

Special Section on Mechanistic and Translational Research on Transporters in Toxicology—Editorial

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The special section, “Mechanistic and Translational Research on Transporters in Toxicology,” features articles contributed by Dr. Lauren M. Aleksunes and some of her former and current collaborators. Dr. Aleksunes presents a comprehensive review of transporter regulation in the placenta during pregnancy complications. The special section also collects one review article focused on the role and regulation of ATP-binding cassette (ABC) transporters in the liver during drug-induced liver injury (DILI) and three original research articles focusing on the regulation of transporters *in vitro* or *in vivo* following exposure to environmental pollutants.

Dr. Aleksunes was the recipient of the Richard Okita Early Career Award given by the Drug Metabolism and Disposition Division of the American Society for Pharmacology and Experimental Therapeutics in 2019 (Fig. 1). The award was established to recognize excellent original research by early-career investigators in drug metabolism and disposition. Dr. Aleksunes was recognized for her mechanistic and translational research on elucidating critical roles of transporters in xenobiotic disposition and in the protection of multiple organs against chemical toxicities. She received both her Pharm.D. and Ph.D. at the University of Connecticut. As a Pharm.D. student, Dr. Aleksunes conducted her University Scholar’s thesis work under the mentorship of Dr. Steven Cohen. She then completed her doctoral work under the mentorship of Dr. José Manautou, followed by postdoctoral training in Dr. Curtis Klaassen’s laboratory at the University of Kansas Medical Center. She became a tenure-track faculty member at the Ernest Mario School of Pharmacy and the Environmental and Occupational Health Sciences Institute at Rutgers University, where she has moved through the ranks to her current position as professor of pharmacology and toxicology and director of the Joint Graduate Program in Toxicology. Her laboratory investigates how drug transporters in the liver, kidneys, brain, and placenta protect against the accumulation and toxicity of pharmaceuticals and environmental chemicals.

The movement of ions, nucleosides, peptides, metabolites, lipids, and other essential nutrients across a biologic membrane relies on specialized membrane-spanning proteins, named membrane transporters. These proteins are categorized into three families: P-type ATPases, ABC transporters, and solute carriers (SLCs). P-type ATPases contain five subfamilies, designated as P1 to P5, and mainly translocate ions and lipids across membrane using the energy derived from ATP hydrolysis. ABC transporters are divided into seven subfamilies, designated from ABC-A to ABC-G, which use ATP as the energy source to translocate various substrates including lipids, sterols, and xenobiotics. SLC transporters consist of over 400 genes that are organized into 66 subfamilies, and they act as facilitative or secondary active transporters. SLC transporters can transport a diverse array of substrates, including nutrients, ions, hormones, and nucleosides, either downhill or uphill against their concentration gradients across biologic membranes using secondary energy sources provided by ion gradients or electrochemical potential differences.

Over the past decades, changes in functional activities or tissue expression of transporters have been directly connected with the onset of an increasing number of human diseases, or indirectly with the disease progression. For example, *ABCC7*, an ABC transporter known as cystic fibrosis transmembrane conductance regulator (CFTR), transports chloride and bicarbonate ions across plasma membranes of epithelial cells to maintain ion and fluid homeostasis in the lung (Smith and Welsh, 1992). Mutations in *ABCC7* alter CFTR’s functional expression and cause cystic fibrosis (Nguyen et al., 2021). Therefore, it is becoming increasingly important to understand the regulation of gene expression of transporters under physiologic and pathophysiologic conditions, as well as their response to therapeutic reagents and environmental pollutants.

Regulation of Placental Efflux Transporters during Pregnancy Complications

The placenta is a developing organ during pregnancy, and it contains the syncytiotrophoblast cell barriers that separate the fetus from the mother’s circulation. The barrier allows the reliable delivery of oxygen, hormones, and nutrients from the mother to the fetus during gestation and the removal of waste from the fetus. Many ABC and SLC transporter proteins are expressed in the syncytiotrophoblast cells of the placenta, which facilitate the transplacental transport of essential nutrients and efflux of harmful xenobiotics. In this review article, Dr. Aleksunes and her colleagues (Kozlosky et al., 2022) critically examine the regulation of efflux transporters in the placenta during medical complications of pregnancy. These complications include inflammation and infection in placenta, hypertensive and metabolic disorders, and fetal growth restriction with gestational age. The review summarizes the importance of up- or downregulation of transporter genes during pathophysiologic conditions in the placenta. The authors highlight that ABC transporters play a critical role in regulating the fetal expo-

ABBREVIATIONS: ABC, ATP-binding cassette; AD, Alzheimer’s disease; CFTR, cystic fibrosis transmembrane conductance regulator; DILI, drug-induced liver injury; NASH, nonalcoholic steatohepatitis; OAT, organic anion transporter; OTA, Ochratoxin A; PFCA, perfluorinated carboxylic acid; SLC, solute carrier.

