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Review

HEME OXYGENASE-1 AND FATTY LIVER DISEASE.

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Summary

Fatty liver diseases are a spectrum of liver pathologies characterized by abnormal hepatocellular accumulations of lipids. This condition may occur in both adults and children, particularly those who are obese or have insulin resistance or following abuse of alcohol consumption. They are classified in Non-Alcoholic Fatty Liver Disease (NAFLD) and Alcoholic Fatty Liver Disease (AFLD). Steatohepatitis is a specific pattern of injury within the spectrum of NAFLD and this pattern is associated with fibrotic progression and cirrhosis. The role of oxidative stress in liver steatosis production and its progression to inflammation leading to steatohepatitis has been discussed in relation to alterations in metabolic and pro-inflammatory pathway. One of the main enzymes responsible for antioxidant activity in the presence of liver damage is the Heme Oxygenase-1(HO-1).The products of the HO-1-catalyzed reaction, particularly carbon monoxide (CO) and biliverdin/bilirubin have been shown to exert protective effects in several organs against oxidative and other noxious stimuli. In this context, it is interesting to note that induction of HO-1 expression contributes to protection against liver damage in various experimental models. The focus of this review is on the significance of targeted induction of HO-1 as a potential therapeutic strategy to protect the liver against fatty liver diseases.

Introduction

Excessive fat accumulation within the hepatocyte is known as hepatic steatosis and such condition has been a prominent feature of some of the most common health problems such as Non-Alcoholic Fatty Liver Disease (NAFLD) and Alcoholic Fatty Liver Disease (AFLD).

AFLD is one of the most prevalent forms of liver disease worldwide and can progress to inflammation (hepatitis), fibrosis/cirrhosis, and ultimately lead to end stage liver injury. The mechanisms, by which ethanol consumption leads to AFLD, are complicated and multiple, and remain poorly understood. In NAFLD the accumulation of intracellular fat results from an imbalance between hepatic fatty acid uptake, lipid synthesis, lipid oxidation, and export *via* VLDL particles.Both NAFLD and AFLD may trig-

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ger a continuous damage to the liver leading to cell injury and progress to their more aggressive or chronic forms like steatohepatitis, liver failure and even irreversible cirrhosis and HepatoCellular Carcinoma (HCC)(1). Liver steatosis is a disease that is not necessarily progressive and is often caused by long-term alcohol consumption. Nevertheless, a wide spectrum of fatty liver diseases has been documented in non-drinkers, ranging from simple steatosis to steatohepatitis. Non-alcoholic steatohepatitis (NASH) is a clinical-pathological condition characterized by a necroinflammatory disorder with the fatty infiltration of hepatocytes(2). NASH is an important clinical entity because it may progress to fibrosis or cirrhosis, with a fatal outcome (3).Patterns of steatosis can be categorized as microvesicular (microsteatosis) and macrovesicular (macrosteatosis) hepatic steatosis (4-7). Microsteatosis refers to tiny lipid vesicles while macrosteatosis refers to a single large fat vacuole (which is greater than the hepatocyte nucleus) in the cytoplasm of the hepatocytes(8). Microsteatosis is usually more severe than simple steatosis and associated with toxin-induced injury, acute viral and metabolic abnormalities (9). Macrosteatosis is generally associated with diabetes, dyslipidemia, obesity, alcohol abuse and hyperlipidemia since it affects determination of insulin resistance (i.e.,interfering insulin signaling) and also increases risk of cardiac complications and cardiovascular disease mortality (10, 11).

Fatty liver might be also caused by several conditions, diseases, or drugs; however, obesity, insulin resistance, and dyslipidemia as well as excess alcohol intake are the most frequent causes of NAFLD or AFLD (12). The natural course of fatty liver is strongly dependent on etiology and comorbidities. For example, in NAFLD, 20%-30% of patients with steatosis will develop NASH, which is associated with increased total and cardiovascular mortality (13). NASH is complicated by liver cirrhosis in 2%-5% of patients (12). Co-occurrence of steatosis and chronic HCV infection has been found to be associated with poorer outcome when compared to patients without steatosis (14)

Oxidative stress is becoming recognized as a key factor in the initiation and progression of chronic liver disease (CLD) such fatty liver diseases and hepatocarcinogenesis.

