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Review

Animal models of drug-induced liver injury☆

Mitchell R. McGill[a,b], Hartmut Jaeschke[c,*]

[a] Dept. of Environmental and Occupational Health, Fay W. Boozman College of Public Health, University of Arkansas for Medical Sciences, Little Rock, AR, USA
[b] Dept. of Pharmacology and Toxicology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA
[c] Dept. of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical Center, Kansas City, KS, USA

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ABSTRACT

Drug-induced liver injury (DILI) presents unique challenges for consumers, clinicians, and regulators. It is the most common cause of acute liver failure in the US. It is also one of the most common reasons for termination of new drugs during pre-clinical testing and withdrawal of new drugs post-marketing. DILI is generally divided into two forms: intrinsic and idiosyncratic. Many of the challenges with DILI are due in large part to poor understanding of the mechanisms of toxicity. Although useful models of intrinsic DILI are available, they are frequently misused. Modeling idiosyncratic DILI presents greater challenges, but promising new models have recently been developed. The purpose of this manuscript is to provide a critical review of the most popular animal models of DILI, and to discuss the future of DILI research.

1. Introduction

Drug-induced liver injury (DILI) is a problem that affects consumers, clinicians, pharmaceutical companies, and regulators. For consumers, it is a marginal but ever-present risk. For clinicians, it is difficult to diagnose and can be difficult to treat. And for the pharmaceutical industry and regulators, it is an obstacle that must be avoided in order to bring a new product to the market and keep it there. DILI is the single most common cause of acute liver failure (ALF) in the US. It has been reported that DILI is responsible for approximately 60% of all ALF cases [1], but that is likely an underestimate; other studies have consistently demonstrated that 10–20% of ALF cases of indeterminate etiology are actually due to DILI [2–4]. DILI is also one of the most common reasons for post-marketing withdrawal of drugs and for new black box warnings throughout the world [5–7].

DILI is usually divided into two types that are commonly referred to as “intrinsic” and “idiosyncratic.” Although there is no universal definition of either, intrinsic DILI is typically said to be dose-dependent and predictable. The toxicity is attributed to chemical properties of the drug rather than some unique aspect of the drug consumer's biology. On the other hand, idiosyncratic DILI (IDILI) is often described as non-dose-dependent (i.e. occurs at low doses), unpredictable, and rare (though the definition of “rare” also varies considerably). It is thought to be determined in large part by genetic variation. In reality, these definitions probably represent two ends of a spectrum. This is clear because the probability of IDILI increases with increasing daily dose [8–10] and the prevalence (and therefore predictability) of toxicity among users of IDILI-causing agents varies from drug to drug. Furthermore, there is some evidence that biological variation can also influence intrinsic hepatotoxicity [11–13].

The models used to study DILI are important. The challenges presented by DILI are due in part to our poor understanding of the mechanisms that drive it. Without knowledge of the mechanisms, it is difficult to develop ways to predict and avoid it. And in order to understand the causes, we need research models that can reproduce it. However, development of appropriate models has been onerous. It has been pointed out that adverse drug reactions that are idiosyncratic in humans are also idiosyncratic in mice [14], and even use of intrinsic hepatotoxicants in animals suffers from pitfalls that must be avoided. While novel in vitro models of DILI with promise for pre-clinical prediction of hepatotoxicity have been introduced, they lack important factors like a complete immune system and cross-talk with other organs. It seems unlikely that they will fully replace animals for research or drug development. In this manuscript, we review the major animal models of DILI and describe promising recent advances. The attributes of ideal DILI models are listed in Table 1, with examples of each.

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* Corresponding author at: Dept. of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical Center, 3901 Rainbow Blvd., MS1018, Kansas City, KS 66160, USA.
E-mail address: hjaeschke@kumc.edu (H. Jaeschke).

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Table 1
Attributes of an ideal model of drug-induced liver injury.

Attribute	Description	Example(s)
Clinical resemblance to human DILI	Doses, time course and/or pathology are similar	APAP overdose, Uetrecht-Pohl model, mitochondriopathy model
Mechanistic resemblance to human DILI	Pathophysiology is similar	APAP overdose, Uetrecht-Pohl model?
Experimental convenience	Animals develop injury in days to weeks	All current models

2. Models of intrinsic DILI

Animal models of intrinsic DILI are straightforward with regard to technique. In most cases, one can simply treat the animals with a large dose of the drug of interest to cause hepatotoxicity. However, the proper use of these models requires a basic understanding of the mechanisms of toxicity in each one. The most common models of intrinsic hepatotoxicity are listed in Table 2. By far, the two most common models in intrinsic DILI research are acetaminophen (APAP) and carbon tetrachloride (CCl_4).

