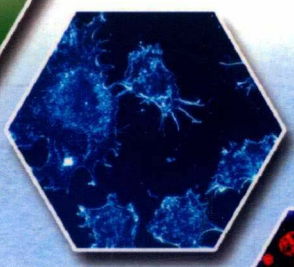
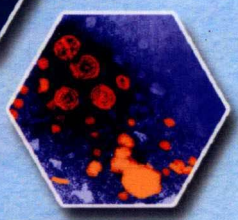
Pathobiology of Hepatocellular Carcinoma and Clinical Impact

Cancer Etiology, Diagnosis and Treatments





Antonio Mazzocca
Pasquale Agosti
Carlo Sabbà

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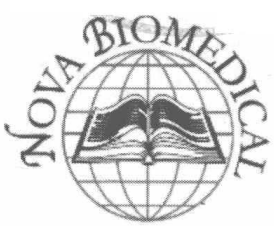

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CANCER ETIOLOGY, DIAGNOSIS AND TREATMENTS

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CANCER ETIOLOGY, DIAGNOSIS AND TREATMENTS

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Author Biography

Antonio Mazzocca, MD, PhD, was born in Barletta, Italy in 1965. After graduating from the Medical School of the University of Bari in 1994, he served as a Navy physician (Medical Officer) in the Italian Navy Medical Corps. Following a PhD in Clinical Pathophysiology at the University of Florence Italy, which he finished in 2001, he moved to the USA, where he continued his postdoctoral research at the laboratory of Alex Toker at Harvard Medical School in Boston for the next three years (2001-2004). Working with Professor Toker, he identified a soluble protein named ADAM9-S secreted by hepatic stromal cells, discovered as important for tumor invasion. His research interest has focused on cell and molecular basis of pathogenic mechanisms underlying liver cancer progression, with particular focus on molecules regulating tumor-stromal interactions. He continued his research on factors involved in cancer progression after moving to Vanderbilt University in 2007. Back to Italy, he was appointed as Assistant Professor of Laboratory Medicine at University of Bari School of Medicine and promoted to Associate Professor in Gastroenterology in 2012 (National Scientific Qualification). Here, he continued his work on hepatic cancer and identified lysophosphatidic acid receptor LPAR6, a protein that supports the growth and tumorigenesis of hepatocellular carcinoma. His research on factors promoting liver cancer growth has proven crucial to understanding the development of cancer and designing anti-cancer drugs. He has published several papers and this is his 1st book. He received several Investigator Awards and he is also the Associate Editor of the Journal of Gastrointestinal Cancer and BMC Cancer. (For further reading please also visit http://www.antoniomazzocca.com/).

Pasquale Agosti, MD, was born in Bari, Italy in 1986. He graduated in Medicine and Surgery at the University of Bari in 2012. He is currently geriatric medical resident at the Interdisciplinary Department of Medicine University of Bari School of Medicine. During the last 2 years, while working in the medical management, he began to show interest in the field of medical research, engaging in clinical and experimental research in the field of hepatology.

Carlo Sabbà, MD, PhD, was born in Bari, Italy in 1952. He graduated in Medicine and Surgery at the University of Bari in 1977. From 1978 to 1981 he did a fellowship for the Italian Research Council. From 1981 he began Assistant Professor in Internal Medicine at the University of Bari. From 1980 to 1983, he was "Visiting Professor" in several Universities of France and in 1983 he got the Italian Board in Internal Medicine. In 1987, he earned his PhD in "Pedagogie des sciences de la sanitè," Universitè Bobigny-Paris France. In 1988, he worked as an Assistant Professor at the Ultrasond Unit Rochester University (NY), USA. From 1988 to 1990, he was "Research Fellow" at the Hepatic Hemodynamic Laboratory and Department of Radiology, Ultrasond Section, New Haven, USA. In 1990, he was "Visiting professor" at the Unit of Ultrasonic Angiology-Guy's Hospital London, Great Britain and in 2001, "Visiting Professor"at the HHT center, Yale University CT, USA. From 1999 to 2010, he continued to work at the University of Bari as Associate Professor and then as Full Professor of Internal Medicine. From 2009, he is Chief of the general internal medicine division at General Hospital of Bari, *Policlinico.* Author of 146 scientific international pubblications indexed on Pub med. His main researchs in the field of hepatology concerned Echo-Color Doppler evaluations of portal hypertension in cirrhotic patients and HCC pathobiology.

