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THE ROLE OF OXIDATIVE STRESS AND ANTIOXIDANT DEFENSE SYSTEM IN THE PATHOPHYSIOLOGY OF LIVER DISEASES AND THEIR IMPORTANCE IN TREATMENT

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Oxidative stress reflects the imbalance between the excessive formation of reactive oxygen/nitrogen species (ROS/RNS) and limited antioxidant defenses. A direct consequence of excessive ROS production derives from its interaction with cellular biomolecules, such as DNA, lipids, and proteins, which are modified and may cause cell death. Besides exogenous sources, such as ionizing radiation, diet, metals, pesticides or other toxic compounds, ROS are also generated endogenously as byproducts of a variety of enzymatic reactions and

metabolic pathways that require molecular oxygen and are likely involved in the pathogenesis of different human diseases including liver diseases. Liver is one of the most critical organs in the body due to its numerous functions. Importantly, the metabolism and detoxification of alcohol and drugs are its main tasks which produce ROS as byproducts. In addition, it is responsible for the storage of vitamins (A, B, D, E, and K), glycogen, and minerals like iron and copper which are involved in ROS-generating reactions. Remarkably, all chronic hepatic disorders, independently

from their etiology, share as a common feature a highly oxidative milieu that perpetuates cellular damage and contributes to the progression of fibrosis, cirrhosis, and ultimately hepatocellular carcinoma, meaning that all could benefit from the same therapeutic strategies aiming to boost the antioxidant defense system [1,2,3].

Reactive oxygen species can be produced by exogenous sources such as alcohol, drugs, virus infection, UV light, radiation, stress, and smoking, or endogenous sources during metabolic pathways in which oxygen is involved. The metabolism of molecules like ethanol, drugs (such as APAP), and FFA in hepatocytes induce an increment in ROS formation in the mitochondria that in turn provokes mitochondrial dysfunction. The accumulated ROS can react with cellular biomolecules (lipids, proteins, and DNA) and alter or impede their functioning. The generation of these oxidized adducts extends oxidative damage and favors cellular death. Moreover, ethanol consumption and lipid-enriched diets can lead to the loss of the intestinal barrier integrity permitting the entry of microbial products or saturated-FA to the circulation that release pathogen-associated molecular patterns (PAMPs)/damage-associated molecular patterns (DAMPs) and trigger the activation of cytokines (Il-1 β , Il-6, Tnf α) leading to inflammation. APAP: acetaminophen; ATP: adenosine triphosphate; Ca²⁺: calcium ion; CYP2E1: cytochrome P450 2E1 oxydase; FFA: free fatty acids; HNE-4: 4-Hydroxynonenal; LPS: lipopolysaccharide; MDA: malonaldehyde; MPT: mitochondrial permeability transition; NQO1: NAD(P)H:

Quinone Oxidoreductase 1; OXPHOS: oxidative phosphorylation system; PAMPs: pathogen-associated molecular patterns; ROS: reactive oxygen species [4,5,6].

Due to the predominance of mitochondrial-origin ROS and the involvement of this organelle in liver diseases, attention will be focused in the strategies to attenuate mitochondrial ROS formation. Hepatocytes are well equipped with non-enzymatic and enzymatic antioxidant defense systems that neutralize free radicals. SOD enzyme is the “first line” defense in reducing superoxide radicals formed in the ETC to H₂O₂ and O₂. CAT is a major H₂O₂ detoxifying enzyme. However, mitochondrial expression of CAT is null as the localization of this enzyme is mainly peroxisomal. Therefore, the degradation of mitochondrial hydrogen peroxide is carried out by other alternative antioxidant enzymes. Mitochondrial glutathione peroxidases (Gpx1,4) and various hydroperoxides (PrxIII, Trx2) catalyze the reduction of H₂O₂ in a chain reaction with GSH as the electron donor, and the subsequent conversion of GSH disulfide (GSSG) back to GSH by the NADPH-dependent glutathione reductase (GR). Hence, mitochondrial GSH (mGSH) protects mitochondria from the lack of catalase, implying that its availability is crucial for the appropriate redox maintenance in this organelle.

