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INVITED REVIEW

Catalase and nonalcoholic fatty liver disease

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Abstract

Obesity and insulin resistance are considered the main causes of nonalcoholic fatty liver disease (NAFLD), and oxidative stress accelerates the progression of NAFLD. Free fatty acids, which are elevated in the liver by obesity or insulin resistance, lead to incomplete oxidation in the mitochondria, peroxisomes, and microsomes, leading to the production of reactive oxygen species (ROS). Among the ROS generated, H_2O_2 is mainly produced in peroxisomes and decomposed by catalase. However, when the H_2O_2 concentration increases because of decreased expression or activity of catalase, it migrates to cytosol and other organelles, causing cell injury and participating in the Fenton reaction, resulting in serious oxidative stress. To date, numerous studies have been shown to inhibit the pathogenesis of NAFLD, but treatment for this disease mainly depends on weight loss and exercise. Various molecules such as vitamin E, metformin, liraglutide, and resveratrol have been proposed as therapeutic agents, but further verification of the dose setting, clinical application, and side effects is needed. Reducing oxidative stress may be a fundamental method for improving not only the progression of NAFLD but also obesity and insulin resistance. However, the relationship between NAFLD progression and antioxidants, particularly catalase, which is most commonly expressed in the liver, remains unclear. Therefore, this review summarizes the role of catalase, focusing on its potential therapeutic effects in NAFLD progression.

Keywords Catalase · Nonalcoholic fatty liver disease · Hydrogen peroxide · Oxidative stress · Steatosis · Steatohepatitis

Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as the accumulation of excessive fat in the liver, with at least 5% of hepatocytes containing triglyceride (TG) or steatosis occurring in at least 5% of the liver volume or weight of patients, who consume less than 30 and 20 g of alcohol per day in men and women, respectively [2]. NAFLD is now the most common liver disease in all age groups, with 14–30% of patients developing the disease because of high obesity and overweight, and has emerged as a serious clinical problem [2].

NAFLD includes a variety of stages from hepatocellular steatosis to inflammatory nonalcoholic steatohepatitis, fibrosis, and cirrhosis [2], and in this review, NAFLD is used as a comprehensive word for these diseases (Fig. 1). The pathogenesis of NAFLD is described in detail below using the "two-hit" model. The first stage of NAFLD is steatosis, which is a simple fatty liver. Steatosis occurs when the cytoplasm of hepatocytes contains more than 5% TG (Fig. 1) [157]. If hepatocyte injury as hepatocyte ballooning and cell death, inflammatory infiltration, and/or fibrosis occurs, nonalcoholic steatohepatitis (NASH) results (Fig. 1) [40]. Cirrhosis is a condition in which hepatocytes are replaced by scar tissue, and 10–29% of patients with NASH develop into cirrhosis within 10 years (Fig. 1) [8].

Most patients with NAFLD exhibit obesity, diabetes, or dyslipidemia, and thus, metabolic syndrome is recognized as the greatest risk factors for NAFLD development [28]. Oxidative stress is also thought to contribute to the progression of simple steatosis to steatohepatitis, fibrosis, and cirrhosis [43], such as by increasing lipid peroxide levels [140]. Antioxidants are abundant in the liver [86], and thus, decreased antioxidant defense is a major factor promoting oxidative stress in patients with NAFLD. Decreases in antioxidant factors including coenzyme Q10, Cu/Zn-superoxide

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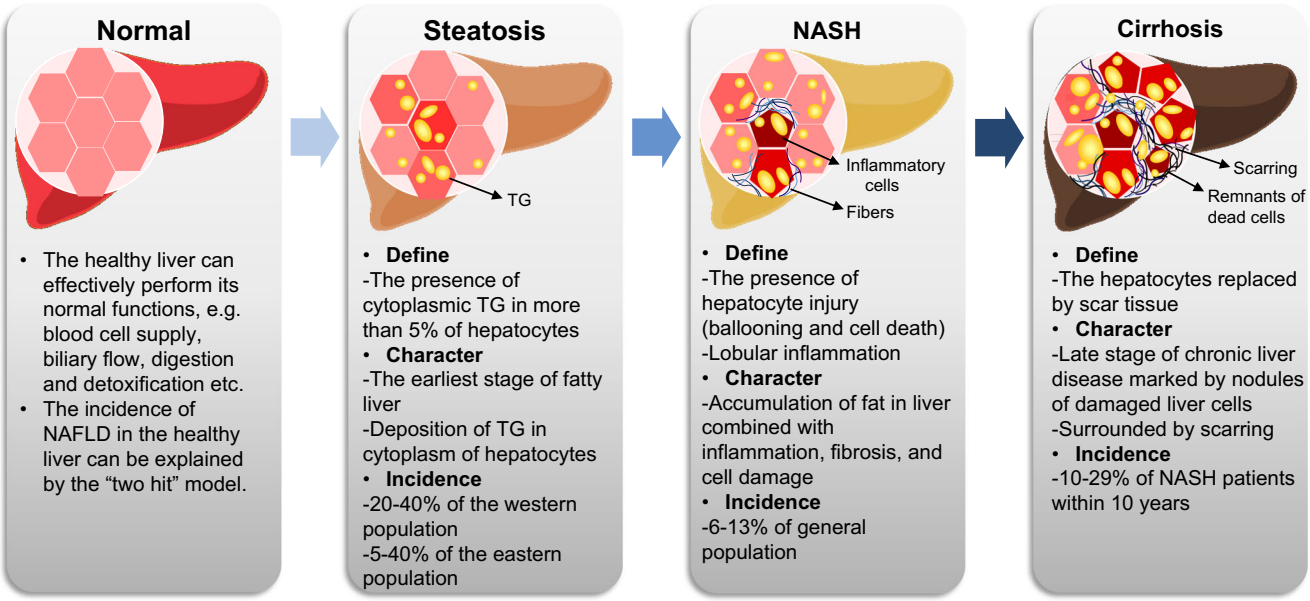

Fig. 1 The diagram of progression of nonalcoholic fatty liver disease. TG, triglyceride

dismutase, catalase, glutathione, and glutathione *S*-transferase correlate with the severity of NAFLD [86, 151, 170]. Machado et al. [97] suggested that expression of antioxidant enzymes was reduced in the liver of NASH mice compared to that of obese steatosis mice, resulting in higher oxidative stress than in obese steatosis mice. The livers of NASH mice showed more fibrosis and inflammation than those of steatosis mice, and indicators of cell death were significantly greater in NASH mice than in steatosis mice. Thus, oxidative stress is an attractive therapeutic target for therapy in patients with fatty liver disease.

