生理学报 *Acta Physiologica Sinica*, June 25, 2025, 77(3): 545–562
DOI: 10.13294/j.aps.2025.0001 CSTR: 32202.14.j.aps.2025.0001 https://actaps.sinh.ac.cn


综 述

# 硬脂酰辅酶A去饱和酶1在代谢性疾病中的功能及相关机制研究进展

孙 钦，邢晓蕊，刘 诚，贾单单*，王 茹*

上海体育大学运动健康学院，上海 200438

**摘 要**：代谢性疾病主要表现为能量稳态失调，是全球面临的重大健康挑战。代谢性疾病人群常伴有与脂质代谢紊乱相关的并发症，如肥胖和非酒精性脂肪性肝病。关注脂质代谢核心基因有助于代谢性疾病及其并发症的防治工作。硬脂酰辅酶A去饱和酶1 (stearoyl-CoA desaturase 1, SCD1)是一种脂代谢关键酶，可将饱和脂肪酸转化为单不饱和脂肪酸，在能量稳态、糖脂代谢、自噬和炎症反应等众多生理和病理过程中发挥关键调控作用。*Scd1*的异常转录和表观遗传激活可通过调控多条信号轴导致脂质异常积累，从而促进肥胖、非酒精性脂肪性肝病、糖尿病和癌症发展。本文全面综述了SCD1作为代谢枢纽基因在常见生理和病理事件中的关键作用，并进一步从转化视角出发讨论了多学科交叉背景下SCD1新型抑制剂的潜在开发路径，以期为靶向SCD1防治代谢性疾病提供新视野和新思路。

**关键词**：代谢性疾病；硬脂酰辅酶A去饱和酶1；糖脂代谢；代谢枢纽

# Advances in the function and mechanisms of stearoyl-CoA desaturase 1 in metabolic diseases

SUN Qin, XING Xiao-Rui, LIU Cheng, JIA Dan-Dan*, WANG Ru*

*School of Kinesiology, Shanghai University of Sport, Shanghai 200438, China*

**Abstract:** Metabolic diseases characterized by an imbalance in energy homeostasis represent a significant global health challenge. Individuals with metabolic diseases often suffer from complications related to disorders in lipid metabolism, such as obesity and non-alcoholic fatty liver disease (NAFLD). Understanding core genes involved in lipid metabolism can advance strategies for the prevention and treatment of these conditions. Stearoyl-CoA desaturase 1 (SCD1) is a key enzyme in lipid metabolism that converts saturated fatty acids into monounsaturated fatty acids. SCD1 plays a crucial regulatory role in numerous physiological and pathological processes, including energy homeostasis, glycolipid metabolism, autophagy, and inflammation. Abnormal transcription and epigenetic activation of *Scd1* contribute to abnormal lipid accumulation by regulating multiple signaling axes, thereby promoting the development of obesity, NAFLD, diabetes, and cancer. This review comprehensively summarizes the key role of SCD1 as a metabolic hub gene in various (patho)physiological contexts. Further it explores potential translational avenues, focusing on the development of novel SCD1 inhibitors across interdisciplinary fields, aiming to provide new insights and approaches for targeting SCD1 in the prevention and treatment of metabolic diseases.

**Key words:** metabolic diseases; stearoyl-CoA desaturase 1; glycolipid metabolism; metabolic hub

---

This work was supported by the National Natural Science Foundation of China (No. 32271226), the National Key R&D Program of China (No. 2020YFA0803800), Shanghai "Science and Technology Innovation Action Plan" Social Development Science and Technology Reach Project (No. 22dz1204600), and Shanghai Municipal Science and Technology Committee of Shanghai Outstanding Academic Leaders Plan (No. 21XD1403200).

*Corresponding authors. WANG Ru: E-mail: wangru@sus.edu.cn; JIA Dan-Dan: E-mail: jiadandan@sus.edu.cn

代谢性疾病流行现状严峻，严重影响全球公众健康，加重医疗负担。代谢性疾病发生和发展的特征之一是脂质代谢功能的失调，以及进一步引发的慢性炎症激活、氧化应激和异常自噬等[1–4]。硬脂酰辅酶A去饱和酶1 (stearoyl-CoA desaturase 1, SCD1)是脂质合成中的关键限速酶，通过产生单不饱和脂肪酸(monounsaturated fatty acids, MUFAs)维持细胞内脂质稳态，协调糖脂代谢、炎症和自噬，是调节代谢的中心因子[5–8]。越来越多的研究表明，SCD1的异常表达与肥胖、非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)和2型糖尿病(type 2 diabetes mellitus, T2DM)等多种代谢性疾病的风险增加有关[9–14]。进一步研究发现抑制SCD1活性能够减弱脂肪酸的再酯化和糖异生，并促进脂肪细胞中*Atgl*和*Hsl*等脂解生物标志物的表达[15]。同时，两项以NAFLD和非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)患者为受试者的临床试验揭示了Aramchol (Arachidyl amido cholanoic acid，一种肝脏SCD1部分抑制剂)能够显著减少肝脏脂质堆积，改善肝纤维化[16–18]。其中，Aramchol通过下调*Scd1*基因表达、上调PPARγ表达，减少肝星状细胞中I型胶原的表达和分泌，最终在NASH患者中达到抗纤维化效果[19]。

综上，探明SCD1如何调控上述复杂信号网络是理解其在代谢性疾病发病机制中作用的核心。因此，本文综述了SCD1作为代谢枢纽基因在生理和病理事件中的关键影响，并进一步讨论了针对多种组织和器官的新型强效SCD1抑制剂用于治疗代谢性疾病的潜在开发路径，以期为靶向SCD1防治代谢性疾病提供新视野。

## 1 SCD1分子特征

SCDs是一类高度保守的脂肪酸去饱和酶家族，亦属于亚铁去饱和酶家族。迄今为止，在小鼠中已鉴定出具有高度氨基酸序列同源性的四种SCD亚型(SCD1~4)，在大鼠中已鉴定出两种SCD同工酶(SCD1~2)[20, 21]。其中，SCD1是一种位于内质网(endoplasmic reticulum, ER)的膜蛋白，具有四个跨膜α螺旋(TM1~TM4)，这些螺旋在结构上呈锥形排列[22]。在跨膜区域，大部分氨基酸是疏水性的，但在TM4的中心位置有一个保守的精氨酸残基(Arg249)以稳定SCD1结构。SCD1的N端和C端位于细胞质侧[22, 23]。在SCD1结构域中，高度保守的组氨酸残基通过结合二价铁离子形成催化中心，通过电子传递参与SCD1的脂肪酸去饱和反应[22–24] (如图1*A*)。此外，SCD1发挥活性需要两个膜内蛋白质的辅助，即细胞色素b5还原酶(b5 reductase, b5R)和细胞色素b5 (cyt b5) [22]。b5R在其N端有一个单个跨膜α螺旋，以及由N端和C端两部分组成的水溶性胞质区域。N端部分结合黄素腺嘌呤二核苷酸(FAD)，C端部分结合NADH [22]。b5R的主要还原因子是cyt b5，它包含一个水溶性胞质区域和C末端的单个跨膜区域，其中含有一个b型血红素，由两个轴向组氨酸配体连接。b5R和cyt b5都通过其单个跨膜区域锚定在ER膜上。从NADH开始，通过b5R和cyt b5，与SCD1相互作用形成电子传递链，催化饱和酰基辅酶A上的双键形成[22, 23]。

SCD1在肝脏、脂肪、胰岛、大脑和骨骼肌等各类组织中广泛表达[25–35] (图2)。在人类、恒河猴、大鼠和小鼠中，SCD1的蛋白质序列同源性为91.3% (图1*B*)，这表明SCD1通过脂质代谢调节机体内稳态的作用在进化上是保守的。SCD1的转录受到如葡萄糖、饱和脂肪酸(saturated fatty acids, SFAs)、胰岛素、固醇调节元件结合蛋白1 (sterol regulatory element-binding protein 1, SREBP1)、过氧化物酶体增殖物激活受体α (peroxisome proliferators-activated receptor α, PPARα)和肝X受体(liver X-receptor, LXR)等营养、激素和环境多种因素的严格调控[36–40]。其中，瘦素、雌激素和多不饱和脂肪酸(polyunsaturated fatty acids, PUFAs)能够抑制*Scd1*基因转录[41–43]。比如，来自脂肪组织的PUFAs通过与启动子区域的60 bp PUFAs反应元件结合可下调小鼠肝脏*Scd1*启动子活性，抑制*Scd1*基因表达[44]。此外，激活LXR可上调人类间充质基质细胞中SCD1蛋白表达，同时防止过量SFAs造成的脂毒性损伤(如氧化应激和炎症反应)[45]。有趣的是，随着SFAs的水平升高，SCD1的蛋白表达和活性被上调，增强机体对SFAs的去饱和化以维持脂质稳态[45, 46]。

## 2 SCD1的生理功能

SCD1广泛调控体内多种生理和病理功能[47]。锚定在ER的整合蛋白SCD1通过催化SFAs的碳9和碳10之间形成顺式双键，将SFAs (如硬脂酸)转化为MUFAs (如油酸)[47, 48]。SCD1能够促进体内的脂质代谢，保护癌细胞免受SFAs引发的脂毒性影响，从而增强肿瘤细胞增殖和再生，提高其存活

