

Contents

List of Contributors

Preface

Acknowledgments

PART ONE: INTRODUCTION

1 Organizational Principles of the Liver

Peter Nagy, Snorri S. Thorgeirsson, and Joe W. Grisham

2 Embryonic Development of the Liver

Kenneth S. Zaret, Roque Bort, and Stephen A. Duncan

PART TWO: THE CELLS

SECTION A: CELL BIOLOGY OF THE LIVER

3 Cytoskeletal Motors: Structure and Function in Hepatocytes

Mukesh Kumar, Arnab Gupta, and Roop Mallik

4 Hepatocyte Surface Polarity

Anne Müsch and Irwin M. Arias

5 Primary Cilia

Carolyn M. Ott

6 Endocytosis in Liver Function and Pathology

Micah B. Schott, Barbara Schroeder, and Mark A. McNiven

7 The Hepatocellular Secretory Pathway

Catherine L. Jackson and Mark A. McNiven

8 Mitochondrial Function, Dynamics, and Quality Control

Marc Liesa, Ilan Benador, Nathanael Miller, and Orian S. Shirihai

9 Nuclear Pore Complex

Michelle A. Veronin and Joseph S. Glavy

10 Protein Maturation and Processing at the Endoplasmic Reticulum

Ramanujan S. Hegde

x

xx

xxi

1

3

14

23

25

27

36

50

62

75

86

94

108

11 Protein Degradation and the Lysosomal System Susmita Kaushik and Ana Maria Cuervo	122
12 Peroxisome Assembly, Degradation, and Disease Rong Hua and Peter K. Kim	137
13 Organelle–Organelle Contacts: Origins and Functions Uri Manor	151
14 Gap and Tight Junctions in Liver: Structure, Function, and Pathology John W. Murray and David C. Spray	160
15 Ribosome Biogenesis and its Role in Cell Growth and Proliferation in the Liver Katherine I. Farley-Barnes and Susan J. Baserga	174
16 miRNAs and Hepatocellular Carcinoma Yusuke Yamamoto, Isaku Kohama, and Takahiro Ochiya	183
17 Hepatocyte Apoptosis: Mechanisms and Relevance in Liver Diseases Harmeet Malhi and Gregory J. Gores	195
SECTION B: THE HEPATOCYTE	207
18 Copper Metabolism and the Liver Cynthia Abou Zeid, Ling Yi, and Stephen G. Kaler	209
19 The Central Role of the Liver in Iron Storage and Regulation of Systemic Iron Homeostasis Tracey A. Rouault, Victor R. Gordeuk, and Gregory J. Anderson	215
20 Disorders of Bilirubin Metabolism Namita Roy Chowdhury, Yanfeng Li, and Jayanta Roy Chowdhury	229
21 Hepatic Lipid Droplets in Liver Function and Disease Douglas G. Mashek, Wenqi Cui, Linshan Shang, and Charles P. Najt	245
22 Lipoprotein Metabolism and Cholesterol Balance Mariana Acuña-Aravena and David E. Cohen	255
SECTION C: TRANSPORTERS, BILE ACIDS, AND CHOLESTASIS	269
23 Bile Acid Metabolism in Health and Disease: An Update Tiangang Li and John Y.L. Chiang	271
24 TGR5 (GPBAR1) in the Liver Verena Keitel, Christoph G.W. Gertzen, Lina Spomer, Holger Gohlke, and Dieter Häussinger	286
25 Bile Acids as Signaling Molecules Thierry Claudel and Michael Trauner	299
26 Hepatic Adenosine Triphosphate-Binding Cassette Transport Proteins and Their Role in Physiology Peter L.M. Jansen	313
27 Basolateral Plasma Membrane Organic Anion Transporters M. Sawkat Anwer and Allan W. Wolkoff	327
28 Hepatic Nuclear Receptors Raymond E. Soccio	337
29 Molecular Cholestasis Paul Gissen and Richard J. Thompson	351
30 Pathophysiologic Basis for Alternative Therapies for Cholestasis Claudia D. Fuchs, Emina Halilbasic, and Michael Trauner	364

