

Contents

Author Index	xi
Abbreviations	xv
 1 Liver Regeneration and Partial Hepatectomy: Process and Prototype	 1
<i>Marie C. DeFrances and George K. Michalopoulos</i>	
1.1 Introduction	1
1.2 Liver Regeneration: Historical Perspective.	1
1.3 Partial Hepatectomy as a Means to Study Liver Regeneration	2
1.4 Three Phases of Liver Regeneration after Partial Hepatectomy	4
1.5 Future Directions	10
 2 Oval Cells, Bone Marrow, and Liver Regeneration	 17
<i>Anna C. Piscaglia, Antonio Gasbarrini, and Bryon E. Petersen</i>	
2.1 Stem Cells: Definition and Properties	17
2.2 Liver Stem Cells and Their Role in Hepatic Regeneration.	21
2.3 Extrahepatic Stem Cells with Hepatogenic Potential: “The Blood of Prometheus”	25
2.4 Clinical Applications of Bone Marrow–Derived Stem Cells in Hepatology.	30
 3 Inflammation and Liver Regeneration.	 39
<i>Johannes G. Bode</i>	
3.1 Introduction	39
3.2 Liver Regeneration and Inflammation: General Aspects.	40
3.3 Liver Macrophages and Their Relevance for Liver Regeneration	41
3.4 Inflammatory Mediators Are Required to Promote Liver Regeneration	44
3.5 Inappropriate Inflammation Impairs Liver Regeneration	46
3.6 Role of NK and NKT-cells for Liver Regeneration: Negative Regulators of Regeneration.	47

4	Lymphotoxin β Receptor and Tumor Necrosis Factor Receptor p55 in Liver Regeneration	53
	<i>Ursula R. Sorg and Klaus Pfeffer</i>	
4.1	The TNF/TNFR Superfamily	53
4.2	Liver Regeneration	56
4.3	TNFRp55 and Liver Regeneration	57
4.4	LT β R and Liver Regeneration.	58
5	The Hepatic Stem Cell Niches	63
	<i>Iris Sawitzka, Claus Kordes, and Dieter Häussinger</i>	
5.1	Introduction	63
5.2	Secreted Factors in the Stem Cell Niche	64
5.3	Physical Contacts of Stem Cells with Their Niche	71
5.4	Identification of Stem Cell Niches	72
5.5	Stem Cell Niches in the Liver	74
6	Stellate Cells in the Regenerating Liver.	85
	<i>Claus Kordes, Iris Sawitzka, and Dieter Häussinger</i>	
6.1	Characterization of Stellate Cells.	85
6.2	Plasticity of Hepatic Stellate Cells	90
6.3	Stellate Cells in Liver Regeneration	90
7	Epigenetics during Liver Regeneration	99
	<i>Claus Kordes, Iris Sawitzka, and Dieter Häussinger</i>	
7.1	Definition and Mechanisms of Epigenetics	99
7.2	Methods to Investigate Epigenetic Mechanisms	103
7.3	Epigenomics in Liver Regeneration	104
7.4	Epigenetics During Stellate Cell Activation	105
8	Hedgehog Signaling and Liver Regeneration	111
	<i>Steve S. Choi and Anna Mae Diehl</i>	
8.1	Introduction	111
8.2	Liver Regeneration after Partial Hepatectomy	112
8.3	Fetal Development of the Liver	112
8.4	Overview of Hedgehog Signaling Pathway	113
8.5	Reactivation of the Hedgehog Pathway after Partial Hepatectomy	115
8.6	Hedgehog Pathway Activation during Repair of Chronic Liver Injury: General Concepts	116
8.7	Hedgehog Pathway Activation and Liver Progenitors in Chronic Injury Models	117

8.8	Hedgehog Pathway Activation and Liver Fibrosis	118
8.9	Hedgehog Pathway Activation and Vascular Remodeling in Injured Livers.	121
8.10	Hedgehog Pathway Activation and Hepatocarcinogenesis	121
9	EGFR, CD95, and the Switch between Proliferation and Apoptosis in Hepatic Stellate Cells. <i>Roland Reinehr and Dieter Häussinger</i>	129
9.1	Introduction.	129
9.2	Liver Cell Proliferation Involves Ligand-dependent EGFR Activation.	130
9.3	Liver Cell Apoptosis Involves EGFR-dependent CD95 Activation	132
9.4	EGFR Activation Can Couple to Both Proliferation and Apoptosis in Hepatic Stellate Cells.	135
10	Angiogenesis and Liver Regeneration. <i>Tobias Buschmann, Jan Eglinger, and Eckhard Lammert</i>	145
10.1	Introduction.	145
10.2	Blood Flow and Cell Types in the Adult Liver.	145
10.3	Angiogenesis in Liver Regeneration	148
10.4	Importance of VEGF for Liver Regeneration	150
10.5	Role of Angiogenesis in Liver Damage/Disease	151
10.6	Questions and Problems	153
11	A Quantitative Mathematical Modeling Approach to Liver Regeneration <i>Dirk Drasdo, Stefan Hoehme, and Jan G. Hengstler</i>	159
11.1	Definition	159
11.2	Methods to Quantify Spatial–Temporal Information in Liver Lobules	161
11.3	Normal Liver Lobule: The Reference State	163
11.4	Quantifying the Regeneration Process: Process Parameters	164
11.5	Mathematical Model	164
11.6	Simulation Results with the Mathematical Model.	169
11.7	Limitations.	171
12	Animal Models for Studies on Liver Regeneration <i>Amalya Hovhannisyan and Rolf Gebhardt</i>	175
12.1	Introduction.	175
12.2	Different Types of Regenerative Processes	175

12.3	Different Types of Animal Models	177
12.4	Surgical Animal Models	179
12.5	Pharmacological Models	180
12.6	Transgenic Models	181
12.7	Immunological Models	186
13	Therapeutic Potential of Bone Marrow Stem Cells in Liver Surgery	191
	<i>Jan Schulte am Esch, Moritz Schmelzle, Günter Fürst, and Wolfram Trudo Knoefel</i>	
13.1	Clinical Scenario	191
13.2	Mechanisms of Hepatic Regeneration	192
13.3	Stem Cells in Liver Regeneration	192
13.4	Mesenchymal or Hematopoietic Stem Cells to Support Liver Regeneration?	193
13.5	BMSC as External Conductors of Liver Regeneration	194
13.6	Stem Cell Treatment in Chronic Liver Disease in Humans	194
13.7	BMSC to Support Liver Proliferation Prior to Hepatectomy	195
	Index	207