Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/pq48qt39

TARGETING FATTY ACID METABOLISM IN OBESITY: ROLE OF FATTY-ACYL-COA SYNTHASE AS A THERAPEUTIC TARGET

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ABSTRACT:
Obesity has emerged as a global pandemic and a primary driver of chronic metabolic diseases, including type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and non-alcoholic fatty liver disease (NAFLD). The pathophysiology of obesity is intrinsically linked to the dysregulation of fatty acid metabolism, which fosters ectopic lipid accumulation, cellular lipotoxicity, insulin resistance, and a state of chronic low-grade inflammation. Central to the control of lipid fate are the fatty-acyl-CoA synthases (ACSLs), a family of isoenzymes that catalyze the activation of long-chain fatty acids to their acyl-CoA thioesters. This activation is the committed step that directs fatty acids towards distinct metabolic pathways, such as mitochondrial β-oxidation for energy production or esterification into complex lipids like triglycerides for storage. Accumulating evidence indicates that the expression and activity of specific ACSL isoforms are significantly altered in obesity. In particular, isoforms such as ACSL1, ACSL4, and ACSL5 have been implicated in adipocyte dysfunction, hepatic steatosis, and skeletal muscle insulin resistance. This review consolidates the current understanding of the role of ACSLs in the pathogenesis of obesity and its metabolic sequelae. We discuss the structure, tissue-specific functions, and regulatory mechanisms of key ACSL isoforms. Furthermore, we explore the therapeutic potential of targeting ACSLs, highlighting emerging pharmacological and genetic strategies aimed at developing isoform-specific inhibitors. By serving as critical nodes in the lipid metabolic network, ACSLs represent promising therapeutic targets for the development of novel interventions to combat obesity and its devastating complications.

KEYWORDS: Obesity, Fatty Acid Metabolism, Acyl-CoA Synthetases, ACSL4, Therapeutic Target, Metabolic Syndrome, Insulin Resistance.

INTRODUCTION:

The prevalence of obesity has reached pandemic proportions over the past few decades, constituting one of the most significant public health challenges of the 21st century. The World Health Organization (WHO) reports that worldwide obesity has nearly tripled since 1975, with over 1.9 billion adults being overweight in 2016, of whom over 650 million were obese (1). This alarming trend is not restricted to developed nations but is also rapidly accelerating in low- and middle-income countries (2). Obesity is a complex, multifactorial chronic disease characterized by excessive adiposity to the extent that it negatively impacts health. It serves as a major gateway to a cluster of non-communicable diseases, including type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD) like hypertension and atherosclerosis, non-alcoholic fatty liver disease (NAFLD), and several types of cancer (3,4). The economic ramifications are staggering, encompassing substantial direct healthcare costs for managing associated comorbidities and indirect costs related to reduced productivity and disability (5).

At the core of obesity's pathophysiology lies a profound dysregulation of energy homeostasis and lipid metabolism (6). In a state of chronic positive energy balance, excess fatty acids are taken up by peripheral tissues. While adipose tissue is specialized for lipid storage, its capacity can be overwhelmed, leading to lipid spillover and accumulation in non-adipose tissues such as the liver, skeletal muscle, heart, and pancreas. This phenomenon, known as ectopic fat deposition, is a key driver of cellular dysfunction (lipotoxicity), which contributes directly to the development of insulin resistance and systemic inflammation (7,8).

The metabolic fate of intracellular fatty acids—whether they are oxidized for energy, stored as triglycerides, or incorporated into structural lipids and signaling molecules—is tightly regulated. A critical control point in this process is the activation of fatty acids through their conversion to fatty acyl-CoA thioesters. This essential enzymatic step is catalyzed by a family of enzymes known as fatty-acyl-CoA synthases (FACS) or long-chain acyl-CoA synthetases (ACSLs) (9). The human genome encodes five major ACSL isoforms (ACSL1, 3, 4, 5, and 6), each with distinct tissue distribution, subcellular localization, and substrate specificities (10). This diversity allows for fine-tuned, tissue-specific regulation of fatty acid metabolism. Emerging evidence from both preclinical models and human studies strongly suggests that the expression and activity of ACSL isoforms are dysregulated in obesity, directly contributing to its metabolic complications (11,12). Consequently, these enzymes have garnered significant attention as potential therapeutic targets. This review aims to synthesize the current literature on the role of ACSLs in obesity, detailing their function in lipid metabolism and exploring the rationale and strategies for targeting them to ameliorate obesity-related metabolic diseases.

