PL-1

Animal Models of Human Disease in Drug Safety Assessment
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Animal models of human disease are widely used to study the pathogenesis of a disease or to test the efficacy of therapeutic treatment. In contrast, such models are rarely used to investigate drug toxicity and the underlying molecular mechanisms. The reasons why toxicologists have been reluctant to utilize non-classical animal models in drug safety assessment are manifold. For example, the use of non-conventional animal models is neither standardized nor required by regulatory authorities. Furthermore, inclusion of novel animal models might create new and unexpected findings which are difficult to interpret. Finally, animal models ideally should closely mimic the human disease in both its etiology, clinical-pathological manifestations, and mechanisms, and this is not always the case. This presentation explores whether such animal models, nevertheless, would offer new insights into molecular mechanisms of toxicity and also provide a predictive tool for safety assessment, in particular for drugs that cause rare and unexpected adverse effects in patients.

Rare but severe adverse drug reactions (ADRs) often become apparent late in drug development or typically in the postmarketing phase. They have in some cases led to the discontinuation of further development or even withdrawal of a newly approved drug from the market. These ADRs are a major problem in drug development because they have remained unpredictable from preclinical studies and because their underlying mechanisms cannot be studied in normal healthy animals. Such idiosyncratic drug reactions are dependent on three major determinants; first, the potential toxicity of the drug molecule (or a reactive metabolite), second, host (patient) susceptibility factors, which are both genetically determined and environmentally regulated, and, third, factors pertaining to the underlying disease (therapeutic indication) [1]. These latter include altered toxicokinetics, but also alterations in gene expression and specific toxic responses to drugs [2]. Two widely known examples of disease-related determinants are the greatly increased susceptibility to sulfa drugs in patients infected with HIV versus non-virally-infected patients and the increased incidence of drug-induced acute liver failure in diabetes patients versus non-diabetes patients.

For this presentation, the focus will be on idiosyncratic drug reactions occurring in the liver. It is often striking that individuals, or subsets of patient populations, will develop liver injury following drug treatment, while healthy populations (and healthy animals) do not exhibit apparent hepatic adverse reactions. One of the reasons to explain this is that these patients exhibit a frequently occurring molecular abnormality, on which a toxic response to a drug is superimposed, often affecting the same molecular target. For example, the rare cases of severe hepatotoxicity associated with drugs used in neurodegenerative diseases (e.g., tacrine, tolcapone) have been associated with possible mitochondrial injury. Indeed, mitochondria from Parkinson or Alzheimer patients often exhibit biochemical defects and decreased activities in complex I or IV, respectively, of the electron transport chain [3]. Although the genetic abnormalities have not yet been identified at the molecular level, these mitochondria are compromised and sensitized to additional cellular stress. Animal models which mimic such mitochondrial abnormalities include gene knockout mice for specific mitochondrial key proteins, mice with specific mtDNA deletions, and rats with acquired mitochondrial abnormalities (e.g., carnitine-deficient rats).

The second paradigm encompasses animal models featuring pro-inflammatory conditions. It has been known that mild inflammation can predispose for mitochondrial toxicity. Indeed, it has been demonstrated in animal models of rheumatoid arthritis that mitochondrial toxicity induced by nonsteroidal anti-inflammatory drugs is enhanced. Furthermore, the release of bacterial lipopolysaccharide, which dramatically alters the proinflammatory cytokine network, can sensitize animals to liver injury induced by a number of drugs [4].

Finally, animal models of type 2 diabetes have been used for assessing the efficacy of antidiabetic drugs, but rarely for toxicity assessment of these drugs. For example, troglitazone has been associated with hepatotoxicity, possibly via mitochondrial damage. It is known that the liver of obese and diabetic animals is more sensitive to developing mitochondrial injury and increased prooxidant stress than healthy animals [5]. Also, animal models of type 2 diabetes have revealed that certain genes related to lipid and glucose metabolism are differentially expressed in the liver of these rats/mice compared to that of normal animals. For example, peroxisome proliferator-activated receptor-γ is highly upregulated in the liver of diabetic mice [6]. Treatment
with thiazolidinediones induces severe hepatic steatosis in diabetic mice, but not in lean controls, and this could set the stage for downstream toxic responses. Again, there are a number of available animal models of type 2 diabetes, including ob/ob mice (deficiency in leptin), db/db mice (deficiency in leptin receptor), KKAY mice (abnormal expression of agouti gene), and high fat diet-induced diabetes in rats.

Taken together, although it is obvious that animal models of human disease respond in a different manner to drugs (with respect to hepatic liability) than normal animals, such models are rarely used in preclinical safety assessment. Despite their limitations (costs, inappropriate model, production of “false positive” data, lack of historical patho data) it is suggested that such models be increasingly used in exploratory and predictive toxicology. They could serve as a powerful tool to help selecting candidates and explaining possible molecular mechanisms of toxicity.

References:


