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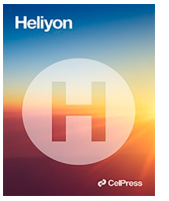

Review article

Role of the angiopoietin-like protein family in the progression of NAFLD

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is the most frequent cause of chronic liver disease, with a range of conditions including non-alcoholic fatty liver, non-alcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma (HCC). Currently recognized as the liver component of the metabolic syndrome, NAFLD is intimately linked to metabolic diseases. Angiopoietin-like proteins (ANGPTLs) comprise a class of proteins that resemble angiopoietins structurally. It is closely related to obesity, insulin resistance and lipid metabolism, and may be the critical factor of metabolic syndrome. In recent years, many studies have found that there is a certain correlation between ANGPTLs and the occurrence and progression of NAFLD disease spectrum. This article reviews the possible mechanisms and roles of ANGPTL protein in the pathogenesis and progression of NAFLD.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological syndrome characterized by excessive hepatic lipid accumulation and hepatic parenchymal cell steatosis in addition to alcohol, viral infections, and other definitive liver injury factors [1]. NAFLD is diagnosed when hepatic steatosis occurs in more than 5% of the liver [2]. The spectrum of NAFLD includes non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH) and its associated cirrhosis and hepatocellular carcinoma (HCC). Its progression is closely related to metabolism, inflammation and tumor [3].

As the social economy has developed rapidly in recent years, people's diet structure and living standards have been constantly changed and improved. The incidence of obesity, hypertension, hyperlipidemia and hyperglycemia continues to rise, and the incidence and detection rate of NAFLD has increased yearly. According to recent articles, the global prevalence of NAFLD has exceeded 30% in recent years and is still increasing. The global prevalence of NASH is about 5% [4].

However, the early onset of NAFLD is relatively insidious, and people lack awareness of the risk of NAFLD, so the proportion of

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active counseling is also low. Moreover, there are few effective early diagnoses of NAFLD, which delay the time to control the progression of the disease and lead to further deterioration of the condition, such as NASH, cirrhosis, and HCC. Currently, the gold standard for diagnosing NAFLD and assessing its progression is liver biopsy [5]. However, liver biopsy has more limitations and is inherently invasive, making it inappropriate for population screening [6]. Controlled attenuation parameter, magnetic resonance imaging (MRI)-based assessment of steatosis helps in the detection of benign lesions (hepatic steatosis) but does not allow evaluation of disease progression [7]. NAFLD fibrosis score (NFS), Fibrosis-4 (FIB-4), and other common scoring systems are common predictors of cirrhosis and long-term liver-related events.

Unfortunately, no scoring system can achieve high accuracy [8]. In clinical practice, clinical imaging tests such as ultrasound, computed tomography, MRI, and FibroScan can also identify increased hepatic parenchymal fat accumulation, but there are still major challenges in detecting early fatty liver disease [9,10]. Therefore, the development of new clinical noninvasive indicators to detect disease and predict disease progression for early intervention is critical for patients with NAFLD.

The angiopoietin-like proteins (ANGPTLs) family currently consists of eight members, ANGPTL1 - ANGPTL8, which play vital roles in lipid metabolism, diabetes, inflammation and tumors. More and more studies focus on the connection between ANGPTLs and the NAFLD disease spectrum. Moreover, ANGPTLs have also become an attractive biomarker for disease prediction or prognosis assessment, and research on the ANGPTLs could yield novel targets for the creation of NAFLD treatment plans in the future. Here, we review the possible roles and mechanisms of ANGPTLs in the pathogenesis and progression of NAFLD, NASH, and HCC.

2. NAFLD and the metabolic syndrome

Observed increased metabolic syndrome incidence is associated with the high incidence of NAFLD. There is a strong bidirectional relationship between NAFLD and metabolic syndrome components. Metabolic disorders may be induced in patients with NAFLD, and metabolic syndrome is an essential risk factor for NAFLD [11] (Fig. 1). To better understand the pathophysiology of this spectrum of diseases and to develop more rational diagnostic criteria, NAFLD was proposed to be renamed Metabolism-Associated Fatty Liver Disease (MAFLD) in 2020. MAFLD is considered a hepatic manifestation of the metabolic syndrome as well as a crucial indicator of

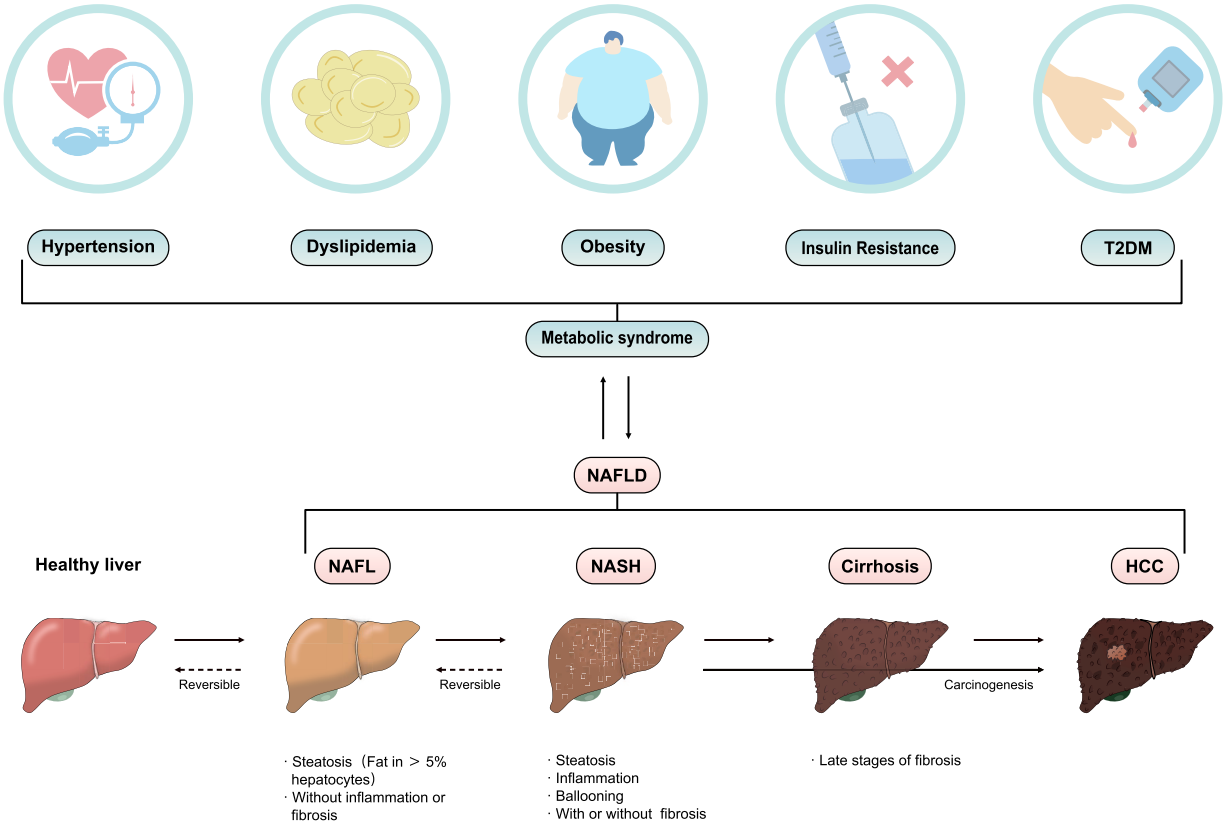

Fig. 1. Relationship between metabolic syndrome and progression of NAFLD disease spectrum. NAFLD has a strong bidirectional association with components of metabolic syndrome. The components of metabolic syndrome associated with NAFLD include obesity, insulin resistance, type 2 diabetes, hyperlipidemia, and hypertension. NAFLD is currently considered the hepatic component of metabolic syndrome, with a spectrum of diseases ranging from NAFL to NASH, which may progress to cirrhosis and HCC. Fatty liver is diagnosed when the fat content of hepatocytes is >5%. In NAFL there is only steatosis without inflammation or fibrosis, whereas in NASH there is inflammation, ballooning, with or without fibrosis in addition to steatosis. Pathologic changes in the early stages of NAFLD are reversible, and the prognosis for late-stage NAFLD is poor.

metabolic dysfunction [12,13]. Similarly, in 2023, metabolic dysfunction–associated steatotic liver disease (MASLD) is proposed as a new designation, and MASLD includes patients with hepatic steatosis and at least one of five cardiometabolic risk factors [14]. Unfortunately, the renaming of the disease has been hotly debated, further academic discussion is needed to assess the subsequent impact, and the outcome of the renaming remains unknown [15].