31 Adaptive Regulation of Hepatocyte Transporters in Cholestasis James L. Boyer	378
SECTION D: NON-HEPATOCTYCE CELLS	391
32 Cholangiocyte Biology and Pathobiology Massimiliano Cadamuro, Romina Fiorotto, and Mario Strazzabosco	393
33 Polycystic Liver Diseases: Genetics, Mechanisms, and Therapies Tatyana Masyuk, Anatoliy Masyuk, and Nicholas LaRusso	408
34 The Liver Sinusoidal Endothelial Cell: Basic Biology and Pathobiology Karen K. Sørensen and Bård Smedsrød	422
35 Fenestrations in the Liver Sinusoidal Endothelial Cell Victoria C. Cogger, Nicholas J. Hunt, and David G. Le Couteur	435
36 Stellate Cells and Fibrosis Youngmin A. Lee and Scott L. Friedman	444
PART THREE: FUNCTIONS OF THE LIVER	455
SECTION A: METABOLIC FUNCTIONS	457
37 Non-alcoholic Fatty Liver Disease and Insulin Resistance Max C. Petersen, Varman T. Samuel, Kitt Falk Petersen, and Gerald I. Shulman	459
38 AMPK: Central Regulator of Glucose and Lipid Metabolism and Target of Type 2 Diabetes Therapeutics Daniel Garcia, Maria M. Mihaylova, and Reuben J. Shaw	472
39 Insulin-Mediated PI3K and AKT Signaling Hyokjoon Kwon and Jeffrey E. Pessin	485
40 Ca²⁺ Signaling in the Liver Mateus T. Guerra, M. Fatima Leite, and Michael H. Nathanson	496
41 Clinical Genomics of NAFLD Frank Lammert	509
SECTION B: LIVER GROWTH AND REGENERATION	521
42 Stem Cell-Fueled Maturation Lineages in Hepatic and Pancreatic Organogenesis Wencheng Zhang, Amanda Allen, Eliane Wauthier, Xianwen Yi, Homayoun Hani, Praveen Sethupathy, David Gerber, Vincenzo Cardinale, Guido Carpino, Juan Dominguez-Bendala, Giacomo Lanzoni, Domenico Alvaro, Eugenio Gaudio, and Lola Reid	523
43 Developmental Morphogens and Adult Liver Repair Mariana Verdelho Machado and Anna Mae Diehl	539
44 Liver Repopulation by Cell Transplantation and the Role of Stem Cells in Liver Biology David A. Shafritz and Markus Grompe	550
45 Liver Regeneration George K. Michalopoulos	566
46 β-Catenin Signaling Satdarshan P.S. Monga	585
47 Polyploidy in Liver Function, Mitochondrial Metabolism, and Cancer Evan R. Delgado, Elizabeth C. Stahl, Nairita Roy, Patrick D. Wilkinson, and Andrew W. Duncan	603

PART FOUR: PATHOBIOLOGY OF LIVER DISEASE	615
48 Hepatic Encephalopathy	617
Roger F. Butterworth	
49 The Kidney in Liver Disease	630
Moshe Levi, Shogo Takahashi, Xiaoxin X. Wang, and Marilyn E. Levi	
50 α1-Antitrypsin Deficiency	645
David A. Rudnick and David H. Perlmutter	
51 Pathophysiology of Portal Hypertension	659
Yasuko Iwakiri and Roberto J. Groszmann	
52 Non-alcoholic Fatty Liver Disease: Mechanisms and Treatment	670
Yaron Rotman and Devika Kapuria	
53 Alcoholic Liver Disease	682
Bin Gao, Xiaogang Xiang, Lorenzo Leggio, and George F. Koob	
54 Drug-Induced Liver Injury	701
Lily Dara and Neil Kaplowitz	
55 Oxidative Stress and Inflammation in the Liver	714
John J. Lemasters and Hartmut Jaeschke	
56 The Role of Bile Acid-Mediated Inflammation in Cholestatic Liver Injury	728
Shi-Ying Cai, Man Li, and James L. Boyer	
57 Toll-like Receptors in Liver Disease	737
So Yeon Kim and Ekihiro Seki	
PART FIVE: LIVER CANCER	747
58 Experimental Models of Liver Cancer: Genomic Assessment of Experimental Models	749
Sun Young Yim, Jae-Jun Shim, Bo Hwa Sohn, and Ju-Seog Lee	
59 Epidemiology of Hepatocellular Carcinoma	758
Hashem B. El-Serag	
60 Mutations and Genomic Alterations in Liver Cancer	773
Jessica Zucman-Rossi and Jean-Charles Nault	
61 Treatment of Liver Cancer	782
Tim F. Greten	
PART SIX: HEPATITIS	793
62 Molecular Biology of Hepatitis Viruses	795
Christopher Seeger, William S. Mason, and Michael M.C. Lai	
63 Immune Mechanisms of Viral Clearance and Disease Pathogenesis During Viral Hepatitis	821
Carlo Ferrari, Valeria Barili, Stefania Varchetta, and Mario U. Mondelli	
64 Clinical Implications of the Molecular Biology of Hepatitis B Virus	851
Timothy M. Block, Ju-Tao Guo, and W. Thomas London	
65 Viral Escape Mechanisms in Hepatitis C and the Clinical Consequences of Persistent Infection	868
Marc G. Ghany, Christopher M. Walker, and Patrizia Farci	
66 Tracking Hepatitis C Virus Interactions with the Hepatic Lipid Metabolism: A Hitchhiker's Guide to Solve Remaining Translational Research Challenges in Hepatitis C	889
Gabrielle Vieyres and Thomas Pietschmann	

