, where aberrant methylation influences CXCR4 expression (Sato et al., 2005). This finding may pave the way for the development of anticancer drugs that target the CXCR4 receptor, which is overexpressed in various cancers. Moreover, the CXCR4 receptor ligand CXCL12, which has also been shown to be regulated by DNA methylation, has a role in tumour invasion and metastasis and may offer another target for anticancer drugs (Kubarek & Jagodzinski, 2007). The *MGMT* gene, which encodes the DNA repair enzyme O6-methylguanine-DNA methyltransferase, plays a prominent role in the repair of DNA lesions caused by alkylating agents. The extent of methylation of the *MGMT* promoter has been shown to correlate with the responsiveness of gliomas to alkylating drugs, such as carmustine and temozolomide (Paz et al., 2004). Lastly, although the oestrogen receptor is also regulated epigenetically, both by DNA methylation and histone modifications (Bovenzi & Momparler, 2001) in cancer, a non-cancer-related event (ischemia) has also been shown to affect the methylation and expression status of the oestrogen receptor in an animal model (Westberry et al., 2008), demonstrating the wide range of genes that may contribute to drug response variations by means of epigenetic regulation.

As reported for the oestrogen receptor, also histone modifications play an important role in the control of genes encoding drug targets and proteins involved in drug ADME. However, it

must not be forgotten that DNA methylation and histone modification are interconnected events. Let's go back then to CYP1A1, this enzyme has been shown to be also under histone modification control, particularly methylation of lysine 4, a H3 histone (3meK4H3) (Okino et al., 2006). Again, in phase I drug metabolism, an increase in CYP2A6 mRNA and protein levels was observed in human hepatocytes in response to dexamethasone. This was shown to be mediated by the hepatic nuclear factor 4α and the glucocorticoid receptor (GR). The binding of the hepatic nuclear factor 4α to the hepatic nuclear factor 4α response element was promoted by the increased acetylation of histone H4, also in response to dexamethasone (Onica et al., 2008). This modification relaxes the chromatin, thereby allowing the binding of DNA-binding proteins. As a response to cisplatin treatment of HeLa cells, specific phosphorylation of Ser-10 at histone H3 is mediated by the p38 mitogen-activated protein kinase pathway. Likewise, cisplatin induces phosphorylation of H3 at Ser-28 and acetylation of histone H4 (Wang & Lippard, 2004). These findings provide a link between the drug response and chromosomal structural alterations through histone modifications.

3.2 The effect of drugs on methylation/deacetylation

Several chemicals are able to affect the epigenome, either as agents used in clinical practice, or causing ADRs. A range of first-generation compounds that target the epigenome, including DNA methyltransferases (DNMTs) and histone deacetylase inhibitors, have met with success in the treatment of haematological disorders. The earliest of these, 5-azacytidine and azacytidine, are chemical analogs of the nucleoside cytidine and its deoxy derivative, 5-aza-2′-deoxycytidine (decitabine). Through incorporation into DNA (during replication) and RNA (during transcription), they inhibit methyltransferases and lead to demethylation of the sequence (Christman, 2002). Other drugs that affect the epigenome have also emerged, such as zebularine, a cytidine analog that inhibits DNA methylation (Bradbury, 2004). Second-generation drugs that target epigenetic enzymes with more tightly defined modes of action are, at time of writing, still in the investigation phase. Some such drugs include MG98, an antisense oligonucleotide that targets the 3′-untranslated region of the maintenance methyltransferase DNMT1, inhibiting it (Goffin & Eisenhauer, 2002); RG108, a small molecule that effectively blocks DNMTs, particularly DNMT1 and inhibits their activity (Suzuki et al., 2010), and psammaplin, a natural product derived from the sea sponge Pseudoceratina purpurea that inhibits DNMTs as well as histone deacetylases (McCulloch et al., 2009). Increasing attention is being paid not only to research on drugs that modify the DNA methylation landscape, but also to developing drugs that affect histone modifications. Histone deacetylase inhibitors have been object of research in anticancer drug development, as they present a potential strategy to reverse aberrant epigenetic changes associated with cancer (Dannenberg & Edenberg, 2006). However, there is also an increasing awareness that commonly used drugs can affect epigenome and cause ADRs. Among the better-documented examples are valproic acid (VPA), hydralazine, and procainamide. Although VPA is an established antiepileptic and mood-stabilizing drug, clinically used since the 1960s, only recently it has been found that VPA is a direct inhibitor of histone deacetylase (Phiel et al., 2001). Furthermore, the resultant increase in histone acetylation caused by VPA was shown to be interrelated with changes in genomic DNA methylation (Milutinovic et al., 2007). Animal and cell culture studies have implicated the epigenetic mode of action of VPA in a wide range of gene expression changes associated with VPA-induced side-effects, such as teratogenicity and cognitive disorders (Fukuchi et al., 2009;

