Metabolomics: Open Access
ISSN: 2153-0769

Cacabelos, Metabolomics 2015, 5:3
DOI: 10.4172/2153-0769.1000e140

Editorial Open Access

Pharmacoepigenomics and the Metabolomics of Drug Efficacy and Safety

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The cost of pharmaceutical treatment in major problems of health (cardiovascular disorders, cancer, brain disorders) represents about 10-15% of direct costs. Less than 30-40% of patients are good responders to conventional drugs; and the misuse and/or abuse of drugs, especially psychotropics, is becoming a major concern in developed countries [1]. Furthermore, the governments of the countries where the public health system assumes the overall costs of their members are very concerned about the sharp increase in health costs, especially in diseases that affect the elderly population. In the scientific community there is a growing discontent with the bureaucratic excesses of the regulatory agencies and the limited incorporation of many procedures that genomic medicine could bring to develop new drugs and optimize the use of drugs commonly consumed worldwide. In between, the medical community continues to use protocols supported by the pharmaceutical industry based on trial and error testing where the only guarantee of quality is a statistical marker. A necessary move in the right direction, according to the scientific development of genomic science, would be to accelerate the incorporation of pharmacogenomics and metabolomics procedures to the development and personalized use of drugs [2,3].

The effects of drugs and their therapeutic outcome in the treatment of a given disease are the result of a network of metabolomic events associated with the binomial interaction of a chemical or biological molecule with a living organism. Pharmacogenomics accounts for 30-90% variability in pharmacokinetics and pharmacodynamics; however, pharmacogenetics alone does not predict all phenotypic variations in drug response. Individual differences in drug response are associated with genetic and epigenetic variability and disease determinants [4].

Epigenomics/epigenetics refers to phenotypic changes with no apparent alterations in structural DNA. Classical epigenetic mechanisms, including DNA methylation, histone modifications, and regulation by microRNAs (miRNAs), are among the major regulatory elements that control metabolic pathways at the molecular level, with epigenetic modifications regulating gene expression transcriptionally and miRNAs suppressing gene expression post-transcriptionally [5,6]. Pharmacoepigenomics deals with the influence that epigenetic alterations exert on drug efficacy and safety, and also on the effects that drugs may have on the epigenetic machinery [4].

