Pharmaceutical Research, Vol. 25, No. 2, February 2008 (© 2007)
DOI: 10.1007/s11095-007-9437-7

Editorial

Membrane Transporters in Drug Disposition

Published online September 11, 2007

Membrane transporters are the gatekeepers for all cells, controlling the flux of crucial endogenous substrates such as sugars, amino acids, nucleotides, and inorganic ions into and out of the cells. Many of these transporters also transport drugs that bear similar structures as their endogenous substrates. Consequently, these transporters crucially influence the absorption, distribution and elimination of drugs in the body.

One important area of investigation in understanding the role of transporters in drug disposition is how these transporters are regulated. Alterations in the function of these drug transporters play an important role in the intra- and inter-individual variability of the therapeutic efficacy and the toxicity of the drugs. As a result, the activity of drug transporters must be under tight regulation so as to carry out their normal duties. Key players involved in the regulation of transporters include hormones, protein kinases, nuclear receptors, scaffolding proteins, and disease conditions. These factors may affect transporter activity at various levels such as when and how often a gene encoding a given transporter is transcribed (transcriptional control). They may also affect how the primary RNA transcript is spliced or processed (RNA processing control) and how the mRNA is then translated in the cytoplasm by ribosomes (translational control). Furthermore, these factors may then determine the destabilization rate of these mRNA molecules in the cytoplasm (mRNA degradation control), and finally they may regulate how the transporter protein is modified and assembled after it has been translated (posttranslational control). This theme issue presents several articles related to the regulation of drug transporters. Wang *et al*. investigated the effects of several pregnancy-related hormones on the mRNA and protein expression of breast cancer resistant protein (BCRP) in human placental BeWo cells. Their data support the hypothesis that BCRP expression in the placenta and other tissues can be regulated by multiple hormones, either independently or cooperatively. Sun *et al*. examined pathways affecting the plasma membrane localization of human organic anion transport polypeptide OATPC. They showed that the membrane expression of OATPC is mediated by Golgi complex and vacuolar H^+-ATPase vesicle mediated membrane sorting pathways. cAMP-PKA regulates sorting process through the Golgi complex but not the vacuolar H^+-ATPase associated vesicular pathway. Zhou *et al*. explored how one transporter can be differentially regulated in different tissues through interacting with different sets of partners.

The studies mentioned above were carried out in cultured cells. The cell culture is a convenient system, in which there is little ambiguity over the identity of the transporter. However such system might not completely reflect the native membrane environment, where several transporters are expressed on the same membrane of the same tissue. Due to the broad substrate specificities of transporters, one compound is often recognized by multiple transporters. In such situation, discrimination between the contributions of multiple transporters is more of a challenge. To meet such challenge, the *in vitro* data have to be validated through *in vivo* studies. Development of knockout or knockdown mice is an effective approach for the *in vivo* investigation of the drug transporters. RNA interference technology provides a convenient method for knockdown research in animals. An example of combining *in vitro* data with *in vivo* studies is presented in this theme issue, in which Sweet *et al* elucidated the role of the renal basolateral transporter, Oat3, in the disposition of methotrexate in both Chinese hamster ovary cells expressing mouse Oat3 and in Oat3 knockout mice.

The research articles featured in this theme issue were contributed by experts in the drug transport field and are examples of the focused efforts in drug transport research. Understanding the contribution of drug transporters in drug disposition will have significant impact on the future design of strategies aimed at maximizing therapeutic efficacy and minimizing drug-related toxicity.

INTERVIEW QUESTIONS

What Do You Think Holds the Key to Your Success as a Pharmaceutical Scientist?

Response. The achievement I have made so far can be attributed to have had great education, great mentors and colleagues, a stimulating environment to work, and many talented, and hard-working post-doctoral fellows and graduate students.

What Do You Consider to be Your Key Research Accomplishments?