2.1. Acetaminophen

APAP is the most commonly used model of intrinsic DILI. It is also the most clinically relevant [15], as APAP overdose is the primary cause of acute liver failure in several countries [1]. As a result, the mechanisms of APAP hepatotoxicity have been well studied, though important gaps remain. The toxicity is initiated by conversion of APAP to an electrophile thought to be *N*-acetyl-*p*-benzoquinone imine (NAPQI) (Fig. 1). That conversion is catalyzed by cytochrome P450 enzymes. NAPQI then binds to sulfhydryl groups on glutathione and proteins. Depletion of GSH makes the cells more susceptible to oxidative stress. The effects of protein binding are less clear, but there is mounting evidence that mitochondrial proteins are the critical targets [16,17]. For example, *N*-acetyl-*m*-aminophenol (AMAP), an isomer of APAP, does not bind to mitochondrial proteins nor cause toxicity in mouse hepatocytes, but does both in human hepatocytes [17]. The protein binding appears to cause inhibition of mitochondrial respiration during APAP toxicity [18] and mitochondrial oxidative stress develops [19–22]. It is thought that the initial oxidative stress activates redox-sensitive MAP kinases that converge on the c-Jun N-terminal kinases 1/2 (Jnk) [23–26], and phospho-Jnk then translocates to mitochondria where it exacerbates the oxidative stress by further inhibiting mitochondrial respiration [27–29]. Although recent data have cast doubt on the Jnk hypothesis [30], the weight of the evidence supports it [31]. Other kinases, such as the receptor interacting protein kinases (Ripk) 1 and 3 have also been demonstrated to be important [32–34]. However, the detailed mechanisms of the involvement of these kinases in APAP toxicity remain to be investigated; a recent study even questioned the relevance of Ripk 3 [35]. Eventually, loss of the mitochondrial membrane potential occurs [36], which causes swelling and rupture of mitochondrial membranes with release of endonucleases [37]. The endonucleases then translocate to the nucleus and cleave nuclear DNA [37,38]. The result is oncotic necrosis [16,39,40].

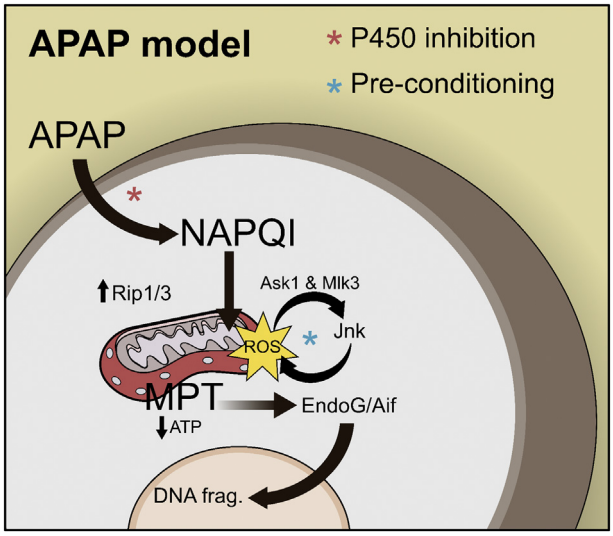

Fig. 1. Mechanisms of acetaminophen hepatotoxicity. Acetaminophen (APAP) hepatotoxicity begins with formation of a reactive metabolite (NAPQI) that binds to proteins. Binding to mitochondrial proteins causes mitochondrial dysfunction and oxidative stress. The initial reactive oxygen species (ROS) activate kinases like the c-Jun N-terminal kinases 1/2 (Jnk), which then exacerbates the mitochondrial oxidative stress. Eventually, the mitochondrial permeability transition (MPT) occurs and mitochondrial polarization and ATP production are lost. The mitochondrial matrix swell and the outer membranes rupture releasing endonucleases (EndoG and AIF) that translocate to the nucleus and fragment nuclear DNA.

