

Liver Regeneration and Carcinogenesis

Molecular and Cellular Mechanisms

Edited by
Randy L. Jirtle

Academic Press

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**Liver Regeneration
and Carcinogenesis**
*Molecular and
Cellular Mechanisms*

*This book is dedicated to my wife Nancy
and my children, Bonnie and James.*

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Preface

The fact that the liver regenerates following injury has been known since ancient times. According to Greek mythology, Prometheus was chained to a rock for defying Zeus by stealing fire from Mount Olympus. He was subjected to an eagle eating his liver during the day, and it regenerated by night. Because of this marked capacity to regenerate and the ability of chemical carcinogens and viruses to transform hepatocytes, the liver is used extensively as a model for investigating the molecular mechanisms of normal cell proliferation and carcinogenesis.

Recently, striking advances have occurred in our understanding of hepatocyte growth regulation and how chemical agents and viruses alter these normal growth regulatory pathways during the genesis of liver tumors. Both *in vitro* and *in vivo* models of neoplastic transformation have established that the pathway to neoplasia has multiple steps. Aberrant expression of proto-oncogenes or the expression of mutant forms of these genes (i.e., oncogenes) can lead to neoplastic transformation. The loss of tumor suppressor gene function is also involved in the development of both rodent and human liver cancer. This book demonstrates that the determination of the factors involved in controlling the regeneration of normal liver has led to a clearer understanding of the mechanisms involved in the formation of various liver diseases, including hepatocellular carcinomas.

The chapters in this book are grouped into three main research areas. The first section of the book covers the subject of liver regeneration. Liver regeneration has been investigated for many years, particularly since 1931 when Higgins and Anderson published a classic paper describing a partial hepatectomy technique in rats that reproducibly stimulates the liver to regeneration. An overview of liver regeneration research both then and now is described in the first chapter by one of the premier scientists in this field of investigation, Dr. Nancy Bucher. The growth factor that plays a central role in stimulating hepatocyte proliferation following liver injury, hepatocyte growth factor, and its receptor (*c-met*) are discussed in Chapters 2 and 3, respectively. The immediate-early response genes that are expressed in the early stages of liver regeneration are described in Chapter 4.

The second section of this book deals with the subject of liver carcinogenesis. The topics were chosen to provide an overview of this immense subject.

Chapter 5 covers the role that hepatic stem cells play in both liver regeneration and carcinogenesis. It is well known that hepatitis virus infection is a major risk factor for the development of human hepatocellular carcinomas. The contribution of hepadnavirus research to our understanding of liver cancer is discussed in Chapter 6. Programmed cell death, apoptosis, has been increasingly shown to be mechanistically involved in liver tumor promotion and carcinogenesis as discussed in Chapter 7. Transforming growth factor β and the suppression of p53-dependent cell cycle checkpoint function as they relate to liver tumor promotion are discussed in Chapters 8 and 9. In Chapter 10 it is postulated that hypomethylation of the DNA may represent an epigenetic mechanism for hepatocyte transformation. The use of transgenic animals to ascertain directly the role of growth factors, oncogenes, etc., in liver carcinogenesis is a powerful molecular technique thoroughly presented in Chapter 11. It is also important to realize that humans vary in their susceptibility to tumor formation. Chapter 12 describes the importance of genetics in the development of liver tumors in both humans and animals.

The final section of this book deals with two vastly different techniques for treating liver cancer. Although hepatocellular carcinoma is one of the most common neoplasms in the world, primary cancer of the liver is relatively rare in the United States. Hepatocellular carcinomas are, however, still of significance in the United States because they are highly lethal; the 5-year survival rate is less than 10%. One method of treating primary and metastatic liver tumors is surgical resection. When the malignancy is not amenable to a simple resection, the whole liver can now be transplanted. These surgical procedures for the treatment of liver cancer are described in Chapter 13. As the genes involved in liver carcinogenesis are elucidated, it becomes more probable that this information will be used to develop successful molecular strategies for cancer treatment. The potential of using gene therapy approaches to treat liver tumors and genetic liver diseases is discussed in Chapter 14.