Nagai et al., 2008; Tung & Winn, 2010). Procainamide, an antiarrythmic sodium channel blocker and hydralazine, a vasodilator used to treat hypertension, did not have well-characterized mechanisms of action when they were first introduced. Mechanistic studies have now shown that procainamide directly inhibits methyltransferases activity, specifically DNMT1 (Lee et al., 2005), whereas hydralazine mainly inhibits DNMT expression (Arce et al., 2006). Consequently, the extensive hypomethylation induced by these drugs alters appropriate protein expression in T cells and triggers a lupus-like autoimmune disease (Chang & Gershwin, 2010; Yung et al., 1996).

The notion that some drug-induced epigenetic marks may have a transgenerational impact is even more alarming. It has been suggested that drugs, such as thalidomide, a sedative–hypnotic and immunomodulatory agent and the synthetic oestrogen diethylstilbestrol may induce transgenerational epigenetic alterations that result in persistent pathological changes in subsequent generations (Holliday, 1998; Newbold et al., 2006). However, given the inadequacy of experimental tools and approaches, solid evidence for true transgenerational epigenetic impact has not been clearly established, although it is an attractive hypothesis to explain such observations.

Other drugs, such as isotretinoin, methylphenidate, tamoxifen, methotrexate and even families of drugs, such as conventional neuroleptics, selective serotonin reuptake inhibitor antidepressant, β-blockers, and chloroquine and fluoroquinolone antibiotics, have all been suggested to affect the epigenome (Csoka & Szyf, 2009). Such conclusions have been based mainly on observations of altered DNA methylation patterns, chromatin remodeling, or substantial changes in gene and protein expression that persist even after therapy has ceased. However, the exact mechanisms through which these drugs influence the epigenome and the consequences of the drug-induced epigenetic reprogramming have not been sufficiently investigated

4. Pharmacogenomics of microRNA

Although sequencing the whole genome and identifying genetic variations, such as SNPs, small insertions, deletions, inversions, variable numbers of tandem repeat (minisatellite), short tandem repeat (microsatellite), and copy number variations (Nakamura, 2009), are important for the understanding of human biology, having information on only these genomic aspects is limiting when attempting to explain interindividual differences in drug response and ADRs. Consequently, researchers have suggested that knowledge and understanding of functional genomics related to gene expression, such as transcriptional and translational processes, be included. One of the first steps to be taken towards understanding the difference in gene expression to identify the variability in drug response is investigating the role of nuclear receptors, or transcription factors, such as the arylhydrocarbon receptor (AhR), peroxisoma proliferator activated receptor (PPAR), pregnane X receptor (PXR) and constitutive androstane receptor (CAR), in the transcription control of genes encoding drug transporters, enzymes and drug targets (Lehmann et al., 1998; Smirlis et al., 2001; Synold et al., 2001; Xie et al., 2000a, 2000b). However the discovery of the world of small regulatory RNAs, or microRNA (miRNA), which are coded in our genomes and implicated in post-transcriptional control, has been more promising. Some researchers classify microRNA regulation as an epigenetic phenomenon (Peedicayil, 2008) but, even if it is closely related to epigenetic phenomena, microRNAs are not themselves epigenetic factors (Chuang & Jones, 2007).

MiRNAs are small, single stranded, 21–23 nucleotide-long, independent functional units of noncoding RNA (Lagos-Quintana et al., 2001; Lau et al., 2001; Lee & Ambros, 2001) which bind to the target transcript in the 3′-untraslated region (3′-UTR) to inhibit the translation of proteins and destabilize their target mRNAs (Baek et al., 2008, Selbach et al., 2008). MiRNAs regulate specific genes broadly involved in multiple pathways, like cell death, cell proliferation, stress resistance and fat metabolism (Ambros, 2003, Lim et al., 2003a, 2003b).

