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Invited Review

Stress of Strains: Inbred Mice in Liver Research

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Inbred mice are the most popular animals used for in vivo liver research. These mice are genetically defined, readily available, less expensive to maintain than larger animals, and enjoy a broad array of commercial reagents for scientific characterization. C57BL/6 mice are the most commonly used strain. However, other strains discussed, including BALB/c, C3H, A/J, and FVB/N, may be better suited to a particular disease model or line of investigation. Understanding the phenotypes of different inbred mouse strains facilitates informed decision making during experimental design. Model systems influenced by strain-dependent phenotype include tissue regeneration, drug-induced liver injury (DILI; e.g., acetaminophen), fibrosis (e.g., carbon tetrachloride, CCl_4), Fas-induced apoptosis, cholestasis, alcohol-induced liver disease and cirrhosis, nonalcoholic fatty liver disease and steatohepatitis (NAFLD/NASH), and hepatocellular carcinoma (HCC). Thoughtful consideration of the strengths and weaknesses of each inbred strain in a given model system will lead to more robust data and a clearer understanding of translational relevance to human liver disease.

Key words: Liver; Mice, Inbred strains; Genotype; Phenotype; Research; Animal experimentation

INTRODUCTION

Inbred mice are widely used in liver disease research because of their genetic homogeneity, reproducibility of results, inexpensive cost compared with larger species, and availability of a wide array of research reagents for in vivo characterization[1]. Because the genetic background (genotype) of inbred mouse strains is tightly controlled, physical features and pathophysiologic responses to experimental challenges (phenotype) can be better predicted. The most popular mouse strain is the C57BL/6 (C57-Black, Black-6, B6) strain. Whereas the B6 mouse is characterized by widespread use, detailed phenotypic understanding, and favored status as the background strain for most genetically engineered models, other strains of mice may be more appropriate to address specific questions in liver research. Moreover, as gene editing becomes more common, investigators may be able to insert specific genetic modifications onto any background strain[2]. This will greatly expand the toolkit of liver researchers by facilitating the study of host–environment interactions across a variety of phenotypic backgrounds. This review introduces a modest sampling of inbred mouse strains commonly used in hepatic research and describes their phenotypes in the context of specific disease models to highlight the importance of strain consideration in any given system. The overall goal is to help reduce investigator stress when selecting strains for liver research.

THE MICE

C57BL/6

A workhorse among mice, the B6 strain is far and away the most widely used in biomedical research. It should be noted that there are multiple substrains of C57BL/6 mice[3]; the C57BL/6J strain from The Jackson Laboratory is the one most investigators refer to as "B6." Both biologic and pragmatic factors contributed to the early popularity of this strain. B6 mice are docile and demonstrate reliable breeding kinetics, although they may suffer higher-than-average rates of pup loss under duress. (B6 dams sometimes eat offspring that die spontaneously, leading to an undeserved reputation as infanticidal cannibals[4].) Later, with the advent of transgenic technologies, B6 mice proved useful in identifying successful introduction of a genetically engineered mutation because their

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black fur contrasted with the white 129 mice favored for germ cell gene knockout. Patchy gray coats in the offspring signaled successful chimerism. Over the years, B6 mice became entrenched in the scientific consciousness for the simple fact that so many previous studies had utilized the strain, and there was a body of literature. B6 mice became famous for being famous. Popularity aside, certain disease conditions are ideally suited for study in B6 mice. Because this strain is more willing to ingest ethanol than others, B6 mice are favored for modeling alcoholic liver disease (ALD)[5]. Slow metabolism leading to diet-induced obesity (DIO), metabolic syndrome, and type 2 diabetes (T2D) facilitates investigation of nonalcoholic fatty liver disease (NAFLD) in this strain[6]. Viral hepatitis research has been advanced by the use of B6 mice transfected with whole or partial genomes of hepatitis B and C viruses[7]. Wild-type (WT) B6 mice are more resistant to chemically induced hepatocellular carcinoma (HCC) than strains such as C3H and DBA, making it possible to identify quantitative trait loci (QTL) associated with the disease in genetically defined hybrids[8,9]. A wide array of genetically engineered mutant mice (GEMM) on the B6 background have provided extensive insights into specific genes and pathways involved in different liver diseases. For these and other reasons, B6 mice are likely to remain the most widely used strain in liver research for years to come.

