To translate pharmacogenetics in geriatrics: towards a personalized medicine

Davide Seripa, Giulia Paroni, Michele Lauriola, Antonio Greco
Geriatric Unit and Gerontology, Geriatrics Research Laboratory, Department of Medical Sciences, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy

Abstract

Geriatric wards represented a very interesting clinical setting in which an increased drugs use rise the prevalence of adverse drug reactions (ADRs) and therapeutic failures (TFs). These are not independent phenomena, but the severe counterposed manifestations of a continuum of phenotypes in which the better drug response is the midpoint. Age-related changes in the regulation of cytochrome P450 (CYP) genes, encoding the most common drug-metabolizing enzymes, might be responsible of the observed age-associated drift towards ADRs and TFs. In this review article, a complete impression of the CYP pharmacogenetics and epigenetics is reported in the context of increasing age, in which epigenetic CYP gene regulation might change. Physiological age-related changes in DNA-methylation, the main epigenetic mechanisms regulating gene expression in humans, results in a physiological decrease in CYP gene expression with advancing age. This may be one of the physiological changes that, together with an increased drug use, contributed to raise the prevalence of severe responder phenotypes in older age.

Materials and Methods

Epigenetics and age

The early concept of molecular biology reporting that DNA is the only source of genetic information, with information flowing from DNA to RNA to proteins is still valid. However, the inter-individual phenotypic variability observed in drug responses cannot be fully explained by known variability in the genes encoding drug metabolizing enzymes (DMEs), transporters (DTs), and receptors (DRs). Thus, an additional source of variation is needed. Studies on monozygotic twins have demonstrated that this is accomplished by epigenetic modifications. Indeed, the concept that interindividual epigenetic differences might be responsible of interindividual differences in drug metabolism has been recently proposed. Current knowledge stated that epigenetic act through two main mechanisms: methylation, at both DNA and protein levels (mainly histones), and microRNA (miRNA) interference, all involved in the regulation of gene expression. Among these mechanisms, DNA methylation is probably the best conserved form of gene regulation through evolution. Although methylation exists as a relatively stable and inheritable modification, it is widely accepted that is the result of long/short-term dynamic methylation/demethylation equilibrium continuing throughout lifespan, but also changing day-by-day in response to environmental stimuli. In particular, DNA methylation is the well known mechanism by which gene silencing is obtained. DNA methylation is catalyzed by the DNA methyltransferase enzymes (DNMTs). In humans, DNMT-1 is known as the maintenance methylase, whereas DNMT-3a and DNMT-3b are de novo methylases. The ten eleven translocation family enzymes, instead, are the enzymes responsible of demethylation process.

The genetic information encoded in DNA did not change with age. Conversely, it is well documented that methylation patterns change with age. Overall, a physiological process towards a global genome hypomethylation and a specific hypermethylation with age is observed. Accordingly, in the context of advancing age, in which a general hypermethylation of the promoter regions is observed, all genes regulated by DNA methylation tended to reduced their expression, including DMEs, DTs and DRs and other genes involved in drug metabolism and distribution. Whereas, it has been largely demonstrated that DNA methylation changes in human cells and tissues with age, data regarding the other two epigenetic mechanisms, histones modification by methylation and miRNA interference, are less clear. Thus, DNA methylation may be the valid mechanisms to explain age-related differences in the overall interindividual variation observed in drug response throughout age-related differences in the regulation of DMEs, DTs and DRs expression.

Genetics, epigenetics and drug response

The perception that inherited factors might contribute to interindividual differences in drug response was not a recent one, but, and currently, this concept is widely accepted and validated. In this context, inherited variants in DME encoding genes, mainly cytochromes P450 (CYPs), may play a major role. Clearly, this great gene diversity results into a high variability in the activity of the encoded enzymes. Potentially, in this system, the cataly-
tic activity of each enzyme differed from each other.

However, modern pharmacology did not completely take advantage from this system since more than 90-95% of the CYP reactions with drugs are catalyzed only by five (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) of the 44 CYP subfamilies (11.36%), with the latter enzyme (CYP3A4) accounting for approximately 50% of the total CYP reactions. The concept of an epigenetic regulation of CYP is not recent. However, DNA methylation appeared as the main epigenetic mechanism to regulate several CYP enzymes in the CYP gene-families 1 (CYP1), 2 (CYP2), 3 (CYP3), the most important families in the adult liver contributing to the metabolism of about 70% of clinically used drugs and 4 (CYP24). Accordingly, inherited variants in CYP genes, as well as inherited changes in the epigenetic regulation of CYP gene expression, might well play the role of those genetic factors moving the drug response to far from the better.