The role of oxidative stress in liver steatosis production and its progression to inflammation leading to steatohepatitis has been discussed in relation to alterations in metabolic and pro-inflammatory transcription factors expression. Increased levels of reactive oxygen species (ROS) and lipid oxidation products and decreased levels of antioxidant enzymes such as superoxide dismutase (SOD) and catalase and antioxidant compounds such as glutathione have been observed in patients of NAFLD/NASH compared with those observed in the healthy subjects (15).

Many studies showed potential beneficial effects of radical-scavenging antioxidants molecules, which are also the basis of other bioactivities and health benefits, such as anticancer, anti-aging, and protective action for cardiovascular diseases, diabetes mellitus, obesity and neurodegenerative diseases (16-21). As far as the cellular injury is triggered, cells activate several mechanisms in the attempt to restore redox balance promoting cell survival(22-24). Among such mechanisms, heme oxygenase (HO) seems to play a major role. HO, the first and the rate-limiting enzyme in the catabolism of heme, is also known as heat shock protein 32. It has been demonstrated that HO-1 is a stress-responsive protein induced by various oxidative agents, and plays a fundamental role against the oxidative process (25-29).

In this review, recent findings on the implications of HO-1 in fatty liver diseases are considered, with particular emphasis placed on targeted HO-1 induction to hepatic protection.

Heme Oxygenase-1 (HO-1)

HO is a widely distributed enzyme in mammalian tissues, and its main function is associated with the degradation of heme to iron, carbon monoxide (CO), and biliverdin, the latter being converted

to bilirubin by the cytosolic enzyme biliverdin reductase (30). There are two HO isoforms, the constitutive HO-2 and the inducible HO-1. HO-1 is up-regulated during alterations in cellular redox and plays a role in numerous of pathological conditions, including metabolic syndrome (31-35). (Figure 1)

HO-1 is a highly attractive and interesting candidate stress-response protein, which may play key role(s) in mediating protection against oxidant-mediated damages. These effects are completed by the intriguing biological activities of the catalytic byproducts, carbon monoxide (CO), iron, and bilirubin(36, 37). In fact, it has demonstrated that overproduction of biliverdin and bilirubin acts as an antioxidative defense mechanism such as LDL oxidation inhibition (38).

An important role of the HO reaction in regulating liver function is to generate CO, which activating the soluble guanylatecyclase triggers an intracellular cyclic guanylyl mono-phosphate (cGMP) increase similar to that attributable to nitric oxide (NO)(39).It was demonstrated that CO, by its inflammatory effects, involves the MAP kinase signaling pathway and acts as an endogenous regulator that is necessary for maintaining microvascular blood flow in the liver (40, 41). Many studies showed that increase of HO-1 activity and expression results in the reversal of oxidative stress and decrease in liver damage (42). Moreover, HO-1 induction by hemin protects against obesity-induced metabolic dysregulation by reducing adipose inflammation (43), which causes mitochondrial dysfunction leading to loss of oxidative capacity and hepatic lipid accumulation (44, 45).The increase of HO-1 expression induces phosphorylation of AMP-activated protein kinase (AMPK), and decrease fatty acid synthase (FAS) resulting in an increase in insulin sensitivity and the lowering of fatty acid levels(46, 47). Moreover, it was recently shown that induction of HO-1 attenuated the development of fatty liver and decreased lipid droplet size in obese mice(48).