The components of metabolic syndrome associated with NAFLD include obesity, diabetes mellitus type 2 (T2DM), hyperlipidemia, and hypertension [16,17]. There are several risks associated with NAFLD such as lipid metabolism disorders, insulin resistance and high plasma C-reactive protein, according to a cohort study of 3170 children [18]. Obesity was a significant risk factor for NAFLD. In obese patients, triglyceride (TG) levels and adipose tissue increased. Excess fatty acids induced Insulin resistance (IR) and impaired insulin clearance in vivo and in vitro, promoting NAFLD development and progression to NASH [19,20]. High blood sugar is not only a risk factor for NAFLD, but also aggravates the condition. A meta-analysis found a prevalence of 55.5% of NAFLD among T2DM patients, confirming that T2DM is a significant risk factor for NAFLD and has the potential to accelerate the progression of NAFLD [21]. The presence of diabetes is also an independent risk factor for the development of cirrhosis and HCC, according to Alexander [22]. NAFLD is often associated with dyslipidemia, which is mainly characterized by a high accumulation of TG in the liver. When the content of TG in the liver reaches $\geq$5%, fatty liver can be diagnosed. Excessive TG accumulates in the liver, causing liver cells to undergo steatosis and inflammation, which can lead to the occurrence of NAFLD and NASH [23]. NAFLD promotes hypertension and is an independent risk factor for cardiovascular death [24]. NAFLD promotes the development of hypertension, which is also a risk factor for NAFLD [25,26]. According to a meta-analysis, 44% of NASH patients had been diagnosed with type 2 diabetes, 72% had dyslipidemia, and 80% were overweight or obese [19,27].

The progression from NAFLD and NASH to HCC is continuous, and many factors can potentially contribute to worsening disease progression. In a cohort study spanning 25 years, the burden of NAFLD associated HCC was found to be significantly higher than that of HCC due to other etiologies, increasing the incidence of HCC [28]. Similarly, during the past 20 years, research from Europe, Southeast Asia, and other regions has demonstrated a sharp rise in the percentage of HCC patients with NAFLD [29,30]. Notably, NAFLD-HCC is poorly differentiated and has a larger tumor size and aggressive phenotype compared to hepatocellular carcinomas originating from other etiologies [31].

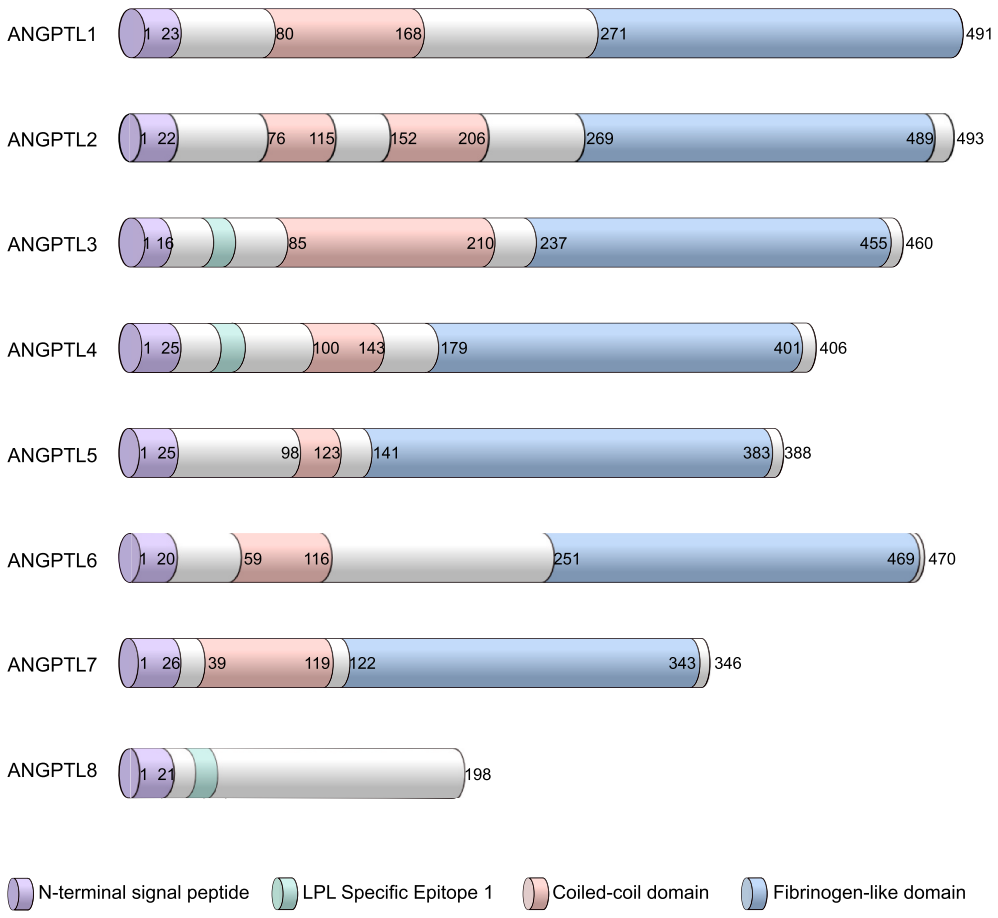

Fig. 2. Schematic representation of ANGPTL protein structure. The ANGPTL family consists of three domains: an N-terminal signal peptide structural domain, one or two N-terminal coiled-coil domains, and a C-terminal fibrinogen-like structural domain.

In summary, the current data consistently show a closely association between NAFLD and the components of metabolic syndrome. With the trend of a globalized epidemic of related metabolic syndromes, NAFLD has become the prevalent chronic liver disease and is emerging as an important cause of liver cancer, liver transplantation, and even liver-related deaths, placing a huge burden on global health and economy [16,32]. These pieces of evidence prove that early identification of NAFLD and early intervention have important practical significance.

2.1. Angiopoietin-like proteins

The eight members of the angiopoietin-like proteins (ANGPTLs) family are secreted glycoproteins that share structural similarities with angiopoietins [33]. ANGPTLs (ANGPTL 1–7) possess an N-terminal signal peptide domain, one or two N-terminal coiled-coil domains (CCD), and a C-terminal fibrinogen-like domain (FLD). The ANGPTL8 is an exception because it lacks an FLD (Fig. 2). Although angiopoietin-like proteins and angiopoietin share similar sequences, ANGPTLs do not bind to angiopoietin-specific receptors tyrosine kinase receptor (Tie) 1 or Tie2, and are therefore also known as "orphan ligands". It is suggested that ANGPTLs function in the organism through mechanisms and signaling pathways different from those of angiopoietins, which also makes the function of ANGPTLs not identical to that of angiopoietins [34]. ANGPTLs exhibit a variety of biological properties that include effects on inflammation [35], lipid metabolism [36], hematopoietic stem cell activity [37], and cancer cell invasion [38].

