REVIEW

Non-alcoholic fatty liver disease and liver secretome

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Abstract Metabolism of carbohydrates and lipids and protein degradation occurs in the liver and contributes to the body's homeostasis by secreting a variety of mediators. Any imbalance in this homeostasis due to excess fat consumption and the pathologic events accompanying lipotoxicity, autophagy dysregulation, endoplasmic reticulum stress, and insulin resistance may cause disturbances in the secretion of the proteins from the liver and their physiologic modifications and interactions with others. Since the liver secretome plays a role in the regulation of fuel metabolism and inflammation not only in the liver per se but also in other organs, the proteins belong to the utmost targets for treating metabolic and inflammatory diseases (e.g., COVID-19), depending on the available and feasible approaches to controlling their biological effects. However, in this era, we still come across new liver-derived proteins but are yet unable to entirely understand the pathologic basis underlying disease progression. This review aims to provide an updated overview of liver secretome biology with explanatory mechanisms with regard to the progression of metabolic and inflammatory liver diseases.

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Metabolic disorders and non-alcoholic fatty liver disease

Metabolic syndrome can be diagnosed if three or more of the following factors are present: fasting glucose ≥ 100 mg/dL, blood pressure ≥ 130/85 mm Hg, triglyceride level ≥ 150 mg/dL, high-density lipoprotein cholesterol level < 40 mg/dL in men or < 50 mg/dL in women, and waist circumference (for Westerners, > 100 cm in men or 88 cm in women; for Asians, > 88 cm in men or > 80 cm in women) (Carr et al. 2016). Metabolic disorders such as diabetes and hyperlipidemia are becoming increasingly common in modern society. Adults in Western countries suffer from obesity (90%), diabetes (50%), and hyperlipidemia (90%) (Le et al. 2017). The major reason for this high prevalence of metabolic disorders is due to increased sedentary lifestyles and excess calorie intake, leading to energy imbalances. Humans maintain their health by regulating lipid metabolic rate via lipogenesis, lipoprotein absorption, and secretion.

The liver is considered the metabolic hub of the body because all ingested nutrients pass through the liver after intestinal absorption. Hence, the liver quickly senses any nutritional changes, which then alters metabolic activities to maintain homeostasis. Therefore, any disturbances in fuel consumption of the liver (e.g., steatosis and steatohepatitis) are often indicators of a metabolic disorder. The hypothalamus is also an essential regulator of energy and weight homeostasis. Evidently, mutant genes contribute to the underlying basis of metabolic disorders (Hochberg and Hochberg 2010). Therefore, metabolic disorders result from various combined factors, including genetic variations, nutritional alternation, and hormonal impairment. Conditions commonly associated with metabolic syndrome include obesity (Cornier et al. 2008), diabetes, and

nonalcoholic fatty liver diseases (Eckel et al. 2010), which will be discussed in more detail.

Obesity

Obesity is defined as abnormal or excessive fat accumulation that presents a risk to health. According to the World Health Organization (WHO), individuals with a body mass index (BMI) over 30 kg/m^2 are considered obese. This cutoff value was determined from the point where the typical metabolic complications of obesity increased twofold. However, among the Asian population, who have a high prevalence of metabolic complications with lower BMI compared with White, Hispanic, or Black populations, the BMI cut-off value is 25 kg/m^2.

A WHO report (2021) mentioned that nearly 2.2 billion adults (40%) worldwide are obese. Another study subdivided obesity by gender, showing that 200 million men and 300 million women worldwide are obese (Polyzos et al. 2019). Data on obesity prevalence among Asians in 2014 showed that about 40% of adults in China, 30% in Japan and India, and 27% in Korea were considered obese (Fan et al. 2017). Of them, more than 39 million were considered morbidly obese (BMI > 40 kg/m^2). Surveillance data from the United States for 2009 and 2010 revealed that more than 15% of children and adolescents were obese, with a consequent increase in pre-diabetic rates (Roth 2015). Data from the Global Obesity Observatory (2021) revealed that seven out of every ten Indian adults and four out of every eleven children are obese (Observatory 2021a), while in Pakistan, six out of every ten adults and five out of every eleven children are obese (Observatory 2021b). A cohort study conducted on 975 Chinese children aged between 6 and 13 years and continued for 6 years afterward showed that obesity increased 2.8 times during adolescence, while another study included 204 Chinese children aged between 6 and 17 years and followed up for 13 years revealed that obesity prevalence increased 5.8 times (Pan et al. 2021). Therefore, obesity will continue to be a severe global health problem due to its rapid increase among children and adolescents.

Studies have shown a linear increase in NAFLD prevalence with increased obesity. In a study of 181 morbidly obese patients with severe average BMI (= 45.1 ± 8.3 kg/m^2), 126 patients (69.6%) exhibited symptoms of NAFLD (Ooi et al. 2021). The study's results showed that more than 33% of obese patients suffered from NAFLD, with more than one-third having bariatric surgery (Machado et al. 2006). NAFLD diagnoses are increasing exponentially in relation to obesity in the United States. For example, 4.17 million cases of NAFLD were reported in 2008, rising to 83.1 million cases in 2015.

Diabetes

Diabetes mellitus (DM) is a chronic disorder that causes abnormal metabolic regulation of glucose as well as vascular and neuropathic complications (Crandall and Shamoon 2020). DM diagnosis depends on the detection of elevated fasting blood glucose levels ($\geq$ 126 mg/dL). There are two types of diabetes: type 1 diabetes (T1D, insulin-dependent or juvenile-onset diabetes) and type 2 diabetes (T2D, non-insulin-dependent or adult-onset diabetes). The pathophysiology of DM can be explained by insulin deficiency and reduced carbohydrate metabolism. Insulin maintains glucose homeostasis by promoting glucose storage in the fed state and releasing it in the fasting state (Crandall and Shamoon 2020). Insulin resistance (IR) is defined as when the signaling pathways of insulin are impaired in principal target organs and tissues such as muscle, fat, and the liver. IR can result in compensatory hyperinsulinemia to maintain normal glucose homeostasis. If compensation is not adequate, hyperglycemia and T2D can eventually develop.

Metabolic syndrome, which includes diabetes, is considered one of the significant life-threatening conditions of the twenty-first century because it can cause serious complications such as cardiovascular disease and stroke. In 2040, it is estimated that 642 million people worldwide will have T2D (Yang et al. 2020), which has shown a linear relationship with elevated BMI, reflecting increasing obesity rates. A meta-analysis using observational data from 20 countries revealed that more than 50% of T2D patients also suffered from NAFLD (Younossi et al. 2019; Targher et al. 2021). The literature suggests a bi-directional relationship between NAFLD and T2D. Moreover, T2D has been proven to be one of the main risk factors for patients developing NAFLD and HCC (Anstee et al. 2013; Powell et al. 2021). The underlying mechanism for high co-incidence of T2D and NAFLD is explained as follows; under IR conditions, adipose tissue becomes dysfunctional, reducing its ability to uptake circulating lipids and enhance lipolysis, even in high-fat diet (HFD) conditions (Yaribeygi et al. 2019). Therefore, these dysfunctional adipose tissues release large amounts of circulating free fatty acids (FFA), which can accumulate in the liver and cause NAFLD (Hammoutene and Rautou 2019).

Non-alcoholic fatty liver disease (NAFLD)

NAFLD is clinically diagnosed if the liver consists of > 5% fat, as monitored by liver imaging or biopsy in the absence of secondary causes of fat accumulation such as chronic alcohol abuse (defined as more than one drink per day for women or two for men) (Carr et al. 2016). NAFLD can encompass a wide variety of liver diseases ranging from simple fatty liver (i.e., simple steatosis) with no inflammation to non-alcoholic steatohepatitis (NASH) with accompanying steatosis,

inflammation, and hepatocyte injury. This can manifest as hepatocytes ballooning with or without fibrosis, which may further proceed to liver fibrosis or liver cancer (Piccinin et al. 2019; Makri et al. 2021). Fibrosis can be histologically categorized into four stages, ranging from stage 0 (no fibrosis) to stage 4 (cirrhosis) (Powell et al. 2021).

NAFLD is currently the most common liver disease globally and has been reported to affect 30% of people over the age of 18 (Hou et al. 2021). A cohort study of 139,056 Koreans between 2011 and 2013 showed an association between a sedentary lifestyle and NAFLD prevalence in young and middle-aged people (Ryu et al. 2015). Another study showed that NAFLD is strongly associated with obesity and T2D (Lonardo et al. 2019). As a consequence of this strong correlation, NAFLD has also become known as metabolic dysfunction-associated fatty liver disease (MAFLD) (Eslam et al. 2020; Makri et al. 2021). As metabolic syndrome becomes more common, so does the incidence of NAFLD (i.e., a worldwide incidence of ~25%, ranging from 13% in Africa to 42% in Southeast Asia). There are expected to be an estimated 100.9 million cases of NAFLD by 2030, a 21% increase from 2015, with a 33.5% prevalence in people above the age of 15 and 28.4% for people of all ages (Estes et al. 2018). Data monitored by national healthcare providers between 1998 and 2015 were gathered, and a new comprehensive analysis was conducted to investigate the prevalence of NASH in various countries and regions. The results of the above-mentioned study revealed that the annual medical costs for treating NAFLD exceeded $100 billion in the United States alone (Mundi et al. 2020).

Pathogenesis of liver diseases

NAFLD, newly named MAFLD, is certainly associated with metabolic dysfunction. Here, the pathogenesis of metabolic diseases will be discussed in the context of lipotoxicity, autophagy dysregulation, endoplasmic reticulum stress, IR, and other targets. In a recent study, the analysis of single-cell RNA transcriptome has been used to find a cell type-specific role in gene expression for the progression of liver diseases including NAFLD (Su et al. 2021).

