Introduction

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Chi Chun Wong and Jun Yu

Abstract

Obesity is fast becoming a major disorder for mankind. Numerous lifestyle factors play a role in the rising obesity epidemic, including changes in the diet and the lack of physical activity. Unfortunately, more than two-thirds of the adult population in developed countries is considered overweight and more than a third of them are obese. In addition to the well-publicized association of obesity with type II diabetes and cardiovascular diseases, emerging evidence indicates that obesity represents a major risk factor for fatty liver diseases and fatty liver disease-associated hepatocellular carcinoma (HCC).

Keywords

Obesity · Non-alcoholic steatohepatitis · Hepatocellular carcinoma · Microbiota · Therapy

C. C. Wong · J. Yu (✉)
Institute of Digestive Disease and Department of Medicine & Therapeutics, State Key Laboratory of Digestive Disease, LKS Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, Hong Kong
e-mail: chichun.wong@cuhk.edu.hk; junyu@cuhk.edu.hk

Obesity is fast becoming a major disorder for mankind. Numerous lifestyle factors play a role in the rising obesity epidemic, including changes in the diet and the lack of physical activity. Unfortunately, more than two-thirds of the adult population in developed countries is considered overweight and more than a third of them are obese. In addition to the well-publicized association of obesity with type II diabetes and cardiovascular diseases, emerging evidence indicate that obesity represents a major risk factor for fatty liver diseases and fatty liver disease-associated hepatocellular carcinoma (HCC).

Non-alcoholic fatty liver disease (NAFLD), defined by the collective features of obesity, diabetes, insulin resistance and dyslipidemia, is the most common cause of chronic liver disease in the West and in Asia. This is particularly true among obese individuals, where its incidence can be as high as 98%. Pathologically, NAFLD comprise of a full spectrum of liver conditions ranging from relatively benign, simple steatosis to more aggressive disease such as non-alcoholic steatohepatitis (NASH). NASH often progresses to cirrhosis, which in turn, predisposes HCC. In fact, NASH is increasingly considered as an important causative factor of HCC. Whilst a relatively small proportion of patients with NAFLD eventually develop cirrhosis and progress to HCC, the rising incidence of obesity coupled with metabolic syndrome means that to a large

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proportion of the general population are susceptible to NASH or NASH-associated HCC.

In the past decade, there has been an enormous research efforts studying the pathogenesis of hepatitis B/C (HBV/HCV)-associated HCC, which broadened our understanding of HBV/HCV-associated HCC. NASH-associated HCC has received less attention thus far; however, we are now beginning to understand its pathogenesis and molecular mechanism of action. One key unifying theme between NASH and NASH-associated HCC is chronic inflammation. Induction of inflammation is a hallmark of NAFLD and plays an important role in disease progression to NASH and cirrhosis. Moreover, chronic inflammation has been casually linked to the development of multiple malignancies. With advances in both basic sciences and biotechnology, much progress has been made in the development of therapeutic targets and drugs in the prevention and treatment of inflammatory conditions and inflammation-associated cancer, and they hold great promise for targeting NASH and NASH-associated HCC.

In this book, we invited researchers and clinicians from different regions to share their expertise in NAFLD, NASH and NASH-associated HCC, to shed new insights and future perspectives on the development of the field. In this regard, this book begins with the description of the epidemiology and etiology of NAFLD and its associated HCC to highlight their rising trend in the developed countries as a result of the obesity epidemic. Inflammation is a key player in the pathogenesis of NAFLD and HCC. The next two chapters describe the role of immune mediators and inflammatory pathways, including cytokines, adipokines and chemokines, which contribute to the development of NAFLD and NASH. Next, an up-to-date overview on the pathogenesis of NAFLD-related HCC is given and the underlying role of metabolic syndrome in the transition of steatosis to NASH, fibrosis and HCC is discussed. Surveillance of NAFLD-related HCC is a major challenge as only a small portion of patients will eventually progress to HCC. Recent advances in the utilization of clinical and genetic biomarkers for the cost effective patient stratification and disease detection is therefore summarized. The first part of the book concludes with a discussion on the role of epigenetic changes, heritable changes in gene expression that are not resulted from alterations in DNA sequence, in NAFLD and HCC, and how might these epigenetic alterations be used for disease diagnosis and prognosis.

The second part of the book focuses on in-depth reviews on current hot topics in NAFLD, NASH and HCC. The gut microbiota is an emerging environmental factor that triggers a multitude of diseases. Intensive efforts have established the microbiota dysfunction as a novel contributor to obesity and liver cancer, and these studies are reviewed to emphasize their diverse roles in disease development. The influence of gut microbiota-derived metabolites on the pathogenesis of NAFLD is first outlined with a focus on microbiota-derived bile acids. This is followed by an overview on the interaction between obesity and microbiota contributing to development of NAFLD. Microbiota dysfunction in HCC is then discussed, highlighting its potential role in the transition from NAFLD to HCC. Another key research area is the role of autophagy in HCC. Autophagy represents a cell survival mechanism that mediates the recycling of dysfunctional cellular components, and impairment of autophagy has a contributory role in NAFLD. As such, targeting autophagy processes will be a novel therapeutic strategy for treating inflammation and cancer in the liver.

The third part of the book aims to capture latest developments in established therapies and future therapeutic strategies for the prevention and treatment of NAFLD, NASH and HCC. It begins with an extensive overview of pre-clinical experimental animal models of NAFLD and NAFLD-associated HCC that can be used for efficacy evaluation of novel therapeutics or treatment modalities, and the pros and cons of each model. This is followed by an up-to-date review of prevention and treatment options for NAFLD, with a focus on management of NAFLD in order to minimize disease progression to cirrhosis and HCC. The current therapies and future therapeutic strategies for the treatment of obesity related HCC is also discussed. Given that obesity, fatty liver and fatty liver-associated HCC are increasingly prevalent in developed countries, this book offers a timely and comprehensive overview on these diseases, and provides perspectives on future strategies for their detection, prevention and treatment.