2.2. ANGPTL1

The ANGPTL family's first member to be found was ANGPTL1, its gene is located on human chromosome 1q24.2 [39,40]. There is widespread expression of ANGPTL1 mRNA in adult tissues, such as liver, muscle, placenta, thyroid, gastrointestinal tract, and adipose tissue [33,40]. NAFLD, especially NASH, is associated with an inflammatory response characterized by hepatocyte ballooning, apoptosis, and infiltration of inflammatory factors due to intracellular fat accumulation, ultimately leading to hepatocyte death. ANGPTL1 has anti-inflammatory activity in various inflammation-related diseases and is an agonistic endothelial TEK tyrosine kinase ligand with stabilizing and anti-inflammatory effects [41].

ANGPTL1, also known as vasopressin, is a critical anti-angiogenic protein that blocks key processes in the angiogenic cascade, such as inhibiting vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (b-FGF) mediated endothelial cell proliferation, migration, tube formation, and adhesion [40]. Developing NASH can result in liver fibrosis and even the development of HCC. Angiogenesis is crucial to the development of HCC since it is a vascular-rich tumor [42]. The development of HCC may be influenced by ANGPTL1 because of its function in regulating angiogenesis. Analysis of ANGPTL1 expression was done on 92 samples of hepatocellular liver carcinoma. The findings demonstrated a negative correlation between ANGPTL1 expression and prognosis, vascular invasion, tumor size, stage, and grade [43]. There is accumulating evidence that cancer stem cells (CSCs) exhibit epithelial-mesenchymal transformation (EMT) features in several cancer types, including liver, lung, and colorectal cancer [44]. At the same time, there is a correlation between sorafenib resistance and EMT. When ANGPTL1 and hepatocyte growth factor (HGF) compete to bind to the methionine receptor, the methionine phosphorylation level is reduced. Slug expression is then inhibited via the protein kinase B (PKB)/extracellular signal-regulated kinase (ERK) regulated Egr-1 pathway, which in turn inhibits sorafenib resistance, EMT and cancer stemness [43]. ANGPTL1 may develop into a new methionine receptor inhibitor and thus be used to treat some types of cancer.

Although the involvement of ANGPTL1 in atherosclerosis, diabetes mellitus, NAFLD, or metabolic syndrome has not been definitively reported, ANGPTL1, as a secreted oncogenic factor, can improve the clinical prognosis of HCC patients by inhibiting angiogenesis and metastasis. These findings also make ANGPTL1 potentially a more attractive biomarker for detecting disease and evaluating cancer prognosis, and are also expected to be a new therapeutic strategy for liver cancer.

2.3. ANGPTL2

In 1999, Kim et al. discovered and cloned angiopoietin-like protein 2 for the first time in human heart tissue, and its gene is located in the region of human chromosome 9q33.3. The ANGPTL2 protein is a 493 amino acid (57 kDa) glycosylated protein that circulates in the body as a secreted protein [45,46]. ANGPTL2 is mainly secreted by adipose tissue, macrophages, and endothelial cells [35]. It is abundantly expressed in the heart, lungs, kidneys, adipose tissue, and skeletal muscle. Hypoxia stimulates its expression and induces endothelial migration and angiogenesis [47]. It was found that ANGPTL2 could induce the activation of downstream signaling pathways that promote inflammation, like AKT and nuclear factor-kappa B (NF-κB) by interacting with integrin α5β1, resulting in the increased expression of inflammation-associated cytokines in adipocytes, which could cause chronic inflammation to develop [48]. Integrins, as functional receptors for ANGPTL2, are profusely expressed on endothelial cells, macrophages and adipocytes [49]. ANGPTL2 derived from these cells is crucial in the association between metabolic disease and adipose tissue inflammation [35]. It was found that ANGPTL2 was abundantly expressed in the visceral adipose tissue of mice with obesity and metabolic disorders, promoting inflammatory responses and insulin resistance [35,49]. Data also suggests that ANGPTL 2 more directly stimulates macrophage pro-inflammatory responses [50]. ANGPTL2 can also further promote the expression of inflammatory mediators via the Foxo1 pathway, thus leading to inflammation and insulin resistance, and plays a critical role in the progression of NAFLD and NASH [49,51]. In addition, after a lifestyle intervention in overweight Japanese men, the researchers assessed their serum ANGPTL2 levels and found that ANGPTL2 was an effective response to obesity, visceral fat loss, and metabolic improvement [52]. Sasaki et al., in mice injected with ANGPTL2 via adenovirus, found increased expression of genes related to lipid metabolism and increased hepatic fatty acid

