Review

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Drug-induced liver injury: Interactions between drug properties and host factors

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Summary

Idiosyncratic drug-induced liver injury (DILI) is a common cause for drug withdrawal from the market and although infrequent, DILI can result in serious clinical outcomes including acute liver failure and the need for liver transplantation. Eliminating the iatrogenic "harm" caused by a therapeutic intent is a priority in patient care. However, identifying culprit drugs and individuals at risk for DILI remains challenging. Apart from genetic factors predisposing individuals at risk, the role of the drugs' physicochemical and toxicological properties and their interactions with host and environmental factors need to be considered. The influence of these factors on mechanisms involved in DILI is multi-layered. In this review, we summarize current knowledge on 1) drug properties associated with hepatotoxicity, 2) host factors considered to modify an individuals' risk for DILI and clinical phenotypes, and 3) drug-host interactions. We aim at clarifying knowledge gaps needed to be filled in as to improve risk stratification in patient care. We therefore broadly discuss relevant areas of future research. Emerging insight will stimulate new investigational approaches to facilitate the discovery of clinical DILI risk modifiers in the context of disease complexity and associated interactions with drug properties, and hence will be able to move towards safety personalized medicine.

Keywords: Drug-induced liver injury; Drug physicochemical properties; Host factors; Drug-host Interaction; Pharmacogenetics; Drug metabolism; Drug clearance; Clinical toxicology.

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Abbreviations: DILI, drug-induced liver injury; HLA, human leucocyte antigen; DAMPs, the damage associated molecular pattern molecules; ADMET, absorption, distribution, metabolism, excretion and toxicity; GST, glutathione-S-transferase; ROS, reactive oxygen species; JNK, c-Jun N-terminal kinase; Nrf-2, nuclear factor erythroid 2-related factor 2; Keap-1, Kelch-like ECH-associated protein 1; mtDNA, mitochondrial DNA; MPT, mitochondrial permeability transition; BSEP, bile salt export pump; ATP, adenosine triphosphate; P-gp, P-glycoprotein; MRP, multidrug resistance-associated protein; NAT2, N-acetyltransferase 2; CYP450, cytochrome P450; GSTM1, glutathione S-transferase Mu 1; GSTT1, glutathione S-transferase theta 1; NSAIDs, non-steroidal anti-inflammatory drugs; GSH, gluthatione; POLG, polymerase (DNA directed), gamma; FXR, farnesoid X receptor; LPS, lipopolysaccharides; MELD, Model for end-stage liver disease; PARP-1, Poly-(ADP-Ribose) Polymerase-1; NAFLD, non-alcoholic fatty liver disease; SOD2, superoxide dismutase 2; GPX1, glutathione peroxidase; NASH, nonalcoholic steatohepatitis; UDPGT, UDP-glucuronosyltransferase; NRTIs, nucleoside reverse transcriptase Inhibitors; PPARγ, peroxisome proliferator-activated receptor gamma; APC, antigen-presenting cell; MHC, major histocompatibility complex.

Introduction

Drug-induced hepatotoxicity is one of the major concerns in medical practice. Although it is relatively uncommon, drug-induced liver injury (DILI) is the leading cause of acute liver failure in the US and a major reason for liver transplantation [1]. Many marketed drugs, herbs and dietary supplements have a potential to cause liver injury. In preclinical studies, about 50% of candidate compounds present hepatic effects at supra-therapeutic dose and face drug attrition [2]. DILI is also a major cause for drug failure in clinical trials and frequently results in regulatory actions and drug withdrawal [3,4].

The incidence of DILI in general populations is about 14–19 per 100,000 inhabitants [5,6], while frequency estimated in a healthcare system is around 30–33 per 100,000 persons [7]. The reported incidence and severity of DILI varies among drugs [6,7], suggesting that drug properties have a role in DILI risk determination. Conversely, drugs with DILI potential cause liver injury only in a small portion of patients indicating that host factors play a major role in DILI development.

DILI is classified into intrinsic *vs.* idiosyncratic liver injury, reflecting a dominant role of drug toxicity (dose-dependent) *vs.* host factors (no dose dependence) in liver injury. With a few exceptions (i.e., acetaminophen), most of DILI experienced in humans are considered idiosyncratic. However, inflammatory stress may influence the dose-response curve towards

sensitization for toxicity at therapeutic doses, making the two DILI types less distinct [8]. Indeed, around 10% of acetaminophen-induced acute liver failure cases occurred at recommended dosage, suggesting host factors modify individual risks of acetaminophen liver injury [9,10]. Besides, drug dosage is a well-known determinant of idiosyncratic DILI [11,12]. Thus, the two entities may rather coincide in human DILI.

The current mechanistic understanding of DILI is depicted in Fig. 1. The key mechanisms in DILI are two-fold: 1) drug/metabolite exposure to a threshold level, determined by the dose and drug handling of the liver, and 2) the adaptive immune response or "alarm-signalling" by the damage associated molecular pattern molecules (DAMPs) [13]. Cellular damage occurs at an intricate balance between toxic drug exposure and defence mechanisms. Once cells are damaged, innate and adaptive responses kick-in and play a significant role in driving tissue inflammation and injury. The degree of local tissue inflammation and injury, in a balance with tissue repair, influences overall tissue damage and determines clinical outcome. Drug exposure and properties of administered drugs play primary roles at the initial stages of cellular damage while host factors drive 'host responses' to toxic insults with the induction of cellular repair programs.

This review will systematically update the current knowledge on drug properties associated with hepatotoxicity, discuss various host factors that may contribute to individuals' DILI risks and clinical phenotypes, and allude to potential drug-host interactions aiming at providing a structured conceptual framework to guide future empirical research in this challenging field.