GSH is exclusively synthesized in the cytosol, thus specific carriers are required to distribute GSH to different compartments including mitochondria. In the liver, GSH is transported into mitochondria via the 2-oxoglutarate carrier

(OGC; Slc25a11) which imports GSH in exchange for 2-oxoglutarate (2-OG). A relevant aspect of GSH transport in hepatic disorders is the dependence of the 2-OG carrier on membrane fluidity which is determined by fatty acid composition and cholesterol content. Increment of the membrane rigidity impairs this transport system, limiting mGSH availability and antioxidant protection. In this sense, previous studies in various models of alcoholic (ASH) and non-alcoholic steatohepatitis (NASH) have reported increased mitochondrial cholesterol which resulted in mitochondrial dysfunction, reduced levels of mGSH and increased susceptibility to cell demise [7,8,9].

Oxidative Stress Caused by Alcohol: Alcohol beverages are widely consumed all over the world; however, excessive alcohol consumption may cause a series of health problems. It was reported that alcohol consumption accounting for an estimated 3.8% of global mortality. Alcoholic liver disease (ALD) may progress from steatosis to more severe liver diseases form, such as hepatitis, fibrosis, and cirrhosis. As a matter of fact, more than 90% heavy drinkers develops fatty liver, and about 30% of heavy drinkers further develops advance forms of ALD. Although pathogenesis of ALD has not been fully elaborated, the direct consequence of ethanol metabolism seems to be related to ROS production, mitochondrial injury and steatosis, which are the common features of acute and chronic alcohol exposure . It is well illustrated that at least three distinct enzymatic pathways are involved in the process of ethanol oxidation. The primary pathway for the ethanol metabolism is

dehydrogenase system. It is initiated by alcohol dehydrogenase (ADH), a NAD⁺-requiring enzyme expressed at high levels in hepatocytes, which oxidizes ethanol to acetaldehyde. Then, acetaldehyde enters the mitochondria where it is oxidized to acetate by aldehyde dehydrogenases (ALDH). The second major pathway to oxidize ethanol is the microsomal ethanol oxidizing system (MEOS), which involves an NADPH-requiring enzyme, the cytochrome P450 enzyme CYP2E1. The MEOS pathway is prompted in individuals who consume alcohol chronically. In addition, infrequently, ethanol can also be oxidized by catalase in peroxisomes. Since this oxidation pathway requires the presence hydrogen peroxide (H₂O₂), under normal conditions, this pathway plays no major role in alcohol metabolism. During the metabolism processes via dehydrogenase system and MEOS system, NADH or NADP⁺ will be produced in bulk, leading to the increase of ROS, which cause oxidative stress resulting in hepatocyte injury, and finally trigger various liver diseases [8,9,10].

The enhanced activation of Nrf2 by pharmacologic molecules or genetic engineering has been shown to protect the liver in different oxidative stress models. For example, in terms of pharmacologic activation of Nrf2, the use of small molecules, such as BHA, oleanolic acid, ursolic acid and CDDO-Im have been reported to show hepatoprotection against liver damage induced by acetaminophen, a famous drug possessing hepatotoxicity. During the process where mitochondria convert acetate into ATP, a significant amount of free radicals are generated, which results in cellular injuries, especially

to mitochondria themselves. Activation of Nrf2 protects mitochondria from oxidative stress via a variety of mechanisms depending on different circumstances, such as increasing antioxidant levels, protecting against mitochondrial permeability transition pore opening, maintaining the mitochondrial redox state, enhancing mitochondrial biogenesis by promoting transcription of nuclear respiratory factor 1 (Nrf1). For fatty liver disease, activation of Nrf2 could facilitate fatty acid metabolism in liver by directly regulating fatty acid metabolism related genes, such as CD36. Regarding the vital role of oxidative stress in chain of liver diseases, various anti-oxidative therapy and antioxidants are proposed to prevent and treat liver diseases. A series of studies have tested the effectiveness of some antioxidants in the treatment of patients with various liver diseases, such as chronic hepatitis C virus infection, alcoholic hepatitis or cirrhosis, and non-alcoholic fatty liver disease (NAFLD). The clinical effects of antioxidants as adjuvants including vitamin E/C, mitoquinone, N-acetylcysteine, polaprezinc silymarin, silibinin and some antioxidant cocktail on chronic hepatitis C patients have been examined has shown clear benefit of antioxidants to interferon based therapy of HCV [11,12,13,14].

