Albumin, an interesting and functionally diverse protein, varies from 'native' to 'effective' (Review)

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Abstract. Human serum albumins (HSAs) are synthesized in the liver and are the most abundant proteins in plasma of healthy human. They play an important role in the pathophysiological processes of the liver and even the whole organism. Previous studies have mainly focused on the regulation of HSAs' expression. However, with the progress of research in recent years, it has been found that the content of circulating albumin cannot fully reflect the biological function of albumin itself. Given the aforementioned fact, the concept of serum 'effective albumin concentration' has been proposed. It refers to the content of albumin that is structurally and functionally intact. Alterations in the molecular structure and function of albumin have been reported in a variety of diseases, including liver disease. Moreover, these changes have been verified to affect the progression of oxidative stress-related diseases. However, the link between albumin structure and function has not been fully elaborated, and the mechanisms by which different forms of albumin affect disease also need to be further investigated. In this context, the present review mainly expounded the biological characteristics and functions of albumin, summarized the different types of post-translational modification of albumin, and discussed their functional changes and possible mechanisms in non-alcoholic fatty liver disease, alcoholic hepatitis, viral hepatitis and different stages of cirrhosis. This will help to improve understanding of the role of albumin in disease development and provide a more comprehensive physiological basis for it in disease treatment.

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Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; AGEs, advanced glycation end products; AH, alcoholic hepatitis; Arg, arginine; CLD, chronic liver disease; Cys, cysteine; Cys-34, cysteine 34; DHA, dehydroalanine; ECAD, extracorporeal albumin dialysis; FcRn, neonatal Fc receptor; HMA, human mercaptalbumin; HNA1, human non-mercaptalbumin 1; HNA2, human non-mercaptalbumin 2; HRS, hepatorenal syndrome; HSAs, human serum albumins; HSA-NO, nitroso-albumin; HUVEC, human umbilical vein endothelial cells; IL-6, interleukin-6; IMA, ischemia-modified albumin; IMAR, IMA/albumin ratio; Leu, leucine; Lys, lysine; MARS, molecular adsorbent recirculating system; NAFLD, non-alcoholic fatty liver disease; ·NO, nitric oxide; PGE_2, prostaglandin E_2; Pro, proline; PTM, post-translational modification; RAGE, AGEs receptor; SAH, severe AH; SBP, spontaneous bacterial peritonitis; TNFα, tumor necrosis factor α; Trp, tryptophan

Key words: human serum albumins, post-translational modification, hepatic disease, albumin function, inflammation

Contents

1. Introduction

Liver is the largest substantive organ of human body, bearing numerous important and complex physiological functions. It is

not only the metabolic center of numerous substances, but also has a variety of physiological functions such as detoxification and immune regulation (1). Chronic liver disease (CLD) is one of the leading causes of death globally, and the associated burden is also rising (2). In recent years, due to changes in lifestyle and dietary habits, the incidence and prevalence of non-alcoholic fatty liver disease (NAFLD) have been increasing (3), and it has gradually become the most common cause of CLD. At present, ~25% of the global population is considered to have NAFLD (4). The risk of liver disease increases as excessive consumption of alcohol increases (5). The number of deaths caused by end-stage liver disease worldwide even is as numerous as 2 million each year (6). At present, liver disease has gradually developed into a global public health problem, and the prevention and treatment of this disease will be the top priority.

At the same time, the liver is also the hub of plasma protein synthesis, glucose and lipid metabolism. It has been suggested that metabolic reprogramming in the liver may influence the progression of liver disease (7). However, albumin, an important protein synthesized and metabolized in the liver, has always been the focus of attention. Its effects on the liver are still being explored. It is known to be introduced as a therapy for the management of hypoalbuminemia and ascites in patients with cirrhosis because of its ability to maintain plasma oncotic pressure (8). Subsequently, numerous clinical trials have found that albumin infusion is beneficial in the treatment of other complications of liver cirrhosis, which can improve the prognosis and/or survival of patients with spontaneous bacterial peritonitis (SBP) (9,10) and hepatorenal syndrome (HRS) (11,12). These benefits have drawn attention to the role of albumin in the organism.

However, due to the incomplete understanding of its structure and function, the use of albumin is also controversial (13,14). When Jalan *et al* (15) verified the correlation between albumin therapy and its function, it was found that not only the quantity of albumin was reduced, but also the quality of albumin was damaged in patients with liver failure. Hence, the concept of 'effective albumin concentration' has been proposed on this basis by them. This further draws attention to albumin's function rather than just quantity. In addition, the study also noted that in patients with liver cirrhosis, the concentration of structurally and functionally intact albumin was lower than that of clinically measured serum albumin (15). More importantly, a previous study has shown that in NAFLD, viral hepatitis and other liver diseases, although the amount of serum albumin is maintained at a normal level, the function of albumin has been altered (16). At the same time, an *in vitro* study has shown that some modifications of albumins themselves may exacerbate disease pathology (17), as these changes affect the binding properties and function of albumin.

Although it has been found that the main structural changes in the post-translational modification (PTM) of albumin are oxidation, glycosylation, nitrosylation and partial truncation of the N- and C-terminal, the relationship between albumin of different PTMs and their functional changes is not clear. Therefore, detection of albumin PTMs and changes in biological function related to PTMs may provide more information on the pathogenesis, diagnosis and treatment of diseases. In addition, in order to further explore the mechanism by which modified albumin affects disease progression, it is needed to conduct clinical trials based on an improved understanding of albumin biology to determine the preventive and therapeutic effect of albumin on liver disease or other diseases. In the present review, previous research findings on albumin modifications were summarized, focusing on their roles in the occurrence and development of liver disease. The aim was to deepen the understanding of albumin modification and its function on the pathogenesis of liver disease, and to provide a rational strategy for the clinical therapy of albumin.

2. Characteristics and structure of human serum albumins (HSAs)

HSA is the most abundant protein in human blood plasma (18). Its concentration is normally 3.5-5 g/dl, accounting for ~50-60% of total plasma protein in healthy adults (19). It is a globular protein composed of 585 amino acid residues with a molecular weight of ~66.5 kDa (20). It is negatively charged at neutral pH and has a half-life of ~21 days (8,18). An albumin molecule contains 35 cysteine (Cys) residues, of which 34 Cys residues form 17 disulfide bonds (S-S) to stabilize the protein's secondary structure, and the Cys residue at site 34 (called Cys-34) (Fig. 1) carries a single free redox-active thiol (-SH) and constitutes the major pool of redox-active thiols in plasma (21,22).

Depending on the status of Cys-34, albumin can exist in both reduced and oxidized forms in plasma. Its reduced form is called human mercaptalbumin (HMA), which accounts for ~70-80% in healthy young individuals, and is the main form of HSA; and the oxidized form can be divided into reversible oxidation and irreversible oxidation, which are called human non-mercaptalbumin 1 (HNA1) and human non-mercaptalbumin 2 (HNA2), respectively. HNA1 is a common reversibly oxidized albumin, which can interact with thiol-containing small molecule compounds (cysteine, homocysteine, glutathione) in the blood, thus it often exists in the form of mixed disulfide compounds, accounting for ~20-30% in healthy young individuals; HNA2 is a highly oxidized form, and its Cys-34 residue is modified with sulfinic or sulfonic acid, which accounts for the least in healthy young individuals, ~2-5%.

