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Commentary

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Exploring the regulatory impact of insulin on type I collagen synthesis in hepatic stellate cells through α5β1 integrin

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Abstract

In the present study by Dodig and colleagues, published in *Metabolism and Target Organ Damage*, the authors investigate the role of insulin in promoting type I collagen synthesis in hepatic stellate cells (HSCs) through α5β1 integrin signaling. Using L-SACC1 transgenic mice, which exhibit hyperinsulinemia and insulin resistance without fasting hyperglycemia, the researchers demonstrate that elevated insulin levels significantly increase type I collagen production in HSCs. This effect is mediated by α5β1 integrin signaling rather than the PI3 kinase pathway. These findings suggest that chronic hyperinsulinemia may preprogram HSCs for enhanced fibrogenesis following liver injury, contributing to advanced fibrosis associated with metabolic disorders such as metabolic dysfunction-associated steatosis liver disease (MASLD) and type 2 diabetes. It further suggests that chronic hyperinsulinemia increases the risk of significant fibrosis burden in chronic liver disease. In this commentary, the strengths and limitations of this study are discussed, along with the potential impact of these findings on current treatment strategies for insulin resistance, endogenous hyperinsulinemia, and exogenous hyperinsulinemia in the development of MASLD and disease progression to fibrosis, cirrhosis, and hepatocellular carcinoma.

Keywords: Insulin resistance, integrins, collagen, fibrosis, cirrhosis, MASLD

THE IMPACT OF HYPERINSULINEMIA ON HEPATIC FIBROSIS

In the pathogenesis of metabolic dysfunction-associated steatosis liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH), insulin resistance is one of the most critical factors that lead to disease initiation and progression[1]. The activity of insulin is mediated by binding to the α-subunit of the insulin receptor, followed by transactivation of the tyrosine kinase of the β-subunit of the insulin receptor. This initiates a cascade of events that lead to a myriad of insulin actions in different cells and tissues[1]. In this process, the carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), a plasma glycoprotein with predominant expression in the liver, stabilizes the insulin receptor complex and increases the rate of its cellular uptake. This leads to insulin's delivery to the degradation and clearance processes primarily mediated in hepatocytes and, to a lesser extent, in renal proximal tubule cells[1].

Hyperinsulinemia and type 2 diabetes (T2DM) have been identified as independent predictors of cardiovascular disease and fibrosis in MASH and MASLD[2]. They are also linked to chronic liver disease and the pathogenesis of cirrhosis and hepatocellular carcinoma (HCC), which, like fibrosis, are all associated with abnormal accumulation of excessive extracellular matrix (ECM), a significant overall predictor of liver-related outcomes[3]. However, the role of hyperinsulinemia in promoting hepatic fibrosis and its impact on HSCs remains unclear.

Previous work has suggested that the activation of hepatic stellate cells (HSCs) plays a role in the development of insulin resistance and diabetes[4]. Specifically, during the early activation process, the PI3K/Akt-p70S6K pathway is a crucial trigger for cellular activation and fibrosis development in MASH[5].

Insulin stimulates the proliferation of HSCs by activating dipeptidyl peptidase IV (DPP-4)[6,7], leading to enhanced expression of α-smooth muscle actin (α-SMA), a marker for HSC activation[5]. The insulin-PI3K/Akt-p70S6K signaling pathway is important in the activation of HSCs induced by serum[5]. A study by Zhang *et al*. a decade ago demonstrated that inhibiting the insulin receptor-mediated PI3K/AKT and ERK pathways can prevent HSC activation[8]. Therefore, it is evident that insulin promotes HSC proliferation by activating both DPP-4 and the PI3K/Akt pathway. A study by Creeden *et al*., using advanced PamGene technology, revealed that insulin receptor kinase activity is significantly increased in HSCs from humans and mice with liver fibrosis[9]. Since HSC activation is a known indicator of liver fibrosis, enhancing insulin sensitivity could have dual effects, potentially benefiting hepatocytes while also triggering or worsening liver fibrosis in the later stages of chronic liver disease.