The genes involved in the pharmacogenomic response to drugs fall into five major categories: (i) genes associated with disease pathogenesis; (ii) genes associated with the mechanism of action of drugs (enzymes, receptors, transmitters, messengers); (iii) genes associated with drug metabolism: (a) phase I reaction enzymes: alcohol dehydrogenases (ADH1-7), aldehyde dehydrogenases (ALDH1-9), aldo-keto reductases (AKR1A-D), amine oxidases (MAOA, MAOB, SMOX), carbonyl reductases (CBR1-4), cytidine deaminase (CDA), cytochrome P450 family (CYP1-51, POR, TBXAS1), cytochrome b5 reductase (CYB5R3), dihydropirimidine dehydrogenase (DPYD), esterases (AADAC, CEL, CES1-3, CES5A, ESD, GZMA, GZMB, PON1, PON2, PON3, UCHL1, UCHL3), epoxidases (EPHX1-2), flavin-containing monooxygenases (FMO1-6), glutathione reductase/peroxidases (GPX1-7, GSR), short-chain dehydrogenases/reductases (DHRS1-13, DHRSX, HSD11B1, HSD17B10, HSD17B11, HSD17B14), superoxide dismutases (SOD1-2), and xanthine dehydrogenase (XDH); and (b): phase II reaction enzymes: amino acid transferases (AGXT, BAAT, CCBL1), dehydrogenases (NQO1-2, XDH), esterases (CES1-5), glucuronosyl transferases (UGT1-8), glutathione transferases (GSTA1-5, GSTK1, GSTM1-5, GSTO1-2, GSTP1, GSTT1-2, GSTZ1, GSTCD, MGST1-3, PTGES), methyl transferases (AS3MT, ASMT, COMT, GNMT, GAMT, HNMT, INMT, NNMT, PNMT, TPMT), N-acetyl transferases (ACSL1-4, ACSM1, ACSM2B, ACSM3, AANAT, GLYAT, NAA20, NAT1-2, SAT1), thioltransferase (GLRX), and sulfotransferases (CHST2-13, GAL3ST1, SULT1A1-3, SULT1B1, SULT1C1-4, SULT1E1, SULT2A1, SULT2B1, SULT4A1, SULT6B1, CHST1); (iv) genes associated with drug transporters: *ABC* genes, genes of the solute carrier superfamily (*SLC*) and solute carrier organic (*SLCO*) transporter family, responsible for the transport of multiple endogenous and exogenous compounds, including folate (*SLC19A1*), urea (*SLC14A1*, *SLC14A2*), monoamines (*SLC29A4*, *SLC22A3*), amino acids (*SLC1A5*, *SLC3A1*, *SLC7A3*, *SLC7A9*, *SLC38A1*, *SLC38A4*, *SLC38A5*, *SLC38A7*, *SLC43A2*, *SLC45A1*), nucleotides (*SLC29A2*, *SLC29A3*), fatty acids (*SLC27A1-6*), neurotransmitters (*SLC6A2* (noradrenaline transporter), *SLC6A3* (dopamine transporter), *SLC6A4* (serotonin transporter, SERT), *SLC6A5*, *SLC6A6*, *SLC6A9*, *SLC6A11*, *SLC6A12*, *SLC6A14*, *SLC6A15*, *SLC6A16*, *SLC6A17*, *SLC6A18*, *SLC6A19*), glutamate (*SLC1A6*, *SLC1A7*), and others; and (v) pleiotropic genes involved in multifaceted cascades and metabolic reactions [2-4].

Epigenetic regulation is responsible for the tissue-specific expression of genes involved in pharmacogenetic processes. Epigenetic changes affect cytochrome P450 enzyme expression, major transporter function, and nuclear receptor interactions. Although this is a still poorly explored field, epigenetic regulation of genes encoding drug-metabolizing enzymes (*CYP1A1*, *1A2*, *1B1*, *1A6*, *2A13*, *2B6*, *2C8*, *2C9*, *2C18*, *2C19*, *2D6*, *2E1*, *2J2*, *2F1*, *2R1*, *2S1*, *2W1*, *3A4*, *3A5*, *3A7*, *3A43*, *UGT1*, *GSTP1*), drug transporters (*ABCB1*/*MDR1*/*P-gp*, *ABCC1*/*MRP1*, *ABCC11*/*MRP8*, *ABCG2*/*BCRP*, *SLC19A1*, *SLC22A8*), and nuclear receptors (*RARB2*, *ESR1*, *NR1I2*, *HNF41*) has been documented in pioneering studies of pharmacoepigenetics [6-8].

DNA methylation and chromatin accessibility of the promoter regions of CYP genes correlate with expression levels of these genes in different tissues. Epigenetic changes in metabolic genes may affect circadian rhythms and secretory patterns of endogenous factors whose dysregulation may alter alter metabolic pathways and drug actions. Exposure to toxicants and pollutants may alter the expression

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Received August 18, 2015; **Accepted** August 23, 2015; **Published** August 25, 2015

Citation: Cacabelos R (2015) Pharmacoepigenomics and the Metabolomics of Drug Efficacy and Safety. Metabolomics 5: e140. doi:10.4172/2153-0769.1000e140

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of metabolic genes contributing to toxicity, disease, and abnormal drug metabolism. Prenatal exposure to drugs and maternal medical conditions are associated with altered neonatal polygenic DNA methylation status, which, in turn, appears to be associated with postnatal pathologies and abnormal responses to conventional drugs. Sex-differential methylation may have medical effects, and different methylation patterns partially explain the sex-based differences in expression of CYP family members, which potentially lead to inborn differences between males and females and their different responses to drugs. DNA hypo- and hyper-methylation interfere with gene regulation resulting in the defective expression of UGTs in human liver. Epigenetic regulation would be one of the mechanisms that determine the tissue-specific expression of UGTs [9].