The tertiary structure of albumin presents a heart shape and can be divided into three similar-sized homologous domains I, II and III, each of which contains two subdomains A and B (Fig. 2) (23). Because of this stable and flexible structure, albumin can bind numerous endogenous and exogenous substances. Nevertheless, albumin structure is prone to modification after enzymatic and non-enzymatic reactions (such as the most common oxidation and carbonylation), but whether the structural changes are related to its biological function is not fully clarified.

3. Synthesis and metabolism of HSAs

Albumin is mostly synthesized by hepatocytes (24), 10-15 g/day (25), and is translated from a single gene as prepro-albumin, which is transported to the Golgi apparatus after the removal of N-terminal propeptide through the endoplasmic reticulum, and continuously is secreted into blood (26). Of these, the rate of albumin synthesis depends on individual nutritional status. Yet, HSA synthesis is also regulated by

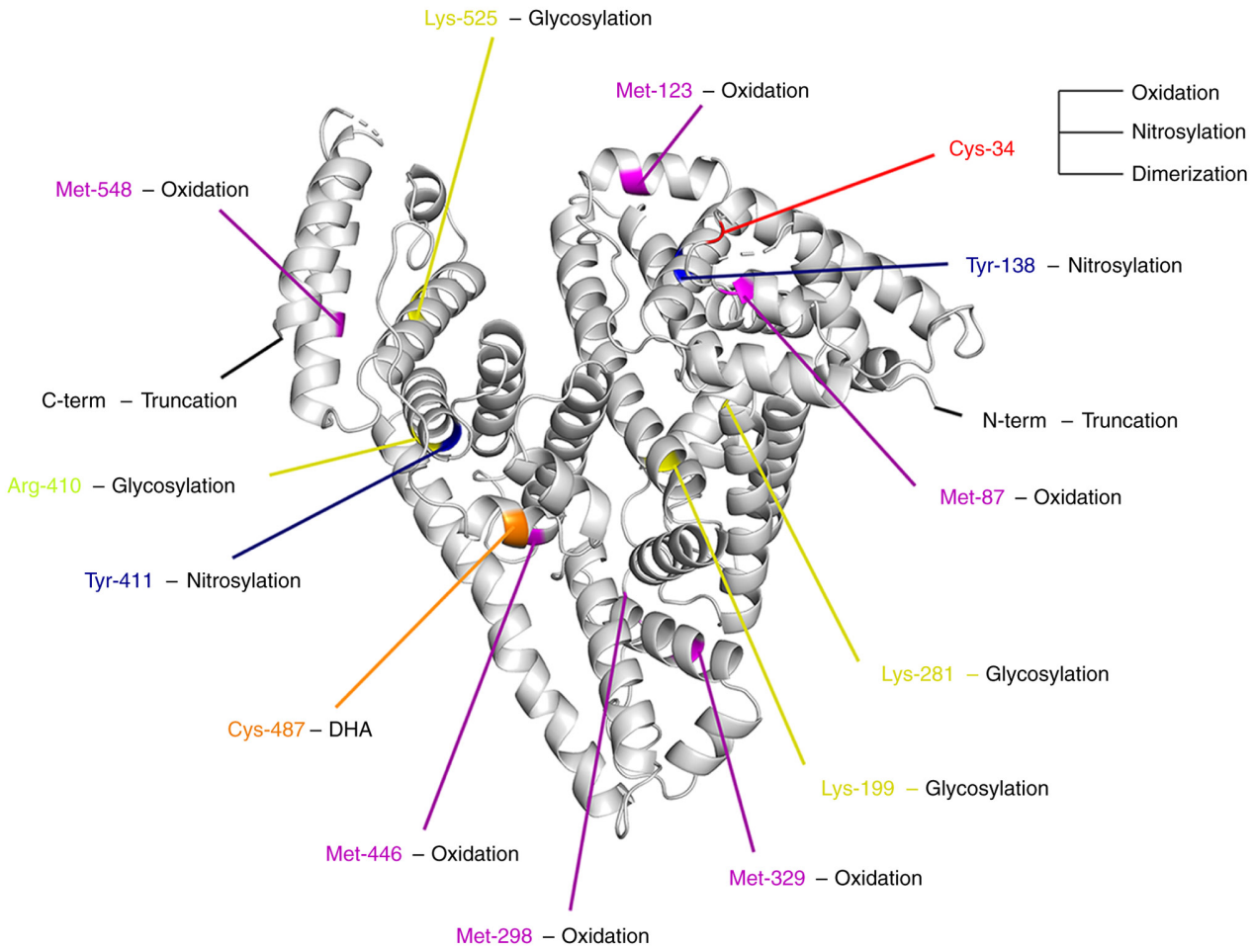

Figure 1. Some common albumin modification sites mentioned in the text.

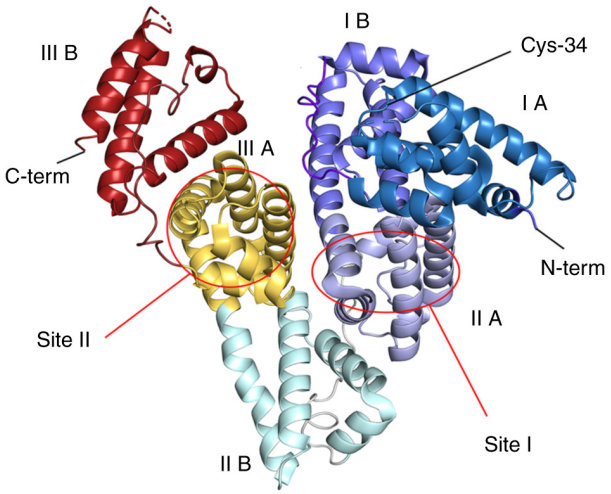

Figure 2. Crystal structure of human serum albumin. Sub-domains are colored as follows: IA, blue; IB, bluish violet; IIA, lila; IIB, reseda; IIIA, yellow; IIIB, red. The approximate locations of Site I and Site II are also shown. The structure of albumin images originates from RCSB PDB database (PDB ID: 7FFR; www.rcsb.org). The illustration was constructed using PyMOL 2.5 (DeLano Scientific LLC).

other factors. For example, HSA production is significantly elevated upon hypoalbuminemia and growth hormone stimulation (27-29); On the contrary, pro-inflammatory cytokines [such as tumor necrosis factor α (TNFα) and interleukin-6 (IL-6)] instead inhibit its synthesis (30).

In addition, the circulation of albumin is closely related to hepatocytes. To be precise, albumin cycle persistence is determined by the continuous uptake and secretion of hepatocytes (31). Albumin is considered as an extracellular molecule, mainly because it is secreted outside the cell as rapidly as cytokines after synthesized in hepatocytes. In turn, numerous types of cells (including endothelial cells and hepatocytes), are able to take up albumin by receptor-mediated endocytosis and break it down by lysosomes (8,32). This process is modulated in a pH-dependent manner by the neonatal Fc receptor (FcRn) (33) that is ubiquitously expressed in a variety of organs and tissues, and FcRn expression in different cells is of varying importance for albumin uptake and metabolism. Among them, FcRn expressed by hepatocytes and endothelial cells was shown to be the main contributor for the maintenance of albumin circulation and the stability of albumin circulating levels (34). Because it mediates the recycling of albumin, FcRn can, in general, transport albumin back into the circulatory system before it is degraded in lysosomes. Hypoalbuminemia occurs when FcRn is absent on these cells. Among them, in capillaries with continuous endothelium, native albumin is transported by an active transcytosis mechanism mediated by the GP60 receptors (Albondin) (31). The affinity of albumin for the GP60 receptor was decreased when the HSA conformation