Current treatment strategies for MASLD and hepatic insulin resistance often involve hypocaloric diets and exercise for MASH resolution, as well as combinations of insulin sensitizers and glucagon-like peptide-1 (GLP-1) receptor agonists[10,11]. Therefore, solely focusing on improving hepatocyte function may pose risks in advanced stages, underscoring the importance of considering the dangers associated with HSC activation when exploring new therapeutic options.

INSULIN ENHANCES COLLAGEN PRODUCTION IN HSCS VIA α SUBUNIT 5 AND THE β SUBUNIT 1 INTEGRIN

The study by Dodig *et al*. investigated the impact of insulin on collagen production in cultured primary HSCs and in the L-SACC1 transgenic mice, representing an established model that mimics hyperinsulinemia without fasting hyperglycemia[12] [Figure 1].

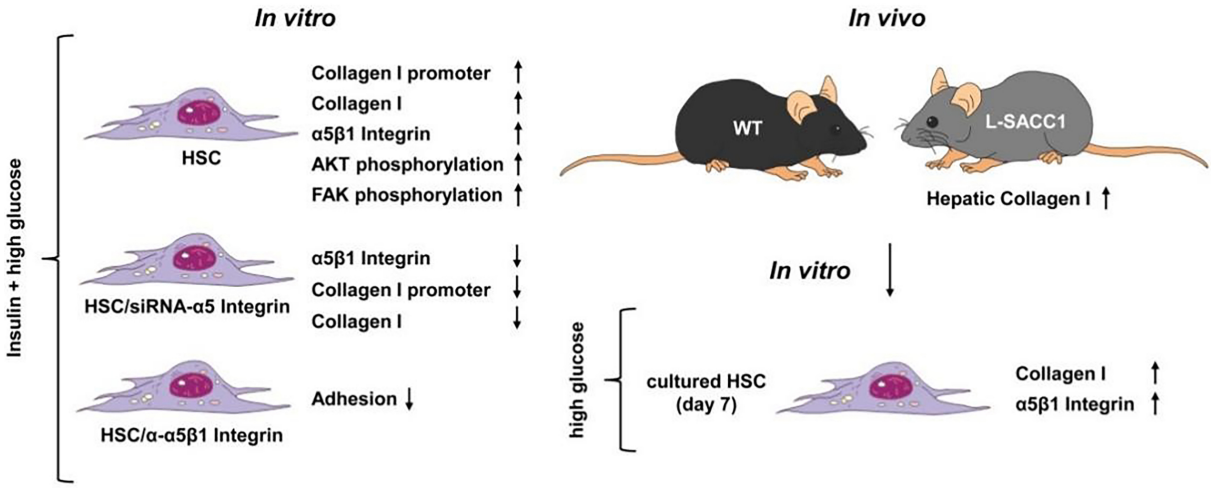

Figure 1. Summary of results and outcomes. The study by Dodig *et al.*[12] investigates the role of insulin in enhancing type I collagen synthesis in primary HSC cultures under high glucose conditions. Insulin treatment significantly increased type I collagen promoter activity and protein levels, particularly at 5 μM, without affecting HSC proliferation. The effects were independent of PI3 kinase signaling despite AKT phosphorylation indicating active pathway engagement. Insulin also promoted HSC adhesion to fibronectin and elevated α5β1 integrin and phosphorylated FAK levels. Knocking down α5 integrin reduced collagen synthesis and inhibited insulin's effects on both α5 integrin and collagen levels. *In vivo* analysis of L-SACC1 transgenic mice showed increased ECM deposition and enhanced type I collagen production by isolated HSCs compared to wild-type controsls. ECM: Extracellular matrix; FAK: focal adhesion kinase; HSC: hepatic stellate cell; WT: wild-type.

In their experimental setup, primary HSC cultures were first confirmed to be pure through immunostaining for specific markers. Interestingly, treatment with insulin significantly increased type I collagen promoter activity and protein levels, especially at a concentration of 5 μM. This effect was only observed in high glucose conditions, while glucose alone did not enhance collagen production without insulin. Importantly, insulin treatment did not affect HSC proliferation.

