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Review

The role of quantitative systems pharmacology modeling in the prediction and explanation of idiosyncratic drug-induced liver injury

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ABSTRACT

Idiosyncratic drug-induced liver injury (iDILI) is a serious concern in drug development. The rarity and multifactorial nature of iDILI makes it difficult to predict and explain. Recently, human leukocyte antigen (HLA) allele associations have provided strong support for a role of an adaptive immune response in the pathogenesis of many iDILI cases; however, it is likely that an adaptive immune attack requires several preceding events. Quantitative systems pharmacology (QSP), an *in silico* modeling technique that leverages known physiology and the results of *in vitro* experiments in order to make predictions about how drugs affect biological processes, is proposed as a potentially useful tool for predicting and explaining critical events that likely precede immune-mediated iDILI, as well as the immune attack itself. DILIsym, a QSP platform for drug-induced liver injury, has demonstrated success in predicting the presence of delayed hepatocellular stress events that likely precede the iDILI cascade, and has successfully predicted hepatocellular stress likely underlying iDILI attributed to troglitazone and tolvaptan. The incorporation of a model of the adaptive immune system into DILIsym would represent and important advance. In summary, QSP methods can play a key role in the future prediction and understanding of both immune-mediated and non-immune-mediated iDILI.

1. Introduction

Drug-induced liver injury (DILI) is remains a key problem in drug development [1]. Of special concern is idiosyncratic DILI (iDILI), which has begun to be identified as separate from direct (or "intrinsic") DILI. In contrast to intrinsic DILI, in which a clear toxic dose–response could be induced by the drug in a majority of the population (*e.g.* acetaminophen), idiosyncratic DILI (iDILI) is characterized by a complex dose–response relationship with only a small minority of the population susceptible to the toxicity [2].

A well-known and studied example of a drug with an iDILI liability is troglitazone. In clinical trials, troglitazone showed generally minor elevations in serum alanine aminotransferases in only a small subset of the population (<2%) [3] and the ability of the drug to cause progressive liver injury was not appreciated; it was therefore approved for diabetes treatment in 1997. While on the market, however, a small number of patients developed severe liver injury after several months of troglitazone treatment, resulting in liver transplant or death; troglitazone was subsequently removed from the market [4,5]. Examples of other drugs associated with iDILI reactions include flucloxacillin, ximelagatran, and lapatinib [6–8].

The preponderance of data support a role for the adaptive immune system in iDILI caused by many and perhaps most drugs. The implication of adaptive immune responses, particularly T cell responses, in iDILI has historically rested largely on phenotypic characteristics of the injury. Particularly, liver injury is characteristically delayed, as would be expected in the development of an antigen-specific T cell response, and injury is generally manifested rapidly on re-challenge, as one might expect for a memory T cell response. This phenotypic evidence has been strongly bolstered by relatively recent data showing HLA associations for liver injury caused by particular drugs, including amoxicillin-clavulanate, ximelagatran, and lapatinib, among others [9]. Because HLA alleles encode major histocompatibility class I or class II proteins that bind and present peptide antigens to CD8+ or CD4+ T cells,

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respectively, the HLA associations implicate a T cell response in the observed injury. More direct evidence of T cell responsiveness has emerged recently through *in vitro* culture of T cells from HLA-typed donors exposed to drugs of interest. Amoxicillin-clavulanate and flucloxacillin-specific T cell lines and clones have been generated and characterized, shedding light on antigen presentation and T cell effector functions [10–12]. Despite these data, there remain many unknowns on the exact nature of T cell mediated DILI, including which subsets of T cells are involved, where the T cells are primed, what the role of regulatory cells might be, and why the majority of individuals, even those carrying the known HLA risk alleles, will not suffer injury.

2. Conceptual framework for T cell-mediated iDILI

It is likely that a series of necessary but not sufficient steps precede the adaptive immune response that is thought to be a characteristic of idiosyncratic DILI. This is based on the prevailing concept that a robust adaptive immune response requires “danger signals” elicited from the target tissues that result from activation of innate immune cells in that tissue [13]. It is therefore likely that the necessary initial steps in a drug-mediated adaptive immune attack on the liver include generation of hepatocyte stress, creation of neoantigens, release of damage associated molecular patterns (DAMPs) and activation of innate immune cells in the liver. Fig. 1 shows a schematic of this proposed iDILI cascade. Reactive metabolite formation has been identified as a potential instigator of the iDILI cascade [14], though it is unclear whether the reactive metabolite is involved in generation of neoantigens, hepatocyte stress, or both processes. Other mechanisms of generating cellular stress, such as bile acid accumulation or mitochondrial toxicity, could also help trigger the idiosyncratic immune response.