THE GLOBAL BURDEN AND PATHOPHYSIOLOGY OF OBESITY:

Obesity is a complex metabolic disease defined by the excessive accumulation of adipose tissue. Its etiology involves a complex interplay of genetic predisposition, environmental factors (including diet and physical activity), and socioeconomic determinants (13). The global surge in obesity is largely attributed to an environment that promotes high-calorie food intake and sedentary lifestyles. The health consequences are severe and wide-ranging. Central obesity, characterized by the accumulation of visceral adipose tissue, is particularly pernicious as this fat depot is more metabolically active and secretes a range of pro-inflammatory adipokines and cytokines that drive systemic inflammation and insulin resistance (14).

Obesity and Type 2 Diabetes Mellitus (T2DM): Obesity is the single most important risk factor for T2DM (15). Ectopic lipid accumulation in skeletal muscle and liver impairs insulin signaling pathways, leading to reduced glucose uptake and increased hepatic glucose production, respectively. Lipotoxicity, mediated by lipid intermediates like diacylglycerols (DAGs) and ceramides, activates protein kinase C isoforms that interfere with insulin receptor substrate (IRS) signaling (16). Furthermore, chronic inflammation originating from hypertrophied adipose tissue exacerbates insulin resistance (17).

Obesity and Cardiovascular Disease (CVD): Obesity promotes CVD through multiple mechanisms. It is a major cause of hypertension, dyslipidemia (characterized by high triglycerides, low HDL cholesterol), and atherosclerosis (3). Adipose tissue dysfunction leads to the release of non-esterified fatty acids, which promote hepatic VLDL production. The chronic inflammatory state associated with obesity contributes to endothelial dysfunction and the development and progression of atherosclerotic plaques (18).

Obesity and Non-alcoholic Fatty Liver Disease (NAFLD): NAFLD, which encompasses a spectrum from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis, is considered the hepatic manifestation of the metabolic syndrome (19). In obesity, increased fatty acid flux to the liver from both diet and adipose tissue lipolysis, coupled with increased de novo lipogenesis, overwhelms the liver's capacity for fatty acid oxidation and export, leading to triglyceride accumulation (steatosis) (20). In a subset of individuals, this progresses to NASH, characterized by inflammation, cellular injury, and fibrosis, which can lead to severe liver disease (21).

FATTY-ACYL-COA SYNTHASES (ACSLs): STRUCTURE, FUNCTION, AND ISOFORMS: Fatty-acyl-CoA synthases catalyze the ATP-dependent esterification of a fatty acid with coenzyme A (CoA) to form a fatty acyl-CoA. This activation reaction is thermodynamically favorable and renders the fatty acid metabolically active for downstream processes (9). The reaction proceeds in two steps: first, the formation of an acyl-adenylate intermediate, followed by the transfer of the acyl group to CoA.

The five principal ACSL isoforms (ACSL1, 3, 4, 5, 6) share a conserved domain structure but exhibit crucial differences that determine their specific roles in metabolism (10, 22). </