Mice are the preferred animal for studies of APAP overdose. Early studies involved multiple species, including rats [41,42], guinea pigs [41], cats [43] and hamsters [44]. However, it is now clear that mice are the best available model [45]. The doses of APAP that cause toxicity in mice and humans are similar; both species develop injury at doses ≥150 mg/kg, while the other species that have been tested are either much more resistant or much more susceptible [41,43,45]. More importantly, the mechanisms of toxicity appear to be the same in mice and humans [15]. There is strong evidence for glutathione depletion [40,46,47], protein binding [2,47,48], mitochondrial damage [16,17,40,47], oxidative stress [40], DNA fragmentation [16,49] and Jnk activation [47] in humans, like mice. On the other hand, rats have less mitochondrial protein binding than mice, despite receiving much higher doses [45], and there is no evidence of mitochondrial damage or oxidative stress in rats [45]. Conveniently, mice are generally easier to work with than other species, and numerous gene knock-out mice and transgenic substrains of mice are available for research purposes. One minor difference between humans and mice is the time course of liver injury; hepatotoxicity develops somewhat faster in mice, peaking around 12–24 h compared to 24–72 h in humans [16,40].

Typically, the mice are fasted for 12–16 h before treatment with 200–300 mg/kg APAP. The primary purpose of fasting is to reduce variation of hepatic GSH levels due to nutritional status; it ensures that

Table 2
Major animal models of intrinsic drug-induced liver injury.

Drug	Favored species	Typical dose	Strengths	Weaknesses
Acetaminophen	Mouse	200–600 mg/kg	Easy to use, clinically relevant	Potential interference with metabolism
CCl_4	Rat, mouse	1–2 mL/kg (10–20 mmol/kg)	Easy to use, can also model chronic DILI	Limited clinical relevance; potential interference with metabolism
Thioacetamide	Mouse, rat	100–300 mg/kg	Easy to use	Limited clinical relevance; potential interference with metabolism
Furosemide	Mouse	200–500 mg/kg	Easy to use	Limited clinical relevance; potential interference with metabolism
Bromobenzene	Mouse, rat	0.5–1 mL/kg (5–10 mmol/kg)	Easy to use	Limited clinical relevance; potential interference with metabolism
Allyl alcohol	Mouse, rat	30–100 mg/kg	Easy to use	Limited clinical relevance; potential interference with metabolism

all the animals have a similar baseline level of glutathione for glutathionylation and glycogen for glucuronidation. However, fasting is not required if higher doses of APAP (400–600 mg/kg) are given. Whether or not fasting the animals makes the model less clinically relevant is debatable. However, almost all research to date that has included a comparison of toxicity or regeneration mechanisms between mice and humans have used fasted mice and found that the mechanisms are similar between species, even in metabolomics experiments where one might expect fasting to alter the results [16,50–53]. One exception might be when studying autophagy. Fasting induces autophagy and may mask potential effects of pharmacological interventions. Thus, studies that showed the hepatoprotective effects of removing damaged mitochondria [54] or protein adducts [55] by autophagy used fed mice.

Several issues must be addressed when using the mouse model of APAP overdose. First, any intervention that reduces P450 expression, inhibits P450 activity, or otherwise reduces protein binding will also prevent or reduce the liver injury (Fig. 1). Many drugs initially thought to protect against APAP through novel mechanisms actually inhibit APAP bioactivation [56–58]. Drug vehicles must also be considered. A classic example is dimethyl sulfoxide (DMSO), which is well known to inhibit Cyps [56,59–61]. To avoid inhibition of APAP bioactivation, interventions should be given at least 1.5 h after a dose of ≤300 mg/kg APAP. Anytime pre- or co-treatment is used, it is important to include vehicle controls, and to assess the effect of the drug(s) and vehicle(s) on either hepatic GSH depletion or protein binding.

A related issue is pre-conditioning. Any intervention that puts stress on hepatocytes prior to APAP treatment can induce expression of antioxidant genes that protect against toxicity (Fig. 1). This phenomenon has been documented with both pharmacologic [62] and genetic interventions [63,64]. For example, liver-specific KO of autophagy genes causes chronic liver injury and repair that activates nuclear factor (erythroid-derived 2)-like 2 (Nrf2) [63]. The increased Nrf2 activity in the liver results in higher baseline GSH levels and thereby protects against APAP overdose [63]. Another example is the use of neutropenia-inducing antibodies 24 h before APAP treatment, which protects against APAP hepatotoxicity [52,65]. However, this protection is not caused by neutropenia as hypothesized but by causing a preconditioning effect due to the phagocytosis of the antibody-tagged, inactivated neutrophils by Kupffer cells, which triggers the extensive induction of defense genes including metallothionein [66]. Metallothionein protects against APAP overdose by assisting in the scavenging of NAPQI [67]. Thus, anytime an intervention or genotype protects against APAP hepatotoxicity, it is important to verify that it is not due to a pre-conditioning effect.

