Biomere

COMMUNITY BLOG

MODELS AND MARKERS TO EVALUATE DRUG INDUCED LIVER INJURY (DILI)

The primary organs that are impacted by drug toxicity are the liver, intestine and kidney that are the primary sites for waste generation and elimination. Drugs administered through various routes (oral, intravenous, intramuscular, etc.) are distributed throughout the body via the vasculature and are metabolized primarily in the liver and intestine before excretion via the kidney or rectum. Since the liver is typically the first organ exposed to a drug in the vasculature, it is the most vulnerable to drug induced toxicity and this effect is known as drug induced liver toxicity (DILI). DILI has a low incidence rate but is the reason for most cases of acute liver failure[1]. In severe cases, a liver transplant may be the only therapeutic option. DILI can be segmented into intrinsic and idiosyncratic types[2] – intrinsic DILI is typically dose dependent and is based on the properties of the drug to cause damage to liver tissues. Intrinsic DILI is more predictable as information is available on the drug structure and function. Idiosyncratic DILI is less predictable and is not dose dependent and is believed to be cause by genetic variation among the human population.

Several models are currently available to detect DILI preclinically including animal models, 2D human hepatocytes, and 3D cell models that can include microfluidics. One of the major challenges with developing animal models to evaluate DILI is that the mechanism of toxicity of drugs is not always clear. Animal models to evaluate DILI caused by specific drugs have been developed – one example is the mouse model for acetaminophen induced DILI2. Acetaminophen is a widely used pain medication which is known to cause liver failure with chronic use and was one of the earlier models of DILI. Typically, to measure DILI, drugs can be injected into rodent models at different doses to evaluate the extent of liver injury that is measured using specific biomarkers and evaluating changes in liver histology. This approach, while straightforward, does not address the question of how the drug causes liver injury[2]. This is critical information that is needed for smarter drug design and improved next-generation therapeutics.

Increasingly, cell-based models are being used to study DILI as these systems are completely human and are increasingly becoming more complex and therefore, more predictive of the *in vivo* state. Cell-based models range from 2D cells to complex organ on chip systems. Human hepatocytes are considered to be the gold standard for evaluating hepatotoxicity in an *in vitro* setting, but it is difficult to source primary human hepatocytes. The HepG2 cell line has been used to form 3D spheroids, but those spheroids are generated from one cell type and do not represent the 3D microenvironment. An alternative source is induced pluripotent stem (iPS) cells that are differentiated into hepatocytes. Co-culture of hepatocytes with endothelial cells, stellate cells, and Kupffer cells can better recapitulate the native environment of the liver and have been used to evaluate DILI[3].

Biomarkers to measure DILI can be broadly divided into two types – biochemical markers and genetic markers. Biochemical markers of DILI are typically measured in serum samples and range from common markers of liver damage such as glutamate dehydrogenase or cleaved K18 (keratin 18) to specific circulating microRNAs or miRs. miR-122 was shown to have some clinical relevance as a marker for DILI[4]. While several biomarkers for liver injury have been reported and evaluated, it has been a challenge to identify a comprehensive biomarker to reliably predict DILI across the board. The ideal biomarkers to measure DILI should be sensitive, reproducible and be truly predictive of DILI as opposed to transient variation in expression levels. Several biomarkers have shown significant variation in circulating biomarker levels across patient cohorts and in some cases, within the same individual sampled at different times4. Genetic markers of DILI are being explored primarily in the context of idiosyncratic DILI and the focus has been on HLA variants[5]. A recent publication has shown the correlation between specific HLA alleles and sensitivity to specific drugs but so far, no single HLA allele has been identified as a marker to predict DILI. GWAS (genome wide association studies) datasets are being used to identify non-HLA related genetic markers to predict DILI but so far, no significant biomarker has been identified. The challenge with identifying genetic markers is compounded by the low prevalence of DILI and the variation across populations. Nevertheless, the availability of GWAS data will continue to fuel the search for genetic markers to predict DILI in clinical trials.

References:

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