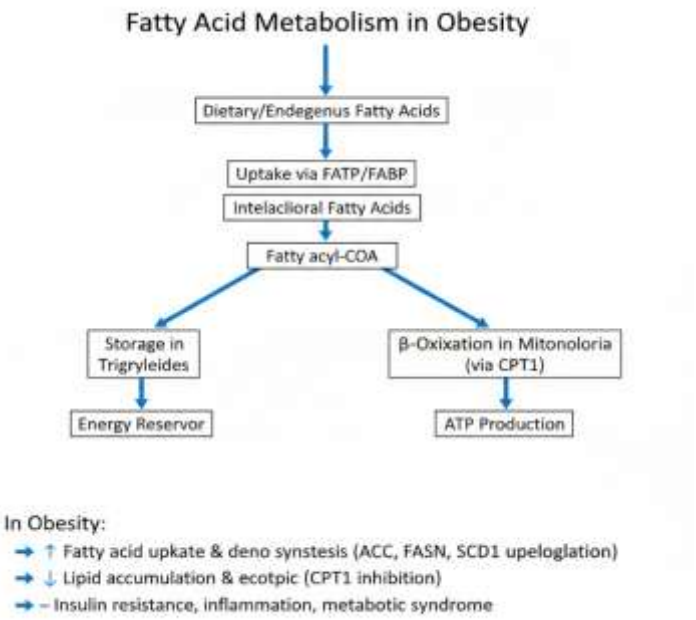
ACSL1: Highly expressed in metabolic tissues such as adipose tissue, skeletal muscle, heart, and liver. ACSL1 is generally associated with promoting fatty acid oxidation and is crucial for systemic energy metabolism. In adipocytes, it is also involved in triglyceride synthesis for lipid storage (23). Its deficiency in muscle leads to impaired fatty acid oxidation and accumulation of intramyocellular lipids (24).

ACSL3: Primarily located on the endoplasmic reticulum and lipid droplets, ACSL3 is abundant in the liver and steroidogenic tissues. It appears to channel fatty acids preferentially towards phospholipid and triglyceride biosynthesis rather than oxidation (25).

ACSL4: This isoform displays a unique substrate preference for long-chain polyunsaturated fatty acids (PUFAs), such as arachidonic acid (AA) and eicosapentaenoic acid (EPA) (26). It is highly expressed in steroidogenic tissues, the brain, and is increasingly recognized for its role in regulating lipid signaling. Critically, ACSL4 is an essential enzyme for ferroptosis, a form of iron-dependent programmed cell death characterized by lipid peroxidation (27). Its role in phospholipid remodeling makes it a key player in membrane dynamics and cellular stress responses.

ACSL5: Found in the small intestine, liver, and adipose tissue, ACSL5 is localized to both mitochondria and the endoplasmic reticulum. It has been implicated in both fatty acid oxidation and triglyceride synthesis. Genetic ablation of ACSL5 in mice leads to reduced adiposity, increased energy expenditure, and improved insulin sensitivity, making it an attractive therapeutic target (28).

ACSL6: Predominantly expressed in the brain, ACSL6 has a preference for very-long-chain fatty acids like docosahexaenoic acid (DHA). It plays a vital role in maintaining the unique phospholipid composition of neuronal membranes, which is essential for normal brain function (29).



DYSREGULATION OF ACSLs IN OBESITY AND METABOLIC DISEASE:

The tissue-specific expression and function of ACSL isoforms are profoundly altered in the setting of obesity and insulin resistance, contributing directly to the pathophysiology of metabolic disease.

In obese humans, the expression of ACSL1 is often paradoxically downregulated in skeletal muscle, which is associated with reduced fatty acid oxidation capacity and contributes to intramyocellular lipid accumulation and insulin resistance (11, 30). In contrast, hepatic ACSL1 expression may be increased, potentially contributing to the elevated triglyceride synthesis seen in NAFLD. Studies have shown that ACSL3 expression is elevated in the livers of obese and diabetic mice, where it promotes hepatic steatosis by directing fatty acids towards triglyceride storage (31). Its association with lipid droplets facilitates the efficient esterification of fatty acids, exacerbating lipid accumulation in the liver.

ACSL4 has emerged as a particularly important player in obesity-associated dysfunction. In adipose tissue, its expression is upregulated in obese mice and humans. This upregulation leads to remodeling of the adipocyte phospholipidome, increasing the content of arachidonic acid-containing phospholipids, which can promote inflammation and adipocyte dysfunction (12, 32). Overexpression of ACSL4 in adipocytes has been shown to impair their insulin sensitivity. Furthermore, its role in ferroptosis links it to cell death pathways that can be activated under conditions of metabolic stress and inflammation common in obesity (33).

The role of ACSL5 is also complex. While its deletion protects against diet-induced obesity (28), some studies show its expression is increased in the livers of patients with NASH, where it may contribute to lipotoxicity and disease progression (34). Its dual role in both anabolic and catabolic pathways suggests its function is highly context-dependent.