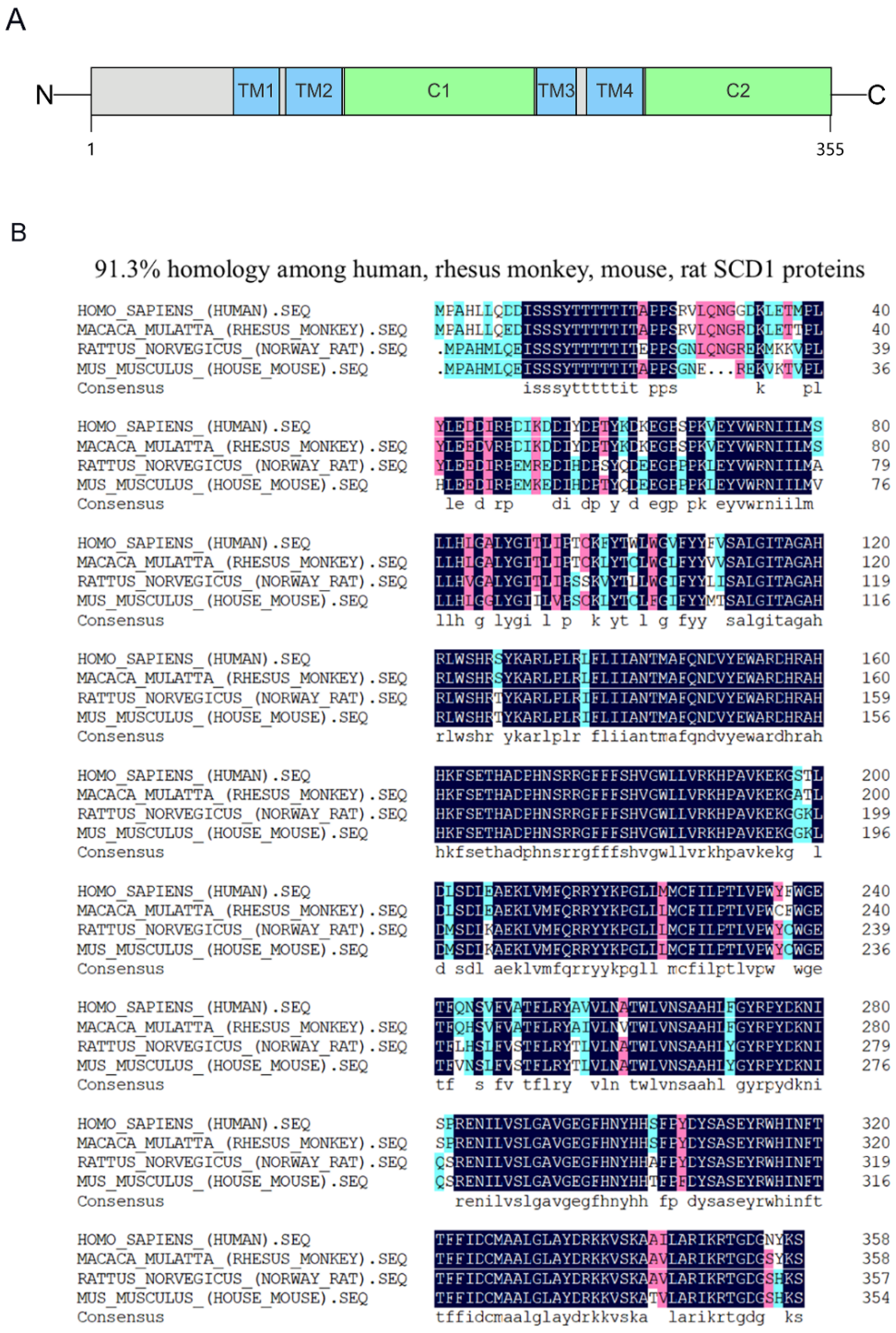


图 1. SCD1分子结构域及在各物种间蛋白序列比对(参考NCBI数据库绘制)

Fig. 1. SCD1 molecular domain map and protein sequence alignment among different species (Drawn by NCBI database). *A*: The molecular structure domain diagram highlights the critical functional regions of the SCD1 protein. N-terminal signal peptide is represented in gray; 4 transmembrane α helices (TM1-TM4) are represented in blue; and 2 histidine clusters (C1-C2) are represented in green. These domains show a high degree of consistency across species. *B*: This alignment compares SCD1 protein sequences from human (NP_005054.3), rhesus monkey (XP_015003410.1), mouse (NP_033153.2) and rat (NP_631931.2). Among the 4 sequences, 2 identical residues are represented in blue; 3 identical residues are represented in red; and 4 identical residues are represented in black.

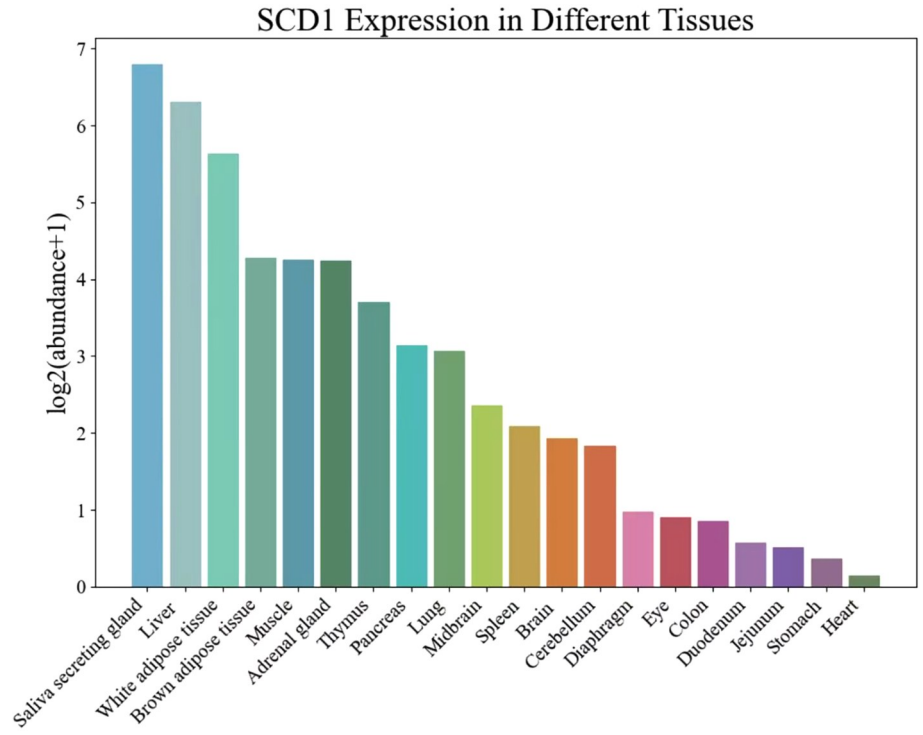


图 2. SCD1小鼠各组织特异性分布(参考NCBI和PaxDb数据库绘制)

Fig. 2. Tissue specific distribution of SCD1 in mice (Drawn by NCBI and PaxDb databases).

率[8, 49, 50]。相反，SCD1的失活将降低透明细胞肾细胞癌的细胞增殖并促使其凋亡[51]。与此同时，SCD1在葡萄糖代谢、自噬和炎症中亦发挥着广泛影响[6, 9, 47, 52, 53]。

### 2.1 SCD1和糖代谢

小鼠全身SCD1敲除可增强骨骼肌、棕色脂肪组织(brown adipose tissue, BAT)和心脏等组织的葡萄糖摄取，促进糖原积累，增强胰岛素敏感性[54, 55]。其中，骨骼肌是人体最大的代谢器官，直接调节全身葡萄糖稳态和胰岛素敏感性[56]。在骨骼肌过表达SCD1小鼠中，骨骼肌胰岛素受体底物1 (insulin receptor substrate 1, IRS1)酪氨酸磷酸化和Akt1丝氨酸473磷酸化水平下调，提示胰岛素信号传导途径受损[54, 55]。相反，在骨骼肌敲除SCD1小鼠中，骨骼肌胰岛素受体、IRS1、IRS2和Akt磷酸化水平上调，GLUT4介导葡萄糖转运增强[54, 55]。其潜在机制可能是SCD1改变了体内如游离脂肪酸(free fatty acids, FFAs)和神经酰胺等脂质含量，进一步抑制了IRS1-Akt信号轴活性及其相关的胰岛素敏感性关键因子(如AMPK和PTP-1B)的激活，最终导致葡萄糖代谢稳态失衡[54, 57, 58]。

高碳水化合物饮食(high carbohydrates diet, HCD)通过SCD1引起肝脏脂质生成，并且这种效应受到SREBP1、碳水化合物反应元件结合蛋白(carbohydrate response element binding protein, ChREBP)和LXR等应答元件的调节[36]。特异性敲除HCD喂养小鼠肝脏SCD1可增强机体葡萄糖摄取，并促进肝脏成纤维细胞生长因子21 (fibroblast growth factor 21, FGF21)的合成和分泌[59]。已知FGF21能够增强全身胰岛素敏感性并调节全身脂质代谢[59]。进一步实验证明，原代肝细胞经油酸处理后PGC-1α表达下调，并部分抑制了SCD1抑制剂诱导的FGF21表达[59]。另有研究发现，在AML12细胞中SCD1的缺失引发ER应激，并通过过量SFAs激活mTORC1-PGC-1α轴增加FGF21蛋白表达[60]。已知胰岛素样生长因子结合蛋白1 (insulin-like growth factor binding protein 1, IGFBP1)作为另一种改善葡萄糖耐量的肝脏细胞因子，能够增强β细胞增殖、胰岛素信号传导和葡萄糖摄取[61]。在HCD化合物喂食期间，SCD1肝脏敲除小鼠肝脏中IGFBP1蛋白水平显著增加[60]。这种IGFBP1水平的变化可能受油酸调节下mTORC1-FGF21信号轴调控[62]。

### 2.2 SCD1和脂代谢

SCD1减弱脂肪组织棕色化。研究发现，敲除脂肪干细胞中*Scd1*基因可增加琥珀酸积累，增强线

粒体复合体II活性，促进脂肪干细胞向米色脂肪细胞的分化[63]。在高脂饮食(high fat diet, HFD)喂养小鼠的腹股沟脂肪(inguinal white adipose tissue, iWAT)中，*Scd1*基因突变上调*Ucp1*和*Pparγ*等产热基因转录，诱导脂肪细胞棕色化，降低iWAT质量[63]。有趣的是，通过冷暴露或激活骨形态发生蛋白(bone morphogenetic proteins, BMP)-Smad轴将上调SCD1蛋白表达，促进Fabp4-Cre-Bmp4$^{LoxP/LoxP}$小鼠皮下脂肪细胞的脂质动员和全身能量代谢，诱导脂肪细胞褐变[64]。其中，通过上调SCD1表达而增加的油酸合成将触发脂解和脂质自噬[64, 65]。不同来源的脂肪组织可能是SCD1缺失时出现代谢差异表型的潜在原因。先前研究发现内脏脂肪质量的增加与机体代谢功能障碍相关，而增加皮下脂肪则可以维护代谢生理稳态[66]。而冷暴露干预促使FFAs的脂解和转化，也可能导致产生不一致的实验结果[67]。此外，在特异性敲除肝脏SCD1的小鼠中发现$\beta_3$-肾上腺素受体($\beta_3$-adrenergic receptor, $\beta_3$-AR)的表达增加和PPARα的激活，伴随着BAT产热和肝脏脂解的显著增加[68]。尽管PPARα诱导脂肪酸β-氧化和产热基因的转录，但小鼠肝脏中PPARα的缺失无法消除肝脏特异性SCD1敲除对脂肪酸氧化增强的效果，提示肝脏SCD1仍然存在PPARα以外的下游靶点[68]。