The most important intracellular antioxidants in the human body are superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase [153]. Catalase is a common enzyme found in all organisms. Catalase is present in peroxisomes, where it decomposes two hydrogen peroxide (H_2O_2) molecules into two H_2O molecules and O_2 ($2H_2O_2 \rightarrow 2H_2O + O_2$). Both catalase and GPX degrade H_2O_2, but GPX has a higher affinity for H_2O_2 compared to catalase [70]. Thus, H_2O_2 is typically decomposed by GPX under normal conditions. However, as the concentration of H_2O_2 increases, catalase shows a greater contribution to H_2O_2 degradation [169]. Additionally, H_2O_2 is relatively stable among reactive oxygen species, and thus, it can easily move away from its production site to show a concentration gradient [133]. Catalase expression in the cardiac mitochondria is elevated by a high-fat diet, which elevates catalase expression to remove excess H_2O_2 produced by increased lipid metabolism [137]. In another report, cytochrome C oxidase and GPX were not significantly involved in the rate of H_2O_2 consumption of highly purified rat liver mitochondria, while H_2O_2 consumption was significantly inhibited by the catalase inhibitor KCN or aminotriazole [142]. Thus, catalase contributes to mitochondrial protection against endogenous or exogenous H_2O_2, and mitochondrial catalase in the liver may be a new therapeutic strategy for liver disease. Most studies on cytosolic catalase have been performed using erythrocytes. Cytosolic catalase in erythrocytes mainly protects erythrocytes from highly exogenous H_2O_2; when catalase was inhibited, GPX did not prevent H_2O_2-induced oxidative stress [139]. Few studies have examined cytosolic catalase in the liver. In 1984, it was reported that purified rat liver cytosolic catalase showed enzymatic activity reaching the levels of purified peroxisome catalase [144]. In 1992, a study of the changes in peroxisomal and cytosolic catalase activity over time indicated that cytosolic catalase can be incorporated into peroxisomes [49]. This means that catalase is mainly present in peroxisomes, but also contributes to decomposition of H_2O_2 generated at other sites in the cell, such as the mitochondria and cytosol, and is essential for overcoming intracellular oxidative stress.

Therefore, we focus our attention on the relationship between catalase and NAFLD, as the role of catalase in fatty liver development is often overlooked. This review discusses the findings of studies on the activity or expression of catalase in NAFLD models.

NAFLD pathogenesis and oxidative stress

NAFLD exhibits excessive accumulation of TG because of excessive influx of free fatty acids (FFAs) and/or increased de novo lipogenesis without significant alcohol consumption [26]. Although the pathogenesis of NAFLD remains unclear, the "two-hit" model is considered as the most probable cause

of NAFLD (Fig. 2) [43]. FFAs in hepatocytes are transmitted from adipose tissue or produced by de novo synthesis [46]. Hepatic FFAs are mainly used for β-oxidation or synthesized into TG, and NAFLD occurs when β-oxidation is reduced and TG synthesis is increased (Fig. 2). Insulin resistance enhances lipolysis in adipose tissue and increases the inflow of FFAs into the liver. Excess FFAs in liver are mostly synthesized as TG because of β-oxidation overload. The mechanisms of excess fat accumulation and insulin resistance in the liver are the "first hit," while the "second hit" are oxidative stress, lipid peroxidation, proinflammatory cytokines, and adipocytokines derived from adipose tissue. When β-oxidation is overloaded in hepatocytes, reactive oxygen species (ROS) are produced, initiating the "second hit" and leading to the development of NASH from simple fatty liver (Fig. 2) [47].

NAFLD pathogenesis is related to hepatic and adipose tissue insulin resistance and underlying metabolic syndrome, which is a combination of conditions such as diabetes, obesity, and dyslipidemia [25, 64]. For example, people who meet the criteria for metabolic syndrome are at least twofold more likely to develop NAFLD compared to normal people, and more than 90% of patients with NAFLD have metabolic syndrome [91, 100]. Obesity is the most important risk factor for NAFLD. In one study, 74% of obese subjects (30–50% overweight, 534 male) developed NAFLD, which was 4.6-fold higher than the rate in normal people (4079 male) [116]. Among patients who are pathologically obese and underwent bariatric surgery for weight loss, 84–96% have steatosis and 2–12% have severe fibrosis or cirrhosis [18, 41, 45, 57]. The prevalence of NAFLD is estimated to be at least twofold more common among those who meet the criteria for metabolic syndrome [91]. Among patients with NAFLD, more than 90% of cases are characterized by metabolic syndrome [100]. Diabetes was reported in 33–50% of patients with NAFLD, while insulin resistance affected as many as 75% of patients [104].

Oxidative stress may trigger the development stage of NAFLD (Fig. 2). Increased oxidative stress, decreased hepatic ATP, and inflammation impair mitochondrial bioenergetics, function, and morphology [140]. Metabolic diseases such as obesity, diabetes, and dyslipidemia and oxidative stress are related and interact. The serum levels of H_2O_2 and malondialdehyde, which are oxidative stress markers, are significantly higher in patients diagnosed with metabolic syndrome and NAFLD than those with only metabolic syndrome [7]. Additionally, the inflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6 were also significantly higher in patients diagnosed with both diseases than in patients diagnosed with metabolic syndrome alone [7]. Excessive FFA flow into the liver leads to saturation of the oxidative pathway and an incomplete β-oxidation pathway. Incomplete β-oxidation in the mitochondria of liver tissue increases mitochondrial ROS, including superoxide, H_2O_2, and hydroxyl radicals, resulting in DNA mutations and lipid peroxidation [125]. Pessayre et al. [125] also suggested that ROS and lipid peroxidation products contribute to mitochondrial dysfunction and hepatic mitochondrial dysfunction contributes to the genesis of NASH lesions. In NAFLD, increased