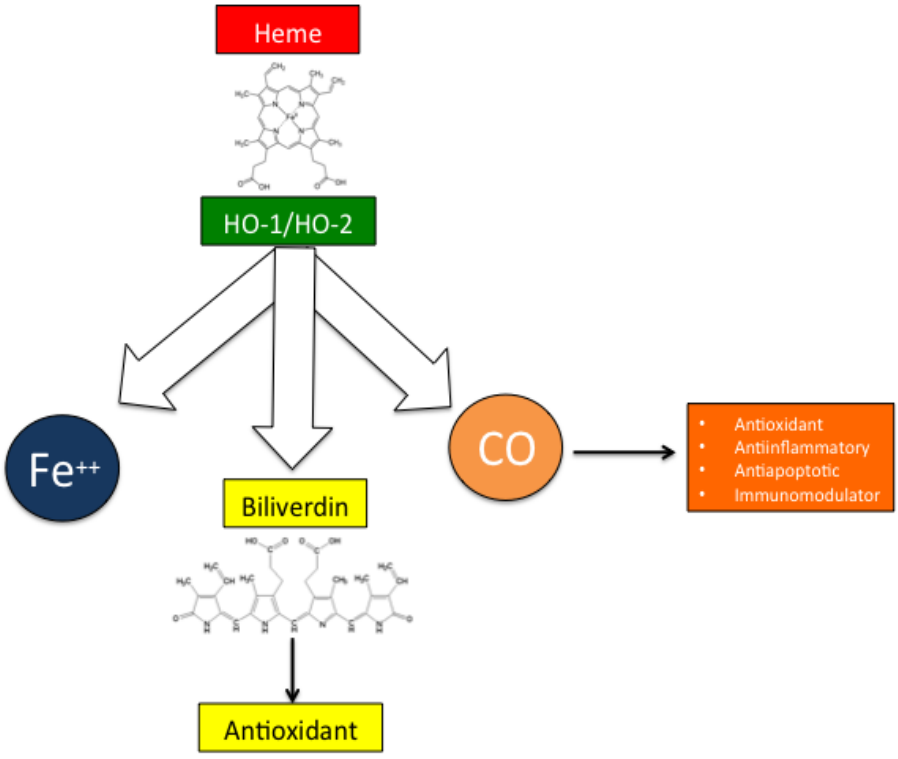

Figure 1. Schematic representation of enzymatic reaction catalyzed by the heme oxygenases isoforms and biological effects of its byproducts.

Finally, HO-1 has been shown to be protective in several disparate models of hepatic injuries (Amersi et al., 1999, 2002).

HO-1 and AFLD

Chronic alcohol exposure and consumption of more than 30 g of pure alcohol was demonstrated to significantly increase the risk of fatty liver disease. (49-51). Susceptibility factors included female sex, obesity, and cigarette smoking as well as coexistence of other hepatic disorders, such as hepatitis B or C virus infection, NAFLD, or hemochromatosis (52).Alcohol is metabolized *via* two main pathways in the liver: the oxidative pathway and the non-oxidative cytochrome P450 2E1 pathway.The first pathway is mediated by the alcohol dehydrogenase (ADH),which converts ethanol to acetaldehyde, and acetaldehyde dehydrogenase (ALDH),which metabolizes to acetate by the mitochondrial enzyme ALDH (53-55).The reactions are both coupled to the reduction of nicotinamide adenine dinucleotide (NAD) to nicotinamide adenine dinucleotide-hydrogen (NADH) (56, 57).Excess NADH has deleterious effects on gluconeogenesis and fatty acid synthesis . Acetaldehyde was found to induce lipogenesis by increasing SREBP-1c expression (58). Increased fatty acid synthesis leads to the accumulation of fatty acid intermediates, such as malonyl-CoA, which suppresses fatty acid transport into the mitochondria and their oxidation by CPT-1 (59) .

The transcription factor for genes PPARα , inhibited by alcohol *via* its metabolite acetaldehyde, is implied in oxidation transport, and export of fatty acids (60-64). In PPARα deficient mice, chronic ethanol feeding was correlated with progressive intrahepatic triglyceride accumulation because there is β-oxidation decrease and alterations in Krebs's cycle and the electron transfer chain (65). Alcohol feeding resulted in dysfunction of ALDH2 and aldehyde accumulation, in a mouse model. Pharmacological activation of ALDH2 reversed alcoholic steatosis in these mice. (66)

Several studies found that HO-1 could defend against ethanol-induced liver damage(67). Alcohol abuse increased the hepatic malondialdehyde (MDA) levels, which is an oxidative stress marker, and the triglyceride, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. The HO-1 inducer hemin,resulted in upregulation of hepatic HO-1 gene expression, reduced ALT and AST levels, triglyceride, the MDA and significantly attenuated the severity of liver injury. A contrary effect was observed with the HO-1 inhibitor zinc protoporphyrin IX (ZnPP-IX) that appears in downregulation of hepatic HO-1 gene expression and could not allay alcoholic hepatic steatosis(68).

