On-Chip Construction of Liver Lobule-like Microtissue and Its Application for Adverse Drug Reaction Assay

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Deskriptoren
Pharmaka; Metabolismus; Enzymassay; Induktion; Arzneimittelwechselwirkung; Enzym; Pathophysiologie; toxische Einwirkung; Bioingenieurwesen; Lab-on-a-Chip-Technologie

MEDICINES:DRUG; METABOLISM; ENZYME-ASSAY; MAGNETIC-INDUCTION; DRUG-INTERACTION; ENZYMES; PATHOPHYSIOLOGY; TOXIC-EFFECT; BIOENGINEERING; LAB-ON-A-CHIP

Abstract
Engineering the liver in vitro is promising to provide functional replacement for patients with liver failure, or tissue models for drug metabolism and toxicity analysis. In this study, we describe a microfluidics-based biomimetic approach for the fabrication of an in vitro 3D liver lobule-like microtissue composed of a radially patterned hepatic cord-like network and an intrinsic hepatic sinusoid-like network. The hepatic enzyme assay showed that the 3D biomimetic microtissue maintained high basal CYP-1A1/2 and UGT activities, responded dynamically to enzyme induction/inhibition, and preserved great hepatic capacity of drug metabolism. Using the established biomimetic microtissue, the potential adverse drug reactions that induced liver injury were successfully analyzed via drug-drug interactions of clinical pharmaceuticals. The results showed that predosed pharmaceuticals which agitated CYP-1A1/2 and/or UGT activities would alter the toxic effect of the subsequently administrated drug. All the results validated the utility of the established biomimetic microtissue in toxicological studies in vitro. Also, we anticipate the microfluidics-based bioengineering strategy would benefit liver tissue engineering and liver physiology/pathophysiology studies, as well as in vitro assessment of drug-induced hepatotoxicity.

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Quelle
Analytical Chemistry * Band 88 (2016) Heft 3, Seite 1719-1727 (9 Seiten, 39 Quellen)

Sprache
EN Englisch

Dokumentart
J Zeitschrift
ED Digital Object Identifier (DOI)

Erscheinungsjahr
2016