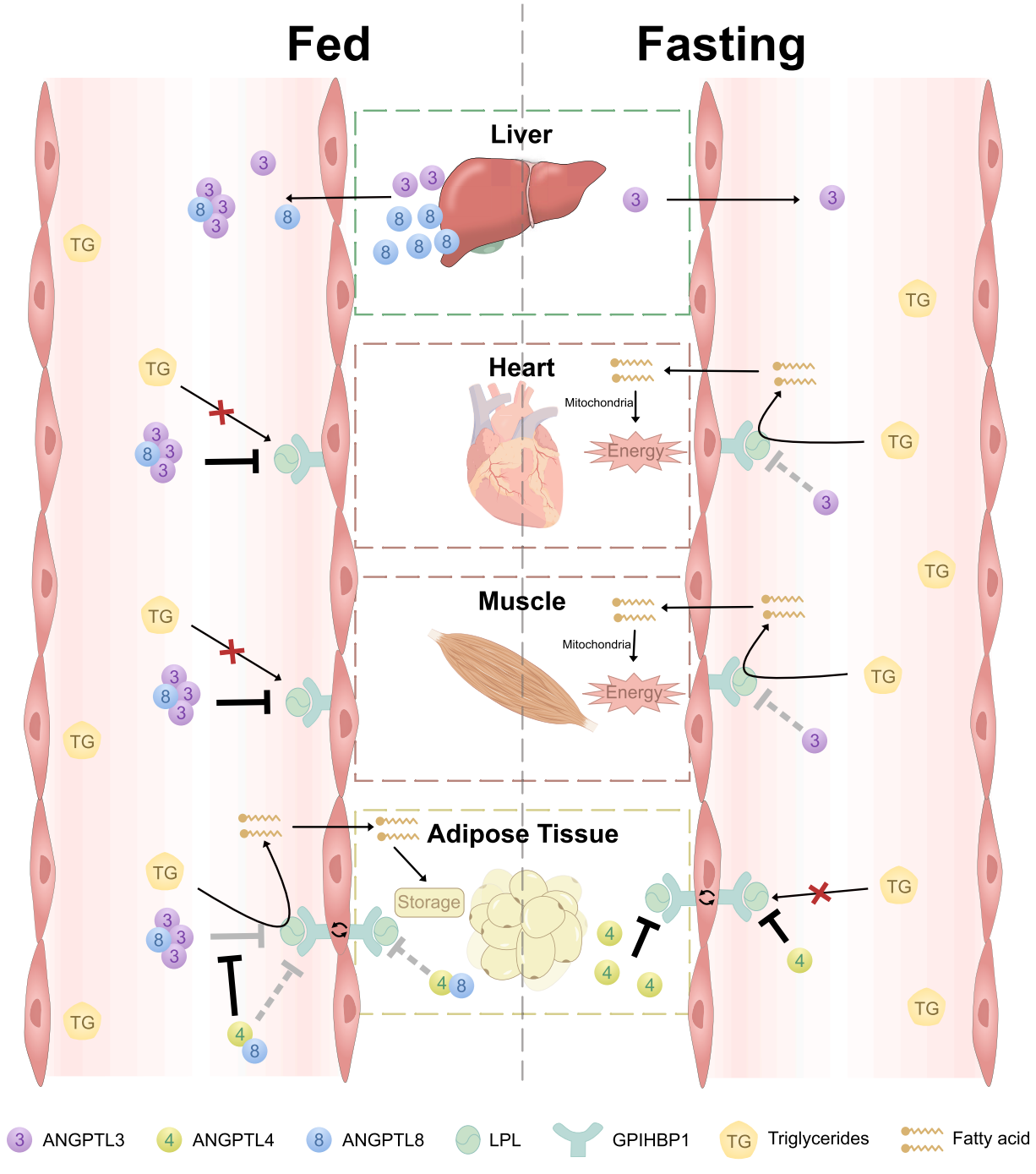

Fig. 3. ANGPTL3-4-8 model regulates LPL activity and directs TG in fasting/eating state. Under fed conditions, both ANGPTL3 and ANGPTL8 are expressed in the liver, circulating ANGPTL3-8 complexes are increased, and LPL in oxidized tissues (e.g., heart, skeletal muscle) is inhibited. In adipose tissue, the ANGPTL4-8 complex is formed, which is less capable of inhibiting LPL than ANGPTL4 and protects LPL from the inhibition of circulating ANGPTL3-8 complexes, thus allowing it to specifically target LPL in oxidized tissue. Under fasting conditions, ANGPTL4 expression was increased and ANGPTL8 expression was decreased in adipocytes. ANGPTL4 locally inhibits LPL activity. Circulating ANGPTL3-8 complex levels were reduced due to decreased hepatic ANGPTL8 expression. weaker inhibition of LPL by ANGPTL3 reduced the inhibition of LPL activity by oxidized tissues, and more energetic substrates were available to the muscle. The transport of LPL from the intercellular space to capillary endothelial cells depends on GPIHBP1, which binds to LPL in the intercellular space and transports it across the surface of endothelial cells to the capillary lumen. LPL, lipoprotein lipase; TG, triglyceride; ANGPTL, angiopoietin-like protein; GPIHBP1, glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1.

synthesis and lipid accumulation, all of which contribute to fatty liver development [50]. A key step limiting the progression of nonalcoholic simple fatty liver to NASH is the hepatic inflammatory response, and the ANGPTL2 mediated signaling pathway plays a crucial role in the high-fat diet-induced hepatic inflammatory response in NASH rats [53].

In addition to its important role in the development of inflammation, ANGPTL2 also has a non-negligible role in tumor progression. Recent studies have shown that sustained activation of ANGPTL2 leads to irreversible pathological tissue remodeling, which in turn causes tumor invasion and metastasis to distal organs and lymph nodes [49]. ANGPTL2 activates the transforming growth factor β (TGFβ)-Smad signaling pathway, causing high expression of EMT-related markers, such as N-cadherin and Slug, as well as low expression of E-calmodulin, which results in higher tumor cell motility and invasiveness, and thus promotes tumor metastasis [54]. ANGPTL2 also activates downstream p38 mitogen-activated protein kinase (P38 MAPK) signaling through integrin α5β1 interactions, increasing matrix metalloproteinase (MMP) expression and activity, thereby promoting extracellular matrix remodeling, and thus tumor invasion and metastasis [48]. The findings of Lin also showed a positive correlation between intrahepatic metastasis and ANGPTL2 expression in individuals with HCC, and that overexpression of ANGPTL2 promoted tumor formation and facilitated hepatocellular carcinoma metastasis in HCC cell lines [55]. In conclusion, ANGPTL2 plays a crucial role in the development and progression of HCC. ANGPTL2, as a secreted protein, can provide a basis for diagnosis and prognosis of the disease by measuring the content of ANGPTL2 in the serum of patients. Inhibition of ANGPTL2 activity in cancer cells may be a potential therapeutic strategy to inhibit tumor growth and metastasis.

2.4. ANGPTL3

Conklin discovered angiopoietin-like protein 3 (ANGPTL3) for the first time in 1999. It is mainly expressed by liver cells and is considered as a hepatokine [56]. The ANGPTL3 gene is located on chromosome 1p3, and the mature protein that hepatocytes secrete is around 70 kDa in molecular weight [57]. Various factors regulate ANGPTL3 expression and regulation, and existing studies have shown that ANGPTL3 is a direct target of liver X receptor (LXR) [58]. LXR is a nuclear receptor that is closely related to lipid metabolism. LXR upregulates ANGPTL3 mRNA expression; in addition, insulin, leptin, and thyroid hormones inhibit ANGPTL3 mRNA expression [59,60]. The main functions of ANGPTL3 are to induce angiogenesis and regulate lipid metabolism [61,62]. By inhibiting the enzymatic activities of lipoprotein lipase (LPL) and endothelial lipase (EL), ANGPTL3 can be extremely important in regulating blood levels of TG and cholesterol [62]. Cleavage of ANGPTL3 is essential for its regulatory role in lipid metabolism [63]. The CCD is a potent inhibitory region for LPL and EL activity. The FLD binds to integrin αvβ3 receptors and is involved in processes such as angiogenesis [64].

ANGPTL3 can synergize with the related ANGPTL4 and ANGPTL8. The ANGPTL3-8 complex has a significant inhibitory effect on LPL (Fig. 3). The plasma levels of TG and cholesterol are lower in ANGPTL3-deficient mice [65]. Ruhanen proposed that hepatocyte-secreted ANGPTL3 binds to αVβ3 on the surface of the same or neighboring cells and affects hepatic TG homeostasis through integrin αVβ3/PI3K/Akt signaling [66]. The authors categorized patients with suspected NAFLD into definitive NASH (5–8), borderline NASH (3 and 4), or simple fatty liver (0–2) based on histological NASH score (range from 0 to 8). And the study examined ANGPTL3 plasma levels in definite NASH, borderline NASH, simple fatty liver, and healthy controls by enzyme-linked immunosorbent assay and found that plasma ANGPTL3 levels were elevated in NAFLD exacerbations, which may be associated with insulin resistance in NASH patients [67]. ANGPTL3 induces adipose tissue lipolysis, releasing free fatty acids and glycerol from adipocytes, which may lead to peripheral and hepatic insulin resistance (IR) and increased intrahepatic fat accumulation [68]. It was found that individuals with NAFLD had higher levels of ANGPTL3 than those without NAFLD, and increased circulating ANGPTL3 levels were associated with progressive increases in hepatocyte fat content, inflammatory stage, and histological and clinical markers of liver injury. In more severe NAFLD and NASH, ANGPTL3 is more involved [69]. Notably, however, circulating levels of ANGPTL3 are also elevated in patients with chronic hepatitis C and hepatocellular carcinoma [70]. It was suggested that chronic liver inflammation may also promote hepatic ANGPTL3 expression [69]. In addition, the c-terminal fibronectin-like structural domain of ANGPTL3 has been shown to be pro-inflammatory [61]. The increase in ANGPTL3 in patients with NAFLD may be associated with increased circulating concentrations of ANGPTL3 as a result of hepatic impairment of varying severity [69]. This discovery suggests that we can conduct more research on the specificity of diagnostic markers and diseases in the future. At the same time, we can also use other methods for differential diagnosis. However, it cannot be denied that ANGPTL3 still has a suggestive effect on the discovery of NAFLD.

Pathologic angiogenesis is involved in the progression of disease progression. ANGPTL3, which is abnormally expressed in human cancers, can induce angiogenesis and stimulate cancer cell growth by binding to integrin αvβ3 receptor [61]. El-Shal found that tumor tissues had more active angiogenesis and higher ANGPTL3 expression than tumor-adjacent tissues, and ANGPTL3 expression levels correlated with clinical stage [70]. Down-regulation of ANGPTL3 through the p38MAPK pathway significantly inhibited the expression of the migration protein marker matrix metallo proteinase-9 (MMP-9), which ultimately suppressed the proliferation and metastasis of HCC cells [71]. This also demonstrates that ANGPTL3 is a viable target for hepatocellular carcinoma treatment and may play a functional role in the proliferation and invasion of HCC.