Response. I would like to mention two of these. The first one is the cloning and identification of the first urea transporter from the kidney during my post-doctoral period at Harvard Medical School. Urea transporters play central role in body water balance. The cloning of this transporter corrected the concept, which had been in the textbook for 20 years that urea moves across cell membrane only through passive diffusion. Since the cloning, the research in urea transport field has been fast moving forward at the molecular level. The second involves the thorough investigation of the regulation of organic anion transporter (OAT), a group of drug transporters, by post-translational modification. OAT is a new family of transporters, responsible for the body disposition of clinically important anionic drugs including anti-HIV therapeutics, anti-tumor drugs, antibiotics, anti-hypertensives, and anti-inflammatories. The expression of OAT is detected in kidney, liver, brain and placenta. OAT dysfunction in these organs may contribute to the renal, hepatic, neurological and fetal toxicity and disease. During the past couple of years, my laboratory has demonstrated that the function of OAT can be regulated by glycosylation, phosphoylation, and interaction with other proteins. Understanding the regulation of these transporters will impact on the future design of strategies aimed at maximizing therapeutic efficacy and minimizing toxicity, and will permit insight into the molecular, cellular and clinical bases of renal, hepatic, neurological and fetal toxicity and disease.

What was the Turning Point in Your Career?

Response. Cloning the first urea transporter cDNA during my post-doctoral period at Harvard Medical School gave me the confidence in pursuing research in membrane transport field. Obtaining my first NIH grant shaped my career. I remain grateful for those who gave me genuine advice on how to write my first NIH grant.

Who are the Individuals Who Most Influenced Your Research Career?

Response. There have been many people who have had important influence on my career. My father had always encouraged me to try the best in what I chose to do. My Ph.D. supervisor Donald Nelson recruited me from China to his laboratory, which changed my life forever. My husband, with his own busy career, has always been supportive of my work. I also have the enormous support from my friends and collaborators.

Pharmaceutical Scientists are Faced with the Dilemma of Having to Publish in Biomedical or Basic Science Journals. Does it Mean Cutting Edge Science will not Likely be Featured in the Pharmaceutical Research?

Response. There are many ways to make Pharmaceutical Research a place where people would want to submit their work in basic science research. In recent years, the journal has made great effort by including scientists in biomedical and basic science field to the editorial board, which is one of the approaches to attract many excellent scientists in biomedical and basic research field to submit their findings.

Where is the Field of Drug Transporters Going, and How Do the Articles in the Theme Section Fill the Gap?

Response. Drug transporters crucially influence the absorption, distribution and elimination of drugs in the body. With more such transporters being identified, future directions aim at elucidating the structural basis of substrate transport of these transporters and the complex mechanisms underlying their regulation. Such information is critical in the design of strategies to maximize therapeutic efficacy of the drugs and to minimize their toxicity. To achieve this goal, detailed characterization of individual transporters using *in vitro* systems has to be combined with their *in vivo* studies using animal models. The articles featured in this theme issue are representatives of such effort.

What is the Key to Developing Successful Collaborative Relationships?

Response. Both sides could offer unique techniques.

What is Your Philosophy of Educating Graduate Students?

Response. Graduate students are at a transition stage from being given answers to providing answers. I tried to give students enough room, allowing them to make mistakes and to grow from these mistakes.

What are the Challenges Facing the Pharmaceutical Sciences?

Response. With more drug transporters being isolated, great advance has been made in their characterization. However, characterization of the transporters in isolation such as in transfected cells only provides part of the picture. *in vivo*, the loss of function of one transporter may result in the up-regulation of another transporter to compensate for the loss. The integration of the *in vitro* data with *in vivo* studies requires development of knockout mouse models. With that tool, the contribution of each transporter to overall disposition of a drug and its therapeutic efficacy can then be more accurately predicted.

Guofeng You received her undergraduate education in Peking Medical University, P.R. China and her Ph.D. in Biochemistry from the Department of Chemistry, Clark University, Worcester, MA, USA. She then worked as a postdoctoral fellow in the Department of Medicine, Harvard Medical School, where she pursued her research in the cloning and characterization of several novel transporter proteins. In 1997, she accepted a position as Assistant Professor in the Department of Medicine, the Mount Sinai School of Medicine, to further her research in the field of drug transport. She is now an Associate Professor in the Department of Pharmaceutics, the Ernest Mario School of Pharmacy, Rutgers-the State University of New Jersey. She has authored many peer-reviewed papers in drug transport and is currently on the editorial Board of *Pharmaceutical Research*. She has recently co-edited with Professor Marilyn Morris a book entitled "Drug Transporters" published by Wiley & Sons, Inc. The book is the first to cover the basic transport mechanisms, clinical implications of transporters in human physiology and disease, and their role in drug therapy.

Guofeng You
Pharmaceutics, Rutgers University,
160 Frelinghuysen Rd,
Piscataway, New Jersey 08854, USA.
email: gyou@rci.rutgers.edu