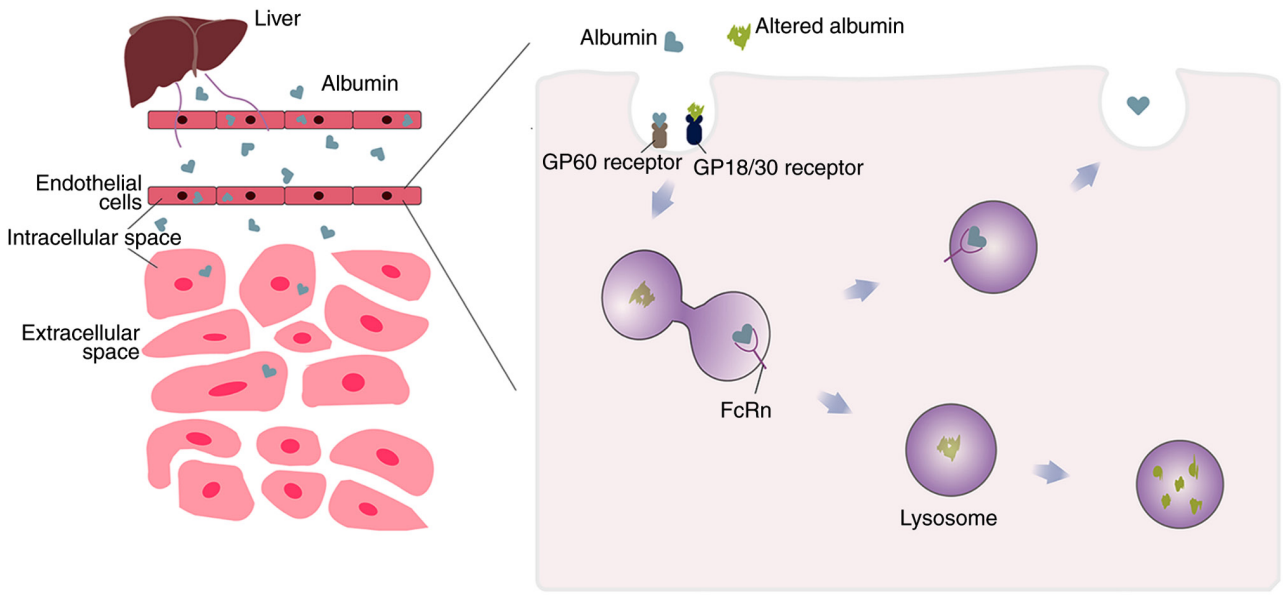

Figure 3. Schematic diagram of the uptake and metabolism pathways of albumin by endothelial cells. Native albumin binds to the GP60 receptor, and after being taken up by endocytosis, FcRn, neonatal Fc receptor can bind to native albumin and return it to the systemic circulation, preventing lysosomal degradation. Differently, altered albumin binds to GP18/GP30 receptors and is internalized and degraded in lysosomes. Some of the data were obtained from Reference 31.

was altered (Fig. 3) (35). But conversely, the endocytosis and degradation of modified albumin is increased by GP18/GP30 (another membrane-associated albumin binding protein (36), both of which are similarly expressed in heart, liver, spleen and numerous other tissues (35).

Furthermore, it has been reported that the cycle life of modified albumin is lower than that of native albumin. On the one hand, the aforementioned GP18/GP30 may act as scavenger receptors that promote the internalization and degradation of modified albumin. On the other hand, it may be related to FcRn. Crystallography and mutation studies have shown that FcRn binds primarily to residues located at domain I and III, of which domain III is the key (37). In addition to being pH-dependent, this interaction also requires hydrogen bonds formed by protonation of the histidine of albumin, which then bind to FcRn interfacial residues (38). However, when PTMs occur in albumin, such as Cys-34 oxidation and Lysine (Lys)-525 glycation, the conformational changes of albumin caused by these site modifications affect the formation of hydrogen bonds due to the proximity to the binding site, resulting in the weakening or disappearance of the binding ability of albumin to FcRn (Fig. 3) (39).

4. Function of albumin

Albumin can ensure the communication between intracellular fluid, extracellular fluid and tissue fluid, and maintain the balance of blood colloid osmotic pressure. This is because albumin accounts for ~70-80% of the total osmotic pressure in plasma and is the main regulator of fluid distribution in the body cavity (40). Initially, it was considered that the benefits of albumin depended on this function. As such, it was introduced in the 1950s as a plasma expander, and was widely used to augment circulating blood volume in patients with burns, shock and blood loss.

Whereas, with the in-depth understanding of the biological function of HSA, it has been discovered that albumin has multiple biological effects, and its non-colloidal function cannot be ignored in addition to the colloidal function. The non-oncotic functions of albumin mainly include antioxidant, anti-inflammatory, molecular transport, endothelial stabilization and immune regulation (Fig. 4) (41). Among them, the antioxidant characteristics of albumin are mainly dependent on its free radical-trapping properties and the possession of a variety of ligand binding sites (42). In terms of free radical-trapping properties, HSA primarily functions through the aforementioned Cys-34 (43). Although the reaction of albumin thiols with oxidants is not particularly fast, the plasma concentrations of albumin are so high, especially considering the limited number of antioxidant enzymes available in the body (42), that Cys-34 provides ~80% of the free thiols groups in plasma (43-45), while the free thiol groups in plasma usually act as the main scavengers of various oxidants (46). Therefore, Cys-34 is still considered extremely important for plasma antioxidant function on the human organism. This is consistent with a recent study reporting that HSA is the main source of free radical-trapping properties in serum (47). Notably, Cys-34 is also closely associated with oxidative stress-related diseases (42,48-50). In addition, the multiple binding sites of albumin also contribute to its antioxidant activity by binding to metal ions, bilirubin and homocysteine (51). For example, HSA can combine with free copper (II) and iron (II) ions to prevent them from participating in the Fenton reactions, which further generate deleterious hydroxyl radicals (52). The binding of bilirubin indirectly plays an antioxidant function, as this complex was shown to be an inhibitor of lipid peroxidation (53,54).

Meanwhile, albumin also binds multiple inflammatory mediators and modulates immune responses in systemic inflammation and sepsis through Toll-like receptor

