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Review

Obesity linking to hepatocellular carcinoma: A global view

Lu Gan, Zhenjiang Liu, Chao Sun*

College of Animal Science and Technology, Northwest A&F University, Yangling, Shaanxi 712100, China

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ABSTRACT

Hepatocellular carcinoma (HCC) is the commonest primary liver cancer and the second leading cause of cancer death worldwide. Obesity is rapidly becoming pandemic and associated with increased carcinogenesis. In this review, we describe the obesity-related factors that influence the development of HCC. We provide evidence of strong links between neural regulation, endocrine and HCC in obesity. We discuss recent advances in our understanding of how adipose tissue alters hepatic metabolism and immune response in HCC development through inter-organ communication. Taken together, our review aims to provides a concise and up-to date summary about the connection between obesity and HCC, with emphasis on the opportunities for effective strategies in preventing the development of HCC in obese individuals.

1. Introduction

Obesity is an important public health concern and is increasingly recognized as a major risk factor for several common types of cancer [1]. Considering the complexity of obesity, which comprised of behavioral, epidemiologic and molecular/metabolic factors, both epidemiologic and preclinical studies have been determined to understand the mechanisms linking obesity and cancer [2]. Moreover, obesity and related co-morbidities are associated with increased risk of adverse treatment effects on liver, which may impact the treatment plan [3]. The liver closely communicates with adipose tissue [4]. Non-alcoholic fatty liver (NAFLD), the hepatic manifestation of the metabolic syndrome, comprises a spectrum of liver diseases including benign steatosis, steatohepatitis, cirrhosis and hepatocellular carcinoma [5]. Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It is the fifth most common cancer with over half a million new cases diagnosed annually worldwide [6]. Moreover, it is now clear that obesity and associated diseases such as type 2 diabetes are well accepted risk factors for the development of HCC. Obesity refers to the excess of adipose tissue and the ectopic secretion of adipocytokines. The abnormal serum levels of adiponectin and leptin predicts the occurrence of HCC and liver-related death in patients with cirrhosis.

In the last decade, it has become evident that obesity-related metabolic inflammation involved in different aspects of HCC progression, including tumor onset, metastatic dissemination and cancer immunemodulation. Since both adipose tissue and liver are affected by obesity, it is not trivial to clarify the impact of obesity in these different aspects of HCC development. Since central neuron, intestinal immune system and endocrine system are partially controlled or modulated by obese adipose tissue, it is important to assess the multi-aspects of obesity in HCC progression.

The aim of this review is to updated early review reports and describe the latest advances of obesity and HCC in decades. We will summarize the most significant data focusing on obesity in mice and human experiments, offering relevant information for the discussion about the role of obesity in HCC development and its possible translational implications.

2. Neural regulation in HCC

2.1. Autonomic nerve system

Obesity is usually heritable to many diseases and causes a wide variety of disorders and effects on the central and peripheral nervous system [7]. Anatomically, the peripheral sympathetic and parasympathetic pathways are separate and the distribution of premotor neurons in higher brain regions often overlaps. In the peripheral nervous system, obesity-driven alterations in the autonomic nervous system prompt imbalances in sympathetic-parasympathetic activity [8]. Moreover, autonomic nerve system plays an important role in the development of multiple cancers via regulating cancer cell proliferation, differentiation, apoptosis, migration and invasion. Coordinated modulation of sympathetic and parasympathetic nervous activities is required for physiological regulation of hepatic function. Studies indicate that liver is innervated by both sympathetic and parasympathetic nerves in HCC [9]. The sympathetic nervous system is also slight and

* Corresponding author.
E-mail address: sunchao2775@163.com (C. Sun).

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has a reduced metabolic rate in obese [10]. Furthermore, sympathetic nervous system plays a significant role in tumor initiation and metastasis. HCC frequently occurs in cirrhotic livers after chronic inflammation, and the sympathetic nervous system is hyperactive in advanced liver cirrhosis [11]. Thus, it is not surprising that obesity may play essential roles in the regulation of autonomic nervous system triggered HCC.

2.2. Leptin resistance

Obesity is characterized by hyperleptinemia and central leptin resistance [12]. Leptin is a hormone produced by peripheral adipose tissue. The ectopic serum leptin level is usually considered as a symbol of metabolic disorder which has contributed to HCC. Somatic mutations of liver leptin receptor contribute to the development of cirrhotic liver and HCC [13]. The ectopic serum leptin level is also a risk factor for microvascular invasion, a known predictor of poor survival in HCC [14]. Recently, studies have report the oncogenic role of hepatic leptin resistance and its potential in increasing tumor invasiveness and migration of HCC [15]. Hepatic leptin resistance is caused by impairment of the leptin-signal transduction mediated by both janus-activated kinase-2 (JAK2) and the mitogen-activated protein kinase (MAPK) pathways [16]. Leptin administration induced a significant suppression of HCC through increasing natural killer (NK) cell number in liver [17]. Thus, obesity directly increases the risk of HCC in which is associated with the ectopic serum leptin and hepatic leptin resistance.