An additional consideration is the mouse strain used for the experiments. There is considerable variation in the extent of liver injury caused by APAP across strains [68]. Common inbred strains used in APAP research are C57Bl/6J, C57Bl/6N, and C3HeB/FeJ. Interestingly, C57Bl/6J mice carry a spontaneous mutation in the nicotinamide nucleotide transhydrogenase (*Nnt)* gene that results in loss of its activity. Normally, Nnt maintains high concentrations of NADPH in the mitochondrial matrix, which is important for several reactions including the reduction of glutathione disulfide (GSSG) back to the reduced form. However, under conditions when the mitochondrial electron transport chain is impaired, the enzyme works in the opposite direction, i.e. Nnt functions to generate more NADH for use in the electron transport chain, which leads to reduction of NADPH levels and consequently lower antioxidant capacity in the mitochondria [69]. In the case of APAP, this means that the push to feed more electrons into the transport chain leads to more reactive oxygen formation in combination with the impaired antioxidant defense. This explains why C57Bl/6N mice with functional Nnt are more susceptible to APAP toxicity than C57Bl/6J mice [70,71]. C3H/HeJ mice carry a spontaneous mutation in the toll-like receptor 4 (*Tlr4*) gene, which makes them less responsive to endotoxin. The C3H/HeJ mice are also less susceptible to APAP toxicity than other C3H substrains, which led one group to propose that Tlr4 is an important mediator of the injury [72]. Although there is no doubt that the extensive necrosis observed after APAP overdose leads to release of damage-associated molecular patterns, which are ligands for a variety of pattern recognition receptors and trigger the transcriptional activation of cytokines and chemokines in the liver [73–75], that interpretation of the data may be incorrect. This sterile formation of inflammatory mediators does cause the recruitment of neutrophils and monocyte-derived macrophages into the liver. However, the function of these inflammatory cells is controversial. There is experimental evidence both for and against a direct exaggerating effect of neutrophils and monocytes on APAP-induced liver injury [73–75], but the preponderance of evidence appears to support the idea that these inflammatory cells are recruited to remove necrotic cells and prepare the liver for recovery [74,75]. These animal data are supported by evidence that monocytes [76] and neutrophils [53] are pro-regenerative after APAP overdose in humans.

2.2. Carbon tetrachloride

CCl_4 is not a drug, but high doses (≥1 mL/kg) do cause reproducible acute liver injury that resembles intrinsic DILI. After APAP, CCl_4 is probably the most common model of xenobiotic-induced acute liver injury. The effects of CCl_4 on the liver are complex and there is debate over which are most important for its hepatotoxicity [77]. However, it is clear that the toxicity is dependent on the P450-catalyzed metabolism to the reactive metabolite trichloromethyl radical ($CCl_3\cdot$) (Fig. 2). Early studies revealed that CCl_4-induced necrosis is limited to the centrilobular area where P450 expression is greatest, that haloalkanes with stronger carbon-halogen bonds that are difficult to break are not hepatotoxic, that ^{14}C from radiolabeled CCl_4 accumulates in the endoplasmic reticulum where P450 activity is greatest, and that young rats with low P450 expression are resistant to CCl_4-induced liver injury [78]. More direct approaches to test the involvement of P450s have since become available and also support that hypothesis [77,79]. Importantly, $CCl_3\cdot$ can alkylate proteins, nucleic acids and lipids, altering their function. Major effects include reduced protein synthesis, steatosis, and altered calcium homeostasis [77]. $CCl_3\cdot$ also reacts with molecular oxygen to form trichloromethylperoxy radical ($CCl_3OO\cdot$). In addition to binding to macromolecules like $CCl_3\cdot$, $CCl_3OO\cdot$ can extract hydrogen from polyunsaturated fatty acids and thereby initiate the