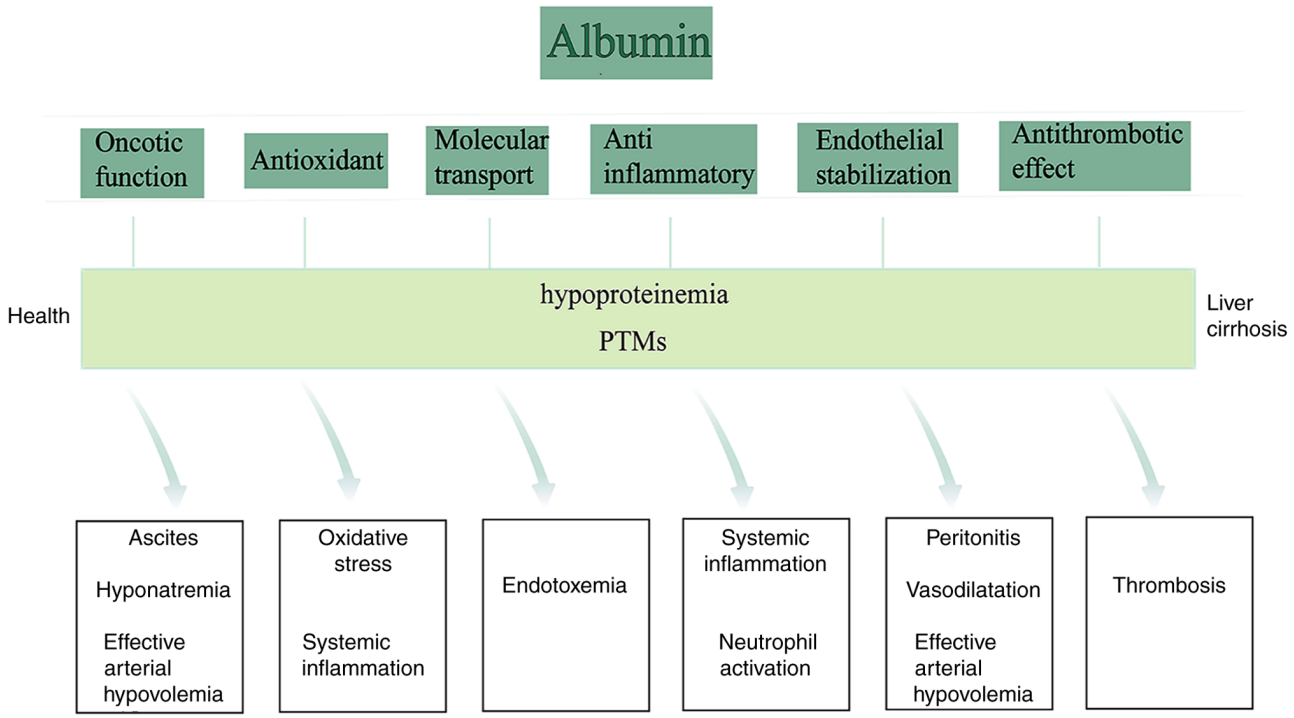

Figure 4. Effect of albumin PTMs in liver cirrhosis. Albumin has a variety of biological functions, but in the case of liver cirrhosis, decreased albumin concentration and PTMs lead to impairment of its function, resulting in clinical complications. PTMs, post-translational modifications.

signaling (55,56). A clinical trial has also demonstrated positive effects of HSA infusion in infected patients with or without liver disease (57-59). Moreover, several *in vitro* and *in vivo* studies supported the beneficial role of albumin in stabilizing the endothelial cell function, which may be due to albumin's antioxidant and inflammation-regulating properties to protect endothelial cells from damage by pro-inflammatory factors (60,61). On the other hand, Cys-34 can also bind nitric oxide (·NO) to form nitroso-albumin (HSA-NO) in a variety of ways (62,63), which can relax blood vessels and inhibit platelet aggregation (8). Albumin can also play a role in transporting these substances, by binding to the aforementioned substances through the binding site. With the gradual understanding of the albumin function, its structural changes in diseases have also gradually been reported, and there may be a certain relationship between the two. In short, other biological effects of albumin in disease are far more important than the maintenance of colloid osmotic pressure alone.

5. PTMs of albumin

Due to the progress of mass spectrometric and chromatographic techniques, the modification of albumin can be detected in an improved way in the human organism, which further deepens individuals' understanding of albumin structure, both in physiological or pathological states. More importantly, on this basis, it has also been found that the different modification states of albumin may affect its own function, and even be related to organ dysfunction *in vivo*. This renders individuals have to pay more attention to the structural integrity of albumin and the structural changes that have occurred. At present, the common modifications that have been reported are mainly oxidation, nitrosylation, glycosylation, truncation and dimerization. In the future, the different modifications and their possible changes in binding capacity and other functions will be summarized by the authors.

Albumin oxidation. Albumin is susceptible to various oxidative modifications, of which sulfhydryl (-SH) oxidation on Cys-34 is the most common PTM. Methionine residues are also the most commonly oxidized amino acids, including Met-87, Met-123, Met-298, Met-329, Met-446 and Met-548 (Fig. 1) (44). Besides, albumin oxidation can also involve other kinds of amino acid residues, such as Lys, Arginine (Arg) and Proline (Pro) (64). Direct oxidation of these amino acid residues may also generate carbonyl derivatives, and the carbonyl content also predicts the oxidative modification of other amino acid residues in albumin (65).

Since Cys-34 is a major contributor to antioxidant activity, oxidation of this site will alter the antioxidant capacity of HSA (Table I). Consistent with this conclusion, it was found that with the increase of HNA-1 level, the antioxidant activity of the body was significantly decreased (42). This is indirectly confirmed by the role of HNA2 in promoting inflammation and oxidative stress (66). In addition, albumin also provides numerous binding sites for exogenous and/or endogenous substances. Therefore, when the conformation of the albumin molecule was changed, the affinity of its binding site would also be changed, ultimately resulting in reducing in ligand binding (Table I). Previous studies demonstrated that cysteinylation of Cys-34 can alter the conformation of the entire domain I as well as the interface between domains I and II (67,68). This may be related to the impaired binding of bilirubin and other ligands by oxidized albumin in advanced liver disease. In addition, Anraku *et al* (59), using *in vitro* experiments, found that HNA1 affects the binding ability of Sites I and II [two specific drug binding sites, located

Table I. Common albumin post-translational modifications and effects on their function.

HSA modifications		HSA functional changes		(Refs.)
Oxidation	Binding capacity	Metal ion binding capacity and fatty acid binding capacity	Decrease	(16)
		Affinity of FcRn	Decrease	(39)
		Warfarin (Site I-ligand)	No effect	(59)
		Ketoprofen (Site II-ligand)	Decrease	(59)
		L(small)-Trp (Site II-ligand) and cefazolin (Site I-ligand)	Decrease	(68)
		Verapamil (Site I and II-ligand)	Increase	(68)
		Dansylsarcosine (Site II-ligand)	Decrease	(70)
		Binding of bilirubin capacity	Decrease	(114)
	Transport function	Fatty acid transport	Decrease	(15)
	Antioxidant function	IMAR	Decrease	(15)
		Free radical scavenging activity	Decrease	(68)
Glycosylation	Binding capacity	Affinity of FcRn	Decrease	(39)
		Ibuprofen and flufenamic acid	Decrease	(84)
		Ketoprofen	Decrease	(85)
		Warfarin	Increase	(84)
		Warfarin	No effect	(86)
		Warfarin	Decrease	(87)
		Hemin affinity	No effect	(88)
		Affinity of bilirubin and long chain fatty acid	Decrease	(88)
		Tryptophan	No effect	(82)
		Tryptophan	Increase	(86)
		Tryptophan	Decrease	(89)
Nitration	Binding capacity	Palmitate	Decrease	(99)
		Polycyclic aromatic hydrocarbon epoxides	Decrease	(101)
Truncation of N-terminal	Antioxidant function	Cobalt binding	Decrease	(103)
		Free radical scavenging ability	Decrease	(104)
Truncation of C-terminal	Binding capacity	Affinity of FcRn	Decrease	(102,105)
Dimerization	Binding capacity	Myristic acid	Decrease	(109)
Dehydroalanine	Antioxidant function	Scavenge free radicals	Increase	(111)

HSAs, human serum albumins; FcRn, neonatal Fc receptor.

in subdomains IIA and IIIA, respectively (69)], with a greater effect on Site II (23,59) (Fig. 4). At the same time, Oettl *et al* (70) used dansylsarcosine (the labeling ligand of HSA Site II) to study and identified that HNA2 levels were correlated with Site II binding capacity. In this way, both HNA1 and HNA2 are closely related to the Site I and/or Site II binding function, although they may have different effects on different ligands. On the other hand, oxidative modifications play an important role in inducing binding of other amino acid residues to ligands. Nagumo *et al* (71) found that with the increase in cysteinylation of Cys-34, other amino acid residues were also oxidized, and these amino acids also played critical roles in ligand binding at sites I and II. These evidences prove that oxidation not only directly affects ligand binding, but also indirectly regulates ligand binding by affecting other amino acid residues.

