World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i9.2136

World J Gastroenterol 2014 March 7; 20(9): 2136-2142
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (10): Alcoholic liver disease

Role of mitochondria in alcoholic liver disease

Fatiha Nassir, Jamal A Ibdah

Fatiha Nassir, Jamal A Ibdah, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Missouri School of Medicine, Columbia, MO 65212, United States

Author contributions: Nassir F reviewed the literature and wrote the manuscript and Ibdah JA provided overall intellectual input into the design, contributed to writing, and edited the final version of the manuscript.

Correspondence to: Jamal A Ibdah, MD, PhD, AGAF, Professor, Director, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Missouri School of Medicine, One Hospital Drive, CE 405, Columbia, MO 65212, United States. ibdahj@health.missouri.edu
Telephone: +1-573-8827349 Fax: +1-573-8844595

Received: October 29, 2013 Revised: December 24, 2013
Accepted: January 14, 2014
Published online: March 7, 2014

Abstract

Alcohol abuse is the leading cause of liver related morbidity and mortality. Chronic or binge alcohol drinking causes hepatic steatosis which can develop to steatohepatitis, cirrhosis and ultimately hepatocellular carcinoma. The pathogenesis of alcoholic liver disease (ALD) is poorly characterized, however several recent studies point to a major role of mitochondria in this process. Mitochondria play a crucial role in cellular energy metabolism and in reactive species formation. Alcohol treatment causes mitochondrial DNA damage, lipid accumulation and oxidative stress. Studies in both animal models and in humans showed that alcohol administration causes changes in the mitochondrial morphology and function suggesting a role of these changes in the pathogenesis of ALD. We review recent findings on mechanisms by which alcohol negatively impacts mitochondrial biogenesis and function and we will discuss the specific intracellular pathways affected by alcohol consumption. Interestingly, recent findings indicate that a large number of mitochondrial proteins are acetylated and that mitochondrial proteins acetylation and sirtuins are modulated by alcohol. Understanding the mechanisms behind alcohol mediated impaired mitochondrial biogenesis and function may help identify potential therapeutic targets for treating ALD in humans.

Key words: Liver; Alcoholic liver disease; Mitochondria; Alcohol; Sirtuins

Core tip: Excessive chronic or binge alcohol consumption causes alcoholic liver disease (ALD) with a spectrum ranging from simple steatosis to steatohepatitis and cirrhosis. One of the characteristics of ALD is the alteration in mitochondrial structure and function. This review summarizes some of the recent findings of the molecular mechanisms involved in the modulation of mitochondrial function and their implication in the development of ALD.

Nassir F, Ibdah JA. Role of mitochondria in alcoholic liver disease. *World J Gastroenterol* 2014; 20(9): 2136-2142 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i9/2136.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i9.2136

INTRODUCTION

Alcohol is widely consumed in most parts of the world and has long been associated with various liver diseases accounting for about 4% of all deaths[1]. The 2011 global status report on alcohol and health (World Health Organization) indicated that 4.5% of the global burden of disease and injury was attributed to alcohol with 7.4% for men and 1.4% for women. In the United States, 50% of the adult population (aged 18 years and over) consumed alcohol on regular basis in 2011 (Summary Health Statistics for United States Adults: National Health Interview Survey, 2011). Excessive chronic or

binge (acute large doses) of alcohol consumption causes hepatic steatosis, which can progress, if drinking continues, to more advanced form of alcoholic liver disease (ALD) such as alcoholic steatohepatitis (SH), hepatic fibrosis and cirrhosis and ultimately hepatocellular carcinoma[2-4]. The pathogenesis of ALD is still poorly understood making the progress in finding treatment slow. One of the characteristics of ALD both in animal models and in patients is the perturbation in the morphology and function of mitochondria. Abnormal mitochondrial and cellular redox homeostasis has been documented in alcoholic steatohepatitis and results in alterations of multiple redox-sensitive signaling cascades[5]. We will review current understandings of the role of alcohol metabolism in the pathogenesis of liver disease and the recent mechanisms involved in ALD with special focus on the mitochondrial changes associated with alcohol consumption and their potential implications in ALD.

SPECTRUM OF ALCOHOLIC LIVER DISEASE

ALD is a multistage disease consisting of hepatic steatosis (fatty liver), alcoholic hepatitis, and chronic hepatitis (inflammation) with hepatic fibrosis (development of scar tissue) or cirrhosis[5,6]. The different stages of ALD are not mutually exclusive and may be present simultaneously in certain individual[7]; alcoholic cirrhosis can develop without precedent of hepatic steatosis or alcoholic hepatitis. Hepatic steatosis is the earliest response to alcohol consumption and develops in 90% of heavy alcohol drinkers[8-10]. Simple hepatic steatosis is usually asymptomatic, reversible and resolve after 4-6 wk of abstinence[11]. With continuous alcohol intake, 20%-30% of patients with steatosis develop alcoholic hepatitis and 16% of patients with steatohepatitis will develop cirrhosis[12,13]. Fibrosis of the liver, a consequence of inflammation, infection or injury, results from excessive accumulation of collagen and other extracellular matrix proteins in the liver which impedes normal function of the liver leading to the development of cirrhosis. Alcohol associated cirrhosis is a consequence of sustained alcohol intake and is characterized by both steatosis and hepatitis with fibrosis[4]. Alcoholic cirrhosis is irreversible and is among the top ten causes of death worldwide. According to the National Institute on Alcohol Abuse and Alcoholism, liver cirrhosis is the 12th leading cause of death in the United States with 29925 death in 2010, about 50% of which are alcohol related[14]. Liver cirrhosis predisposes the HCC, it is seen in about 80% of HCC patients[15,16]. In the US, HCC is the most rapidly growing cause of cancer-related mortality, particularly among men ages 40 to 60 years[17,18].