BALB/c

As ornery as B6 are docile, animal handlers would probably prefer to see the Bagg albino c-strain (BALB/c) decline in popularity. Unfortunately for the caretakers, BALB/c remains a popular strain for numerous types of studies, particularly those where their Th2-polarized immune system serves as a stark contrast to the Th1-centric C57BL/6[10]. Additionally, sensitivity to carbon tetrachloride (CCl_4) and other hepatotoxins makes the BALB/c strain a favorite in studies of acute chemical injury and liver fibrosis[11]. Continued use of BALB/c mice across a range of liver disease models means that the animal facility first aid kit will need to remain well stocked.

C3H

Along with CBA and DBA/2 strains, C3H mice have a high susceptibility to both chemically induced and spontaneous HCC[12]. Historically, this strain also showed unusually high sensitivity to Gram-negative bacterial infections but resistance to lipopolysaccharide (LPS; endotoxin) toxicity. Subsequently, it was learned that this was due to a spontaneous mutation in toll-like receptor 4 (TLR4)[13]. The mutation occurred in mice at The Jackson Laboratory (C3H/HeJ) but not at other facilities (C3H/HeN, C3H/HeOuJ) producing a natural model to study TLR4 function[14]. C3H mice form half of the equation in the generation of B6C3F1 hybrids used in most NTP studies[15].

A/J

Small and lean, A/J mice often are used to evaluate genetic resistance to NAFLD in the context of DIO and other metabolic challenges. In this regard, they serve as a metabolic foil to the B6 strain, which is prone to obesity and fatty liver[16]. To study genetic determinants of these divergent metabolic phenotypes, chromosome-substitution strain or "consomic" mice have been made between B6 and A/J strains, which bear the inbred genome of the parental strain with the exception of a complete chromosome from the donor strain. (In most cases, A/J is the chromosome donor, and B6 is the recipient.) Using this approach, QTL specifying lean versus obese phenotypes have been localized to chromosomes 6 and 17[17,18]. In addition to metabolic research, A/J mice develop chronic hepatitis and HCC that are histologically indistinguishable from human chronic viral hepatitis when infected with the enterohepatic bacterium *Helicobacter hepaticus*[1]. This remains the only WT mouse model of infectious liver cancer employing a native murine pathogen.

FVB/N

This strain was saved from declining popularity by its large embryos for easy pronuclear injection and permissiveness to embryonic stem cell transfection at the dawn of the GEMM era. To this day, a large number of transgenic mice remain on the FVB/N background ("transgenic" = new gene added, "knockout" = existing gene inactivated). FVB mice are prone to multiple forms of cancer, and carcinomas in particular (tumors of epithelial origin), a stroke of luck for oncology scientists relying on transgenic approaches[19]. In addition to transgenic modeling, WT FVB/N animals also are employed in certain metabolic and toxicology studies[20].

THE MODELS

Liver Regeneration

As the only visceral organ capable of full regeneration following significant loss of functional mass, the liver is the gold standard to model tissue development and maturation. The most widely applied model is two thirds (or ~70%) partial hepatectomy, although regeneration studies following chemical and other types of injury are also employed[21]. Whereas different strains of mice have been used in liver regeneration research, surprisingly few studies have directly compared responses between strains. Liver regeneration is delayed in C3H/HeJ mice compared with C3H/HeN, which has been attributed to differences in sinusoidal blood flow; however, this is not driven exclusively by TLR4 because $TLR4^{-/-}$ mice show normal regenerative capacity compared with WT B6 controls[22].

Drug-Induced Liver Injury: Acetaminophen

As a primary center of xenobiotic processing and elimination, the liver is highly susceptible to acute toxicity and drug-induced liver injury (DILI). This section highlights acetaminophen (APAP) toxicity as a representative model. Mice given a single high dose of APAP undergo centrilobular necrosis resulting in very high ALT and AST levels within 24 h, similar to human overdose[23]. Injury is exacerbated if mice are fasted prior to dosing due to depleted levels of reduced glutathione. Whereas early work suggested that outbred Swiss–Webster mice exhibited apoptosis following APAP challenge, subsequent work showed that caspase 3 activation was minor in these mice and that the pathophysiology of the injury was equivalent with C57BL/6 mice in terms of lesions and biomarkers[24]. Even within the B6 line, there are substrain differences in APAP sensitivity, as C57BL/6N mice show more vulnerability than C57BL/6J[3]. Mechanisms accounting for these different phenotypes remain to be elucidated.