Lipotoxicity

One of the most well-known disease progression mechanisms in NAFLD is steatosis. When a hepatocyte's ability to synthesize triglycerides overwhelms its ability to dispose of them, triglycerides will accumulate inside them as fat. Although triglycerides are not toxic per se, their precursors, such as fatty acids and other metabolic byproducts, such as reactive oxygen species (ROS), are toxic to hepatocytes. The accumulation of these byproducts is known as lipotoxicity

(Yoon et al. 2021). Because of impaired lipid metabolism, NAFLD patients experience inter- and intrahepatic lipid buildups such as enhanced hepatic FFA intake and very-low-density lipoprotein synthesis, dysregulation of triglyceride export, and reduced levels of high-density lipoproteins and cholesterol in the blood (Katsiki et al. 2016). Inflammation also promotes cytokine production, gut-derived products (e.g., lipopolysaccharide), and hepatotoxic mediators, which can aggravate NAFLD if hepatocytes are exposed to them (Diehl and Day 2017).

FFAs are hydrophobic, which increases their permeability across the cell membranes. However, a few transport proteins facilitate their transport (e.g., plasma membrane fatty acid-binding protein) and fatty acid translocases such as CD36 (Rada et al. 2020). The fatty acid translocase CD36 has a high-affinity receptor for long-chain FFAs, contributing to enhanced fat surge, excessive lipid storage, and metabolic dysfunction. These proteins are also involved in lipid metabolisms such as fat intestinal absorption and fatty acids consumption by muscle, adipose tissue, and liver (Rey et al. 2020). An exome-wide association study revealed that increased levels of VLDL were adversely found in T2D patients (Liu et al. 2017).

NADP+-dependent aldo–keto reductase family 1, member 10 (AKR1B10), also named as ARL-1 protein, is mainly expressed in the small intestine and colon (Gallego et al. 2007). The levels of AKR1B10 were found to be higher in patients with HCC (Heringlake et al. 2010) or adenocarcinoma of the lung (Fukumoto et al. 2005), renal cancer, and breast cancer (Ma et al. 2012; Kanno et al. 2019). The studies have proven that AKR1B10 is involved in regulating lipotoxicity and de novo-lipogenesis; lipid peroxidation produces electrophilic carbonyls, aggravating DNA damage by interacting with nucleophiles and causing carcinogenesis and apoptosis (Luo et al. 2011; Ye et al. 2019).

Autophagy dysregulation

The liver is the primary organ involved in the detoxification of chemicals within the body. Maintaining homeostasis between the generation of new proteins and the destruction of damaged proteins in eukaryotic cells involves two main pathways: the ubiquitin–proteasome system (UPS) for short-lived proteins and the autophagy-lysosomal pathway for longer-lived proteins (Martinet et al. 2009). Several articles have reported on the correlation between autophagy and lipid metabolism. Autophagy causes the transfer of intracellular materials, such as denatured proteins, fat droplets, and dysfunctional mitochondria, to the lysosomes for their destruction. As a "housekeeper" of cellular contents, autophagy not only inhibits the progression of steatosis and fatty hepatitis but also prevents hepatocyte injury (Kwanten et al. 2014). However, the fizzy lifestyle and intense caloric

food intake have increased the obesity ratio, negatively affecting the regulation of autophagy.

Before analyzing the possible pathogenic mechanism of NAFLD driven by dysfunctional autophagy, it is necessary to review how the intracellular contents are controlled. Lipid accumulation in the hepatocytes could result in decreased autophagic activity, bile acid fluctuations, increased endoplasmic reticulum (ER) stress, inflammatory response, and disturbed gut microbiota, all of which can contribute to NAFLD progression (Friedman et al. 2018; Yueh et al. 2020). The relationships between autophagic imbalance and hepatic diseases have been studied (Kwanten et al. 2014; Kim and Kim 2020). In addition, the consequential excessive storage of lipids in hepatocytes due to impaired autophagy has been shown to cause apoptosis, exacerbating NAFLD (Tanaka et al. 2016).

There are three types of autophagy: macro-autophagy, micro-autophagy, and chaperone-mediated autophagy (Amir and Czaja 2011). Lipid droplets (LDs) of various sizes are metabolized by macroautophagic engulfment (Singh et al. 2009). Macroautophagy occurs when autophagosomes and lysosomes fuse together (Amir and Czaja 2011). Autophagosomes, submerged cytosolic double-membrane structures attached with lysosomal enzymes, degrade the cellular constituents, and then autophagy-related genes (Atgs) are responsible for regulating the overall process (Czaja 2011). Atg knockout mice exhibited a fourfold increase in liver mass due to the failure to degrade appropriate cellular components (Czaja

2011). While lysosomal lipase degrades lipoproteins via endocytosis, macroautophagy activates the cleavage of triglycerols and cholesterols stored in hepatocytes and releases FFAs through a process known as "lipophagy." In addition, chaperone-mediated autophagy stimulates LDs' metabolism, resulting in lipolysis via either cytosolic lipases or macroautophagy (Zhang et al. 2020).

To function properly as the primary initiative for autophagy, autophagosomes need to be formed. This step is mediated by the unc-51-like kinase 1 (ULK1), serine/threonine-protein kinase. One of the possible mechanisms underlying autophagy dysfunction in NAFLD is due to the inhibition of ULK1 by mTOR. Research has shown that chronic caloric intake is directly related to mTOR activation, which leads to the complex formation of mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) (Chung and Chung 2019). Phosphorylation by mTORC1 of ULK1 at Ser758 and Ser757 in human and mouse cells, respectively, interferes with AMP-activated protein kinase (AMPK)-binding ULK1 phosphorylation and inhibits its activation. Since autophagy initiation by ULK1 is inhibited via mTORC1 activation, the action of autophagy is reciprocally regulated by mTORC1 (Fig. 1) (Kim and Guan 2015). Studies have shown that Atg7 knockdown and reduced LC3-II cause decreased levels of autophagic flux with hepatomegaly (Kim et al. 2013; Tsai et al. 2017). Regarding protease enzymes, calpain 2 expression was found to increase compared to that of calpain 1. Research has also shown that calpain 2 activation leads to the loss of Atg3 and Atg7 activities, decreasing

Fig. 1 On the left, increased caloric intake affects the mTORC1, AMPK and ULK1 network and inhibits autophagy. On the right, the activation of calpain-2 results in the loss of Atg3 and Atg7 required to activate autophagy. The loss of function would result in decreased autophagy activity. *mTORc1* mammalian target of rapamycin complex 1, *ULK1* Unc-51-like kinase 1, *Atg3* autophagy related 3, and *Atg7* autophagy related 3
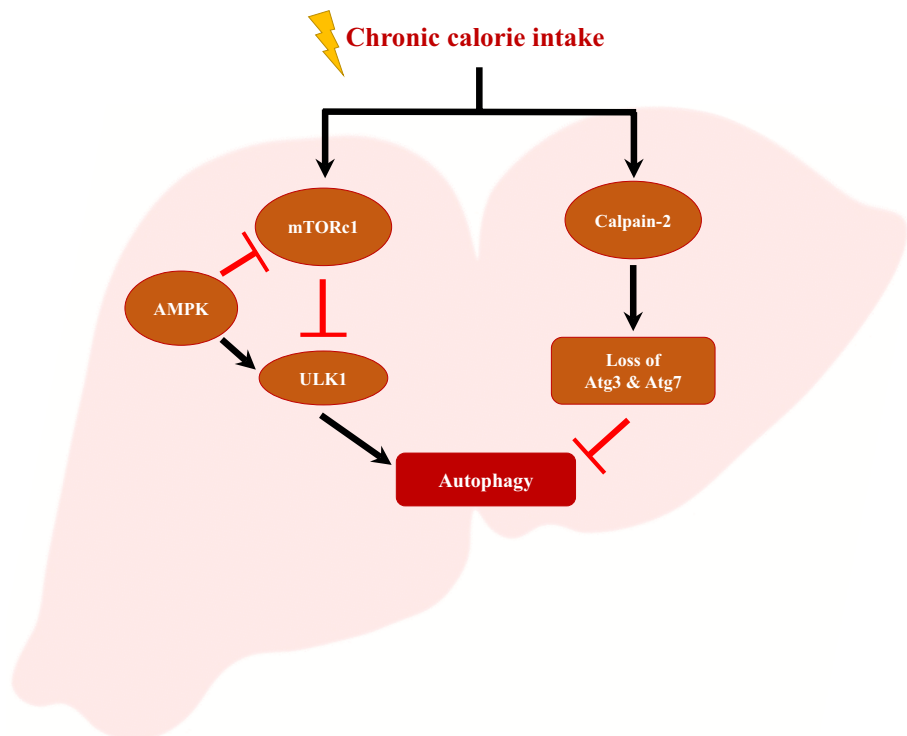
autophagy in hepatocytes with the progression of fatty liver and IR (Kim et al. 2008) (Fig. 1).

Another mechanism proposed for the inhibition of macroautophagy in hepatocytes results from the dysregulation of a protease called autophagy-related protein 4B (ATG4B) and RAS-related protein-8b (Rab-8b), which is mediated with liver X receptor α (LXRα) (Kim et al. 2020). In this event, LXRα transcriptionally induces the *MIRLET7A* and *MIR34A* genes to inhibit ATG4B and Rab-8B, suppressing mitochondria biogenesis and fuel consumption. Persistent over-activation of LXRα (due to HFD feeding and/or excessive calorie intake), therefore, worsens NAFLD (Kim et al. 2021).