SCD1调控体内SFAs和MUFAs水平变化能够作为脂质信号显著影响细胞代谢健康。人类和动物的研究发现，富含SFAs的西方饮食将异常提高体内SFAs水平，并引发慢性炎症。这进一步干扰代谢稳态，促进各类代谢性疾病的发生和发展[69–71]。相反，富含MUFAs的地中海饮食存在抗炎效果，可诱导M2型巨噬细胞极化和抑制NOD样受体热蛋白结构域相关蛋白3 (NOD-like receptor thermal protein domain associated protein 3, NLRP3)炎症小体激活，以及抑制SFAs诱导的胰岛素抵抗和肝脏脂肪变性[72–74]。因此，由SCD1内源性合成的MUFAs在调节组织脂质稳态方面具有关键且独特的功能。

### 2.3 SCD1和炎症

脂肪酸长期以来被认为可调节组织炎症[75, 76]。SCD1通过调节MUFAs和SFAs间的平衡，对炎症和应激反应存在显著影响[77]。SFAs作为Toll样受体(Toll-like receptor, TLRs)家族成员等细胞表面免疫受体的配体，可促进炎症过程[70]。SFAs也可转化为鞘氨醇等中间物质，间接产生促炎效应[6, 78]。SFAs在包括巨噬细胞、内皮细胞、脂肪细胞和β细胞等多种类型细胞中均发挥促炎效应[6]。而MUFAs通过激活抗炎机制(如促进M2巨噬细胞极化和脂肪细胞IL-10分泌)能够逆转SFAs对脂肪和肝脏组织的不良影响[79]。重要的是，SCD1活性增强可通过促进巨噬细胞中MUFAs积累进而减少由髓样分化因子88 (myeloid differentiation factor 88, MyD88)介导的炎症反应[80]。动物研究表明通过核呼吸因子2 (nuclear respiratoty factor 2, NRF2)-SREBP1-SCD1/2信号轴控制MUFAs代谢能够减轻MyD88驱动的TLRs诱导的巨噬细胞炎症[80]。除此之外，SCD1也可通过增强DNA甲基化来控制炎症基因的表达，从而抑制*Il4ra*、*Il6st*和*Tgfb1*转录，最终减缓炎症过程[81]。相反，当使用化学抑制剂抑制脂肪细胞中SCD1活性时，脂肪酸如硬脂酸的水平将上调，这会显著加剧包括IL-6、单核细胞趋化蛋白-1 (monocyte chemotactic protein-1, MCP-1)和趋化因子配体5 (regulated on activation, normal T-cell expressed and secreted, RANTES)在内的炎症标志物分泌，最终引发细胞发生炎症应激[82]。

总而言之，SCD1能够减弱上述如SFAs、MyD88和TLRs等各种炎症因子促炎症作用[83]。然而，目前尚不清楚累积的MUFAs如何解决MyD88驱动的炎症，需待未来进一步研究。

### 2.4 SCD1和自噬

在营养缺乏条件下，自噬在蛋白质、脂滴(lipid droplets, LDs)和糖原的分解代谢中起着关键作用，以维持正常代谢平衡[84, 85]。自噬的特征是通过包裹部分细胞质和需要降解的细胞器及蛋白质形成自噬体[86, 87]。自噬体与溶酶体融合，分解其内容物，以维持细胞内稳态和器官更新[86, 87]。脂质是细胞膜结合的信号分子，通过特异性招募调控膜变形、扩展和囊泡运输的细胞质蛋白效应因子，介导自噬小体组装和形成[88]。其中，SCD1调控哺乳动物细胞和组织中的脂肪酸构成，并显著下调自噬水平[7]。在小鼠胚胎成纤维细胞中SCD1缺失阻碍了Akt磷酸化激活，随后增加叉头盒蛋白O1 (Forkhead box O1, FOXO1)核转位，最终激活*Atg4b*、*Atg12*和*Becn1*等自噬相关基因的转录[89]。有趣的是，这种在SCD1抑制下的自噬诱导并不依赖于经典mTOR信号调控[89]。此外，去乙酰化酶3 (Sirtuin 3, SIRT3)和NADH：泛醌氧化还原酶B9亚基(NADH: ubiquinone oxidoreductase subunit B9, NDUFB9)通过调节SCD1表达，从而调控各组织自噬、分化和炎症等生物事件[41, 52, 90, 91]。

## 3 SCD1水平异常诱发代谢性疾病的流行病学证据

日益增加的流行病学研究证据表明，*Scd1*基因遗传多态性与代谢性疾病风险因素显著相关，如体脂分布异常、胰岛素抵抗和慢性炎症[92–96]。在一项基于2152名成年人的队列研究中，*Scd1*基因中包含rs1502593的两种常见连锁遗传型与代谢综合征(metabolic syndrome, MetS)患病率增加显著相关[97]。SCD1潜在高概率的错义多态性已被多项研究报道与代谢性疾病发生有关[93, 94, 97]。一项关于*Scd1*基因多态性与糖尿病潜在机制的体外研究中，功能获得性rs2234970多态性通过增强mRNA稳定性，抑制蛋白降解，能够提高SCD1蛋白表达和酶活性[98]。这与随后胰岛素抵抗风险增加显著相关，表明rs2234970多态性的变异将进一步增加糖尿病的患病风险[98, 99]。

上述流行病学证据表明，单核苷酸多态性导致SCD1的不同突变及其后续功能改变可能对包括肥胖、MetS和糖尿病在内的多种代谢性疾病的发生存在显著影响[24, 100]。

## 4 SCD1与代谢性疾病

SCD1的异常表达和活性改变与肥胖、NAFLD和糖尿病等多种代谢疾病的风险增加相关[9–11, 13, 14, 101]。重要的是，SCD1可能通过调节脂质产生在各组织器官间实现“对话”(crosstalk)，在各种代谢疾病中扮演调控分子信号网络的核心角色。并且，其下游脂质产物不仅影响能量代谢，也可作为信号分子来调节生理和病理功能。目前，已有众多研究报道SCD1相关信号轴(见表1)，其是影响糖脂代谢、炎症反应和自噬异常的共通枢纽[49, 57, 102, 103]

表1. SCD1影响不同代谢性疾病的机制

Table 1. The mechanisms by which SCD1 affects different metabolic diseases

| Diseases | Signaling axis | Effects of SCD1 on metabolic diseases |
|---|---|---|
| Obesity | NDUFB9[91]<br>FOXO1[104]<br>AMPK-ACC[26]<br>NRF2-SREBP 1[105] | Excess MUFAs production through SCD1 promotes lipogenesis, leading to hypertrophy and proliferation of adipocytes, which promotes fat accumulation and leads to lipid toxicity. |
| NAFLD | STAT3[106]<br>ADGRF1[107]<br>FGF1-SREBF1[108]<br>AMPK-SREBP1[109]<br>NcDase-Wnt[27]<br>SIRT3[90] | Overactivity of SCD1 reduces fatty acid oxidation and increases lipid deposition in the liver, contributing to the development of hepatic steatosis, lipid accumulation, and insulin resistance. Furthermore, SCD1 plays a role in promoting inflammation and oxidative stress by altering the fatty acid composition. |
| Diabetes | PPAR-RXR[110]<br>AKT-mTOR[62]<br>AMPK-SIRT1[102]<br>SREBP1[111] | High SCD1 activity promotes elevated triglyceride levels and indirectly affects insulin signaling sensitivity. On the other hand, SCD1 is able to maintain the number and size of lipid droplets in β cells and the structure and function of islets. |
| Cancer | AKT-GSK3β [112]<br>mTOR-SREBP1 [113]<br>METTL16-YTHDC2 [114]<br>Wnt-IGHM [115]<br>PI3K-AKT-mTOR [49]<br>FBW7-NRA41 [13]<br>XBP1-CHOP [116] | SCD1 promotes tumor proliferation, growth, migration, invasion and metastasis by maintaining the lipogenesis of cancer cells. |

NAFLD: non-alcoholic fatty liver disease; INSIG1: insulin-induced gene 1; SREBP1: sterol regulatory element-binding protein 1; AMPK: adenosine 5′-monophosphate (AMP)-activated protein kinase; ACC: acetyl-CoA carboxylase; NRF2: nuclear respiratory factors 2; NcDase: neutral ceramidase; SIRT3: Sirtuin 3; PI3K: phosphoinositide 3-kinase; mTOR: mammalian target of rapamycin; FBW7: F-box and WD repeat domain-containing 7; NRA41: nuclear receptor subfamily 4 group a member 1; CHOP: C/EBP-homologous protein; Bax: BCL2-associated X; NDUFB9: NADH: ubiquinone oxidoreductase subunit B9; STAT3: signal transducer and activator of transcription 3; ADGRF1: adhesion G protein-coupled receptor F1; FGF1: fibroblast growth factor 1; RXR: retinoid X receptor; METTL16: methyltransferase-like protein 16; YTHDC2: YTH domain containing 2; MUFAs: monounsaturated fatty acids.