Antioxidants for Prevention and Treatment of Alcoholic Liver Diseases:

An obvious avenue of alcoholic liver diseases (ALD) prevention would be abstinence; however, abstinence is not easy to maintain due to the high rate of recidivism in alcoholics. As mentioned above, ALD develops from simple steatosis to more severe disease forms

including hepatitis, fibrosis, cirrhosis, and even hepatocellular carcinoma, which implies that preventing disease development at the early stage would be more effective than receiving treatment at end-stage of liver disease. Notably, TNF, a group of cytotoxic pro-inflammatory cytokines, is thought to play a vital role in initiation of liver damage. Increasing evidence has indicated that oxidative stress might act together with endotoxins to increase TNF production. Increased circulating TNF- α stimulates TNF- α receptors of cell surface, which leads to activation of the stress-related protein kinases JNK and IKK β , resulting in increased production of additional inflammatory cytokines, and reduced insulin sensitivity. Consequently, the inhibition of TNF is regarded as a therapy to block fatty liver and relieve liver injury. Pharmacological and genetic manipulation of TNF have been attempted to treat liver disease. For example, anti-TNF antibodies or knocking out TNF-R1 have been treated to mice to protect against the development of ALD. However, since liver regeneration requires low “basal” contents of TNF, down regulating but not blocking totally TNF activity is a preferred therapeutic intervention for liver disease. With better understanding of the mechanism that regulates the initiation and advancement of ALD, antioxidant therapy could be developed as directed therapy to prevent or treat ALD. It has been demonstrated that many food and plants, such as vegetables, fruits, tea, cereals, medicinal plants, microalgae, edible macro-fungi, and wild flowers, have abundant natural antioxidants, and possess the ability of eliminating free radicals and protecting the

liver from oxidative stress, and thus might be beneficial for liver diseases [15].

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XÜLASƏ

QARACİYƏR XƏSTƏLİKLƏRİNİN PATOFİZİOLOGİYASINDA OKSİDATİV STRESS, ANTIOKSİDANT MÜDAFİƏ SİSTEMİNİN ROLU VƏ MÜALİCƏDƏ ƏHƏMİYYƏTİ

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Oksidləşdirici stress reaktiv oksigen/azot növlərinin (ROS/RNS) həddindən artıq formalaşması və məhdud antioksidant müdafiə sistemi arasında balanssızlığı əks etdirir. Həddindən artıq ROS-un istehsalı onun dəyişdirilmiş və hüceyrə ölümünə səbəb ola bilən DNT, lipidlər və zülallar kimi hüceyrə biomolekulları ilə qarşılıqlı təsirindən irəli gəlir. İonlaşdırıcı şüalanma, pəhriz, metallar, pestisidlər və ya digər zəhərli birləşmələr kimi ekzogen mənbələrdən başqa, ROS həm də molekulyar oksigen tələb edən və müxtəlif insan xəstəliklərinin patogenezinə iştirak edən müxtəlif fermentativ reaksiyaların və metabolik yolların əlavə məhsulları kimi endogen şəkildə əmələ gəlir.

Qaraciyər çoxsaylı funksiyalarına görə orqanizmin ən kritik orqanlarından biridir. Spirtli içkilərdə və narkotik kimi maddələrin mübadiləsində və detoksifikasiyada ROS –un əlavə məhsul kimi istehsalı onun əsas vəzifələrindən biridir. Bundan əlavə qaraciyər vitaminlərin (A, B, D, E və K), glikogenin və ROS-u yaradan reaksiyalarda iştirak edən dəmir və mis kimi mineralların saxlanması cavabdehdir.

