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Perspective

The interplay between the muscle and liver in the regulation of glucolipid metabolism

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The liver, adipose tissue, and skeletal muscle work not only independently but also collaboratively to maintain glucose and lipid homeostasis under different nutritional and environmental conditions (da Silva Rosa et al., 2020). Dysfunctions of these active metabolic and endocrine tissues lead to a variety of metabolic, cardiovascular, and cerebrovascular disorders, including type 2 diabetes mellitus (T2DM), atherosclerosis, metabolic-associated fatty liver disease (MAFLD; also previously known as non-alcoholic fatty liver disease), and stroke (Wang et al., 2020). Here, we summarize the interaction between the liver and muscle in the regulation of glucolipid metabolism and discuss the key metabolic factors that mediate their crosstalk in the context of physiological (fasting and postprandial state) and pathological conditions (obesity, T2DM, and MAFLD).

The crucial roles of the liver in systemic glucose and lipid homeostasis

The liver regulates the metabolic pathways of glucose uptake and storage (glycolysis and glycogen synthesis) and glucose production (gluconeogenesis and glycogenolysis) (Petersen et al., 2017). Apart from glucose metabolism, hepatocytes are also responsible for lipid homeostasis via the regulation of lipid uptake, fatty acid esterification, fatty oxidation, and triacylglycerol (TG) secretion (Heeren and Scheja, 2021). Maintenance of glucose and lipid balance requires interorgan communication. The Cori cycle (lactate–glucose cycle) and the Cahill cycle (glucose–alanine cycle) are examples of such interactions in glucose metabolism (da Silva Rosa et al., 2020).

The effects of hepatic glucolipid metabolism on the muscle

Liver disease has an impact on skeletal muscle functions. Sarcopenia is commonly observed in patients with MAFLD and is closely associated with the severity of steatosis and fibrosis. Muscle mass loss can be accelerated by hyperammonemia-induced myotoxic and physical inactivity. The latest study by Okun et al. (2021) also demonstrated that improved liver function could reverse skeletal muscle atrophy. Interestingly, alleviation of hepatic insulin resistance (IR) has been shown to improve insulin sensitivity in skeletal muscle.

Lipid droplets, as a major organelle for lipid storage and metabolism, are important for lipid metabolic homeostasis. The accumulation of intramyocellular lipids leads to the buildup and dysregulation of deleterious lipid intermediates such as diacylglycerols (DAGs) and ceramides, which inhibit insulin signaling in skeletal muscle by activating proinflammatory/stress pathways, increasing reactive oxygen species production, and triggering the protein kinase C pathway (Aquilano et al., 2016). In addition, the accumulation of bioactive lipids (such as ceramides and DAGs) blocked insulin-mediated mammalian target of rapamycin (mTOR) activation and subsequent anabolic action in skeletal muscle in aging and obese conditions (Rivas et al., 2016).

Hepatokines

Hepatokines are hepatocyte-secreted proteins that play a key role in maintaining glucolipid metabolic homeostasis through autocrine, paracrine, and endocrine mechanisms. We will discuss several major hepatokines involved in glucolipid metabolism via the interplay with skeletal muscle as below.

As a high-affinity calcium-binding protein, fetuin-A plays an influential role in the dynamic homeostasis of calcium and affects bone remodelling (Yamasandhi et al., 2021). Higher serum fetuin-A levels have been linked to obesity, MAFLD, and T2DM in various clinical epidemiological studies (Yamasandhi et al., 2021). Similarly, fetuin-B can induce IR in myotubes and hepatocytes (Wang et al., 2022).

A human study found that serum apolipoprotein J (ApoJ) level was strongly associated with IR independent of obesity, and a reduction in ApoJ level

Table 1 Summary of hepatokines and their influence on muscle glucolipid metabolism.