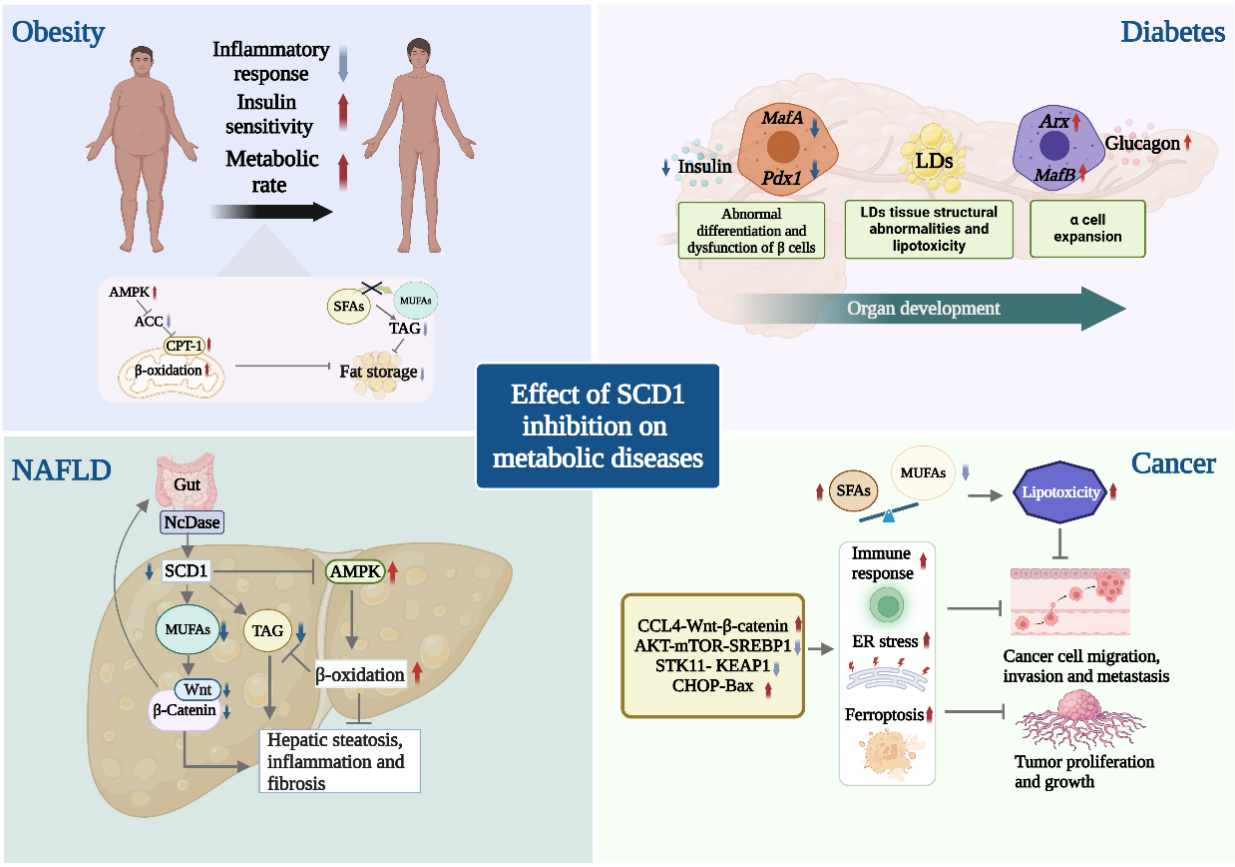


图 3. 抑制SCD1在各类代谢性疾病中的作用

Fig. 3. The impact of SCD1 inhibition on various metabolic diseases. Inhibition of SCD1 improves obesity by activating the AMPK-ACC signaling axis, increasing β-oxidation of fatty acids in mitochondria and reducing lipid synthesis through decreased conversion of MUFAs. This mechanism also enhances hepatic fatty acid oxidation, improves hepatic lipid accumulation, and alleviates hepatic steatosis in NAFLD, while attenuating the fibrosis and inflammation responses driven by the NcDase-Wnt-β-Catenin signaling axis in non-alcoholic steatohepatitis (NASH). Furthermore, loss of SCD1 adversely affects islet structure and functionality, reducing the number and size of LDs in β-cells, thus exacerbating susceptibility to lipotoxicity, and accelerating structural and functional changes associated with type 2 diabetes mellitus (T2DM). Eventually, it leads to abnormal differentiation and dysfunction of β-cells. Additionally, inhibiting SCD1 suppresses ER stress, ferroptosis, and immune responses in cancer cells, hindering their proliferation, migration, invasion, and metastasis. TAG, triacylglyceride; LDs, lipid droplets; NcDase, neutral ceramidase; SFAs, saturated fatty acids; ER stress, endoplasmic reticulum stress. The other abbreviaions are the same as those in Table 1.

(图3)。因此，深入理解SCD1在各种代谢性疾病中的调控机制对于疾病治疗具有深远的临床意义。

### 4.1 SCD1和肥胖

SCD1是体重调节的关键因子。Cruz-Color等研究者对38名肥胖患者进行脂肪组织活检，发现SCD1在皮下和内脏脂肪组织高表达，其中皮下脂肪组织中SCD1的表达随身体质量指数的增加呈显著上升趋势[117]。全身SCD1基因敲除小鼠能够抵抗HFD引起的肥胖，同时胰岛素敏感性和新陈代谢率增强[118]。SCD1基因缺失ob/ob小鼠(*Scd1*$^{-/-}$ leptin$^{ob/ob}$)低代谢表型逆转，能量消耗显著增强，肝脏脂质沉积显著减少[119]。然而，与leptin$^{ob/ob}$小鼠相比，*Scd1*$^{-/-}$ leptin$^{ob/ob}$小鼠表现出胰岛素抵抗、低胰岛素血症和高血糖，伴随出现异常胰岛功能[118]。基于此，SCD1在肥胖进程中可能发挥双重作用：SCD1缺失减轻了肥胖表型，但伴随胰岛功能障碍和糖代谢紊乱[118]。近期研究也发现SCD1缺乏将引起胰岛内β细胞向α细胞分化，胰岛微结构破坏并出现胰岛功能障碍[28]。其中，SCD1参与调节关键β细胞基因(如*Pdx1*和*MafA*)启动子甲基化状态，抑制SCD1会导致低甲基化并改变β细胞染色体内的甲基化水平分布[28]。同时，在INS-1细胞中过表达SCD1将增

加SFAs向MUFAs转化[104, 120]。棕榈油酸作为MUFAs之一，能够增强FoxO1转录活性，使INS-1细胞对棕榈酸引起的脂毒性侵害具有抵抗力，从而保护它们免受脂毒性诱发的ER应激和细胞凋亡[104, 120]。有趣的是，特异性敲除小鼠肝脏SCD1能够降低肝脏脂肪生成酶活性，减少肝糖异生，从而避免HCD而不是HFD导致的(皮下和内脏)脂肪组织的脂质堆积，改善小鼠肥胖和胰岛素抵抗[121]。已知肝脏*Scd1*启动子甲基化水平与全身脂肪含量和血清瘦素水平显著正相关，并受到高胆固醇饮食和HFD的正向调节[122]。这提示我们SCD1功能可能具有组织特异性作用，并且在肝-脂肪轴的组织间“对话”中存在关键作用，是肝脏-脂肪轴间交流的介质[123]。

过表达小鼠骨骼肌中SCD1显著减弱AMPK磷酸化，AMP/ATP比例降低，小鼠表现出对HFD诱导的脂质积累和胰岛素抵抗的易感性[26]。在正常原代人骨骼肌细胞中，过表达SCD1将减少45%油酸氧化，并且细胞内甘油三酯和磷脂水平分别增加22%和27%[9]。同时，AMPK和ACC2磷酸化水平受到抑制，导致肌细胞脂肪酸氧化率下降[9, 124]。此外，与正常人相比，在重度肥胖患者骨骼肌中，SCD1显著增加与脂肪酸氧化率下降、甘油三酯合成增加以及MUFAs水平上升呈显著正相关，这可能是受表观遗传和/或遗传机制驱动[9, 31]。

### 4.2 SCD1、NAFLD和NASH

NAFLD包括其更严重程度的NASH全球患病率高达20%~25%，是全球重大公共卫生问题[125]。NAFLD主要特征是肝脏脂肪变性、胰岛素抵抗、线粒体功能障碍、炎症和氧化应激[126, 127]。SCD1作为临床上肝脏脂代谢稳态的生物标志物，在NAFLD发生和发展中起着重要作用[123]。随着脂肪酸在脂肪组织或肝细胞中的过度累积，肥胖人群患NAFLD的风险显著增加[128]。能量过剩会启动肝脏AMPK-SREBP1信号轴中SREBP1c的裂解和核转位，随后其与SCD1启动子内SRE基序相结合，引起肝细胞甘油三酯的积累[109]。而特异性敲除肝脏SCD1能够减少肝脏脂质合成，保护小鼠免受过量碳水化合物诱发的肝脏脂肪变性[121]。

伴随NASH发展，肝脏将发生一系列异常病理变化，尤以肝细胞肿胀、胰岛素抵抗、炎症反应和肝脏纤维化为主要特征[129, 130]。此外，与组织再生相关信号通路将异常激活，这会促进贮脂细胞诱导肝脏纤维化[131]。动物和临床研究表明，肝脏纤维化导致肝硬化和肝功能衰竭，并且促进肝癌的发展[132–134]。已知中性神经酰胺酶(neutral ceramidase, NcDase)-SCD1-β-链蛋白(β-Catenin)形成的反馈回路通过调节细胞内鞘氨醇和FFAs水平，促进NASH中的炎症和纤维化[27]。在HFD喂养下，NcDase将减少调节肠道微生物群组成的小肠免疫球蛋白A (immunoglobulin A, IgA)的产生，从而降低NASH小鼠肠道中瘤胃菌科的定植[27]。瘤胃球菌已知能够抑制SCD1的表达，从而减少小鼠肝脏和回肠中MUFAs生成[27]。总体来说，NcDase缺失通过改变肠道微生物群落抑制SCD1的表达，进而产生增强Wnt活性和β-Catenin核转运的SFAs。过量SFAs引起Wnt脂酰化和β-Catenin激活，诱发HFD下肝脏炎症反应[27, 135]。并且，这将激活HFD喂养的小鼠肝脏中纤维化基因(如*Il-6h*和*ACTA2*)表达[27]。重要的是，Wnt蛋白正向促进NcDase活性，这将最终形成NcDase-SCD1-Wnt之间的正反馈循环，加剧NAFLD病程[27]。在另一项关于肠道微生物刺激肝脏再生的研究中，由肠道微生物产生的短链脂肪酸(short-chain fatty acids, SCFAs)通过门静脉运输到肝脏，并在那里转化为SFAs。SFAs随后通过促进肝细胞中SCD1表达来激活肝细胞增殖[136]。值得注意的是，SCD1的表达被发现与肝切除术后人肝脏的增殖和再生呈正相关[136]。类似地，通过siRNA抑制SCD1显著降低了HepG2细胞的增殖以及肝细胞类器官中的细胞周期标志物[136]。基于此，通过改变特定肠道微生物特征和肝脏SCD1表达，诱导NASH中肝部分再生并改善肝功能似乎是一个值得探索的治疗途径[136]。然而，应当注意的是，SCD1表达和酶活性的增加可能会导致肝细胞脂质氧化减弱和炎症反应上调，这会间接加剧NASH的进程[19, 109]。因此，未来需要进一步探索肠道微生物与其宿主之间这种复杂相互作用背后的分子机制。此外，SCD1的激活在多大程度上能够促进肝细胞的增殖和再生，而不加剧NASH或肝细胞癌发展，值得进一步研究。