In conclusion, an increasing body of research indicates that ANGPTL3 is crucial for biological processes including angiogenesis and lipid metabolism, as well as in pathological changes such as diabetes, liver disease, and cancer. Differential expression of ANGPTL3 in diseases such as NAFLD, NASH, and HCC may be a potential biomarker for identifying the stage of disease onset or progression.

2.5. ANGPTL4

ANGPTL4 is localized at 19p13.3 and encodes a secreted glycoprotein containing 406 amino acids. In addition to high expression in

adipose tissue and liver, ANGPTL4 is also widely expressed in the kidney, intestine, placenta and heart [72,73]. Studies have shown that ANGPTL4 acts locally in adipose tissue to inhibit LPL activity as well as modulate TG uptake [74]. Apart from its function in the metabolism of lipids, ANGPTL4 also has a role in the metabolism of glucose, regulating insulin sensitivity and glucose tolerance [75,76], as well as inflammation and angiogenesis [77]. Natural full length ANGPTL4 (fANGPTL4) exists as a dimer or tetramer complex, which can be cleaved by pro-protein convertases, forming two polypeptide structures, nANGPTL4 and cANGPTL4, and functions independently of each other, nANGPTL4 is mainly responsible for inhibiting LPL, while cANGPTL4 is involved in stimulating lipolysis within adipocytes, wound healing, regulation of vascular permeability and angiogenesis, and may be a regulator of tumorigenesis [78,79].

Altun et al. found that serum ANGPTL4 levels were lower in patients with hepatic steatosis. And the reduced ANGPTL4 levels may be a cause of fatty liver [80]. NASH pathology has been reported to be ameliorated by enhanced PPAR signaling in the liver [81,82]. ANGPTL4 is a target of PPAR and may be involved in the process by which PPAR ameliorates the pathophysiology of NASH. Teratani found that ANGPTL4 relieves free cholesterol accumulation in hepatic stellate cells and may be a crucial factor in the development of liver fibrosis in NASH patients. For the therapy of NASH, ANGPTL4 may therefore be a new and promising target [83].

ANGPTL4 is present in various tumors. However, the role of ANGPTL4 in hepatocellular carcinoma is also controversial. Li H et al. found that serum ANGPTL 4 was higher in HCC patients compared to healthy controls and correlated with intrahepatic metastasis and histologic grading [84]. ANGPTL4 also confers anoikis resistance by stimulating integrin-mediated signaling and activating downstream PI 3 K and ERK pathways [85]. And the latest study also proved that high expression of ANGPTL4 is closely related to HCC. Knockdown of ANGPTL4 significantly inhibited the proliferation of HCC cells [86]. Nevertheless, Ng et al. discovered the reverse: ANGPTL4 mRNA expression was lower in HCC patients' tumor tissues than in non-tumor tissues [87]. It was also demonstrated that overexpression of ANGPTL4 enhanced apoptosis and thus inhibited tumor growth, and also inhibited the motility of HCC cells by suppressing the expression of ROCK1 and the formation of polymerized stress fibers, thus inhibiting the invasion of tumor cells [87]. In addition, this study found that ANGPTL4 treatment could inhibit HCC progression by promoting tumor cell apoptosis, inhibiting tumor motility and angiogenesis, and disrupting the favorable tumor microenvironment [87]. It is worth noting that the association between ANGPTL4 and HCC is not specific for NAFLD and is equally suggestive for other causes of hepatocellular carcinoma associated with viral infections. However, the potential association between ANGPTL4 and NASH associated HCC should be supported by studies of NAFLD, but this has not been clearly reported in the literature yet, and further studies are needed. However, the disease involves complex pathophysiological processes, and in practical clinical work, several tests are needed for differential diagnosis. We believe that ANGPTL4 still has some reference significance for the detection and treatment of NAFLD and its related diseases.

It has been suggested that the reason for this contradiction of ANGPTL4 lies in its post-translational modification status and different tissue environments. Moreover, different fragments of ANGPTL4 have different functions and roles in tumors, respectively, and these functions have yet to be thoroughly investigated. Although the role of ANGPTL4 in liver disease remains controversial, differential expression of ANGPTL4 in disease may be a potential biomarker for determining the stage of disease onset or progression, and the complex mechanism of action of ANGPTL4 opens up the possibility of its possible clinical application, providing a viable option for the therapeutic management of illnesses like NAFLD and HCC.

2.6. ANGPTL5

The ANGPTL5 gene is located on chromosome 11 (11q22) and encodes 388 amino acids [88]. Adipose tissue is the primary site of ANGPTL5 expression, it is also slightly expressed in the heart, ovary, testis, and skin [33,89]. Some findings suggest that ANGPTL5 may not regulate angiogenesis compared to most ANGPTLs [90]. ANGPTL5 dysfunction mutation can markedly reduce plasma TG concentration, suggesting that ANGPTL5 and TG regulation may be tightly connected [91]. Alghanim recently discovered that the concentration of plasma ANGPTL5 was higher in obese individuals than in non-obese people. Plasma ANGPTL5 concentrations were increased in obese type 2 diabetics compared to non-obese type 2 diabetics [79]. By using multiple logistic regression analysis, Hammad et al. confirmed in 2020 that adolescents with higher plasma ANGPTL5 levels were 3.5 times more likely than other adolescents to be obese. They also found that increased ANGPTL5 was linked to an increased risk of obesity, suggesting that ANGPTL5 may be a marker of advanced obesity [92]. All of these findings suggest that ANGPTL5 concentrations may be closely associated with lipid metabolism disorders, obesity, and diabetes. As such, ANGPTL5 is anticipated to be a potent biomarker or a crucial treatment tool for metabolic illnesses. Few studies have examined ANGPTL5's relevance in tumors. Analysis of the Human Protein Atlas database showed that ANGPTL5 was highly expressed in hepatocellular carcinoma tissues [93]. ANGPTL5 is poorly understood in terms of its function and mechanism. Whether ANGPTL5 can be used as a diagnostic and prognostic tool in NAFLD and other related metabolic diseases needs further evaluation.

2.7. ANGPTL6

Encoded on human chromosome 19p13.2, ANGPTL6 is a hepatocyte-derived circulating factor, also referred to as angiopoietin-related growth factor (AGF) or angiopoietin-related protein 5 [34,94]. The majority of ANGPTL6 in vivo is secreted by hepatocytes, with secondary expression detected in the brain, adrenal glands, and hematopoietic cells [95,96]. The ANGPTL6 contributes to wound healing and epidermal proliferation. It promotes the proliferation and migratory capacity of endothelial cells by binding to integrin receptors to activate ERK 1/2 and endothelial-type nitric oxide synthase (eNOS) systems [97,98].

Apart from its angiogenic properties, ANGPTL6 controls the metabolism of lipids, glucose, and energy [99]. ANGPTL6 knockout mice develop obesity even in a standard mouse diet and have reduced core temperature and oxygen consumption [100]. In mice

transgenic for ANGPTL6, this performance was completely reversed. Exogenous ANGPTL6 transduced by adenovirus reduced body weight and increased insulin sensitivity in dietary obese patients [100]. In addition, recombinant ANGPTL6 protein reduced hepatocytes' glucose production [101]. It is possible to treat obesity, diabetes, and metabolic syndrome by targeting ANGPTL6. However, ANGPTL6 levels in serum were shown to be considerably higher in patients with metabolic syndrome compared to healthy individuals in another investigation [102]. In addition, during the study, it was found that increased serum ANGPTL6 levels preceded the development of the metabolic syndrome, as well as changes in serum levels of triglycerides, and glucose [102]. These results seem to be at odds with the functional role that ANGPTL6 has been shown to play in the fight against obesity and insulin resistance. Further investigation in this area is therefore necessary.