Hepatokine	Influence	References
Fetuin-A	Inhibits the translocation of Glut4 in mouse C2C12 myoblasts in response to insulin stimulation	Goustin et al. (2013)
ApoJ	Binds to LRP2 on skeletal muscle and improves insulin sensitivity	Seo et al. (2020)
Adropin	Enhances the phosphorylation of Akt and promotes the translocation of GLUT4	Gao et al. (2015)
SeP	Enhances the phosphorylation of IRS1 at Ser307 to inhibit insulin signal transduction	Misu et al. (2010)
FGF21	Increases Akt phosphorylation and insulin sensitivity; increases Glut4 in skeletal muscle	Pereira et al. (2017); Yano et al. (2022)
HPS	Induces IR via the EGFR/JNK pathway	Jung et al. (2018)
LECT2	Activates the JNK signaling pathway and IR	Lan et al. (2014)
PEDF	Inhibits tyrosine phosphorylation of IRS1, dual loop phosphorylation–activation of Akt, and GLUT4 translocation	Carnagarin et al. (2016)
ANGPTL3	Inhibits lipoprotein lipase	Kersten (2014)

promoted insulin sensitivity in T2DM (Seo et al., 2018). Free fatty acids might activate ApoJ secretion via the surface low-density lipoprotein receptor-related protein-2 (LRP2) receptor megalin, thereby impairing hepatic insulin sensitivity (Bradley et al., 2019). Hepatic ApoJ deletion induces IR and subsequent glucose intolerance in skeletal muscle (Seo et al., 2020).

Adropin is encoded by the clock-controlled energy homeostasis-associated gene and is mainly expressed in the liver. It helps to alleviate IR, maintain normal glucose tolerance, and reduce lipid deposition in the liver (Kumar et al., 2008). In skeletal muscle cells, adropin enhances the phosphorylation of protein kinase B (Akt), leading to the translocation of glycogenesis and glucose transporter 4 (GLUT4) to the cell surface, thereby enhancing glucose absorption and usage by the muscle (Gao et al., 2015). Moreover, adropin is involved in regulating the propensity of carbohydrate oxidation in skeletal muscle, limiting incomplete fatty acid oxidation and promoting carbohydrate oxidation, thus further raising the coenzyme A/acetyl coenzyme A ratio and improving mitochondrial function (Gao et al., 2014).

Selenoprotein P (SeP) has been rediscovered as a hepatokine that contributes to the pathology of T2DM and aging-related diseases, such as exercise resistance in skeletal muscle and insulin secretory failure in pancreatic beta cells (Takamura, 2020). SeP increased the mRNA expression of gluconeogenic enzymes (*Pck1* and *G6pc*), resulting in a 30% increase in glucose release from the liver and reducing glucose absorption in myocytes (Takamura, 2020).

Clinical research has shown that fibroblast growth factor 21 (FGF21) analogues can lessen liver fibrosis and enhance insulin sensitivity (Flippo and Potthoff, 2021). Increased risks of sarcopenia, as well as low muscle mass and strength, were strongly correlated with elevated serum FGF21 levels in the elderly (Jung et al., 2021).

Hepassocin (HPS), also known as fibrinogen-like 1 or hepatocyte-derived fibrinogen-related protein-1, is derived from the liver (Hara et al., 2000). Demchev et al. (2013) found that HPS knockout mice exhibited elevated hepatic gluconeogenesis and fasting hyperglycemia. In skeletal muscle, HPS affects glucose homeostasis through different mechanisms. The effect of HPS on muscle IR was abrogated by siRNA-mediated suppression of the c-Jun N-terminal kinase (JNK) pathway (Jung et al., 2018).

Leukocyte cell-derived chemotaxin 2 (LECT2) facilitates IR in skeletal muscle through the activation of the JNK signaling pathway (Lan et al., 2014). Pigment epithelium-derived factor inhibits the phosphorylation of insulin receptor substrate 1 (IRS1) and Akt and, subsequently, GLUT4 translocation (Carnagarin et al., 2016).