Fibrosis: Carbon Tetrachloride

Compared with humans and other animal species, mice mount weak fibrotic responses even in the face of severe liver injury. CCl_4, once a common compound in dry cleaning and a major cause of morbidity among workers in that industry[25], is now primarily employed in mouse research as an inducer of fibrosis. CCl_4 is metabolized into toxic intermediates by the cytochrome P450 enzyme CYP2E1, which is concentrated in centrilobular hepatocytes. Central degeneration and/or necrosis may occur at high challenge concentrations. Interestingly, zone 1 (periportal) hepatocytes also undergo coagulative necrosis, and CCl_4-induced fibrosis is highly portocentric with frequent portal–portal but rare portal–central bridging[26]. Hepatocytes undergo a combination of apoptotic and oncotic necrosis, resulting in rapid cell dropout, scarring, and fibrosis. This portal pattern of fibrosis is distinct from that seen in ALD and NAFLD featuring a primarily perivenular/pericellular ("chickenwire") pattern of collagen deposition[27,28]. BALB/c mice are most susceptible to CCl_4 toxicity, although B6 and C3H mice also may show degenerative and fibrotic changes[11]. For this reason, investigators studying mechanisms and intervention of liver fibrosis/cirrhosis frequently turn to the CCl_4 model in BALB/c mice. Thioacetamide invokes similar changes and is processed in a manner similar to CCl_4[29]. Bile duct ligation also invokes fibrosis resulting from severe cholestasis (see section on Cholestatic Hepatitis).

Apoptosis

The liver is an especially valuable tissue for the study of apoptosis given the readiness of programmed cell loss and replacement in this compartment. Fas ligand (CD95) binding to the Fas receptor, which is expressed at moderate to high levels in up to 25% of hepatocytes, results in activation of the canonical Fas-associated death domain[30]. This is a generalized model for extrinsic programmed cell death that may occur via other pathways including TNFRSF1A associated via death domain[31]. C3H mice have a higher susceptibility to Fas-induced apoptosis than C57BL/6 and FVB/N mice, a finding attributed to increased levels of caspase and proapoptotic mitochondrial inner membrane proteins in the former[32].

Cholestatic Hepatitis

Bile salts are proinflammatory when encountered outside of their appropriate niche. Cholestasis is associated with hepatitis in humans and in mouse models. Knockout of the multidrug resistance-2 gene ($Mdr2^{-/-}$) impairs bile salt secretion and results in intrahepatic cholestasis and hepatitis[33]. However, strain background influences this phenotype. $Mdr2^{-/-}$ mice on an FVB/N background develop severe chronic hepatitis that progresses to HCC, whereas the disease is muted in mice on a B6 background[34]. FVB mice also were used to demonstrate that common bile duct ligation results in the most extreme cholestatic disease (including prominent fibrosis), followed by chemical injury with CCl_4, 3,5-diethoxycarbonyl-1,4-dihydrocollidine, and -naphthyl-isothiocyanate[35].

Alcoholic Liver Disease

Most studies of ALD utilize B6 mice because of their willingness to ingest ethanol compared with other strains[36]. However, in a comparison of 12 inbred strains, high alcohol ingestion resulted in dramatic variation in hepatic steatosis and inflammation[37]. NZW/Lacj was most sensitive, whereas Wsb/Eij was resistant. Among the more common strains tested, BALB/c showed intermediate ALD sensitivity, whereas C3H/HeJ and FVB/N were more resistant. It is noteworthy that 129S1Svimj mice, which have inherent defects in iron metabolism, were resistant to the high alcohol diet, demonstrating that not all types of liver injury are additive.

Baffled by NAFLD and NAFL and NASH

NAFLD is a relatively recent clinical construct arising out of the need to characterize liver disease associated with the epidemic of obesity, metabolic syndrome, and T2D. Originally, NAFLD was somewhat synonymous with benign hepatic steatosis (fatty liver), whereas the more aggressive nonalcoholic steatohepatitis (NASH) was a distinct subcomponent. Today, many investigators use the term NAFL (nonalcoholic fatty liver) to connote uncomplicated hepatic lipidosis, joining NASH as a distinct entity under the NAFLD umbrella. Others hedge

