Prediction of Toxic Endpoints: Fact or Fantasy?

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Many marketed or under development drugs induce lipid disorders, constituting major risk factors for hepatic injury. Drug-induced lipid disorders are often unpredictable in preclinical stages, and related adverse events have led to post-market withdrawal of drugs. In particular, phospholipidosis (DIPL) and steatosis (DIST) are considered possible alarms for early Drug Induced Liver Injury. Chemical structure-based models for the prediction of liver toxicity have only modest performance, highlighting that there is no simple relationship between chemical features and toxicity. Bioassays for small molecules that assess their cytotoxicity and potential for inducing mitochondrial dysfunction in liver cell lines are routinely run in pharmaceutical companies, however, often profiled known hepatotoxic compounds did not show activity even when tested at high concentrations.

The paper presents the evaluations of the ability of lipidomic fingerprints to predict DILI for a set of well characterized marketed drugs that have also been tested in other bioassays. More precisely, the 3D tissue culture of primary human hepatocytes co-cultured with Kupffer cells will be used. These cells performance are stable up to 14 days in term of basal metabolism and xenobiotic metabolic capability, and they can be drug-treated for long time in sub-chronic conditions. Kupffer cells strongly regulate the hepatocyte functions, therefore their presence in the culture give a model much more similar to the in vivo system. Furthermore, the currently used cell system (HepG2 or HEPARG) express only partially the xenobiotic metabolized enzyme systems. This means that the effects of xenobiotics on lipid metabolism, on these cell cultures, lack the information related to the role of hepatic metabolite(s).

It is shown that any chemically-induced change/modification of a cellular function is reflected in several modifications of lipid content. The lipid profile consists of more than 40,000 different lipid molecules which composition is very sensitive to cellular perturbations, modifications, alterations induced by diseases and/or by pharmacological treatments. Therefore a lipid profile is a fingerprint for adverse effects or potential biomarkers in hepatocyte model to exploit negative (or positive) effects during their first line of therapeutic protocol.