Work on miRNA knock-down and miRNA transfections has recently shown that approximately one third of the miRNA targets are translationally repressed in a cell display mRNA destabilization (Baek et al., 2008, Selbach et al., 2008). Consequently, miRNAs fine-tune protein output in the cell by translationally repressing and destabilizing the target mRNA (Baek et al., 2008; Mishra et al., 2007; Selbach et al., 2008). Other evidence suggests that a gain, or loss in miRNA function is associated to disease progression and prognosis (Lu et al., 2005; Mishra et al., 2007), as several studies have now established that miRNAs are expressed differently in human cancers than in normal healthy tissue (Calin et al., 2004; He et al., 2007; Lu et al., 2005).

4.1 Effect of polymorphisms in miRNA in drug response and adverse drug reactions

Polymorphisms in the miRNA regulatory pathway (miR-polymorphisms) are a novel class of functional polymorphisms present in the human genome. MiR-polymorphisms reside at, or near to, a miRNA binding site of a functional gene, influencing its expression by interfering with miRNA function (Bertino et al., 2007; Mishra et al., 2007, 2008). Several groups worldwide have acknowledged the role of miR-polymorphisms, suggesting a strong association between miR-polymorphisms and disease progression, as well as with drug response. Indeed, a single miR-polymorphism can potentially affect the expression of multiple genes involved in pathways regulating drug absorption, metabolism, disposition and may affect the overall clinical efficacy of a drug and/or resistance to that drug.

An analysis of the publicly available SNP database revealed the presence of a relatively high level of variations in the 3′-UTRs of miRNA target genes (Saunders et al., 2007) demonstrating that some of these variations may interfere with the function of miRNA and are potential miR-polymorphisms with the capacity to affect the expression of miRNA targets (Barnes et al., 2007; Kertesz et al., 2007; Mishra et al., 2007). MiRNA mutation (miR-mutations) can be defined as a mutation that interferes with miRNA function. MiR-polymorphisms and miR-mutations can be present either in heterozygous, or homozygous forms in a population. These variants in the human genome may take the form of insertions, deletions, amplifications, or chromosomal translocations, resulting in loss, or gain of miRNA site/function (Mishra et al., 2007). Functional miR-polymorphisms, or mutations, may create, or destroy, a miRNA binding site within a target mRNA and affect gene expression by interfering with the function of a miRNA (Bertino et al., 2007; Mishra et al., 2007, 2008).

Recently, the role of miRNA in drug-resistance/sensitivity has been investigated. It was functionally demonstrated that a polymorphism in a miRNA binding site could lead to drug-resistance/drug sensitivity (Bertino et al., 2007; Mishra et al., 2007, 2008). For example, a C>T SNP present in the 3′-UTR of dihydrofolate reductase gene (DHFR) was originally identified in a case–control study of childhood leukaemia patients to occur with 14.2% allelic frequency in the Japanese population (Goto et al., 2001). Later it was demonstrated that the

SNP is present near a miR-24 miRNA-binding site in human DHFR. The C>T SNP near the miRNA-binding site acts as a loss-of-function mutation and interferes with miR-24 function. The loss of miR-24 function results in high steady-state levels of DHFR mRNA and protein levels leading to drug resistance (Mishra et al., 2007). Interestingly, loss of miR-24 function, due to the SNP, led to a twofold increase in the half-life of the mRNA target. This observation not only explained the corresponding increase in DHFR mRNA and protein levels, but also suggested that the target mRNA destabilization could be a principle mechanism of action of a miRNA (Mishra et al., 2007). This finding may also be useful in predicting the clinical outcome of methotrexate treatment in clinical settings. Consequently, various miR-polymorphisms, located in many important genes that are drug targets, may affect drug response in patients and may lead to drug resistance and/or drug sensitivity and even unexpected toxicity.

This new insight has introduced a novel and promising field of research: Pharmacogenomics of miRNA, that holds new possibilities for tailor-made medical therapy. MiRNA pharmacogenomics can be defined as the study of miRNAs and polymorphisms affecting miRNA function in order to predict drug behaviour and improve drug efficiency (Bertino et al., 2007; Mishra et al., 2008). There are several reasons why miRNA pharmacogenomics have strong clinical implications: miRNAs are attractive drug targets, are differentially expressed in abnormal cells in all different diseases versus normal cells and regulate the expression of several important proteins in the cell (Calin et al., 2002; Iorio et al., 2005) supporting the hypothesis that miRNA polymorphisms, located near the miRNA-binding site of important genes involved in the drug pharmacokinetics and pharmacodynmics, have the potential to affect drug behaviour. Therefore, these miR-polymorphisms are potential predictors of drug response in the clinical setting and will hopefully lead to the development of more accurate methods of determining appropriate drug dosages based on a patient's genetic make-up and decrease the likelihood of drug overdose (Bertino et al., 2007)

