Free Radical Biology and Medicine ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Review Article

Oxidative stress and hepatic Nox proteins in chronic hepatitis C and hepatocellular carcinoma

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ARTICLE INFO

Article history:
Received 1 January 2014
Received in revised form
16 April 2014
Accepted 18 April 2014

Keywords:
Cancer
HCV
Inflammation
NADPH oxidase
Reactive oxygen species
Free radicals

ABSTRACT

Hepatocellular carcinoma (HCC) is the most common liver cancer and a leading cause of cancer-related mortality in the world. Hepatitis C virus (HCV) is a major etiologic agent of HCC. A majority of HCV infections lead to chronic infection that can progress to cirrhosis and, eventually, HCC and liver failure. A common pathogenic feature present in HCV infection, and other conditions leading to HCC, is oxidative stress. HCV directly increases superoxide and H_2O_2 formation in hepatocytes by elevating Nox protein expression and sensitizing mitochondria to reactive oxygen species generation while decreasing glutathione. Nitric oxide synthesis and hepatic iron are also elevated. Furthermore, activation of phagocytic NADPH oxidase (Nox) 2 of host immune cells is likely to exacerbate oxidative stress in HCV-infected patients. Key mechanisms of HCC include genome instability, epigenetic regulation, inflammation with chronic tissue injury and sustained cell proliferation, and modulation of cell growth and death. Oxidative stress, or Nox proteins, plays various roles in these mechanisms. Nox proteins also function in hepatic fibrosis, which commonly precedes HCC, and Nox4 elevation by HCV is mediated by transforming growth factor β. This review summarizes mechanisms of oncogenesis by HCV, highlighting the roles of oxidative stress and hepatic Nox enzymes in HCC.

Contents

Abbreviations: 8-OHdG, 8-hydroxydeoxyguanosine; ALT, alanine aminotransferase; AP-1, activator protein 1; BHA, butylated hydroxyanisole; CD81, cluster of differentiation 81; CXCL10, C-X-C motif chemokine 10; CYP, cytochrome P450; DCF, dihydrodichlorocarboxyfluorescein; DEN, diethylnitrosamine; DPI, diphenyleneiodonium; Duox, dual oxidase; EMT, epithelial–mesenchymal transition; ER, endoplasmic reticulum; F/ARFP, frameshift/alternate reading frame protein; FoxMI, Forkhead box M1; GAG, glycosaminoglycans; GSH, glutathione; H2AX, H2A histone family, member X; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HSC, hepatic stellate cell; IFN, interferon; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; LDLR, low-density lipoprotein receptor; LPC, liver progenitor cell; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; MPT, membrane permeability transition; NAC, *N*-acetylcysteine; NALP3, NACHT, LRR, and PYD domains-containing protein 3; NF-κB, nuclear factor κB; Nox, NADPH oxidase; Nrf, nuclear factor erythroid-2-related transcription factor; NS, nonstructural; OCLN, occludin; OGG1, 8-oxoguanine glycosylase; PDTC, pyrrolidine dithiocarbamate; PI3K, phosphoinositide 3-kinase; PPAR, peroxisome proliferator-activated receptor; pRb, retinoblastoma protein; Rac, Ras-related C3 botulinum toxin substrate; RNS, reactive nitrogen species; ROS, reactive oxygen species; SCID, severe combined immunodeficient; SOD, superoxide dismutase; SR-B1, scavenger receptor class B type I; STAT, signal transducer and activator of transcription; SVR, sustained virological response; TGF, transforming growth factor; TLR, Toll-like receptor; TNFα, tumor necrosis factor α; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; UTR, untranslated region

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http://dx.doi.org/10.1016/j.freeradbiomed.2014.04.020
0891-5849/

Introduction

Oxygen is essential for the life of aerobic organisms. During aerobic respiration, O_2 is reduced to H_2O through a series of electron transfer reactions occurring in mitochondria that drive ATP synthesis. In addition, reactive oxygen species (ROS)[1] are formed. Although ROS are often associated with toxicity, not all biological ROS generation is harmful, and ROS participate in specific, reversible biochemical reactions in redox signaling. For example, reversible thiol oxidation of protein tyrosine phosphatases and peroxiredoxins by H_2O_2 that produces cysteine sulfenic acid intermediates is well characterized [1]. Even an overproduction of reactive species is not necessarily harmful and could confer some benefit to the organism producing them. A clear example would be the burst of superoxide anion ($O_2^{\bullet -}$) produced by NADPH oxidase 2 (Nox2) in phagocytes during inflammation, which is critical for the destruction of microbes within phagosomes; absence of a functional Nox2 protein complex leads to chronic and frequent infections, as well as dysregulated inflammation in patients with chronic granulomatous disease [2]. Nevertheless, aberrant levels of ROS that overwhelm the body's antioxidant defenses can result in pathogenic changes and tissue injury, and a shift in redox status is associated with diverse disease conditions.