Key points

- Individual risks and clinical phenotypes of DILI are likely determined by a multi-faceted interplay between drugs' physicochemical and toxicological properties, host factors and the interactions among them.
- Drug properties contributing to initial cell damage include surpassing a threshold dose, physicochemical characteristics such as lipophilicity, formation of reactive metabolites, induction of oxidative stress, mitochondrial hazard and inhibition of hepatic transporters.
- Age, gender, genetic factors, pubertal development, hormonal and nutritional status, pregnancy, co-medications, underlying conditions and the gut microbiome influence key mechanistic components of DILI which can be classified into four categories: drug handling, toxicological responses, inflammation and immune responses, and the balance of tissue damage and repair.
- Further investigations on drug-host interactions are needed to integrate the drug signature data with patient clinical data that would enable the discovery of clinical DILI risk modifiers and their interactions with drug properties as to move towards safety personalized medicine.
- Developing new investigational approaches, involving bioinformatics and computer science may enhance the transferability of information and facilitate inter-disciplinary research in the field.

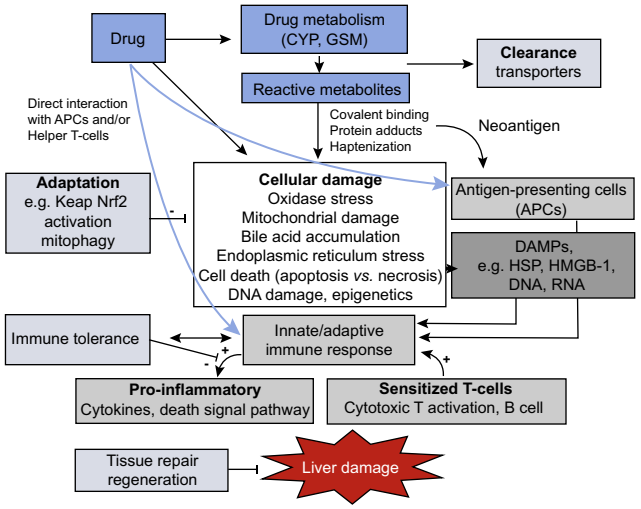

Fig. 1. Current mechanistic understanding in the initiation and progression events relevant to idiosyncratic drug-induced liver injury. Two mechanistic cascades, (A) Sterile inflammation caused by drug-induced cytotoxicity *vs.* (B) Immune response via antigen presenting cells (APCs) and/or helper T-cells. Drugs/reactive metabolites exert direct toxicity or form adducts leading to haptenization. Cells respond by activating adaptive pathways. Injured hepatocytes release "danger signals", such as the damage associated molecular patterns molecules (DAMPs) which favour the release of pro-inflammatory cytokines to induce a T/B-cell response against hepatocytes. The HLA associations discovered in GWAS suggest that the adaptive immune response is an upstream event. The innate immune system can either co-stimulate the adaptive immunity or modulate the degree of inflammation and regeneration.

Drug properties related to DILI risk in humans

Drugs within a therapeutic class differ regarding their hepatic liability, suggesting that physicochemical and toxicological drug properties affect DILI risk. Typical examples are thiazolidinediones, of which troglitazone was withdrawn from market due to fatal hepatotoxicity, while rosiglitazone and pioglitazone were less harmful to the liver. Among drug properties, factors contributing to initial cell damage include surpassing a threshold dose, physicochemical characteristics, reactive metabolites formation, oxidative stress, mitochondrial hazard and inhibition of hepatic transporters.

Threshold dose

Idiosyncratic DILI is considered dose-independent; most DILI cases occur at therapeutic dose in an individual despite being well tolerated in the general populations. However, in preclinical testing, hepatotoxicity is often predicted at high drug exposure leading to several stress responses in hepatocytes [14]. The conventional concept of dose independency is being challenged [15]. Uetrecht firstly suggested that idiosyncratic DILI was rarely observed with drugs given at daily doses of $\leqslant$10 mg [16] and many drugs withdrawn from market or issued with a boxed warning (e.g. nimesulide, bosentan) due to hepatotoxicity, were prescribed at daily doses $\geqslant$50 or 100 mg [17,18]. Moreover, DILI patients in large cohorts from Spain and Iceland [6,19] and 81% of non-acetaminophen DILI patients undergoing liver transplantation in the United States received medications with daily doses of $\geqslant$50 mg [1]. Therefore, a significant association between daily dose and poor DILI outcome (i.e. liver failure,

transplantation and death) exists and was also found in a systematic survey based on pharmaceutical databases [11]. These evidences suggest that surpassing a threshold dose is associated with an increased risk of triggering liver injury among the treated patients. Daily dose alone is, however, inadequate to reliably predict DILI risk from individual drugs because a majority of compounds needs $\geqslant$50 mg to achieve efficacy [21].

Lipophilicity

A drug's physicochemical property is known to affect cellular uptakes and ADMET (absorption, distribution, metabolism, excretion and toxicity). Chen *et al.* [12] explored the impact of lipophilicity in combination with daily dose and found oral medications at high daily doses ($\geqslant$100 mg) and a lipophilicity of logP $\geqslant$3 to be significantly associated with severe DILI. Their study demonstrated that both factors could individually predict hepatotoxicity, while the ''rule-of-two'', which combines dose and lipophilicity, performs better than daily dose alone, thus increasing the positive predictive value from 85% to 96% while decreasing the negative predictive value from 55% to 39%. Higher lipophilicity could enhance DILI risk by facilitating drug uptake from blood into hepatocytes, which conditions hepatic metabolism and may result in a greater amount of reactive metabolites, subsequently leading to an interaction with mitochondrial membranes and hepatocanalicuar transport [13,22]. Besides lipophilicity, other physiochemical properties as molecular weight and total polar surface area associate with *in vivo* toxicological outcomes [23,24].