Although hepatic steatosis is found in 90% of heavy alcohol drinkers, the severe forms of ALD such as fibrosis and cirrhosis develop only in 30% of individuals with heavy alcohol intake suggesting that other factors are involved in the progression of the disease. The possible risk factors that can affect the development of liver injury include the dose[19], duration[20], type of alcohol consumed[21], drinking patterns[22], gender[4,23], ethnicity[4,24], and associated risk factors, including obesity[25,26] and genetic factors[27,28].

METABOLISM OF ALCOHOL IN THE LIVER

When consumed, 90% of ingested alcohol is absorbed in the upper GI tract and diffuse throughout the body[29,30]. Studies both in humans[31,32] and animals[33-35] have shown that both short and long term ethanol treatment can disrupt the epithelial barrier of the GI tract which results in increased intestinal permeability and enhanced movement of luminal antigens such as bacteria and endotoxins into the portal circulation[36,37]. This can lead to Kupffer cells activation in the liver and cytokine release which may consequently results in liver injury and ALD[38,39]. The liver is the main organ responsible for metabolizing ingested alcohol; therefore it is more susceptible to alcohol related injury. Alcohol is metabolized in the liver by both oxidative and non-oxidative pathways. Briefly, the oxidative pathways of alcohol metabolism involve three enzymes, alcohol dehydrogenase (ADH) in the cytosol, cytochrome P450 2E1 (CYP2E1) in the peroxisomes and catalase in the microsomes[29,40]. ADH is present in the cytosol where it converts alcohol to acetaldehyde and other metabolites. In this reaction nicotinamide adenine dinucleotide (NAD^+) is reduced by two electrons to NADH generating a highly reduced environment in hepatocytes. The increased NADH/NAD ratio favors hepatic triglyceride accumulation. In addition, excess NADH may promote fatty acid synthesis. Acetaldehyde inhibits protein synthesis and may be linked to tumor development[41]. Cytochrome P450 enzymes (Cyp2E1, 1A2, and 3A4) present mainly in microsomes and endoplasmic reticulum also contribute to alcohol metabolism into acetaldehyde at high concentration of ethanol. Catalase in the peroxisomal pathway requires hydrogen peroxidase (H_2O_2) to oxidize alcohol into acetaldehyde and water. Acetaldehyde is a highly reactive and toxic byproduct to hepatocytes that may contribute to tissue damage because it forms a variety of protein and DNA adducts that promote glutathione depletion, lipid peroxidation, and mitochondrial damage[40,41]. It also contributes to the changes in the redox state of the cell and the formation of reactive oxygen species (ROS)[41]. The acetaldehyde produced from alcohol oxidation is rapidly metabolized into NADH and acetate by aldehyde dehydrogenase (ALDH) in mitochondria. The product of acetaldehyde breakdown is rapidly removed from the liver and is metabolized into CO_2 *via* the TCA cycle in the heart, skeletal muscle and the brain. Genetic variations in ADH and ALDH influence the susceptibility of developing alcoholism and alcohol related injury. The nonoxidative pathway is minor in normal conditions and leads to the formation of fatty acid ethyl ester

(FAEE) and phosphatidyl ethanol (PEth). The products of the nonoxidative pathway have pathological and diagnostic significance. Both PEth and FAEE are poorly metabolized; they accumulate in the liver and interfere with cell signaling. Because of their intermediate half-life and tendency to accumulate, non-oxidative ethanol metabolites can be used as biomarkers for alcohol consumption[42]. A second nonoxidative pathway occurs at high circulating levels of alcohol and involves phospholipase D (PLD), which converts phosphatidylcholine to generate phosphatidic acid (PA) and subsequently phosphatidyl ethanol[40]. Phosphatidyl ethanol is poorly metabolized and its effects on the cell are unknown, however it might interfere with the production of PA and disrupt cell signaling[40].