ACSLs AS THERAPEUTIC TARGETS FOR OBESITY MANAGEMENT:

The central role of ACSLs in dictating fatty acid fate makes them highly attractive therapeutic targets for metabolic diseases. The goal of targeting ACSLs is not to broadly inhibit all fatty acid activation but to selectively modulate the activity of specific isoforms in specific tissues to achieve a desired metabolic outcome, such as increasing fatty acid oxidation or reducing the synthesis of lipotoxic lipid species (35).

Isoform-Specific Pharmacological Inhibition: The development of potent and selective small-molecule inhibitors for ACSL isoforms is a major area of research. For example, ACSL4 inhibitors are being actively investigated, not only for metabolic diseases but also for cancer, due to its role in

ferroptosis (36, 37). An effective ACSL4 inhibitor could potentially reduce inflammation and improve adipocyte function in obesity. Similarly, inhibiting hepatic ACSL3 could reduce triglyceride synthesis and ameliorate steatosis. Triacsin C is a well-known natural product that inhibits multiple ACSL isoforms (1, 3, and 4) and has been a useful tool compound, but its lack of selectivity limits its therapeutic potential (38). The development of isoform-specific inhibitors remains a significant challenge due to the structural similarity of the active sites across the ACSL family.

Genetic and Molecular Approaches: Preclinical studies using genetic knockout or knockdown approaches have provided compelling proof-of-concept for targeting ACSLs. As mentioned, ACSL5 knockout mice are lean and insulin-sensitive (28). Liver-specific knockdown of ACSL3 has been shown to protect against diet-induced hepatic steatosis (31). Antisense oligonucleotides (ASOs) or small interfering RNAs (siRNAs) offer a potential therapeutic modality to specifically reduce the expression of a target ACSL isoform in a particular organ, such as the liver (39).

Combination Therapies: Given the metabolic complexity of obesity, combination therapies are likely to be more effective. Targeting an ACSL isoform could be combined with other therapeutic approaches, such as GLP-1 receptor agonists, which reduce appetite and improve glucose control, or with inhibitors of other key enzymes in lipid metabolism like acetyl-CoA carboxylase (ACC) or stearoyl-CoA desaturase-1 (SCD1) (40, 41). For example, combining an inhibitor of hepatic lipogenesis with a therapy that enhances peripheral fatty acid oxidation could provide a synergistic benefit for treating NAFLD and improving insulin sensitivity.

CHALLENGES AND FUTURE DIRECTIONS:

While targeting ACSLs holds great promise, several challenges must be overcome. A primary hurdle is the development of truly isoform-selective inhibitors. High-resolution crystal structures of the different ACSL isoforms are needed to facilitate rational drug design (42). Another challenge is the potential for metabolic compensation. Inhibiting one pathway of fatty acid metabolism may lead to the upregulation of another, potentially negating the therapeutic benefit. For example, blocking fatty acid esterification might shunt fatty acids towards other pathways that could generate different lipotoxic species (43).

Furthermore, there is a translational gap between rodent models and human physiology. The metabolic regulation and relative importance of different ACSL isoforms may differ between species, highlighting the need for careful validation in human-derived systems and well-designed clinical trials (44).

Future research should focus on a deeper understanding of the regulatory networks that control ACSL expression and activity in health and disease. The application of systems biology approaches, including transcriptomics, proteomics, and metabolomics, will be crucial for elucidating the precise consequences of modulating specific ACSL isoforms in different tissues (45). Personalized medicine approaches, potentially using genetic markers to predict which patients would respond best to an ACSL-targeted therapy, could also enhance therapeutic efficacy (46). Ultimately, a multi-pronged approach that combines lifestyle interventions with targeted pharmacotherapies will be necessary to combat the obesity epidemic.

CONCLUSION:

Obesity and its associated metabolic disorders are driven by a fundamental dysregulation of fatty acid metabolism. Fatty-acyl-CoA synthases are positioned at a critical control point, activating fatty acids and directing them towards their ultimate metabolic fate. The tissue-specific expression and distinct functions of the ACSL isoforms provide a unique opportunity for therapeutic intervention. Mounting evidence implicates the dysregulation of specific isoforms, particularly ACSL1, ACSL3, ACSL4, and ACSL5, in the pathogenesis of insulin resistance, adipocyte dysfunction, and NAFLD. Selective modulation of these enzymes offers a promising strategy to restore metabolic homeostasis. While significant challenges remain, particularly in developing isoform-specific inhibitors, continued research into the biology of ACSLs is paving the way for a new class of therapeutics to address the profound and growing public health crisis of obesity.