Alcoholic liver disease (ALD), including alcoholic hepatitis, is the most prevalent liver disease worldwide. ALD is defined by the accretion of neutral lipids and lipid metabolism disruption prior to liver damage. Obesity is another risk factor for ALD development; the incidence of ALD increases by 2–3 times in individuals with steatosis (Parker et al. 2019). Alcohol-induced, kynurenine-mediated AhR activation in hepatocytes is responsible for autophagy inhibition, exacerbating liver steatosis. The importance of different types of cells involved in the NAFLD progression has also been demonstrated at the molecular levels (Jin 2020; Kumar et al. 2021). Studies have provided detailed insights into the role of metabotropic interactions in hepatic parenchymal (hepatocytes) and non-parenchymal cells. These interactions negatively affect autophagy, and therefore mitochondrial activity and biogenesis, via various nuclear receptors as lipid or sensors/or amino acid metabolites in aggravating alcoholic and non-alcoholic liver diseases, either pathological or non-pathological pathways (Choi et al. 2019, 2021).

Endoplasmic reticulum (ER) stress

Hepatocytes have numerous ERs, similar to other secretory cells, because of their protein synthesis capability. ER is involved in the folding of secreted and transmembrane proteins, a process achieved with the assistance of chaperone proteins. The ER also houses enzymes that synthesize cholesterol and triacyl-glycerides (TAG) for energy storage (Little et al. 2007). However, increased levels of saturated fatty acids trigger the excess storage of misfolded or unfolded proteins in the ER lumen, a process known as ER stress. In order to restore homeostasis, ER stress accelerates the unfolded protein response (UPR), a signal transduction pathway located in the ER lumen, which is also known as the regulator of ER proteostasis surveillance (Wang and Kaufman 2016). UPR adaptively stimulates the increased expression of ER proteins, including ER membrane proteins, to extend the organelle space and produce more chaperone proteins required for protein folding. Additionally, UPR activation reduces the total protein synthesis, thereby lessening

the workload of the ER, enhancing the secretion of folded proteins, and eliminating misfolded proteins via autophagy and ER-associated protein degradation (ERAD) (Hetz et al. 2020). The ERs' physiological activity shears the inter-progressive relationship between ER stress and fatty acid synthesis. Chronic ER stress is also associated with NAFLD as it contributes to lipid accumulation, inflammation, and hepatocyte apoptosis (Liu et al. 2021).

The UPR acts as an ER stress sensor through various major pathways: protein kinase RNA-like ER kinase (PERK), eukaryotic translation initiation factor 2α(eIF2α), inositol-requiring protein 1 α(IRE1α), X-box binding protein 1 (XBP1), and activating transcription factor 6α(ATF6) (Xu et al. 2021). Both PERK and IRE1α are widely known as type I transmembrane proteins with the same ER luminal and cytosolic Ser/Thr kinase domains. However, ATF6α is a type II transmembrane protein and has a cytosolic cyclic AMP response element-binding protein (CREB) ATF with a basic leucine zipper domain (Oslowski and Urano 2011). In the resting state, an ER chaperone known as immunoglobin binding protein (BiP) binds to IRE1α or PERK. This binding deactivates the ER stress sensors pathway. When the ERs are stressed, unfolded or misfolded proteins accumulate. BiP binds to these unfolded or misfolded protein peptides, thereby deactivating the ER stress sensors pathway. Alternatively, the unfolded proteins bind directly to IRE1α or PERK activated after unbinding from BiP (Hetz et al. 2020).

PERK activation results in the phosphorylation of eukaryotic translation initiation factor 2α (eIF2α), which reduces the general protein translation to relieve the ER workload. eIF2α selectively enhances the production of the stress-inducible transcription factor, ATF4. It activates to express the genes associated with amino acid metabolism, antioxidative response, autophagy, and ER protein folding. The chronic activation of ATF4 stimulates the expression of transcription factor C/EBP homologous protein (CHOP) (Li et al. 2018). Usually, CHOP remains dormant; however, under persistent stresses such as increased toxins, metabolic inhibitors, and nutrient deprivation, CHOP is activated and arrests the growth and induction of DNA damage-inducible gene 153 (GADD153) (Batchvarova et al. 1995). The overexpression of CHOP sensitizes hepatocytes to apoptosis by promoting ER stress, whereas the opposite was shown with decreased CHOP expression. Therefore, decreased CHOP levels attenuate ER stress-induced apoptosis in the liver (McCullough et al. 2001).

IRE1α contains ribonuclease and kinase domains within the cytosolic region. Under ER stress conditions, the activation of IRE1α leads to the stimulation of the ribonucleolytic activity of itself, resulting in a small intron being excised from the XBP1 mRNA (Fig. 2). This process is known as non-conventional splicing. This excision/splicing causes a shift in the translational reading frame,

Fig. 2 On the left, chronic caloric intake causes TG accumulation and then activates IRE1α, causing cleavage of XBP1 to XBP1s, which promotes unfolded protein response in early phase. On the right during late phase, IRE1α activate TRAF2 which activate ASK, leading to JNK phosphorylation. NF-κB inhibits the phosphorylation of JNK. Persistent activation of JNK, however, leads to Bim activation, which triggers apoptosis. *TG* triglyceride, *IRE1α* inositol-requiring transmembrane kinase/endoribonuclease 1α, *TRAF2* tumor necrosis factor receptor-associated factor 2, *ASK1* apoptosis signal kinase 1, *NF-κB* nuclear factor-κB, *JNK* c-Jun N-terminal kinase, and *Bim* bcl-2-interacting mediator of cell death
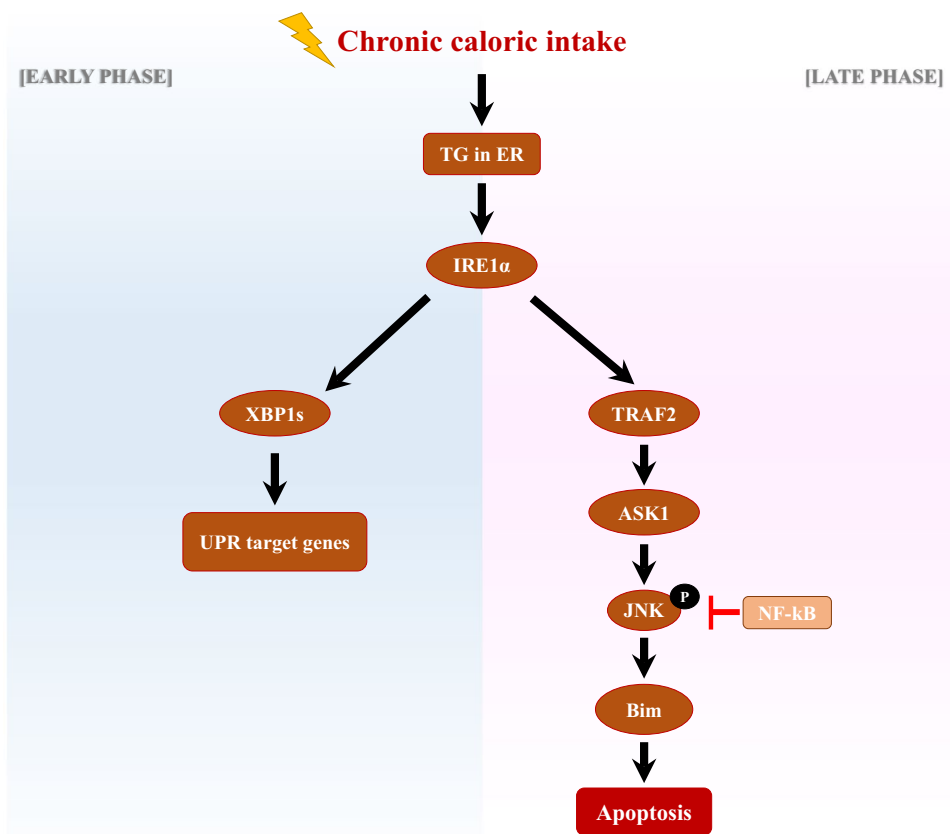
leading to the production of an active XBP1 transcription factor, XBP1s. It also upregulates genes related to protein folding, translocation, and secretion, as well as degradation (Calfon et al. 2002). Additionally, IRE1α exerts its ribonucleolytic activity on mRNAs in the ER membrane, encoding specific secretory proteins such as proinsulin or IRE1α itself. This process, which reduces the abundance of mRNA and the protein folding load, is known as regulated IRE1-dependent decay (RIDD) (Deng et al. 2013). Under chronic and excessive ER stress, IRE1α activates Jun amino-terminal kinase (JNK) and apoptosis signal kinase 1 (ASK1) by engaging the adaptor protein and tumor necrosis factor receptor-associated factor 2 (TRAF2) (Calfon et al. 2002). JNK phosphorylation stimulates proapoptotic Bcl-2 only-like protein 11 (Bim), which ultimately induces apoptosis. Studies have shown that nuclear factor kappa B (NF-κB) inhibits JNK activation, preventing the induction of apoptosis in normal cells. However, prolonged stress conditions mean that apoptosis through JNK activation prevails in the antiapoptotic function by NF-κB. Stimulating proapoptotic BH3-only proteins transcriptionally or post-transcriptionally leads to proapoptotic Bax and Bak stimulation by antagonizing antiapoptotic members (Fig. 2) (Hetz et al. 2006).

ATF6 is translocated from the ER to the Golgi apparatus under ER stress conditions. In the Golgi apparatus, ATF6 is split, and a fragment known as the basic leucine zipper domain (bZip) transcription factor is released. This transcription factor induces gene expression after being translocated inside the nucleus. Both bZip and XBP1s act similarly to the one described above (Lee et al. 2002).