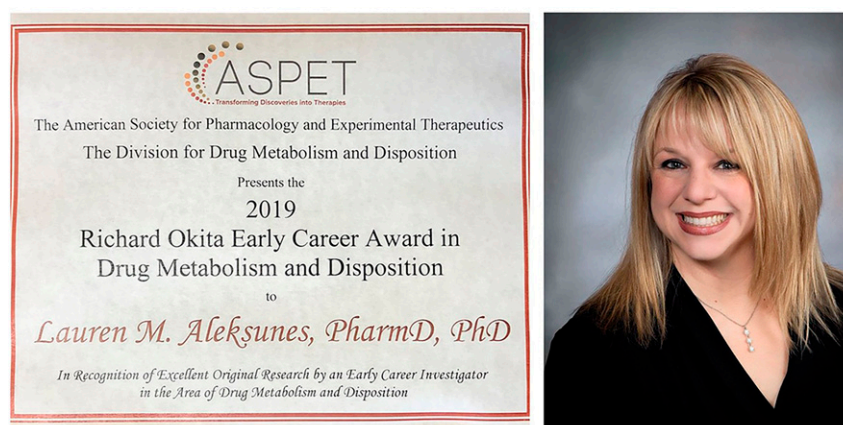


Fig. 1. Dr. Lauren M. Aleksunes was the recipient of the Richard Okita Early Career Award given by the Drug Metabolism and Disposition Division of the American Society for Pharmacology and Experimental Therapeutics in 2019. Photos are reproduced with permission from Dr. Lauren M. Aleksunes.

tures of drugs and environmental pollutants. With some exceptions, diseases during pregnancy can reduce the expression of efflux transporters and increase the potential risk of placental accumulation and fetal exposure of xenobiotics.

Regulation of ABC Transporters during DILI

Being the largest digestive organ in the body, the liver is responsible for removing metabolic wastes and detoxifying most xenobiotics and, consequently, is a prime target for the toxicity of many drugs. While hepatotoxicity of acetaminophen, one of the most widely used analgesic drugs, is well-recognized, virtually all classes of pharmacological therapeutics can cause liver injury. The liver expresses many membrane transporter proteins. ABC transporters are expressed at both the sinusoidal and canalicular membranes of hepatocytes and are involved in drug efflux from hepatocytes. In contrast, SLC transporters, including organic anion transporting polypeptides and organic anion transporters (OATs), are localized on the sinusoidal membrane of hepatocytes and mediate drug uptake from blood into hepatocytes. Together with metabolizing enzymes in the liver, these transporters play a key role in determining the concentrations of a drug and its metabolites in hepatocytes and contribute to DILI. In this special section, Dr. José Manautou and his long-term collaborator, Dr. Carolina Ghanem from the University of Buenos Aires (Ghanem and Manautou, 2022), provide a comprehensive summary on the “Role and Regulation of Hepatobiliary ATP-Binding Cassette Transporters during Chemical-Induced Liver Injury.” As stated above, Dr. Manautou was the predoctoral mentor of Dr. Aleksunes, and is currently the Boehringer-Ingelheim Pharmaceuticals, Inc. chair in mechanistic toxicology and department head of pharmaceutical sciences and professor of toxicology at the University of Connecticut. Drs. Manautou and Ghanem critically review recent advances in the study of drug transporters and DILI by examining the contribution of hepatic ABC transporters to and the impact of transporter alteration on overall toxicity outcome of DILI. The review article calls attention to the study of the knowledge gaps in the epigenetic regulation of liver transporter expression, drug-host interactions, and the role of gastrointestinal microbiota in interindividual differences in DILI susceptibility, as well as the combined contributions of all these factors to DILI.