Albumin glycosylation. Glycation is also called non-enzymatic glycosylation (72). *In vivo*, the Amadori products produced by glucose-modified albumin are the predominant modification of glycated albumin (73), and this modification mainly occurs at multiple sites corresponding to Lys and Arg residues, among which Lys residues are the most common (64,74). Currently, the glycation of Lys-281, Lys-199 and Lys-525 has been confirmed (Fig. 1) (75-77). However, in a previous study, Lys-525 was considered to be the main site of non-enzymatic glycosylation of HSA, with a higher contribution to overall glycosylation than other sites *in vivo* (76). In addition, when early glycation adducts such as Amadori products undergo a series of oxidation, rearrangement, and cross-linking to form alpha-oxoaldehydes, such as methylglyoxal and glyoxal, can also react with the free amino group of albumins to form the advanced glycation end products (AGEs) (78,79). For the AGEs produced by methylglyoxal modification, Arg-410 is the predominant site of modification, and at the same time, Arg-114, Arg-186, Arg-218 and Arg-428 are also slightly modified (80,81). Since Arg-410 is not only necessary for

albumin-associated esterase activity but also the binding site for ketoprofen and diazepam (80,82). Therefore, the modification of Arg-410 caused by methylglyoxal will reduce the esterase activity of albumin and the binding ability of the aforementioned drugs. It is worth noting that the AGEs generated by methylglyoxal modification cause albumin functional changes and may be related to the pKa value of the microenvironment, but the pKa value appears to have little effect on which residues are more likely to be glycosylated (80,83).

In fact, it has also been found that the conformational and binding activity of albumin modified with early glycation adducts are changed (Table I). Glycated albumin has been reported to have a reduced affinity for drugs such as ibuprofen and ketoprofen (84,85), but the ability of glycated albumin to bind to warfarin remains controversial (86,87). In addition, *in vitro* experiments revealed that the affinity of glycated albumin to bilirubin and long-chain fatty acids also changed significantly, with the affinity of bilirubin reduced by ~50% (88). However, Bohney and Feldhoff (82) noted that the binding of Tryptophan (Trp) (the Site II ligand) was unaffected by glycation albumin, but in another study its affinity for glycation albumin was reduced (89). These conflicting data need to be further validated in different diseases. At the same time, similar to cysteinylation of Cys-34, glycation induces structural changes in the region surrounding the ligand binding site, such as the local structure around Trp -214 (90).

Most of the current research on albumin glycation has focused on the study of diabetes and its complications. However, it has also been reported that the level of circulating AGEs in the plasma was increased in cirrhotic patients without diabetes (91). Furthermore, given that the liver is also the main site of AGE metabolism (92), in advanced liver disease, further accumulation of AGEs and activation of intrahepatic cells to produce cytokines would trigger more damaging effects on the liver due to a reduction in hepatic effective liver volume/mass (91,93). Clinically, AGEs have been proven to cause fibrosis in other organs (94,95). Of note, an *in vitro* experiment also demonstrated that AGEs exacerbate liver injury and fibrosis in bile duct-ligated rats, but not in normal rats (96). This still requires further investigation of the clinical significance of glycosylated albumin in the pathophysiology of liver disease.

Albumin nitrosylation. Nitrosylation of Cys-34 is another important PTM. Under physiological conditions, the formation of HSA-NO is considered to be the main mode of natural storage of ·NO in human plasma (97). This combination not only prolongs the biological activity of ·NO, but also enables albumin to exert antithrombotic effects due to the regulatory effect of ·NO on thrombosis (98).

However, under pathological conditions, such as liver cirrhosis, elevated local tissue ·NO concentrations have been reported to lead to increased HSA-NO production and decreased palmitate binding (99); moreover, due to the instability of ·NO, it is be apt to react with superoxide anion radicals to form peroxynitrite (ONOO-) (100). The nitration of HSA tyrosine by $ONOO^-$ has been demonstrated, and Tyr-138 and Tyr-411 (Fig. 1) are particularly sensitive to this modification (101). Nitrotyrosination is a pathological PTM that may alter albumin structure and function (Table I). Previous studies have pointed out that both Tyr-138 and Tyr-411 are located at the ligand binding site, which may be related to the impaired binding ability of this form of albumin (99,101). It remains unclear how HSA-NO and nitrotyrosination generated under pathological conditions affect the organism, and the mechanisms by which these alters play a role in disease remain to be further explored.

Truncation of N- or C-terminal. Physiologically, the C-terminal domain of albumin contributes to molecular stability and is critical for its binding to FcRn (102). Besides, the N-terminal metal ion binding site of albumin can chelate free metal ions, which plays an important role in the antioxidant activity of albumin to a certain extent (103). In some diseases, a small fraction of circulating HSA may be truncated at the N- and/or C-terminal. Naldi *et al* (104) found that the most abundant form of N-terminal truncation in cirrhosis patients is the absence of Asp-Ala residues. This truncation affects the antioxidant capacity of HSA due to its antioxidant effects (Table I). The most abundant C-terminal truncations is the absence of Leucine (Leu) residues, which often reduce albumin stability and shorten its half-life (Table I) (105). In addition, based on the ability of the N-terminal of albumin to bind cobalt, when oxidative stress or other pathological conditions occur, ischemia-modified albumin (IMA) is subsequently produced, which indicates a decrease in the metal-binding ability of the N-terminal of albumin (103,106).

Dimerization. When oxidative stress increases, HSA can dimerize by forming intermolecular disulfide bonds on Cys-34 (107). Naldi *et al* (108) demonstrated that HSA can be divided into homo- and hetero-dimeric. Just as its name suggests, the former refers to the binding of two identical monomers, such as two albumins lacking C-terminal Leu residue. On the contrary, it is called hetero-dimeric if unidentical monomers are combined. As dimerization reduces free Cys-34 residues, it adversely affects the antioxidant and binding capacity of HSA (Table I) (109). In addition, Naldi *et al* (108) also identified that HSA dimer may be a new potential biomarker for CLD. One study also pointed out that HSA homo-dimeric may be associated with prognosis in decompensated cirrhosis (Table II) (110), but its biological consequences are uncertain.

Dehydroalanine (DHA) conversion. Cys can be converted to DHA when exposed to alkaline and/or thermal conditions. Bar-or *et al* (111) have reported that this modification change was observed on Cys-487 (Fig. 1) of albumin. Furthermore, they found that this transformation can enhance the degradation rate of HSA, but may disrupt the ligand binding capacity of Cys-487 and nearby sites.

6. Role of albumin PTMs in different liver diseases

Liver cirrhosis. Liver cirrhosis, characterized by persistent liver damage and systemic inflammation and increased oxidative stress, is a classic example of HSA structural and functional changes caused by disease states. As early as ten years ago, Domenicali *et al* (112) found that the structural abnormalities of HSA in hospitalized patients with

Table II. Most common PTMs of HSA in different liver diseases and their detection and analysis methods.