Gα12 overexpression is promoted by ER stress via the IRE1-Xbp1 pathway, which subsequently feeds forward an ER stress-induced vicious cycle in the hepatocytes. Thus, ER stress-induced Gα12 induction may cause hepatocyte death, leading to drug-induced liver disease symptoms. This process is notable because Gα12 overexpression can initiate arachidonate 12-lipoxygenase (ALOX12)-dependent lipid peroxide generation via Rho-associated kinase 1 (ROCK1), facilitating polyunsaturated fatty acids (PUFA) peroxidation, hepatocyte ferroptosis, and eventually fibrosis (Tak et al. 2022). The dysregulation of miR-15a aids in the induction of ALOX-12. ER stress has also been shown to cause liver fibrosis in activated hepatic stellate cells (HSCs), as indicated by the significant association between ER stress and HSC activation in animal models and patients (Gupta et al. 2010). At the molecular level, ER stress-induced dysregulation of primary-miR-18a processing leads to SMAD2

overexpression via the direct phosphorylation of hnRNPA1 at the Thr51 site by PERK (Koo et al. 2016). In cancer biology, sorafenib resistance is attained by ER stress via the upregulation of PMK2 by miR-188-5p/hnRNPA2B (Zhou et al. 2021).

Collectively, under physiological ER stress levels, the UPR sensors are activated to maintain homeostasis, resulting in a reduction of protein synthesis, increased protein folding, promotion of autophagy, and increased degradation of misfolded proteins. However, when the ER stress level exceeds the threshold, ER stress-mediated cell death and apoptosis are initiated (Hughes and Mallucci 2019).

Insulin resistance

IR is primarily responsible for the pathogenesis of T2D, NAFLD, and its more severe form, NASH (Holt et al. 2006). The hepatic IR augmented by FFA influx and the overstimulation of pro-inflammatory cytokines and lipid intermediates in the liver is explained by the impediment to the phosphorylation of insulin receptors (Petito-da-Silva et al. 2019). However, the exact mechanism of IR is still debatable and is hypothesized on the consequences of following events in the body. As per the traditional "two-hit" hypothesis, hepatic lipid deposition is secondary to an inactive/desk-bound lifestyle, having HFD intake that leads to obesity, and a consequent triggering of IR, which serves as a first fundamental hit to sensitize the liver, and subsequently activates inflammatory cascades (Rada et al. 2020).

Others

Excessive caloric intake unbalances hepatic physiological functioning due to the dysfunction of organelles, which can cause a variety of metabolic syndromes, including diabetes, fatty liver disease, and obesity. An electron shift occurs between substrates to oxygen, whereby protons are eliminated from the mitochondrial complex and maintain a chemiosmotic gradient that further boosts ATP production due to ATP synthase activity (Li et al. 2000). Recent studies have revealed that patatin-like phospholipase domain-containing protein 3 (PNPLA3) is associated with central fat accumulation (Trepo et al. 2016). Central fat accumulation also releases chronic inflammatory mediators, such as cytokines, and disrupts the insulin-glucagon balance (Liu et al. 2020). Another recent study has confirmed that phosphorylation of the iroquois homeobox gene 3 (IRX3, a protein involved in tissue/organ patterning or development) by the JNK leads to obesity and macrophage infiltration (Yao et al. 2021). To date, it is well established that macrophagic infiltration is involved in the progression of NAFLD and liver steatosis (Lefere et al. 2020).

The literature has shown that the most commonly used mouse models for obesity and NAFLD (Koo et al. 2017). HFD-induced obesity and hyperglycemia in animals result in elevated levels of Gα13 in skeletal muscle. In addition, a new scientific explanation for Gα13 has recently provided a new molecular mechanism for diabetes when the liver is compromised. In response to hyperglycemic stimuli, the challenged liver tissues show a decrease in Gα13 levels in both mice and humans. Secretome analysis has revealed that a decrease of Gα13 promotes the production of inter-a-trypsin inhibitor heavy chain 1 (ITIH1) in the liver. The circulation of ITIH1 is then associated with IR in peripheral tissues, including skeletal muscle and adipose tissue. Mechanistically, the reduced Gα13 levels in hepatocytes activate O-GlcNAc transferase induction, which is responsible for IR, via the stabilization of ITIH1 and its binding with HA (Kim et al. 2019).

The ligands that specifically activate G protein-coupled receptor (GPCR) coupling to Gα_{12} members (the ligands of which include sphingosine-1-phosphate (S1P), lysophosphatidic acid, angiotensin II (Ang II), thrombin, and endothelin-1) enhance liver fibrosis (Alexander et al. 2021). Of the Gα_{12} members, Gα_{12} has the potential transforming ability, cell proliferation, migration, and inflammation (Suzuki et al. 2009). Since Gα_{12} acts through GPCRs, resulting in enhanced signaling cascades (Suzuki et al. 2009), changes in Gα_{12} levels amplify or dampen the biological and physiological processes (Okashah et al. 2020). Gα_{12} overexpression in activated HSCs promotes liver fibrosis because of the downregulation of miR-16 and miR-29a (Huang et al. 2015; Kim et al. 2018), which is directly related to JNK-dependent ATG12-5 (Kim et al. 2018; Wible et al. 2019). Therefore, GPCR substrates, G proteins, and related dysregulation of microRNA mediators can all potentially contribute to NAFLD, ALD, and liver fibrosis.

In another study, E2 and ERα were found to be mutually associated with Gα_{12} in patients with HCC and their overall prognoses. However, ERα expressions were reported to have an inverse relationship to Gα_{12} in cell-based experiments and human tissue (Yun et al. 2022). Ligand-mediated activation of ERα restrains Gα_{12} gene transactivation, leading to microRNA-141 and -200a downregulation via the Gα_{12}–RhoA axis (Yun et al. 2022) and promotes the amoeboid movement of cancer cells. In this paper, Gα_{12} antagonism by ERα can be explained by the gender discrepancy in HCC prognosis.

Roles of liver secretome

In association with the above pathologic factors, recent attention was paid to the roles of liver secretory proteins in liver disease progression since they play diverse roles in regulating fuel metabolism and inflammatory processes in

different cells and organs. In this section, we will discuss the representative liver secretory proteins associated with metabolic and inflammatory liver diseases (Table 1).

Proteins associated with acute phase response proteins and proinflammation

Fetuins A and B

Fetuins belong to the cystatin family and protease inhibitors and are considered acute phase response proteins (Brown and Dziegielewska 1997). Fetuin-A (α2-Heremans-Schmid glycoprotein, AHSG, Alpha-2-HS-glycoprotein) is efficiently expressed in serum, liver, tongue, and placenta (Denecke et al. 2003). Fetuin-B is majorly expressed in the liver, with serum concentrations of about 0.01 g/l and 0.3 g/l in humans and mice, respectively (Denecke et al. 2003). Fetuin levels were positively related in patients with elevated glucose contents, obesity (Peter et al. 2018), NAFLD, and T2D. Hence, fetuin was proposed as a potential biomarker for IR (Meex et al. 2015). Interestingly, enhanced fetuin-A levels were directly related to the loss of hepatic Gα13 and were related to chronic inflammation (Kim et al. 2019). Fetuin-A and B were also elevated in patients with liver steatosis. In contrast, fetuin A was found lowest in the patients with the final stage of alcoholic liver cirrhosis as compared to the initial stages (Prystupa et al. 2016). The circulating levels of fetuin-A were thus directly related to hepatic fat content, while both fetuin-A and B positively correlated with glucose area under the curve and oral glucose tolerance test results (Peter et al. 2018). In the same study and another one, fetuin-A stimulated IR in association with FFA through TLR_4 (Pal et al. 2012; Peter et al. 2018). Fetuin-B is primarily released from the hepatocytes, and the levels were also elevated in T2D patients; consistently, HepG2 cells treated with fetuin-B showed enhanced lipid accumulation (Meex et al. 2015; Zhou et al. 2019). Mechanistically, fetuin-B decreases the phosphorylation of 5'-adenosine monophosphate-activated protein kinase (AMPK) (Zhou et al. 2019).

Serum amyloid A-2 protein

Serum amyloid A (SAA) belongs to four homologous alpha-helical amphipathic proteins encoded at chromosomes 7 and 11 in mice and humans, respectively. C-reactive proteins (CRP) and SAA subtypes are increased > 1000 times in the case of inflammation. CRP and SAA are primarily regulated by IL-1 and TNF-α in the presence of IL-6. SAA4 is mainly expressed in the liver. Apoe$^{-/-}$ mice fed with a high fat, high cholesterol diet (HFHCD) for 12 weeks showed elevated levels of SAA by inhibiting liver-specific ATP-citrate lyase. HFHCD feeding for 12 weeks resulted in chronic systemic inflammation and raised 1.3-fold plasma concentrations of SAA (Samsoondar et al. 2017). In another study, enhanced SAA levels were reported in obese humans and mice, and their respective livers showed elevated SAA2 mRNA levels (Chiba et al. 2009). Similar results were obtained using Apoe$^{-/-}$ mice (Chiba et al. 2009). The loss of hepatic Gα 13 in mice resulted in elevated ITIH1 and SAA2 levels. Both ITIH1 and SAA2 seem to be related to obesity, T2D, and NAFLD (Kim et al. 2019).

A number of studies showed a the strong association of SSA with the severity of COVID-19, emphasizing its prognostic value for COVID-19 (Goncalves and Sesterheim 2021; Zinellu et al. 2021). Two meta-analysis studies also validated its positive correlation in COVID-19 patients (Zhang et al. 2021; Zinellu et al. 2021). Mechanistically, one paper described the enhancement of amyloid formation of SAA in vitro in its nine-residue segment located at the C-terminus of the envelope protein of SARS-CoV-2 (Jana et al. 2021). It remains to be established whether the virus-induced upregulation of amyloid formation aggravates COVID-19.