ROLE OF MITOCHONDRIA IN LIVER PHYSIOLOGY

Mitochondrial structure

Mitochondria are organelles with double membrane structure. The outer membrane delimits the intermediate space while the inner membrane delimits the mitochondrial matrix. The structure of the inner membrane is highly complex and consists of the complexes of the electron transport system, the ATP synthetase complex, and transport proteins. The matrix contains a highly concentrated mixture of enzymes involved in the oxidation of pyruvate and fatty acids (FAs) in TCA cycle. Eukaryotic cells contain nuclear and mitochondrial DNA (mtDNA) genomes sequestered into distinct subcellular compartments. Human mtDNA is found in the matrix and consists of 13 structural genes that encode subunits essential for respiratory complexes Ⅰ, Ⅲ, Ⅳ, and Ⅴ of the mitochondrial respiratory chain involved in the generation of ATP. Each mitochondrion contains 5-10 copies of mtDNA and each cell contains a high copy number of mtDNA. It is considered that the number of normal mtDNA copies must fall below 20%-40% of basal levels to induce mitochondrial dysfunction and the adverse effects. The mitochondrial matrix possesses an incomplete mitochondrial DNA repair system, and is highly sensitive to ROS-induced oxidative damage due to its proximity to the inner mitochondrial membrane where most of the ROS are produced[43-45].

Mitochondrial function

Mitochondria are the power producer of the cell which plays a central role in the generation of energy from nutrient oxidation. Hepatocytes are rich in mitochondria; each hepatocyte contains about 800 mitochondria occupying about 18% of the entire cell volume. Mitochondria have a unique role in the liver compared to other organs as they participate in glucose, lipids and protein metabolism. Mitochondria play an essential role in the cell as they provide the majority of cellular energy in the form of ATP; generate and regulate ROS; buffer cytosolic Ca^{2+} and regulate apoptosis. Carbohydrates and fats are oxidized in the mitochondria to produce energy. Glucose is converted into pyruvate within the cytosol, transported to the mitochondria where it is converted to acetyl-CoA. Acetyl-CoA undergoes TCA cycle resulting in CO_2, water and energy. FAs in the liver originate from the diet, adipose tissue lipolysis, or hydrolysis of intracellular stores or *de novo* lipogenesis. These free FAs (FFAs) are metabolized through oxidation, ketogenesis or esterification into triglyceride. Together with the muscle, the liver is the main site for mitochondrial fatty acid oxidation. The oxidation of FFAs occurs mainly in the mitochondria of hepatocytes where FFAs are converted by carnitine palmitoyltransferase-1 (CPT1) into acylcarnitine which is transported into the mitochondrial matrix. FFAs oxidation into acetyl-coenzyme A (acetyl-CoA) and its subsequent oxidation by the TCA cycle generates reduced NADH and reduced flavine-adenin dinucleotide ($FADH_2$). NADH and $FADH_2$ are the electron donor and transfer the hydrogen/electron to an oxygen molecule, *via* a variety of redox components in complex Ⅰ through Ⅳ in the mitochondrial respiratory chain located in the inner mitochondrial membrane[46]. The flow of electron in the respiratory chain is coupled with pumping of protons from the mitochondrial matrix into the inter-membrane space, thus creating an electrochemical gradient across the membrane[46]. When ATP is low, protons re-enter the matrix trough ATP synthase and the energy released initiates ATP synthesis[46]. Although most of the electrons end up in water, the insulation of complexes Ⅰ and Ⅲ of the respiratory chain from oxygen in not perfect[46]. Excessive electron flow to the respiratory chain results in accumulation and leakage of electrons at these two sites which react with oxygen to produce ROS[47]. About 1%-2% of mitochondrial oxygen consumption results in ROS production under normal condition[48], 90% of cellular ROS are produced in the mitochondria[49]. Mitochondria play an important role in ROS homeostasis as they are the main site for ROS generation but can also be a target for excessive ROS exposure. The ROS production occurs through reduction of oxygen to superoxide (O^{2-}) by complex Ⅰ and Ⅲ of the electron transfer chain (ETC). Under normal conditions Mn-SOD located in the matrix of mitochondria converts the O^{2-} to H_2O_2 which is subsequently reduced to H_2O. ROS production in mitochondria is upregulated in conditions where increased NADH and increased membrane potential is not coupled with an increase in ATP production. Excessive production of ROS exceeding the cell's antioxidant defenses can damage components of the cells such as lipids, proteins and nucleic acids (particularly mtDNA) leading to oxidative stress and ultimately apoptosis. This can be observed in conditions of increased oxidation of FFAs such as in NASH[50] and when levels of NADH are augmented due to alcohol metabolism in alcoholic steatohepatitis[45].