their bets with the parenthetical NAFL(D). NASH was originally defined by three histologic criteria: steatosis, inflammation, and hepatocyte ballooning degeneration[38]. Those same three criteria are graded by pathologists semi-quantitatively to form the NAFLD activity score (NAS). Under the current rubric, steatosis (0–3), hepatocyte ballooning (0–2), and inflammation (0–3) each receives an individual score, for an overall NAS range from 0 to 8[38]. Fibrosis is a frequent outcome of chronic NASH and is considered by many an integral aspect of the disease. Scoring criteria on a 0–4 scale have been described for fibrosis, but this remains an addendum to the NAS and is not typically included within it[38]. Unfortunately, human NAS scoring does not translate well to mouse models. In particular, hepatocyte ballooning degeneration is lacking in most murine fatty liver models, especially those relying on diet-induced or genetically defined obesity[39]. This is not an insignificant consideration because hepatocyte ballooning reflects lipotoxicity and represents an inflection point in the transition from clinically static to progressive fatty liver disease[40]. In most DIO mouse models, excess fat is stored in discrete membrane-bound lipid droplets primarily in the form of triglycerides (i.e., benign steatosis). Sometimes this is superimposed with glycogen-mediated cytoplasmic hydropic degeneration ("cloudy swelling"), particularly in diets supplemented with excess sugars, leading to an erroneous interpretation of ballooning degeneration. There are mouse models that do produce bona fide ballooning degeneration, but these tend to rely on direct oxidative injury rather than caloric overload, and animals typically lose rather than gain weight due to hepatotoxicity. As such, they may recapitulate histologic but not metabolic features of the human disease. Here we consider a sampling of models that rely on caloric overload (in the form of excess fats and/or sugars) versus direct oxidative stress (with or without concomitant high-fat/sugar feeding).

Obesity Models of Fatty Liver Disease

Most diet-induced and genetic obesity models (e.g., *ob/ob* mice) produce NAFL but not NASH[39]. However, these models do a good job of reproducing systemic metabolic conditions associated with the human disease (e.g., obesity and insulin resistance). Fatty liver phenotypes in genetic and diet-induced models frequently (though not always) correlate with visceral adiposity. Because B6 mice are highly susceptible to DIO and fatty liver, an overwhelming majority of NAFLD studies in WT mice use the C57BL/6 strain[41]. In contrast, A/J mice fall at the other end of the spectrum, resisting both DIO and NAFLD. For this reason, studies into genetic determinants of basal metabolism and obesity-associated diseases often contrast findings in these two strains[42]. The extreme difference in obesity propensity between B6 and A/J mice has led to the development of chromosome-substitution strain (or consomic) mice on a C57BL/6 background with the exception of one A/J chromosome in order to localize genetic determinants in a systematic way[43]. Interestingly, the hybrid F1 offspring of B6 and A/J mice develop spontaneous insulin resistance and NAFL in a parent-specific fashion, suggesting an additional contribution of epigenetic imprinting to strain-dependent obesity phenotypes[44]. In a rare study contrasting B6 mice to a strain other than A/J, it was shown that high-fat diet feeding to C57BL/6 resulted in extrahepatic adiposity, liver inflammation, and fibrosis, whereas BALB/c mice developed benign steatosis only; these attributes were attributed in part to different immune cell populations reflecting known strain biases toward a Th1 (B6) or Th2 (BALB/c) phenotype[45].

Oxidative Injury Models of Fatty Liver Disease

In order to induce lipotoxicity sufficient to result in hepatocyte ballooning in mice, experimental challenge beyond a high-fat/high-sugar diet usually is required. Some investigators add a hepatotoxin such as CCl_4 to the mix to enhance oxidative liver injury and increase fibrosis[46]. Others forego the obesity component and feed mice a methionine–choline deficient (MCD), which induces NASH-like disease through loss of phosphatidylcholine precursors required for proper mitochondrial function and oxygen free radical scavenging (SAMe; glutathione)[47]. Although livers from MCD mice recapitulate the histologic features of NASH[48], animals lose rather than gain weight, and insulin resistance and other system-wide metabolic dysfunctions associated with human NASH are not reproduced. Indeed, fat accumulation itself in this model is attributable to hepatocyte distress and not caloric overload. The *Mdr2*$^{-/-}$ mouse, which develops cholestatic liver disease and severe oxidative stress, also displays histologic features consistent with NASH in conjunction with body wasting[49]. The STAM™ mouse model relies on an injection of streptozotocin to destroy pancreatic islet cells early in life, followed by a high-fat diet. This produces severe hyperglycemia due to insulin depletion, resulting in NASH-like lesions in the liver; however, the model often is criticized because low insulin levels are more consistent with type 1 (juvenile) diabetes rather than insulin resistance and hyperinsulinemia associated with T2D and metabolic syndrome[50]. Because of severe cellular injury and inflammation, oxidative stress-based models also tend to induce more fibrosis than DIO models[51]. Almost all of the studies using the aforementioned strategies utilize B6 mice, and it is difficult to find strain comparisons. However, one study found that C57BL/6N mice on an MCD diet developed

