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MINI REVIEW

The role of ROS-induced autophagy in hepatocellular carcinoma

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Summary Hepatocellular carcinoma (HCC) is a main cause of cancer-related mortality and its etiology is not fully understood. As prominent factors that regulate cellular homeostasis, both reactive oxygen species (ROS) and autophagy are considered to play an essential role in the liver carcinogenesis. However, the crosstalk between ROS and autophagy is not well characterized in the pathogenesis of HCC. This review summarizes the roles of autophagy in ROS-mediated hepatocarcinogenesis and discusses the role of ROS-induced autophagy in HCC cell fate decision following treatment with chemotherapeutic agents in preclinical settings, which may allow the identification of novel strategies for the treatment of HCC.

Introduction

Reactive oxygen species (ROS) are defined as oxygen metabolites and oxygen-containing materials with reactive properties that are derived from oxidative metabolism, including superoxide anion (O_2-) and hydroxyl radical ($OH-$) as well as nonradical molecules such hydrogen peroxide (H_2O_2). These reactive species can be produced as a byproduct of metabolic reactions in mitochondria, the NADPH oxidase system, peroxisomes and endoplasmic reticulum, among which mitochondria are regarded as the dominant source of cellular ROS [1]. The detoxification of ROS is performed by several endogenous antioxidant enzymes, such as superoxide dismutase (SOD), catalase and glutathione peroxidase; thus, the generation and degradation of ROS in the cell maintain in a state of equilibrium under physiological conditions [2]. In normal concentration, ROS act as crucial second messengers that are involved in various signal transductions that regulate cellular growth, proliferation and differentiation. However, redox imbalance causes excessive production of ROS that exceeds the capacity of the cell to remove, which leads to oxidative stress and plays a crucial role in the occurrence and development of cancer [3].

Autophagy is an evolutionarily conserved cellular process whereby cytoplasmic components, such as damaged organelles and aggregated proteins, are delivered to autophagosomes for degradation and recycling, and is

Abbreviations: 8-OHdG, 8-Hydroxydeoxyguanosine; FFAs, free fatty acids; HBV/HCV, hepatitis B/C virus; HBx, HBV X protein; HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis; ROS, reactive oxygen species; SOD, superoxide dismutase.

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responsible for the maintenance of cellular homeostasis and viability [4]. Excess ROS cause mitochondria dysfunction and biomolecules oxidation (DNA, lipids and proteins), thus triggering carcinogenesis; whilst autophagy induction acts as a buffer system to moderate ROS and mitigate oxidative stress [5]. ROS and autophagy interact to keep cellular homeostasis, either redox or autophagy dysregulations are associated with tumor initiation and maintenance [6]. Hepatocellular carcinoma (HCC) is a major cause of cancer-related death and its etiologic factors including viral infections, obesity and alcohol abuse, are widely considered to induce oxidative stress and thus participate in hepatocarcinogenesis [7,8]. However, the crosstalk between ROS and autophagy in the development of HCC remain unclear. Furthermore, recent studies have revealed that in diverse HCC chemotherapies ROS-mediated autophagy acts in two opposing functions: the cell survival promotion that known as a mechanism of chemotherapy resistance [9,10]; and the cell death induction, defined as autophagic cell death, which might be beneficial to antitumor treatment [11,12]. Thus, a better understanding of the interplay between ROS and autophagy in the pathogenesis of HCC may provide a novel strategy for the treatment of this disease.

ROS-induced mitochondrial dysfunction and oxidative stress

HCC is associated with chronic liver damage due to viral infection, alcohol abuse and obesity. These risk factors can increase ROS production via interference with the mitochondrial electron transport, thus leading to oxidative stress [13,14].