Insulin signaling via the PI3 kinase pathway was confirmed by observing AKT phosphorylation. However, inhibition of this pathway by wortmannin did not alter collagen promoter activity, indicating that insulin's effects were independent of PI3 kinase signaling. The role of α subunit 5 and the β subunit 1 (α5β1) integrin in insulin-induced collagen synthesis was also explored. The authors found that insulin enhanced HSC adhesion to fibronectin and increased levels of α5β1 integrin alongside phosphorylated focal adhesion kinase (FAK). Knocking down α5 integrin resulted in decreased type I collagen levels and inhibited the insulin-mediated increase in both α5 integrin and collagen synthesis. Additionally, analysis of liver samples from L-SACC1 transgenic mice showed increased ECM deposition compared to wild-type mice. HSCs isolated from these hyperinsulinemic mice exhibited higher levels of type I collagen and α5 integrin without differences in activation or proliferation compared to controls. Overall, these results suggested that hyperinsulinemia enhanced type I collagen synthesis in HSCs through an α5β1 integrin-dependent mechanism, contributing to liver fibrosis development.

α5β1 integrin is a type of cell surface receptor that plays a crucial role in cell adhesion, migration, and signaling. It is a complex of two subunits that specifically binds to fibronectin, an ECM protein that is important for maintaining tissue structure and facilitating cellular interactions with the surrounding environment. Previous work has demonstrated that α5β1 integrin is involved in regulating cell behavior, including proliferation, differentiation, and survival in various biological processes. It has been shown to play significant roles in wound healing, tissue remodeling, and fibrosis development. In the context of liver disease, α5β1 integrin has already been implicated in the activation of HSCs, which are key players in liver

fibrosis. The present work has highlighted that research into α5β1 integrin's signaling pathways may provide insights into therapeutic targets for conditions characterized by abnormal fibrosis or tissue remodeling, such as MASLD and other chronic liver diseases.

The strengths of the data presented in this study are multifaceted and contribute significantly to our understanding of the role of insulin in HSC activation and collagen synthesis. Firstly, the use of primary HSC cultures enables a more physiologically relevant assessment of insulin's effects compared to immortalized cell lines. The purity of these cultures was rigorously validated through immunostaining, ensuring that the observed effects can be confidently attributed to HSCs rather than other cell types. Secondly, the study employed a range of experimental approaches, including chloramphenicol acetyltransferase (CAT) reporter assays and western blot analyses, to demonstrate that insulin significantly increases type I collagen promoter activity and protein levels. This comprehensive methodology strengthens the reliability of the findings by corroborating results across different techniques. Additionally, the investigation into insulin signaling pathways revealed that while AKT phosphorylation indicated active PI3 kinase signaling, insulin's effect on collagen synthesis was independent of this pathway. This insight highlights a novel mechanism involving α5β1 integrin signaling, suggesting alternative therapeutic targets for managing liver fibrosis.

Importantly, the use of L-SACC1 transgenic mice enhances the strength of these data by providing an *in vivo* model. The L-SACC1 transgenic mouse model mimics hyperinsulinemia without fasting hyperglycemia. It harbors six copies of a liver-specific dominant negative phosphorylation-defective Ser503Ala mutant in CEACAM1, which triggers the development of chronic hyperinsulinemia resulting from blunted hepatic clearance of insulin, visceral obesity, and glucose intolerance[13,14]. The transgene is driven under the regulatory control of parts of the human apolipoprotein A-1 promoter, which directs the expression of the transgene exclusively in the liver[13,15]. The observation that these mice exhibited increased ECM deposition and higher levels of type I collagen reinforces the relevance of hyperinsulinemia as a contributing factor to liver fibrosis. Lastly, the study's findings have important clinical implications, as they suggest that targeting α5β1 integrin signaling may offer new strategies for preventing or treating liver fibrosis associated with metabolic disorders such as T2DM and MASLD.

