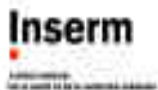


Human hepatoma HepaRG cells : a unique model system for xenobiotic metabolism and toxicity studies



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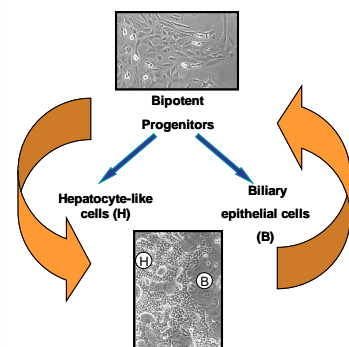
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INTRODUCTION

Recently, a new human hepatoma cell line named HepaRG has been established. These cells, derived from a human liver carcinoma, are characterized by a high pattern of differentiation after 2 weeks at confluency in presence of 2% DMSO (Gripon et al., PNAS, 2002).

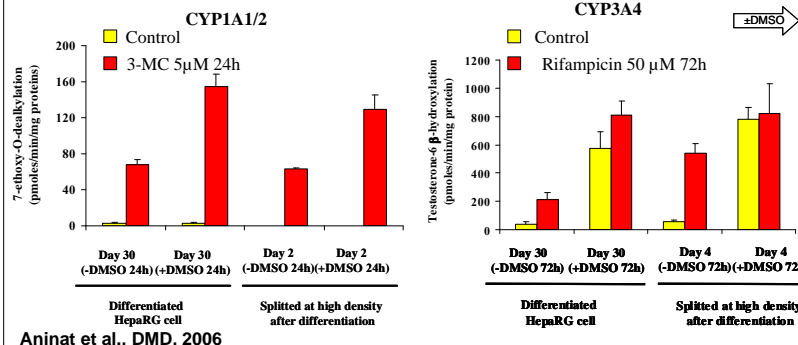
The aim of this work was to analyze the expression of the main xenobiotic metabolizing enzymes and drug transporters in HepaRG cells and to determine whether these cells could mimic human hepatocytes in drug metabolism and toxicity studies.

Fig 1. Differentiation and Transdifferentiation of hepatocyte-like cells through bipotent progenitors



Cerec et al., Hepatology, 2007

Fig. 2 Drug metabolism activities. HepaRG cells were cultured for 30 or 33 days. At day 15, 2% DMSO was added to the culture medium until day 30. Then the cells were cultured the last 24h (day 31) or 72h (day 33) without 2% DMSO or were seeded at high density and cultured for 24h or 72h with or without 2% DMSO.



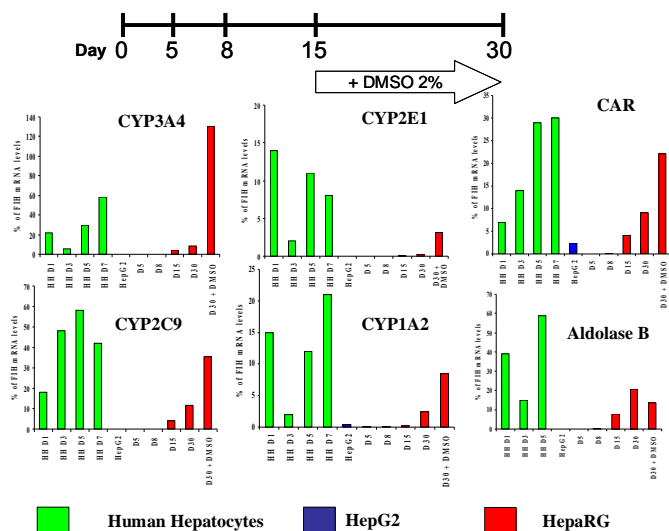
Aninat et al., DMD, 2006

Fig 3. mRNA expression of several transporters. Transcripts were measured in confluent HepG2 and undifferentiated proliferating (P) or differentiated (D) HepaRG cells. The values are expressed as percentages compared to 1-day human hepatocyte cultures.

	HepG2		HepaRG	
	%	P	D	
BSEP	0	0	5 – 30	
OATP-C	0	0	10	
NTCP	0	0	10	
OCT1	0	0	50	
MDR1	150	150	240	
MRP2	110	50	50	
MRP3	80	150	190	

Le Vée et al., Eur. J. Pharm. Sci., 2006

Fig. 4 Comparative expression of cytochromes P450 mRNA in HepaRG cells, HepG2 cells and in human hepatocytes. HepaRG cells were seeded at low density and cultured for 5, 8, 15 and 30 days in the presence of 2% DMSO between days 15 and 30. Results are expressed as percentage compared to freshly isolated hepatocytes (FIH) arbitrarily set at 100%. FIH correspond to a pool of 3 different cell populations. Results are the mean of two independent experiments in duplicate.



Aninat et al., DMD, 2006

Fig. 5 Comparative cytotoxicity of aflatoxin B₁ to subconfluent HepG2 and differentiated HepaRG cells after a three days treatment. Cells viability was estimated by a standart MTT test. The values were normalized to untreated cells and expressed as mean ± SD (n= 3 cultures).

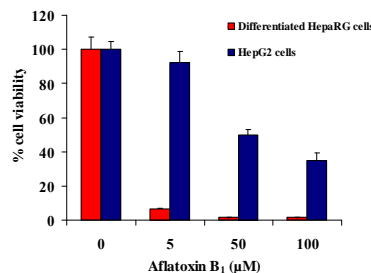
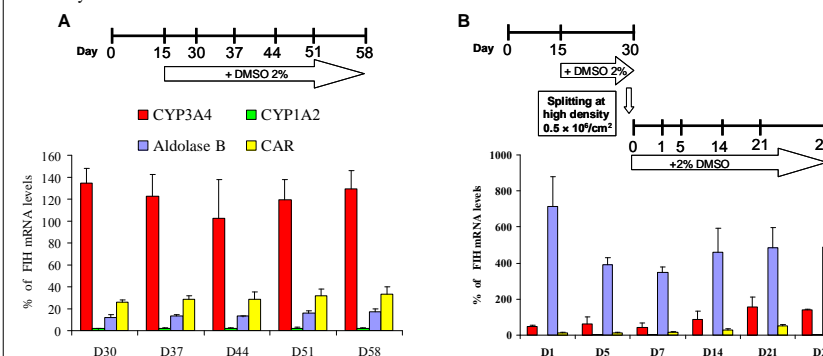


Fig. 6 Long-term expression of CYP3A4, CYP1A2, CAR and Aldolase B transcripts. (A) HepaRG cells were seeded at a low density and cultured for 15, 30, 37, 44, 51 and 58 days in the presence of 2% DMSO between days 15 and 58 or (B) HepaRG cells were seeded at high density and cultured for 1, 5, 7, 14, 21 and 28 days in the presence of 2% DMSO. Results are expressed as percentage compared to freshly isolated hepatocytes (FIH) arbitrarily set at 100%.



CONCLUSIONS

We report for the first time that a human hepatoma cell line is able to express the major CYP-related activities as well as other liver-specific functions. These unique functional properties make HepaRG cells a suitable model for metabolism and acute and chronic hepatotoxicity studies of chemicals.