4.2 MiRNA expression and drugs

Even though each miRNA appears to regulate the expression of tens to hundreds of different genes at time of writing, there are only a few examples demonstrating the relevance of miRNA in the regulation of proteins involved in drug metabolism, transporting and targeting. In CYP research, miR-27b expression was found to be lower in breast cancer tissues than in neighbouring healthy tissue ($P < 0.0005$). This expression profile correlated inversely with CYP1B1 expression and, *in vitro* studies, showed the involvement of miR-27b in the post-transcriptional regulation of CYP1B1 (Tsuchiya et al., 2006). Human CYP2E1 expression, an important CYP450 isoform from a pharmacologically and toxicological point of view, is regulated by miR-378, mainly via translational repression (Mohri et al., 2010). Again, CYP24 by miR-125b post-transcriptionally, which serves as a possible mechanism for the high CYP24 expression in tumour tissues, since CYP24 catalyzes the inactivation of 1α,25-dihydroxyvitamin D3 (calcitriol), which exerts antiproliferative effects (Komagata et al., 2009). Moreover, the transcription factor pregnane X receptor, which regulates the expression of a number of CYP members, including CYP3A4, was shown to be regulated by miR-148a (Takagi et al., 2008). The miR-148a–dependent decreases in pregnane X receptor protein attenuated the induction of CYP3A4 mRNA ($P < 0.05$) and protein levels ($P < 0.010$).

As to drug transporters, ABCG2 expression was found to be inhibited by miR-519c in a parental S1 colon cancer cell line. However, this inhibition was lost in the drug-resistant counterpart due to a shorter 3′-UTR in these cells, most likely responsible for the resistance (To et al., 2008). There was a similar effect on drug resistance in the multidrug resistant cell lines (A2780DX5 and KB-V1.27), where miR-27a and miR-451 led to overexpression of P-glycoprotein (P-gp) (Zhu et al., 2008). Again, some researchers reported that miR-451 regulates P-gp expression in doxorubicin-resistant MCF-7 cells (Kovalchuk et al., 2008). There is other evidence on miRNA and anticancer agents, such as tamoxifen (Cittelly et al., 2010), cisplatin (Bian et al., 2011; Imanaka et al., 2011), 5-fluorouracil (Shah et al., 2011; Valeri et al., 2010) and other anticancer drugs (Giovannetti et al., 2011).

Other examples involve the role of miRNA as regulators of nuclear receptors. Peroxisome proliferator-activated receptor gamma (PPARγ) has gained considerable interest as a therapeutic target during chronic inflammatory diseases. Indeed, the pathogenesis of diseases such as multiple sclerosis, or Alzheimer, might be associated with impaired PPARγ expression. Jennewein and colleagues have provided, *in vitro*, evidence of the PPARγ mRNA destabilization through miRNA 27b binding *PPARγ* 3′-UTR, which is induced by inflammatory response (Jennewein et al., 2010). Hepatocyte nuclear factor (HNF) 4α is a key transcription factor regulating endo/xenobiotic-metabolizing enzymes and transporters and this nuclear factor was down-regulated, *in vitro*, by miR-24 and miR-34a, affecting the metabolism and cellular biology (Takagi et al., 2010). Glucocorticoids (GCs) exert profound effects on a variety of physiological processes, including adaptation to stress, metabolism, immunity, and neuronal development. Vreugdenhil et al. tested the hypothesis that miRNA might control GR activity by reducing GR protein levels in neuronal tissues and found that miRNA 18 and 124a not only reduced GR-mediated events, but also decreased GR protein levels, providing a better understanding of the etiology of stress-related diseases as well as the efficacy of GC therapy (Vreugdenhil et al., 2009). When considered as a whole, these results indicate a possibility of intervening in the drug response mechanisms by modulating miRNA expression but many hurdles must be overcome before finding methodologies or agents (anti-miRNA) capable of efficiently modulating miRNA expression (Thai et al., 2010).

