Biomaterials 33 (2012) 5187–5197

Contents lists available at SciVerse ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

The prediction of drug metabolism using scaffold-mediated enhancement of the induced cytochrome P450 activities in fibroblasts by hepatic transcriptional regulators

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ARTICLE INFO

Article history:
Received 27 March 2012
Accepted 4 April 2012
Available online 26 April 2012

Keywords:
Human dermal fibroblast
Cytochrome P450
Transcriptional regulator
Scaffold
Drug metabolism

ABSTRACT

A reliable, reproducible, and convenient *in vitro* platform for drug metabolism determination and toxicity prediction is of tremendous value but still lacking. In the present study, a collection of 24 hepatic transcription factors and nuclear receptors in different combinations were surveyed, and 10 among them were finally selected to induce the expression and enzyme activities of cytochrome P450 (CYP) 3A4, 1B1, and 2C9 in human dermal fibroblasts (HDFs). The expression and activities of these CYPs in the induced HDFs were higher than those in commonly used hepatoma cell lines. High CYP expression and activities could be further enhanced by culturing the induced HDFs either as spheroids or into several kinds of scaffolds, particularly the tri-copolymer scaffold composed of gelatin, chondroitin and hyaluronan. More strikingly, there showed a synergistic effect of seeding and culturing the spheroids into the tri-copolymer scaffold. Scanning electron microscopy and confocal microscopy disclosed well accommodation of these spheroids inside the scaffolds and displayed a high survival rate. Moreover, the spheroid/scaffold constructs could metabolize an anti-hypertension drug nifedipine into oxidized nifedipine, showing their applicability in studying drug metabolism. This study presents a strategy to induce the expression and enzyme activities of critical CYPs in HDFs, and may have potential to establish an *in vitro* platform to study drug metabolism and to predict the possible human risk of drug toxicity.

1. Introduction

The concern of drug safety is a serious issue for the public and health organizations, while a critical challenge to the pharmaceutical industry. Many drugs have been withdrawn from the market, and over 40% of marketing candidate drugs terminated due to unexpected toxic effects [1,2]. This outcome represented a severe harm to the patients and a huge loss of money from the industry. For decades, drug-induced hepatotoxicity accounted for around 30% of drug withdrawals from the market [1,3,4]. Apparently the traditionally used toxicity assays based on animal studies have failed to recognize the potential human risk of hepatotoxicity of these compounds during their development. Animal tests are expensive and of low throughput, yet frequently of questionable

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doi:10.1016/j.biomaterials.2012.04.014