MITOCHONDRIAL ALTERATION IN ALD

Recent studies have suggested that chronic ethanol administration causes changes in the mitochondrial morphology and function in both animal models and humans. The mitochondria are often enlarged and altered and these structural changes are associated with the development of fatty liver in the rat[51] suggesting that chronic ethanol treatment affects hepatic energy metabolism. With the exception of one study that showed an increase in mitochondrial respiration in mice[52], most studies in rats and in humans have shown altered mitochondrial respiration. The mechanism behind the species difference between the rat and mouse is unknown. Hepatocytes isolated from mice fed ethanol containing diet showed lower fatty acid oxidation and increased lipid synthesis. In the rat, chronic ethanol administration alters mitochondrial oxidative phosphorylation in the liver by inhibiting the synthesis of proteins of the respiratory complexes[53]. Lower oxidation capacity in combination of the reducing environment induced by ethanol creates conditions of O^{2-} formation and ROS production. As mentioned above, mtDNA, which encodes the subunits of the electron transport chain and the ATP synthase, is vulnerable to ROS due its proximity to the source (the inner membrane) of cellular ROS. Damage of mtDNA will in turn impair cellular energy metabolism and enhances ROS formation. Strong evidence indicates that oxidative stress and dysregulation of redox-sensitive signaling pathways are central to the pathobiology of ALD. It has been shown that a single dose of ethanol was able to damage mtDNA and cause cell toxicity[45]. Other abnormalities that have been described as a result of ethanol treatment are decreases in ATP levels. Oxidative stress can cause cellular apoptosis *via* both mitochondria-independent (involving death receptor of the tumor necrosis factor (TNF) receptor gene family) and mitochondria-dependent (caused by intracellular stresses such DNA damage and ROS) pathways. Hepatocyte apoptosis has been observed in patients with alcoholic hepatitis[54]. One of the mechanisms proposed to explain alcohol-induced hepatocyte apoptosis is the release of cytochrome C in the cytosol where it promotes caspases activation. The role of alcohol in ROS production, the induction of the mitochondrial cell death pathway and the possible mechanisms involved have been recently discussed in[55].

Acetylation is an important posttranslational modification that regulates proteins. Recently, sirtuins, a family of NAD^+ dependent deacetylases have been identified. In mammals, sirtuins are a family of seven proteins (SIRT1-7) that have been shown to be involved in longevity, DNA repair and the control of metabolic enzymes. Three sirtuins SITR3, SIRT4 and SIRT5 are localized within the mitochondrial matrix[56]. Interestingly, SIRT3-deficient mice show increased mitochondrial protein hyperacetylation but not SIRT4 and SIRT5 deficient mice suggesting that SIRT3 is a major mitochondrial deacetylase[57,58]. Chronic alcohol consumption induces a global acetylation of proteins mainly mitochondrial proteins indicating a role of the acetylation of mitochondrial proteins in mitochondrial biology. At least 20% of mitochondrial proteins are acetylated including proteins of TCA cycle, oxidative phosphorylation, β-oxidation and the urea cycle[59]. Therefore, Sirtuins have been implicated in the regulation of mitochondrial number, turnover and activity and have been proposed to play a role in the pathogenesis of alcoholic liver disease[60]. Chronic ethanol administration impairs hepatic lipid metabolism pathways largely by modulating SIRT1 (a nuclear sirtuin) and causes development of fatty liver. Ethanol decreases hepatic SIRT1 in rodent models suggesting a role of ethanol and SIRT1 in the regulation of mitochondrial energy metabolism and mitochondrial biogenesis. SIRT1 regulates lipid metabolism by deacetylating the sterol regulatory element-binding protein-1c (SREB-1c) and PPARγ coactivator 1α (PGC-1α); thus it increases fatty acid synthesis and decreases fatty acid β-oxidation (deacetylation of PGC-1α increases its activity; deacetylation of SREBP-1c decreases its activity). In addition, evidence suggests that mitochondrial biogenesis is regulated at least in part by PGC-1α suggesting that ethanol mediated reduced deacetylation of PGC-1α would inhibit mitochondrial biogenesis[61]. More recent studies, have demonstrated that chronic alcohol treatment specifically induced a small noncoding micro RNA (miRNA) (miR-217) in AML-12 hepatocytes and in mouse livers[62]. Ethanol induced expression of miR-217 reduced SIRT1 expression which in turn results in an increase in lipogenic enzymes [acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), and stearoyl-coenzyme A desaturase 1 (SCD1)] and a decrease in genes involved in fatty acid oxidation [PPARα, PGC-1α, and acyl-CoA oxidase (*AOX*)][60,62]. In addition miR-217 modulation of SIRT1 has been recently shown to regulate lipin-1 which is a crucial regulator of hepatic lipid metabolism[62]. Lipin-1 deficiency aggravated the defect in fatty acid oxidation and lipoprotein secretion induced by alcohol in mice fed the modified Lieber-DeCarli ethanol-containing low-fat diets for 4 wk[62] suggesting a role of this microRNA in the development of ALD. It is not known how alcohol induces miR-217 but it is suggested that the products of ethanol metabolism, acetaldehyde and acetate, may play a role in this process[62].

Recent studies suggest that sirtuins can modulate ROS levels. As mentioned above, mitochondria are involved in the generation of ROS as well as in the defense against ROS. In addition, mitochondria are themselves target for ROS damage and cell fate. Mitochondrial SIRT3 deacetylates and activates enzymes involved in maintaining physiological ROS levels. SIRT3 reduces ROS species levels through deacetylation and activation of the antioxidant enzyme superoxide dismutase (SOD)[63,64]. SIRT1 is essential for ROS-mediated apoptosis in embryonic stem cells by facilitating mitochondrial localization of p53[65]. SIRT1 also inactivates the P65 subunit of NF-κB through direct acetylation, NF-κB inhibition suppresses the inducible nitric oxide synthase

(iNOS) and nitrous acid production and thus may lower cellular ROS levels[66].