2.3. Circadian rhythm

Circadian rhythm controls many physiological processes such as the sleep-wake cycle, metabolism and hormone secretion which adapted to 24 h day-night periodicity. Deregulation of these rhythms is associated with a number of pathogenic conditions including depression, diabetes, metabolic syndrome and cancer. The circadian clock system in the liver also plays important roles in regulating metabolism and energy homeostasis [18–20]. Melatonin, primary secreted by the pineal, inhibits HCC progression by reducing lncRNA-CPS1-IT1-mediated EMT suppression [21]. Kettner et al. identify the disruption of normal circadian rhythmicity as an independent risk factor for HCC [21,23]. Loss of circadian rhythm for IGF-I in liver is also associated with cirrhotic liver and HCC [24]. Moreover, some drugs are more effectively delivered to HCC patients at a circadian rhythm-modulated rate [25]. Taken together, circadian rhythm will be an important factor for considering the regulator mechanism and treatment of HCC in future (Fig. 1).

3. Molecular metabolism in HCC

3.1. Hepatokines and metabolism

Hepatokines are proteins secreted from hepatocytes that can influence metabolism both locally and in distant organs through autocrine, paracrine and endocrine signaling. Hepatocytes secrete more than 500 hepatokines including angiopoietin-like protein 4 (ANGPTL4), fibroblast growth factor 21 (FGF21), leukocyte cell-derived chemotaxin 2 (LECT2), retinol-binding protein 4 (RBP4), sex hormone-binding globulin (SHBG) [26–30]. Obesity-induced liver steatosis elevated the serum level of fetuin-A, a hepatokine released from fatty liver [31]. Moreover, studies have identified that obesity accelerates the secretion of hepatokines and induces liver steatosis [32–34]. There is no doubt that liver steatosis is associated with the development of HCC. In turn, liver steatosis and HCC induce ectopic hepatokines secretion and play an alternative role in pathogenesis of obesity. Accordingly, further studies need to determine the causality of obesity and HCC especially in the development of liver steatosis.

3.2. Adipocytokines

Adipocytokines play important roles in adipose tissue homeostasis, especially in obesity-associated disorders such as NAFLD and their complications including HCC. Adipocytokines, such as adiponectin, leptin and adiposin, have been fully determined by numerous studies that regulate HCC via signal pathways and metabolic processes [35–37]. Here, we focus on a few other adipocytokines which have potential and clinical relevance but remains unclear until today. Obesity increased serum visfatin, a pro-inflammatory adipocytokine, which is associated with poor prognosis of HCC [38]. Resistin is primarily produced by adipocytes and is involved in NAFLD and non-alcoholic steatohepatitis (NASH) [39,40]. Chemerin is a protein secreted by adipose tissue and liver and is correlated with NAFLD features, but the regulatory mechanism remains unclear [41,42]. In obesity, adipose tissue secreted a rich source for adipocytokines which have been identified its clinical relevance. We only briefly discuss a few other adipocytokines and their potential role in HCC as this topic has been excellently reviewed recently.

3.3. Omics research

Omics studies such as transcriptomics, genomics, proteomics, and lipidomics are novel methodologies which are gaining importance to develop new therapeutic approaches in diseases. Recently, integrative multi-omics analysis has been processed in HCC to identify novel biomarkers and therapeutic targets. Protein tyrosine phosphatase receptor type D (PTPRD), a tumor suppressor gene, is homozygously deleted and epigenetically downregulated in HCC [43]. Considering the complicated relationship of obesity and HCC, the comprehensive multi-omics characterization of individuals may improve clinical decision-making, facilitate personalized medicine. Recent studies provide evidence that the earliest detectable pathogenic mechanisms are mitochondrial energetic and structural dysfunction and lipotoxicity, HCC appears to be a late consequence of the progression of obesity and NAFLD [44]. The lipidomics may be more precise approach in discovering the mechanisms of obesity and HCC. However, few studies suggest the important role of glycerolipids, glycerophospholipids and sphingolipids in HCC development. Thus, there still need more precise data to determine the key molecular or metabolite in the development of HCC.

4. Immune response in HCC

4.1. Immune cells in liver

Obesity is associated with systemic inflammation especially NASH and NAFLD that increase risk of HCC. The immune cells accumulate in liver and secret numerous immune factors which aggravate carcinoma [45–47]. The percentage and absolute number of liver NK cells decrease significantly during the development and progression of HCC [48]. In obese, T cell killing was lower than that required to directly inhibit HCC proliferation [49]. Studies clarify the cellular and molecular mechanisms that coordinate the innate immune response to tissue damage and cell death in the liver [50]. The adaptive immune system, including type1 helper T cells (Th1 cells), cytotoxic T lymphocytes (CTLs), and dendritic cells (DCs), plays important roles in development of HCC [51].

4.2. Intestinal immunity

Liver and intestine are closed tissues and coordinate systemic homeostasis. The intestinal immune system contains largest number of immune cells of tissues in the body and it is continually exposed to a wide range of antigens and potential immune stimulus [52]. Recently, growing evidence has implicated the intestinal immune system as an important contributor to metabolic disease. Obesity predisposes to