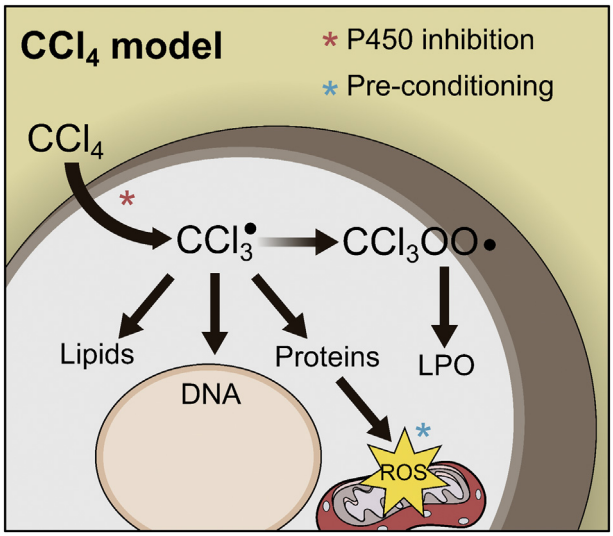

Fig. 2. Mechanisms of carbon tetrachloride hepatotoxicity. Carbon tetrachloride (CCl_4) is converted to a radical ($CCl_3\cdot$) that binds to proteins, DNA and lipids. This causes mitochondrial damage and oxidative stress. $CCl_3\cdot$ can also react with O_2 to form $CCl_3OO\cdot$, which initiates the lipid peroxidation (LPO) chain reaction that damages cell membranes.

chain reaction known as lipid peroxidation (LPO). It appears that both alkylation and LPO are required for the hepatotoxicity of CCl_4 [77]. Like APAP, acute CCl_4 hepatotoxicity involves mitochondrial damage and mitochondrial DNA depletion in addition to LPO [79].

Rats are likely the best animals for studies of CCl_4 hepatotoxicity when resemblance to humans is important. Although the rat is the least susceptible rodent species [80], there is evidence that metabolism of CCl_4 is lower in both rats and humans than in other species [81] and it has been observed that the histopathology of CCl_4 toxicity in rats is like that in humans [82]. Nevertheless, mice are often used for convenience and because of the availability of gene knock-out mice and transgenic substrains.

Many considerations for the APAP hepatotoxicity model of DILI are the same for CCl_4. Again, any intervention that alters P450 expression or activity will likely affect the injury (Fig. 2). The importance of P450-mediated bioactivation of CCl_4 has been directly demonstrated using P450 inhibitors in multiple studies [79,83]. Thus, as for APAP, we recommend post-treatment when using any pharmacologic interventions. It has also been demonstrated that Nrf2 is activated in mouse liver tissue after acute CCl_4 treatment [84] and that it protects against CCl_4 [85]. Thus, it is likely that preconditioning effects that further upregulate antioxidant genes would protect (Fig. 2). Finally, major differences between mouse sub-strains have also been reported for CCl_4-induced liver injury. For example, C57Bl/6N mice develop more severe injury, but also recover much faster due to differences in the response of macrophages [86].

One application of CCl_4 that sets it apart from APAP is that it can also be used to model chronic liver disease (CLD), such as alcohol associated liver diseases and fatty liver diseases. Lower doses (0.5–0.8 mL/kg) given twice per week over the course of 2–4 weeks will cause persistent liver injury with inflammation and fibrosis. Any intervention strategy, especially plant extracts with unknown composition, used in the chronic model of CCl_4-induced toxicity has to be tested for its potential effects on P450-dependent metabolism. CCl_4 is also often included as a second “hit” in two-hit models of CLD. Although most alcoholics and obese patients develop fatty liver, a minority progress to fibrosis or cirrhosis. The two-hit hypothesis of CLD is that fatty liver is merely the first hit, and one or more additional insults are required to drive disease progression [87]. Thus, CCl_4 treatment is often mixed with other treatments as the second hit [87–90]. A promising novel model of non-alcoholic steatohepatitis (NASH) was recently developed using this approach. When C57Bl/6J mice were fed a high-fat Western diet combined with once per week exposure to a low dose of CCl_4 (0.2 mL/kg) they developed steatosis and late-stage fibrosis by 12 weeks, with progression to hepatocellular carcinoma (HCC) by 24 weeks [90,91]. This appears to be the first mouse model to reproduce nearly all the histopathological and transcriptomic features of human NASH [90].