Together the recent findings point to a major role of mitochondria in alcohol induced hepatic fat accumulation. Alcohol consumption results in inhibition of PPAR-α and stimulation of SREBP-1C and the transformation of liver from an oxidizing to a fat-storing organ. Alcohol also induces reactive oxygen species levels and causes liver injury and apoptosis in part by regulating sirtuins levels and enzymes of the antioxidant defense.

CONCLUSION

Alcohol has deleterious effects on liver function. Ethanol and its metabolites destroy the liver over time. Mitochondria play an important role both in hepatic alcohol metabolism and in the bioenergetics of the hepatocyte. In this review we have outline the mechanisms by which alcohol negatively impacts mitochondrial function. The observed changes in mitochondrial function and the alteration in redox status and their implication in alcohol induced hepatic steatosis and the progression of liver disease have been discussed. We also reviewed some of the recent pathways involved in the development of ALD. Future research into the mechanism by which alcohol modulates mitochondrial biogenesis and function are critical for the development of biomarkers and the identification of potential therapeutic targets for the prevention and treatment of human ALD.

REFERENCES

1 **Rehm J**, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 2009; **373**: 2223-2233 [PMID: 19560604 DOI: 10.1016/S0140-6736(09)60746-7]

2 **Bergheim I**, McClain CJ, Arteel GE. Treatment of alcoholic liver disease. *Dig Dis* 2005; **23**: 275-284 [PMID: 16508292 DOI: 10.1159/000090175]

3 **Miranda-Mendez A**, Lugo-Baruqui A, Armendariz-Borunda J. Molecular basis and current treatment for alcoholic liver disease. *Int J Environ Res Public Health* 2010; **7**: 1872-1888 [PMID: 20622998 DOI: 10.3390/ijerph7051872]

4 **Mann RE**, Smart RG, Govoni R. The epidemiology of alcoholic liver disease. *Alcohol Res Health* 2003; **27**: 209-219 [PMID: 15535449]

5 **Morris EM**, Rector RS, Thyfault JP, Ibdah JA. Mitochondria and redox signaling in steatohepatitis. *Antioxid Redox Signal* 2011; **15**: 485-504 [PMID: 21128703 DOI: 10.1089/ars.2010.3795]

6 **MacSween RN**, Burt AD. Histologic spectrum of alcoholic liver disease. *Semin Liver Dis* 1986; **6**: 221-232 [PMID: 3022386 DOI: 10.1055/s-2008-1040605]

7 **Lefkowitch JH**. Morphology of alcoholic liver disease. *Clin Liver Dis* 2005; **9**: 37-53 [PMID: 15763228 DOI: 10.1016/j.cld.2004.11.001]

8 **Crabb DW**. Pathogenesis of alcoholic liver disease: newer mechanisms of injury. *Keio J Med* 1999; **48**: 184-188 [PMID: 10638142 DOI: 10.2302/kjm.48.184]

9 **Méndez-Sánchez N**, Almeda-Valdés P, Uribe M. Alcoholic liver disease. An update. *Ann Hepatol* 2005; **4**: 32-42 [PMID: 15798659]

10 **Arteel G**, Marsano L, Mendez C, Bentley F, McClain CJ. Advances in alcoholic liver disease. *Best Pract Res Clin Gastroenterol* 2003; **17**: 625-647 [PMID: 12828959 DOI: 10.1016/S1521-6918(03)00053-2]

11 **Mendenhall CL**. Anabolic steroid therapy as an adjunct to diet in alcoholic hepatic steatosis. *Am J Dig Dis* 1968; **13**: 783-791 [PMID: 5672729 DOI: 10.1007/BF02233094]

12 **Pateria P**, de Boer B, MacQuillan G. Liver abnormalities in drug and substance abusers. *Best Pract Res Clin Gastroenterol* 2013; **27**: 577-596 [PMID: 24090944 DOI: 10.1016/j.bpg.2013.08.001]

13 **Deleuran T**, Grønbaek H, Vilstrup H, Jepsen P. Cirrhosis and mortality risks of biopsy-verified alcoholic pure steatosis and steatohepatitis: a nationwide registry-based study. *Aliment Pharmacol Ther* 2012; **35**: 1336-1342 [PMID: 22490057 DOI: 10.1111/j.1365-2036.2012.05091.x]

14 **Murphy SL**, Xu JQ, Kochanek DK. Deaths: Final data for 2010. NVSR Volume 61, Number 04. Available from: URL: http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_04.pdf

15 **Llovet JM**, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907-1917 [PMID: 14667750 DOI: 10.1016/S0140-6736(03)14964-1]

16 **Fattovich G**, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; **127**: S35-S50 [PMID: 15508101 DOI: 10.1053/j.gastro.2004.09.014]

17 **Jemal A**, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; **59**: 225-249 [PMID: 19474385 DOI: 10.3322/caac.20006]

18 **El-Serag HB**, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 2007; **132**: 2557-2576 [PMID: 17570226 DOI: 10.1053/j.gastro.2007.04.061]