Formation of reactive metabolites

Several lines of evidence suggests that the formation of reactive metabolites play a central role in the pathogenesis of idiosyncratic DILI [25]. Reactive metabolites can covalently bind proteins to form drug-protein adducts that might trigger immune-mediated reactions or exert direct toxicity [26,27]. Cholestasis may also be a consequence of the canalicular secretion of reactive metabolites or disintegration of labile glutathione and/or glucuronide conjugates thereby damaging cholangiocytes or triggering an immune response. However, for a given drug, there is no clear-cut correlation between the potential to form reactive metabolites in experimental conditions and the actual incidence of hepatotoxicity in humans [28]. Obach *et al.* [29] measured the formation of reactive metabolites *in vitro* and found that metabolism-dependent covalent binding with liver microsomes cannot distinguish hepatotoxic and non-hepatotoxic drugs. Another experimental study tested approximately 100 Merck drug candidates and found no correlation between liver toxicity observed from *in vivo* animal studies and the extent of covalent binding [30]. Within a given drug class, specific chemical structures can render the compound distinctly hepatotoxic. For instance, ebroditine, an antiulcer drug pharmacologically related to famotidine, carries a bromobenzene ring which undergoes metabolic activation to reactive epoxides [31]. Likewise, temafloxacin and trovafloxacin share a unique difluorinated side chain that does not occur in other quinolones with much less hepatotoxicity [32].

Oxidative stress

Oxidative damage in the liver could be a consequence of cytosolic oxidant stress after drug metabolism or could arise from oxidant stress directly generated in mitochondria and the subsequent inflammatory cell response by injured hepatocytes. Oxidative stress is caused by an imbalance of reactive oxygen species (ROS) formation (c-Jun N-terminal kinase, JNK) and its detoxification by antioxidant defence systems (Nrf2/Keap1) [33]. The balance of products of oxidative stress, protective cellular defence and cytokines modulating inflammation may be critical for DILI susceptibility, severity and extent of injury. Increased ROS can directly damage DNA, proteins, enzymes, and lipids in cells and tissues and induce immune-mediated liver damage. Some drugs (e.g. valproic acid) can induce enhanced generation of ROS by interrupting the homeostasis of mitochondria respiratory chain and triggering JNK signalling pathway, to subsequently activate mitochondrial permeability and death of hepatocytes [33]. Recent reports suggest drug-induced oxidative stress also significantly correlate with DILI risk. Xu *et al.* identified ROS generation along with mitochondrial damage and intracellular glutathione depletion, as most important indicators contributing to hepatotoxicity as determined by high content imaging in primary human hepatocyte cultures [34].

Mitochondrial liability

Mitochondrial dysfunction plays a critical role in the pathogenesis of DILI by alteration of metabolic pathways and damage to mitochondrial components [33,35]. Drugs such as stavudine and amiodarone can induce steatosis/steatohepatitis by severely altering mitochondrial function. Mitochondrial damage could trigger hepatic necrosis and/or apoptosis, leading to activation of cell death signalling pathways such as JNK when a critical mitochondrial death threshold is surpassed [35,36]. This view challenges the traditional paradigm, indicating that cell death is rather an active process involving mitochondria thereby determining the fate of cells as opposed to overwhelming biochemical injury [36]. Specifically, drugs can impair mitochondrial respiration (valproic acid) and/or β-oxidation (aspirin, tamoxifen), trigger mitochondrial membrane disruption (diclofenac) and damage mtDNA (tacrine) [37–39]. Interestingly, Porceddu *et al.* [40] reported a significant association between loss of mitochondrial integrity and the potential to cause DILI, based on the analysis of 124 chemicals/drugs.

Inhibition of BSEP and other hepatobiliary transporters

Hepatobiliary transporters, and particularly the canalicular adenosine triphosphate (ATP)-dependent bile salt export pump (BSEP), are responsible for the biliary excretion of several organic compounds including bile acids. An impaired function of BSEP determines the accumulation of cytotoxic bile acids in hepatocytes leading to the induction of oxidative stress and/or apoptosis and necrosis by FAS-mediated pathways [41]. Drugs and/or metabolites with capacity to inhibit BSEP *in vitro* have potential to cause DILI as has been shown by Morgan *et al.* using BSEP-inverted vesicles [42]. Although this approach enables preclinical drug testing with some drugs shown to be potent BSEP inhibitors and have either been withdrawn from the market (troglitazone) or received warnings (imatinib) for hepatotoxicity, others (pioglitazone, simvastatin) have a low potential for DILI risk. Hence, BSEP inhibitory potency alone is insufficient for determining DILI risk and additional factors should be considered. Recently, Aleo *et al.* demonstrated that drugs which carry

a more serious DILI risk influence both BSEP and mitochondrial activities [43]. Mitochondrial dysfunction would result in impaired ATP production, and in conjunction with BSEP inhibition, might explain the synergistic link between mitochondria and ATP-dependent transporters such as BSEP in DILI.

The hepatic canalicular transporter P-glycoprotein (P-gp) is a well-known determinant in multidrug resistance in chemotherapy [44]. Other hepatobiliary transporters of the multidrug resistance protein (MRP) family are also involved in the excretion of conjugated organic anions, bilirubin and drug metabolites. Recent studies suggest that the consideration of MRP2/3/4 inhibition could improve the correlation with DILI risk in humans as compared with BSEP inhibition alone [45], suggesting that defects in transporters function modify drug disposition. Owing to the fact that hepatocytes are highly polarized and transporters function either bi- or mono-directional, the host and drug interactions may lead to different phenotypes of DILI (i.e. cholestasis, hepatocellular, steatosis).

Host factors modifying DILI risks and clinical phenotypes

Host factors contributing to individual susceptibility and clinical phenotypes of DILI have not been systematically investigated. In this section, we will provide cross-disciplinary view over host factors influencing key mechanistic components of DILI, classified into four categories: drug handling, toxicological responses, inflammation and immune responses, and imbalance of tissue damage and induction of repair processes.