ANGPTL3 is a distinctive constituent of the angiopoietin-like (ANGPTL) protein cluster and is exclusively synthesized in the liver, thereby categorizing it as a hepatokine (Kersten, 2017). Its chief function is to repress lipoprotein lipase, an enzyme accountable for hydrolysing circulating triglycerides (TGs) within the capillaries situated in adipose and muscular tissues (Kersten, 2014).

In summary, numerous hepatokines play a considerable role in skeletal muscle glucolipid metabolism (Table 1 and Figure 1), and further research is needed to investigate the specific mechanisms and roles to be targeted for future therapy.

The effect of skeletal muscle metabolism on the liver

Dysfunction of skeletal muscle also has a negative impact on liver homeostasis. According to two previous meta-analyses, patients with sarcopenia had a ∼1.5-fold higher risk of MAFLD than control subjects (Pan et al., 2018).

Beneficial effects of exercise-induced glucolipid metabolism in the liver

Epidemiological studies have demonstrated that regular exercise reduces the risk of T2DM via multiple mechanisms, such as activation of adenosine monophosphate-activated protein kinase, calmodulin-dependent protein kinases, and Akt, which are known to promote GLUT4 translocation to the cell membrane for glucose uptake (Evans et al., 2019). In addition, aerobic exercise reduces hepatic GLUT2 mRNA expression and improves hepatic IR in diabetic rats (Simões et al., 2020).

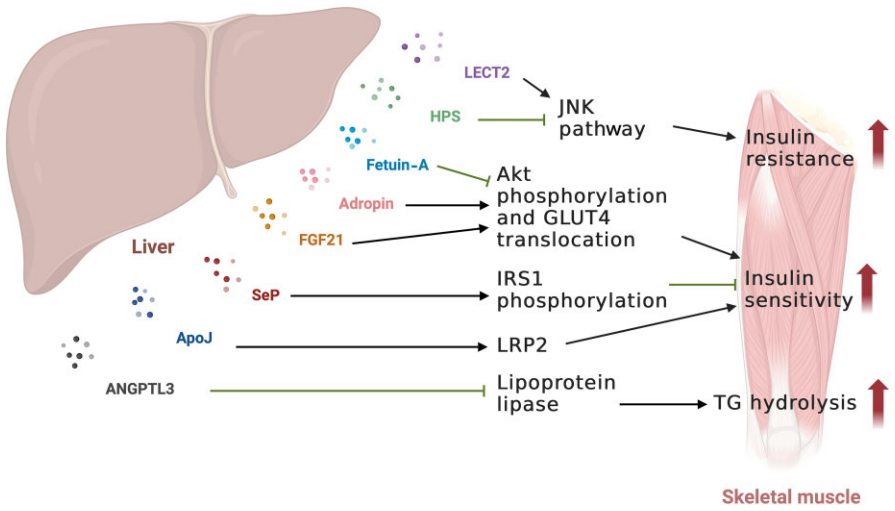

Figure 1 The roles of hepatokines in the regulation of skeletal muscle glucolipid metabolism. The green blunt arrow represents inhibition, while the black and thick red arrows represent promotion.

Aerobic workouts can also enhance lipoprotein lipase activity and fatty acid oxidation in the liver, thereby reducing hepatic lipid accumulation (Zheng and Cai, 2019). Studies have shown that aerobic exercise significantly increases the expression levels of hepatic peroxisome proliferator-activated receptor-γ (PPAR-γ), carnitine palmitoyl transferase-1, and medium-chain acyl-CoA dehydrogenase and improves hepatocyte ultrastructure, consequently reducing hepatic lipid deposition (Zheng and Cai, 2019).

Myokines

By creating local (auto/paracrine) and distant (endocrine) effects, myokines (muscle-derived hormones) and hepatokines (liver-derived hormones) can form interconnected networks. As summarized in Table 2 and Figure 2, myokines play a crucial role in metabolism.