Abbreviations

ADH3	alcohol dehydrogenase 3
ALDH2	aldehyde dehydrogenase 2
AFP	alpha-fetoprotein
AFP-L3	lens culinaris agglutinin -reactive alpha-fetoprotein
ALPPS	hypertrophy-inducing strategy for staging hepatectomy
ALT	alanine transaminase
Ang-1	angiopoietin 1
AOS	consensus statement from the Asian Oncology Summit 2009
AP	activator protein
APC	adenomatous polyposis coli
ATX	autotaxin
BCLC	Barcelona Clinic Liver Cancer system
BMI	body mass index
BRCA2	breast cancer type 2
CCl4	carbon tetrachloride
CCN1	matricellular protein cysteine-rich protein 61
CD	cluster of differentiation
CIN	chromosomal instability
CK	cytokeratin
CKI	cyclin-dependent kinase inhibitor
CGH	comparative genomic hybridization
CLIP	Cancer of the Liver Italian Program score
COX	cyclooxygenase
CP	Child Pugh score
CTP	Child-Turcotte-Pugh score
CSCs	cancer stem cells

CT	computed tomography
CTGF	connective tissue growth factor
CUPI	Chinese University Prognostic Index
DCP	des gamma carboxy prothrombin
DEN	diethylnitrosamine
DMN	dimethylnitrosamine
DNs	dysplastic nodules
DNMTs	DNA methyltransferases
DWI	diffusion weighted imaging
EASL	European Association for the Study of the Liver
ECM	extracellular matrix
ECOG	Eastern Cooperative Oncology Group performance status test
ELF	enhanced liver fibrosis test
EORTC	European Organisation for Research and Treatment of Cancer
EpCAM	epithelial cell adhesion molecule
EGF	epidermal growth factor
EGFR/ ERBB	epidermal growth factor receptor
ER	estrogen receptor
ET-1	endotelin 1
FAK	focal adhesion kinase
FDA	US Food and Drug Administration
FGF	fibroblast growth factor
FLR	future liver remnant
FLT3	fms related tyrosine kinase 3
GGT	gamma-glutamyl transpeptidase
GPC3	glypican-3
GRB2	growth factor receptor-bound protein 2
GSK	glycogen synthase kinase
GST-M1	glutathione s-transferase mu 1
GST-T1	glutathione s-transferase theta 1
GSTP1	glutathione s-transferase pi 1
GTP	guanosine-5'-triphosphate
HAI	hepatitis activity index
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HER	human epidermal growth factor receptor

HGDNs	high-grade dysplastic nodules
HGF	hepatocyte growth factor
HIF-1A	hypoxia-inducible factor 1-alpha
HPCs	hepatic stem cells
HSP-70	*heat shock protein 70*
HURP	hepatoma-up-regulated protein
ICG	indocyanine green
IGF2R	insulin-like growth factor 2 receptor
IFN	interferon
IL	interleukin
JIS	Japan Integrated Staging score
JNK	c-Jun N-terminal kinases
KRT19	keratin 19, type 1
LAK	lymphocytes with recombinant interleukin-2
LCSGJ	Liver Cancer Study Group of Japan
LOH	loss of heterozygosity
LPA	lysophosphatidic acid
LPAR	lysophosphatidic acid receptor
LPC	lysophosphatidylcholine
LRP	lipoprotein receptor-related protein
LTx	liver transplantation
MAPK	*mitogen-activated protein kinases*
MCP-1	monocyte chemotactic protein-1
M-CSF	macrophage colony-stimulating factor
MDCT	multidetector computed tomography
MELD	model for end-stage liver disease score
MFBs	myofibroblasts
MMPs	metalloproteases
mRECIST	modified *Response Evaluation Criteria In Solid Tumors*
MRI	magnetic resonance imaging
mRNA	messenger *ribonucleic acid*
MRNs	macroregenerative nodules
MSCs	mesenchymal stem cells
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NCCN	National Comprehensive Cancer Network
NF-kβ	nuclear factor kappa-light-chain-enhancer of activated B cells
NK	natural killer
NS	nonstructural *protein*

OV-6	oval cell marker antibody
p160ROCK/ ROCK 1	rho-associated, coiled-coil-containing protein kinase 1
PCNA	proliferating cell nuclear antigen
PCR	polymerase chain reaction
PDGF	platelet derived growth factor
PDGFR	platelet derived growth factor receptor
PEI	percutaneous ethanol injection
PIAF	cisplatin (platinol) with interferon, doxorubicin, and 5-fluorouracil
PI4KII	phosphatidylinositol 4-kinase type 2 alpha
PIVKA-II	vitamin K absence or antagonist-II
PPAR-γ	peroxisome proliferator-activated receptor gamma
PTEN	phosphatase and tensin homolog
PT INR	prothrombin time international normalized ratio
PTMA	prothymosin-alpha
PVE	portal vein embolization
PVT	portal vein thrombosis
RAMP3	receptor activity modifying protein 3
RAN	ras-related nuclear protein
RasGEF	ras guanine nucleotide exchange factors
RASSF1	ras association domain family member 1
RECIST	*Response Evaluation Criteria In Solid Tumors*
RFA	percutaneous radiofrequency ablation
RhoC	ras homolog *gene* family, member C
ROS	reactive oxygen species
SERCA	sarcoplasmic/endoplasmic reticulum calcium ATPase
SERPINE1	serpin peptidase inhibitor, clade E 1
sFRP1	secreted frizzled-related protein 1
SOCS-1	suppressor of cytokine signaling 1
STAT-1	signal transducer and activator of transcription 1
TAF9	TATA box binding protein-associated factor
TEMs	tetraspanin-enriched microdomains
TERC	telomerase RNA component
TGF	transforming growth factor
Th	T helper lymphocytes
TACE	hepatic artery chemoembolization
TIMP	tissue inhibitor inhibitors of metalloproteases
TIN2	TERF1-interacting nuclear factor 2