Host factors influencing drug handling

Factors that modify the level of exposure to the reactive metabolites and/or alter the disposition of the drug may critically influence the development of DILI. In individual cases, drug therapy adjustments appear to change a drug's hepatotoxic potential; e.g. reducing the dose of mianserin [46] and prolonged dose intervals of gefitinib [47] eliminated risk of hepatotoxicity while atorvastatin dose escalation increased the risk of hepatotoxicity [20]. These observations underpin the need of surpassing a threshold dose to induce DILI in a unique susceptible individual [20]. Inter-individual differences in drug tissue concentration are further influenced by oral bioavailability, volume of distribution, visceral blood flow, drug metabolism, nutritional status, excretion/transport, age and genetic and epigenetic factors.

Aging is known to influence the pharmacokinetics of drugs due to decreased renal function and cytochrome-mediated hepatic metabolism, while reduced conjugation reactions seem to be restricted to older frail patients [48]. Hence, older age likely enhances DILI susceptibility. This concept, however, has not been supported by data from large national DILI registries. In the Spanish DILI Registry 46% of DILI patients were $\geqslant$60 years of age and the US Drug-Induced Liver Injury Network (DILIN) reported 18.5% of DILI patients to be 65 years or older [49,50]. In a population-based study done in Iceland, a relationship between DILI incidence and increasing age was observed, probably related to a greater exposure to polypharmacy in older subjects [6]. Apparently, the type of liver injury differed with age with younger patients presenting more frequently hepatocellular damage as compared to cholestatic/mixed injury seen in the old [49,51]. The risk of developing valproic acid-induced hepatotoxicity with fatal outcomes is higher in children below the age of two [52]. Hepatotoxicity induced by isoniazid appears to be more frequent in older patients. A retrospective study in 3377 adults receiving isoniazid therapy demonstrated that the DILI incidence was about two-fold amongst 35–49 years old and almost five-fold in $\geqslant$50 years old patients as compared to the 25–34 years old ones [53].

Furthermore, gene expression of drug metabolizing enzymes and transporters vary significantly among individuals, being influenced by genetic variants, epigenetic alterations, age, gender, hormones, nutrition, alcohol, and co-medications [54]. Genetic polymorphisms of drug metabolizing enzymes are estimated to influence the clinical outcome in 20–25% of all drug therapies [54]. Some racial differences in DILI caused by anti-tuberculosis drugs have been attributed to variants of drug metabolizing genes coding for NAT2, CYP2E1, GSTM1 and GSTT1 [55]. Thus, polymorphisms of drug metabolizing enzymes and transporters are considered as one of the key contributors in an individual's DILI risk [56].

Gender, pubertal development, sex hormones, pregnancy and growth hormone levels also influence drug metabolizing enzymes [57]. For instance, men have a higher clearance rate of acetaminophen than women due to higher glucuronidation rates, while CYP3A4, a major drug metabolizing enzyme, is expressed at a higher rate in women [58]. Furthermore, cytokines released in systemic infection inflammation significantly represses activities of cytochrome P450 monooxygenases and transporters [59,60]. Consequently, in patients with systemic inflammatory response syndrome, detoxification processes may significantly decrease possibly requiring dose adjustment.

Lifestyle, disease conditions, and co-medications also modify individual's drug handling capability. Alcohol and high fat diets are known to induce CYPs 2E1 and 4A. Alcohol-induced increase in CYP2E1 has been associated with an increased risk of acetaminophen-induced liver injury in humans, which is explained by an increased generation of the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI) [61]. Malnutrition and cellular senescence could result in decreased xenobiotic clearance and subsequently lead to slower drug elimination and higher drug plasma levels. Additionally, several marketed drugs are known to inhibit/induce specific drug metabolizing enzymes and transporters [62], which potentially alter reactive metabolite formation, drug conjugation, and/or drug elimination, and therefore modifying an individual's DILI risk [61,62].

Host factors modifying toxicological responses

Drugs initiate cellular damage through diverse mechanisms: reactive metabolite formation, which leads to covalent binding to cellular proteins, oxidative stress, endoplasmic reticulum stress, mitochondrial injury, DNA damage, epigenetic modifications, and/or inhibition of bile acid excretion (Fig. 1). Various patients' host factors may influence toxicological responses and modify the risks of developing cellular damage.

Specifically, risk of inducing cellular damage through reactive metabolites is affected by cellular detoxification mechanisms. Patients with genetic defects in GST were reported to have an increased risk of developing DILI caused by anti-tuberculosis drugs [63], NSAIDs and antibacterials [64]. Slow acetylators of NAT2 were also associated with moderate to severe DILI related to anti-tuberculosis drugs [65]. Thus, at a given amount of

reactive metabolite formation, those with diminished cellular detoxification are at a higher risk of developing DILI.

Induction of cellular oxidative stress is another major toxicological insult caused by drugs. The degree of drug-induced oxidative insult may be modified by host's pre-existing increased cellular oxidants, increased substrates for oxidative reactions (e.g., steatosis, lipid peroxidation), and/or decreased anti-oxidants. Patients with functional polymorphisms in mitochondrial superoxide dismutase and glutathione peroxidase have a higher risk of developing DILI, especially for those culprit drugs that are hazardous for mitochondria and/or form highly reactive intermediates [63,66]. Other host factors influencing cellular oxidative stress are listed in Table 1 [26,67,68]. A female-specific susceptibility to oxidative stress in idiosyncratic DILI has been reported [49].

Host factors influencing mitochondrial functions are listed in Table 1 [26,69,70]. In normal mitochondrial biology, significant amount of ROS is produced and usually appropriately detoxified

Table 1. Overview of drug/host factors influencing specific mechanisms involved in idiosyncratic drug-induced liver injury.