Nevertheless, it should be noted that other members of the integrin family also play a significant role in liver fibrosis by increasing cellular contractility and transforming growth factor-β (TGF-β) activity. For example, blocking or deleting α8β1 has been shown to effectively reduce ongoing hepatic fibrosis[16].

LIMITATIONS OF THE STUDY

While the study provides valuable insights into the role of insulin in promoting type I collagen synthesis in HSCs, it is important to acknowledge several limitations that may impact the interpretation and generalizability of the findings. Firstly, primary HSC cultures offer a physiologically relevant context for assessing insulin's effects, but they are still limited by the constraints of *in vitro* studies. The culture conditions may not fully replicate the intricate microenvironment of the liver, including interactions with other cell types such as hepatocytes, immune cells, and ECM components. These interactions can greatly influence HSC behavior and function. Therefore, results observed in isolated cultures may not completely reflect what happens *in vivo* under physiological or pathological conditions. Secondly, while the use of L-SACC1 transgenic mice provides a valuable model for studying hyperinsulinemia without fasting hyperglycemia, it may not encompass all aspects of human metabolic disorders. The genetic modifications specific to these mice could introduce variables that are not present in human patients with T2DM or MASLD. Additionally, MASLD is a complex condition involving genetic and environmental factors,

triggered by dysregulation in lipid metabolism and hepatic immune responses. The L-SACC1 model is better suited to investigate hepatic inflammation rather than hepatic fibrosis in MASLD pathogenesis, compared to other rodent models[17]. Therefore, caution is advised when extrapolating findings from this animal model to human pathophysiology. It would be beneficial to validate these important findings in other, potentially more suitable, rodent MASLD models as well[17]. Furthermore, while the L-SACC1 mice serve as an important experimental model for studying hepatic insulin resistance, it is important to note that they do not develop diabetes[13]. This suggests that additional tissues must be involved in the development of overt T2DM and subsequent hepatic fibrogenesis.

Additionally, the study identified α5β1 integrin signaling as a key mediator of insulin's profibrotic effects on HSCs, but did not explore other potential signaling pathways that could contribute to collagen synthesis. In particular, investigating MAPK pathways such as ERK1/2 and p38 MAPK could provide further insights into how insulin influences HSC activation and fibrogenesis since these pathways have been implicated in various cellular responses related to growth factors and cytokines. Important factors such as the cellular communication network factor 2 (CCN2), previously known as connective tissue growth factor (CTGF), and TGF-β were not investigated[18]. To gain a comprehensive understanding of insulin's effects on HSCs, employing high-throughput techniques like RNA sequencing (NGS) or proteomics could elucidate global changes at both gene expression and protein levels following insulin treatment.

Furthermore, while the study tested various concentrations of insulin and found significant effects on collagen production, it mainly focused on a single concentration (5 μM) for detailed analysis. This raises questions about dose dependency and whether higher or lower concentrations could lead to different outcomes in terms of HSC activation and collagen synthesis. The study also did not assess the long-term effects or consequences of chronic insulin exposure on HSCs and liver fibrosis progression. Understanding how sustained hyperinsulinemia affects cellular behavior over time is crucial for evaluating its role in chronic liver diseases. Longitudinal studies would provide deeper insights into how continuous exposure influences HSC activation states and fibrogenesis.

Another notable limitation of this study is the lack of analysis regarding potential gender differences in the response of HSCs to insulin and collagen synthesis. Gender can significantly influence metabolic processes, hormonal regulation, and the pathophysiology of various diseases, including liver disorders[19].