19 **Savolainen VT**, Liesto K, Männikkö A, Penttilä A, Karhunen PJ. Alcohol consumption and alcoholic liver disease: evidence of a threshold level of effects of ethanol. *Alcohol Clin Exp Res* 1993; **17**: 1112-1117 [PMID: 8279675 DOI: 10.1111/j.1530-0277.1993.tb05673.x]

20 **Bellentani S**, Saccoccio G, Costa G, Tiribelli C, Manenti F, Sodde M, Saveria Crocè L, Sasso F, Pozzato G, Cristianini G, Brandi G. Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group. *Gut* 1997; **41**: 845-850 [PMID: 9462221 DOI: 10.1136/gut.41.6.845]

21 **Becker U**, Grønbaek M, Johansen D, Sørensen TI. Lower risk for alcohol-induced cirrhosis in wine drinkers. *Hepatology* 2002; **35**: 868-875 [PMID: 11915033 DOI: 10.1053/jhep.2002.32101]

22 **Lu XL**, Luo JY, Tao M, Gen Y, Zhao P, Zhao HL, Zhang XD, Dong N. Risk factors for alcoholic liver disease in China. *World J Gastroenterol* 2004; **10**: 2423-2426 [PMID: 15285035]

23 **Sato N**, Lindros KO, Baraona E, Ikejima K, Mezey E, Järveläinen HA, Ramchandani VA. Sex difference in alcohol-related organ injury. *Alcohol Clin Exp Res* 2001; **25**: 40S-45S [PMID: 11391047 DOI: 10.1111/j.1530-0277.2001.tb02371.x]

24 **Stewart SH**, Connors GJ. Ethnicity, alcohol drinking and changes in transaminase activity among heavy drinkers. *J Natl Med Assoc* 2007; **99**: 564-569 [PMID: 17534015]

25 **Iturriaga H**, Bunout D, Hirsch S, Ugarte G. Overweight as a risk factor or a predictive sign of histological liver damage in alcoholics. *Am J Clin Nutr* 1988; **47**: 235-238 [PMID: 3341254]

26 **Naveau S**, Giraud V, Borotto E, Aubert A, Capron F, Chaput JC. Excess weight risk factor for alcoholic liver disease. *Hepatology* 1997; **25**: 108-111 [PMID: 8985274 DOI: 10.1002/hep.510250120]

27 **Uhl GR**, Liu QR, Walther D, Hess J, Naiman D. Polysubstance abuse-vulnerability genes: genome scans for association, using 1,004 subjects and 1,494 single-nucleotide polymorphisms. *Am J Hum Genet* 2001; **69**: 1290-1300 [PMID: 11704927 DOI: 10.1086/324467]

28 **Reed T**, Page WF, Viken RJ, Christian JC. Genetic predisposition to organ-specific endpoints of alcoholism. *Alcohol Clin Exp Res* 1996; **20**: 1528-1533 [PMID: 8986199 DOI: 10.1111/j.1530-0277.1996.tb01695.x]

29 **Levitt MD**, Li R, DeMaster EG, Elson M, Furne J, Levitt DG. Use of measurements of ethanol absorption from stomach and intestine to assess human ethanol metabolism. *Am J Physiol* 1997; **273**: G951-G957 [PMID: 9357840]

30 **Norberg A**, Jones AW, Hahn RG, Gabrielsson JL. Role of variability in explaining ethanol pharmacokinetics: research and forensic applications. *Clin Pharmacokinet* 2003; **42**: 1-31 [PMID: 12489977 DOI: 10.2165/00003088-200342010-00001]

31 **Bjarnason I**, Peters TJ, Wise RJ. The leaky gut of alcoholism: possible route of entry for toxic compounds. *Lancet* 1984; **1**: 179-182 [PMID: 6141332 DOI: 10.1016/S0140-6736(84)92109-3]

32 **Robinson GM**, Orrego H, Israel Y, Devenyi P, Kapur BM. Low-molecular-weight polyethylene glycol as a probe of gastrointestinal permeability after alcohol ingestion. *Dig Dis Sci* 1981; **26**: 971-977 [PMID: 7297377 DOI: 10.1007/BF01314757]

33 **Mathurin P**, Deng QG, Keshavarzian A, Choudhary S, Holmes EW, Tsukamoto H. Exacerbation of alcoholic liver injury by enteral endotoxin in rats. *Hepatology* 2000; **32**: 1008-1017 [PMID: 11050051 DOI: 10.1053/jhep.2000.19621]

34 **Keshavarzian A**, Farhadi A, Forsyth CB, Rangan J, Jakate S, Shaikh M, Banan A, Fields JZ. Evidence that chronic alcohol exposure promotes intestinal oxidative stress, intestinal hyperpermeability and endotoxemia prior to development of alcoholic steatohepatitis in rats. *J Hepatol* 2009; **50**: 538-547 [PMID: 19155080 DOI: 10.1016/j.jhep.2008.10.028]

