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EDITORIAL

Disease, Drug Metabolism, and Transporter Interactions

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Drug metabolism is a highly complex process involving the cooperative function of drug transporter proteins and drug-conjugating and -metabolizing enzymes, as well as targeted programs of gene activation and the proteasomal degradation pathway. The transport and metabolism of drugs in intestine and liver mediates the systemic delivery of therapeutic compounds, protects the body from drug toxicity, and initiates droves of signaling cascades that collectively work to maintain the body's homeostatic conditions. The multifaceted nature of drug homeostasis requires a high level of regulation on multiple levels, and thus a disturbance in homeostatic conditions can have major detrimental effects on patient health. There are several disease states (inflammation/diabetes/morbid obesity/cancer) that can profoundly alter key drug transport and/or drug metabolic pathways in liver and intestine. However, the specific molecular mechanisms responsible for producing aberrant drug handling by the body are only beginning to be fully understood. This special theme issue of *Pharmaceutical Research* entitled "Disease, Drug Metabolism and Transporter Interactions" focuses on the molecular impact that specific pathological states have upon the transport and metabolism of drugs in the body, with particular emphasis on disease states that affect the entero-hepatic system. Experts from multiple fields have presented the most recent advances pertaining to the effect of disease states on signaling cascades, drug transporter function and expression, gene transcription, and cellular stress with the intent of presenting novel therapeutic targets to aid in the treatment, prevention and diagnosis of potentially fatal diseases.

The liver and intestine are the primary sites of drug metabolism in the body and therefore disease states that alter hepatic and intestinal regulatory pathways are potentially lethal. Nuclear receptor proteins (NRs) are the primary regulators of the expression of genes encoding drug metabolizing enzymes and several key drug transporter proteins. Thus, a great deal of past and present research is dedicated to the full understanding of NR-mediated pathways and NR expression profiles in both healthy and pathological states. The article "Hepatocyte Nuclear Factor 4 Alpha and Farnesoid X Receptor Co-regulates Gene Transcription in Mouse Liver on a Genome-wide Scale" (Thomas *et al.*) examines the cooperative and independent functions of the nuclear receptors farnesoid x receptor (FXR, NR1H4) and Hepatocyte nuclear factor 4 alpha (HNF4α, NR2A1) on a genome-wide scale in mouse liver. These two NR proteins are critical for proper hepatic function and further elucidation of their interactions with one another may aid in the discovery of therapeutic targets in the treatment of diseases such as cholestasis and hepatocellular carcinomas. Kittayaruksakul *et al.*, further explore the field of NR biology in the article "Identification of Three Novel Natural Product Compounds that Activate PXR and CAR and Inhibit Inflammation." Long before modern medicine, herbal remedies were utilized in the treatment of various illnesses. As homeopathic medicine is growing in popularity, it is becoming increasingly important to more thoroughly characterize these compounds and their effects on drug metabolism and transport on the molecular level. The preganane x receptor (PXR, NR1I2) has a very flexible ligand-binding domain that exhibits broad specificity and is a key positive regulator of drug metabolism. Ligand-activated PXR is also a strong negative regulator of inflammatory signaling pathways in liver and intestine. These characteristics make PXR an excellent candidate in the study of potential anti-inflammatory compounds in these tissues. Unraveling the molecular basis of anti-inflammatory effects of novel PXR herbal-derived agonists is seen as a fruitful area of research in the near future.

Alongside NR-mediated gene activation programs, other liver- and intestine-enriched transcription factors (TFs) play key regulatory roles in drug metabolism and transport, often times in cooperation with NR proteins. The article "Pregnancy Represses

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Induction of Efflux Transporters in Livers of Type I Diabetic Mice" (Aleksunes, *et al.*) outlines the highly cooperative role of NRs and other TFs in the regulation of drug efflux proteins in pregnant mice with type I diabetes. To further the study of TFs, Kulkarni *et al.*, examined the novel regulatory roles of the transcription factor Nrf2 in hepatic steatosis in the article "Caloric Restriction-mediated Induction of Lipid Metabolism Gene Expression in Liver is Enhanced by Keap-1 Knockdown." Caloric-restriction induces fatty-acid oxidation and therefore reverses the effects of hepatic steatosis. Understanding the mechanism by which Nrf2 enhances fatty-acid oxidation in hepatic steatosis could present a therapeutic target in the treatment of other systemic hyperlipidemias. Kulkarni *et al.*, also examined the effects of caloric restriction on hepatic nuclear receptor, transcription factor and drug transporter expression profiles in the article "Effect of Caloric Restriction and AMPK Activation on Hepatic Nuclear Receptor, Biotransformation Enzyme, and Transporter Expression in Lean and Obese mice." Nrf2 primarily functions as a regulator of endogenous antioxidant cascades within the body and therefore acts as a prospective therapeutic target in disease states in which oxidative stress plays a primary factor, such as diabetes. The article "Divergent Effects of Sulforaphane on Basal and Glucose-Stimulated Insulin Secretion in β-Cells: Role of Reactive Oxygen Species and Induction of Endogenous Antioxidants" (Fu *et al.*) examines the effect of sulforaphane (SFN), a plant derived antioxidant, on basal and glucose-stimulated insulin production as well as the effect of SFN on Nrf2 activity.