In conclusion, the veritable explosion of scientific information that has occurred recently in liver biology encompasses many research disciplines. This book is an attempt to bring these diverse research results together in a coherent manner. Scientists who will benefit from this book include toxicologists, virologists, molecular biologists, cell biologists, cancer biologists, pharmacologists, pathologists, surgeons, and gastroenterologists who are interested in furthering their understanding of the molecular mechanisms controlling liver regeneration and hepatocellular carcinogenesis.

I would like to thank Ms. Charlotte Brabants at Academic Press for her continued support and patience, the contributors of this book for writing their chapters when it is increasingly difficult to find the time for such

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Randy L. Jirtle

Contents

Contributors xvii

Preface xxi

1

Liver Regeneration Then and Now

Nancy L. R. Bucher

- I. Landmarks 1
- II. Normal Adult Rat Liver 2
- III. Liver Regeneration 3
- IV. Hepatocyte Priming 5
- V. Regeneration Signals 7
 - A. Hormones 7
 - B. Growth Factors 12
 - C. Cytokines 17
 - D. Interactions 18
- VI. Conclusions 19
- References 19

2

Hepatocyte Growth Factor (HGF) and Its Receptor (Met) in Liver Regeneration, Neoplasia, and Disease

George K. Michalopoulos

- I. Introduction 27
- II. Structural and Functional Aspects of HGF and the HGF Receptor 28
- III. HGF Localization 30
 - A. In Liver 30
 - B. In Extra Hepatic Tissues 31

IV. Liver and the Processing of HGF	32
A. HGF and Liver Regeneration	33
V. HGF and the Early Proteolytic Events Following Partial Hepatectomy	37
VI. HGF Localization	40
A. In Liver Embryogenesis	40
B. In Liver Disease	41
C. In Liver Carcinogenesis	42
VII. Summary	43
References	44

3

Structure and Functions of the HGF Receptor (c-Met)

Paolo M. Comoglio

Elisa Vigna

I. Hepatocyte Growth Factor and Scatter Factor	51
II. HGF Receptor	53
A. Encoding by the <i>c-met</i> Oncogene	53
B. Post-translational Modifications	54
C. Positive and Negative Regulation	55
D. Signal Transduction	57
E. Tissue Distribution and Subcellular Localization	59
III. Regulation of <i>c-met</i> Expression	60
IV. Role of HGF in Tissue Regeneration and Embryogenesis	61
V. Role of <i>c-met</i> in Carcinogenesis	62
References	63

4

Expression and Function of Growth-Induced Genes during Liver Regeneration

Rebecca Taub

I. Liver Regeneration: The Important Questions	71
II. Immediate-Early Gene Expression in Hepatic Cells	72
III. Modification of Preexisting Transcription Factors	

- Immediately Following Partial Hepatectomy Turns
on Immediate-Early Genes 76
- IV. Induction Patterns of 70 Genes Following Partial
Hepatectomy Define the Temporal Course
of Liver Regeneration 78
- V. Transcription Factors Induced in the
Regenerating Liver 80
- A. The LRF-1/JunB Story 80
- B. RNR-1, a Novel Nuclear Receptor That Acts
through the NGFI-B Half-Site 82
- VI. Immediate-Early Genes Involved in Signal
Transduction 84
- A. PRL-1, a Member of a Novel Class of
Protein-Tyrosine Phosphatases 84
- VII. Immediate-Early Genes That Are
Secreted Proteins 86
- VIII. Liver-Specific Immediate-Early Genes:
Relationship to the Maintenance of Hepatocyte
Differentiation and Metabolism 87
- A. Identification of CL-6 88
- IX. Immediate-Early Genes in H35 Cells That Are
Expressed as Delayed-Early Genes
in Regenerating Liver 89
- A. Delayed-Early Genes That Encode RNA
Binding Proteins 89
- X. Conclusions 91
- References 93

5

Stem Cells and Hepatocarcinogenesis

Snorri S. Thorgeirsson

- I. Introduction 99
- II. Cellular Biology of the Hepatic Stem Cell
Compartment 101
- A. Experimental Systems *in Vivo* 101
- B. Experimental Systems *in Vitro* 102
- III. Neoplastic Development in the Liver 104
- A. Hepatic Stem Cells and
Hepatocarcinogenesis 104
- B. Transformation of Liver Derived Epithelial
(Oval) Cells 106
- IV. Conclusions 108
- References 109

6

Contributions of Hepadnavirus Research to Our Understanding of Hepatocarcinogenesis