Epigenetic modifications are associated with drug resistance [4]. This is especially important in cancer, cardiovascular disorders (hypertension), brain disorders (epilepsy, schizophrenia, depression, Parkinson's disease), infections, metabolic/endocrine disorders (diabetes) and anesthesia. Chemotherapy resistance remains an important problem in cancer. The acquisition of drug resistance is tightly regulated by post-transcriptional regulators such as RNA-binding proteins (RBPs) and miRNAs, which change the stability and translation of mRNA encoding factors involved in cell survival, proliferation, epithelial-mesenchymal transition, and drug metabolism [10].

Alterations in chromatin acetylation and DNA double-strand breaks (DSBs) in some types of cancer are accompanied by different responses to therapy. Patients with high levels of acetyl-histone H3 at lys9 (H3K9ac), which is associated with enhanced transcription and nuclear decondensation, fail to respond to therapy or experience disease recurrence shortly after therapy, and patients who respond poorly to therapy have increased accumulation of DNA DSB, indicating genomic instability [11]. About two-thirds of all breast cancers are ERα-positive and can be treated with the antiestrogen tamoxifen, and over 30% of women treated with tamoxifen develop drug resistance [12]. Aberrant DNA methylation, together with other pharmacogenetic factors, is thought to play a role in this resistance [4].

Several epigenetic drugs have been approved by the FDA to circumvent some of these problems [13-15]. Among novel epigenetic drugs, bromodomain and extraterminal (BET) domain proteins have emerged as promising therapeutic targets in glioblastoma and many other cancers [16]. Small-molecule inhibitors of BET bromodomain proteins reduce expression of several oncogenes required for glioblastoma multiforme (GBM) progression [17]. Long noncoding RNAs (lncRNAs) are important epigenetic regulators with critical roles in cancer initiation and malignant progression. The expression of a recently identified subset of GBM-specific lncRNAs is regulated by BET proteins. Treatment of specific cancer cells with BET bromodomain inhibitors reduces levels of the tumor-promoting lncRNA HOX transcript antisense RNA and restores the expression of several other onco-cells down-regulated lncRNAs. Several miRNAs are involved in the chemosensitivity of cancer cells.

Epigenetic changes in drug transporters may also affect drug metabolism and drug resistance. This is especially important when epigenetic modification affects the multidrug resistance 1 (*MDR1*, *ABCB1*) gene product P-glycoprotein (P-gp), an ATP binding cassette transporter which extrudes multiple endogenous and exogenous substrates from the cell, playing important roles in normal physiology and xenobiotic distribution and bioavailability [18]. Three CpG islands within a 1.15- kb region characterize the chromatin landscape surrounding the transcriptional start site of the *ABCB1* gene [19]. Hypermethylation of this region is correlated with *ABCB1* gene silencing and the inability of chemotherapeutic agents to activate *ABCB1* transcription [20]. Induced expression of the Abcb1 drug transporter often occurs in tumors in response to chemotherapy. Increased *ABCB1* transcript expression coincident with acquisition of resistance to epirubicin or paclitaxel is temporally associated with hypomethylation of the *ABCB1* downstream promoter in the absence of gene amplifications or changes in mRNA stability [21].

Circulating miRNA is emerging as promising diagnostic biomarkers for different types of cancer, and RNA-interference (RNAi) and gene silencing are attractive therapeutic strategies in diverse medical conditions. RNAi agents such as small-interfering RNA (siRNA) and miRNA have strong potential as therapeutic agents for the treatment of a broad range of diseases such as malignancies, infections, autoimmune diseases and neurological diseases that are associated with undesirable gene expression. Several clinical trials of RNAi therapeutics have been conducted with limited success so far [22-26].

