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Metformin Pharmacogenomics: Biomarkers to Mechanisms

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Pharmacogenomics is the study of the contribution of inheritance to variation in drug response—variation that can range from a loss of the desired therapeutic effect at one end of the spectrum to an adverse drug reaction at the other (1,2). The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) recently sponsored a workshop on the pharmacogenomics of metformin, the most widely prescribed drug for the treatment of type 2 diabetes. Metformin displays wide variation in efficacy and occasional serious adverse reactions (3). A report of that workshop is published in this issue (4). Pawlyk et al. (4) provide an overview of the current status of metformin pharmacogenomics as well as insight into the current state of pharmacogenomics as a discipline. Pharmacogenomic information is increasingly being implemented clinically and is being used to adjust drug dosage or to avoid adverse drug reactions (5). At the same time, pharmacogenomic research has moved from a focus on the contribution of genetics to variation in processes that we already understand—for example, drug metabolism and known drug target(s)—to also become a tool for discovery by using techniques as diverse as genome-wide association studies (GWAS), next-generation DNA sequencing, genomic studies of patients enrolled in very large clinical consortia, or the addition to genomic information of other, complementary "omics" data sets. Application of these techniques has made it possible to move beyond merely identifying biomarkers to obtaining novel mechanistic insights. Several of these experimental approaches have already been applied to study inherited variation in metformin response or were suggested by participants in the NIDDK workshop. There has already been significant progress in our understanding of metformin pharmacogenomics, particularly with regard to its pharmacokinetics, i.e., factors that determine the concentration of drug that reaches its target(s). However, many questions remain unanswered, especially with regard to metformin pharmacodynamics, i.e., targets for the drug, downstream signals from those targets, and mechanisms of drug action.

Metformin, unlike most drugs, does not undergo biotransformation. It is not metabolized (6). However, it is transported into and out of cells and organs (7–9). There have been successful pharmacogenomic studies of metformin transporter genes such as *OCT1* (*SLC22A1*), *MATE1* (*SLC47A1*), and *MATE2* (*SLC47A2*) (Fig. 1) (7–9). However, even though *OCT1* encodes the major metformin transporter in the liver and is functionally genetically polymorphic, and even though common genetic polymorphisms in the *MATE1* and *MATE2* genes have been associated with altered metformin-related glucose-lowering effect, the practical clinical utility of these transporter gene polymorphisms remains to be demonstrated. The same is true of polymorphisms identified during a candidate gene study of 40 genes in potential metformin target pathways, such as the AMP-activated protein kinase pathway (10).

There are now many examples in which GWAS have been applied successfully to study drug response, both efficacy and adverse drug reactions, in the setting of large prospective clinical trials (11,12). Many population-based pharmacogenomic GWAS have also been performed. The one large metformin response GWA study that has been published, the Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) study (13–15), a population-based study, reported a genome-wide association "signal" on chromosome 11 in an area containing seven genes, including the *ATM* (ataxia telangiectasia mutated) gene. However, functional validation of a possible role for *ATM* in metformin response remains a subject of controversy (16,17). As a result, although pharmacogenomic studies of metformin have already helped us to understand the role of inheritance in its pharmacokinetics (Fig. 1), and although intriguing initial results have been obtained, the clinical utility of those observations remains to be demonstrated, and the critical question of clinically relevant genetic variation in targets for the drug also remains unanswered. However, if

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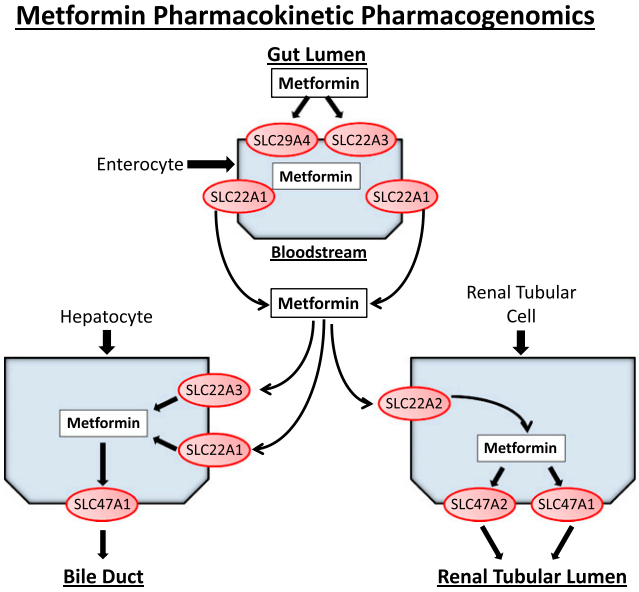

Figure 1—Schematic representation of the cellular locations of SLC transporters that contribute to metformin pharmacokinetics. It has been reported that the genes encoding SLC22A1, MATE1, and MATE2 are genetically polymorphic and that these polymorphisms contribute to individual variation in metformin pharmacokinetics (7–9). SLC22A1 = OCT1, SLC22A2 = OCT2, SLC22A3 = OCT3, SLC29A4 = ENT4, SLC47A1 = MATE1, and SLC47A2 = MATE2.

the suggestions made at the NIDDK workshop can be implemented—such as the creation of a large national or international consortium for metformin pharmacogenomic studies or complementing pharmacogenomic studies with other "omics" techniques (e.g., metabolomics)—we might anticipate future insight into mechanisms of metformin action and potentially the identification of novel drug targets for the treatment of type 2 diabetes. In addition, although the use of metformin to treat or prevent cancer was not addressed during the NIDDK workshop, pharmacogenomic studies might also contribute to that expanding clinical application of metformin (18). As a result, implementation of the recommendations and suggestions contained in the report by Pawlyk et al. (4) might help make it possible to identify and validate biomarkers with clinical utility for better individualizing metformin dosage and use. Equally important, the results of such studies might also have the potential to provide insight into mechanism(s) of action of this very important drug and, as a result, the possible identification of novel drug targets for the treatment of type 2 diabetes.

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