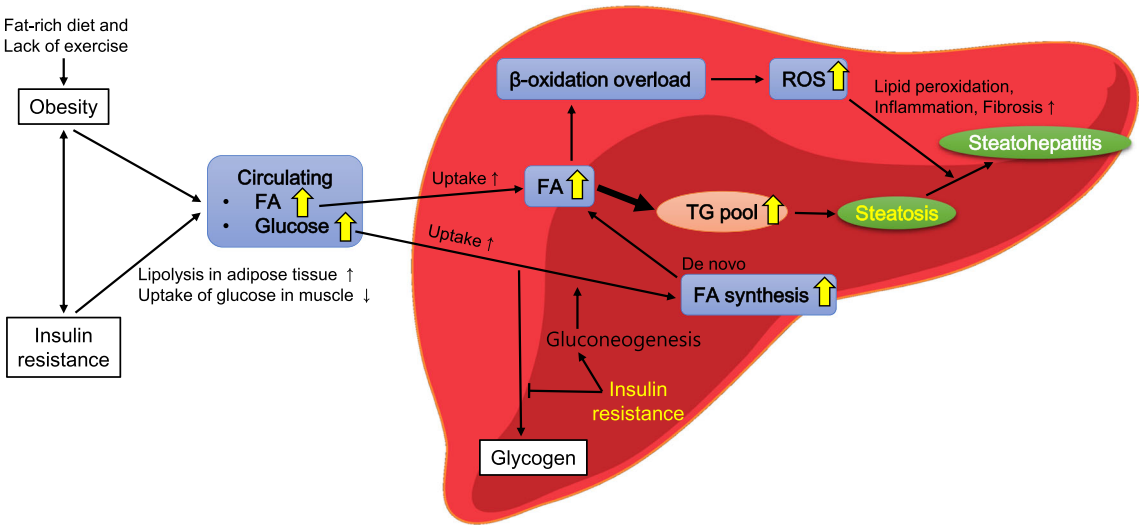

Fig. 2 Mechanisms during the progression to nonalcoholic steatohepatitis by obesity and insulin resistance. The development of NASH is primarily initiated by risk factors including rich food and lack of exercise that cause obesity and insulin resistance. Obesity leads to hyperglycemia and hyperlipidemia and further contributes to insulin resistance in adipose tissue and muscle. Insulin resistance promotes lipolysis in adipose tissue and inhibits uptake of glucose in muscle, further increasing circulating FA and glucose. FA and glucose, which are excessively infused into the liver, undergo oxidation overload and are mainly used for TG synthesis. On the other hand, ROS produced by overload of β-oxidation induces lipid peroxidation, inflammation, and fibrosis and develops steatosis to NASH. FA, fatty acid; TG, triglyceride; ROS, reactive oxygen species

expression and activity of cytochrome P450 2E1 (CYP2E1) is an important source of ROS, which is the starting point of oxidative stress and continuously deteriorates the function of hepatic mitochondria [14]. Additionally, elevated microsomal CYP4A enzymes promoted ROS production in steatosis and ablation of the CYP4A gene in an animal model of steatohepatitis decreased hepatic inflammation and fibrosis [87, 184].

NAFLD pathogenesis and insulin/IGF-1 signaling

Insulin-like growth factor-1 (IGF-1) is mainly secreted in hepatocytes by growth hormone (GH) [147]. The main function of IGF-1 via IGF receptors (IGF1R, IGF2R) in the liver is organ development, growth, and regeneration, and it regulates the cell cycle progression, proliferation, and differentiation of hepatocytes [76]. In general, IGF-1 protects liver function and is known to play a very important role in hepatic hormonal regulation and metabolism [36, 37, 130].

Among the various physiological functions of IGF-1, it plays a role in chronic liver disease process from simple fatty liver to cirrhosis, hepatitis, and hepatocellular carcinoma [1, 112]. Abundant data suggest the role of IGF-1 in the development of chronic liver disease and that IGF-1 administration can reduce fibrosis and improve overall liver function. Efstratiadis et al. [48] showed that IGF-1 levels were low in patients with metabolic syndrome and that IGF-1 is an independent prognostic factor for hepatic steatosis. The results of Völzke et al. [171] and Galiano et al. [56] showed that liver steatosis is associated with low serum IGF-1, and IGF-1 levels were further decreased during the progression to NASH. Interestingly, in the case of adult GH deficiency, GH replacement therapy significantly reversed NASH and reduced inflammation and oxidative stress markers [158], indirectly indicating that IGF-1 has an NAFLD-improving effect in humans.

Additionally, IGF-1 concentration may be important in the pathogenesis of T2DM by regulating the insulin sensitivity or maintenance of beta cell mass [147]. Sandhu et al. [143] showed that elevated serum IGF-1 levels are associated with a decreased risk of developing T2DM. It is unclear whether insulin resistance causes fatty liver or if fatty liver causes hepatic and peripheral (muscle, adipose tissue) insulin resistance. However, there is a close relationship between NAFLD and hepatic insulin resistance and decreased systemic insulin sensitivity. Insulin resistance induces excessive accumulation of TG in hepatocytes by increasing the release of FFAs from adipose tissue. Particularly, it has been shown that hepatic insulin resistance was found to be more important in NAFLD pathogenesis than muscle or adipose tissue insulin resistance using a tissue-specific insulin-resistant mouse model [19]. Hepatic insulin resistance is associated with impaired glycogenesis and increased gluconeogenesis and glycogenolysis [24, 35]. Marchesini et al. [98] reported that the glucose disposal rate, a measure of insulin sensitivity, was reduced by 45–50% in NAFLD compared to that in normal subjects. Additionally, insulin resistance promotes the progression from simple steatosis to NASH and becomes more severe as it progresses to NASH [58, 100]. Hyperinsulinemia directly induces oxidative stress and promotes the secretion of components of the extracellular matrix associated with hepatic stellate cell proliferation and fibrosis progression [121, 154].

In summary, IGF-1 improves insulin resistance, reduces ROS, enhances mitochondrial function, and reduces TG accumulation in hepatocytes. However, little is known about the direct association between IGF-1 and catalase activity. However, IGF-1-deficient mice treated with IGF-1 have been reported to have increased hepatic catalase activity, while other antioxidant enzymes were unchanged [118]. Thus, GH and IGF-1 treatments have shown the potential for liver and mitochondrial protection and antioxidant effects, suggesting the clinical applicability of these hormones. Further studies are needed to clarify the exact mechanism of GH or IGF-1 in regulating catalase activity.

When lipid peroxidation is increased by excessive ROS in hepatocytes, inflammatory cytokines, which promotes apoptosis and inflammation, such as TNF-α, IL-6, and IL-1, are induced in Kupffer cells [13, 140, 167]. ROS, together with the products of lipid peroxidation, increases the secretion of TNF-α, which plays an important role in cell death, inflammation, and fibrosis [13]. TNF-α increases the lipid peroxidation of mitochondrial membranes, exacerbating and further inducing oxidative stress [156]. In vitro studies showed that IL-6 promotes insulin resistance through a variety of mechanisms [73, 78, 148], and human studies have also demonstrated the role of IL-6 in the pathogenesis of type 2 diabetes mellitus (T2DM) [82, 128, 132, 165]. The role of IL-6 in NAFLD pathogenesis is unclear, as the results of studies on the relationship between IL-6 levels and NAFLD are controversial [4, 56, 66, 88, 163, 172]. However, because insulin resistance is included in the "first hit" of NAFLD pathogenesis, the effect of IL-6 on NAFLD is relatively predictable. IL-1α and IL-1β play crucial roles in the conversion from steatosis to steatohepatitis [72].

Serum IL-1 levels are significantly higher in patients with NAFLD with increasing histological grades and severity of fibrosis [83]. The role of various cytokines including TNF-α, IL-6, IL-8, IL-1, and IL-18 in the development of insulin resistance and NAFLD has been widely studied [69, 174, 178]. Recent studies also suggested that inflammation caused by oxidative stress associated with cytokine activation is a cause of NASH development [115]. In conclusion, oxidative stress also increases inflammation and develops NAFLD in the liver tissue through systemic circulation.

