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Role of cell membrane transporters in the pharmacological treatment of Sickle cell anemia

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The pharmacological management of any disease can be complex due the multitude of factors driving pharmacokinetic (PK) and pharmacodynamic (PD) properties of drugs. Sickle cell anemia (SCA) is particularly difficult to manage due to the complex pathophysiology that affects multiple organ systems. In order to improve current therapies and develop new drugs for the treatment of SCA, it is important to understand factors that modulate PK and PD. Recent studies have demonstrated that cell membrane transport proteins encoded by the family of ATP-binding cassette (ABC) genes and solute carrier (SLC) genes play an integral role in regulating PK and PD properties of oncology drugs. Transporters mediate cellular uptake and efflux of substrates which influence drug disposition as well as targeted and off-target drug effects. Variation in transporter function or expression contributes to inter-patientvariability in drug response and drug-drug or drug-food interactions. The oncology field is moving rapidly to further examine the impact of ABC and SLC transporters on drug distribution, toxicity, efficacy, and interactions for investigational and approved drugs. Likewise, pharmacological studies of commonly used drugs in hematology may help to improve treatment for SCA. Hydroxyurea, currently the only FDA-approved drug for the treatment of SCA, induces fetal hemoglobin expression and decreases sickle cell-related morbidity. However, PK and PD properties of hydroxyurea vary widely between patients, and the source of inter-patient variability remains largely unknown. Studies to elucidate PK and PD properties of hydroxyurea are needed. Data implicating transporters in the modulation of hydroxyurea pharmacology will be presented including (i) identification of specific transporters and (ii) demonstration of how transporter deficiency alters hydroxyurea PK. From these findings, it is evident that additional studies are warranted to investigate the role of transporters as determinants of hydroxyurea PK and PD responses. Knowledge gained from these and similar studies of hematological drugs may be particularly applicable for optimizing individual dosing regimens, predicting individual drug response, and avoiding drug-drug or drug-food interactions. All of which can help to improve the pharmacological treatment for SCA.

Biography

Aisha L Walker completed her PhD at Georgia Regents University (formerly known as Medical College of Georgia). During her Postdoctoral studies at St. Jude Children's Research Hospital, she has conducted research focused on investigating the pharmacology of hydroxyurea for the treatment of sickle cell disease. Her recent publications are the first to identify transporters as modulators of hydroxyurea cellular uptake which impact the disposition of hydroxyurea. She continues to investigate cellular and molecular mechanisms involved in the pharmacological treatment of sickle cell disease as an Assistant Professor in the Department of Biology at Texas Woman's University.

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