Charles E. Rogler

Leslie E. Rogler

Deyun Yang

Silvana Breiteneder-Geleef

Shih Gong

Haiping Wang

- I. General Overview of Hepadnavirus Animal Models and Hepatocarcinogenesis 113
- II. Hepatitis B Virus Envelope Protein (HBsAg) Transgenic Mice 117
 - A. HBsAg (Line 50-4) Transgenic Model of Hepatocarcinogenesis 117
 - B. Noncytopathic HBsAg Transgenic Mice: Role of Cytokines in Gene Regulation 118
- III. Woodchuck Hepatitis Virus (WHV) Model of Hepatocarcinogenesis 122
 - A. Toxic Oxygen Radicals and WHV Persistent Infection 122
 - B. Insertional Mutagenesis 122
 - C. Integration and Human HCC 125
 - D. Analysis of Precancerous Lesions and HCCs: The Case for a Role of IGF2 in Tumor Promotion 125
- IV. Hepadnavirus X Gene Encodes an Oncogenic Transcriptional Transactivator 129
 - A. Background 129
 - B. X Gene Transactivation Mechanism 131
 - C. *In Vitro* Assays for Hepadnavirus Transforming Activity 132
 - D. HBx Transgenic Mice Develop HCC 132
- V. Conclusions 134
- References 134

7

Apoptosis and Hepatocarcinogenesis

Rolf Schulte-Hermann

Bettina Grasl-Kraupp

Wilfried Bursch

- I. Apoptosis and Other Types of Active Cell Death 141

II. Active Cell Death in the Liver	145
A. Detection and Quantification	145
B. Models	146
C. Duration of Apoptosis in the Liver	151
III. Biochemical and Molecular Aspects of Apoptosis	152
A. Events Associated with Cell Killing	153
B. Events Associated with Preparation for Active Cell Death	154
C. Signal Factors	156
IV. Active Cell Death in the Stages of Hepatocarcinogenesis	158
A. Cancer Prestages in the Liver	158
B. Kinetic Aspects of Cell Proliferation and Death in Cancer Prestages	160
C. Active Cell Death and Initiation	161
D. Active Cell Death and Tumor Promotion	163
E. Active Cell Death and Tumors	165
V. Conclusions	166
References	167

8

Liver Tumor Promotion and the Suppression of p53-Dependent Cell Cycle Checkpoint Function

Yingchun Zhang

Chia Chiao

Laura L. Byrd

David G. Kaufman

William K. Kaufmann

I. Introduction	179
II. Mechanisms of Cell Cycle Control	180
III. Cell Cycle Checkpoints, Lifespan Extension, and Genetic Instability	181
IV. Isolation of EL/EGV Hepatocytes and Promotion of Hepatocarcinogenesis <i>in Vitro</i>	183
V. Immortal Rat Hepatocytes Require PB for Clonal Expansion	186
VI. Mechanisms of Promotion of Hepatocarcinogenesis by Phenobarbital	191
VII. Conclusions	193
References	194

9

Mechanisms of Liver Tumor Promotion

Jeremy J. Mills

Randy L. Jirtle

Ivan J. Boyer

I. Introduction	199
II. Stages of Liver Carcinogenesis	201
A. Initiation	201
B. Promotion	202
C. Progression	203
III. Cell Cycle Regulation and Liver Carcinogenesis	204
A. Cyclins and Cyclin-Dependent Kinases	205
B. Rb Gene	206
C. p53 Gene	207
IV. TGF β and Liver Carcinogenesis	208
A. TGF β and TGF β Receptors	210
B. M6P/IGF2 Receptor	212
C. Experimental Results	214
V. Apoptosis and Liver Carcinogenesis	216
VI. Summary	217
References	218

10

Hypomethylation of DNA: An Epigenetic Mechanism That Can Facilitate the Aberrant Oncogene Expression Involved in Liver Carcinogenesis

Jennifer L. Counts

Jay I. Goodman

I. Introduction	227
II. Epigenetics	230
III. DNA Methylation	230
IV. Working Hypothesis and Experimental Model	235
V. Liver Tumor Promotion: A Role for Hypomethylation of DNA	236
VI. Methyl Deficient Diets	238
VII. DNA Damage and Altered DNA Methylation	240