5. Complementary approaches

Even if the process of understanding the mechanisms responsible for variable responses to the powerful therapeutic agents have been accelerated by these new approaches, the identification of a particular phenotype unequivocally from an equivocal genotype still remains a challenge. Nebert et al. report several reasons why no example can be cited in which a single genotype is always associated with a phenotype in all individuals within all human populations (Nebert & Vesell, 2004). Indeed, there is always a reason why a genomic event, or another phenomenon might override a single DNA variant site somewhere in a gene (Nebert & Vesell, 2004). Therefore, studies on drug response are expanding beyond genomics to new horizons encompassing trascriptomics, metabonomics, proteomics and mathematical models, to become a systems-based discipline, or system biology approach. Even if much still remains to be done in the field of genomics to better understand the exact role of the genotype in the development of the phenotype e.g. through gene-gene interactions resulting from particular stimuli that affect a complex circuitry of pathways, ending in a response by the cell, or organism, these new fields are very promising to

understand and predict variation in drug response phenotype. Trascriptomics refers to the study of gene transcripts (Kiechle & Holland-Staley, 2003), generally analyzed by cDNA expression microarrays. Such cDNA expression studies have led to a number of exciting breakthroughs in basic science. For example, microarray analysis of certain tumours has been successful in correlating particular expression patterns with patient prognosis (Macgregor, 2003). Microarrays of cDNA expression have also been used effectively as predictors of success for hormone responsiveness, hormone non-responsiveness, clinical outcomes and anticancer chemotherapeutic drugs (Domchek & Weber, 2002; Liu & Karuturi, 2004), even if other phenotypes may also be directly related to drug response. One of those phenotypes is the level of metabolites, not drug metabolites, but rather all small molecules that can be accurately assayed in the organism. These thousands of small molecules i.e. the metabolome, may also be altered by drug exposure and, consequently, able to predict variation in drug response. Metabonomics or metabolomics refers to the study of metabolite profiling, or metabolome i.e. the repertoire of small molecules present in cell, tissues, organs and biological fluids (Dettmer & Hammock, 2004; Lindon et al., 2004; Maddox et al., 2006; Plumb et al., 2003; Reo, 2002; Schmidt, 2004a, 2004b; van der Greef et al., 2007). The metabonome represents a real time integrated response to all endogenous and all exogenous stimuli (drugs, chemical exposures, occupation, lifestyle, nutrition, age, gender). Therefore, metabonomics might provide a sensitive means to follow an individual patient's phenotype as a function of all these stimuli. Recently, metabonomics has achieved major new advances due to novel, highly sensitive techniques for the measurement of urinary metabolite profiles. The analytical data in these studies are derived from electrospray mass spectrometry coupled to gas chromatography, liquid chromatography, or mass spectrometry time-of-flight (Plumb et al., 2002). The metabolites measured include, not only those from drugs, but hundreds of small-molecular weight compounds present in synthetic and degradation pathways.

Animal model studies, using the metabonomic approach have been reported to perform a study of drug-induced hepatotoxicity. Hepatotoxicity is a common and potentially serious adverse reaction to drugs, such as acetaminophen (Fontana & Quallich, 2001; Watkins et al., 2006). In this metabolomic study, male Sprague-Dawley rats were treated with acetaminophen and both pre and post-drug exposure urine samples were subjected to Nuclear Magnetic Resonance (NMR) analysis. A model was then developed that used pre-drug metabolomic data to predict both ratios of acetaminophen glucuronide conjugate to parent drug and post-acetaminophen hepatotoxicity (Clayton et al., 2006).

Clinical studies using metabonomics are still in the teething stage. For example, one study focused on metabolic profiles of antipsychotic drugs and used a specialized lipidomic platform to measure more than 300 lipid metabolites for the evaluation of global lipid changes in schizophrenia after treatment with three commonly prescribed atypical antipsychotics: olanzapine, risperidone and aripiprazole (Kaddurah-Daouk et al., 2007). A major side-effect associated with the use of these drugs is weight gain. Effects of the three antipsychotic drugs on lipid biochemical pathways were then evaluated by comparing metabolic profiles at baseline with post treatment assays. Phosphotidylethanolamine concentrations were elevated after treatment with all three drugs. Olanzapine and risperidone affected a much broader range of lipid classes than did aripiprazole, with an increase in about 50 lipids after exposure to these drugs, but not after aripiprazole therapy.