Ceruloplasmin

Ceruloplasmin (Cp) belongs to glycoproteins (~ 150 kDa) and is primarily produced in the liver; Cp acts as the eighth binding atom of copper ions to the apo ceruloplasmin (Wolf and Griffiths 1982). Thus, Cp serves as a serum ferroxidase and transporter for copper (Wolf and Griffiths 1982). The amount of transferrin (FeIII) is a primitive sign to assess the iron concentrations in serum. The oxidation of FeII to FeIII by serum ferroxidase follows a zero-order reaction, and therefore a reduced Cp level lowers iron content in the blood (Roeser et al. 1970; Vachette et al. 2002). Studies have also shown that inherited Cp loss and low hepcidin serum levels lead to aceruloplasminemia (Kono 2012); Aceruloplasminemia is associated with diabetes and liver cancer because of intrusion in glucose metabolism due to hemochromatosis (iron toxicity) (Niederau et al. 1996; Cairo et al. 2001). The findings of another study showed that aceruloplasminemia is associated with increased iron storage in the liver and brain with low serum Cp levels (Loréal et al. 2002; Finkenstedt et al. 2010). A cohort study including 328 NAFLD patients showed that Cp gene mutation was related to hyper-ferritinemia, liver siderosis, and fibrosis (Corradini et al. 2021). Cp variants-associated hyperferritinemia and specific mutation of gene rs61733458 were reported in NAFLD patients (Pelucchi et al. 2021). The levels of Cp were lower in children with higher NAFLD scores, which may be due to the inability of the liver to produce Cp in the patients (Nobili et al. 2013). In another study, however, Cp levels were increased in the states of mild to severe steatosis (Liu et al. 2022). HFD-fed Gα13 LKO mice showed elevated Cp levels (i.e., a 2.2-fold change) (Kim et al. 2019).

Table 1 Representative liver secretory proteins and their functions

Proteins	Reported activities	Expression	References
Proteins associated with acute phase response protein and proinflammation			
Fetuin-A	• Raised serum levels in liver fibrosis, NAFLD and T2D • Fetuin-A promotes IR and raises blood glucose by activating TLR4 • Gα13 hepatic knockout leads to the surge of fetuin-A • Fetuin-A levels were reported lowest in patients with severe alcoholic liver cirrhosis	Hepatocytes	Pal et al. (2012), Meex et al. (2015), Prystupa et al. (2016), Peter et al. (2018) and Kim et al. (2019)
Fetuin B	• Elevated concentrations reported in T2D and hepatic steatosis • Fetuin B inhibits LXR-SREBP1c and increases fatty acid oxidation, enhances IR and blood sugar levels	Hepatocytes	Meex et al. (2015), Peter et al. (2018) and Zhou et al. (2019)
Serum Amyloid A-2 protein (SAA2)	• 1.3-fold plasma concentrations elevated after treating mice with the HFHCD diet • Serum SAA2 levels increased in obese patients • Gα13 loss results in SAA2 upregulation	Liver	Chiba et al. (2009), Samsoondar et al. (2017), Kim et al. (2019)
Ceruloplasmin (Cp)	• Aceruloplasminemia positively related to diabetic and HCC patients • Mutation in Cp genes resulted in hyper-ferritinemia and fibrosis • Cp levels were found lower in children with higher NAFLD score due to hepatic inability to produce Cp • Gα13 loss results in Cp overexpression	Liver and lungs	Niederau et al. (1996), Cairo et al. (2001), Nobili et al. (2013), Kim et al. (2019) and Corradini et al. (2021)
Alpha-1-acid glycoprotein (AGP)	• In NAFLD patients, AGP shows a positive correlation with collagen • AGP desialyation raises its expression in liver diseases • Levels of AGP showed a severity-dependent increase in patients with mild to severe steatosis • HFD-fed primary hepatocytes of Gα13 showed a pronounced surge of AGP	Hepatocytes	Serbource-Goguel et al. (1983), Younossi et al. (2017), Kim et al. (2019) and Liu et al. (2022)
Hemopexin (HPX)	• Increased heme toxicity in animals and humans was observed with reduced levels of HPX • Loss of Gα13 positively regulates HPX levels • HPX knockout mice exhibit overstimulation of ROS and TLR4 receptors resulting in chronic inflammation • HPX levels were found elevated in HCC patients compared to those with cirrhosis without HCC or with fibrosis	Liver	Debruyne et al. (2010), Lin et al. (2015), Vinchi et al. (2016) and Kim et al. (2019)

Table 1 (continued)

Proteins	Reported activities	Expression	References
Binding carrier of hormones or lipids			
RBP4	• Its levels were found to be raised in obesity and T2D • Serum RBP4 showed controversial results in NAFLD patients • RBP4 increases IR by the stimulation of JNK and TLR4 • The levels of RBP4 were found elevated by the loss of Gα13	Hepatocytes and adipocytes	Graham et al. (2006), Wu et al. (2008), Nobili et al. (2009), Norseen et al. (2012), Kim et al. (2019), Zhong et al. (2019) and Wang et al. (2020)
Precursors of receptor ligands or hormones			
Angiopoietin-like protein 1 (ANGPTL1)	• In-vitro studies showed that ANGPTL1 inhibits the hepatocyte's growth factor-induced MET phosphorylation • It was also found to be involved in the suppression of metastasis of hepatoma cells, whereas its serum levels were reduced in HCC • ANGPTL1 expressions were reduced in colorectal carcinoma	Vascularized tissue and colon cells	Kuo et al. (2013), Chen et al. (2016) and Chang et al. (2022)
ANGPTL2	• ANGPL2 expressed in patients with HCC, also in thyroid cancer and lung carcinoma	Hepatocytes	Gao et al. (2015), Wei et al. (2017) and Yang et al. (2019)
ANGPTL3	• The serum concentration of ANGPTL3 reduced in obese patients • Single or multiple dose treatments of ANGPTL3 reduced plasma HDL, LDL and increased plasma TAG	Hepatocytes	Musso et al. (2012) and Graham et al. (2017)
ANGPLT4	• Obese patients showed enhanced serum levels • Loss of ANGPTL4 results in inhibition of lipoprotein lipase and raised HDL levels • HCC and ER stress leads to diminished ANGPTL4 levels	Liver and adipose tissues	Romeo et al. (2007), Romeo et al. (2009), Lichtenstein et al. (2010), Singh et al. (2021) and Spitler et al. (2021)
ANGPTL6	• ANGPTL6 knockout mice showed weight gain, increases in rectal temperature, basal metabolic rate, food intake, enhanced HDL and TAG, and aggravated IR and blood glucose levels • ANGPTL6 serum concentrations were raised in NAFLD and T2D	Hepatocyte-induced circulating factors	Oike et al. (2005), Ebert et al. (2009) and Ma et al. (2019)
ANGPTL8/betatrophin	• ANPTL8 is commonly known as HCC-associated protein and increased in T2D and liver steatosis with elevated TAG, IR, and glucose levels • ANGPTL8 inhibits AMPK-mediated activation of SREBP1c and results in HCC progression	Liver	von Loeffelholz et al. (2017) and Wang et al. (2018)

Table 1 (continued)

Proteins	Reported activities	Expression	References
Fibroblast growth factor 1 (FGF1)	• Elevated in obese patients as well as in liver fibrosis and biliary proliferation • Administration of FGFR1 antagonist results in the protection against hepatic fibrosis	Hepatic stellate cells	O'Brien et al. (2022)
FGF2	• In BDL mice, administration of FGF2 ameliorates liver fibrosis • FGF2 levels were found elevated in patients with HCC	Hepatic stellate cells and adipocytes	Jim-No et al. (1997) and Sato-Matsubara et al. (2017)
FGF 19, FGFR4 and beta-klotho	• FGFR4 impaired signaling results in diminished expression of FGF19 • FGF19 serum levels were in parallel to bile acid in NASH patients • ER stress elevates the b-klotho and FGF19 in patients with HCC	Ileum, liver, and cholangiocytes	Miura et al. (2012) and Jiao et al. (2018)
FGF21	• FGF21 analog leads to amelioration of steatosis, inflammation, and IR • Deficiency of CYP2E1 activates the PPARα-FGF21 axis, increasing the adipose browning with reduced obesity	Liver and Pancreas	Zarei et al. (2020), Su et al. (2021) and Zhang et al. (2022)
Pigment epithelium-derived factor (PEDF)	• PEDF synergizes the breast cancer proliferation • Hepatic metastasis was negatively regulated with PEDF • PEDF levels were higher in T2D with CKD, and with the loss of Gα13 LKO, PEDF levels were increased	Hepatocytes and adipocytes	Fitzgerald et al. (2012), Hui et al. (2014), Protiva et al. (2015) and Kim et al. (2019)
Hepassocin (HPS)	• Serum analysis showed elevated in patients with T2D and NAFLD • ER-stress in primary hepatocytes increased HPS in a dose-dependent manner	Liver	Wu et al. (2013), Jung et al. (2018), Abdelmoemen et al. (2019) and Watt et al. (2019)
Angiotensinogen	• Gα13 LKO primary hepatocyte analysis showed a 2.583-fold increase in angiotensinogen • Angiotensinogen-induced ER stress and ROS are primitive culprits in HTN	Liver, kidney, and heart	Furmanik and Shanahan (2017), Dikalov and Dikalova (2019) and Kim et al. (2019)
Coagulation factors & proinflammatory mediators			
Plasma Protease C1 inhibitors (C1 INH)	• Deficiency of C1 INH causes congenital hereditary angioedema type I • Excessive bradykinin production is a sign of genetic deficiency of C1 INH • Primary hepatocytes fed up with HFD in Gα13 LKO showed elevated expression of C1 INH • C1 INH levels were reduced in patients with COVID-19, T2D, and steatosis	Liver	Clermont et al. (2011), Oschatz et al. (2011), Ivanov et al. (2019), Kim et al. (2019), Medjeral-Thomas et al. (2021), Karnaukhova (2022) and Subudhi et al. (2022)