Prediction of the precipitating events, for example characterization of hepatocellular stress and resulting innate immune responses, can be accomplished through the use of quantitative systems pharmacology (QSP) modeling. QSP modeling is a computer modeling technique that incorporates known biology and physiology in order to better understand *in vitro* data. By placing those data in the proper biological context, QSP models seek to provide better predictions of how a biological system would react to a given stimulus [15]. QSP modeling is common in research on drug efficacy, but recently it has been adopted as a tool for exploration of potential drug toxicity.

3. QSP models as gateways to iDILI

Strong evidence to support the proposed initiating events for iDILI has come from studies that have utilized DILIsym®, a QSP platform model of DILI that harnesses the physiology of the liver in order to translate *in vitro* toxicity data to predictions of a drug's potential to cause DILI. DILIsym has been developed by the DILI-sim Initiative, a pre-competitive consortium of pharmaceutical companies with the mandate to create a software tool that can predict DILI during clinical drug development (http://www.dilisym.com/). The DILIsym software contains a PBPK sub-model that describes drug distribution into the liver as well as several sub-models that describe physiological processes occurring within the liver. Among these sub-models are bile acid homeostasis and disruption; mitochondrial activity and toxicity; reactive metabolite generation and disposition; oxidative stress; inflammation mediated by the innate immune system; and the overall hepatocyte life cycle.

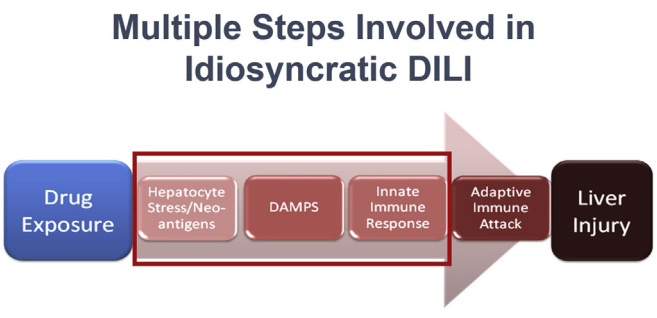

Fig. 1. Schematic of the steps involved in the proposed framework for the initiation of adaptive immune-mediated idiosyncratic DILI responses.

Other QSP approaches to predicting DILI have tended to focus on the case of acetaminophen. Recent work has been done in constructing an agent-based model of the liver that represents acetaminophen toxicity; this model also represents some inter-individual variability in response that could aid in prediction of rare hepatotoxicity [16]. Other approaches have used QSP modeling to predict the likelihood that an acetaminophen overdose would progress to liver failure based on a patient's aminotransferase levels and plasma acetaminophen concentration at the time of presentation [17]. These approaches may improve management of acetaminophen hepatotoxicity, which constitutes a considerable proportion of DILI cases. The approach to improve prediction of patient outcomes based on measurable biomarkers is potentially extensible to other compounds but may require distinct QSP models. Further, the lack of mechanistic representation of toxicity within the cell, suggests these models may be most applicable on clinical presentation and less suited for drug development.

A different approach that uses an intracellular mechanistic representation to explain hepatotoxicity has also been explored. This approach used hepatocyte-derived gene expression data to bridge the gap between predicted exposure and predicted toxicity. This approach successfully predicted rat and patient responses to acute azathioprine overdose [18]. Because this model also uses a PBPK approach, it appears well-suited to evaluate the effect of subject characteristics (*e.g.*, age, weight, sex) on exposure and thereby, on response to hepatotoxins. However, it does not appear to include response variability related to the mechanism of toxicity. It will be informative to see this approach applied to other compounds, in order to determine if a common QSP model can address multiple pathways or if the abundance of gene expression patterns requires a distinct QSP model for each compound. Additionally, while the rat toxicity predictions suggest that QSP modeling can apply gene expression profiles to predict liver response, the multiplicity of gene expression patterns and their nebulous relationship to functional tissue changes suggests the need for additional compound modeling.

Contrastingly, DILIsym has used the inputs generated by mechanistic *in vitro* assays to explain intrinsic toxicity by several molecules across different mechanisms of toxicity. The reactive-metabolite mediated toxicity of methapyrilene in rats was correctly predicted by DILIsym, and species differences were explained as well [19]. DILIsym also predicted the species differences in the bile-acid mediated toxicity of bosentan, and properly compared the DILI-generating bosentan to a non-DILI-risk drug, telmisartan [20]. DILIsym also correctly predicted the difference in toxicity between tolcapone (rare DILI risk) and entacapone (no DILI risk), both of which are mitochondrial toxins *in vitro* [21]. These examples suggest that DILIsym can predict cellular stress from numerous mechanisms that might serve as an initiating event for an adaptive immune attack.

DILIsym facilitates predictions of hepatotoxicity based on inputs from mechanistic *in vitro* toxicity assays. The assays currently used for DILIsym inputs include transporter vesicle assays that yield a K_i