### 4.3 SCD1和糖尿病

研究发现，SCD1的活性增强与T2DM的发生和发展呈正相关[137, 138]。一项近3000人的大型社区前瞻性队列研究发现，SCD1活性与糖尿病的发病率呈显著正相关[139]。然而，最近的证据发现，SCD1表达增加也可能帮助人类抵抗T2DM。已知脂毒性影响胰岛β细胞的DNA甲基化，导致β细胞

功能障碍以及加剧T2DM[102]。因此，肥胖糖尿病患者中SCD1蛋白表达或活性的提高可能是机体减轻脂毒性的一种代偿方式[140]。SCD1的激活可以加速酰基辅酶A去饱和，恢复细胞内脂肪酸水平正常化，这能够缓解肥胖个体因过量SFAs引起的脂毒性[141]。并且，长链SFAs对人类EndoC-βH1 β细胞具有显著脂毒性，而SCD1在这些细胞中的过表达可以逆转SFAs对β细胞结构和功能的负面影响，如ER应激和LDs形成减少[142, 143]。然而，当下调SCD1时，AMPK被激活，进而上调NAD-依赖性去乙酰化酶Sirtuin-1 (SIRT1)的表达[102]。SIRT1导致DNA甲基转移酶1 (DNA methyltransferase 1, DNMT1)去乙酰化，引起β细胞DNA全局甲基化水平下降，最终影响β细胞LDs形态结构以及对脂毒性的抵抗力[102]。SCD1活性也影响胰岛β细胞的自噬小体-溶酶体融合阶段[144]。抑制SCD1活性将改变INS-1E细胞膜磷脂组成，引发异常自噬小体-溶酶体融合和自噬清除缺陷[144]。这些效应加剧了INS-1E细胞对棕榈酸诱导损伤的易感性[144]。同时，这种变化干扰了ER的正常功能，将引发线粒体介导的细胞凋亡，抑制β细胞增殖及其功能，最终导致胰岛β细胞死亡[144]。

此外，SCD1还作为胰腺-肝脏轴中介“对话”因子，调节肝脏代谢灵活性。例如，研究发现胰腺分泌的胰岛素通过肝脏SCD1产生棕榈油酸，能够激活Wnt-β-Catenin通路活性以调节肝脏代谢稳态以及胰岛素敏感性[145]。

综上所述，SCD1在肥胖和糖尿病中发挥不同作用的潜在解释可能是：当体内出现代谢应激或胰岛素敏感性受损时，SCD1会被诱导表达。一旦应激恢复正常，作为保护者的SCD1水平会相应地下调。另一方面，全身性SCD1抑制对肥胖的积极影响可能以β细胞的脂毒性为代价[28, 118]。全身*Scd1*基因敲除导致小鼠胰岛中LDs的大小和数量减少，中性脂质积累降低，这会减弱脂质储存能力，并降低小鼠胰岛β细胞对脂毒性的抵抗力[146]。总之，SCD1在肥胖和糖尿病中的作用是错综复杂的。实验模型的差异(人类或啮齿动物样本)、组织类型(脂肪组织或胰岛)以及遗传特征和代谢功能障碍(肥胖或T2DM)都可能导致上述不一致的研究结果。

### 4.4 SCD1和癌症

SCD1通过调节肿瘤细胞脂肪代谢，在肿瘤发生、发展、侵袭和转移中发挥着关键作用[8]。临床上已发现在卵巢癌、胃癌、结直肠癌和胰腺癌中SCD1表达水平均显著升高[10, 147, 148]。在肺癌和乳腺癌中，SCD1高水平表达与不良预后显著相关[149]。其中，SCD1的上调通过增加MUFAs合成，保护癌细胞免受SFAs脂毒性的侵害，促进癌细胞迁移和肿瘤再生长[49]。研究证实，经油酸处理后癌细胞可逆转由SCD1活性抑制引起的癌细胞凋亡和生长抑制[112, 150]。除此之外，SCD1还参与调控肿瘤细胞的压力和生存过程，如铁死亡。铁死亡是一种铁依赖性、由细胞膜上脂质过氧化物过量累积引发的程序性细胞死亡形式[151]。值得注意的是，脂代谢是影响铁死亡的关键调节通路之一[152]。作为调控脂质代谢的关键介质，SCD1在癌细胞抵御铁死亡中起关键作用[8]。已知SCD1通过PI3K-Akt-mTOR途径赋予癌细胞抵抗活性氧(reactive oxygen species, ROS)诱导的铁死亡，从而促进癌症复发[49]。最近的研究发现，人类结肠癌中LINC01606 (一种致癌基因)显著上调，通过与miR-423-5p相互作用来增强SCD1的表达，激活经典Wnt/β-Catenin信号通路，促进癌细胞生长和干细胞化，并抑制铁死亡[115]。与此同时，Wnt/β-Catenin信号转导又反过来通过转录因子结合IGHM增强子3 (transcription factor binding to IGHM enhancer 3, TFE3)增加LINC01606的转录，形成正反馈调节回路，进一步抑制铁死亡并增强癌细胞干性(癌症干细胞的自我更新和分化的能力)[115]。

未折叠蛋白反应(unfolded protein response, UPR)是一种生存机制，由ER中未折叠或错误折叠蛋白质的积累而触发。然而，异常水平的UPR与癌症的发生和发展显著相关[153]。SCD1可能也参与调节应激反应途径，这些途径促进肿瘤生长和转移[154]。先前的研究表明，抑制肿瘤SCD1导致糖原合酶激酶β (glycogen synthase kinase 3β, GSK3β)去磷酸化活化，GSK3β是Akt通路的下游靶点，通过诱导β-Catenin和细胞周期蛋白D1降解来阻止癌细胞增殖[112]。类似地，在人类癌细胞中，抑制SCD1表达会触发UPR介导的Xbp1 mRNA剪接、eIF2α磷酸化以及C/EBP同源蛋白(C/EBP homologous protein, CHOP)表达增加等事件，最终诱导CHOP依赖的癌细胞凋亡[116]。最近，Ben-David等研究者通过高通量筛选鉴定出小分子PluriSIns，其能够抑制人类多能干细胞(human pluripotent stem cells, hPSCs)中SCD1活性。PluriSIns处理后导致棕榈酸积累和油酸转化减少，引起hPSCs的ER应激，促

进癌细胞凋亡[155]。总体而言，SCD1的异常激活能够促进肿瘤生长、转移、免疫逃逸以及癌症发展中对治疗的抵抗[156]。

## 5 靶向SCD1的疾病治疗新策略

随着对SCD1研究的不断深入，靶向SCD1治疗代谢性疾病已受到广泛关注。不同研究相继揭示了SCD1活性抑制在NAFLD、T2DM及癌症等代谢性疾病治疗中的显著疗效[8, 16, 123]。通过合成具有极低半抑制浓度($IC_{50}$，即物质抑制特定生物或生化功能的效力的量度，数值越低，药物性能越好)的合成类化合物抑制SCD1能够有效改善代谢性疾病。例如，在NASH患者二期临床试验中发现口服Aramchol能够改善患者肝脏纤维化、增强肝功能以及血糖控制[18]。重要的是，Aramchol表现出了良好的耐受性和安全性[18, 19]。此外，患者在口服Aramchol后糖化血红蛋白(HbA1c)水平得到显著改善，这表明了Aramchol在治疗T2DM中的潜在重要临床价值[18, 157]。与此同时，天然化合物如小檗碱和姜黄素等传统中草药也被证明能够有效调节SCD1活性，展现出独特的临床治疗潜力[109, 158, 159]。但值得注意的是，鉴于SCD1广泛表达于多种组织和器官中，全身抑制SCD1可能引起系列不良效应(如扰乱细胞内的脂质稳态)，从而损害正常机体生理功能。因此，需更加注重SCD1抑制剂长期使用的安全性、有效性和剂量优化性，为代谢性疾病治疗提供有力且稳定的治疗。未来或可进一步开发针对特定组织SCD1活性抑制策略的设计，如研发针对肝脏、脂肪组织和骨骼肌的纳米颗粒和脂质纳米颗粒等组织特异性纳米级药物递送方式(一种基于生物纳米结构的给药方式，主要存在基于脂质或聚合物或白蛋白的三类纳米药物，已用于癌症和基因治疗)(见图4)，从而精确靶向特定组织，最大限度提高药物疗效并减少对其他组织产生潜在副作用[160–162]。

## 6 总结与展望

SCD1作为一个代谢枢纽因子，其表达受到转录和表观遗传的调控，通过控制MUFAs转化来协调糖脂代谢、炎症和自噬等生物过程。在生理病理条件下，抑制SCD1能够促进脂肪组织棕色化，减少脂质积累以及增强脂解，在代谢和能量稳态中发挥关键作用。此前已有多种SCD1抑制剂在临床前模型测试中显示出良好的抗肿瘤效果。例如，

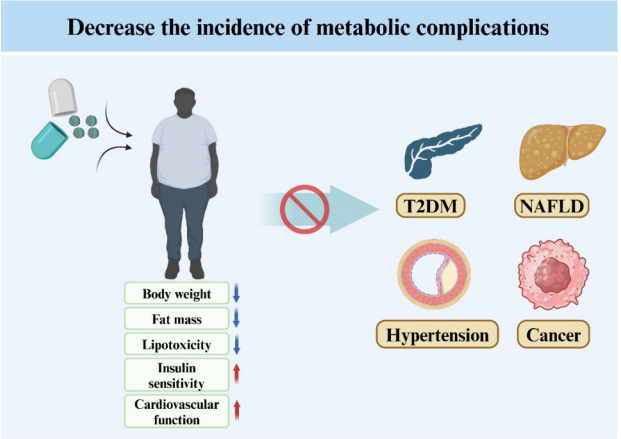


图 4. 特异性精准抑制SCD1改善多种代谢性疾病病理状态

Fig. 4. Precise amelioration of various metabolic disease pathologies through specific SCD1 inhibition. As a key factor in metabolic diseases and their complications, SCD1 is expected to become an important target for the treatment of obesity, diabetes and cardiovascular diseases by developing tissue-specific SCD1 delivery drugs to safely and effectively improve the excessive accumulation of lipids, insulin resistance, inflammation and cardiovascular risk in patients with metabolic diseases. NAFLD: non-alcoholic fatty liver disease; T2DM: type 2 diabetes mellitus.