TNF	tumor necrosis factor
TNM	Tumor, Node, Metastasis system
TRF1-2	telomeric repeat factor 1-2
TTP	tristetrapolin
US	ultrasonography
VEGF	vascular endotelial growth factor
VEGFR	vascular endotelial growth factor receptor
WHO	World Health Organization

Preface

This book describes the pathobiology of hepatocellular carcinoma underlining its clinical impact in terms of diagnosis, prognosis and novel therapeutic management. In Europe, the common background of HCC is generally viral or alcoholic cirrhosis, however, an increasing number of HCCs develops on inflammatory conditions such as NASH or NAFLD related to metabolic syndrome. The process of carcinogenesis in cirrhotic patients is a multistep process ranging from regenerative to dysplastic nodules characterized by specific alterations including genetic or epigenetic abnormalities. In this context, the tumor microenvironment (i.e., immune and inflammatory response and stromal reaction) is crucial for the transition from the dysplastic nodule to HCC. Extracellular matrix proteins, tetraspanins, ADAMs, TGF-β and the lysophosphatidic acid (LPA) signaling axis are just few examples of mediators that will be reviewed in this book as paradigms in the process of HCC development and progression. The growing knowledges in the complex crosstalk between HCC cells and microenvironment and in the signaling pathways involved will make possible novel target therapies and patient outcome improvements.

Introduction to Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC) is considered the sixth most common cancer worldwide and the third malignancy as cause of cancer-related death. In the last 30 years, in USA, there has been a significant increase of HCC incidence (which probably reflects HCV incidence) that is still growing. To date, lung, breast, prostate and colorectal cancer are considered the "four big killer" in USA. However, a predictive study shows that HCC will become the third leading cause of cancer-related deaths by 2030 [1]. This may seem surprising considering the predicted reduction of incidence of both HBV and HCV infection, but it is not surprising considering the increased lifespan of chronic HCV patients and the emerging HCC risk factors. What is really changing is the fraction of HCC not related to common risk factors and so the significant increasing incidence of metabolic conditions such as diabetes, obesity and metabolic syndrome could explain HCC increase. HCC will become a very frequent tumor strongly influenced by life style. Accordingly, liver steatosis or NASH can be considered precancerous conditions. Several environmental and biological factors are involved in liver cancer development, but many studies are necessary to understand better its pathobiology. Therefore, aim of this book is to overview most of the actual knowledge about the pathobiology underlying HCC development and progression and how this knowledge may improve the management of HCC patients.

Reference

[1] Lola Rahib, Benjamin D. Smith, Rhonda Aizenberg, Allison B. Rosenzweig, Julie M. Fleshman, Lynn M. Matrisian. 2014. "Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States." *Cancer Res* 74:2913-21.

Contents

Chapter 1

Pathobiology of HCC: The Role of Risk Factors

The Role of the Known Environmental Risk Factors

Inflammation, regeneration and fibrosis are the three common features of liver cirrhosis, which is the most common background for HCC development. Known factors associated with an increased risk for HCC are hepatitis B or hepatitis C chronic infection, ethanol chronic consumption, non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), aflatoxin B1 or other food contaminant fungal toxins. Other factors less commonly associated are hereafter listed and include hemochromatosis, primary biliary cirrhosis, Wilson's disease, α1 antitrypsin deficiency, porphyria cutanea tarda, glycogen storage diseases, citrullinemia, tyrosinemia, autoimmune hepatitis and alagille syndrome of infants. Liver cirrhosis is considered a pre-malignant condition, but not all cirrhotic patients have similar cancer risk. For example, cirrhotic patients with older age, male gender, and severity of hepatopathy have an increased risk of developing HCC. Co-infections such as HBV and HCV, HCV and HIV, or HCV plus alcohol greatly increase the cancer risk. Most cases of HCC (about 80%) occur in sub-Saharan Africa or in Eastern Asia. Other high-rate areas include Senegal, Gambia and South Korea. Southern European countries including Italy are medium-rate areas. Also, the incidence of HCC can vary largely among populations living in the same region. For instance, HCC rates are 2 times higher in Asians than in African Americans