ANGPTL6 is also an attractive therapeutic target for antitumor therapy [103]. By analyzing the CCLE database, Bai et al. found that ANGPTL6 had high protein expression in HCC cell lines and was differentially expressed between tumor and normal tissues [93]. In another study, ANGPLT6 was found to be significantly increased in both pericarcinoma tissues and serum of hepatocellular carcinoma and enriched in the extracellular matrix of hepatocellular carcinoma, suggesting that ANGPLT6 plays an important role in hepatocellular carcinoma development and progression [104]. The above findings suggest that ANGPTL6 is both an independent risk factor and a prognostic factor for hepatocellular carcinoma, with a strong potential to predict hepatocarcinogenesis. In conclusion, ANGPTL6 is a promising new biomarker for diagnosing metabolic diseases and cancers and assessing prognosis.

2.8. *ANGPTL7*

One member of the ANGPTL family that has received less research attention is ANGPTL7, a secretory circulating cytokine. It is also known as cornea derived transcript 6 (CDT6) and was first discovered in the corneal stroma [105]. The ANGPTL7 gene is located on human chromosome 1p36.22 and is expressed in neural tissue, cone cornea, trabecular meshwork [106]. ANGPTL7 overexpression induces collagen expression and plays a pathogenic role in glaucoma [107]. Obese patients have increased levels of ANGPTL7 in

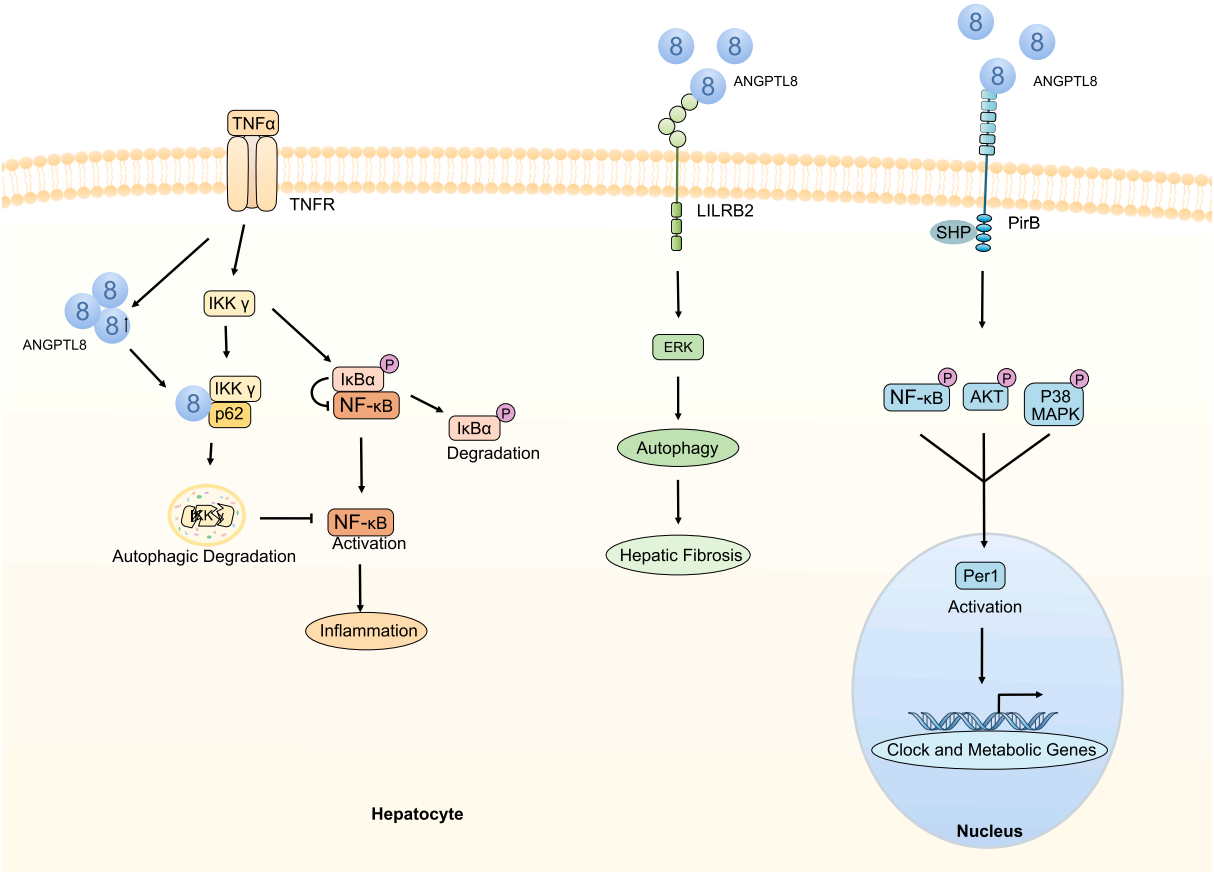

Fig. 4. The role of ANGPTL8 in liver cells. In hepatocytes, intracellular ANGPTL8 inhibits NF-κB activation by promoting the formation of the ANGPTL8-p62-IKKγ complex and subsequent degradation of IKKγ autophagy, which in turn suppresses inflammation. ANGPTL8 promotes NAFLD-associated liver fibrosis by activating LILRB2/ERK signaling in hepatic stellate cells. ANGPTL8 also activates the PirB receptor and reduces SHP phosphatase activity. This process promotes the phosphorylation of p38 MAPK, NF-κB, and AKT, leading to activation of Per1, which results in the transcription of clock and metabolic genes. IKKγ, IκB kinase γ; NF-kB, nuclear factor-kappa B; p38MAPK, p38 mitogen-activated protein kinase; SHP, small heterodimer partner.

plasma and adipose tissue, while physical activity reduces ANGPTL7 levels [108]. According to recent research, ANGPTL7 can promote insulin resistance and T2DM through a variety of pathways. As a result, ANGPTL7 may offer a novel therapeutic target for the management of such conditions [109]. Given that type 2 diabetes mellitus is an independent risk factor for adverse clinical events in patients with nonalcoholic fatty liver disease (including events such as progressive liver fibrosis and cirrhosis), ANGPTL7 may also provide a new idea for the treatment of NAFLD.

ANGPTL7 is a strong target gene of the WNT/β-catenin signaling pathway and a potential target in oncology and regenerative medicine. Studies have shown that ANGPTL7 is a pro-angiogenic factor that promotes angiogenesis, increases tumor invasiveness, and promotes its distant metastasis by promoting endothelial cells' motility, proliferation, and invasiveness [110]. However, Lim's findings indicated that ANGPTL7 could have anti-angiogenic qualities because it dramatically decreased the development of hepatic metastases and angiogenesis [111]. A recent study found that ANGPTL7 was differentially expressed in hepatocellular carcinoma and normal tissues, and ANGPTL7 was significantly positively correlated with liver tumor stage and significantly negatively correlated with tumor grade. Compared with normal tissues, ANGPTL7 was significantly hypermethylated in tumor tissues. In addition, this study found that ANGPTL7 expression levels in hepatocellular carcinoma patients were associated with a favorable prognosis [93]. The role of ANGPTL7 in cancer progression remains unclear due to differences in the results observed between studies. However, differential expression of ANGPTL7 in cancer could be a useful diagnostic for evaluating the cancer's stage of carcinogenesis or advancement.

2.9. ANGPTL8

Angiopoietin-like protein 8 (ANGPTL8), also known as Betatrophin, lipasin, refeeding induced in fat and liver (RIFL), or TD26 [112, 113]. The ANGPTL8 gene, located on human chromosome 19p13.2, is a 22 kDa protein that is mainly expressed in liver and adipose tissue and circulates in human plasma [112,113]. The findings suggest that hepatic ANGPTL8 acts in an endocrine manner, whereas adipose ANGPTL8 acts in an autocrine or paracrine manner [114]. ANGPTL8 expression is regulated by fasting/feeding signaling. ANGPTL8 levels were reduced in the fasted state and significantly increased in the fed state [115]. There is a n-terminal domain in ANGPTL8 that is needed to inhibit LPL activity, but a structural domain at the c-terminus is absent [116]. Nevertheless, ANGPTL8 still plays an important role in regulating the liver clock, LPL activity, lipid metabolism, and inflammatory pathways.