2.3. Other drugs and xenobiotics

Thioacetamide (TAA) induces hepatotoxicity in mice and rats at doses ≥100 mg/kg. It is converted to the metabolites TAA S-oxide and S,S-dioxide by cytochrome P450 enzymes [92–94] and the S,S-dioxide initiates toxicity by binding to lipids and proteins. Few studies have directly addressed species differences in TAA hepatotoxicity, but values for serum ALT reported in the literature are typically much higher for mice than rats despite treatment with similar doses. Very few studies have investigated the pathophysiology of TAA hepatotoxicity, so not much is known about it. Other poorly studied model hepatotoxicants are furosemide, bromobenzene, and allyl alcohol. Similar to APAP, CCl_4 and TAA, these drugs are converted to reactive metabolites that bind to proteins [95–98] or can induce lipid peroxidation [99] to cause hepatocyte necrosis. Finally, there are other xenobiotics that induce liver injury in rodents, but are not models of DILI per se. For example, the combination of endotoxin and an inhibitor of gene expression causes apoptotic death [100], which does not appear to be a common characteristic of intrinsic DILI [16,101].

2.4. Summary

APAP is the archetype of intrinsic DILI, and APAP overdose in mice is by far the most common model. CCl_4 is also popular, and has the advantage of being useful for studies of chronic DILI and fibrosis. However, consideration of the basic mechanisms of toxicity is important when using either APAP or CCl_4. Reactive metabolite formation and protein binding are common features of almost all available animal models of intrinsic DILI. Some form of oxidative stress and mitochondrial damage are also involved in both the APAP and CCl_4 models, and in several less common intrinsic DILI models [102–104]. Thus, intrinsic DILI appears to involve reactive metabolites, oxidative stress and mitochondrial damage in most cases.

3. Models of idiosyncratic DILI

The study of IDILI in animals poses greater technical challenges. Achieving an adverse reaction to a drug that is known to cause IDILI in humans typically requires a pre-treatment or genetic alteration designed to pre-dispose the animals to injury. Of course, any such pre-treatment has the potential to affect the clinical relevance of the model. The three major approaches that have been used so far involve either induction of inflammation, suppression of immune tolerance, or genetic manipulation of mitochondrial function. These models are summarized in Table 3.

3.1. Inflammagen model

In the inflammagen model, animals are either pre-treated, co-treated, or post-treated with bacterial lipopolysaccharides (LPS) in order to induce inflammation. The model was based on observations made as far back as the 1940s, when it was discovered that pre-treatment with antibiotics reduces the hepatotoxicity of CCl_4 [105]. Similar reports led to the hypothesis that IDILI is due in part to variation in exposure of humans to LPS [106]. That hypothesis has evolved to the idea that any randomly occurring inflammatory stimulus can precipitate IDILI. The first direct evidence to support that idea came from experiments with chlorpromazine (CPZ), a tricyclic antipsychotic. CPZ is now rarely used but was once a common cause of drug-induced liver disease. Therapeutic doses cause liver function impairment and elevated serum alkaline phosphatase (ALP) in approximately 40% of all users [107,108], and liver disease in approximately 1% [108]. However, extensive efforts for decades to develop an animal model of CPZ hepatotoxicity brought little success. Finally, Buchweitz et al. [109] were able to reproduce the clinical chemistry of human CPZ hepatotoxicity in rats by adding a 2 h pre-treatment with LPS. Since then, the inflammagen model has been used to induce reproducible liver injury in rodents using relatively low doses of several other drugs that cause IDILI in humans including diclofenac [110], halothane [111],

Table 3
Major animal models of idiosyncratic drug-induced liver injury.

Model	Strategy	Strengths	Weaknesses
Inflammagen model	LPS co-administration	Easy to use	Poor resemblance to human IDILI
Uetrecht-Pohl model	Compromised immune tolerance	Time course and pathology resemble human IDILI	No liver failure
Subclinical mitochondriopathy	Compromised ROS defense	Time course resembles human IDILI	Poor reproducibility

amiodarone [112], ranitidine [113] and trovafloxacin [114].