Liver disease	The PTMs present	Analytical/detection approaches	Year	(Refs.)
Liver cirrhosis	HNA1; HNA2; HNA1 high proportion	RP-LC-HRMS	2018	(55)
	Oxidized albumin and AGEs	HPLC	2004	(91)
	HSA-DA; HSA-L; HSA-CYS; HSA-SO_2H; HSA-GLYc	RP-LC-MS	2013	(104)
	Albumin Homodimers	RP-LC-MS	2016	(110)
	HSA-DA; HSA-L; HSA-CYS; HSA-SO_2H; HSA-GLYc	RP-LC-MS	2014	(112)
	HNA1; HNA2	SEC-SAXS-MALS	2021	(113)
ACLF	HNA1; HNA2; HNA2 high proportion	RP-LC-HRMS	2018	(55)
	Albumin homodimers	RP-LC-MS	2016	(110)
	HNA2	HPLC	2016	(119)
AH	HSA-Da; HSA-L; HSA-GLYc; HSA-CYS; HSA-SO_2H	RP-LC-MS	2017	(17)
	HNA1; HNA2; HNA2 high proportion	RP-LC-HRMS	2018	(55)
	HSA-DA; HSA-L; DHA; HSA-SO_2H; HSA-CYS	RP-LC-MS	2016	(120)
NAFLD	AGEs	HPLC	2018	(126)
Viral hepatitis	/	/	/	/

PTMs, post-translational modifications; HSAs, human serum albumins; NAFLD, non-alcoholic fatty liver disease; ACLF, acute-on-chronic liver failure; AGEs, advanced glycation end products; AH, alcoholic hepatitis; HNA, human non-mercaptalbumin; DHA, dehydroalanine.

liver cirrhosis, mainly included cysteinylation of Cys-34 (HSA-CYS), sulfinylation (HSA-SO_2H), partial truncation of the N/C-terminal (HSA-DA and/or HSA-L), glycosylation (HSA-GLYc), and a combination of these isoforms (Table II). Among them, cysteinylation and glycosylation were the most common (112). Over the past few years, a significant decrease in HMA accompanied by an increase in HNA1 and HNA2 has been well documented in advanced liver disease (112,113). In addition, Watanabe *et al* (91) also verified that serum oxidized albumin levels increased with the severity of liver disease. However, in patients with liver cirrhosis, in addition to changes in the molecular structure of albumin, impaired albumin binding function has also been gradually discovered. Interestingly, there may be some connection between the two.

In liver cirrhosis, various modifications of albumin have been reported to affect ligand binding ability. For example: Severe oxidation of albumin impairs the ability of albumin to bind bilirubin, possibly due to the high affinity of bilirubin to HMA (114). Moreover, it has been pointed out that the fatty acid binding capacity of HSA is also severely impaired in patients with liver cirrhosis, while the reduction of this ability is greater in patients with acute-on-chronic liver failure (ACLF) and may be due to the accumulation of AGEs (15). In fact, the chelation capacity of metal ions in patients with liver cirrhosis is only 50% that of healthy individuals, and it develops and progresses with increasing severity of cirrhosis in these patients (15,41). Notably, a recent study have also demonstrated that in patients with chronic liver failure, a marked opening of the structures of HSA domains I and III was observed with increased levels of fatty acids and bilirubin in the organism (113). This may further affect the binding function of HSA. In addition, in the previous albumin modification section, PTMs on different amino acid residue and their effects on sites were also mentioned in the patients with liver cirrhosis. All these evidences demonstrated that there are certain connections between amino acid residue modifications, molecular conformation changes, and function changes in albumin, and understanding these is a prerequisite for improved study of the role of albumin PTMs in disease.

Furthermore, certain studies have suggested that modified albumin may contribute to systemic inflammation (31,55,61,115-117). Magzal *et al* (61) found that hemodialysis patients exposed to oxidative stress had hypoalbuminemia and albumin modifications (the highest proportion of HNA1 in isolated albumin), and further revealed that these modifications triggered an inflammatory response in human umbilical vein endothelial cells (HUVEC) (Fig. 5). In addition, the pro-inflammatory properties of modified albumin are also associated with glycosylation *in vivo*. A study clarified that AGEs promote the release of pro-inflammatory factors such as TNFα in HUVEC (115). Not surprisingly, modified albumin plays a similar role in liver cirrhosis characterized by oxidative stress. For example, Bernardi *et al* (31) pointed out that the elevated levels of HNA1 and HNA2 were correlated with the severity of liver cirrhosis and the degree of systemic inflammation (HNA1 played a major role). This has been confirmed in a previous study (55). In addition to that, the study prepared HNA1 and HNA2 *in vitro* and demonstrated that HNA1 could induce cytokine storm in leukocytes and induces systemic inflammation in decompensated liver cirrhosis by triggering an inflammatory response signaling pathway in peripheral blood mononuclear cells; excitingly, the aforementioned study also identified that this pathway may be mediated by p38-MAP kinase (Fig. 5) (55). Although the aforementioned study did not elucidate the receptors that mediate p38-MAP kinase activation in response to HNA1, it is equally important, which means that there are new insights into the mechanism of action of oxidized albumin. At the same time, circulating HNA1 upregulates the expression of prostaglandin E_2 (PGE_2), which has been shown to drive cirrhosis-related immunosuppression (116,117). It indicated that circulating HNA1 appears

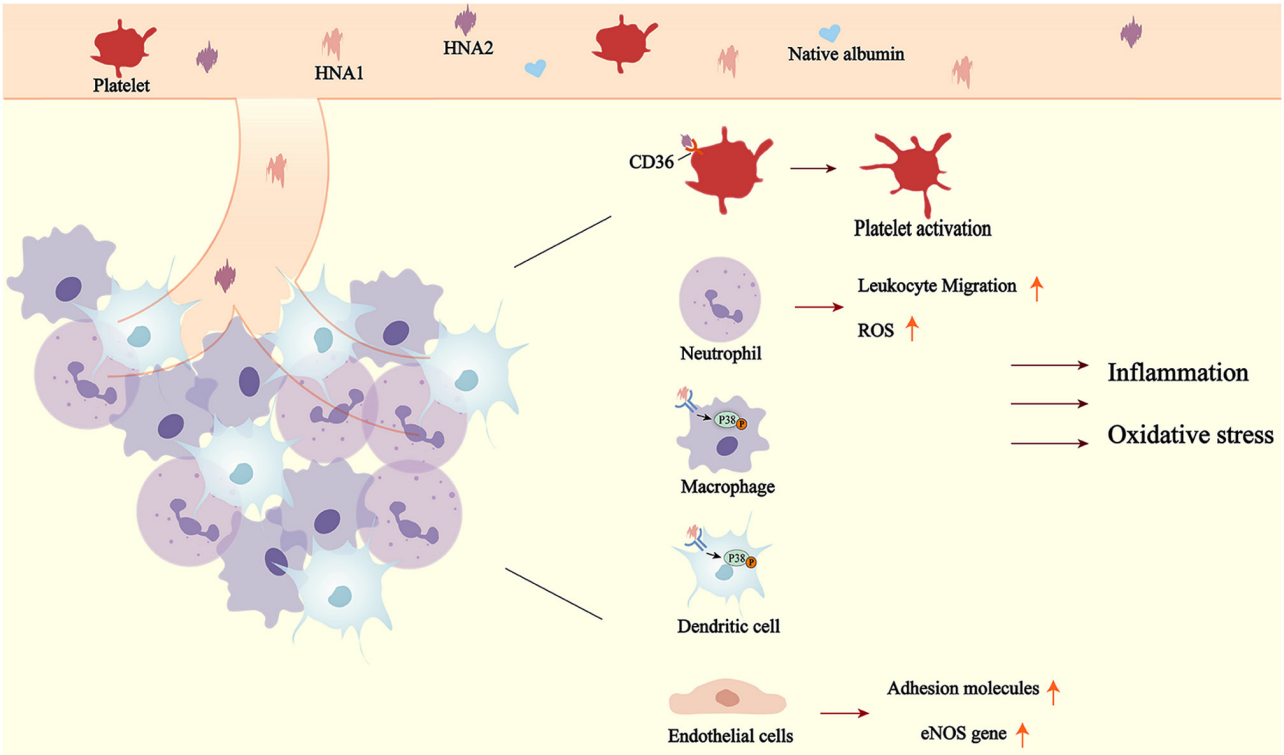

Figure 5. Oxidized albumin causes systemic inflammation by regulating different cells. HNA2 promotes inflammation and oxidative stress by activating platelets through CD36 receptor. HNA1 mediates inflammation in peripheral blood mononuclear cells such as macrophages and dendritic cells through phosphorylation of P38 MAP pathway, but its receptor remains unclear. In addition, oxidized albumin can further aggravate systemic inflammation and oxidative stress by activating neutrophils and promoting endothelial damage. HNA, human non-mercaptalbumin; ROS, reactive oxygen species.