Human exercise induces the release of glucose from the liver in response to muscle-derived interleukin-6 (IL-6) (Severinsen and Pedersen, 2020). The positive effects of IL-6 on glucose and insulin homeostasis are maintained in obesity, as evidenced by the fact that IL-6 therapy increases Akt signaling and decreases gluconeogenic gene expression in the livers of mice given either low- or high-fat diets (Peppler et al., 2019). Conversely, IL-6 appears to cause IR (Kim et al., 2008). Researchers found that IL-6 enhances signal transducer and activator of transcription 3 (STAT3) activation via mTOR, leading to cytokine signaling 3 (SOCS-3) overexpression, which inhibits insulin signaling in hepatocytes (Kim et al., 2008).

Serum irisin concentrations were found to be inversely related to hepatic TG content in a cross-sectional study of obese Chinese adults (Perakakis et al., 2017). In streptozotocin–high-fat diet-induced type 2 diabetic mice, irisin effectively reduced fasting glucose levels, as well as hepatic TG content and glucose output, while increasing hepatic glycogen synthesis and storage (So and Leung, 2016). Irisin inhibited phosphoenolpyruvate carboxykinase (PEPCK) and glucokinase expression by the phosphatidylinositol 3-kinase (PI3K)/Akt/Forkhead box O1 (FOXO1) pathway and enhanced glycogen synthesis through PI3K/Akt/glycogen synthase kinase-3 (GSK3)-mediated activation of glycogen synthase (Perakakis et al., 2017).

Muscle fibres express and produce myostatin (MSTN), which is also known as GDF-8, a member of the transforming growth factor β superfamily (Sharma et al., 2015). In addition to promoting muscle growth, blocking MSTN offers protection against fatty liver and enhances IR in mice (Merli and Dasarathy, 2015). Recent studies indicated that MSTN may significantly contribute to the onset of diabetes. For instance, serum MSTN levels were higher in children and adults with type 1 diabetes mellitus (T1DM) than in healthy individuals (Dial et al., 2020; Efthymiadou et al., 2021).

Furthermore, myonectin exhibits positive correlations with TG, fasting insulin, and IR index but forms a negative relationship with the insulin sensitivity index. This pattern suggests a potential risk of IR in the absence of a sufficient myonectin level (Li et al., 2018). Several amino acid-related molecules, such as β-aminoisobutyric acid (BAIBA), have been reported to activate skeletal muscle function and effective in improving IR as well as lipid and glucose disorders (Kamei et al., 2020).

Myokines are closely related to metabolic diseases. Future research should focus on the specific mechanisms of exercise on skeletal muscle and plasma concentrations of myokines, which is expected to be a more promising point for diagnosing and treating these metabolic diseases.

Limitations of existing research

With the increasing prevalence of metabolic diseases such as T2DM, obesity, and MAFLD, it is crucial to understand the complex interactions between different organs. Based on the literature findings, the communication between the muscle and liver plays a critical role in the control of glucose, lipid, and energy homeostasis throughout the body. Multiple clinical studies have indicated that skeletal muscle and the liver mutually affect the development of disorders of each other. There is also a wealth of research on liver and muscle secretory proteins, which can act alone or in combination with others to regulate insulin sensitivity and mitochondrial function under metabolic stress conditions. Dysregulated crosstalk between the liver and muscle increases the prevalence of metabolic diseases.

However, it is imperative to acknowledge the limitations of these studies and

Table 2 Summary of myokines and their influence on glucolipid metabolism.