HO-1 and NAFLD

NAFLD has become the most common cause of elevated liver enzymes in the Western World, affecting 30%-40% of men and 15%-20% of women in the general population (69) and up to 70% of type 2 diabetics (70). It is now considered the hepatic manifestation of the metabolic syndrome, which comprises metabolic disorders, including overweight or obesity hypertension, insulin resistance, and dyslipidemia(71, 72). An imbalance between hepatic fatty acid uptake, lipid synthesis, lipid oxidation, and export *via* VLDL particles are the most common cause of intracellular lipid accumulation in NAFLD. Several studies have stressed the importance of adipose tissue lipolysis in the development of hepatic steatosis and in the increase total fat mass,(73, 74) which is alsoassociated with excess fatty acid uptake into the liver.

The hallmark in the pathogenesis of the disease is the accumulation of triglycerides (TGs) in hepatocytes, followed by increased vulnerability to hepatocyte injury. The pathogenesis involves the "two-hits" hypothesis proposed by day in 1998 (75). The "first hit" is characterized by accumulation of TGs derived from the esterification of free fatty acid (FFA) and glycerol which arises from an disproportion of supply, formation, consumption and hepatic oxidation and disposal of TG (76). Donnely *etal*(77) demonstrated that in NAFLD, the major sources of FFA are adipose tissue lipolysis (59%) and *de novo*lipogenesis (26%) and less so from

diet (15%). The impaired suppression of lipolysis in adipose tissue by insulin due to insulin resistance causes an influx of FFA from adipose tissue in NAFLD (76).Following accumulation of TG in hepatocytes, there is increased susceptibility to inflammatory injury, and this constitutes the "second hit" in the pathogenic pathway. The injury is mediated by increased expression of inflammatory cytokines like tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1β. TNF-α;adipokynes for example leptin and adiponectin which are respectively pro-inflammatory and anti-inflammatory(75, 76); oxidative stress and mitochondrial dysfunction, endoplasmic reticulum stress and gut-derived endotoxemia from bacterial overgrowth among others (75, 76). Fibrosis is the final stage or the "third hit" resulting from an imbalance between the rate of hepatocyte death and hepatocyte regeneration. There is inhibition of hepatocyte proliferation due to oxidative stress. This results in activation of hepatic stellate cells and differentiation into myofibroblasts, which in turn produce excessive matrix and also stimulate recruitment of hepatic progenitor cells (78). The latter proliferate to differentiate into hepatocytes and cholangiocytes, and they can also produce chemokines, which attract inflammatory cells to the liver. This alternate repair response gives rise to distortion in liver architecture with presence of a variable fibrosis, regenerative nodules, and inflammatory cell infiltration(75, 76). A complex interaction of multiple genetic predispositions and environmental factors determine which patient with NAFLD will progress from simple steatosis to NASH and liver cirrhosis (79) .

Several studies suggest that HO-1 forms a cytoprotective module with SIRT1 and together ,within hepatocytes , decrease steatohepatitis, hepatic fibrosis and cardiovascular dysfunction. (80) The HO-1 induction in the liver reduces insulin resistance, diet-induced metabolic imbalance, and hepatic lipid deposition, ROS and also prevents the development of hepatic fibrosis; these effects are mediated by activation of SIRT1 gene expression. SIRT1 is a class III protein deacetylase, a crucial cellular survival protein in combating metabolic imbalance (81).This interaction, between HO-1 and SIRT1 in NAFLD, could develop new biomarkers and therapeutic strategies to fight hepatic dysfunction. This will result in improved quality of life and life expectancy in the obese, insulin resistant patient. (80)

HO-1 and NASH

The estimated prevalence of NASH is 3% -5% in general population (82) , of which about 30% ~ 50% of individuals demonstrate advanced fibrosis or cirrhosis within a decade (78) .Oxidative stress has a principal role in the pathogenesis of NAFLD, Non-alcoholic steatohepatitis (NASH) and hepatic steatosisin fact levels of lipid peroxide are increased in both liver injury(83).This condition is caused by various deleterious processes resulting from an imbalance between the excessive formation of pro-oxidants like ROS and RNS, and lacking of antioxidant defences(84). This imbalance leads oxidative insult and so causes cell death and tissue damage (85).