Research has indicated that men and women may exhibit different susceptibilities to conditions such as T2DM and MASLD. These differences can arise from variations in hormone levels, such as estrogen and testosterone, which have been shown to modulate insulin sensitivity and fibrosis progression in the liver. For instance, estrogen is known to exert protective effects against liver fibrosis, while testosterone may have a more complex role that varies with context[19]. In studies involving animal models or human subjects, gender differences can also affect the activation state of HSCs and their response to profibrotic stimuli like insulin. It is plausible that male and female HSCs could respond differently to hyperinsulinemia due to intrinsic biological factors or varying expression levels of insulin receptors and downstream signaling molecules. The absence of gender-based analysis in this study limits the ability to generalize findings across populations. It is well-accepted that there are many factors resulting in gender differences in liver fibrosis, including various genetic, hormonal, immunological, metabolic, and lifestyle-related factors such as alcohol consumption, diet, and sedentary behavior[19].

In summary, the present study offers valuable insights and establishes a solid framework, laying a strong foundation for future research efforts. By validating important findings in other models and addressing the

limitations discussed, this study ultimately sets the stage for further exploration and validation of related concepts. Specifically, there is a need for further investigation into the impact of α5β1 integrin on the development of insulin resistance and hepatic fibrogenesis.

IMPACT ON THE CLINICAL MANAGEMENT OF INSULIN RESISTANCE AND DIABETES

The findings of this study have significant implications for the clinical management of patients with insulin resistance and related diseases, such as T2DM and MASLD. By elucidating the role of hyperinsulinemia in promoting type I collagen synthesis through α5β1 integrin signaling in HSCs, the research highlights a potential therapeutic target for mitigating liver fibrosis progression. Clinicians may consider strategies that specifically aim to modulate insulin levels or block α5β1 integrin signaling pathways to reduce fibrogenesis in at-risk populations. Furthermore, understanding the mechanisms by which insulin influences HSC activation can inform dietary and lifestyle interventions designed to improve insulin sensitivity, ultimately helping to prevent or slow the advancement of chronic liver diseases. By inhibiting α5β1, it may be possible to reduce HSC activation and proliferation, ultimately diminishing the deposition of ECM components that characterize fibrotic tissue. Additionally, specific antagonists or monoclonal antibodies against α5β1 could disrupt its interaction with fibronectin, thereby preventing the progression of fibrosis. Furthermore, combining α5β1 targeting strategies with existing therapies could enhance overall treatment efficacy and improve patient outcomes in individuals suffering from liver fibrosis. Therefore, focusing on α5β1 integrin presents a novel therapeutic avenue that warrants further investigation in clinical settings. As such, the study underscores the importance of personalized treatment approaches that take into account individual metabolic profiles, paving the way for more effective management strategies tailored to patients suffering from insulin resistance and its associated complications.

RESEARCH AGENDA NECESSARY FOR TRANSLATING FINDINGS OF THIS STUDY INTO CLINICAL PRACTICE FOR DIABETES AND LIVER DISEASE MANAGEMENT

In order to effectively translate the findings regarding hyperinsulinemia and its role in promoting type I collagen synthesis via α5β1 integrin signaling in HSCs into clinical practice, a focused research agenda is essential. This agenda should begin with mechanistic studies that further elucidate the specific pathways involved in insulin-mediated HSC activation and collagen production, including potential interactions with other profibrotic factors such as TGF-β and CCN2/CTGF. Additionally, it will be important to conduct preclinical studies using both male and female animal models to investigate gender differences in response to hyperinsulinemia, thereby ensuring that therapeutic strategies are inclusive and effective across diverse populations. Following this, clinical trials should be designed to evaluate the efficacy of pharmacological agents targeting α5β1 integrin or insulin modulation on liver fibrosis progression in patients with insulin resistance or metabolic disorders. For example, previous studies have shown that a rationally designed protein, called ProAgio, which targets αvβ3, can induce apoptosis *in vitro* and effectively deplete activated HSC *in vi*vo[20]. Additionally, the α8β1 and α11β1 integrins, selectively expressed in HSC, have been identified as new therapeutic targets for hepatic fibrosis[21]. A pan-αv inhibitor that targets arginine-glycine-aspartate-binding integrins has been found to attenuate fibrosis in a choline-deficient, amino-acid-defined, high-fat diet model, a well-established model of MASH[22]. Furthermore, Pliant Therapeutics has developed the small molecule αvβ1 inhibitor PLN-1474, which has been acquired by Novartis AG and will soon be tested for its beneficial effects in end-stage liver fibrosis resulting from MASH[23].