Transporter Gene Expression and Responses to Environmental Pollutants

Ochratoxin A (OTA) is produced by various fungi and is a common mycotoxin found in a wide variety of food commodities. OTA is a genotoxic carcinogen that can form DNA adducts via quinone formation to cause oxidative DNA lesions and induce nephrotoxicity in animal species (Bui-Klimke and Wu, 2015). OTA is thought to be linked with human Balkan endemic nephropathy, chronic interstitial nephropathy, and urothelial track cancers. OTA can bind to the brain and cause depletion of striatal dopamine, which is a prime culprit in Parkinson’s disease. Results from *in vitro* studies also suggested that OTA exposure may contribute to the development of Alzheimer’s (AD) and Parkinson’s diseases (Zhang et al., 2009). Human exposure to OTA can occur through food ingestion. In this special section, Dr. Nathan J. Cherrington and his colleagues (Jilek et al., 2022) investigate the alterations in expression of renal transporters during nonalcoholic steatohepatitis (NASH) in mice and their impact on OTA disposition and subsequent nephrotoxicity. Dr. Cherrington is a close collaborator with Dr. Aleksunes. He is currently an associate dean for research at the College of Pharmacy, the director of the Southwest Environmental Health Sciences Center, and the director of the Arizona Board of Regents Center for Toxicology at the University of Arizona. In the current investigation, Dr. Cherrington’s group found that the expression of OAT1-5 in NASH mice was decreased by about half relative to expression in healthy mice. The accumulation of OTA in proximal convoluted tubule cells through OAT-mediated uptake was decreased and the renal excretion of OTA was robustly increased in NASH mice. As a result, the attenuated renal OAT transporter expression in NASH mice protected against renal toxicity. The research emphasized the importance of understanding the alterations of transporter expression and their

influence on drug efficacy, as well as on the systemic clearance or toxicity of drugs and environmental pollutants in NASH or other diseases.

Unwanted human wastes can contaminate water, air, and food and become environmental pollutants. Constant exposure to environmental pollutants can result in harmful long-term health consequences and is a leading risk factor to human health (Peters et al., 2021). Perfluorinated carboxylic acids (PFCAs) possess excellent heat and chemical resistance and are widely used in many consumer products. PFCAs can undergo OATP-mediated active uptake to accumulate in the liver (Zhao et al., 2017) and stay a long period of time in the body, causing adverse effects on human health. In a study of the effects of PFCAs at the molecular level, Dr. Julia Yue Cui and her colleagues report that “PFCAs with increasing carbon chain lengths upregulate amino acid transporters and modulate compensatory response of xenobiotic transporters in HepaRG cells” (Lim et al., 2022). Dr. Cui graduated from the University of Kansas Medical Center under the mentorship of Dr. Curtis Klaassen and has been a close collaborator with Dr. Aleksunes. She is currently an associate professor in toxicology at the University of Washington Department of Environmental and Occupational Health Sciences. She is also the director of the University of Washington Environmental Health and Microbiome Research Center and the Genomics, Bioinformatics and Biostatistics, and Microphysiological System Core of the University of Washington Interdisciplinary Center for Exposures, Diseases, Genomics and Environment and previously held the Sheldon D. Murphy Endowed Chair in Toxicology and Environmental Health. In the current study, Dr. Cui identifies over 30 common target genes associated with the treatment of all three PFCAs tested. Of those, most of the regulated genes are involved in amino acid transport and carbohydrate metabolism. The regulation of PFCA-mediated transporter genes in HepaRG cells likely activates the nuclear factor erythroid 2-related factor, but not the peroxisome proliferator-activated receptor α or the constitutive androstane receptor. The authors demonstrate that the PFCAs with a longer carbon chain regulates a greater number of genes than the PFCAs with a shorter chain in HepaRG cells and appear to be the most potent modulator in hepatic transcriptomic response.

In the second investigation, on the “Effect of Chronic Cadmium Exposure on Brain and Liver transporters and drug metabolizing enzymes in male and female mice genetically predisposed to Alzheimer’s Disease” (Wang et al., 2022), Dr. Cui and her colleagues used an AD mouse model to investigate the effects of cadmium exposure on the transcriptomes of transporter and drug-metabolizing genes in the liver and brain to elucidate the interactions of a genetic risk factor (the apolipoprotein E4 (ApoE) allele—the strongest known genetic risk factor for AD) with exposures to environmental pollutants. Cadmium has been extensively used in industry (e.g., Ni/Cd batteries) and is generally present at low levels in the environment. Exposure to cadmium can result in a diverse array of adverse effects on human health, such as cancer, anemia, kidney and liver damages, and cardiovascular diseases. Cadmium can thoroughly penetrate the central nerve system and act as a neurotoxicant associated with increased risks of AD. In this investigation, Dr. Cui and colleagues showed that cadmium can alter the transcriptomes of both the liver and brain in a sex- and ApoE genotype-dependent manner.

In summary, this special section on “mechanistic and translational research on transporters in toxicology” provides a snapshot of the current state of research on three related topics: placental efflux transporters during pregnancy complications, ABC transporters in DILI, and transporter expression in response to environmental pollutants. This special section also highlights the importance of research on xenobiotic transporters and the contributions by Dr. Lauren M. Aleksunes and her collaborators to the field.

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