NASH is a chronic progressive liver disease, characterized by steatosis, balloon degeneration, inflammation, and fibrosis (86). The mechanisms that underlie the pathogenesis of NASH remain still unclear, however the explanation most accepted contemplates the two hit hypotheses (87),

in which the critical "hit" is caused by hepatocellular apoptotic response associated with oxidative stress (88-91) in the transition from benign steatosis to steatohepatitis. Indeed, it was possible to understand that within NASH pathogenesis in the first step there has been a metabolic disturbance characterized by an increase of free fatty acids and de novo lipogenesis, leading to steatosis; the "second hit" includes oxidative stress, decreased hepatic ATP production, and induction of proinflammatory cytokines, which triggers necroinflammation leading to the progression of steatohepatitis. Therefore, it conceivable that during the second hit, oxidative stress plays a key role through the formation of proinflammatory cytokines(92, 93).Increased for-

mation of proinflammatory cytokines and stellate cell activation leads to fibrosis and collagen deposition, dysregulation of lysosomal metabolism, and endoplasmic reticulum stress, leading to apoptotic and necrotic cell death (93-95).

Aprevious study focused on the relationship between the mRNA levels of HO- 1 and the evolution of simple steatosis to NASH and it was observed that the levels of HO-1 expression wasparticularly higher in NASH patients than in simple steatosis and in control group.

Positive associations were observed with HO-1 and the degree of NASH since the HO-1 expression and the severity of NASHconcomitantly increased. A similar correlation emerged between the amount of HO-1 and hepatic iron accumulation, in fact, the levels of HO-1 were low in samples in which histological analysis indicated no detectable iron and gradually increased as the iron granules were much more visible. NASH patients with iron grades of 0 or 1 tended to have higher HO-1 expression levels than simple steatosis patients with the same iron grades, this result may be due to the higher levels of lipid peroxidation found in NASH subjects.

Another significant correlation was found between mRNA HO-1 and tissue ferritin levels, and between mRNA HO-1 and hepatic iron concentrations(96). The evolution of simple steatosis in NASH is based on mechanisms which involve multiple cellular adaptations to the oxidative stress when fatty acid metabolism is altered.Products of the HO reaction, CO, biliverdin, and divalent iron, are generated in comparable amounts in both Kupffer cells and hepatocytes; they are biologically active, as such the subject of several studies developed about the regulation of hepatobiliary function (97).The increase of HO-1 expression in parallel to to the progression ofNASH represents an index ofliver disease progression in which the variation of the HO -1 expression is connected to clinical worsening until the onset of fibrosis. However, the involvement of HO-1 has been observed in other liver diseases different from NASH(98, 99). Interestingly studies in a mouse model in which liver damage was induced by lipopolysaccharide (LPS) have shown that in the mice sensitized with a hepatocytes-specific transcription inhibitor d-galactosamine (GalN), the HO-induction led to a prolongation of survival, but not the protection from liver damage, which appeared to be dependent on down-regulation of cytokine synthesis (100).

They were also highlighted potential pro-oxidant consequences of HO activity. The HO reaction releases iron, which could be involved in deleterious reactions that compete with iron reutilization and sequestration pathways. The induction of HO activity may have both pro- and anti-oxidant sequelae depending on cellular redox potential, and the metabolic fate of the heme iron. Several studies indicate that the HO-1 expression exhibits distinct alterations between different stages of liver disease in humans. The sequence of pathogenic events during steatohepatitis progression involves early lipid accumulation and lipid peroxidation in hepatocytes, followed by liver cell injury and inflammation, and eventually conspicuous hepatic fibrosis (101).