Myokine	Influence	Reference
IL-6	Increases hepatic phosphorylation of Akt and decreases hepatic gluconeogenic gene expression	Peppler et al. (2019)
Irisin	Inhibits hepatic gluconeogenesis via the PI3K/Akt/FOXO1 pathway and increases glycogenesis via the PI3K/Akt/GSK3 pathway	Liu et al. (2015)
MSTN	Increases liver fatty acid oxidation in MSTN -deficient mice	Zhang et al. (2012)
Myonectin	Activates the PI3K/Akt/mTOR pathway to suppress autophagy in mouse liver	Seldin et al. (2013)
BAIBA	Increases hepatic β-oxidation through PPAR-α	Roberts et al. (2014)

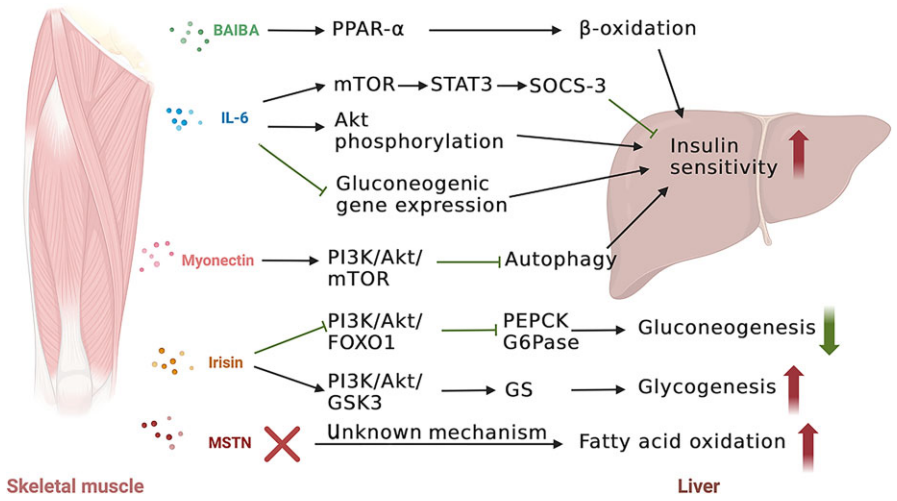

Figure 2 The roles of myokines in the regulation of liver glucolipid metabolism. The green blunt and thick green arrows represent inhibition, while the black and thick red arrows represent promotion. G6Pase, glucose-6-phosphatase; GS, glycogen synthase.

the challenges that need to be overcome in future investigations.

First, establishing a cause-and-effect relationship is challenging due to the complexity of the liver–muscle crosstalk. Numerous studies have demonstrated the correlation between the liver–muscle interaction and glycolipid homeostasis, but the causality is not clearly established. Hence, further investigations incorporating rigorous experimental designs are warranted to elucidate the underlying mechanisms.

Second, previous studies typically focused solely on either the liver or muscle, neglecting the dynamic interplay between these two organs. Future research should adopt a more comprehensive perspective and consider the effects of both organs on metabolism.

Third, many myokines and hepatokines remain to be discovered, and their mechanisms of action are not yet fully clarified. For instance, IL-7 plays a potential role in myogenesis, IL-15 has an impact on fat deposition, and IL-8 potentially stimulates skeletal muscle angiogenesis (Pedersen, 2013). However, it remains unknown whether these myokines also influence liver glucolipid metabolism. Furthermore, other conditions like inflammation, aging, and genetics could interfere with the impact of these myokines and hepatokines on metabolism, adding another layer of complexity.

Last, related drug research is still at the early stages, such as MSTN antagonists (Eilers et al., 2021), and there is a significant lack of relevant clinical trials. A better understanding of the muscle–liver interplay might contribute to the development of novel therapeutic strategies. Due to variations in genetics and lifestyle the treatment strategies may differ among different patients.

In summary, although the current research has provided significant insights into the relationship between the liver and muscle in glucolipid homeostasis, there are certain limitations that should be addressed in future investigations.

Summary and perspective

In recent years, various hepatokines were found to regulate skeletal muscle glucolipid metabolism (Figure 1). Fetuin-A, FGF21, and ApoJ are three examples. They are involved in regulating glucose uptake and insulin sensitivity in the muscle. Considering the amount of research focused on hepatokines, there is a promising prospect of identifying the muscle–liver communication pathway as a potential target for therapeutic interventions in metabolic diseases.