Table 1. Inbred Mice in Commonly Used Models of Human Liver Disease With Overall Strengths and Weaknesses

Strain	Commonly Used Models	Strengths	Weaknesses
C57BL/6	Liver regeneration (PH) DILI Cholestasis/fibrosis (BDL) ALD NAFLD (susceptible) "NASH" (MCD) KO models	Best-characterized inbred strain Most KO models on B6 background Willingly ingest alcohol Metabolically susceptible to obesity-associated diseases (NAFLD)	Pup mortality higher than other strains Immune models limited to Th1 type Sometimes defaulted to even when another strain is better suited
BALB/c	Fibrosis (CCl_4, TAA)	More fibrosis than other strains Th2 foil to Th1-biased B6 when comparing immune responses	Can be difficult to handle
C3H	Apoptosis (Fas) LPS/sepsis HCC (DEN, AFB1)	TLR4 functionality can be selected Highly susceptible to chemically induced HCC	Prone to spontaneous preneoplastic and neoplastic liver lesions
A/J	NAFLD (resistant) Chronic hepatitis and hepatitis-associated HCC (*Helicobacter hepaticus*)	Resistance to obesity-associated diseases serves as a foil to B6 Only model of infectious chronic hepatitis and HCC by a murine pathogen (*H. hepaticus*)	Outside of metabolic studies, not as well characterized as other strains
FVB/N	Cholestatic hepatitis (*Mdr2*$^{-/-}$) Transgenic models	Large and readily transfectable embryo facilitates transgene insertion	Not as well characterized as other strains

AFB1, aflatoxin B1; ALD, alcoholic liver disease; BDL, bile duct ligation; CCl_4, carbon tetrachloride; DEN, diethylnitrosamine; DILI, drug-induced liver injury; HCC, hepatocellular carcinoma; *H. hepaticus*, *Helicobacter hepaticus*; KO, knockout; LPS, lipopolysaccharide; MCD, methionine choline-deficient diet; MDR, multidrug resistant; NAFLD, nonalcoholic liver disease; NASH, nonalcoholic steatohepatitis; PH, partial hepatectomy; TAA, thioacetamide.

more severe lesions including steatosis and fibrosis than did C3H/HeN mice[52]. A related model utilizes a diet deficient in cholate and folate (CFD). In a comparison of seven strains on the CFD diet, it was found that WSB/EiJ developed the most severe disease, whereas A/J, C57BL/6, and C3H/HeJ were more resistant[53]. These phenotypes were attributed at least in part to endogenous iron metabolism[54]. It is interesting to note that WSB/EiJ mice are resistant to alcohol-induced liver injury but highly sensitive to MCD diet, highlighting the importance of genetic background when assessing responses to different liver challenges.

Hepatocellular Carcinoma

The impact of mouse strain on HCC susceptibility has received an excellent recent review elsewhere and will not be covered in depth here[55]. C3H mice are well known for their high incidence of both spontaneous and chemically initiated hepatocellular tumors, whereas C57BL/6, BALB/c, and A/J mice are more resistant. B6C3F1 hybrids (like those used in NTP studies) show an intermediate phenotype, with C3H-like high tumor volume but B6-like low multiplicity[56]. In a two-hit chemical initiation–promotion comparison, it was found that C3H mice were highly susceptible both to diethylnitrosamine (DEN) initiation and phenobarbital (PB) promotion, BALB/c were resistant to initiation but sensitive to promotion, and B6 mice resisted both[57]. Tumor-susceptible DBA/2 mice also are sensitive to DEN/PB initiation–promotion[58]. Strain differences in HCC risk occur at the level of promotion and not initiation, as few differences in metabolism and adduct formation are noted immediately after challenge with common hepatocarcinogens including DEN and aflatoxin B1[59]. Interestingly, C3H and HCC-susceptible CBA mice show high metallothionein responses to zinc and copper exposure, whereas HCC-resistant B6 mice respond weakly to similar metal ion challenge[60].

CONCLUSION

Selection of inbred mouse strain may be just as important as choosing a model in the investigation of liver disease in vivo. C57BL/6 mice are an excellent choice for some but not all models, and this strain should not simply be defaulted to based on prior literature. Other strains have unique characteristics that may make them best suited for studies of liver regeneration, toxicity, infection, metabolic disease, and cancer (see Table 1). It cannot be stressed enough that choosing the right strain will reward the investigator with better outcomes and a higher relevance to human liver disease.

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