35 **Keshavarzian A**, Choudhary S, Holmes EW, Yong S, Banan A, Jakate S, Fields JZ. Preventing gut leakiness by oats supplementation ameliorates alcohol-induced liver damage in rats. *J Pharmacol Exp Ther* 2001; **299**: 442-448 [PMID: 11602653]

36 **Parlesak A**, Schäfer C, Schütz T, Bode JC, Bode C. Increased intestinal permeability to macromolecules and endotoxemia in patients with chronic alcohol abuse in different stages of alcohol-induced liver disease. *J Hepatol* 2000; **32**: 742-747 [PMID: 10845660 DOI: 10.1016/S0168-8278(00)80242-1]

37 **Lambert JC**, Zhou Z, Wang L, Song Z, McClain CJ, Kang YJ. Prevention of alterations in intestinal permeability is involved in zinc inhibition of acute ethanol-induced liver damage in mice. *J Pharmacol Exp Ther* 2003; **305**: 880-886 [PMID: 12626662 DOI: 10.1124/jpet.102.047852]

38 **Adachi Y**, Bradford BU, Gao W, Bojes HK, Thurman RG. Inactivation of Kupffer cells prevents early alcohol-induced liver injury. *Hepatology* 1994; **20**: 453-460 [PMID: 8045507 DOI: 10.1002/hep.1840200227]

39 **Nanji AA**, Khettry U, Sadrzadeh SM. Lactobacillus feeding reduces endotoxemia and severity of experimental alcoholic liver (disease). *Proc Soc Exp Biol Med* 1994; **205**: 243-247 [PMID: 8171045 DOI: 10.3181/00379727-205-43703]

40 **Zakhari S**. Overview: how is alcohol metabolized by the body? *Alcohol Res Health* 2006; **29**: 245-254 [PMID: 17718403]

41 **Yu HS**, Oyama T, Isse T, Kitagawa K, Pham TT, Tanaka M, Kawamoto T. Formation of acetaldehyde-derived DNA adducts due to alcohol exposure. *Chem Biol Interact* 2010; **188**: 367-375 [PMID: 20813101 DOI: 10.1016/j.cbi.2010.08.005]

42 **Maenhout TM**, De Buyzere ML, Delanghe JR. Non-oxidative ethanol metabolites as a measure of alcohol intake. *Clin Chim Acta* 2013; **415**: 322-329 [PMID: 23178443 DOI: 10.1016/j.cca.2012.11.014]

43 **Bohr VA**, Anson RM. Mitochondrial DNA repair pathways. *J Bioenerg Biomembr* 1999; **31**: 391-398 [PMID: 10665528 DOI: 10.1023/A:1005484004167]

44 **Bogenhagen DF**. Repair of mtDNA in vertebrates. *Am J Hum Genet* 1999; **64**: 1276-1281 [PMID: 10205257 DOI: 10.1086/302392]

45 **Mansouri A**, Gaou I, De Kerguenec C, Amsellem S, Haouzi D, Berson A, Moreau A, Feldmann G, Lettéron P, Pessayre D, Fromenty B. An alcoholic binge causes massive degradation of hepatic mitochondrial DNA in mice. *Gastroenterology* 1999; **117**: 181-190 [PMID: 10381926 DOI: 10.1016/S0016-5085(99)70566-4]

46 **Fromenty B**, Pessayre D. Inhibition of mitochondrial beta-oxidation as a mechanism of hepatotoxicity. *Pharmacol Ther* 1995; **67**: 101-154 [PMID: 7494860 DOI: 10.1016/0163-7258(95)00012-6]

47 **Murphy MP**. How mitochondria produce reactive oxygen species. *Biochem J* 2009; **417**: 1-13 [PMID: 19061483 DOI: 10.1042/BJ20081386]

48 **Boveris A**, Chance B. The mitochondrial generation of hydrogen peroxide. General properties and effect of hyperbaric oxygen. *Biochem J* 1973; **134**: 707-716 [PMID: 4749271]

49 **Balaban RS**, Nemoto S, Finkel T. Mitochondria, oxidants, and aging. *Cell* 2005; **120**: 483-495 [PMID: 15734681 DOI: 10.1016/j.cell.2005.02.001]

50 **Begriche K**, Igoudjil A, Pessayre D, Fromenty B. Mitochondrial dysfunction in NASH: causes, consequences and possible means to prevent it. *Mitochondrion* 2006; **6**: 1-28 [PMID: 16406828 DOI: 10.1016/j.mito.2005.10.004]

51 **Gordon ER**. Alcohol-induced mitochondrial changes in the liver. *Recent Dev Alcohol* 1984; **2**: 143-158 [PMID: 6729159]

52 **Han D**, Ybanez MD, Johnson HS, McDonald JN, Mesropyan L, Sancheti H, Martin G, Martin A, Lim AM, Dara L, Cadenas E, Tsukamoto H, Kaplowitz N. Dynamic adaptation of liver mitochondria to chronic alcohol feeding in mice: biogenesis, remodeling, and functional alterations. *J Biol Chem* 2012; **287**: 42165-42179 [PMID: 23086958 DOI: 10.1074/jbc.M112.377374]