Therapeutic approaches focused on regulating miRNAs are a promising approach for treating cancer since aberrant expression of miRNAs is critically implicated in cancer initiation and progression. Under chronic cardiac stress, miRNAs act as critical regulators of cardiac tissue remodeling and represent a new class of therapeutic targets in patients suffering from heart failure. siRNA silencing has also been used as a potential therapeutic option in experimental models of mental disorders. Antisense oligonucleotides, miRNA sponges, and CRISPR/Cas9 genome editing systems are being investigated as tools for regulating miRNAs. However, delivery concerns and technical problems are major obstacles for the progress and clinical application of this novel therapeutic strategy.

miRNAs contribute to active DNA demethylation control in normal and disease development, based on recent findings in stem cells and cancer [27]. Several miRNAs target genes encoding epigenetic regulation; for instance, miR-29, -29c, -370, and -450A target DNMT3A, and miR-29, -148, and -29b target DNMT3B, inducing hypomethylation and expression of tumor suppression genes; let-7a, miR-26a, -101, -138, and -124 target EZH2, decreasing histone methylation and increasing expression of tumor suppressor genes; miR-449 and -874 target HDAC1, inducing growth arrest by decreasing histone acetylation; miR-1 and -155 target HDAC4, promoting myogenesis and impairing transcriptional activity of B-cell lymphoma 6 (BCL6); miR-627 and -155 target JMJD1A, decreasing histone demethylation and hypoxic gene expression; miR-132 and -483-5p target MECP2, promoting demethylation and cell differentiation [28,29].

Recent studies support the conclusions that: (i) epigenetic changes are common phenomena in physiological and pathological conditions; (ii) epigenetic variation is sex- and age-dependent, and affects life expectancy and longevity; (iii) sex differences in DNA methylation and chromatin structure are involved in the sex-dependent effects/actions of endogenous (transmitters, hormones, enzymes) and exogenous factors (nutrients, drugs, xenobiotic agents); (iv) DNA methylation influence phenotype differences, such as susceptibility to certain diseases and pathogens, and response to drugs and xenobiotic agents; (v) epigenetic modifications are associated with drug resistance; (vi) epigenetic modifications are reversible and can be potentially targeted by pharmacological and dietary interventions; (vii) epigenetic drugs can reverse epigenetic changes in gene expression and might open future avenues for the treatment of major problems of health; (viii) a series of epigenetic drugs have been developed, including DNA

methyltransferase inhibitors (nucleoside analogs, small molecules, bioproducts, antisense oligonucleotides, miRNAs), histone deacetylase inhibitors (short-chain fatty acids, hydroxamic acids, cyclic peptides, benzamides, ketones, sirtuin inhibitors, sirtuin activators), histone acetyltransferase modulators, histone methyltransferase inhibitors, histone demethylase inhibitors, and non-coding RNAs (miRNAs) with potential effects against major problems of health; (viii) RNAi agents, such as small-interfering RNA (siRNA) and miRNA, have strong potential as therapeutic agents for the treatment of a broad range of diseases; (ix) pharmacoepigenomics deals with the influence that epigenetic alterations may exert on genes involved in the pharmacogenomic network responsible for the pharmacokinetics and pharmacodynamics of drugs (efficacy and safety), as well as the effects that drugs may have on the epigenetic machinery; (xi) genes involved in the pharmacogenomic process include pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes which are susceptible to epigenetic modifications leading to altered expression of proteins and enzymes, with the consequent effects on the therapeutic outcome; and (xii) although the information available at present on the pharmacoepigenomics of most drugs is very limited, growing evidence indicates that epigenetic changes are determinant in the pathogenesis of many medical conditions and in drug response and drug resistance; consequently, pharmacoepigenetic studies should be incorporated in the future as routine procedures for the proper evaluation of efficacy and safety issues in drug development and clinical trials [1-4].

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