Meanwhile, the muscle also produces myokines capable of influencing liver functions (Figure 2), including irisin, IL-6, etc. These myokines can promote glucose and lipid metabolism in the liver, thus contributing to metabolic homeostasis. Because exercise can increase myokine levels, this may provide a therapeutic strategy for metabolic diseases that is easier for patients to adhere to.

In conclusion, it is apparent that factors derived from the muscle and liver present significant potential for the management of metabolic diseases, but much more detailed molecular mechanisms regarding this intricate signaling system remain to be elucidated. Additionally, investigating the communication between organs to comprehend the intricate dynamics between muscle and liver tissues will be helpful to explore potential therapeutic solutions for various metabolic diseases.

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References

Aquilano, K., Baldelli, S., La Barbera, L., et al. (2016). Adipose triglyceride lipase decrement affects skeletal muscle homeostasis during aging through FAs–PPARα–PGC-1α antioxidant response. Oncotarget *7*, 23019–23032.

Bradley, D., Blaszczak, A., Yin, Z., et al. (2019). Clusterin impairs hepatic insulin sensitivity and adipocyte clusterin associates with cardiometabolic risk. Diabetes Care *42*, 466–475.

Carnagarin, R., Dharmarajan, A.M., and Dass, C.R. (2016). PEDF attenuates insulin-dependent molecular pathways of glucose homeostasis in skeletal myocytes. Mol. Cell. Endocrinol. *422*, 115–124.

da Silva Rosa, S.C., Nayak, N., Caymo, A.M., et al. (2020). Mechanisms of muscle insulin resistance and the cross-talk with liver and adipose tissue. Physiol. Rep. *8*, e14607.

Demchev, V., Malana, G., Vangala, D., et al. (2013). Targeted deletion of fibrinogen like protein 1 reveals a novel role in energy substrate utilization. PLoS One *8*, e58084.

Dial, A.G., Monaco, C.M.F., Grafham, G.K., et al. (2020). Muscle and serum myostatin expression in type 1 diabetes. Physiol. Rep. *8*, e14500.

Efthymiadou, A., Vasilakis, I.A., Giannakopoulos, A., et al. (2021). Myostatin serum levels in children with type 1 diabetes mellitus. Hormones *20*, 777–782.

Eilers, W., Cleasby, M., and Foster, K. (2021). Development of antisense-mediated myostatin knockdown for the treatment of insulin resistance. Sci. Rep. *11*, 1604.

Evans, P.L., McMillin, S.L., Weyrauch, L.A., et al. (2019). Regulation of skeletal muscle glucose transport and glucose metabolism by exercise training. Nutrients *11*, 2432.

Flippo, K.H., and Potthoff, M.J. (2021). Metabolic messengers: FGF21. Nat. Metab. *3*, 309–317.

Gao, S., McMillan, R.P., Jacas, J., et al. (2014). Regulation of substrate oxidation preferences in muscle by the peptide hormone adropin. Diabetes *63*, 3242–3252.

Gao, S., McMillan, R.P., Zhu, Q., et al. (2015). Therapeutic effects of adropin on glucose tolerance and substrate utilization in diet-induced obese mice with insulin resistance. Mol. Metab. *4*, 310–324.

Goustin, A.S., Derar, N., and Abou-Samra, A.B. (2013). Ahsg-fetuin blocks the metabolic arm of insulin action through its interaction with the 95-kD β-subunit of the insulin receptor. Cell. Signal. *25*, 981–988.

Hara, H., Uchida, S., Yoshimura, H., et al. (2000). Isolation and characterization of a novel liver-specific gene, hepassocin, upregulated during liver regeneration. Biochim. Biophys. Acta *1492*, 31–44.

Heeren, J., and Scheja, L. (2021). Metabolic-associated fatty liver disease and lipoprotein metabolism. Mol. Metab. *50*, 101238.