Table 1 (continued)

Proteins	Reported activities	Expression	References
Xanthine oxidase/dehydrogenase XOR/D	• CDAHFD-fed NAFLD mice showed elevated XO plasma levels • Primary hepatocytes treated with HFD showed a rise in XOR/D levels • GLUT9 and SLC2A9 deficiency showed increased XOR/D activity	Liver and kidney	DeBosch et al. (2014), Kim et al. (2019) and Kawachi et al. (2021)
Mannose Binding Protein C (MBP-C)	• MBP-C aggravates the complement system and promotes tissue damage (thromboembolic system) in COVID-19 patients, and hepatic loss of Gα13 results in MBP-C enhanced expressions	Liver	Kim et al. (2019) and Asselta et al. (2022)
Structural proteins in association with ECM			
Inter-α-trypsin inhibitor heavy chain 1 (ITIH1)	• HFD-fed to transgenic Alzheimer's disease mice showed a 1.54-fold increase in ITIH1 levels • The deficiency of ITIH1/ITIH3 altered the mice's behavior • LPS primed HFD mice showed reduced ITIH1 levels • ITIH1 levels were found higher in patients with T2D and NAFLD	Liver	Goulding et al. (2019), Kim et al. (2019), Manuel et al. (2019) and Wang et al. (2021)
ITIH2	• HFD-fed mice showed a positive relation with ITIH2 in Alzheimer's disease • ITIH2 was found reduced in patients with breast cancer • Significantly diminished ITIH2 levels were observed in LPS primed HFD mice showed • Gα13 loss results in enhanced expression of ITIH2	Liver	Hamm et al. (2008), Kim et al. (2019), Manuel et al. (2019) and Wang et al. (2021)
ITIH4	• COVID-19 patients showed decreased ITIH1, ITIH2, and ITIH4, whereas ITIH1 and 2 were overexpressed in COVID-19 patients • ITIH4 levels decreased in patients with T2D and NAFLD	Liver	Kim et al. (2019), Demichev et al. (2021a) and Geyer et al. (2021)

In addition, copper and Cp showed positive correlations in COVID-19 patients (Hackler et al. 2021). In particular, surviving patients exhibited much higher mean serum copper and CP levels compared to non-survivors (Hackler et al. 2021), suggestive of their potential use as prognostic markers for COVID-19 progression.

Alpha-1-acid glycoprotein-1

Alpha-1-acid glycoprotein (AGP), also known as *orsomucoid* (ORM), is a 44 kDa acute phase response protein and is the most abundantly occurring protein. AGP is mainly secreted by the hepatocytes, and the consequential human serum levels vary between 0.5 and 1.2 g/l (Ceciliani and Pocacqua 2007). It exists in two forms, AGP1 and AGP2. AGP has anti-inflammatory and immunomodulatory, antineutrophil, and anti-complementary effects in cases of inflammation, infection, and tissue grievance; however, the exact mechanism involved in this activity is still in debate (Ceciliani et al. 2002). Previously, it was believed that cytokines release is the major factor for the elevated expression of the AGP and its release from the hepatocytes. In the study, AGP levels were elevated after treatment with phenobarbital. Interestingly, endogenous secretion of IL-1 and IL-6 does not play a major role in the induction of AGP (Gauldie et al. 1987). After asialation, AGP levels were increased in patients suffering from severe liver diseases (Serbource-Goguel et al. 1983). More than a four-fold AGP increase was found in mild steatosis, whereas a sevenfold increase was observed in patients with severe steatosis (Liu et al. 2022). Of note, primary hepatocytes from HFD-fed Gα13 LKO mice showed enhanced expression of AGP1 (Kim et al. 2019), suggesting its association with the Gα13/12 signaling pathway. In another study, AGP1 positively correlated with the percent changes of collagen in the liver of NAFLD patients, whereas a negative relationship was found with apolipoprotein C-II in the fatty liver (Younossi et al. 2017).

Hemopexin

Hemopexin (HPX, 60 kDa) is the plasma glycoprotein with heme binding capability. HPX is majorly found in the liver and belongs to the acute phase responsive proteins. In the case of injury with inflammation, their levels are found to be significantly higher (Fiorito and Tolosano 2022). Analysis of 163 patients showed raised hemopexin articulation with lymph node ratio, venous invasion, and lymphatic invasion (Suzuki et al. 2020). Sickle mice (Hx-null) showed increased ROS and stimulation of Toll-like receptor 4 signaling mechanisms as well as cytokines, whereas the administration of HPX attenuated inflammatory and macrophage-activating pathways (Vinchi et al. 2016). The consequences

of experiments using animal and patient samples exhibited reduced levels of hemopexin and decreased neutralized heme in patients with acute respiratory distress syndrome, burns, or premature infants; however, beneficial outcomes were observed after treatment with hemopexin (Lin et al. 2015).

The results of another study show that long-term subarachnoid hemorrhage is the primitive culprit for the cytotoxicity of heme and lower levels of HPX (Garland et al. 2016). HPX was elevated in patients with HCC, compared to those with either cirrhosis without HCC or fibrosis, and healthy volunteer groups (Debruyne et al. 2010). A mouse model with hemorrhagic shock was protected by treatment with either haptoglobin or hemopexin. Moreover, these treatments protect the kidney from injury associated with a high level of plasma hemoglobin (Graw et al. 2016).

Binding carrier of hormones or lipids

Retinol binding protein 4

Retinol-binding protein 4 (RBP4) is a polypeptide chain having a molecular weight of 21 kD and belongs to the lipocalin family. RBP4, majorly produced in the liver, acts as a serum carrier protein for vitamin A transport. Patients suffering from obesity or those with impaired glucose metabolism, IR (Graham et al. 2006; Haider et al. 2007), and T2D (Graham et al. 2006; Wu et al. 2008) showed elevated serum RBP4 levels, whereas this change was reversed with diet-associated weight loss, bariatric surgery, and exercise (Haider et al. 2007). However, in the case of NAFLD, some study results showed direct relation of RBP4 to NAFLD (Zhong et al. 2019), but others did an inverse relationship of RBP4 with NAFLD (Nobili et al. 2009; Wang et al. 2020). RBP4 leads to the activation of pro-inflammatory cytokines in mice and humans and interrupts insulin signaling by the stimulation of JNK and TLR4 molecular pathways (Norseen et al. 2012). Adipose-$Glut4^{-/-}$ mice showed a 2.5-fold increase in serum concentration of RBP4 compared to the control. The resultant increase of RBP4 activates hepatic expression of a gluconeogenic enzyme (i.e., phosphoenolpyruvate carboxykinase), disturbing muscle insulin signaling (Yang et al. 2005).

Precursors of receptor ligands or hormones

Angiopoietin-like proteins

Angiopoietin-like proteins (ANGPTLs), highly hydrophobic paracrine factors, are ramified into eight members. Of them, ANGPTL 1–7 share structural resemblance and serve as ligands for Tie receptors (TieI or Tie1) (Oike et al. 2003). ANGPTLs are majorly expressed in various organs, such as the liver, kidneys, vascular system, and hematopoietic

system, and are involved in the regulation of angiogenesis, inflammation, and lipid metabolism (Tabata et al. 2009; Chen et al. 2016). Studies have proved that ANGPTL 1 and 2 were related to hepatocellular carcinomas (Chen et al. 2016; Carbone et al. 2018). In addition, ANGPTLs are found to have a regulatory impact on lipid metabolism and angiogenesis, being considered therapeutic candidates for metabolic syndrome (Li and Teng 2014). Serum ANGPTL4 levels were raised in obese patients with or without T2D; correspondingly, the levels of ANGPTL3 were decreased respectively (Cinkajzlová et al. 2018). Both ANGPTL 3 and 4 are highly expressed in the liver, whereas ANGPTL4 hepatic expression is 10% of the adipose tissue (Koishi et al. 2002; Romeo et al. 2009). ANGPTL4 is also known as hepatic fibrinogen/angiopoietin-related protein. Studies have proven that the deletion of ANGTL4 in mice and its mutational loss in patients leads to decreased triglycerides and elevated high-density lipoproteins levels via inhibition of lipoprotein lipase activity, protecting patients against obesity, T2D, NAFLD, and steatosis (Romeo et al. 2007, 2009; Singh et al. 2021; Spitler et al. 2021). Physiologically ANGPTL4 expression is raised because of fasting, cold, exercise, and fatty acid-activated peroxisome proliferator-activated receptors (Lichtenstein et al. 2010). In another study, ANGPTL4 significantly diminished foam cell formation, inflammatory gene expression, and ER stress (Lichtenstein et al. 2010). A study focused on the effect of ANGPTL6 (also known as an angiopoietin-related growth factor) against obesity and IR reveals that ANGPTL6$^{-/-}$ mice showed a significant increase in the body weight leading to obesity on a normal chow diet. Interestingly, loss of ANGPTL6 raised the rectal temperature, basal metabolic rate, and food intake, consequently raising serum cholesterol and TAG levels. Furthermore, mice have developed IR with elevated glucose levels (Oike et al. 2005). ANGPTL6 serum levels were found to be raised in T2D and NAFLD patients (Oike et al. 2005; Ebert et al. 2009; Ma et al. 2019). ANGPTL8/betatrophin is commonly named as HCC-associated protein, TD26, or lipasin, and is found majorly in the liver and visceral adipose tissue. Elevated ANGPTL8 levels were reported in human liver steatosis and enhanced TAG levels in plasma (von Loeffelholz et al. 2017; Wang et al. 2018). TD26 mechanistically binds with the nuclear form of SREBP1, leading to elevated lipid production and tumor cell proliferation (Wang et al. 2018). ANGPTL8, in combination with ANGPTL3, acts as an inhibitor of lipoprotein lipase (Kovrov et al. 2019).