67 Nucleoside Antiviral Agents for HCV: What's Left to Do?	906
Franck Amblard, Seema Mengshetti, Junxing Shi, Sijia Tao, Leda Bassit, and Raymond F. Schinazi	
68 Hepatitis E Virus: An Emerging Zoonotic Virus Causing Acute and Chronic Liver Disease	915
Xiang-Jin Meng	
69 Biological Principles and Clinical Issues Underlying Liver Transplantation for Viral-Induced End-Stage Liver Disease in the Era of Highly Effective Direct-Acting Antiviral Agents	926
Michael S. Kriss, James R. Burton, Jr., and Hugo R. Rosen	
70 Time for the Elimination of Hepatitis C Virus as a Global Health Threat	935
John W. Ward, Alan R. Hinman, and Harvey J. Alter	
PART SEVEN: HORIZONS	953
71 Genome Editing by Targeted Nucleases and the CRISPR/Cas Revolution	955
Shawn M. Burgess	
72 Imaging Cellular Proteins and Structures: Smaller, Brighter, and Faster	965
Aubrey V. Weigel and Erik Lee Snapp	
73 Liver-Directed Gene Therapy	979
Patrik Asp, Chandan Guha, Namita Roy Chowdhury, and Jayanta Roy Chowdhury	
74 Telomeres and Telomerase in Liver Generation and Cirrhosis	992
Sonja C. Schätzlein and K. Lenhard Rudolph	
75 Toxins and Biliary Atresia	1000
Michael Pack and Rebecca G. Wells	
76 The Dual Role of ABC Transporters in Drug Metabolism and Resistance to Chemotherapy	1007
Jean-Pierre Gillet, Marielle Boonen, Michel Jadot, and Michael M. Gottesman	
77 Stem Cell-Derived Liver Cells: From Model System to Therapy	1015
Helmuth Gehart and Hans Clevers	
78 Extracellular Vesicles and Exosomes: Biology and Pathobiology	1022
Gyongyi Szabo and Fatemeh Momen-Heravi	
79 Integrated Technologies for Liver Tissue Engineering	1028
Tiffany N. Vo, Amanda X. Chen, Quinton B. Smith, Arnav Chhabra and Sangeeta N. Bhatia	
80 Pluripotent Stem Cells and Reprogramming: Promise for Therapy	1036
James A. Heslop and Stephen A. Duncan	
81 Chromatin Regulation and Transcription Factor Cooperation in Liver Cells	1043
Ido Goldstein	
82 Drug Interactions in the Liver	1050
Guruprasad P. Aithal and Gerd A. Kullak-Ublick	
83 Metabolic Regulation of Hepatic Growth	1058
Wolfram Goessling	
84 The Gut Microbiome and Liver Disease	1062
Lexing Yu, Jasmohan S. Bajaj, and Robert F. Schwabe	
85 Lineage Tracing: Efficient Tools to Determine the Fate of Hepatic Cells in Health and Disease	1069
Frédéric Lemaigre	
86 The Hepatocyte as a Household for <i>Plasmodium</i> Parasites	1075
Vanessa Zuzarte-Luis and Maria M. Mota	
Index	1081