Jung, H.W., Park, J.H., Kim, D.A., et al. (2021). Association between serum FGF21 level and sarcopenia in older adults. Bone *145*, 115877.

Jung, T.W., Chung, Y.H., Kim, H.C., et al. (2018). Hyperlipidemia-induced hepassocin in the liver contributes to insulin resistance in skeletal muscle. Mol. Cell. Endocrinol. *470*, 26–33.

Kamei, Y., Hatazawa, Y., Uchitomi, R., et al. (2020). Regulation of skeletal muscle function by amino acids. Nutrients *12*, 261.

Kersten, S. (2014). Physiological regulation of lipoprotein lipase. Biochim. Biophys. Acta *1841*, 919–933.

Kersten, S. (2017). Angiopoietin-like 3 in lipoprotein metabolism. Nat. Rev. Endocrinol. *13*, 731–739.

Kim, J.H., Kim, J.E., Liu, H.Y., et al. (2008). Regulation of interleukin-6-induced hepatic insulin resistance by mammalian target of rapamycin through the STAT3–SOCS3 pathway. J. Biol. Chem. *283*, 708–715.

Kumar, K.G., Trevaskis, J.L., Lam, D.D., et al. (2008). Identification of adropin as a secreted factor linking dietary macronutrient intake with energy homeostasis and lipid metabolism. Cell Metab. *8*, 468–481.

Lan, F., Misu, H., Chikamoto, K., et al. (2014). LECT2 functions as a hepatokine that links obesity to skeletal muscle insulin resistance. Diabetes *63*, 1649–1664.

Li, K., Liao, X., Wang, K., et al. (2018). Myonectin predicts the development of type 2 diabetes. J. Clin. Endocrinol. Metab. *103*, 139–147.

Liu, T.Y., Shi, C.X., Gao, R., et al. (2015). Irisin inhibits hepatic gluconeogenesis and increases glycogen synthesis via the PI3K/Akt pathway in type 2 diabetic mice and hepatocytes. Clin. Sci. *129*, 839–850.

Merli, M., and Dasarathy, S. (2015). Sarcopenia in non-alcoholic fatty liver disease: targeting the real culprit? J. Hepatol. *63*, 309–311.

Misu, H., Takamura, T., Takayama, H., et al. (2010). A liver-derived secretory protein, selenoprotein P, causes insulin resistance. Cell Metab. *12*, 483–495.

Okun, J.G., Rusu, P.M., Chan, A.Y., et al. (2021). Liver alanine catabolism promotes skeletal muscle atrophy and hyperglycaemia in type 2 diabetes. Nat. Metab. *3*, 394–409.

Pan, X., Han, Y., Zou, T., et al. (2018). Sarcopenia contributes to the progression of nonalcoholic fatty liver disease-related fibrosis: a meta-analysis. Dig. Dis. *36*, 427–436.

Pedersen, B.K. (2013). Muscle as a secretory organ. Compr. Physiol. *3*, 1337–1362.

Peppler, W.T., Townsend, L.K., Meers, G.M., et al. (2019). Acute administration of IL-6 improves indices of hepatic glucose and insulin homeostasis in lean and obese mice. Am. J. Physiol. Gastrointest. Liver Physiol. *316*, G166–G178.

Perakakis, N., Triantafyllou, G.A., Fernández-Real, J.M., et al. (2017). Physiology and role of irisin in glucose homeostasis. Nat. Rev. Endocrinol. *13*, 324–337.

Pereira, R.O., Tadinada, S.M., Zasadny, F.M., et al. (2017). OPA1 deficiency promotes secretion of FGF21 from muscle that prevents obesity and insulin resistance. EMBO J. *36*, 2126–2145.

Petersen, M.C., Vatner, D.F., and Shulman, G.I. (2017). Regulation of hepatic glucose metabolism in health and disease. Nat. Rev. Endocrinol. *13*, 572–587.