Moreover, incorporating lifestyle interventions, such as dietary modifications and exercise regimens, into these trials could provide insights into comprehensive management approaches for improving metabolic health alongside liver function. Finally, establishing biomarkers for early detection of fibrosis and monitoring treatment responses will be crucial for optimizing patient outcomes. By pursuing this multi-

pronged research agenda, we can bridge the gap between laboratory discoveries and clinical applications, ultimately enhancing the management of patients at risk for chronic liver disease associated with insulin resistance.

CONCLUSIONS

In conclusion, the study provides significant insights into the role of hyperinsulinemia in promoting type I collagen synthesis in HSCs through α5β1 integrin signaling. By demonstrating that insulin enhances collagen production under high glucose conditions independently of the PI3 kinase pathway, the research highlights a novel mechanism by which insulin can contribute to the development of liver fibrosis. The findings emphasize the importance of targeting α5β1 integrin signaling as a potential therapeutic strategy for managing chronic liver diseases associated with insulin resistance and metabolic disorders. Overall, this study lays the groundwork for further exploration into how hyperinsulinemia influences HSC activation and fibrosis progression, ultimately informing more effective clinical interventions for patients at risk of liver-related complications. Future work should focus on elucidating the precise molecular mechanisms underlying the interaction between hyperinsulinemia and α5β1 integrin signaling in HSCs, while also investigating potential gender differences in these responses. Additionally, clinical studies are needed to evaluate therapeutic approaches that target α5β1 integrin or modulate insulin levels to prevent or reverse liver fibrosis in patients with insulin resistance and related metabolic disorders, considering the varying effects observed between male and female patients. The findings of the study enhance previous knowledge and provide a clearer understanding of how hyperinsulinemia can directly influence fibrosis through specific signaling pathways in HSCs. Ultimately, advancing our understanding of these pathways may lead to innovative treatment options that improve patient outcomes and reduce the burden of liver disease in populations affected by metabolic dysfunctions. Moreover, collaborative efforts between researchers and clinicians will be essential to validate these findings and translate them into practical applications that might enhance patient care and management strategies in the long term.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

