

Advances in PHARMACOLOGY

Drug-induced Liver Injury

Edited by

ANUP RAMACHANDRAN

Department of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center, Kansas City, KS, United States

HARTMUT JAESCHKE

Department of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center, Kansas City, KS, United States

Serial Editor

S.J. ENNA

University of Kansas Medical Center, Kansas City, KS, United States

Managing Editor

LYNN LeCOUNT

University of Kansas Medical Center, School of Medicine, Kansas City, KS, United States





Contents

	ntributors eface	ix xiii
1.	Primary hepatocytes and their cultures for the testing of drug-induced liver injury Vânia Vilas-Boas, Axelle Cooreman, Eva Gijbels, Raf Van Campenhout, Emma Gustafson, Steven Ballet, Pieter Annaert, Bruno Cogliati,	1
	and Mathieu Vinken	
	 Introduction Hepatic architecture as the benchmark for liver-based in vitro modeling Induction of dedifferentiation during primary hepatocyte isolation Counteracting dedifferentiation during primary hepatocyte cultivation Testing of drug-induced cholestatic liver injury in primary hepatocyte cultures Conclusion Acknowledgments Conflict of interest References 	2 3 6 8 16 20 21 22 22
2.	Cell death in drug-induced liver injury Andrea lorga and Lily Dara	31
	 Introduction Modes of cell death Conclusions Acknowledgment Conflict of interest References 	34 35 60 61 61
3.	Drug-induced liver injury in obesity and nonalcoholic fatty liver disease Julien Allard, Dounia Le Guillou, Karima Begriche, and Bernard Fromenty	75
	 Introduction Pathophysiology of NAFLD Experimental models of NAFLD 	76 77 79

vi	Contents

	4. Drug-induced hepatotoxicity in obesity and NAFLD	80
	5. Conclusion	96
	Acknowledgments	97
	Conflict of interest	98
	References	98
4.	Role and mechanisms of autophagy in alcohol-induced	
₹.	liver injury	109
	Xiaojuan Chao and Wen-Xing Ding	
	1. Introduction	111
	2. Alcohol metabolism	111
	3. Autophagy	112
	4. Autophagy in ALD mouse models	115
	5. Potential therapeutic approaches to treat ALD by modulating autophagy	118
	6. Conclusion	123
	Acknowledgments	125
	Conflict of interest	125
	References	125
	Further reading	131
5.	Mechanisms of idiosyncratic drug-induced liver injury	133
	Jack Uetrecht	
	1. Introduction	135
	2. Involvement of reactive metabolites in the mechanism of IDILI	138
	3. Immune system involvement in IDILI	139
	4. Other proposed mechanisms of IDILI	143
	5. Animal models that can be used for mechanistic studies of IDILI	150
	6. Implications for prevention and treatment	152
	7. Conclusion	156
	Acknowledgment	156
	Conflict of interest	156
	References	156
6.	Idiosyncratic drug-induced liver injury in patients: Detection,	
6.	Idiosyncratic drug-induced liver injury in patients: Detection, severity assessment, and regulatory implications	165
6.		165
6.	severity assessment, and regulatory implications	165
б.	severity assessment, and regulatory implications Paul B. Watkins	

Contents

	4.	Rating severity of IDILI	173
	5.	Outcome of an IDILI event	174
	6.	Death or transplant	176
	7.	Chronic DILI	176
	8.	Predicting IDILI course	177
	9.	Diagnosing IDILI	179
	10.	Detecting IDILI potential of new drugs in clinical trials	181
	11.	The FDA approach to assess liver safety in clinical trials	183
	12.	Causality assessment in clinical trials	186
	13.	Conclusion	189
	Refe	erences	189
7.	Ace	etaminophen hepatotoxicity: A mitochondrial perspective	195
	Anι	ıp Ramachandran and Hartmut Jaeschke	
	1.	Introduction	196
	2.	Mitochondria in APAP overdose	197
	3.	Mitochondrial protein adducts in APAP hepatotoxicity	198
	4.	APAP induced mitochondrial oxidative and nitrosative stress	200
	5.	Consequences of mitochondrial oxidative/nitrosative stress in the cytosol	204
	6.	Mitochondrial amplification of injury	206
	7.	The end game: Mitochondrial permeability transition and subsequent	
		cellular necrosis	207
	8.	Mitochondria in adaptation and recovery after APAP overdose	209
	9.	Role of mitochondria-derived damage-associated molecular patterns	
		in injury and recovery	210
	10.	Relevance of APAP-induced mitochondrial dysfunction to humans	211
		Conclusion	212
		nowledgments	212
		flict of interest statement	213
	Refe	erences	213
8.	Bio	markers of drug-induced liver injury	221
	Mite	chell R. McGill and Hartmut Jaeschke	
	1.	Introduction	222
	2.	The problem of low prevalence in DILI biomarker development	223
	3.	Biomarkers of DIL+ diagnosis	226
	4.	Biomarkers of DIL1 prediction	227
	5.	Biomarkers of DILI prognosis	228

11	ı	i	
v	,	,	

References

	Content
6. Mechanistic biomarkers	
7. Conclusion	23
Acknowledgments	233
Conflict of interest	233
References	233
neierences	234
9. Mechanisms and biomarkers of liver regeneration after	
drug-induced liver injury	241
Melissa M. Clemens, Mitchell R. McGill, and Udayan Apte	2-11
1. Introduction	242
2. Etiology and prognosis of acute liver injury	24.2
3. Major differences between hepatectomy and hepatotoxicity	243
4. Regeneration after drug-induced liver injury	244
5. Biomarkers of liver regeneration	253
6. Conclusion	253
Conflict of interest statement	255
Acknowledgments	255
References	255
Further reading	262
10 Evaluation and treatment of the control of the c	
10. Evaluation and treatment of acetaminophen toxicity	263
Erik S. Fisher and Steven C. Curry	
1. Introduction	264
2. Acute acetaminophen ingestions	264
3. Chronic APAP oral ingestions	270
4. Conclusion	270
Conflict of interest	271

271