Fibroblast growth factors (FGF families)

Armelin (1973) and Gospodarowicz (1975) were the scientists who introduced the world to fibroblast growth factors (FGFs). Up till now, four members of the family have been discovered, which undergo alternative splicing and yield seven functionally distinct receptors (i.e., FGFRs 1b, 1c, 2b, 2c, 3b, 3c, and 4) with distinct ligand binding properties. The FGF family has been found to regulate energy metabolism (Ornitz and Itoh 2022). FGFR subfamilies are responsible for the release of 18 FGFs that are capable of interacting with the tyrosine kinase with the help of various cofactors (Schumacher and Guo 2016). Canonical FGFs are also paracrine FGFs which mainly exert their functions by binding with heparin. FGF19 and its subunits, i.e., FGF19, FGF21, and FGF23, interact with α-klotho, resulting in its endocrine function (Goetz et al. 2007; Ornitz and Itoh 2015; Yanucil et al. 2022). These three members are involved in endocrine functions and thus regulate bile acid, carbohydrate, lipid metabolism, cell proliferation, differentiation, and survival (Ornitz and Itoh 2015).

The study conducted using bile duct ligation (BDL) in wild-type, and Mdr$^{-/-}$ mice followed by treatment with FGFR1 antagonist (AZD4547) leads to reduced FGF1 and miR-16, resulting in a protective effect against BDL-induced hepatic fibrosis, biliary proliferation, and inflammation (O'Brien et al. 2022). FGF2 is of two types; one is a low molecular weight FGF2, whereas the other is a high molecular weight form. Administration of low molecular weight FGF2 in CCl$_4$-induced fibrotic mice led to the downregulation of Delta-like 1 via the p38 mitogen-activated protein kinase pathway, showing ameliorative effects against fibrosis (Pan et al. 2015). In another study, FGF2 treatment of mice with BDL triggers cytoglobin activation inhibits myofibroblastic human HSCs and ameliorates liver fibrosis (Sato-Matsubara et al. 2017). FGF via FGF receptor 4 (FGFr4) modulates signal transduction between Wnt16 and Dlc, activating notch signaling and leading to hepatocellular carcinoma by initiating niche formation (Lee et al. 2014). FGF19, FGF21, and FGF23, the members of FGF19, are highly expressed in the liver. These ligands are found to regulate the bile acid (BA), fatty acid, glucose, and phosphate metabolism via binding with βKlotho homologous single-pass transmembrane proteins and stimulate FGFr4 (Kurosu et al. 2007). Serum FGF19 and bile acid concentrations were found to be raised in NASH subjects, although adiponectin levels were significantly lowered (Bechmann et al. 2013). It has also been shown that decreased FGF19 and BA concentrations were associated with impaired FXR and FGFr4 signaling (Jiao et al. 2018) (Table 1). Recently, a randomized control study was performed in NAFLD patients with a score of 4 or higher, stage 1–3 fibrosis, and at least 8% liver fat content and the patients were treated with the analog of FGF19 at the dose of 3 or 6 mg for twelve weeks, which led to decreased hepatic fat contents (Harrison et al. 2018). ER stress caused elevated levels of βKlotho and FGF19 in the sera of patients with HCC (Miura et al. 2012). FGF21 and its analogs activated liver FA oxidation, significantly reducing fat buildup in the liver and improving IR.

In addition, the treatments resulted in enhanced levels of adiponectin and exhibited insulin-sensitizing, anti-fibrotic, anti-inflammatory, and anti-steatosis effects (Zarei et al. 2020). CYP2E1 level may be important in FGF21 expression; a deficiency of CYP2E1 is necessary for the activation of the PPARα-FGF21 axis and is effective in the reduction of obesity (Zhang et al. 2022).

Pigment epithelium-derived factor

Pigment epithelium-derived factor (PEDF) is an endogenous glycoprotein belonging to the serine protease inhibitor family, released by the adipocytes, retinal epithelial pigment, hepatocytes, and skeletal myocytes. It also contains an extracellular matrix binding protein site (Uehara et al. 2004; Fitzgerald et al. 2012). PEDF is a regulator of angiogenesis inhibition, immunomodulation, and neurotrophic and has antioxidant activity, antivasopermeability, and anti-tumor activity (Kawaguchi et al. 2010). Studies using human primary melanocytes, as well as an in vivo model, showed higher levels of PEDF and microphthalmia-associated transcription factor expression (Fernández-Barral et al. 2014). PEDF increased the proliferation of breast cancer cells embedded in the mouse brain (Fitzgerald et al. 2012). PEDF was negatively associated with hepatic metastasis in patients with stage II (Uehara et al. 2004) (Table 1). Overexpression of PEDF stimulates NaAsO2-induced apoptosis with an increase of p53 (Zhang et al. 2019). PEDF knockout mice showed elevated expression of the genes related to the Wnt/βcatenin pathway (Protiva et al. 2015). Moreover, the levels of PEDF were significantly enhanced in T2D patients with chronic kidney diseases (Hui et al. 2014).

Hepassocin

Hepassocin (HPS) is known as a hepatocyte-derived fibrinogen-related protein (HFREP-1) and is a liver-specific gene involved in hepatic regeneration (Ou et al. 2017). HPS/liver fibrinogen-related gene-1 expressions were reduced in HCC patients and mice treated with streptozotocin (Ou et al. 2017). The results of another study show that HNF1a interacts with IL-6/IL-6R/STAT3 trajectory and upregulates the HPS promoter transcriptional factors, resulting in the upholding of homeostases such as growth and repair, like the IGFBP-1, G6Pase, and a-fibrinogen promoters (Yu et al. 2009). The study design included patients with T2D (Group I), NAFLD (Group II), and both (Group III). The serum analysis revealed a significantly higher concentration of HPS in group III patients compared to groups I and II (Abdelmoemen et al. 2019). Another study, including 199 patients with NAFLD, showed higher levels of HPS compared to the control, and similar results were also observed in mice fed with HFD. However, the HPS knock-down mice produced by using short hairpin

RNAs targeting HPS showed recovery from the steatosis with decreased NAFLD activity score. Mechanistically, overexpression of HPS in HepG2 cells leads to fat accumulation by modulating the extracellular signal-regulated kinase 1/2 (ERK1/2)-dependent pathway (Wu et al. 2013). Palmitate-induced ER stress in primary hepatocytes showed dose-dependent increase of HPS via stimulation of C/EBPβ-mediated transcriptional factor (Jung et al. 2018; Watt et al. 2019).

Angiotensinogen

Hypertension is one of the most prevalent contributors to worldwide disease and socioeconomic burden with poor understanding (Brouwers et al. 2021). Various organs (i.e., kidneys, heart, liver, vessels, and immune cells) were found to be involved in the development and aggravation of hypertension under several mechanisms, such as oxidative stress and inflammation, obesity, and diabetes (Hossain et al. 2007).

ER stress is the primitive culprit in cardiovascular diseases because of its regulatory characteristics in vascular cell phenotype, dedifferentiation, calcification, and apoptotic mechanisms leading to hypertension and atherosclerosis (Furmanik and Shanahan 2017). ER stress leads to cardiovascular dysfunction and tissue damage (Furmanik and Shanahan 2017). The result of the study validates that reduction/inhibition of ER stress results in the amelioration of hypertension by protecting vascular dysfunction (Carlisle et al. 2016), cardiac impairment, and pulmonary hypertension (Spitler et al. 2013). SIRT 3 acts as a regulator of enzymatic antioxidant activity in mitochondria. The results of studies show that sirtuin 3 (SIRT 3) expression gets reduced in older age (i.e., > 65 years) with resultant hypertension and that metabolic diseases are also responsible for the declined/inactivity due to elevated NADH and acetyl-CoA intensities (Dikalova et al. 2017). SIRT 3 knockout mice experienced hypertension. Diminished SIRT 3 expressions because of hyperacetylation consequently result in oxidative stress in mitochondria (Dikalova et al. 2017). Recent studies specifically focused on mitochondrial interference for hypertension management (Miller Jr 2020). Administration of MitoQ10, a mitochondrial-specific antioxidant, controlled elevated blood pressure in rats by improving endothelial function and decreasing hypertrophy (Graham et al. 2009). In another study, hepatic loss of Gα13 leads to increased expressions of angiotensinogen (2.583-folds) (Kim et al. 2019).

Coagulation factors and proinflammatory mediators

Plasma protease C1 inhibitors (C1 INH)

C1 INH is an acute-phase protein known as a protease inhibitor primarily expressed in the liver. It belongs to the

serine protease inhibitor family with a molecular weight of 105 kDa. Its physiological functions in plasma include the superintendence of various proteolytic functions such as the complement, coagulation, and fibrinolytic pathways (Davis III 1988). Pathogenesis of various diseases shares a common feature of stimulating the complement system in plasma, and the resultant proinflammatory effects produce vasoactive peptides such as C3a, C5a (anaphylaxis), and bradykinin. The deficiency of C1 INH causes a major hereditary disease named hereditary angioedema (Ivanov et al. 2019; Karnaukhova, 2022). The anticipated ratio of hereditary angioedema pervasiveness is 1 out of 50,000 persons without any distinguishable ethnic differences, while untreated patients experience severe attacks (Zuraw 2008).