Mechanistic factors	Drug properties		Host responses	
	Specific factors	Examples	Specific factors	Examples
Threshold dose	Daily dose [11,12]	Duloxetine, gefitinib, bosentan, tacrine, leflunomide, methotrexate	Drug absorption and hepatic delivery	Gastric emptying, gastrointestinal transit, nutrition, aging, atherosclerosis, portal hypertension
	Bioavailability*[12]	Vancomycin, aminoglycosides, rifaximin, cromoglicate		
	Long half-life	Azithromycin, tamoxifen	A reduced drug clearance (i.e., prolongs half-life)	High body fat, elderly, renal dysfunction, hepatic dysfunction
Covalent binding	Significant hepatic metabolism [119]	Atorvastatin, tacrolimus, disulfiram, terbinafine	Hepatic drug metabolism	Genotypes of drug metabolizing enzymes, age [120], sex [57], Inducers/inhibitors of drug metabolizing enzymes (e.g., co-medications, alcohol, and diets)
	Reactive metabolite generation [38]	Acetaminophen, trovafloxacin+, isoniazid, phenytoin, carbamazepine, valproic acid, diclofenac	Impaired cellular proteins, repair/ degradation [121,122]	Reduction of thioredoxin/thioredoxin reductase, glutathione reductase, methionine sulfoxide reductase
Oxidative stress	Increase intracellular (e.g. mitochondria) oxidants [33]	Acetaminophen, troglitazone+, flutamide, nimesulide+, valproic acid, diclofenac	Increase cellular oxidants	Obesity/insulin resistance/NAFLD, advanced cellular senescence
			Increase lipid peroxidation	Fatty liver
			Depletion of antioxidants	Aging, obesity/insulin resistance/ NAFLD, genotypes related to cellular antioxidation (e.g., SOD2, GPx1) [26], nutrition, lack of estrogens [123]
Mitochondrial liability	Impair mitochondrial respiration [38]	Paroxetine, valproic acid, troglitazone+, nefazodone+	Mitochondrial dysfunction	Genetic variants of mitochondrial enzymes, age, sex, sex hormones, advanced cellular senescence (e.g., insulin resistance/NASH, chronic inflammation)
	Inhibit beta-oxidation [38]	Amineptine+, ibuprofen, valproic acid, minocycline, aspirin		
	Trigger mitochondrial membrane disruption [26]	Ciprofloxacin, diclofenac, indomethacin		
	Damage mitochondrial mtDNA [26]	Tacrine, tamoxifen, stavudine and other NRTIs	Impair mitochondrial DNA repair	Genotypes of mitochondrial DNA polymerase γ [73]
Hepatic transporters inhibition	Inhibit BSEP [42]	Troglitazone+, bosentan, erythromycin, estradiol, simvastatin, rifampin, imatinib, nefazodone+	Hepatic transporter regulations	Genotypes related to transporters (e.g., BSEP, MRP2/3/4), co-medications, release of bacterial endotoxin due to increased intestinal permeability, altered hepatic FXR (e.g., NASH [124], bile acid pool and components [125])
	Inhibit other hepatic transporters (e.g., MDR3/ MPR2/MPR3/ MPR4) [42]	Itraconazole (MDR3), zafirlukast (MRP2), atorvastatin (MRP3/4), indomethacin (MRP3/4)	Impair energy supply for hepatic transporters	Aging, cellular senescence/ mitochondrial dysfunction

(*Continued on next page*)

Table 1 (*Continued*)

Mechanistic factors	Drug properties		Host responses	
	Specific factors	Examples	Specific factors	Examples
Inflammation and immune responses	Anti-inflammatory drugs	Aspirin [126], coxibs [127], statins [128]	Pro-inflammatory conditions	Increased influx of LPS (e.g., alcohol abuse, intestinal diseases) [86,87], altered microbiome [129], chronic inflammatory diseases and viral infections, obesity [130], progesterone [81], depletion of bile acid pool [131]
			Anti-inflammatory conditions	Estrogens [81], androgens [26], co-medications (anti-inflammatory drugs)
	Anti-TNFα drugs and other biological products	Azathioprine, leflunomide, tacrolimus, adalimumab, infliximab	Modify immune responses	HLA, sex [27], sex hormones [132], co-medications (e.g., immunosuppressant, immunomodulator), epigenetic alterations (e.g., hydralazine and procainamide)[133], gut microbiota [129]
	Immunosuppressants and immunomodulators	Glucocorticoids, opioids [134], antihistamines [135], statins [136]		
Tissue injury and repair	Dominant induction of necrosis *vs.* apoptosis	Acetaminophen, troglitazone[+], flutamide, diclofenac	Apoptosis *vs.* necrosis	Sex [106], sex hormones [106], cellular energy supply [137]
	Impair tissue repair	Hydralazine derivatives (histone acetylation inhibition) [97], sympathetic stimulants [138, 139]	Tissue repair	Aging [103], advanced cellular senescence [103], co-medications [93], altered FXR [140], sex [141], sex hormones [142]

[*]Drugs of very low bioavailability were associated with few DILI reports (e.g., acarbose).
[+]Drugs that were withdrawn from markets worldwidely or in some countries.

[71]. However, mitochondrial aging, partly due to accumulated oxidative mitochondrial DNA damage [38], may be affected by other host factors such as over-nutrition (e.g., obesity, insulin resistance, diabetes, and NASH) and alcohol [38,72]. Damaged mitochondrial DNA is repaired and maintained by mitochondrial DNA polymerase γ, encoded by the nuclear gene *POLG*. A recent gene-association study showed that about 50% of cases with valproate-induced liver injury were heterozygous for *POLG* substitution mutations and its odds ratio was estimated as high as 24 [73]. Individuals with carnitine deficiency were also associated with an increased risk of valproate-induced liver injury [74] while carnitine appears to be protective against valproate-induced liver injury and improve survival in severe cases.