It is acknowledged that 80% of HCC results from infection with hepatitis B (HBV) and C (HCV) virus, which are involved in carcinogenesis via mitochondrial damage and oxidative stress [15]. Virus proteins induce ROS overproduction through several independent pathways related to mitochondria [13]. For example, the HBV X protein (HBx) directly interacts with mitochondria and targets voltage-dependent anion channel 3, altering the mitochondrial membrane potential and electron transport system, leading to an enhanced production of ROS [16,17]. Actually, the c-terminal region from HBx truncation is required for ROS production and associated with increased venous invasion and metastasis in HCC [13]. In addition, the activation of cytosolic calcium signaling pathways induced by HBV proteins can promote mitochondrial calcium uptake; in consequence, increased levels of ROS stimulate expression of transcription factors NF-κB and STAT3 that assist in viral replication [18,19]. Compared with HBV, HCV proteins similarly trigger ROS generation by disrupting the mitochondrial electron transport [20,21] and modulating calcium signaling [22]. In particular, NADPH oxidases and cytochrome P4502E1 (CYP2E1) are identified as additional sources of ROS in HCV-infected hepatocytes, but their involvement in HBV-induced oxidative stress has yet to be investigated [23]. Accordingly, these results indicate that virus-induced mitochondrial ROS production is beyond redox regulation and renders hepatic tissue more accessible for oxidative damage. Moreover, the HBx and NS5A protein are main factors for HBV and HCV induced-oxidative stress, respectively.

It has been well established that alcohol contributes to liver carcinogenesis by induction of oxidative stress [24]. Ethanol metabolism by alcohol dehydrogenase causes the production of ROS and acetaldehyde. This reaction increases mitochondrial NAD(P)H and thus may exacerbate ROS generation via interference with the electron transfer system [14]. Another main source of ROS is the ethanol-inducible cytochrome P4502E1, which converts ethanol to acetaldehyde and produces ROS in hepatocytes [25]. In hepatoma cells over-expressing P4502E1, the cytotoxicity of ethanol was increased compared to control cells [26], suggesting the intensive oxidative stress in ethanol-associated HCC. Thus, chronic ethanol consumption increases both the protein level and activity of P4502E1 and subsequently causes oxidative stress, involving in hepatic neoplasia [27]. Besides, excess alcohol impairs antioxidant defences through antioxidant enzymes depletion and genetic variations, contributing to overwhelming oxidative stress [28], which may favor the emergence of HCC in patients with alcoholic liver disease.

In nonalcoholic steatohepatitis (NASH), mitochondrial dysfunction participates in the induction of oxidative stress, which might accelerate the progression of NASH to HCC [29]. Accumulated free fatty acids (FFAs) or lipids in the liver are regarded as the main factor for ROS production in NASH. Under normal conditions, FFA β-oxidation in mitochondria provides hepatocytes with energy via the electron transport chain and oxidative phosphorylation, whereas excessive FFAs compromise this process and thus increase dramatically ROS levels [30]. Moreover, ROS generation is elicited in the presence of cytochrome P4502E1 by respiratory chain disruption and mitochondrial abnormality [31]. Also, ROS can inhibit mitochondrial antioxidant enzymes such as SOD, attenuating the antioxidant capacity, which further augments oxidative stress and creates a vicious circle [32].

In summary, HCC risk factors can induce mitochondrial ROS production by several mechanisms:

- mitochondrial electron transport disruption;
- cytochrome P4502E1 abnormal activation;
- antioxidant enzymes depletion.

Sustained redox dysregulation causes hepatocytes death and tissue damage through ROS-induced mitochondrial dysfunction, which in turn augments the production of ROS, resulting in a vicious cycle where increased oxidative damage probably plays a major pathogenic role in the liver carcinogenesis.

Oxidative DNA damage and hepatocarcinogenesis

Previous studies have shown that virus infection can increase the level of 8-Hydroxydeoxyguanosine (8-OHdG), a useful marker of oxidative DNA damage, in HBV transgenic mice and HCV-infected patients with chronic liver disease [33,34]. Further analyses of serum found that patients with HCV-related HCC had significantly higher 8-OHdG levels and reactive oxygen metabolites compared to HBV-related HCC, indicating that HCV infection is more likely to induce hepatic oxidative stress [35]. Also, the more accumulation of

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