The human relevance of the inflammagen model is probably limited. One issue is that the timing of LPS treatment is important. Using this model, some drugs cause liver injury when LPS is administered as a pre-treatment [109,113], while others require very late post-treatment [112]. Such exact timing of increased LPS exposure seems unrealistic in humans. Uetrecht and Naisbitt [115] have described other major problems. First, the time from initiation of therapy to IDILI for a given drug is usually similar across patients. If exposure to LPS was a precipitating factor then one would expect that timing to be random because not all patients on a particular drug would encounter high levels of LPS after the same time period. Instead, the delay in injury is probably the time required to mount an adaptive immune response to a hapten or some other epitope created as a result of the drug [116]. Second, liver injury in the inflammagen model appears to be driven by an innate immune response, as it primarily involves neutrophils [113]. The best example to illustrate that comes from APAP toxicity where the mechanism of APAP toxicity alone can be compared with the injury induced by LPS + APAP. Although an APAP dose close to the threshold of toxicity (150 mg/kg) can be aggravated with LPS pre-treatment [117], the time course of the injury is completely different. The delayed injury in the LPS + APAP experiment is consistent with a late neutrophil-mediated injury, which does not occur with APAP alone [118]. Thus, the LPS + drug toxicity is mainly a neutrophil-mediated toxicity, which is not typical for IDILI. In humans, IDILI is driven by lymphocytes. Third, sensitivity to toll-like receptor ligands including LPS falls precipitously after initial exposure, which likely limits their effects [9]. Finally, intestinal permeability is increased in patients with inflammatory bowel disease and they have elevated serum endotoxin values as a result [119], yet there is currently no evidence for increased risk of IDILI among patients with inflammatory diseases.

4. Suppression of immune tolerance ("Uetrecht-Pohl model")

A recently developed approach to model IDILI in animals is to suppress immune tolerance in the liver (Fig. 3). This approach is based on Temple's corollary, which states that all drugs that cause serious IDILI in a few patients also cause much higher incidences of mild liver injury that spontaneously resolves despite continued treatment. The fact that most patients adapt to the initial mild injury strongly suggests that immune tolerance develops and prevents progression to liver failure. That led to the hypothesis that breakage of immune tolerance is necessary to develop a complete IDILI model. Consistent with that, Metushi et al. [120] observed that the idiosyncratic hepatotoxicant amodiaquine causes delayed-onset mild liver injury in female C57Bl/6J mice that spontaneously resolves, and that resolution occurred after an increase in programmed cell death 1 protein (Pd-1) positive T cells in the liver. Importantly, Pd-1 is critical for development of immune tolerance. The authors later discovered that the injury appeared to be worse in Pd-1 KO (Pd-$1^{-/-}$) mice [121], and that co-treatment of Pd-$1^{-/-}$ mice with an antibody against cytotoxic T-lymphocyte-associated protein 4 (CTLA4) on regulatory T cells prevented injury resolution [121]. At the same time, Chakraborty et al. [122] used a similar approach to delay resolution of halothane hepatotoxicity. Importantly, histology in both studies more closely resembled that of human IDILI than previous models [121,122]. Finally, a recent follow-up study demonstrated that the Pd-$1^{-/-}$-anti-CTLA4 mouse model can also reproduce troglitazone and tolcapone IDILI, and can distinguish between hepatotoxic and non-hepatoxic drugs of the same class [14].

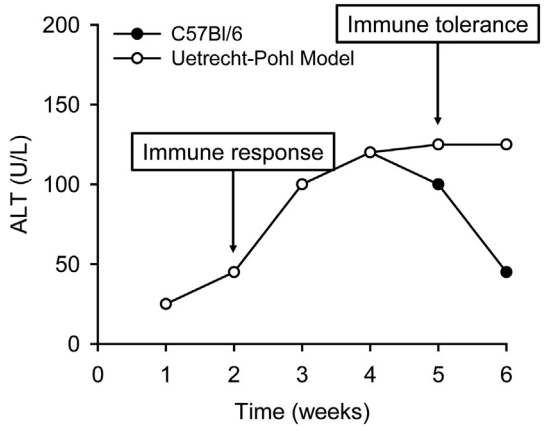

Fig. 3. Importance of immune tolerance in idiosyncratic DILI. In WT C57Bl/6 mice, daily treatment with idiosyncratic hepatotoxicants causes delayed-onset transient liver injury. In the Uetrecht-Pohl model, various strategies are used to reduce regulation of the adaptive immune system and therefore prevent development of immune tolerance, and those mice experience ongoing liver injury. Results from that model have demonstrated that immune tolerance is a likely explanation for the transient nature of most IDILI in humans; loss of tolerance may explain why only some cases of IDILI are severe.