Inhibition of bile acid transporter leads to intrahepatocellular bile acid accumulation while inhibition of phosphatidyl choline excretion (MDR2/3) alters bile composition and leads to cholangiocyte injury [75]. As shown in Table 1, hepatic transporters are influenced by genetic variations, co-medications, bacterial endotoxins and the farconoid xenosensing receptor (FXR), which functions as a bile acid sensor and acts as a key regulator of metabolic processes [41].

Bile acids salts are anionic detergents and highly toxic to the cells. In bile, mixed micelle formation with cholesterol, phospholipids, bile pigments, proteins, and inorganic electrolytes protects cholangiocytes from the toxic detergent effect of bile acid salts. Dysfunction of MDR3/ABCB4 (phosphatidyl choline translocation across canaliculus membranes, regulated by FXR) has been associated with clinical cholestasis, presumably via inhibition of micelle formation, releasing free bile acids salts in bile [76]. Patients with primary biliary cirrhosis and extrahepatic bile obstruction have decreased biliary bicarbonate secretion measured by positron emission tomography [77,78], suggesting a potential susceptibility to drugs influencing bile components (i.e., itraconazole) [78].

Host factors modulating inflammation and immune responses

Innate/adaptive immune response plays a key role in inducing inflammation and determining the degree of 'injury' (Fig. 1). Host factors known to modulate inflammation and immune response which, in turn, may influence DILI susceptibility will be discussed below.

Several genetic variants in the HLA regions were identified as risk factors for DILI [56]. Carriers of the HLA-B*57:01 genotype are at an 80-fold increased risk of flucloxacillin-induced DILI [79]. DILI caused by other drugs (e.g. lumiracoxib, lapatanib, ticlopidine, amoxicillin-clavulanate and ximelagatran) are also associated with HLA genotypes [21]. Even causal drugs not accompanied by hypersensitivity features show the association with the HLA haplotypes, suggesting an important role of the immune system in DILI [21].

Gender and sex hormones are well-known to influence inflammation and immune response. An immune-mediated DILI model showed gender bias in immune response and inflammation; more severe hepatitis, more antibody production, and a higher level of pro-inflammatory hepatic cytokines in females *vs.* males [80]. Indeed, females with DILI are at a higher risk of developing acute liver failure or requiring liver transplantation [19,49]. In halothane-induced DILI, estrogens reduce liver injury in mice while progesterone exacerbates the damage possibly by modulating inflammation and immune response. Indeed, increased hepatic neutrophils and up-regulated hepatic mRNA levels of pro-inflammatory cytokines were noted with

progesterone pre-treatment whereas estradiol resulted in the opposite effects [81].

Racial differences in inflammation and immune response are also known. African-Americans are at a higher risk of developing chronic DILI (defined as persistent liver alteration beyond six months of DILI recognition), while Asians are associated with earlier development of liver-related death or liver transplantation [82]. Potential race-associated genetic variants enhancing inflammation or adaptive immune response are warranted future investigations.

Immune and inflammatory responses are also influenced by medications co-administered at the time of drug exposure. Previous data-mining using a large spontaneous adverse event reporting system discovered latent associations between reduced reporting frequency of liver events and various co-reported medications. Among the identified medications, anti-inflammatory agents and immunosuppressants were disproportionally prevalent [83,84]. Despite the preliminary nature of these observations, the associations suggest that the concomitant use of anti-inflammatory and immunosuppressant agents may modulate host immune response and inflammation and impact DILI occurrence. Other host factors potentially influencing inflammation and immune response are listed in Table 1.

The gut–liver axis plays a role in DILI. Increased intestinal permeability due to damaged intestinal mucosal barrier increases hepatic endotoxin influx, which in turn activates Kupffer cells and the production of pro-inflammatory cytokines, arachidonic acid metabolites and ROS in the liver [85]. In experimental models, intestine-derived endotoxin or co-administration of LPS enhances liver injury induced by chemicals [86,87], while decreased intestinal permeability reduced liver injury [88]. Likely, a disrupted mucosal barrier induced by drugs (e.g. NSAID), alcohol abuse, or intestinal disorders as seen with celiac disease and inflammatory bowel disease, or acute enterocolitis can act synergistically enhancing liver damage caused by hepatotoxic drugs [14].

Whether pre-existing chronic liver diseases enhances the risk of hepatotoxicity is hampered by the fact that recrudescence of inflammation can go undistinguished from true injury induced by a drug. A few examples, however, suggest potential enhancement of drug hepatotoxicity by existing chronic inflammation (or chronic viral infection). A previous retrospective study showed that patients with pre-existing chronic liver injury are at an increased risk of acute liver injury following acetaminophen overdose [89]. Severe DILI cases caused by anti-retroviral medications are more commonly observed among patients co-infected with hepatitis B and/or C virus [90]. Further, chronic hepatitis C virus infection, human immunodeficiency virus (HIV) infection, and autoimmune disease were associated with an increased risk of DILI caused by anti-tuberculosis drug therapy [91,92].

Host factors modifying cell death, tissue injury and repair

The balance between tissue injury and repair needs to be considered with impaired tissue repair worsening the condition leading to poor clinical outcome. This concept is supported by clinical studies, where the impact of co-medications on DILI outcome in patients with acetaminophen-associated liver injury was examined [93,94]. Briefly, co-medications with drugs which ameliorate liver injury and/or enhance liver repair in animal experiments (e.g., statins, fibrates, β-blockers, NSAIDs) were associated with a decreased likelihood of fatality (or lower MELD scores) among acetaminophen-associated liver injury while co-medications with drugs enhancing liver injury and/or impairing liver regeneration (i.e., sympathetic stimulants) were associated with an increased likelihood of fatality [93,94]. Potential beneficial impacts of lipid lowering drugs (i.e., statins, fibrates) and anti-inflammatory agents (e.g., NSAIDs, immunosuppressants) are associated with improved clinical outcomes in patients diagnosed with dyslipidemia and collagen diseases among DILI cases [94,95].

