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Commentary

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Pharmacogenomics and Drug Metabolizing Enzymes

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Introduction

Pharmacogenomics is the combination of pharmacology and genomics. It is the study of genome role in drug response. Pharmacogenomics studies how a person's genetic composition influences their pharmacological reaction. It studies the impact of acquired and inherited genetic variation on drug response in patients by correlating gene expression or single nucleotide polymorphisms with pharmacokinetics and pharmacodynamics. Pharmacogenomics strives to establish reasonable methods for optimizing medication therapy based on a patient's genotype in order to achieve maximal efficacy while minimizing side effects. It is envisaged that by utilizing pharmacogenomics, pharmaceutical drug therapies may be able to depart from the "one dose fits all" strategy. Pharmacogenomics also aims to reduce the trial and error technique of prescription by allowing doctors to consider their patients' genes, how these genes function, and how this may affect the success of their present or future medicines. These approaches promise the upcoming advanced personalized medicine where the drugs and their combinations are optimized for close subsets of patients and even for unique genetic sequence of each individual. Genes are the building blocks of the protein molecules. Each gene instructs different functional protein. Similarly, certain genes could be linked with specific diseases. There are several approved and known genes responsible for the drug metabolism and their response. Drugs are metabolized in many parts of the body including the liver, intestine, lungs and kidneys. The liver being the primary site for drug metabolism, it functions are detoxification, excretion of xenobiotics and deactivation of procarcinogens. The metabolizing enzymes convert the lipid soluble components to more water soluble components. The most prevalent enzymes essential for metabolism of many drugs are cytochrome P450 enzymes.

Cytochrome P450 (Cyp450) Enzymes

Cytochrome P450 is a hemeprotein responsible for metabolism of several drugs and xenobiotics. It is a group of around 50 enzymes that are found and are spread throughout the body, exhibiting their considerable participation in chemical activations and deactivations. Among which six enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) metabolize 90% of the drugs. CYP450 enzymes also play an important role in cholesterol production, synthesis of steroids and prostacyclins and also play a key role in detoxification of chemicals. The most important and abundantly found enzymes are CYP3A4 and CYP2D6. CYP3A4 enzyme is found in liver and intestinal tissues and involves in extrahepatic metabolism. CYP enzymes are responsible for most of the phase I metabolic reactions. Drugs that are metabolized in small intestine undergo phase I metabolism by CYP3A4. Some drugs do not have CYP activity, although, the drugs with CYP activity could inhibit, or induce a specific enzymatic pathway resulting in the alteration of metabolism of parallelly administered agents and some drugs may even cause drug interactions. Grapefruit juice locally acts on the small intestine; it is CYP3A4 inhibitor, inhibiting the enzyme leads to high systemic levels of CYP3A4 active drugs. The variations in gene within the enzymes and diet can influence the activity of the CYP enzymes. In addition to diet and genetic variations, smoking can alter the enzymatic functions; for smoking activates CYP1A2 which increases the drug metabolism resulting lowering the drug levels in the body. CYP1A1 is mainly expressed in lungs, mammary glands, placenta and lymphocytes. This enzyme function involves deactivation of procarcinogens. CYP1A1 is inhibited by cigarette smoke. CYP1A2 enzyme is mainly found in liver, it is induced by cigarette smoke, some foods like cruciferous vegetables and drugs like omeprazole induce the activity of CYP1A2. Theophylline, caffeine, imipramine, paracetamol and phenacitin are the drugs that are metabolized by CYP1A2. When the enzyme activity is induced resulting in altering requirements for metabolizing theophylline among asthmatics. Non-steroidal anti-inflammatory drugs (NSAIDs), the hypoglycemic agent tolbutamide, phenytoin and the angiotensin-II receptor antagonist losartan are the drugs metabolized by CYP2C9. CYP2D6 enzyme metabolizes most of the drugs such as anti-arrhythmics such as flecanide and encainide, tricyclic antidepressants, some beta-blockers and a number of selective serotonin re-uptake inhibitors. CYP2E1 is in charge of metabolizing alcohol and carbon tetrachloride along with the halogenated anaesthetic agents such as halothane, diethyl ether, enflurane, trichloroethylene, chloroform, isoflurane and methoxyflurane. In addition the enzyme also plays a role in breaking down the low molecular weight toxins and carcinogens. CYP3A4 enzyme plays a key role in breaking down over 120 drugs. Among the drugs, the enzyme metabolizes sedatives, antidepressants, anti-arryhthmics, anti-histamines, calcium channel blockers, anti-microbials and protease inhibitors.

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