53 **Wei YH**, Chen YS, Lee JF, Huang JY, Lee CH. Effect of ethanol intake on rat liver mitochondrial respiration and oxidative phosphorylation. *Proc Natl Sci Counc Repub China B* 1990; **14**: 61-68 [PMID: 2247534]

54 **Natori S**, Rust C, Stadheim LM, Srinivasan A, Burgart LJ, Gores GJ. Hepatocyte apoptosis is a pathologic feature of human alcoholic hepatitis. *J Hepatol* 2001; **34**: 248-253 [PMID: 11281553 DOI: 10.1016/S0168-8278(00)00089-1]

55 **Huang JY**, Hirschey MD, Shimazu T, Ho L, Verdin E. Mitochondrial sirtuins. *Biochim Biophys Acta* 2010; **1804**: 1645-1651 [PMID: 20060508]

56 **Hirschey MD**, Shimazu T, Jing E, Grueter CA, Collins AM, Aouizerat B, Stančáková A, Goetzman E, Lam MM, Schwer B, Stevens RD, Muehlbauer MJ, Kakar S, Bass NM, Kuusisto J, Laakso M, Alt FW, Newgard CB, Farese RV, Kahn CR, Verdin E. SIRT3 deficiency and mitochondrial protein hyperacetylation accelerate the development of the metabolic syndrome. *Mol Cell* 2011; **44**: 177-190 [PMID: 21856199 DOI: 10.1016/j.molcel.2011.07.019]

57 **Lombard DB**, Alt FW, Cheng HL, Bunkenborg J, Streeper RS, Mostoslavsky R, Kim J, Yancopoulos G, Valenzuela D, Murphy A, Yang Y, Chen Y, Hirschey MD, Bronson RT, Haigis M, Guarente LP, Farese RV, Weissman S, Verdin E, Schwer B. Mammalian Sir2 homolog SIRT3 regulates global mitochondrial lysine acetylation. *Mol Cell Biol* 2007; **27**: 8807-8814 [PMID: 17923681 DOI: 10.1128/MCB.01636-07]

58 **Kim SC**, Sprung R, Chen Y, Xu Y, Ball H, Pei J, Cheng T, Kho Y, Xiao H, Xiao L, Grishin NV, White M, Yang XJ, Zhao Y. Substrate and functional diversity of lysine acetylation revealed by a proteomics survey. *Mol Cell* 2006; **23**: 607-618 [PMID: 16916647 DOI: 10.1016/j.molcel.2006.06.026]

59 **Sack MN**, Finkel T. Mitochondrial metabolism, sirtuins, and aging. *Cold Spring Harb Perspect Biol* 2012; **4**: [PMID: 23209156]

60 **Fernandez-Marcos PJ**, Auwerx J. Regulation of PGC-1α, a nodal regulator of mitochondrial biogenesis. *Am J Clin Nutr* 2011; **93**: 884S-8890 [PMID: 21289221 DOI: 10.3945/jcn.110.001917]

61 **Yin H**, Hu M, Zhang R, Shen Z, Flatow L, You M. MicroRNA-217 promotes ethanol-induced fat accumulation in hepatocytes by down-regulating SIRT1. *J Biol Chem* 2012; **287**: 9817-9826 [PMID: 22308024 DOI: 10.1074/jbc.M111.333534]

62 **Qiu X**, Brown K, Hirschey MD, Verdin E, Chen D. Calorie restriction reduces oxidative stress by SIRT3-mediated SOD2 activation. *Cell Metab* 2010; **12**: 662-667 [PMID: 21109198 DOI: 10.1016/j.cmet.2010.11.015]

63 **Kincaid B**, Bossy-Wetzel E. Forever young: SIRT3 a shield

against mitochondrial meltdown, aging, and neurodegeneration. *Front Aging Neurosci* 2013; **5**: 48 [PMID:24046746 DOI: 10.3389/fnagi.2013.00048]

64 **Chae HD**, Broxmeyer HE. SIRT1 deficiency downregulates PTEN/JNK/FOXO1 pathway to block reactive oxygen species-induced apoptosis in mouse embryonic stem cells. *Stem Cells Dev* 2011; **20**: 1277-1285 [PMID: 21083429 DOI: 10.3389/fnagi.2013.00048]

65 **Han MK**, Song EK, Guo Y, Ou X, Mantel C, Broxmeyer HE. SIRT1 regulates apoptosis and Nanog expression in mouse embryonic stem cells by controlling p53 subcellular localization. *Cell stem cell* 2008; **2**: 241-251 [PMID: 18371449 DOI: 10.1016/j.stem.2008.01.002]

66 **Lee JH**, Song MY, Song EK, Kim EK, Moon WS, Han MK, Park JW, Kwon KB, Park BH. Overexpression of SIRT1 protects pancreatic beta-cells against cytokine toxicity by suppressing the nuclear factor-kappaB signaling pathway. *Diabetes* 2009; **58**: 344-351 [PMID: 19008341 DOI: 10.2337/db07-1795]

P- Reviewers: Muzyk AJ, Stachowska E
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Liu XM

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1007-9327