to mediate cirrhosis immunosuppression through PGE_2, but the exact mechanism remains unclear. These evidences all indicated that HNA1 is actively involved in the systemic inflammatory response in patients with decompensated cirrhosis. Although some mechanisms have not been fully elucidated, it is worth noting that modified albumin has been revealed to be an important factor in the increase of systemic inflammation in various oxidative stress-related diseases, including cirrhosis.

ACLF. ACLF is the cause of death in most patients with liver cirrhosis and is characterized by high levels of systemic inflammation and high short-term mortality (118). Changes in albumin have also been reported in patients with ACLF, which differ from those during cirrhosis. A clinical study revealed that HNA2 levels in patients with ACLF were markedly higher than those in patients with stable cirrhosis and acute decompensation (AD), and were significantly associated with ACLF severity and survival (Table II), suggesting that HNA2 may be a biomarker of liver failure (119). It is currently understood that patients with ACLF has a higher level of inflammation than that of AD, implying that systemic inflammation levels may affect the composition of oxidized albumin. At the same time, Jalan *et al* (15) demonstrated that IMA/albumin ratio (IMAR) was increased in patients with ACLF. Furthermore, the aforementioned study also provided evidence of other impaired albumin binding: A significantly lower fatty acid binding function. Interestingly, a negative correlation was identified between IMAR and the fatty acid binding coefficients at Sites I and II. This indicated that the binding functions between sites may interact and restrict each other. As with liver cirrhosis, Oettl *et al* (114) found that the binding of albumin to bilirubin and other ligands may be impaired in patients with ACLF, possibly due to the presence of oxidized albumin. Another study found that albumin dimer was also increased in patients with severe ACLF (Table II) (110), but its role in ACLF was unclear. In conclusion, the level of systemic inflammation may affect the composition of oxidized albumin, with HNA2 predominating in ACLF with high systemic inflammation and HNA1 in liver cirrhosis, and the conversion between the two forms may be used to monitor disease progression. Due to the rapid onset and progression of ACLF, it has not been reported whether the aforementioned modified albumin has a role in promoting oxidative stress and systemic inflammation during its development, but the structural and functional changes of albumin have been shown to be closely related to the prognosis of ACLF (15,110).

Alcoholic hepatitis (AH). AH is a unique alcoholic liver disease caused by long-term excessive drinking, and severe AH (SAH) is based on AH with severe progressive inflammation and high mortality. PTMs albumin has also been frequently detected in these diseases. Naldi *et al* (120) found that the relative amount of native albumin decreased more significantly in AH than in cirrhosis. At the same time, in addition to the common PTMs such as N/C-terminal truncation and cysteinylation, two regions of intense signal (likely a Cys oxidation, but not sure which specific residue) and DHA were also found in multi-charged mass spectra (Table II). This signal was absent in liver cirrhosis, possibly due to modification caused by different levels of oxidative stress and inflammation.

While in SAH patients, the most prominent oxidized albumin was HNA2, which was higher than in cirrhotic patients and healthy subjects (55). In fact, N- or C-terminal truncation and glycosylation forms were also found in plasma samples from patients with SAH (Table II) (17). Simultaneously, Das *et al* (121) showed that serum levels of IMA, advanced oxidized protein products and AGEs were higher in patients with SAH compared with alcoholic cirrhosis and healthy controls, and were positively correlated with urinary albumin, which may predict patient prognosis. However, whether these changes occur in AH has not been elucidated.

Nevertheless, only a small number of studies have attempted to confirm the mechanism of the aforementioned clinical phenomenon. A previous study by Das *et al* (17) showed that circulating neutrophils were activated in patients with SAH, along with the induction of oxidative stress in healthy neutrophils by albumin purified from plasma of patients with SAH, and the most prominent oxidized albumin in patients with SAH was HNA2, suggesting that it may be HNA2 that induces persistent oxidative stress and inflammation as well as systemic complications in patients with SAH by regulating neutrophil activation (Fig. 5). Further, recently, Bhat *et al* (66) not only used purified albumin from plasma of patients with SAH, but also oxidized albumin prepared *in vitro*, and it was found that HNA2 may trigger platelet activation through CD36 receptors, promote inflammation and oxidative stress, and contribute to disease severity in patients with SAH (Fig. 5). These findings suggested that HNA2 plays an important role in exacerbating oxidative stress and inflammation in SAH with severe inflammatory responses. And the removal of these PTM albumins may be a strategy for the treatment of AH and SAH. Although different from the form of oxidation that plays a role in cirrhosis, these studies point to the role of oxidized albumin in contributing to the aforementioned pathological conditions.

NAFLD. NAFLD is one of the most common CLDs in the world. Studies have shown that oxidative stress and inflammation are key mediators of NAFLD, and these mediators may affect the PTMs of albumin (122,123). Sun *et al* (123) found increase of IMA in NAFLD. In addition, it has been reported that NAFLD can promote the formation of AGEs, which, on the one hand, may be associated with oxidative stress and the production of inflammatory compounds. On the other hand, it may also be related to the formation of alpha-glyoxaldehydes induced by glucotoxicity and lipotoxicity of NAFLD (124,125). Whereafter AGEs can participate in the oxidative stress and inflammation of NAFLD by combining with the AGEs receptor (RAGE) to promote the occurrence of hepatic steatosis (hepatocyte steatosis) and even fibrosis and form a positive feedback loop (Table II) (125,126). This is consistent with the study by Pereira *et al* (127) that AGEs can monitor the progression of mild, moderate and severe NAFLD according to the grade of steatosis (127). Therefore, as aforementioned, in addition to HNA1 and HNA2, AGEs may also promote systemic inflammation in liver disease.

In addition, Ge *et al* (16) pointed out that fatty acid binding ability and metal binding ability of albumin were impaired to varying degrees in patients with NAFLD. However, it has not been reported what modification caused the impaired binding ability, but these impairments predate conventional biochemical markers such as liver function, which means that in the early stage of oxidative stress disease, even if serum albumin level has not been abnormal, changes in the ability of albumin to bind may predict these diseases early.

Viral hepatitis. Viral hepatitis is a major global health problem and the resulting liver cirrhosis and liver cancer are the leading causes of human death. According to Yavuz *et al* (128), the serum IMA concentration increased in patients with hepatitis B virus-related CLD, which was correlated with the degree of liver fibrosis. Similarly, this view was also confirmed by Cakir *et al* (129). Although oxidized albumin has not been reported in patients with viral hepatitis, a study has shown that their albumin binding capacity is impaired (16). In the early stages of viral hepatitis, Ge *et al* (16) found that the binding capacity of albumin to metal ions and fatty acids is reduced. In addition, the impairment of albumin to fat binding capacity is more severe in patients with hepatitis than in patients with NAFLD. However, the reason for the changes in albumin binding capacity is unclear, and it has been suggested that it may be due to hepatocytes steatosis, viral infection, and/or inflammation response that induces conformational changes in the albumin molecule (16). Moreover, further research is needed to determine whether these changes affect the progression of hepatitis.