Though the primary site of drug metabolism is the liver, drug uptake is an equitably important facet of drug metabolism and drug delivery. The study of uptake transporters is especially prevalent in the field of cancer research as transporter proteins are primarily responsible for the therapeutic potential of anti-cancer drugs as well as chemotherapy resistance. Though this is a critical area of research, the profile of drug transporter proteins in various types of cancer remains largely unknown. The article "Organic Anion Transporting Polypeptides Expressed in Pancreatic Cancer May Serve as Potential Diagnostic Markers and Therapeutic Targets for Early Stage Adenocarcinomas" (Hays *et al.*) provides insight to the expression of crucial drug uptake transporters in pancreatic cancer that may not only provide potential drug targets but also potential markers for early diagnosis in a disease with an extremely high mortality rate.

One prominent molecular characteristic of patients with certain types of cancer is reduced hepatic drug clearance. The inability of patients to successfully excrete chemotherapeutic agents adds to the complexities of successfully treating cancer. Therefore, a thorough understanding of the molecular mechanism(s) that govern reduced drug clearance could provide possible molecular targets to alleviate suppressed metabolic abilities, allowing the patients to be safely treated. Kaceveska *et al.*, presents a possible molecular pathway in the article "Extra-hepatic cancer represses hepatic drug metabolism via interleukin (IL)-6 signaling." Along with reduced hepatic drug clearance, cancer patients often develop resistance to chemotherapeutic agents through unknown molecular mechanisms. Williams *et al.*, explore a possible underlying mechanism of chemotherapy resistance in the article, "Role of Intracellular Calcium in Proteasome Inhibitor-induced Endoplasmic Reticulum Stress, Autophagy and Cell Death." A complete understanding of the mechanisms underlying drug resistance to proteasome inhibitors, like Bortezomib, would provide molecular targets for further drug design allowing more effective treatment of patients with cancers like multiple myeloma.

Though drug metabolism is an essential process required to sustain life, there are certain conditions in which an increase in the activation of drug metabolizing cytochrome (CYP) P450s can increase the potential for toxicity or intensify the symptoms of a disease. For example, Acetaminophen (APAP) is metabolized via CYP P450s to reactive metabolites that if accumulated initiate mitochondrial dysfunction, oxidative stress and alterations in the expression of hepatic drug transporters. McGill *et al.*, present a comprehensive evaluation of APAP metabolism, toxicity, and the formation of intermediates and reactive metabolites in the expert review "Metabolism and Disposition of Acetaminophen: Recent Advances in Relation to Hepatotoxicity and Diagnosis." Inhibition of CYP P450 activity has also been proven to be beneficial in certain cancers. Blake *et al.*, demonstrates that the selective inhibition of CYP2A13 reduces the biotransformation of the procarcinogen NKK and therefore presents a novel therapeutic strategy to reduce the risk of lung cancer in tobacco users. The article "Benzylmorpholine Analogs as Selective Inhibitors of Lung Cytochrome P450 2A13 for the Chemoprevention of Lung Cancer in Tobacco Users" (Scott *et al.*) presents an analysis of 24 different 4-benzylmorpholine analogs that have the potential to selectively inhibit CYP2A13 activity.

Drug metabolism is a highly complex system involving simultaneous cooperation of multiple organs and cellular processes. In the healthy patient, most drugs are transported into the liver, enzymatically altered, and then removed from the body by one of several methods. Disease states have differential effects on healthy metabolic regulatory systems; therefore it is crucial to continue elucidating the molecular profile of drug transporters and drug metabolizing and conjugating enzymes as well as the underlying signaling cascades and molecular targets specific to each disease state. This theme issue of Pharmaceutical Research presents some of the most recent advances in the interaction between disease states and metabolic regulatory pathways. Each article presents possible molecular targets and underlying mechanisms that provide valuable insight for researchers. It is highly possible that this insight will allow for the development of new drugs allowing for a more efficient means to treat patients with evolving or untreatable illnesses.

Jeffrey Staudinger is Professor in the Department of Pharmacology and Toxicology at the University of Kansas School of Pharmacy in Lawrence, Kansas. He received his B.S.(1987, Biology) from Nebraska Wesleyan University and his M.S. (1994, Biochemistry and Molecular Biology) and Ph.D. (1996, Biochemistry and Molecular Biology) from the University of Texas Graduate School of Biomedical Sciences. His professional experience includes Postdoctoral Research Fellow (1996–1999), Nuclear Receptor Group, GlaxoWellcome Research; Senior Postdoctoral Fellow (2000–2001), Department of Pharmacology, Toxicology and Experimental Therapeutics, University of Kansas Medical Center; Assistant Professor (2001–2006), Department of Pharmacology and Toxicology, University of Kansas School of Pharmacy; and Associate Professor (2006-present), Department of Pharmacology and Toxicology, University of Kansas School of Pharmacy. Dr. Staudinger's laboratory is interested in basic regulatory mechanisms in toxicology. He works primarily with mice and tissue culture as model systems to investigate two major questions: (1) What role do ligand-activated transcription factors play in regulating xenobiotic homeostasis? (2) What signal transduction pathways interface with ligand-activated transcription factors in mediating xenobiotic homeostasis. Dr. Staudinger has been a member of the American Society for Pharmacology and Experimental Therapeutics (ASPET) since 2004 in the Drug Metabolism, Molecular Pharmacology, and Toxicology divisions. He is a member of the American Association for the Advancement of Science, American Society for Biochemistry and Molecular Biology, and International Society for the Study of Xenobiotics. He also serves on the Editorial Advisory Board for *Molecular Pharmaceutics*.