Despite the success of the Uetrecht-Pohl model to date, there are potential problems. First, it is a relatively new approach and requires further validation with other IDILI-causing drugs. Second, although there is evidence of sustained liver injury in this model, true liver failure has not yet been reported with the model. Finally, the strategies used to break immune tolerance in mice are extreme; it is unlikely to be so severe in humans, so other factors may need to be considered. Nevertheless, the available data are promising.

4.1. Subclinical mitochondriopathy

Although there is widespread agreement that IDILI involves the adaptive immune system, it has been noted that associations with HLA variants are weak and cannot fully explain IDILI risk in patients [116]. As a result, it has been suggested that non-immune-mediated mechanisms may also be important. Interestingly, Ong et al. [123] reported that mice with partial deficiency of the mitochondrial superoxide dismutase 2 (Sod2$^{+/-}$) developed mild liver injury as indicated by both serum ALT and histology after treatment with 30 mg/kg/day troglitazone for four weeks but WT mice did not. That result led to the hypothesis that some IDILI can be explained by increased susceptibility of patients with subclinical mitochondrial dysfunction. However, attempts to reproduce those results have had mixed success. Another group reported that the increase in ALT after chronic troglitazone treatment did not differ between WT and Sod2$^{+/-}$ mice [124]. In addition, attempts to mimic the troglitazone study with other drugs have resulted in only limited evidence for liver injury [125–127]. As a result, the Sod2$^{+/-}$ model has fallen out of favor. Associations between *SOD2* variants and IDILI in humans have been discovered [128], but those variants have not been reported in more recent genome-wide association studies [129].

4.2. Summary

Of the currently available animal models for IDILI, the Uetrecht-Pohl model appears to be the most similar to humans. Although early results look promising, challenges remain. There is still no complete model of serious IDILI with development of liver failure. Furthermore, although the Uetrecht-Pohl model suggests that loss of immune tolerance is likely an important part of the mechanisms of IDILI, we do not know what would cause that in humans. It is also possible that other, as yet unknown mechanisms play a role. An additional issue with all of the available models is that they have largely been designed with hepatocellular IDILI in mind. These models should also be validated for modeling of cholestatic and mixed IDILI.

5. Differences in drug metabolism between animals and humans

Drug metabolism, and especially cytochrome P450-mediated metabolism, should be a major consideration when working with any model of DILI. It should be clear from our discussion of intrinsic DILI models that many depend upon metabolism to form a reactive metabolite. The prevailing view of IDILI is that it too depends upon reactive metabolites, which bind to proteins and create neoantigens that elicit an immune response (though other mechanisms have also been proposed) [116,130]. Importantly, there are dramatic species differences in metabolism. Although the common experimental models (mice, rats, dogs, and monkeys) all express homologs of the major P450s in humans, not all homologs have the same substrate specificity. In fact, CYP2E1 is the only human P450 that is functionally conserved across species [131]. Generally, mice bear the greatest resemblance in overall P450 function to humans among common research species, while rats are the most strikingly different [131]. Rats tend to have low P450 activity compared to other species, which may explain why they are less susceptible to some hepatotoxicants. Differences in expression or function of other enzymes can also be important. For example, dogs are poor acetylators because they lack *N*-acetyltransferase (Nat) genes [132] and the high incidence of idiosyncratic sulfonamide toxicity in dogs may be a result of that [133], while cats are poor glucuronidators and are highly susceptible to APAP hepatotoxicity because they lack functional Ugt1a6 [134]. Overall, it is critical to consider species differences in drug metabolism when using animal models of DILI.

6. Conclusions

DILI is a major clinical and regulatory problem. Many of the challenges presented by DILI are due to poor understanding of the mechanisms of toxicity caused by different drugs. Although reasonably good models of intrinsic DILI exist, they are often misused. A thorough understanding of what is known about the basic mechanisms of injury caused by intrinsic hepatotoxicants is necessary to ensure proper use. While IDILI is more difficult to reproduce in animals, the Uetrecht-Pohl model involving breakage of immune tolerance appears to be a major step forward. Overall, substantial progress is being made in our understanding of DILI using animal models, but considerable work remains to be done.

Transparency document

The Transparency document associated with this article can be found, in online version.

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Conflict of interest

The authors have no conflict of interest to declare.

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