7. Therapeutic effects of albumin in different clinical pathways

Various evidences indicate that structurally or functionally altered albumin has multiple biological properties, especially oxidized albumin, which provides strong evidence for the removal of structurally and/or functionally incomplete albumin from plasma of patients with different liver diseases, or the replacement of these albumin with native albumin. At present, albumin-related treatment mainly includes intravenous infusion and extracorporeal albumin dialysis (ECAD). The former is suitable for some complications of advanced liver disease; the latter is mainly used in patients with ACLF. However, the mechanism by which these albumin-based treatments function *in vivo* remains controversial.

Intravenous infusion of albumin. It has been reported that albumin infusion is suitable for patients with SBP, HRS and paracentesis-induced circulatory dysfunction (130,131). In these cases, albumin infusion has been shown to reduce the incidence of other complications and prolonged patient survival (10-12,132). But the complications of the aforementioned diseases are all characterized by hypovolemia. Therefore, after the infusion of albumin, only its main osmotic function can be initially shown. However, Jalan *et al* (15) and Chen *et al* (57) discovered that albumin infusion can improve the survival rate of patients with cirrhosis complicated by SBP, which may be related to the detoxification function of albumin. Previous studies have also shown that administration of human albumin in patients with stable cirrhosis and ascites provides short term improvements in albumin binding and detoxification function. Similarly, there has recently been increasing evidence that the beneficial effects of HSA on effective blood

volume were also related to its non-osmotic functions, which can indirectly improve cardiac contractility and peripheral vascular resistance in rats (133). Similar effects have been observed in patients with decompensated cirrhosis (134).

Due to HSA's ability to resist oxidative stress, it is gradually being applied in various diseases and showing some benefits. These benefits, though, remain controversial. For patients with liver disease, on the one hand, several studies have shown that infusion of albumin reduces systemic inflammatory responses and exhibits immunomodulatory properties that further improve survival. For examples, a clinical study showed that after 12 weeks of continuous infusion of albumin at 1.5 g/kg, markers of systemic inflammatory response (like IL-6) were alleviated in patients with decompensated cirrhosis (134). Furthermore, O'Brien *et al* (117) found that PGE2-mediated immune dysfunction associated with liver cirrhosis was improved after albumin infusion, indicating the regulation of immune responses by albumin. This was also previously confirmed in the ANSWER randomized controlled trial (135), which showed that long-term weekly administration of albumin (40 g/biw for 2 weeks, then 40 g/w for 18 months) in patients with decompensated cirrhosis can reduce the incidence of complications, thereby improving the overall survival rate. Interestingly, albumin has also been found to be potentially beneficial for hyponatremia (136) and hepatic encephalopathy (137,138). On the other hand, however, there are studies that suggest that the effect of albumin may not be so strong. A recent clinical study revealed that targeted albumin infusion did not attenuate systemic inflammation or improve cardiac function in patients with decompensated cirrhosis (139). Another trial suggested that infusing albumin to normal levels in patients with advanced liver disease may not provide additional benefit (13). A meta-analysis also confirmed this view (140).

From a holistic perspective, these discrepant results may be related to the quantity, duration, and/or quality of albumin infusion. Currently, the timing and amount of albumin infusion remain a matter of debate. In addition, the uneven quality of commercial albumin may also be one of the reasons. Certain studies have found that the structure and binding function of albumin from different manufacturers have been damaged to varying degrees, and even different batches of albumin manufactured by the same manufacturer have differences (141-143), which will affect the treatment effect of HSA. Notably, these damages are also affected by, for example, storage time and temperature (144). How to improve the quality of commercial albumin and standardize therapeutic dosage is an open question.

ECAD. Albumin dialysis system is a common artificial liver support therapy, among which molecular adsorbent recirculating system (MARS) is the most widely used (145). Although the ability of MARS to remove toxins from patients has been widely demonstrated (41,146), how it alleviates disease status through albumin remains controversial.

On the one hand, Jalan *et al* (15) found that MARS treatment had little effect on IMAR levels. This is contrary to the current hypothesis that clearing of excess toxins (it can bind to albumin and impair albumin function) from the circulation promotes regeneration of native functional albumin, enabling the transport and detoxification of more toxins, suggesting that MARS treatment cannot 'regenerate' albumin. On the other hand, however, Klammt *et al* (147) demonstrated that MARS treatment may be associated with improved albumin binding function rather than just elimination of some toxicants. In addition, Oettl *et al* (148) revealed that MARS can lead to the transfer of HNA1 to HMA (lasting ~24 h), while HNA2 was not significantly affected. Although this transfer lasts for ~1 day, it is not yet fully understood whether the change in the redox form of albumin is beneficial for disease prognosis. But Jalan *et al* (15) previously demonstrated that MARS treatment did not provide a significant survival benefit for patients with ACLF. This may be related to the persistence of HNA2, as another study showed that the proportion of HNA2 was associated with ACLF prognosis (114). Thus, while MARS alters the oxidative state of HNA1 *in vivo*, HNA2 is closely associated with short-term survival, which may explain this paradox. Therefore, follow-up studies should pay more attention to the ratio of reversible and irreversible albumin damage after MARS treatment, and analyze the overall function of circulating albumin on this basis to improve the treatment level and the quality of life of patients.

8. Conclusion and perspectives

Albumin is considered an important antioxidant molecule in the organism. However, in diseases characterized by enhanced systemic inflammatory responses and oxidative stress, such as liver cirrhosis, structural and functional impairment of HSA occurs. Although there is currently evidence that the structural changes of albumin may be related to its binding function, the differences in PTMs, the effects of modifications at different site on different ligands, and how these effects change the overall biological function of albumin remain unclear in different diseases. Further discussion is required. More importantly, the effect of albumin conformational changes on disease progression also needs to be further confirmed. At present, the research on oxidative modification is relatively extensive, while the extent to which other modifications affect liver disease has not been clearly reported. In conclusion, it is required to further explore the relationship between albumin structure and biological function to provide new insights into the occurrence and development of liver diseases.

At the same time, the treatment of HSA is quite expensive. Moreover, HSA is not easy to store and is easily contaminated by pathogens. Therefore, recombinant albumin as its replacement is the future direction of development. However, only a few studies have proved its anti-inflammatory effect *in vitro*, and its clinical significance still needs to be further explored.

Finally, the proposal of 'effective albumin concentration' also makes individuals to realize that the treatment of albumin is not only aimed at increasing serum albumin levels. In particular, recent studies have also demonstrated that 'effective albumin concentration' can improve stratification of patients with liver cirrhosis, and is improved compared with serum total albumin in assessing the prognosis of patients with AD and ACLF. However, how to establish a sound albumin treatment strategy and develop other new treatment methods for patients with advanced liver disease on the basis of testing

'effective albumin' is a problem that can be explored in the future.

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Authors' contributions

JQ and YF conceived and designed the review. JQ, NW, TL and MT drafted the manuscript. NW, CL, SM, HC and HB analyzed the data. NW, LW, YF and JQ contributed materials/analysis tools. LW was involved in revising the manuscript. NW wrote the first draft of the manuscript. YF and JQ modified and reviewed the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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