Mechanisms regulating the activity and expression of catalase

Mammalian catalase expressed in humans, rats, and mice is a 240-kDa heme-containing protein of tetramers. It is encoded by a single structural gene that is highly evolutionarily conserved [15, 111, 134, 136], approximately 33 kb in length, and comprises 13 exons and 12 introns [111, 134, 136]. Catalase expression in mammals is regulated in a tissue-specific manner [38, 103]. Catalase expression levels between tissues, with the highest levels found in the liver, kidney, and blood and lowest levels found in the connective tissue and brain [5, 123, 141]. Catalase is known to be expressed or activated by multiple mechanisms such as genetic, epigenetic, and posttranscriptional processes as well as transcription factors [61]. During the past decade, peroxisome proliferator-activated receptor gamma (PPARγ), organic cation transporter 1 (Oct-1), nuclear respiratory factor (Nrf), and CCAAT-enhancer-binding protein beta (C/EBPβ) have been identified as catalase transcription factors [61].

First, PPARγ is the most well-known activator of transcription of catalase gene and is involved in catalase expression in humans, rats, and mice [61]. The PPAR-response element was detected in the rodent catalase promoters [59, 117] and catalase expression was increased by PPARγ agonists (e.g., 15-deoxy delta prostaglandin J2, pioglitazone, rosiglitazone) in rat oligodendrocytes, cardiomyocytes, fibroblasts, and astrocytes [17, 32, 77, 180]. In addition, the expression of catalase was reduced in the neurons of PPARγ mutant mice, and expression of the prosurvival gene was impaired, leading to further damage resulting from oxidative stress [185]. In human melanocytes, catalase expression was also decreased when PPARγ was inhibited, whereas catalase levels were increased when 2,4,6-octatrienoic acid, a PPARγ activator, was administered [54].

Oct-1 and Nrf are potential activators for catalase expression. The POU (Pit-1, Oct, and Unc)-domain transcription factor Oct1 (POU2F1) regulates target genes, such as peroxiredoxin 2, interferon-activated gene 202B, and tissue inhibitor of metalloproteinase 3, and acts as a sensor of oxidative and metabolic stress [162]. In experiments using human hepatocellular carcinoma cell lines, POU2F1 bound to the catalase promoter at the octamer consensus sequence ATTAAATA and increased the expression of catalase [135]. Hypermethylation of the Oct1 promoter also reduced the expression of Oct1 and subsequently reduced the expression of catalase protein in hepatocarcinoma cells exposed to H_2O_2 [135]. Nrf2, a pleiotropic transcription factor involved in cell defense against oxidative stress, was reported to increase the expression of several antioxidant enzymes including catalase [168]. The expression of catalase in cells such as cardiac fibroblasts, macrophages, and cardiomyocytes isolated from $Nrf2^{-/-}$ mice was significantly lower than that in wild-type (WT) mice [187–189].

Taniguchi et al. [161] showed that C/EBPβ is involved in catalase gene activity by demonstrating that C/EBPβ binds to multiple initiation sites (CCAAT boxes and GT boxes) in the rat reuber hepatoma cell line and regulates gene transcription in the catalase promoter.

Finally, in addition to the various transcription factors identified, recent studies have shown that Akt/protein kinase B in the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) signaling pathway is important in the expression of catalase by modulating the activity of forkhead box O3a (FoxO3a). The FoxO3a transcription factor mainly regulates the expression of antioxidant enzymes such as catalase and mitochondrial SOD in rodents. Suppression of FoxO3a in cardiomyocytes isolated from rat reduced catalase mRNA and protein expression [159] and decreased catalase protein levels in rat vascular smooth muscle cells [90]. Inhibition of the PI3K/Akt pathway inhibited FoxO3a phosphorylation and blocked translocation outside the nucleus. mRNA and protein expression of catalase was increased when LY294002, a PI3K inhibitor, was used to treat rat vascular smooth muscle cells and human MCF-7 cancer cells [60, 90]. FoxO3a regulates catalase expression in cooperation with the transcriptional coactivators PPARγ coactivator 1 (PGC1α) and NAD-dependent deacetylase sirtuin1 (Sirt1). PGC1α is a regulatory factor for mitochondrial function and oxidative metabolism and is involved in regulating gene transcription involved in ROS detoxification. In double-knockout FoxO3a and PGC1α mouse embryonic fibroblast cells, catalase, SOD, and peroxiredoxins were decreased, while there was no effect on catalase expression in these cells with PGC1α single KO and FoxO3a overexpression. Thus, FoxO3a requires PGC1α to induce catalase expression [119]. Sirt1 is also involved in FoxO transcriptional activity and catalase expression. FoxO3a and PGC1α are activated by Sirt1-mediated deacetylation to increase FoxO3a/ PGC1α complex formation and regulate catalase expression [113, 120]. Upon exercise-stimulated Sirt1 activity in the cardiac and adipose tissues of rats, FoxO3a and catalase were increased [53] and Sirt1 inhibition of human proximal tubular cell lines decreased catalase expression, whereas overexpression of Sirt1 increased catalase expression [65].

Although various transcription factors that regulate catalase expression have been identified, further studies of the role of transcriptional regulatory elements in catalase gene expression by oxidative stress such as H_2O_2 are needed.

Catalase and oxidative stress in liver

As described above, not all cases of simple fatty liver progress to steatohepatitis. To produce inflammation and fibrosis in the

simple fatty liver, a major stimulant known as "oxidative stress" is needed [129]. The production of ROS in hepatocytes occurs in the mitochondria [63], microsomes [172, 173], and peroxisomes; particularly, H_2O_2 is produced in the peroxisomal β-oxidation process when mitochondrial β-oxidation is saturated by fatty acid excess or damaged [166]. H_2O_2 is not a radical because it has no unpaired electrons. Therefore, it is relatively less reactive than ROS, but when combined with iron, severe damage can occur. Hydroxyl radical (•OH) is the most toxic and dangerous form of ROS. The hydroxyl radical is among the most powerful oxidizing agents and can react unselectively and rapidly with the surrounding chemicals as soon as it is produced. This hydroxyl radical is generated by the Fenton reaction, and H_2O_2 is the substrate for the Fenton reaction. In the Fenton reaction, iron(II) (Fe^{2+}) is oxidized by hydrogen peroxide into iron(III) (Fe^{3+}) to form a hydroxyl radical and hydroxide ion (OH^-). In 1999, Bonkovsky et al. [20] found that hemochromatosis gene mutations were increased in patients with NASH. Hemochromatosis is a stimulating factor that accumulates iron in hepatocytes and causes oxidative damage by activating the Fenton reaction [152]. Thus, if H_2O_2 is not removed by catalase, hydroxyl radical is generated, resulting in additional oxidative stress.