Thus, metabonomics might well help the physician to provide each patient with personalized drug therapy and avoid toxicity, consequently minimizing the risk of ADRs. This new form of metabolite profiling would resemble what clinical pharmacology has done previously, with the difference that it would be several orders of magnitude more sensitive in detecting subtle toxicity, or other ADRs, long before these become clinically evident. Changes in an individual's metabolite profile might warrant an aggressive regimen, for example, to prevent, or impede the onset of arthritis, or renal disease, long before clinical symptoms appear. It seems practicable that, in the distant future, metabonomics will go hand in hand with genomics to revolutionize and individualize drug therapy.

Proteomics is the study of all proteins encoded by the genome (Tuma, 2004). Although a recent study (Rual et al., 2004) estimated an average of 2 to 3 human proteins per gene, others have estimated that the true number of proteins per gene might be considerably higher. Even though proteomics has not yet been widely applied to the study of drug response, it is however, both conceivable and feasible, that, in the future, proteomic investigators might identify certain protein profiles, similar to ways in which metabonomics can identify certain metabolite profiles, which might be useful in predicting ADRs long before they become overt.

6. Future challenges

The purpose of this chapter is to provide an overview of the development of Pharmacogenetics and the scientific advances that have contributed to the continuing evolution of this discipline. Therefore, the ultimate approach in this field would be the union of genomic, trascriptomic, metabonomic and proteomic data as well as clinical diagnosis and pharmacological treatment response to build a computational cellular, or organ model. If the model is sufficiently accurate and detailed, it will then be possible, firstly to predict the behaviour of a system given any disturbance within it, secondly, gene regulatory networks could be redesigned to create new system properties. This second possibility could take on an extremely important role in Pharmacogenomic research for the development of new drugs.

However, to fully realize the potential of this approach and new insights, a number of issues and challenges must be met. First and foremost, researchers should continue training on systems biology. This will require developing new global technologies for genomics, trascriptomics, proteomics, metabolomics and phenotyping. It will also involve the development of software able to capture, store, analyze, graphically display, integrate, model and disperse the global data sets of systems biology. We must learn how to determine the nature of proteins and gene regulatory networks and their integrations and how to integrate many types of data as well as analyze and integrate global data sets across the dynamic transitions of development, or physiological responses. We also must deal with the challenge of providing access for the laboratories practicing small science to these global technologies and powerful computational tools. Lastly, access to biological samples from a large number of healthy and diseased subjects must be made available so as to begin the global correlative studies able to establish the foundational framework of predictive medicine and pave the way for moving forward into preventive medicine. There is, however, little doubt that the application of Systems Biology will significantly advance our ability to individualize drug therapy over the next few years.

7. Conclusions

Although Pharmacogenetics and Pharmacogenomics hold out the promise of leading to individualized therapy, to date, relatively few Pharmacogenetic/Pharmacogenomic tests are currently used in the clinical setting and even those that are used are done so less frequently than indicated. Even if there has recently been an increase in the awareness on the part of the Food and Drug Administration of the necessity to integrate genomic data into regulatory review (http://www.fda.gov/cder/genomic/), the goal of individualized prescribing still remains an arduous task. Therefore, Pharmacogenetics and/or Pharmacogenomics requires further research in various areas of science and the development of the capability to integrate them so as to be able to treat each patient as they deserve i.e. as the complex, unique and fascinating individual they really are.

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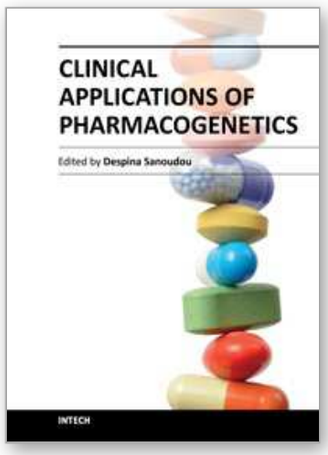
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The rapidly evolving field of Pharmacogenetics aims at identifying the genetic factors implicated in the inter-individual variation of drug response. These factors could enable patient sub-classification based on their treatment needs thus expediting drug development and promoting personalized, safer and more effective treatments. This book presents Pharmacogenetic examples from a broad spectrum of different drugs, for different diseases, which are representative of different stages of evaluation or application. It has been designed so as to serve both the unfamiliar reader through explanations of basic Pharmacogenetic concepts, the clinician with presentation of the latest developments and international guidelines, and the research scientist with examples of Pharmacogenetic applications, discussions on the limitations and an outlook on the new scientific trends in this field.

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