A939572、MF-438和CAY10566等SCD1抑制剂在多种癌症类型(如胰腺癌、食管癌、乳腺癌和肝癌等)中显著降低了肿瘤细胞存活率，抑制了肿瘤生长[163–165]。然而，值得注意的是，当前SCD1的临床转化十分有限，SCD1抑制剂的临床应用仍然存在诸多挑战：1)现有SCD1抑制剂存在一定的脱靶效应，存在药物相关毒性问题。已知全身SCD1抑制或缺乏会对各种器官，特别是皮肤和眼睛产生不良影响(皮腺功能下降和视力衰退)[166]；2)对组织器官内特定靶标信号与SCD1的相互作用尚不清楚。研究发现皮下脂肪组织中SCD1特异性缺失引起葡萄糖转运蛋白1 (glucose transporter 1, GLUT1)上调，但不清楚SCD1如何调控GLUT1蛋白表达[167]；3)由于不同癌症类型和亚型对SCD1的依赖程度不同，目前缺乏合适的个体化治疗策略来治疗代谢性疾病患者群体。STK11/KEAP1共突变的肺腺癌对SCD1抑制剂更为敏感，这表明在这类癌症患者中，SCD1抑制剂可能更为有效[168]。

因此，为了解决这些问题，研究者们首先需开发特异性更高、靶点更准确的SCD1抑制剂，通过跨学科合作揭示更多结构信息和潜在的抑制机制，

为合理设计下一代SCD1抑制剂提供理论依据。其次，临床上也可根据生物学背景(如组织类型和疾病特征)联合信息与计算科学(如计算机模拟和基于AI的医疗数据建模)技术，尝试SCD1抑制剂和其他药剂(如自噬抑制剂)的组合治疗，设计有效的个性化治疗策略。已有部分研究显示，SCD1与铁死亡抑制剂联合使用较单一药剂治疗在肠癌中表现出更好的疗效[169]。此外，通过脂质组学鉴定SCD1衍生的新型下游脂质介体将有助于阐明SCD1复杂的代谢和信号网络。类似于胰高血糖素样肽-1受体，这些脂质介体的功能操纵能够为开发针对SCD1的小分子药物提供新的洞见，它们能够对抗代谢性疾病并改善多个组织和器官的系统代谢。

总之，SCD1作为代谢枢纽基因，其抑制剂的开发用于治疗各种代谢性疾病具有可观前景，特别是对于肥胖、糖尿病、NAFLD和NASH等代谢性疾病。

## 参考文献


1 Tamarit-Rodriguez J. Regulatory role of fatty acid metabolism on glucose-induced changes in insulin and glucagon secretion by pancreatic islet cells. Int J Mol Sci 2024; 25 (11): 6052.

2 Cao LQ, Xie Y, Fleishman JS, Liu X, Chen ZS. Hepatocellular carcinoma and lipid metabolism: Novel targets and therapeutic strategies. Cancer Lett 2024; 597: 217061.

3 Han Y, Sun Q, Chen W, Gao Y, Ye J, Chen Y, Wang T, Gao L, Liu Y, Yang Y. New advances of adiponectin in regulating obesity and related metabolic syndromes. J Pharm Anal 2024; 14(5): 100913.

4 Zhu G, Cao L, Wu J, Xu M, Zhang Y, Wu M, Li J. Comorbid intersections of cancer and cardiovascular disease and targets for natural drug action: Reprogramming of lipid metabolism. Biomed Pharmacother 2024; 176: 116875.

5 Paton CM, Ntambi JM. Biochemical and physiological function of stearoyl-CoA desaturase. Am J Physiol Endocrinol Metab 2009; 297(1): E28-E37.

6 Liu X, Strable MS, Ntambi JM. Stearoyl CoA desaturase 1: role in cellular inflammation and stress. Adv Nutr 2011; 2 (1): 15-22.

7 Ntambi JM, Miyazaki M. Regulation of stearoyl-CoA desaturases and role in metabolism. Prog Lipid Res 2004; 43 (2): 91-104.

8 Sen U, Coleman C, Sen T. Stearoyl coenzyme A desaturase-1: multitasker in cancer, metabolism, and ferroptosis. Trends Cancer 2023; 9(6): 480-489.

9 Hulver MW, Berggren JR, Carper MJ, Miyazaki M, Ntambi JM, Hoffman EP, Thyfault JP, Stevens R, Dohm GL, Houmard JA, Muoio DM. Elevated stearoyl-CoA desaturase-1 expression in skeletal muscle contributes to abnormal fatty acid partitioning in obese humans. Cell Metab 2005; 2(4): 251-261.

10 Piccinin E, Cariello M, Moschetta A. Lipid metabolism in colon cancer: Role of liver X receptor (LXR) and stearoyl-CoA desaturase 1 (SCD1). Mol Aspects Med 2021; 78: 100933.

11 Suppli MP, Rigbolt KTG, Veidal SS, Heebøll S, Eriksen PL, Demant M, Bagger JI, Nielsen JC, Oró D, Thrane SW, Lund A, Strandberg C, Kønig MJ, Vilsbøll T, Vrang N, Thomsen KL, Grønbæk H, Jelsing J, Hansen HH, Knop FK. Hepatic transcriptome signatures in patients with varying degrees of nonalcoholic fatty liver disease compared with healthy normal-weight individuals. Am J Physiol Gastrointest Liver Physiol 2019; 316(4): G462-G472.

12 Yang B, Ding F, Wang FL, Yan J, Ye XW, Yu W, Li D. Association of serum fatty acid and estimated desaturase activity with hypertension in middle-aged and elderly Chinese population. Sci Rep 2016; 6: 23446.

13 Ye Z, Zhuo Q, Hu Q, Xu X, Mengqi L, Zhang Z, Xu W, Liu W, Fan G, Qin Y, Yu X, Ji S. FBW7-NRA41-SCD1 axis synchronously regulates apoptosis and ferroptosis in pancreatic cancer cells. Redox Biol 2021; 38: 101807.

14 Ducheix S, Peres C, Härdfeldt J, Frau C, Mocciaro G, Piccinin E, Lobaccaro JM, De Santis S, Chieppa M, Bertrand-Michel J, Plateroti M, Griffin JL, Sabbà C, Ntambi JM, Moschetta A. Deletion of stearoyl-CoA desaturase-1 from the intestinal epithelium promotes inflammation and tumorigenesis, reversed by dietary oleate. Gastroenterology 2018; 155(5): 1524-1538.e9.

15 Dragos SM, Bergeron KF, Desmarais F, Suitor K, Wright DC, Mounier C, Mutch DM. Reduced SCD1 activity alters markers of fatty acid reesterification, glyceroneogenesis, and lipolysis in murine white adipose tissue and 3T3-L1 adipocytes. Am J Physiol Cell Physiol 2017; 313(3): C295-C304.

16 Ratziu V, Yilmaz Y, Lazas D, Friedman SL, Lackner C, Behling C, Cummings OW, Chen L, Petitjean M, Gilgun-Sherki Y, Gorfine T, Kadosh S, Eyal E, Sanyal AJ. Aramchol improves hepatic fibrosis in metabolic dysfunction-associated steatohepatitis: Results of multimodality assessment using both conventional and digital pathology. Hepatology 2025; 81(3): 932-946.

17 Safadi R, Konikoff FM, Mahamid M, Zelber-Sagi S, Halpern M, Gilat T, Oren R. The fatty acid-bile acid conjugate Aramchol reduces liver fat content in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2014; 12(12): 2085-2091.e1.

18 Ratziu V, de Guevara L, Safadi R, Poordad F, Fuster F, Flores-Figueroa J, Arrese M, Fracanzani AL, Ben Bashat D, Lackner K, Gorfine T, Kadosh S, Oren R, Halperin M, Hayardeny L, Loomba R, Friedman S, Sanyal AJ. Aramchol in patients with nonalcoholic steatohepatitis: a randomized, double-blind, placebo-controlled phase 2b trial. Nat Med 2021; 27(10): 1825-1835.

19 Bhattacharya D, Basta B, Mato JM, Craig A, Fernández-Ramos D, Lopitz-Otsoa F, Tsvirkun D, Hayardeny L, Chandar V, Schwartz RE, Villanueva A, Friedman SL. Aramchol downregulates stearoyl CoA-desaturase 1 in hepatic stellate cells to attenuate cellular fibrogenesis. JHEP Rep 2021; 3 (3): 100237.

20 Castro LF, Wilson JM, Gonçalves O, Galante-Oliveira S, Rocha E, Cunha I. The evolutionary history of the stearoyl-CoA desaturase gene family in vertebrates. BMC Evol Biol 2011; 11: 132.

21 Mihara K. Structure and regulation of rat liver microsomal stearoyl-CoA desaturase gene. J Biochem 1990; 108(6): 1022-1029.

22 Shen J, Wu G, Tsai AL, Zhou M. Structure and mechanism of a unique diiron center in mammalian stearoyl-CoA desaturase. J Mol Biol 2020; 432(18): 5152-5161.

23 Bai Y, McCoy JG, Levin EJ, Sobrado P, Rajashankar KR, Fox BG, Zhou M. X-ray structure of a mammalian stearoyl-CoA desaturase. Nature 2015; 524(7564): 252-256.

