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Role of innate immune mechanisms in drug disposition

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Abstract

Activation of innate immune components such as Toll-like receptor (TLR)s during diseases such as infectious diseases, cancer, metabolic diseases and liver disorders are associated with disruptions in metabolism and clearance of drugs. Impairment of drug metabolism/clearance can cause adverse effects of drugs. Thus, understanding the mechanism by which TLRs disrupt drug metabolism is important to develop effective strategies to prevent undesirable effects of drugs in patients with activated immune responses. Drug disposition is regulated by drug metabolizing enzymes (DMEs) and transporters primarily present in the liver. We have previously shown that activation of TLRs reduce the expression of DME/transporter genes. Expression of these genes is regulated by basal transcription factors as well as by nuclear receptors which bind to the promoters of these genes. We hypothesize that activation of TLRs recruit downstream adaptor proteins, leading to induction of cell-signaling components (c-Jun N-terminal kinase (JNK) and NF-κB) to reduce the expression of nuclear receptors leading to reduced expression of DMEs/transporter genes. We determined the role of the bacterial receptors, TLR2 (for gram-positive bacteria) and TLR4 (for gram-negative bacteria), their downstream adaptor proteins (TIRAP and TRIF), cell-signaling components and nuclear receptors in the regulation of DMEs/transporters. Pharmacokinetc and pharmoacodynamic studies with clinically-relevant medications were also performed. These studies establish the role of innate immune components as novel regulators of drug metabolism/clearance. These regulators can be targeted to prevent or reduce the undesirable effects of drugs in patients.

Biography

Ghose received her Ph.D. from University of Notre Dame, IN, followed by post-doctoral training in Baylor College of Medicine in Houston, Texas. She is an Assistant Professor in the University of Houston, TX and published several articles in peer-reviewed journals and authored a book chapter. She has presented in National/international meetings and serves in the Editorial Board of reputed journals.