Epigenetic modifications of host chromatin may impair regeneration following injury [96,97]. Loss of histone acetylation results in impaired liver regeneration in mice after toxic injury [96]. Impaired histone acetylation induced by todralazine (a hydralazine derivative) also results in impaired liver regeneration, which was correlated with clinical cases of drug-induced acute liver failure [97]. Additionally, nutritional deficiencies cause epigenetic modifications, which potentially alter individual susceptibility to hepatotoxicity. Deficiencies of folic acids, vitamin B12, and choline induce methyl donor depletion, contributing to hypomethylation of genes in cellular metabolism and hepatocyte differentiation [98–100]. Folic acid deficiency is associated with more severe liver damage in ethanol-fed micropigs [101,102] while folic acid supplementation has been associated with a reduced reporting frequency of liver events across different agents with hepatotoxic potential in previous data-mining analyses [83,84].

Age-related decline of mitochondrial function may also compromise energy supply for cellular metabolism and tissue regeneration [71,103]. In patients with hepatitis A, a likelihood of poor clinical outcomes increases with increased age [104]. Decompensated cirrhosis is another factor of poor outcome. Such patients require specific care in the selection of medications, and drugs with significant hepatic metabolism should be avoided [105].

Toxic insults can induce different forms for cell death. Unlike apoptosis, necrotic cell death leads to plasma membrane disturbance and subsequent releases of its cellular contents, which may induce an inflammatory response. Sexual dimorphism was observed in such cell death regulations in other systems [106,107]. An immune-mediated nephritis mouse model evidenced more apoptosis in females but more necrosis in males. The observed gender-biased in cell death was partially mediated by estrogen and Poly-(ADP-Ribose) Polymerase-1 (PARP-1) [106]. In one recent clinical analysis of DILI cases, the frequency of apoptosis was increased in women at a given injury pattern [108]. Further investigations are warranted to delineate the suspected sex difference in cell death and its clinical relevance.

Drug-host interaction: what do we know and what should we know, and how should we approach it

Both drug properties and host factors are multi-layered, influencing multiple mechanisms, and likely interact at multiple levels to determine DILI susceptibility, clinical phenotypes and outcome. Table 1 provides a structured summary of drug properties and host factors relevant to human DILI, which is organized based on mechanistic elements. Some combinations of drugs and host factors may exert additive interactions on DILI risks, which may explain clinical observations of high-risk populations for specific agents. A few examples with suggested mechanisms are provided in Table 2. A previous data-mining analysis showed that

Table 2. Specific drug-host interactions influencing risks of idiosyncratic drug-induced liver injury [14].

Causative DILI agent	Drug properties	Host responses		Possible consequence of drug-host interaction
		Known risk factors	Suggested mechanisms	
Valproic acid	• High solubility, extensive metabolism	• Young age (in particular <2-3 years) • Antiepileptic co-medication	• Different CYP2C9 enzyme activity among developmental stages in children • Enhance 4-ene-valproic acid metabolite formation by inducing CYP activities (CYP2A6, CYP2C9)	• Enhanced reactive metabolite generation
	• Mitochondrial liability	• Metabolic defects (impaired hepatic mitochondrial functions) • Genetic variations in *POLG* (mitochondrial DNA polymerase γ)	• Valproic acid undergoes β-oxidation and competes with endogenous lipids for enzymes and the mitochondrial CoA pool in this pathway. • Impaired mitochondrial DNA replication	• Mitochondrial damage
Atorvastatin	• High lipophilicity	• Older age	• Reduction in drug clearance	• Threshold dose
	• Extensively metabolized by CYP3A4 • Reactive metabolites	• Genotypes of drug metabolizing enzymes • Co-medications (e.g. ketoconazole, nefazodone, ritonavir, erythromycin)	• Functional CYP3A4 polymorphisms • Inducers/inhibitors of CYP3A4	• Enhanced reactive metabolite generation
	• Immunomodulation	• Women, older age	• Autoimmune phenotype	• Autoimmune hepatitis triggered by statins
Diclofenac	• High solubility • Extensive metabolism • Enterohepatic circulation	• Genotypes of drug metabolizing enzymes and transporters • Co-medications	• Underlying genetic polymorphisms in drug metabolizing enzymes (*CYP2C8, UDPGT 2B7, GST*), and hepato-canalicular transporters (*BSEP, MRP2, MRP4*) • Inducers/inhibitors of drug metabolizing enzymes and transporters.	• Enhanced reactive metabolite generation and/or • Delayed clearance of drug/ metabolites in hepatocytes, increase hepatic exposure
	• Formation of acyl glucuronide and oxidative electrophilic quinine imines metabolites	• Genotypes of anti-oxidant system	• Polymorphisms of *SOD2* and *GPX1*	• Impaired anti-oxidation
	• Mitochondrial liability	• Preexisting diseases: osteoarthritis, rheumatoid arthritis, viral infections, diabetes mellitus	• Pre-existing mitochondrial dysfunction: • Electrophiles derived from reactive metabolites causing mitochondrial dysfunction	• Mitochondrial damage
	• Interaction with APC via MHC type II molecule	• HLA genotype [PPARγ-associated SNP, rs17036170: OR(95%CI) of 11.3(4.9-25.9)]	• Innate and adaptive immune mediated	• Enhanced immune response
	• Intestinal toxicity	• Gut microbiome • Pre-existing chronic inflammatory conditions	• Increased LPS influx due to compromised mucosal barrier, induced by diclofenac • Modulation of hepatic inflammation via C-reactive protein	• Enhanced hepatic inflammation
Amoxicillin clavulanate	• High solubility • Multi-drug regimens • Poor metabolism • Biliary excretion	• Older men (>65 years)	• Impaired drug clearance and prolonged exposure of the bile duct cells to the drug metabolite through canalicular excretion	• Predominant cholestatic/ mixed injury among older subjects
	• Interaction with APC via MHC type II molecule	• Repeated prescription • HLA genotypes: North Europe, DRB1*1501-DRB1*0602 and HLA-A*0201; Spanish, hepatocellular injury: HLA-A*3002 (OR = 6.7) and HLA-B*1801 (OR = 2.9), cholestatic injury: DRB1*1501-DRB1*0602 • Racial disparities: Northern *vs.* Southern Europeans Caucasian	• Innate and adaptive Immune mediated	• Enhanced immune response