The role of catalase in protecting cells and tissues against oxidative stress has been extensively studied. As expected, overexpression of catalase in murine fibroblasts, human bronchial epithelial cells, and human umbilical vein epithelial cells was shown to be resistant to toxicity of H_2O_2 and oxidant-mediated injury from exposure to hyperoxia [50, 95, 182]. Additionally, transgenic mice overexpressing catalase were protected following myocardial injury caused by administration of adriamycin and hypertension because of norepinephrine or angiotensin treatment [74, 179]. Thus, catalase plays a role in cellular antioxidant defense mechanisms by suppressing the accumulation of H_2O_2 [68]. According to Ho et al. [68], the degree of antioxidant activity of catalase depends on the type of tissue, and catalase showed an excellent ability to remove H_2O_2 from the liver. This is consistent with a report showing catalase is very highly expressed in the liver [39].

Therefore, catalase is thought to play a very important role in NAFLD and NASH. Abundant experimental results obtained using cells, animals, and humans support this prediction.

Catalase and NAFLD: in vivo and in vitro studies

According to the results of Spitz et al. [150], catalase activity was increased by 20-fold with increase in H_2O_2 concentrations in Chinese hamster fibroblasts. Overexpression of catalase (up to 80%) in *Drosophila melanogaster* did not affect the lifespan of the fly but conferred strong resistance to H_2O_2 [175]. As described above, this supports that catalase is closely related to oxidative stress resistance caused by H_2O_2 (Table 1).

HepG2 cells treated with various concentrations of H_2O_2 (0, 0.25, 0.5, and 1 mM) for 24 h increased the mRNA expression of catalase in a dose-dependent manner [108]. After overexpression of catalase in the cytosol or mitochondria of HepG2 cells, Bai et al. [11] measured intracellular H_2O_2 levels induced by exogenously added H_2O_2 or antimycin A, which led to cytotoxicity and apoptosis. As a result, both cytosolic catalase and mitochondrial catalase were shown to equally decrease H_2O_2 and protect cells from cytotoxicity or apoptosis induced by oxidative stress.

In animal experiments that led directly to the induction of fatty liver using H_2O_2, catalase activity in the liver was significantly increased, while GSH and GPX were significantly lower than in the control group [122]. In this experiment, catalase plays a major role in H_2O_2 decomposition compared to GSH or GPX. Low molecular weight fucoidan extracted from the brown seaweed *Laminaria japonica* Areschoug is known to contribute to the prevention of metabolic syndrome such as diabetes, obesity, hyperlipidemia, and fatty liver. The experimental results of Zheng et al. [186] showed that catalase activity was increased in *db/db* mice treated with fucoidan at 80 mg/kg/day by gavage for 7 weeks, resulting in decreased lipotoxicity-related oxidative stress, thus preventing NAFLD. Thus, obesity/diabetes-induced NAFLD can be prevented by inhibiting oxidative stress via catalase activation. Brady et al. [21] observed that the hepatic mitochondrial and peroxisomal oxidative capacities of obese mice were increased and catalase activity was significantly elevated compared to those of lean mice. The oxidative capacities indicate mitochondrial oxygen consumption (ng-atoms of O consumed/min per mg of protein) and peroxisomal palmitoyl-CoA oxidation (nmol/min per mg of peroxisomal protein). In agreement with the results of Brady et al. [21], Murphy et al. [109] reported that catalase activity and β-oxidation in the peroxisomal fraction of liver from obese mice were increased compared to those in lean mice.

Because oxidative stress contributes to NAFLD (NASH, fatty liver), researchers have examined whether the loss of catalase increases the susceptibility to the disease. Despite feeding of normal diet, catalase KO (CKO) mice showed higher fatty liver compared to the WT mice as age increased [61], and the high-fat diet caused liver injury in only 2 weeks in CKO mice [127]. In a comparison of young (7 weeks) WT mice and old (16 months) WT mice, hepatic H_2O_2 increased and hepatic steatosis, hepatocyte apoptosis, and hepatic fibrosis were reported as hepatic aging parameters [3]. To confirm whether catalase affects the fat accumulation in the liver, first, we administrated a high-fat diet to WT and CKO mice for 4 weeks; fat accumulation was increased in the CKO mice but not in WT mice (Fig. 3a). Next, we analyzed liver

Table 1 Summary of the main characteristics of findings of catalase related to NAFLD

Study	Model	Treatment	Analysis	Response related to catalase	Ref.
In vitro	Chinese hamster fibroblast	10, 20, 30, 40, or 50 μM H_2O_2	Spectrophotometry	Catalase activity increased 20-fold by H_2O_2	[150]
	HepG2	0.25, 0.5, or 1 mM H_2O_2	qRT-PCR	Increased mRNA expression of catalase	[108]
	HepG2	100 μM H_2O_2 or 15 μM antimycin A	Spectrophotometry	Overexpression of catalase in cytosol or mitochondria led to decreased H_2O_2 and protected cells from cytotoxicity or apoptosis	[11]
In vivo	*Drosophila melanogaster*	1.47, 2.35, 2.94, or 5.88 mM H_2O_2	Enzymatic analysis	Overexpression of catalase showed strong resistance to H_2O_2	[175]
	Wistar rats	H_2O_2 (16 mg/kg, i.p., 30 days with 1 day interval)	Enzymatic analysis	Catalase activity of liver was increased, but not GSH and GPX	[122]
	db/db mice	Low molecular weight fucoidan (80 mg/kg/day, gavage, 7 weeks)	ELISA kit	Increased catalase activity and decreased lipotoxicity-related oxidative stress	[186]
	ob/ob mice		Spectrophotometry	Increased hepatic mitochondrial and peroxisomal oxidative capacities and catalase activity	[21]
	ob/ob mice		Spectrophotometry	Increased catalase activity and β-oxidation in peroxisomal fraction	[109]
	Catalase KO mice		Hematoxylin and eosin staining	Progressive fatty liver	[67]
	Catalase KO mice	60% fat HFD	Morphometric and immunohistochemical analysis	Caused liver injury in only 2 weeks	[127]
Study	Design of patients		Sample, analysis	Response related to catalase	Ref.
Human	6 NASH, 6 cirrhosis by HCV, 6 cirrhosis by PBC		Liver biopsy, microarray	mRNA expression of catalase was downregulated in NASH	[151]
	15 steatosis		Liver biopsy, blood, spectrophotometry	Reduced catalase activity of liver and antioxidant capacity of blood	[170]
	35 NAFLD		Blood, spectrophotometry	Reduced catalase activity	[42]
	26 NAFLD		Blood, spectrophotometry	Reduced erythrocyte catalase	[146]
	51 NASH		Blood, spectrophotometry	Reduced catalase activity	[181]
	17 pediatric NASH		Liver biopsy, RT-qPCR	Increased mRNA expression of catalase	[44]
	16 NAFLD		Liver biopsy, blood, spectrophotometry	Increased catalase activity of liver	[124]
	6 NASH		Liver biopsy, qRT-PCR	Increased catalase activity	[12]
	36 NASH		Liver biopsy, qRT-PCR	Increased catalase activity	[108]
	26 NAFLD (including 4 NASH)		Liver biopsy, qRT-PCR	Increased mRNA expression of catalase	[79]
	28 NAFLD (17 steatosis, 11 NASH)		Liver biopsy, qRT-PCR	Increased mRNA expression of catalase	[9]

*For abbreviations, see the text

extracted from 5-, 10-, and 37-week-old WT and CKO mice fed normal chow diet. As a result, there were no morphological differences in the liver between WT and CKO mice aged 5 and 10 weeks, but we observed fatty liver in CKO mice aged 37 weeks (Fig. 3b). Consistent with previous studies [67, 127], these findings suggest that CKO mice were more vulnerable to nonalcoholic fatty liver, which can be caused by a high-fat diet or aging, compared to WT mice.