REFERENCES:

1. World Health Organization. Obesity and overweight. Geneva: WHO; 2021 [cited 2025 Sep 21]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
2. Popkin BM, Adair LS, Ng SW. Global nutrition transition and the pandemic of obesity in developing countries. Nutr Rev. 2012;70(1):3-21.
3. GBD 2015 Obesity Collaborators. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med. 2017;377(1):13-27.
4. Blueher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol. 2019;15(5):288-298.
5. Okunogbe A, Nugent R, Spencer G, Ralston J, Wilding J. Economic impacts of overweight and obesity: current and future estimates for 161 countries. BMJ Glob Health. 2021;6(10):e006325.
6. Frayn KN. Adipose tissue as a buffer for daily lipid flux. Diabetologia. 2002;45(9):1201-10.
7. Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. N Engl J Med. 2014;371(12):1131-41.
8. Unger RH, Clark GO, Scherer PE, Orci L. Lipid homeostasis, lipotoxicity and the metabolic syndrome. Biochim Biophys Acta. 2010;1801(3):209-14.
9. Faergeman NJ, Knudsen J. Role of long-chain fatty acyl-CoA esters in the regulation of metabolism and in cell signalling. Biochem J. 1997;323(Pt 1):1-12.
10. Soupene E, Kuypers FA. Mammalian long-chain acyl-CoA synthetases. Exp Biol Med (Maywood). 2008;233(5):507-21.
11. Poppelreuther M, Fenselau H, Gancheva S, et al. Acyl-CoA synthetase expression in human skeletal muscle is reduced in obesity and insulin resistance. Physiol Rep. 2023;11(17):e15817.
12. Killion EA, Reeves AR, El Azzouny MA, et al. A role for long-chain acyl-CoA synthetase-4 (ACSL4) in diet-induced phospholipid remodeling and obesity-associated adipocyte dysfunction. Mol Metab. 2018;7:113-123.
13. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. Lancet. 2011;378(9793):804-14.
14. Tchernof A, Després JP. Pathophysiology of visceral obesity. Clin Investig Med. 2013;36(2):E109-17.
15. Abdullah A, Peeters A, de Courten M, Stoelwinder J. The magnitude of the association between overweight and obesity and the risk of developing diabetes: a meta-analysis of prospective cohort studies. Diabetes Res Clin Pract. 2010;89(3):309-18.
16. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. J Clin Invest. 2016;126(1):12-22.
17. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature. 2017;542(7640):177-185.
18. Libby P, Buring JE, Badimon L, et al. Atherosclerosis. Nat Rev Dis Primers. 2019;5(1):56.
19. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med. 2018;24(7):908-922.
20. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest. 2005;115(5):1343-51.
21. Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. Lancet. 2021;397(10290):2212-2224.
22. Jia Y, Li Q, Zhang J. ACSL family and their roles in metabolism. J Biomed Res. 2021;35(5):371-381.
23. Li LO, Klett EL, Coleman RA. Acyl-CoA synthetases, fatty acid metabolism and disease. Biochim Biophys Acta. 2010;1801(3):246-51.
24. Grempler R, Kretzschmar T, Wu L, et al. Skeletal muscle-specific knockout of ACSL1 impairs exercise-induced CPT1b translocation and lipid oxidation. J Lipid Res. 2015;56(11):2131-42.
25. Poppelreuther M, Rudolph B, Du C, et al. The N-terminal region of acyl-CoA synthetase 3 is essential for both the localization on lipid droplets and the function in fatty acid uptake. J Lipid