24 Wang H, Klein MG, Zou H, Lane W, Snell G, Levin I, Li K, Sang BC. Crystal structure of human stearoyl-coenzyme A desaturase in complex with substrate. Nat Struct Mol Biol 2015; 22(7): 581-585.

25 Thürmer M, Gollowitzer A, Pein H, Neukirch K, Gelmez E, Waltl L, Wielsch N, Winkler R, Löser K, Grander J, Hotze M, Harder S, Döding A, Meßner M, Troisi F, Ardelt M, Schlüter H, Pachmayr J, Gutiérrez-Gutiérrez Ó, Rudolph KL, Thedieck K, Schulze-Späte U, González-Estévez C, Kosan C, Svatoš A, Kwiatkowski M, Koeberle A. PI(18:1/18:1) is a SCD1-derived lipokine that limits stress signaling. Nat Commun 2022; 13(1): 2982.

26 Dziewulska A, Dobosz AM, Dobrzyn A, Smolinska A, Kolczynska K, Ntambi JM, Dobrzyn P. SCD1 regulates the AMPK/SIRT1 pathway and histone acetylation through changes in adenine nucleotide metabolism in skeletal muscle. J Cell Physiol 2020; 235(2): 1129-1140.

27 Gu X, Sun R, Chen L, Chu S, Doll MA, Li X, Feng W, Siskind L, McClain CJ, Deng Z. Neutral ceramidase mediates nonalcoholic steatohepatitis by regulating monounsaturated fatty acids and Gut $IgA^+$ B Cells. Hepatology 2021; 73(3): 901-919.

28 Dobosz AM, Janikiewicz J, Krogulec E, Dziewulska A, Ajduk A, Szpila M, Nieznańska H, Szczepankiewicz AA, Wypych D, Dobrzyn A. Inhibition of stearoyl-CoA desaturase 1 in the mouse impairs pancreatic islet morphogenesis and promotes loss of β-cell identity and α-cell expansion in the mature pancreas. Mol Metab 2023; 67: 101659.

29 Ran H, Zhu Y, Deng R, Zhang Q, Liu X, Feng M, Zhong J, Lin S, Tong X, Su Q. Stearoyl-CoA desaturase-1 promotes colorectal cancer metastasis in response to glucose by suppressing PTEN. J Exp Clin Cancer Res 2018; 37(1): 54.

30 Shi W, Wang J, Li Z, Xu S, Wang J, Zhang L, Yang H. Reprimo (RPRM) mediates neuronal ferroptosis via CREB-Nrf2/SCD1 pathways in radiation-induced brain injury. Free Radic Biol Med 2024; 213: 343-358.

31 Olichwier A, Sowka A, Balatskyi VV, Gan AM, Dziewulska A, Dobrzyn P. SCD1-related epigenetic modifications affect hormone-sensitive lipase (Lipe) gene expression in cardiomyocytes. Biochim Biophys Acta Mol Cell Res 2024; 1871(1): 119608.

32 Ji C, Guo Y, Liu Y, Xu S, Zhao S, Luo X, Qiu F, Huang R, Xu Q, Zheng R, Xia M, Zhao Y, Ren J, Qiu Y. Inhibition of ceramide *de novo* synthesis ameliorates meibomian gland dysfunction induced by SCD1 deficiency. Ocul Surf 2021; 22: 230-241.

33 Zhou Z, Liang S, Zhou Z, Liu J, Zhang J, Meng X, Zou F, Zhao H, Yu C, Cai S. TGF-β1 promotes SCD1 expression via the PI3K-Akt-mTOR-SREBP1 signaling pathway in lung fibroblasts. Respir Res 2023; 24(1): 8.

34 Lin L, Hu M, Li Q, Du L, Lin L, Xue Y, Zheng F, Wang F, Liu K, Wang Y, Ye J, Jiang X, Wang X, Wang J, Zhai J, Liu B, Xie H, You Y, Wang J, Kong X, Feng D, Green DR, Shi Y, Wang Y. Oleic acid availability impacts thymocyte preprogramming and subsequent peripheral T(reg) cell differentiation. Nat Immunol 2024; 25(1): 54-65.

35 Takao K, Iizuka K, Liu Y, Sakurai T, Kubota S, Kubota-Okamoto S, Imaizumi T, Takahashi Y, Rakhat Y, Komori S, Hirose T, Nonomura K, Kato T, Mizuno M, Suwa T, Horikawa Y, Sone M, Yabe D. Effects of ChREBP deficiency on adrenal lipogenesis and steroidogenesis. J Endocrinol 2021; 248(3): 317-324.

36 Iizuka K, Bruick RK, Liang G, Horton JD, Uyeda K. Deficiency of carbohydrate response element-binding protein (ChREBP) reduces lipogenesis as well as glycolysis. Proc Natl Acad Sci U S A 2004; 101(19): 7281-7286.

37 Sampath H, Flowers MT, Liu X, Paton CM, Sullivan R, Chu K, Zhao M, Ntambi JM. Skin-specific deletion of stearoyl-CoA desaturase-1 alters skin lipid composition and protects mice from high fat diet-induced obesity. J Biol Chem 2009; 284(30): 19961-19973.

38 Ntambi JM. Regulation of stearoyl-CoA desaturase by polyunsaturated fatty acids and cholesterol. J Lipid Res 1999; 40 (9): 1549-1558.

39 Ntambi JM. The regulation of stearoyl-CoA desaturase (SCD). Prog Lipid Res 1995; 34(2): 139-150.
40 Hellemans KH, Hannaert JC, Denys B, Steffensen KR, Raemdonck C, Martens GA, Van Veldhoven PP, Gustafsson JA, Pipeleers D. Susceptibility of pancreatic beta cells to fatty acids is regulated by LXR/PPARalpha-dependent stearoyl-coenzyme A desaturase. PLoS One 2009; 4(9): e7266.
41 Biddinger SB, Miyazaki M, Boucher J, Ntambi JM, Kahn CR. Leptin suppresses stearoyl-CoA desaturase 1 by mechanisms independent of insulin and sterol regulatory element-binding protein-1c. Diabetes 2006; 55(7): 2032-2041.
42 Bryzgalova G, Lundholm L, Portwood N, Gustafsson JA, Khan A, Efendic S, Dahlman-Wright K. Mechanisms of antidiabetogenic and body weight-lowering effects of estrogen in high-fat diet-fed mice. Am J Physiol Endocrinol Metab 2008; 295(4): E904-E912.
43 Sampath H, Ntambi JM. Polyunsaturated fatty acid regulation of genes of lipid metabolism. Annu Rev Nutr 2005; 25: 317-340.
44 Cao H, Gerhold K, Mayers JR, Wiest MM, Watkins SM, Hotamisligil GS. Identification of a lipokine, a lipid hormone linking adipose tissue to systemic metabolism. Cell 2008; 134(6): 933-944.
45 Dalla Valle A, Vertongen P, Spruyt D, Lechanteur J, Suain V, Gaspard N, Brion JP, Gangji V, Rasschaert J. Induction of stearoyl-CoA 9-desaturase 1 protects human mesenchymal stromal cells against palmitic acid-induced lipotoxicity and inflammation. Front Endocrinol (Lausanne) 2019; 10: 726.
46 Yang C, Lim W, Bazer FW, Song G. Down-regulation of stearoyl-CoA desaturase-1 increases susceptibility to palmitic-acid-induced lipotoxicity in human trophoblast cells. J Nutr Biochem 2018; 54: 35-47.
47 AM AL, Syed DN, Ntambi JM. Insights into stearoyl-CoA desaturase-1 regulation of systemic metabolism. Trends Endocrinol Metab 2017; 28(12): 831-842.
48 Dobrzyn P, Jazurek M, Dobrzyn A. Stearoyl-CoA desaturase and insulin signaling--what is the molecular switch? Biochim Biophys Acta 2010; 1797(6-7): 1189-1194.
49 Luis G, Godfroid A, Nishiumi S, Cimino J, Blacher S, Maquoi E, Wery C, Collignon A, Longuespée R, Montero-Ruiz L, Dassoul I, Maloujahmoum N, Pottier C, Mazzucchelli G, Depauw E, Bellahcène A, Yoshida M, Noel A, Sounni NE. Tumor resistance to ferroptosis driven by Stearoyl-CoA Desaturase-1 (SCD1) in cancer cells and Fatty Acid Biding Protein-4 (FABP4) in tumor microenvironment promote tumor recurrence. Redox Biol 2021; 43: 102006.
50 Listenberger LL, Han X, Lewis SE, Cases S, Farese RV, Jr., Ory DS, Schaffer JE. Triglyceride accumulation protects against fatty acid-induced lipotoxicity. Proc Natl Acad Sci U S A 2003; 100(6): 3077-3082.
51 von Roemeling CA, Marlow LA, Wei JJ, Cooper SJ, Caulfield TR, Wu K, Tan WW, Tun HW, Copland JA. Stearoyl-CoA desaturase 1 is a novel molecular therapeutic target for clear cell renal cell carcinoma. Clin Cancer Res 2013; 19 (9): 2368-2380.
52 Zhang N, Wang Y, Zhang J, Liu B, Deng X, Xin S, Xu K. N-glycosylation of CREBH improves lipid metabolism and attenuates lipotoxicity in NAFLD by modulating PPARα and SCD-1. FASEB J 2020; 34(11): 15338-15363.
53 Sampath H, Ntambi JM. The role of stearoyl-CoA desaturase in obesity, insulin resistance, and inflammation. Ann N Y Acad Sci 2011; 1243: 47-53.
54 Rahman SM, Dobrzyn A, Lee SH, Dobrzyn P, Miyazaki M, Ntambi JM. Stearoyl-CoA desaturase 1 deficiency increases insulin signaling and glycogen accumulation in brown adipose tissue. Am J Physiol Endocrinol Metab 2005; 288(2): E381-E387.
55 Rahman SM, Dobrzyn A, Dobrzyn P, Lee SH, Miyazaki M, Ntambi JM. Stearoyl-CoA desaturase 1 deficiency elevates insulin-signaling components and down-regulates protein-tyrosine phosphatase 1B in muscle. Proc Natl Acad Sci U S A 2003; 100(19): 11110-11115.
56 Merz KE, Thurmond DC. Role of skeletal muscle in insulin resistance and glucose uptake. Compr Physiol 2020; 10(3): 785-809.
57 Kim E, Lee JH, Ntambi JM, Hyun CK. Inhibition of stearoyl-CoA desaturase1 activates AMPK and exhibits beneficial lipid metabolic effects *in vitro*. Eur J Pharmacol 2011; 672(1-3): 38-44.
58 Dobrzyn A, Dobrzyn P, Lee SH, Miyazaki M, Cohen P, Asilmaz E, Hardie DG, Friedman JM, Ntambi JM. Stearoyl-CoA desaturase-1 deficiency reduces ceramide synthesis by downregulating serine palmitoyltransferase and increasing beta-oxidation in skeletal muscle. Am J Physiol Endocrinol Metab 2005; 288(3): E599-E607.
59 Aljohani A, Khan MI, Bonneville A, Guo C, Jeffery J, O'Neill L, Syed DN, Lewis SA, Burhans M, Mukhtar H, Ntambi JM. Hepatic stearoyl CoA desaturase 1 deficiency increases glucose uptake in adipose tissue partially through the PGC-1α-FGF21 axis in mice. J Biol Chem 2019; 294 (51): 19475-19485.
60 Sinha RA, Singh BK, Zhou J, Xie S, Farah BL, Lesmana R, Ohba K, Tripathi M, Ghosh S, Hollenberg AN, Yen PM. Loss of ULK1 increases RPS6KB1-NCOR1 repression of NR1H/LXR-mediated Scd1 transcription and augments lipotoxicity in hepatic cells. Autophagy 2017; 13(1): 169-186.
61 Petersson U, Ostgren CJ, Brudin L, Brismar K, Nilsson PM. Low levels of insulin-like growth-factor-binding protein-1 (IGFBP-1) are prospectively associated with the inci-