Catalase and NAFLD: human studies

Clinical studies examining the expression or activity of catalase in fatty liver occurrence showed conflicting results (Table 1).

Several studies reported that antioxidant enzyme activity is decreased as fatty liver worsens and the defense mechanism against oxidative stress in the cytosol and mitochondria is damaged. Screekumar et al. [151] collected liver samples from patients with NASH in the absence of other (viral, drug/toxin, autoimmune, or metabolic) causes of steatosis, cirrhosis by hepatitis C virus (HCV), cirrhosis by primary biliary cirrhosis (PBC), and normal subjects through biopsy and measured hepatic gene expression by high-density synthetic oligonucleotide microarray analysis. In the analysis of hepatic gene expression, the mRNA expression of catalase was significantly downregulated in patients with NASH compared to that in all other groups. Videla et al. [170] analyzed the parameters associated with oxidative stress in the liver for 31 patients with NAFLD. Catalase activities in patients with NASH were significantly reduced by 42 and 48% compared with patients with simple fatty liver and normal subjects, respectively, while changes in hepatic GPX activities were not observed. These changes promote CYP2E1 activity, which increases the production of ROS, free radicals, and reactive mediates, and increased CYP2E1 activity in the liver inactivates SOD and catalase as the disease progresses [87, 93], making the liver more susceptible to oxidative stress. In other in vitro experiments, the enhancement of CYP2E1 activity was shown to cause catalase inactivation and disease progression [51, 81]. Additionally, antioxidative capacity in the blood of patients with NASH was reduced, supporting further lowering of the ferric-reducing ability of plasma (FRAP) values, compared to that of patients with simple fatty liver [170]. FRAP is a simple method for determining the antioxidant capacity by measuring the degree of reduction of ferric to ferrous at low pH using

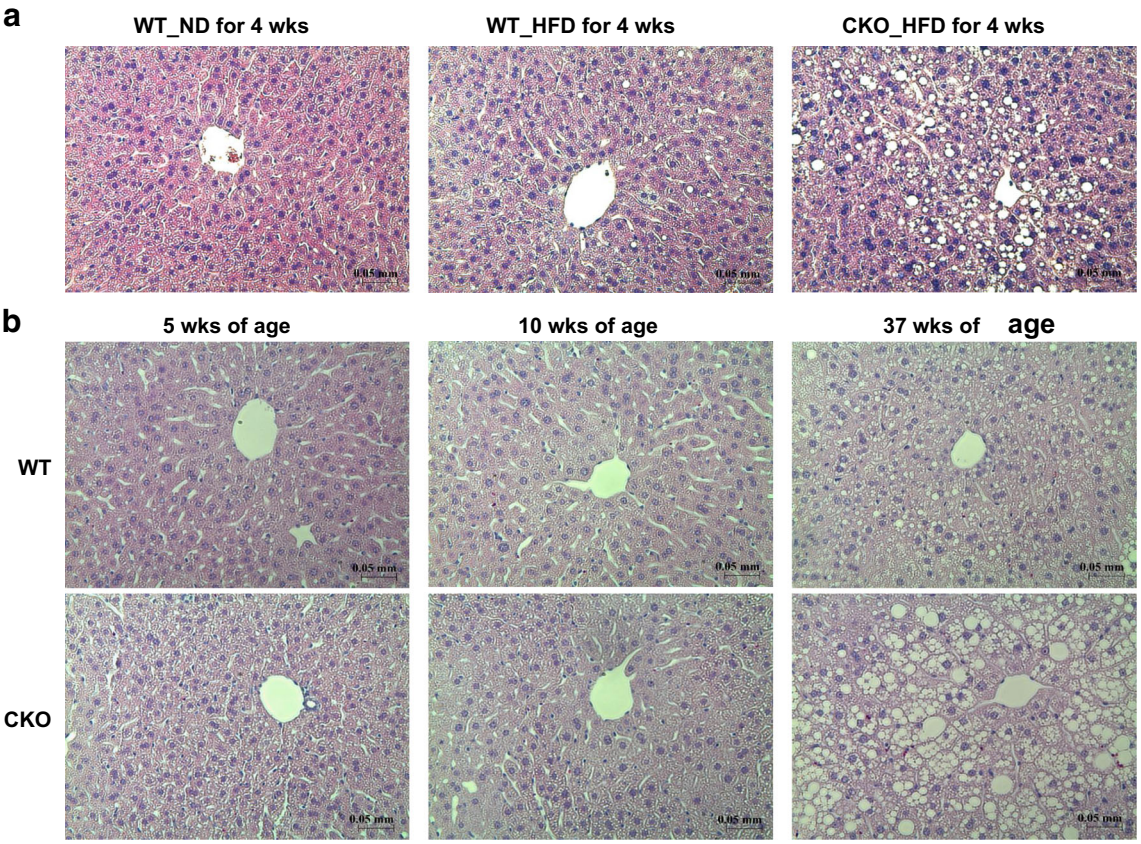

Fig. 3 Histopathological difference in liver of wild-type (WT) and catalase KO (CKO) mice. **a** Hematoxylin and eosin-stained liver sections isolated from mice fed normal diet (ND) or high-fat diet (HFD) (× 200). **b** Liver was extracted from 5-, 10-, and 37-week-old WT and CKO mice fed ND and H&E stained (× 200)

colorimetric assay. In another experiment using blood from 35 patients with NAFLD, catalase activity was reduced by approximately 18.5% compared to that from normal subjects [42]. Because type IV collagen, a marker of fibrosis, was increased in these patients, patients with NAFLD were considered as NASH models rather than a model of simple fatty liver. Additionally, erythrocytic catalase activity was significantly reduced in patients with various stages (17 mild, 7 moderate, and 2 severe) of fatty liver compared to that in normal subjects [146], and 51 patients with NASH also showed significantly decreased systemic catalase activity compared to healthy subjects [181]. Das et al. [42] found that blood is resistant to oxidative stress because it contains various antioxidants such as catalase, SOD, GPX, glutathione *S*-transferase, and glutathione reductase (GSR), but excessive production of superoxide radical can inactivate catalase.