Rivas, D.A., McDonald, D.J., Rice, N.P., et al. (2016). Diminished anabolic signaling response to insulin induced by intramuscular lipid accumulation is associated with inflammation in aging but not obesity. Am. J. Physiol. Regul. Integr. Comp. Physiol. *310*, R561–R569.

Roberts, L.D., Boström, P., O'Sullivan, J.F., et al. (2014). β-aminoisobutyric acid induces browning of white fat and hepatic β-oxidation and is inversely correlated with cardiometabolic risk factors. Cell Metab. *19*, 96–108.

Seldin, M.M., Lei, X., Tan, S.Y., et al. (2013). Skeletal muscle-derived myonectin activates the mammalian target of rapamycin (mTOR) pathway to suppress autophagy in liver. J. Biol. Chem. *288*, 36073–36082.

Seo, J.A., Kang, M.C., Ciaraldi, T.P., et al. (2018). Circulating ApoJ is closely associated with insulin resistance in human subjects. Metabolism *78*, 155–166.

Seo, J.A., Kang, M.C., Yang, W.M., et al. (2020). Apolipoprotein J is a hepatokine regulating muscle glucose metabolism and insulin sensitivity. Nat. Commun. *11*, 2024.

Severinsen, M.C.K., and Pedersen, B.K. (2020). Muscle–organ crosstalk: the emerging roles of myokines. Endocr. Rev. *41*, 594–609.

Sharma, M., McFarlane, C., Kambadur, R., et al. (2015). Myostatin: expanding horizons. IUBMB Life *67*, 589–600.

Simões, E.S.L.L., Santos de Sousa Fernandes, M., Kubrusly, M.S., et al. (2020). Effects of aerobic exercise protocol on genes related to insulin resistance and inflammation in the pancreas of ob/ob mice with NAFLD. Clin. Exp. Gastroenterol. *13*, 223–234.

So, W.Y., and Leung, P.S. (2016). Irisin ameliorates hepatic glucose/lipid metabolism and enhances cell survival in insulin-resistant human HepG2 cells through adenosine monophosphate-activated protein kinase signaling. Int. J. Biochem. Cell Biol. *78*, 237–247.

Takamura, T. (2020). Hepatokine selenoprotein P-mediated reductive stress causes resistance to intracellular signal transduction. Antioxid. Redox Signal. *33*, 517–524.

Wang, D., Wu, M., Zhang, X., et al. (2022). Hepatokine Fetuin B expression is regulated by leptin–STAT3 signalling and associated with leptin in obesity. Sci. Rep. *12*, 12869.

Wang, H.H., Lee, D.K., Liu, M., et al. (2020). Novel insights into the pathogenesis and management of the metabolic syndrome. Pediatr. Gastroenterol. Hepatol. Nutr. *23*, 189–230.

Yamasandhi, P.G., Dharmalingam, M., and Balekuduru, A. (2021). Fetuin-A in newly detected type 2 diabetes mellitus as a marker of non-alcoholic fatty liver disease. Indian J. Gastroenterol. *40*, 556–562.

Yano, K., Yamaguchi, K., Seko, Y., et al. (2022). Hepatocyte-specific fibroblast growth factor 21 overexpression ameliorates high-fat diet-induced obesity and liver steatosis in mice. Lab. Invest. *102*, 281–289.

Zhang, C., McFarlane, C., Lokireddy, S., et al. (2012). Inhibition of myostatin protects against diet-induced obesity by enhancing fatty acid oxidation and promoting a brown adipose phenotype in mice. Diabetologia *55*, 183–193.

Zheng, F., and Cai, Y. (2019). Concurrent exercise improves insulin resistance and nonalcoholic fatty liver disease by upregulating PPAR-γ and genes involved in the beta-oxidation of fatty acids in ApoE-KO mice fed a high-fat diet. Lipids Health Dis. *18*, 6.