The advent of the human genome project has lead to the identification of a number of genes encoding important drug transporters and receptors and considerable progress has been made in understanding their molecular characteristics. In fact, since their roles in drugs and metabolites transport inward and outward of the cells, in the recent years their pharmacogenetics has been well studied. Now, it becomes clear that some transporters are responsible for drug transport and effect in various tissues, and may be key determinants of the pharmacokinetic characteristics of a drug, i.e., intestinal absorption, tissue distribution and elimination. However, no clear data are available regarding the epigenetic regulation of these genes, thus suggesting a minor role in age-related changes in the response to drug treatments. It must be noted that a number of gene superfamilies encoding drug transporters/receptors has been recently identified. However, none of these families showed a polymorphic level comparable with those observed in the CYP gene superfamily, thus still remains the point of intervention for pharmacogenetics, with drug transporters and receptors playing a minor role.

Translating pharmacogenetics in clinical practice

Several recent papers confirmed the usefulness of pharmacogenetics in the clinical practice, really making pharmacogenetics cross-sectional to several disciplines.

For example, it has been recently demonstrated that CYP2C9 genotyping may be useful to identify subgroups of patients who potentially are at increased risk of gastroduodenal bleeding when treated with CYP2C9-metabolized non-steroidal anti-inflammatory drugs. A more wide role may be identified for CYP2D6 genotyping that may influence: 1) the clinical efficacy of donepezil, an acetyl cholinesterase inhibitor commonly used in the treatment of mild-to-moderate Alzheimer’s disease (AD), being useful in clinical practice in identifying patient subgroups with AD who have different clinical response to donepezil treatment and ii) levels of sedation and analgesia in post-operative pain treatment. Accordingly, the cross-sectional role of CYP2D6 genotyping in the identification of responder/non-responder patients to CYP2D6-metabolized drug has been well documented.

It is noteworthy that all these reported clinical applications may be investigated for their role in a geriatric setting by the simple analysis of CYP gene epigenetic regulation by methylation by using commercially available kits.


discussion and conclusions

The better response to a given drug lies in the midpoint of a continuum of phenotypes in which ADRs and TFs are simply the severe counterperused manifestations. The genetics variability underlying the CYP enzymatic system is the basis of this range of phenotypes on which a number of environmental and physiological factors act to modeling the final phenotype observed in clinical practice. Physiological age-related changes in DNA-methylation, the main epigenetic mechanism regulating gene expression in humans, resulted in a progressive genome-wide demethylation and increased promoter regions hypermethylation through the genome, resulting in a progressive physiological gene silencing. It is also clear that in the context of aging, all genes regulated by DNA methylation tended to be reduced in their expression, including CYP and other genes encoding proteins involved in drug metabolism and distribution. This may be one of the physiological changes that, together with an increased drug use, contributed to raised the prevalence of severe responder phenotypes in the geriatric settings.

It is clear that an increased comorbidity is responsible of an increasing number of concomitant therapies, but not sufficient to justify the increased prevalence of ADRs and TFs observed in geriatric practice. Accordingly, CYP genetic variability, the basis of the interindividual difference in the response to drugs, did not change during lifespan. Thus, to justify the pharmacological condition of a geriatric setting, longitudinal factors changing with age possibly influencing CYP genetics must be identified. Accordingly, the introduction of a physiological mechanism regulating CYP gene expression according to age fill this gap and explained as CYP genetics may be dynamic, assuming a longitudinal role in influencing the prevalence of severe responder phenotypes.

Epigenetic processes regulating gene expression, in particular DNA methylation, well plays this role. DNA methylation is the epigenetic mechanism of gene regulation most conserved by evolution, and the main mechanism by which gene silencing is obtained. It is also well demonstrated that DNA methylation is the dynamic process by which environmental and physiological process might influence gene expression. This means that a progressive reduction of CYP gene expression is expected with advancing age, resulting in unbalanced drug metabolism and a different prevalence of responder phenotypes in a geriatric setting. If this is true, then really pharmacogenetics may be longitudinal, suitable to evaluate longitudinal changes in drug metabolism according to increasing age, thus permitting the application of pharmacogenetics in a geriatric setting. Basically, we did not need further research or knowledge. Up to date, we have all acknowledged needed to translate pharmacogenetics in a geriatric setting. The status of what we know and what we need to know is the base for the clinical applications of pharmacogenetics, in which personalized drug treatments constituted the main aim, in particular in patients attending a geriatric ward.

references