In this progression of 'fibrosing steatohepatitis', fibrosis begins in a centrizonal, pericellular location, with fibrotic strands enveloping lipid-laden hepatocytes. Two interrelated processes promoting fibrogenesis in presence of liver injury are oxidative stress and the resultant liberation of cytokines. Moreover, depletion of GSH impairs mitochondria and antioxidant defences as a result of generation of pro-oxidants by lipid oxidases (102, 103). Oxidative damage is prominent in the liver of humans with NASH (104), these findings are consistent with the proposal that hepatocytes are the major site of lipid peroxidation in experimental steatohepatitis; this is also consistent with a proposed role for the generation of pro-oxidants from cytochrome-P450 lipid oxidases and/or mitochondria, both of which are abundant in this cell type and less conspicuous in non-parenchymal cells (105). HO-1 can be activated by exposure to products of lipid peroxidation. The temporal sequence of steatosis/lipid peroxidation, followed by liver cell injury, inflammation, HO-1 upregulation and fi-

brosis is consistent with the clue that lipid peroxidation may be mechanistically involved in the development of fibrosis.Although functional outcome caused by an elevation of hepatic HO-1 expression in cirrhosis has not been fully understood, the current findings led us to consider a pathophysiologic role of HO-1 induction for controlling activities of heme enzymes. Further clinical studies are needed to address whether combined actions of local hemodynamic forces, cytokines, hypoxia, and other unidentified factors could cause alterations in hepatic HO-1 expression under the progression of steatohepatitis(96).

The nuclear factor-erythroid 2-related factor-2 (Nrf2), an important cytoprotective transcription factor, since it functions as a defense system in the development of NASH. For this reason Nrf2 may be a novel therapeutic target for the prevention and treatment of fatty liver and NASH .

It has been shown that curcumin, a phenolic compound derived from the rhizome of Curcuma longa (106), is involved in activation of Nfr2 (107, 108), showing anti-inflammatory and antioxidant activity and anticancer. In turn the Nfr2 is involved in the expression of several antioxidant agents such as GSH, glutathione peroxidase, glutathione synthesis, HO-1, NAD (P) H quinine oxidoreductase 1, glutamate cysteine ligase and many other factors (109-111). It was, in fact, provedwithin studies conducted in mice that the levels of Nrf2 increases during the development of NAFLD and NASH and in correlation to the severity of disease (112). Furthermore, the $Nrf2^{-/-}$livers suffered more oxidative stress than their wild-type counterparts as assessed by a significant depletion of reduced glutathione that was coupled with increases in oxidized glutathione, MDA, and inflammation(113).

Recently, several lines of evidence have suggested that curcumin inhibits oxidative stress and inflammation by triggering Nrf2 signaling. For instance, dietary curcumin increases Nrf2 expression at the transcriptional and translational levels, suggesting that Nrf2–Keap1 interaction enables Nrf2 to translocate to the nucleus (107, 108). Activated Nrf2 binds to the antioxidant-responsive element and initiates the transcription of genes coding antioxidants against oxidative/ nitrative stress and inflammation (114). In addition, it was demonstrated that curcumin could improve insulin resistance, reduce liver MDA levels and increase hepatic GSH content, SOD activity and HO-1 expression, thus confirming the antioxidant effect of curcumin in NASH model rats induced by a high-fat diet. In conclusion, curcumin treatment attenuated insulin resistance, serum lipids, oxidative stress, and liver inflammation in rats with NASH induced by high-fat diet. (115). The results obtained to datesuggest that Nrf2 is involved in NASH and may be a novel therapeutic target for the prevention and treatment of fatty liver disease.

In addition to cytoprotective properties of HO-1, the regulatory mechanisms of this gene have been revealed. A heme-binding factor Bach1 functions as a transcriptional repressor of the gene encoding HO-1. Bach1 forms complexes with small Maf proteins and competes against NF-E2 related factor (Nrf2),which as said, is the major transcriptional activator of *HO-1,* (116)which in turn binds cis-acting antioxidant response element (ARE) enhancers and induces expression of protective antioxidant genes (117). Further studies conducted on mice have shown that have revealed a hepatoprotective role of Bach1 ablation in LPS-induced liver injury(118).Moreover it was showed that HO-1 induction by Bach1 ablation may ameliorate oxidative stress and inflammation, the second hit in NASH pathogenesis and may repress the transition from bland steatosis to steatohepatitis. Surprisingly, in addition to reduction in hepatic damage, Bach1 ablation significantly diminished hepatic steatosis following MCD feeding (119).

Bach1 ablation in mice leads to significant up-regulation of HO-1 mRNA as well as its activity. This was in keeping with several studies that showed data about hepatic expressions of HO-1 mRNA and protein were constitutively high in the absence of Bach1(116).

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