In contrast to the above reports, studies have shown that as the fatty liver is aggravated, catalase activity increases. RT-qPCR analysis of pediatric nonalcoholic steatohepatitis livers revealed a 12.7-fold increase in mRNA expression of catalase compared to that in controls, with no change in GPX and GSR [44]. In 2005, catalase activity in the livers of NAFLD patients was increased by approximately 30% compared to those in normal livers, but there was no difference between the erythrocytes of patients with NAFLD and those of normal subjects [124]. Perlemuter et al. [124] explained that these results indicate that circulating antioxidant defenses did not reflect hepatic peroxidation and that oxidative stress occurs in the liver of NAFLD patients. Baker et al. [12] and Moya et al. [108] reported that catalase activity was increased in the livers of 6 and 36 patients with NASH, respectively, compared to that in normal livers. Kohjima et al. [79] analyzed fatty acid metabolism and antioxidant-related gene expression using liver tissue samples from 26 patients with NAFLD (including 4 patients with NASH). As a result, genes involved in fatty acid oxidation and catalase were overexpressed in patients with NAFLD, which is considered to neutralize ROS produced by fatty acid oxidation. Strikingly, the mRNA expression of catalase was elevated by tenfold in patients with NAFLD compared to that in normal subjects, whereas glutathione synthetase (GSS) was not changed [79]. These results are similar to the results of Desai et al. [44].

The expression levels of catalase in normal, steatosis, and NASH were 0.21, 1.21, and 1.08 (mean of mRNA level of gene compared to that of β-actin), respectively, and significantly enhanced in patients with NAFLD compared to those in normal subjects [9]. These results suggest that catalase expression is altered by the fatty liver stage, although there was no statistical difference between steatosis and NASH. Increased catalase activity in the livers of NASH may be related to increased peroxides, which are produced in the peroxisomes of the fatty liver by increased fatty acid oxidation [20]. This suggests that excessive fatty acids provided by consumption of a high-fat diet increase fatty acid oxidation and thus catalase activity.

Catalase and NAFLD: role of catalase in the development of NAFLD

Based on the above results, the inhibitory effect of catalase on the progression of NASH is shown in Fig. 4. When the concentration of H_2O_2 is increased in hepatocytes, it can diffuse to other cell organelles because of the concentration difference. H_2O_2 induces oxidative stress through the Fenton reaction and leads to lipid peroxidation, inflammation, fibrosis, and cell

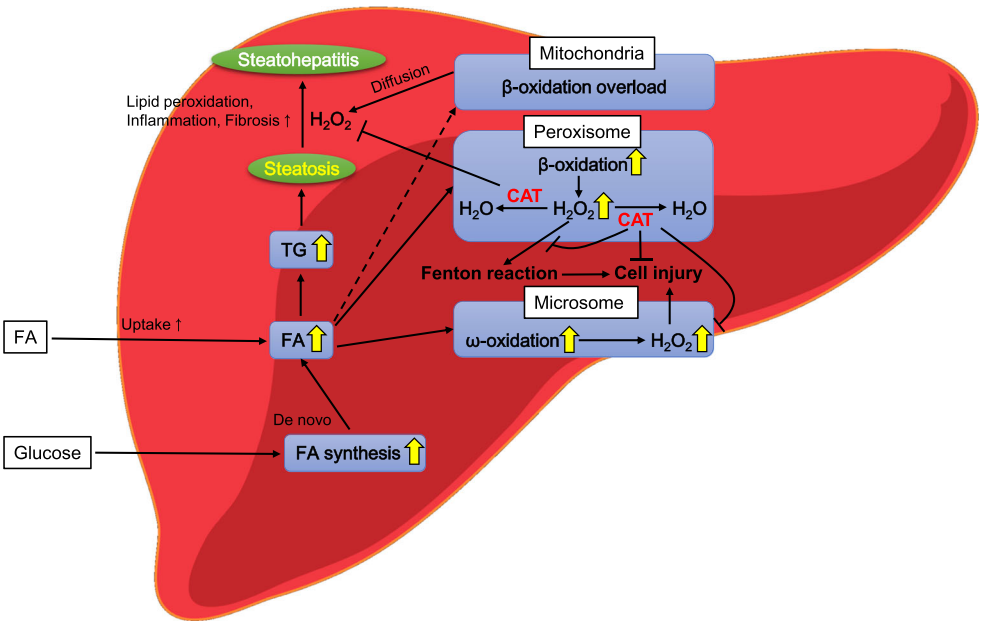

Fig. 4 Mechanisms of catalase function to suppress development of NAFLD. If excessive FFAs in the liver persist, the β-oxidative function of mitochondria becomes overloaded and oxidations of FFAs are activated in peroxisomes and microsomes compensatively. Thus, H_2O_2 is generated in peroxisomes and microsomes, and at the same time, catalase is activated in peroxisomes to decompose H_2O_2. Catalase suppresses the development of steatosis into NASH by blocking Fenton reaction, lipid peroxidation, inflammation, fibrosis, and cell injury by H_2O_2. FA, fatty acid; TG, triglyceride; CAT, catalase

injury. Additionally, steatosis develops into NASH through a combination of oxidative stress and TG pools, which is increased by excessive FFAs (Fig. 4). Catalase can disrupt this sequence of procedures. Particularly, catalase, which shows increased activity when the H_2O_2 concentration is high, can prevent NAFLD from becoming more severe.

In most cell and animal experiments, the activity or expression of catalase was measured during H_2O_2 treatment or steatosis induced by obesity. Because oxidative stress is initiated during an early stage of steatosis, consistently high catalase activity is observed. In a clinical study, catalase expression or activity in patients with NAFLD was not consistent because the process was analyzed at different stages of NAFLD. Thus, catalase has different functions in NAFLD and NASH. Importantly, our research group recently demonstrated that elimination of catalase easily causes steatosis in mice by promoting excessive lipid accumulation. This suggests that catalase plays a protective role as an antioxidant in the livers of NASH, given that oxidative stress is an important therapeutic or preventative target for patients with NASH.

During catalase overexpression in liver disease, the exact mechanism of the main upstream signaling is unclear. Only phenomenological results (catalase activity or mRNA levels up- or downregulated) have been reported for the expression of catalase associated with NAFLD. Catalase activity or mRNA expression increases with H_2O_2 treatment (by ROS stimulation) [108, 122, 150]. A study of human subjects showed that catalase expression differs according to the stage of NAFLD, which is mainly increased in the early stage of NAFLD and decreased in the terminal stage of NASH. Although this may be because many cells are destroyed and become nonfunctional, the exact mechanism of catalase in regulating NAFLD requires further analysis.

NAFLD has been associated with hepatocellular carcinoma (HCC) because of its synergistic interactions with other risk factors of HCC such as chronic HCV infection. HCC is the most common primary liver cancer type, accounting for 85% of liver cancers [101]. HCV and hepatitis B virus (HBV) infection account for approximately 54.9 and 9.5% of HCC cases, respectively, and are a major cause of HCC [183]. Wnt, mitogen-activated protein kinase cascade, and Ras are major molecular biomarkers of HCC pathogenesis, and ROS has been implicated in HCC [101]. The pathogenesis mechanism of HCC known to date is that the oxidative stress is increased in the pre-HCC stage in which hepatic steatosis is present and further exacerbated by the viral core protein [94, 106, 107]. These events ultimately compromise the mitochondrial and cell signaling pathways. At the same time, the viral core protein induces cell proliferation through a mitogen-activated protein kinase pathway containing c-Jun N terminal kinase, p38, and extracellular signal-regulated kinase [80, 101]. Eventually, excessive oxidative stress and abnormal cell proliferation cause HCC. Thus, it has been suggested that oxidative stress contributes to the progression and worsening of HCC and viral hepatitis [110, 155].