ANGPTL8 overexpression induces resetting of the liver clock in mice, and ANGPTL8 in mice interacts with the plasma membrane paired immunoglobulin-like receptor (PirB) and induces the expression of period circadian protein homolog 1 (Per1) through upregulation of p38 MAPK, NF-κB, and AKT phosphorylation levels, leading to increased expression of Per1 (Fig. 4). The deletion of Per1 can also impair the peripheral clock's resetting mediated by ANGPTL8 [117]. The role of ANGPTL3 and 4 in inhibiting LPL activity has been demonstrated. Through interaction with ANGPTL3 and ANGPTL4, ANGPTL8 has also been shown to be an important regulator of LPL activity. ANGPTL8 can form complexes with ANGPTL3 and ANGPTL4, and the LPL inhibitory activity of the ANGPTL3-8 complex is higher than that of ANGPTL3, whereas the LPL inhibitory activity of the ANGPTL4-8 complex is lower than that of ANGPTL4 [118]. In addition, the ANGPTL4-8 complex markedly reduced the LPL inhibitory actions of both the ANGPTL4 and ANGPTL3-8 complexes. An improved ANGPTL3-4-8 model of the partitioning of triglycerides between oxidized and adipose tissues has recently been proposed [119] (Fig. 3). ANGPTL8 can be thought of as a molecular switch that regulates the flow of circulating TG during the feeding-fasting cycle to suit the demands of the body.

Studies have shown that ANGPTL8 is essential for the development of various metabolic diseases. Reducing ANGPTL8 improves obesity and dyslipidemia, prevents lipid-induced insulin resistance, and prevents hepatic TG accumulation and steatosis [120]. Lee demonstrated that ANGPTL8 levels were markedly higher in patients with NAFLD compared to those without NAFLD, regardless of diabetes and obesity status [121]. This suggests that ANGPTL8 may be a potential biomarker for NAFLD. Similar results were obtained in the study of Hong, and hepatocyte lipid content was not correlated with obesity or IR, suggesting that ANGPTL8 may be a predictor of the severity of NAFLD [122].

ANGPTL8 also plays a role in inflammatory diseases. It was found that the extracellular effects of ANGPTL8 are not the same as the intracellular effects in inflammation. Abu-Farha et al. showed that intracellular ANGPTL8, together with p62 and autophagy receptors, forms an ANGPTL8-p62-ikkγ complex, which promotes autophagic degradation of the IκB kinase γ (IKKγ) and negatively regulates IKKγ-mediated phosphorylation and degradation of the NF-κB-binding inhibitor κBα (i-κBα), thereby negatively regulates NF-κB, a key transcription factor in the inflammatory signaling cascade, which plays an anti-inflammatory role in the cell [123] (Fig. 4). TNFα is an important factor in the inflammatory process after injury and is a signaling activator of NF-κB, and researches have indicated that TNFα can regulate ANGPTL8 expression [113]. In addition, it was recently demonstrated that ANGPTL8 is a pro-inflammatory factor that accelerates the progression of NAFLD to liver fibrosis through the LILRB2/ERK signaling pathway [124] (Fig. 4). ANGPTL8 levels were increased in both cirrhosis and HCC patients [125,126], and recent studies have further confirmed that ANGPTL8 expression is higher in HCC tumor tissues than in matched normal tissues. Moreover, In HCC patients, ANGPTL8 expression was also shown to be positively linked with tumor size [127]. ANGPTL8 may have a role in the development of HCC by promoting the growth of tumors and cell proliferation. Overall, these studies suggest that ANGPTL8 is potentially involved in the development and disease progression of NAFLD, NASH, liver fibrosis, and HCC. Although some of the mechanisms have not been fully clarified, and further studies are needed to evaluate this possibility, it is undeniable that ANGPTL8 has the potential to be a promising biomarker for the disease and progression of NAFLD-related diseases and provides an important idea for the remission and treatment of NAFLD.

3. Therapy

3.1. Lifestyle change

As a disease that develops in parallel with obesity, hyperglycemia, dyslipidemia, and hypertension, NAFLD must be prevented and treated by emphasizing lifestyle improvement, including dietary control and exercise, to stabilize the body's energy metabolism self-regulation mechanism and prevent and control the occurrence and development of NAFLD. Exercise is an effective means of losing weight and preventing metabolic diseases. Hannah et al. found that the progression of fatty liver lesions can be slowed in NAFLD patients with 3%–5% weight loss; with 5%–7% weight loss, reversal of fibrosis is possible [128]. Plasma ANGPTL4 levels are generally stable, but circulating ANGPTL4 increases after exercise. In exercising mice, ANGPTL4 mRNA was found to be basally expressed and induced at higher levels in the liver than in muscle, and also in adipose tissue after exercise than in muscle [129]. It has been found that during exercise, ANGPTL4 can activate AMPK to hydrolyze TGs in brown adipose tissue to generate heat for energy [130]. A three-month aerobic exercise intervention study found that exercise was effective in reducing serum ANGPTL8 levels in obese compared to non-obese individuals [131]. Animal studies have shown that energy intake restriction extends lifespan, delays cardiac aging, and improves insulin resistance in mice [132]. Although the transcription of ANGPTL3 did not change significantly during food restriction, ANGPTL8 was significantly repressed, whereas ANGPTL4 was up-regulated due to elevated circulating glucocorticoid levels [133,134]. A study by Kersten et al. found that dietary restriction raised ANGPTL4 in white adipose tissue, which promotes fat consumption and reduces fat storage [135].

From the current study, exercise, dietary restriction, etc. can affect the level of ANGPTLs, thereby regulating the relevant physiological processes, and ultimately improving lipid metabolism disorders, etc., which is another way to regulate lipid metabolism, prevent and improve the development of metabolic syndrome and NAFLD.

Table 1
Characteristics and main functions of angiopoietin-like proteins.

Name	Chromosome (human)	Main tissue/organ expression	Main function(s)	NAFLD Disease Spectrum Association
ANGPTL1	1	Liver, muscle, placenta, thyroid, gastrointestinal tract (no esophagus), adipose tissue	Anti-angiogenesis, anti-apoptosis, tumor suppression	Serum concentrations are negatively associated with disease progression and clinical outcomes in HCC; In vitro inhibition of the HGF receptor.
ANGPTL2	9	Heart, kidney, lung, adipose tissue, adipose tissue, skeletal muscle	Pro-angiogenesis, glucose/lipid metabolism, proinflammation, cancer development	Promote hepatic inflammatory response; Increased expression in HCC; Positively correlated with HCC intrahepatic metastasis.
ANGPTL3	1	Liver	Pro-angiogenesis, lipid metabolism, pro-inflammation, cancer development	Circulating levels are elevated in patients with NAFLD, NASH, and HCC; Promote proliferation and invasion of HCC cells.
ANGPTL4	19	Liver, adipose tissue, kidney, intestine, placenta, heart	Angiogenesis, inflammation, lipid/glucose metabolism, cancer development	Increased or decreased expression levels in NAFLD patients; Differentially expressed in HCC compared to non-tumor tissues; Regulate HCC tumor growth and metastasis.
ANGPTL5	11	Adipose tissue, heart	Expansion of hematopoietic stem cells, lipid metabolism	Closely related to obesity, diabetes, lipid metabolism; Increased expression in HCC tumor tissues.
ANGPTL6	19	Liver	Pro-angiogenesis, lipid/glucose metabolism, pro-inflammation, cancer development	Preventing the development of obesity and IR.
ANGPTL7	1	Central nervous, system, keratoconus cornea,	Angiogenesis, lipid metabolism, proinflammation, cancer development	Promoting insulin resistance and T2DM; Correlation with liver tumor stage and grade.
ANGPTL8	19	liver, adipose tissue	Regulation of the liver clock, Lipid metabolism, pro/anti-Inflammation, cancer development	Improve obesity and dyslipidemia and prevent insulin resistance; Increased expression in NAFLD patients, positively associated with disease severity; Accelerated progression of NAFLD to liver fibrosis; Increased expression in HCC, positively correlated with tumor size.