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Conflicts of interest

The author is Associate Editor of the journal *Metabolism and Target Organ Damage*. The author was not involved in any steps of editorial processing, notably including reviewers' selection, manuscript handling and decision making.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Aldroubi BG, Najjar JA, Youssef TS, et al. Cell-specific regulation of insulin action and hepatic fibrosis by CEACAM1. *Metab Target Organ Damage*. 2024;4:34. DOI PubMed PMC
2. Chandrasekaran P, Weiskirchen R. Diabetes mellitus and heart disease. *Metab Target Organ Damage*. 2024;4:18. DOI
3. Lonardo A, Ballestri S, Baffy G, Weiskirchen R. Liver fibrosis as a barometer of systemic health by gauging the risk of extrahepatic disease. *Metab Target Organ Damage*. 2024;4:41. DOI
4. Bourebaba N, Marycz K. Hepatic stellate cells role in the course of metabolic disorders development - a molecular overview. *Pharmacol Res*. 2021;170:105739. DOI PubMed
5. Cai CX, Buddha H, Castelino-Prabhu S, et al. Activation of insulin-PI3K/Akt-p70S6K pathway in hepatic stellate cells contributes to fibrosis in nonalcoholic steatohepatitis. *Dig Dis Sci*. 2017;62:968-78. DOI PubMed
6. Kaji K, Yoshiji H, Ikenaka Y, et al. Dipeptidyl peptidase-4 inhibitor attenuates hepatic fibrosis via suppression of activated hepatic stellate cell in rats. *J Gastroenterol*. 2014;49:481-91. DOI PubMed
7. Kaya D, Kaji K, Tsuji Y, et al. TGR5 activation modulates an inhibitory effect on liver fibrosis development mediated by anagliptin in diabetic rats. *Cells*. 2019;8:1153. DOI PubMed
8. Zhang F, Zhang Z, Kong D, et al. Tetramethylpyrazine reduces glucose and insulin-induced activation of hepatic stellate cells by inhibiting insulin receptor-mediated PI3K/AKT and ERK pathways. *Mol Cell Endocrinol*. 2014;382:197-204. DOI PubMed
9. Creeden JF, Kipp ZA, Xu M, et al. Hepatic kinome atlas: an in-depth identification of kinase pathways in liver fibrosis of humans and rodents. *Hepatology*. 2022;76:1376-88. DOI PubMed PMC
10. Kitsios K, Trakatelli CM, Antza C, Triantafyllou A, Sarigianni M, Kotsis V. Treatment of metabolic (dysfunction)-associated fatty liver disease: evidence from randomized controlled trials-a short review. *Metab Syndr Relat Disord*. 2024;22:703-8. DOI PubMed
11. Jiang Y, Wu L, Zhu X, Bian H, Gao X, Xia M. Advances in management of metabolic dysfunction-associated steatotic liver disease: from mechanisms to therapeutics. *Lipids Health Dis*. 2024;23:95. DOI PubMed
12. Dodig M, Li M, Dasarathy S, et al. Insulin increases type I collagen synthesis in hepatic stellate cells via α5β1 integrin. *Metab Target Organ Damage*. 2024;4:49. DOI
13. Poy MN, Yang Y, Rezaei K, et al. CEACAM1 regulates insulin clearance in liver. *Nat Genet*. 2002;30:270-6. DOI PubMed
14. Park SY, Cho YR, Kim HJ, et al. Mechanism of glucose intolerance in mice with dominant negative mutation of CEACAM1. *Am J Physiol Endocrinol Metab*. 2006;291:E517-24. DOI PubMed
15. Walsh A, Ito Y, Breslow JL. High levels of human apolipoprotein A-I in transgenic mice result in increased plasma levels of small high density lipoprotein (HDL) particles comparable to human HDL3. *J Biol Chem*. 1989;264:6488-94. PubMed
16. Nishimichi N, Tsujino K, Kanno K, et al. Induced hepatic stellate cell integrin, α8β1, enhances cellular contractility and TGFβ activity in liver fibrosis. *J Pathol*. 2021;253:366-3. DOI PubMed PMC
17. Kohli R, Feldstein AE. NASH animal models: are we there yet? *J Hepatol*. 2011;55:941-3. DOI PubMed
18. Weiskirchen R, Tacke F. Liver fibrosis: from pathogenesis to novel therapies. *Dig Dis*. 2016;34:410-22. DOI PubMed
19. Jamalinia M, Lonardo A, Weiskirchen R. Sex and gender differences in liver fibrosis: pathomechanisms and clinical outcomes. *Fibrosis*. 2024;2:10006. DOI
20. Turaga RC, Satyanarayana G, Sharma M, et al. Targeting integrin αvβ3 by a rationally designed protein for chronic liver disease treatment. *Commun Biol*. 2021;4:1087. DOI PubMed PMC
21. Yokosaki Y, Nishimichi N. New therapeutic targets for hepatic fibrosis in the integrin family, α8β1 and α11β1, induced specifically on activated stellate cells. *Int J Mol Sci*. 2021;22:12794. DOI PubMed PMC
22. Ulmasov B, Noritake H, Carmichael P, Oshima K, Griggs DW, Neuschwander-Tetri BA. An inhibitor of arginine-glycine-aspartate-binding integrins reverses fibrosis in a mouse model of nonalcoholic steatohepatitis. *Hepatol Commun*. 2018;3:246-61. DOI PubMed PMC
23. Slack RJ, Macdonald SJF, Roper JA, Jenkins RG, Hatley RJD. Emerging therapeutic opportunities for integrin inhibitors. *Nat Rev Drug Discov*. 2022;21:60-78. DOI PubMed PMC