Res. 2012;53(5):888-900.
26. Golej DL, Gorkiewicz T, Goralczyk A, et al. Acyl-CoA synthetase 4 (ACSL4) is a key enzyme for arachidonic acid-containing phosphatidylinositol synthesis in prostate cancer cells. J Lipid Res. 2011;52(4):784-95.
27. Doll S, Proneth B, Tyurina YY, et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. Nat Chem Biol. 2017;13(1):91-98.
28. Bowman TA, O'Keeffe KR, D'Aquila T, et al. Acyl-CoA synthetase 5 (ACSL5) ablation in mice increases energy expenditure and insulin sensitivity and delays fat absorption. Mol Metab. 2016;5(3):221-232.
29. Jia Y, Li Q, Zhang J. ACSL6 in brain development and diseases. J Biomed Res. 2021;35(5):382-389.
30. Hames KC, Khemka VK, Hou L, et al. Acyl-CoA synthetase-1 is required for the incorporation of exogenous fatty acids into skeletal muscle lipids. J Lipid Res. 2016;57(5):829-38.
31. Bu SY, Mashek MT, Mashek DG. Suppression of long chain acyl-CoA synthetase 3 decreases hepatic de novo fatty acid synthesis through decreased transcriptional activity of SREBP1c. J Biol Chem. 2009;284(44):30340-7.
32. Wu L, Feng Y, Che L, et al. Long-chain acyl-CoA synthetase 4 is a new regulator of triglyceride synthesis in 3T3-L1 adipocytes. J Lipid Res. 2017;58(1):72-83.
33. Li C, Dong X, Du W, et al. ACSL4 is a novel biomarker and potential therapeutic target of colorectal cancer. Clin Cancer Res. 2018;24(17):4279-4290.
34. Miquilena-Colina ME, Lima-Cabello E, Sánchez-Campos S, et al. Hepatic fatty acid transporters are downregulated in the absence of the cannabinoid CB2 receptor. Dis Model Mech. 2011;4(1):108-18.
35. Ellis JM, Li LO, Wu PC, Koves TR, Ilkayeva O, Stevens RD, et al. Adipose tissue acyl-CoA synthetase-1 directs fatty acids toward beta-oxidation and is required for cold thermogenesis. Cell Metab. 2010;12(1):53-64.
36. Feng H, Schinzel AC, Chen X, et al. A specific ACSL4 inhibitor discovers an intracellular role for ACSL4 in ferroptosis. Nat Cell Biol. 2020;22(7):855-865.
37. Ding K, Liu C, Li L, et al. Acyl-CoA synthetase ACSL4: an essential target in ferroptosis and fatty acid metabolism. Chin Med J (Engl). 2023;136(13):1574-1581.
38. Igal RA. Stearoyl-CoA desaturase-1: a novel key player in the mechanisms of cell proliferation,programmed cell death and transformation. Carcinogenesis. 2010;31(9):1509-15.
39. Watts GF, Ooi EM. Antisense oligonucleotides: a new dawn for the management of hypercholesterolemia? Circulation. 2012;126(17):2059-61.
40. Tong M, DeMaro JA, Jacobs RL, et al. The Acetyl-CoA Carboxylase Inhibitor, ND-646, Reduces Hepatic Steatosis, Improves Insulin Sensitivity, and Modulates Dyslipidemia in Rats. Hepatology. 2017;66(3):793-806.
41. Nauck MA, Meier JJ. Glucagon-like peptide 1 and its derivatives in the treatment of diabetes. Regul Pept. 2005;128(2):135-48.
42. Hisanaga Y, Ago H, Nakagawa N, et al. Structural basis of the substrate-specific two-step catalysis of long chain fatty acyl-CoA synthetase 1. J Biol Chem. 2004;279(30):31717-26.
43. Young PA, Senkal CE, Obeid LM. The role of fatty acid metabolism in cancer. Br J Pharmacol. 2018;175(1):31-47.
44. Martin B, Ji S, Maudsley S, Mattson MP. "Control" laboratory rodents are metabolically morbid: why it matters. Proc Natl Acad Sci U S A. 2010;107(14):6127-33.
45. Yugi K, Kubota H, Hatano A, Kuroda S. Trans-omics: how to reconstruct biochemical networks from multi-omics data. Trends Biotechnol. 2016;34(4):276-290.
46. Sookoian S, Pirola CJ. The genetic epidemiology of nonalcoholic fatty liver disease. Ann Hepatol. 2019;18(2):233-241.