mitochondrial liability was more prevalent among the drugs with an increased pediatric reporting frequency, while cholestatic manifestation, high lipophilicity and biliary excretion were more common among the drugs associated with a higher reporting frequency in the elderly, which might be explained by interactions between specific drug properties and age-biased attributes [51]. Drug-host interactions also appear to exist between specific drug properties and host genetic variants. Lucena *et al.* found that *SOD2Ala/Ala* genotype was associated with an increased risk of developing cholestatic/mixed injury induced by drugs with mitochondrial hazard [66]. Ulzurrun *et al.* suggested positive interaction between drugs containing a carbocyclic system with aromatic rings (e.g. NSAIDs) and a genetic variant, *ABCC11 c.133 CC* in DILI susceptibility [109]. Lastly, sexual dimorphism (XX *vs.* XY) may contribute gender-specific susceptibility of neurons and splenocytes to different cytotoxic agents, suggesting gender bias in cellular toxicological responses [110]. Whether hepatocytes or cholangiocytes exerts similar gender-biased toxicological responses requires future investigation.

Collectively, a conceptual framework explaining the relevance of drug-host interactions in human DILI is depicted in Fig. 2. The proverb of "the blind men and the elephant" teaches us the manifold nature of truth; in the story, every one of the blind men touches different parts of the elephant and describes it differently without knowing that all stems from the same animal. Through this analogy, we intent to highlight the different mechanisms underlying human DILI. Future investigations targeting drug-host interactions in an integrative system analysis will favour unravelling the determinants that overlap and potentiate each other on DILI. In this regard, recent progress in differentiating induced pluripotent stem cells makes it possible to develop patient-specific hepatocytes as a "host dependent" assay system to investigate drug-host interactions [111]. On the other hand, introducing advanced bioinformatics methodologies, machine learning [112], topic modelling [113], network analysis [114] and deep learning techniques [115] to clinical analysis will unmask hidden patterns/associations. Inter-disciplinary translation integrating preclinical knowledge, drug properties and clinical phenotype is of critical importance for a better understanding of human DILI. Development of standardized nomenclature, electronic form of knowledge base for hepatotoxic drugs and drug properties [116], ranking/classification of post-marketing safety profiles [117], and bioinformatics infrastructure to support discovery-driven research will enhance the transferability of information and facilitate inter-disciplinary research in the field.

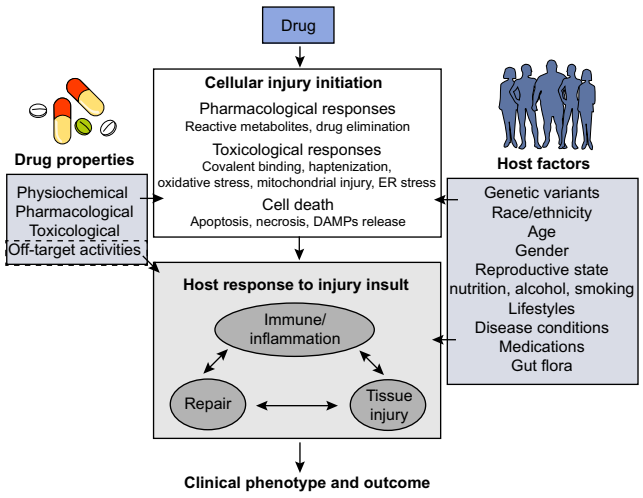

Fig. 2. Conceptual framework explaining drug-host interactions in human DILI. Two key players in DILI, drug and host factors may interact in a multifaceted manner at different functional pathways and determine individual susceptibility, clinical phenotype and outcome. Mechanisms involved in the initiation of cellular injury are likely drug specific and may occur as consequence of the interaction between specific drug properties and host-specific activities. Once injury is established host responses to the injury insult (i.e., immune response, inflammation, tissue injury and repair) are mainly determined by host factors. Such responses are likely modulated by various host factors such as age, gender, genetic factors, lifestyles, disease conditions and co-medications.

Perspectives

This review aimed at highlighting current knowledge on drug properties, host factors and drug-host interactions in human DILI and identifying knowledge gaps to stimulate future investigation. As individual risks and clinical phenotypes of DILI are likely determined by a multi-faceted interaction between drug properties and host factors, a new paradigm of DILI studies should be directed to address not only host factors or drug properties alone but their interactions. Developing new investigational approaches involving bioinformatics and computer science may become crucial in such future investigations. Indeed, preclinical safety assessment is currently based on the paradigm "high doses in healthy animals". However, biological responses to drug treatment will inevitably differ in disease. Therefore, the utility of experimental models that simulate host conditions should be considered [118].

Current knowledge is still limited and insufficient for accurate DILI risk prediction. Further investigations targeting drug-host interactions will enable establishing patient's risk stratification and the development of a safety personalized medicine.

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Conflict of interest

The authors disclose the following: The views presented in this article do not necessarily reflect those of the U.S. Food and Drug Administration.

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