Maraqlıdır ki, bütün xroniki qaraciyər xəstəlikləri, etiologiyasından asılı olmayaraq hüceyrə zədələnməsini davam etdirən fibroz, sirroz və nəticədə hepatosellülar karsinomanın irəliləməsinə töhfə verən yüksək oksidləşdirici mühiti bölüşür. Hepatositlərdə etanol, dərmanlar (məsələn, APAP) və FFA kimi molekulların metabolizmi mitoxondriyada ROS əmələ gəlməsinin artmasını sürətləndirir ki, bu da öz növbəsində mitoxondrial disfunksiyaya səbəb olur. Yığılmış ROS, hüceyrə biomolekulları (lipidlər, zülallar və DNT) ilə reaksiya verə bilər və onların fəaliyyətini dəyişdirir və ya maneə törədə bilər. Bu oksidləşmiş əlavələrin əmələ gəlməsi oksidləşdirici zərəri genişləndirir və hüceyrə ölümünə səbəb olur.

Açar sözlər: qaraciyər xəstəlikləri, patofiziologiya, oksidativ stress, antioksidant müdafiə sistemi, müalicə

РЕЗЮМЕ

РОЛЬ ОКСИДАТИВНОГО СТРЕССА И СИСТЕМЫ ANTIОКСИДАНТНОЙ ЗАЩИТЫ В ПАТОФИЗИОЛОГИИ ЗАБОЛЕВАНИЙ ПЕЧЕНИ И ИХ ЗНАЧЕНИЕ В ЛЕЧЕНИИ

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Окислительный stress отражает дисбаланс между избыточным образованием активных форм кислорода/азота (ROS/RNS) и ограниченной антиоксидантной защитой. Прямое следствие избыточного производства ROS вытекает из его взаимодействия с клеточными биомолекулами, такими как ДНК, липиды и белки, которые модифицируются и могут

вызывать гибель клеток. Помимо экзогенных источников, таких как ионизирующее излучение, диета, металлы, пестициды или другие токсичные соединения, ROS также генерируются эндогенно как побочные продукты различных ферментативных реакций и метаболических путей, которые требуют молекулярного кислорода и вероятно участвуют в патогенезе различных заболеваний человека, включая заболевания печени.

Печень является одним из важнейших органов в организме из-за ее многочисленных функций. Важно отметить, что метаболизм и детоксикация алкоголя и наркотиков являются ее основными задачами, которые производят ROS в качестве побочных продуктов. Кроме того, она отвечает за хранение витаминов (А, В, D, Е и К), гликогена и минералов, таких как железо и медь, которые участвуют в реакциях, генерирующих ROS. Примечательно, что все хронические заболевания печени, независимо от их этиологии, имеют в качестве общей черты высокоокислительную среду, которая увековечивает повреждение клеток и способствует прогрессированию фиброза, цирроза и, в конечном счете, гепатоцеллюлярной карциномы, что означает, что все могут выиграть от одних и тех же терапевтических стратегий, направленных на усиление системы антиоксидантной защиты.

Активные формы кислорода могут вырабатываться экзогенными источниками, такими как алкоголь, наркотики, вирусная инфекция, УФ-свет, радиация, стресс и курение, или эндогенными источниками в ходе метаболических путей, в которых участвует кислород. Метаболизм молекул, таких как этанол, лекарства (например, АРАР) и FFA в гепатоцитах, вызывает увеличение образования ROS в митохондриях, что в свою очередь провоцирует митохондриальную дисфункцию. Накопленные ROS могут реагировать с клеточными биомолекулами (липидами, белками и ДНК) и изменять или затруднять их функционирование. Образование этих окисленных аддуктов продлевает окислительное повреждение и способствует клеточной смерти.

Ключевые слова: *заболевания печени, патофизиология, оксидантный стресс, антиоксидантная система защиты, лечение*