In fact, the precise mechanism of antioxidant enzyme disruption in HCC is unknown, but a unique pathological character of HCC is the dramatic downregulation of antioxidant enzymes that constitute the most important free radical scavenger systems such as catalase, SOD, and GPX [27, 92, 114], and HBV or HCV infection reduces antioxidative defense in patients. Kumar et al. [84] measured antioxidant parameters in the blood of 25 patients with chronic viral hepatitis including HCV and HBV. As a result, the catalase activity in the chronic viral hepatitis group was significantly lower than that in the healthy group, but GPX activity was significantly increased and SOD activity was not different. In another study using blood from HCC patients, there was no difference in catalase activity in patients with HBV, while GPX activity was significantly decreased; in patients with HCV, there was no difference in GPX activity, while catalase activity was significantly decreased [94]. In 13 HCC tissue samples infected with HBV, catalase and GPX activities were significantly decreased compared to those in normal tissues. Additionally, catalase activity in the liver tissue of patients with HCC was lower in both tumor tissue and tumor-free tissue compared to that in healthy liver tissues [16].

Changes in the antioxidant systems of cancer cells during tumor growth result in various outcomes, but the antioxidant system is clearly compromised. Thus, a variety of natural and synthetic antioxidants have been used to treat HCC, although it is not known whether these agents can suppress the abnormal regulation of cellular redox by HCC and reduce viral replication [96]. Therefore, improving the antioxidant system in the body by increasing catalase activity may help inhibit tumor worsening.

Chen et al. produced the first transgenic mouse model [*Tg*(*CAT*)] in which expression of catalase was increased in all tissues using an 80-kb genomic DNA fragment containing 5′ and 3′ flanking regions as well as the human catalase gene [29]. This [*Tg*(*CAT*)] mouse showed catalase activity that was up to fourfold higher than in the WT littermates with similar characteristics such as growth rate, body weight, body composition, and fertility [30]. The levels of other major antioxidant enzymes such as SOD and GPX did not differ from those of the WT [30]. Hepatocytes and skin fibroblasts isolated from [*Tg*(*CAT*)] mice showed strong resistance to H_2O_2 but were sensitive to γ-irradiation [30]. Overexpression of catalase in the heart inhibited oxidative injury by doxorubicin, ischemia-reperfusion, and hypoxia-reoxygenation in vivo [74, 89]. Overexpression of catalase in pancreatic islets of mice inhibited STZ-induced diabetes and islets showed resistance to H_2O_2 [177]. Kidney-specific catalase overexpression inhibited ROS generation and apoptosis in the kidneys of STZ-induced diabetic mice [22]. Overexpression of catalase in the heart of mice prolonged the lifespan and inhibited

cardiac protein damage and contractile defects due to aging [176]. Overexpression of catalase has been reported to be more susceptible to radiation, but has more advantages such as antioxidant, antidiabetic, and extended life span. However, a liver-specific catalase overexpression model has not been reported, and further experiments are needed to determine the mechanism of catalase overexpression in the liver.

Summary and future perspective

Because there are no effective therapeutic drugs, the current therapy for NAFLD relies on weight loss and exercise. However, a variety of insulin-sensitive substances, antioxidants, and drugs have been shown to be beneficial. One of the most popular agents is vitamin E. Recent randomized clinical trials comparing vitamin E to placebo showed that vitamin E can be used as a primary drug in adults with fatty liver [85, 145]. However, it is unknown whether vitamin E is effective in diabetic patients with hepatitis, simple hepatitis, or liver cirrhosis due to hepatitis. There are also no data regarding the safety of long-term treatment with high-dose antioxidants [71]. Metformin is an antidiabetic agent that lowers blood glucose and insulin resistance. Nondiabetic patients with NAFLD were tested to determine the effects of metformin compared to vitamin E, resulting in a marked weight loss effect in the metformin group [23]. However, metformin with rosiglitazone did not show any improvement in patients with NASH compared to rosiglitazone alone [164], and metformin did not improve histological features in patients with pediatric NASH [85]. Additionally, Marchesini et al. [99] found that metformin was not superior to dietary intervention and lifestyle changes. Glucagon-like peptide-1 receptor (GLP-1R) agonists are a relatively new class of drugs for treating type 2 diabetes, and typically include liraglutide. Liraglutide has been reported to be not only beneficial as an anti-diabetes agent but also effective in patients with NAFLD by causing weight loss and inducing antioxidant and anti-inflammatory effects [55, 102, 105, 138]. However, while liraglutide administration has been reported to be effective for weight loss and glycemic control, it has no effect on fatty liver contents [126, 160] and has not been shown to affect hepatic fibrosis [149]. Previous studies suggested that liraglutide can improve NAFLD indirectly through obesity and diabetic improvement, but it may not be suitable for directly treating NAFLD. A dietary phenolic compound, resveratrol, is known to have a wide range of positive health effects, including antioxidant, anti-inflammatory, anti-cancer, anti-obesity, anti-diabetes, and anti-aging effects. Resveratrol was shown to prevent metabolic diseases by upregulating fatty acid oxidation and insulin sensitivity, uncoupling protein 2, and inhibiting lipogenic genes and oxidative stress through various experiments using animals and cells [6, 10, 31, 33, 75, 131]. However, it is difficult to determine the dose-dependency of the effects of resveratrol on NAFLD in mouse [34] and rat [62] experiments, and thus, the appropriate dose of resveratrol to treat NAFLD cannot be evaluated. Additionally, the results of Foruzan et al. [52] showed that when patients with NAFLD were administered 500 mg per day of resveratrol for 12 weeks, the levels of inflammation markers and hepatocyte apoptosis were reduced when lifestyle modifications were also made [52]. Thus, resveratrol alone is not an effective therapeutic material, and additional studies are needed to evaluate its clinical application. There is no effective drug for the wide variety of patients with different characteristics.

Because catalase is an antioxidant enzyme that orchestrates adaptation to intracellular redox perturbation, it may be effective for reducing oxidative stress caused by not only NAFLD but also obesity and diabetes. To date, however, few studies have examined the development of NAFLD, focusing on catalase function. It is essential to understand the oxidative stress and antioxidant system according to the detailed stages of NAFLD and to establish a method for effective expression of antioxidants. Increasing the activity of catalase in combination with weight loss and exercise therapy may be a natural method for overcoming the limitations of monotherapy.

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