Mechanistically, when FXII triggers and brings conformational changes during its interaction with negatively associated surfaces, leading to the production of activated form FXII (FXIIa). The resultant product (FXIIa) converts plasma prekallikrein to plasma kallikrein, which stimulates FXII, causing a positive feedback loop of FXII activation and producing bradykinin via breaking down the high molecular weight kininogen (Müller and Renné 2008). Bradykinin further initiates inflammatory pathways, which leads to enhanced vascular permeability, vasodilation, and chemotaxis of neutrophils. Moreover, FXIIa also activates coagulation pathways by converting FXI into FXIa, which activates the Ca^{+2}-associated proteolytic cleavage and results in thrombin production, fibrin, and fibrin clot formation (Leeb-Lundberg et al. 2005).

C1 INH is a primitive inhibitor of various complement proteases such as C1r, C1s, and mannose-binding lectin–associated serine protease (MASP1 and 2), plasma kallikrein, and coagulation factor XIa and XIIa (Zuraw 2008). Studies also strengthen the concept that excessive bradykinin production is directly related to the genetic deficiency of C1 INH (Oschatz et al. 2011). C1 INH-deficient patients are classified as HAE type I, whereas patients with dysfunctional C1 INH protein with normal C1 INH plasma antigen levels are considered HAE type II (Bl 2008). C1 INH gains much attention in COVID-19 treatment because systemic complement stimulation and local complement-triggering effect lead to a severe acute respiratory syndrome, resulting in hyperinflammation and thrombosis (Afzali et al. 2022, van de Veerdonk et al. 2022). C1 INH and α2 M levels were reduced in patients with COVID 19, where as the levels of ITIH4 were raised (Medjeral-Thomas et al. 2021).

Recently, a significant reduction in levels of C1 INH in COVID-19 patients was reported in several studies (Demichev et al. 2021b). Hence, C1 INH gains much attention in COVID-19 treatment due to its potential inhibitory activity against SARS-CoV-2-induced hyperinflammation and hypercoagulation (Afzali et al. 2022, van de Veerdonk et al. 2022). Based on these, its therapeutic applicability to

alleviate the severity of COVID-19 pathogenesis, as mediated by the reversal of SARS-CoV-2-induced proinflammatory and prothrombic events, was proposed by researchers (Thomson et al. 2020; Adesanya et al. 2021). Recent ongoing clinical trials will ultimately evaluate the use of C1 INH treatment for COVID-19 patients (Mansour et al. 2021).

Abnormal activation of the complement system leads to increased liver damage, resulting in aggravation of hepatic steatosis and ischemic reperfusion hepatic injury with fatty liver (Wlazlo et al. 2013). The results of NAFLD patients with obesity show that C1 INH levels were found to be decreased in patients with steatosis and NASH (Subudhi et al. 2022). Interestingly, the results of a recent study reported that the hepatic loss of Gα13 showed 3.2-fold increased secretion of C1 INH in HFD-fed primary hepatocytes (Kim et al. 2019). Intravitreal injection of C1 INH in streptozotocin-induced diabetic rats significantly reduced the retinal vascular permeability by inhibiting the plasma kallikrein (Clermont et al. 2011). The exact role of C1 INH in NAFLD and diabetes is still in debate and is an undiscovered area.

Xanthine oxidase/dehydrogenase

Xanthine oxidase and dehydrogenase are interchangeable forms of the same enzyme, xanthine oxidoreductase (Pacher et al. 2006). XO mainly regulates the deprivation of purines into uric acid, during which it produces two moles of superoxide and one mole of H_2O_2 (Furuhashi 2020). SLC2A9 gene in GLUT-9 knockout mice experienced elevated urea levels, blood pressure, dyslipidemia, and whole body fat, whereas the administration of xanthine oxidase inhibitor results in recovery of all the above-mentioned parameters (DeBosch et al. 2014). Another study showed that elevated levels of xanthine oxidase were responsible for IR and high sensitivity-C-reactive protein levels in adults (Washio et al. 2017). Increased plasma XO was reported in CDAHFD-induced mice with NASH and was involved in vascular injury in NAFLD/NASH mice (Kawachi et al. 2021). XO expression was raised and reported in primary hepatocytes of Gα13 LKO mice (Kim et al. 2019).

Mannose-binding protein C

Mannose-binding protein (MBP), also known as mannose-binding lectin, can interact with high-density sugar existing on the surface of bacteria, fungi, and parasites, stimulating the antibody-independent complement system (Ikeda et al. 1987). MBP is produced in the liver and is of two types MBP-A and MBP-C (Drickamer et al. 1986). Complement fixation activated by the serine protease, such as MBP-associated serine protease-2 (MASP-2), cleaves and downregulates the complement system (Thiel et al. 1997). The study

results show that the MBL-activated complement system aggravates tissue damage, such as the thromboembolic system in COVID-19 patients (Asselta et al. 2022), showing that the MBL-activated complement system aggravates tissue damage in COVID-19 patients (Asselta et al. 2022).

Structural proteins in association with ECM

Inter-α-trypsin inhibitor heavy chain

Inter-α-inhibitors (IαI), commonly known as inter-α-trypsin inhibitors, are protein-glycosaminoglycan-protein complexes, acute phase response proteins, and have relative concentrations ranging from 150 to 500 μg/l in human plasma (Zhuo et al. 2004). IαI consist of light chains, bikunin, and heavy chains (H1-H5) combined with the chondroitin sulfate chain (Saguchi et al. 1996; Hamm et al. 2008). Two heavy chains (H1 and H2) are the predominant bikunin form, and a single bikunin and pre-α-inhibitor (H3) are present in the blood. The anti-proteolytical activity of IαI belong to the bikunin (Saguchi et al. 1996; Zhuo et al. 2004). HFD fed to triple transgenic Alzheimer's disease showed a 1.54-fold increase in the ITIH1 level and also elevated ITIH2 positively correlated with the disease progression (Wang et al. 2021). Reduced expression (70%) of ITIH2 was reported in breast cancer patients (Hamm et al. 2008). The results showed that the genetic loss of Ambp/bikunin, required for the activation of ITIH1, ITIH3, and ITIH4, leads to the mood alternation in the mice by the loss of ITIH1/ITIH3, whereas ITIH4 deficiency had no effect on the moods and behavior disorder in mice (Goulding et al. 2019). The cluster analysis of uterine LPS-primed mice fed on HFD showed reduced expressions of ITIH1 and ITIH2 (Manuel et al. 2019).

The hepatic Gα13 knockout mice showed a 2.7-fold increase in ITIH1, and ITIH1 was overexpressed in mice with diabetes and NAFLD with hyperglycemia. However, ITIH4 levels were reduced (Kim et al. 2019). The results of GWAS analysis found that ITIH3/ITIH1 genes were directly related to brain health; higher levels would cause more damage to the brain tissue (Gadd et al. 2022). Proprotein convertase subtilisin/kexin type 9 (PCSK9) has shown interaction with high-density lipoproteins in coronary artery disease, and interestingly, crosslinking mass spectrometry analysis identifies the interaction of PCSK9 with ITIH1 (hyaluronan binder) and apoA1 in immunoHDL (Burnap et al. 2021).

A recent study shows that ITIH4, after cleavage, forms a noncovalent inhibitory complex and acts as a protease that is dependent on the ITIH4 von Willebrand factor A domain. ITIH4 impedes mannan-binding lectin–associated serine protease (MASP) 1 and 2 and kallikrein. ITIH4 and MASP complex downregulate the breaking of C2 and C4 by inhibiting the contact of scissile bonds to the active binding site,

leading to acting as protease inhibitors (Pihl et al. 2021). Astonishingly, results were observed in proteomics analysis of COVID-19 patients in which expressions of acute phase proteins ITIH1, ITIH3, and ITIH4 were downregulated (Demichev et al. 2021a); however, another study showed overexpressed ITIH1 and ITIH2, whereas ITIH4 was downregulated in COVID-19 patients (Geyer et al. 2021).

Recently, proteomics analysis of COVID-19 patients' sera confirmed the association of poor prognosis with low levels of ITIH2 (Demichev et al. 2021a). Interestingly, the same family member proteins, ITIH3 and ITIH4, were found to be reduced in older patients with COVID-19 (Demichev et al. 2021b). In separate survival analyses, levels of ITIH4 increased in patients who failed to survive. This data agrees with a lower abundance of ITIH3 and ITIH4 in the nonsurvivors and a higher abundance of ITIH1 and ITIH2 in the survivor group (Völlmy et al. 2021). Since ITIH4 was shown to act as a protease inhibitor for mannan-binding lectin-associated serine protease-1 (MASP-1), MASP-2, and plasma kallikrein, ITIH4 may be utilized as a therapeutic target to prevent SARS-CoV-2-induced hyperinflammation, which depends on the complement and kinin-kallikrein pathways.

Summary

The consumption of excess fat and the resultant accompanying lipotoxicity, autophagy dysregulation, ER stress, and insulin resistance may cause disturbances in the secretion and modifications of the proteins and their interactions with other proteins and/or structures. This ultimately leads to cell death mechanisms. This article attempted to provide an updated overview of liver secretome biology with explanatory mechanisms with regard to metabolic liver diseases so that it may be of help in treating patients and overcoming the economic burden.

Declarations

Conflict of interest Authors have no conflict of interest.

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