3.2. Treatment related to NAFLD

Summarizing the evidence provided so far, it is clear that the ANGPTL family plays a very important role in the pathogenesis and progression of metabolic diseases, including NAFLD-related diseases (Table 1). Certain substances, components, drugs, or means can modulate the content of ANGPTLs or their mediated signaling pathways, etc., to exert their corresponding biological effects, potentially providing ideas for the prevention and treatment of NAFLD.

Berberine exerts anti-inflammatory activity in NAFLD rats by attenuating high-fat diet-induced hepatic inflammatory responses through modulation of the ANGPTL2 pathway [53]. Dihydroartemisinin (DHA) is the main antimalarial compound. Wu et al. demonstrated that DHA inhibits the expression of ANGPTL2 and has an inhibitory effect on HCC [136]. Studies on ANGPTL3 are more abundant, several substances can directly or indirectly reduce the expression of ANGPTL3. Among them, monoclonal antibodies (Evinacumab) and antisense oligonucleotides (vupanorsen) can directly target ANGPTL3 to exert a therapeutic effect and have entered the clinical research stage [137–139]. Tangeretin was shown to significantly inhibit ANGPTL3 promoter activity and attenuate the transcription of ANGPTL3 mediated by the transcription LXRα, thereby decreasing the concentration of ANGPTL3 [140]. Statin therapy also reduces ANGPTL3 concentrations by decreasing LXR activation, which in turn reduces plasma cholesterol and TG levels [141]. Paeoniflorin ameliorates dyslipidemia in animal models through the GALNT2-ANGPTL3-LPL pathway [142]. Xiao discovered that Undaria pinnatifida (UP) soluble fiber could alleviate hyperlipidemia by modulating the ANGPTL3-LPL pathway [143].

Gusarova and Vatner found that targeting ANGPTL8 expression with monoclonal antibodies and antisense oligonucleotides improved lipid metabolism and prevented NAFLD and hepatic insulin resistance [120,144]. Royal jelly fatty acids inhibit ANGPTL8 expression by reducing HNF4α protein in human hepatocellular carcinoma HepG2 cells, thereby inhibiting the associated biological effects [145]. In addition, it was found that metformin, a safe and widely used antidiabetic drug, inhibited the expression of ANGPTL8, thereby protecting the livers of wild-type HFD-fed mice from fibrosis [124]. Notably, there is growing evidence that oligomerization of ANGPTLs is important for their functioning [146]. Thus, finding tiny peptides or compounds that specifically interfere with ANGPTL oligomerization will also hopefully provide new drug candidates for targeting ANGPTLs. Although it cannot be applied in the clinic at present, with the gradual maturation of technologies such as gene editing and RNA interference, in the future, it is also likely to become one of the important therapeutic strategies. In conclusion, targeting ANGPTL for the treatment of related metabolic diseases including NAFLD is a promising therapeutic strategy. ANGPTLs for the treatment of NAFLD and its related diseases are summarized in Table 2.

4. Conclusions and future perspectives

NAFLD is one of the most common chronic diseases, the onset and progression of which are closely associated with the components of the metabolic syndrome and develop in parallel with them. With the increase in the number of patients with metabolic diseases such as diabetes mellitus and obesity, the incidence of NAFLD is gradually increasing, and it has become one of the major worldwide public health issues in the 21st century. The prognosis of advanced NAFLD is very poor, but its early pathological changes are reversible, so early detection, diagnosis, and treatment of the risk factors of NAFLD are essential, not only to improve the quality of life of patients and prolong life expectancy, but also to reduce the global health economic burden.

In order to achieve early detection, diagnosis and treatment, regular medical checkups have become one of the most important means of NAFLD screening. At present, the gold standard for NAFLD diagnosis is still liver biopsy, but it cannot be widely used due to

Table 2
Methods or substances related to ANGPTLs for the treatment of NAFLD and its related diseases.

Therapy	Method/Substance	Action pathway	effect	Reference(s)
Lifestyle change	Exercise	Increased ANGPTL4 levels and decreased ANGPTL8 levels	Prevent and slow down the progression of NAFLD lesions	[129–131]
	Dietary restriction	Increased ANGPTL4 levels and decreased ANGPTL8 levels	Promotes fat burning, reduces fat storage, prevents and treats NAFLD	[132–135]
Treatment related to NAFLD	Berberine	Regulating the ANGPTL2 pathway	Reducing the inflammatory response of the liver	[53]
	Dihydroartemisinin (DHA)	Inhibition of ANGPTL2 expression	Inhibitory effect on HCC	[136]
	Monoclonal antibodies and antisense oligonucleotides	Direct targeting of ANGPTLs	Improve lipid metabolism and play a role in NAFLD prevention and treatment	[120, 137–139,144]
	Tangeretin	Adjusting the LXRα-ANGPTL3-LPL Pathway	Prevention and treatment of dyslipidemia and related diseases	[140]
	Statin	Reduces ANGPTL3 concentration by decreasing LXR activation	More effective lipid-lowering effect	[141]
	Paeoniflorin	Regulating the GALNT2-ANGPTL3-LPL Pathway	Improvement of dyslipidemia	[142]
	Undaria pinnatifida (UP)	Regulating the ANGPTL3-LPL Pathway	alleviate hyperlipidemia	[143]
	Royal jelly fatty acids	Reduction of HNF4α protein to inhibit ANGPTL8 expression	Improvement of abnormal lipid metabolism	[145]
	Metformin	Inhibition of ANGPTL8 expression	Prevention of liver fibrosis	[124]
	gene editing and RNA interference	Specific targeting of ANGPTLs	Exercise the corresponding biological effects to improve NAFLD	[146]

its invasive nature. Non-invasive diagnostic methods are still the focus of future research. The expression level of ANGPTL can be affected by the NAFLD disease spectrum, and by jointly detecting the levels of different ANGPTL isoforms in the NAFLD disease spectrum, it may provide a new test for the early diagnosis of NAFLD in the clinic, and then early prevention and treatment can be implemented. In addition, ANGPTLs play an important role in the key processes and mechanisms of the pathogenesis and progression of NAFLD, and the development of new drugs targeting ANGPTLs and their related pathways will have a broad research prospect and clinical application value. However, there are many subtypes of the ANGPTL family, which type of ANGPTL plays a major role in NAFLD disease onset and progression, in addition, whether there are different ANGPTL molecules playing major roles in different stages of NAFLD, what are the key targets and specific mechanisms of their actions, and whether there are any other interactions between different ANGPTL molecules are still to be further studied and explored. We also believe that these efforts can help us better understand the physiological and pathological significance of the ANGPTL family, and look forward to breakthroughs in relevant therapies targeting this family.

Data availability statement

The authors declare that no data associated with our study has been deposited into a publicly available repository since no data was used for the research described in the article.

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CRediT authorship contribution statement

Xin Su: Writing – original draft, Visualization, Investigation. **Qinchen Xu:** Writing – original draft, Validation, Investigation. **Zigan Li:** Validation, Investigation. **Yidan Ren:** Validation, Investigation. **Qinlian Jiao:** Validation, Investigation. **Lina Wang:** Writing – review & editing, Supervision, Project administration. **Yunshan Wang:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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