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Author
Giacomini, Kathleen M

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The Use of Drug Transporters as Therapeutic Targets

Kathleen M. Giacomini, PhD
Professor and Co-Director
UCSF-Stanford Center of Excellence in Regulatory Sciences and Innovation
UCSF School of Pharmacy
San Francisco, California

H&O What is the role of transporters in cell biology?

KG Transporters are proteins that play a role in bringing small molecules—such as endogenous compounds, vitamins, amino acids, nutrients, and drugs—across biological membranes. Transporters may mediate influx or efflux, or they may be bidirectional. Bidirectional transporters facilitate the movement of substrates across membranes in either direction from the intracellular to the extracellular compartments or vice versa. Transporters that are predominantly influx bring substrates into the cell. Transporters acting as efflux pumps protect organs by pumping drugs and other substances out of the cell.

My research focuses mostly on transporters on the plasma membrane or the cell membrane. It encompasses 3 major areas: transporters in absorption, distribution, metabolism, and elimination (known as ADME), the pharmacogenomics of transporters, and the endogenous role of transporters that have been predominantly characterized as drug transporters. I work on the solute carrier superfamily, which contains almost 400 transporters throughout the human genome. They are clustered into 52 families. Each transporter is unique and does something different.

H&O What is the goal of your research?

KG Within the areas of pharmacogenomics and ADME, the goal is to determine how transporters may affect variation in drug response and drug levels. For example, there may be genetic variants in transporters that people carry that cause them to respond differently to a given drug. Another goal is to determine the endogenous role of those transporters that have been predominantly characterized as drug transporters. Many transporters play a significant role in normal human physiology as well as in disease. I would like to know what these transporters do when they are not interacting with drugs.

H&O In what ways do transporters act on drugs?

KG Drug transporters can act in several ways, which are specific to each organ. In the intestines, some transporters bring drugs into the body and enhance their absorption. Other transporters in the intestine protect the body against ingested toxins from plants and animals. These transporters modulate drug absorption by pumping the drugs out of the intestine or keeping them in the intestinal lumen. Transporters can bring drugs into the liver where they can be metabolized. In the kidneys, transporters can actively eliminate drugs so that they are excreted in the urine. Sometimes transporters may serve to facilitate reabsorption of drugs in the kidneys. Within the blood-brain barrier, transporters can bring drugs into the brain or keep them out.

H&O How are transporters used as therapeutic targets?

KG The use of transporters as therapeutic targets is an interesting new field of study. In 2015, my colleagues and

I published an article in *Nature Reviews Drug Discovery* describing more than 80 transporters that have mutations in more than 100 Mendelian diseases. Each one of these mutations could be targeted to treat the disease. Transporters therefore represent a host of new therapeutic targets for treating rare diseases.

Transporters can also be targeted to treat more common diseases. Diabetes is one example. It is possible to target transporters in the kidney that reabsorb glucose. The body wants to conserve glucose. Targeting these transporters will prevent the body from doing so, and the glucose will be spilled into the urine. The gliflozins are a new class of drugs that target the sodium-glucose cotransporter 2 (SGLT2) in the kidney and prevent the reabsorption of glucose.

In rapidly dividing cancer cells, it may be possible to target nutrient transporters. Targeting these transporters could prevent the tumors from attaining essential nutrients so that they die.

H&O How can genetic variations in transport genes impact drug response?

KG There are several ways. Missense or nonsynonymous variants in transporters can lead to changes in amino acids. These variants can alter the structure of the transporter protein, and perhaps how it interacts, binds to, or translocates the drug substrates. In patients with a nonsynonymous variant, the transporter may interact less effectively with the drug that it normally translocates.

Other genetic variants will affect the expression level of the transporters. For example, a transporter that is usually expressed at a very high level may be expressed at a much lower level in people with a particular genetic variant. Many genetic variants are turning up in genome-wide association studies.

H&O How do transporter polymorphisms impact clinical drug response?