Hepatitis C virus (HCV) is a major etiologic agent of severe liver diseases, including cancer. HCV perturbs the host redox status by increasing production of ROS and reactive nitrogen species (RNS), and oxidative stress has emerged as a common pathogenic feature in numerous in vitro and in vivo studies on HCV. Several sources of ROS contribute to hepatic oxidative stress during HCV infection, including hepatocyte and nonhepatocyte sources, and oxidative stress is likely to contribute to HCV-associated liver cancer through multiple mechanisms. This review summarizes the mechanisms of hepatocarcinogenesis by HCV, highlighting the role of oxidative stress and hepatic Nox enzymes in hepatocellular carcinoma (HCC).

Hepatocellular carcinoma

HCC is a malignant epithelial tumor of the parenchymal liver cell that accounts for 70–85% of primary liver cancers [3]. A majority of HCC cases occur in developing countries, with the highest prevalence in sub-Saharan Africa and eastern Asia. HCC rates are low in developed countries, with the exception of Japan. HCC is the second leading cause of cancer-related mortality in the world [4]. Disease prognosis is poor; 5-year survival rates of ~11% have been reported, even in developed countries [5–7]. Unlike many cancers that have declined over the years, HCC is still on the rise [8]. In the United States, the incidence rates of HCC tripled in both men and women from 1995–1997 to 2005–2007; death rates for liver cancer also increased [9]. Increases in HCC incidence rates were most prominent among Hispanic, black, and white middle-aged men between 2000 and 2005 [9,10]. Higher overall HCC incidence and mortality rates were also found among Asians/Pacific Islanders compared to other groups tested, indicating significant health disparities among populations [9]. A 10-fold increase in the prevalence of HCC was reported among U.S. military veterans with HCV infection from 1996 to 2006 [11]. In 2009, 22,620 new cases of liver and intrahepatic bile duct cancers and 18,160 deaths were estimated in the United States [8]. Worldwide, an estimated 748,300 new liver cancer cases and 695,900 liver cancer-related deaths occurred in 2008 [12].

Risk factors for HCC include viral hepatitis, alcohol abuse, aflatoxin exposure, and obesity, as well as nonalcoholic fatty liver disease [4]. Among these, viral hepatitis is the most important risk factor for HCC; together, hepatitis B virus (HBV) and HCV are responsible for 78% of HCC worldwide [13]. Although the highest rates of HCC are found in areas where HBV is endemic, the increasing incidence of HCC, particularly in developed countries, has been largely attributed to the prevalence of HCV infection. For example, HCV infection is found in approximately 80% of HCC cases in Japan and about half of HCC cases in the United States [14,15]. Unlike HBV, for which there is a vaccine, there is no vaccine that can prevent the spread of HCV infection, and this is probably contributing to the rising incidence of HCV-associated HCC. The odds ratio for developing HCC is 11.5 among HCV-infected individuals [16].

HCV induces HCC

HCV is an enveloped, positive-sense RNA virus of the Flaviviridae family that was discovered in 1989 [17]. HCV is transmitted through blood, and common risk factors for HCV infection include having received blood, blood products, or organs before 1992; injection drug use; birth to an infected mother; sex with an infected person; and occupational exposure. A majority of HCV-infected individuals do not clear the virus and become chronically infected. It is estimated that approximately 170 million individuals are chronically infected with HCV worldwide, including 4 million in the United States [18,19]. Baby boomers, or people who were born between 1945 and 1965, are more likely to have hepatitis C than others; a National Health and Nutrition Examination Survey estimated that among the noninstitutionalized, civilian U.S. population who had chronic HCV infection, approximately 66% were baby boomers who would now have been living with chronic hepatitis C for several decades [20]. It has also been estimated that approximately 50% of individuals with chronic HCV infections are undiagnosed in the United States [20].

Please cite this article as: Choi, J; et al. Oxidative stress and hepatic Nox proteins in chronic hepatitis C and hepatocellular carcinoma. *Free Radic. Biol. Med.* (2014), http://dx.doi.org/10.1016/j.freeradbiomed.2014.04.020