KG Here is an example of a well-known polymorphism that affects drug response. A transporter in the liver, organic anion transporting polypeptide 1B1/SLCO1B1 (OATP1B1), has a common polymorphism that results in an amino acid change. The polymorphic transporter, with the amino acid change, is less effective in transporting its substrates. OATP1B1 interacts with statins by bringing them into the liver, where they can access their target and, importantly, be metabolized. The polymorphic transporter of OATP1B1 takes up statins less effectively, decreasing their access to the liver. Higher drug levels are then achieved because the statins cannot be metabolized or are metabolized at a much slower rate. The high levels of statins can lead to muscle toxicity, a major toxicity of statins that led to the withdrawal of cerivastatin from the market.

H&O What is the endogenous role of membrane transporters?

KG Many transporters transport endogenous molecules such as glucose, amino acids, and nucleoside analogues. However, some transporters take up foreign substances (xenobiotics), such as environmental toxins and drugs. For transporters that have been predominantly characterized as drug transporters, their endogenous role is not yet known. Research in this area has just begun. For example, in 2014, we published an article showing that the organic cation transporter 1 (OCT1), which is characterized almost exclusively as a drug transporter, is the major transporter for vitamin B_1 (thiamine) in the liver. Prior to our work, the transporter's function was thought to be in transporting drugs and various foreign molecules into the liver so they could be metabolized.

H&O Are there any examples in which drug transporters have been used to develop therapies for hematology/oncology?

KG It is possible to target transporters that are highly expressed in tumors. Transporters can be used as delivery systems to deliver drugs to tumors. Chemotherapies can be modified to interact with these transporters and use the transporters to gain access to the tumor cells. An example is oxaliplatin, a platinum agent used primarily in the treatment of colorectal cancer. Data suggest that oxaliplatin accesses the tumor through organic cation transporters expressed on the tumor cell. Another example is methotrexate, which uses the reduced folic acid carrier to gain access into leukemia cells and other cells.

H&O What are the clinical implications of your research?

KG Our research will impact the delivery of precision medicine. Genetic variants in transporters can change a patient's risk for drug toxicity and/or modulate the efficacy of the drug. Knowing that a patient has a particular genetic variant could allow treatment to be modified, either by providing a lower dose of a certain drug or by changing treatment to a different drug.

Understanding the endogenous role of transporters will help us comprehend why human disease develops and progresses, allowing the identification of new drug targets. As an example, genome-wide association studies have revealed a host of transporters that are involved in

uric acid disposition. New drugs have been developed to target these transporters.

Our research may also provide information about drug-drug interactions, which may be mediated by transporters.

H&O Are there any new insights into the role of drug transporters?

KG Yes, there are many new insights, but I will give you one example. There are very interesting discoveries coming from studies of gout. Human glucose transporter 9 (GLUT9) was known to transport fructose and glucose. GLUT9 was recently shown to be an excellent transporter for uric acid in genome-wide association studies and follow-up studies in cells. GLUT9 therefore represents a potential target for the treatment of gout (although no drugs are yet on the market). It is another example of a transporter with unexpected activity. Our recent work on metformin highlights an important role for GLUT2, another member of the glucose transporter family, in response to this antidiabetic drug.

H&O What are some future areas of study?

KG More attention will be focused on the endogenous role of drug transporters. Genetic variants in transporters at genome-wide level significance have been shown to impact the risk for various human diseases, such as cancers, diabetes, and cardiovascular disease. It is not yet known how genetic variation in many of these transporters can exert these effects. There is a wealth of information that biologists can mine to understand the role of transporters in human disease and even physiologic traits.

Another new area will be targeting the mutant transporters seen in rare Mendelian diseases, which currently lack treatment options. The role of transporters in biological systems will also be explored. For example, an amino acid transporter works in concert with enzymes to synthesize proteins for amino acid, and glucose transporters work with enzymes to metabolize glucose. Transporters do not work in isolation, and understanding their role in pathways and as part of biological systems is critical.

Disclosure

Dr Giacomini is a cofounder of a start-up biotech company, Apricity Therapeutics, Inc, which is focused on using transporters to improve delivery of anticancer drugs to tumors.

Suggested Readings

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