dence of type 2 diabetes and impaired glucose tolerance (IGT): the Söderåkra Cardiovascular Risk Factor Study. Diabetes Metab 2009; 35(3): 198-205.

62 O'Neill LM, Phang YX, Liu Z, Lewis SA, Aljohani A, McGahee A, Wade G, Kalyesubula M, Simcox J, Ntambi JM. Hepatic oleate regulates insulin-like growth factor-binding protein 1 partially through the mTORC1-FGF21 axis during high-carbohydrate feeding. Int J Mol Sci 2022; 23(23): 14671.

63 Liu K, Lin L, Li Q, Xue Y, Zheng F, Wang G, Zheng C, Du L, Hu M, Huang Y, Shao C, Kong X, Melino G, Shi Y, Wang Y. Scd1 controls *de novo* beige fat biogenesis through succinate-dependent regulation of mitochondrial complex II. Proc Natl Acad Sci U S A 2020; 117(5): 2462-2472.

64 Zou Y, Wang YN, Ma H, He ZH, Tang Y, Guo L, Liu Y, Ding M, Qian SW, Tang QQ. SCD1 promotes lipid mobilization in subcutaneous white adipose tissue. J Lipid Res 2020; 61(12): 1589-1604.

65 Lee YS, Olefsky J. Chronic tissue inflammation and metabolic disease. Genes Dev 2021; 35(5-6): 307-328.

66 Chau YY, Bandiera R, Serrels A, Martínez-Estrada OM, Qing W, Lee M, Slight J, Thornburn A, Berry R, McHaffie S, Stimson RH, Walker BR, Chapuli RM, Schedl A, Hastie N. Visceral and subcutaneous fat have different origins and evidence supports a mesothelial source. Nat Cell Biol 2014; 16(4): 367-375.

67 Straat ME, Jurado-Fasoli L, Ying Z, Nahon KJ, Janssen LGM, Boon MR, Grabner GF, Kooijman S, Zimmermann R, Giera M, Rensen PCN, Martinez-Tellez B. Cold exposure induces dynamic changes in circulating triacylglycerol species, which is dependent on intracellular lipolysis: A randomized cross-over trial. EBioMedicine 2022; 86: 104349.

68 Miyazaki M, Dobrzyn A, Sampath H, Lee SH, Man WC, Chu K, Peters JM, Gonzalez FJ, Ntambi JM. Reduced adiposity and liver steatosis by stearoyl-CoA desaturase deficiency are independent of peroxisome proliferator-activated receptor-alpha. J Biol Chem 2004; 279(33): 35017-35024.

69 Burr SD, Chen Y, Hartley CP, Zhao X, Liu J. Replacement of saturated fatty acids with linoleic acid in western diet attenuates atherosclerosis in a mouse model with inducible ablation of hepatic LDL receptor. Sci Rep 2023; 13(1): 16832.

70 Garcia-Martinez I, Alen R, Pereira L, Povo-Retana A, Astudillo AM, Hitos AB, Gomez-Hurtado I, Lopez-Collazo E, Boscá L, Francés R, Lizasoain I, Moro M, Balsinde J, Izquierdo M, Valverde Á M. Saturated fatty acid-enriched small extracellular vesicles mediate a crosstalk inducing liver inflammation and hepatocyte insulin resistance. JHEP Rep 2023; 5(8): 100756.

71 Lalrinzuali S, Khushboo M, Dinata R, Bhanushree B, Nisa N, Bidanchi RM, Laskar SA, Manikandan B, Abinash G, Pori B, Roy VK, Gurusubramanian G. Long-term consumption of fermented pork fat-based diets differing in calorie, fat content, and fatty acid levels mediates oxidative stress, inflammation, redox imbalance, germ cell apoptosis, disruption of steroidogenesis, and testicular dysfunction in Wistar rats. Environ Sci Pollut Res Int 2023; 30(18): 52446-52471.

72 Shahidi F, Ambigaipalan P. Omega-3 polyunsaturated fatty acids and their health benefits. Annu Rev Food Sci Technol 2018; 9: 345-381.

73 Toscano R, Millan-Linares MC, Lemus-Conejo A, Claro C, Sanchez-Margalet V, Montserrat-de la Paz S. Postprandial triglyceride-rich lipoproteins promote M1/M2 microglia polarization in a fatty-acid-dependent manner. J Nutr Biochem 2020; 75: 108248.

74 Yang ZH, Pryor M, Noguchi A, Sampson M, Johnson B, Pryor M, Donkor K, Amar M, Remaley AT. Dietary palmitoleic acid attenuates atherosclerosis progression and hyperlipidemia in low-density lipoprotein receptor-deficient mice. Mol Nutr Food Res 2019; 63(12): e1900120.

75 Qian C, Xu D, Wang J, Luo Y, Jin T, Huang L, Zhou Y, Cai Z, Jin B, Bao H, Wang Y. Toll-like receptor 2 deficiency ameliorates obesity-induced cardiomyopathy via inhibiting NF-κB signaling pathway. Int Immunopharmacol 2024; 128: 111551.

76 Rogero MM, Calder PC. Obesity, inflammation, Toll-like receptor 4 and fatty acids. Nutrients 2018; 10(4): 432.

77 Flori E, Mastrofrancesco A, Ottaviani M, Maiellaro M, Zouboulis CC, Camera E. Desaturation of sebaceous-type saturated fatty acids through the SCD1 and the FADS2 pathways impacts lipid neosynthesis and inflammatory response in sebocytes in culture. Exp Dermatol 2023; 32(6): 808-821.

78 Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. J Clin Invest 2006; 116(11): 3015-3025.

79 Ravaut G, Légiot A, Bergeron KF, Mounier C. Monounsaturated fatty acids in obesity-related inflammation. Int J Mol Sci 2020; 22(1): 330.

80 Hsieh WY, Zhou QD, York AG, Williams KJ, Scumpia PO, Kronenberger EB, Hoi XP, Su B, Chi X, Bui VL, Khialeeva E, Kaplan A, Son YM, Divakaruni AS, Sun J, Smale ST, Flavell RA, Bensinger SJ. Toll-like receptors induce signal-specific reprogramming of the macrophage lipidome. Cell Metab 2020; 32(1): 128-143.e5.

81 Malodobra-Mazur M, Dziewulska A, Kozinski K, Dobrzyn P, Kolczynska K, Janikiewicz J, Dobrzyn A. Stearoyl-CoA desaturase regulates inflammatory gene expression by changing DNA methylation level in 3T3 adipocytes. Int J Biochem Cell Biol 2014; 55: 40-50.

82 Ralston JC, Metherel AH, Stark KD, Mutch DM. SCD1 me-

diates the influence of exogenous saturated and monounsaturated fatty acids in adipocytes: Effects on cellular stress, inflammatory markers and fatty acid elongation. J Nutr Biochem 2016; 27: 241-248.
83 Wang R, Sun Q, Wu X, Zhang Y, Xing X, Lin K, Feng Y, Wang M, Wang Y, Wang R. Hypoxia as a double-edged sword to combat obesity and comorbidities. Cells 2022; 11 (23): 3735.
84 Park K, Lee MS. Current status of autophagy enhancers in metabolic disorders and other diseases. Front Cell Dev Biol 2022; 10: 811701.
85 Kim KH, Lee MS. Autophagy--a key player in cellular and body metabolism. Nat Rev Endocrinol 2014; 10(6): 322-337.
86 Zhang W, Zou M, Fu J, Xu Y, Zhu Y. Autophagy: A potential target for natural products in the treatment of ulcerative colitis. Biomed Pharmacother 2024; 176: 116891.
87 Parzych KR, Klionsky DJ. An overview of autophagy: morphology, mechanism, and regulation. Antioxid Redox Signal 2014; 20(3): 460-473.
88 Dall'Armi C, Devereaux KA, Di Paolo G. The role of lipids in the control of autophagy. Curr Biol 2013; 23(1): R33-R45.
89 Tan SH, Shui G, Zhou J, Shi Y, Huang J, Xia D, Wenk MR, Shen HM. Critical role of SCD1 in autophagy regulation via lipogenesis and lipid rafts-coupled AKT-FOXO1 signaling pathway. Autophagy 2014; 10(2): 226-242.
90 Zhang T, Liu J, Shen S, Tong Q, Ma X, Lin L. SIRT3 promotes lipophagy and chaperon-mediated autophagy to protect hepatocytes against lipotoxicity. Cell Death Differ 2020; 27(1): 329-344.
91 Zhu S, Zhang J, Wang W, Jiang X, Chen YQ. Blockage of NDUFB9-SCD1 pathway inhibits adipogenesis : Blockage of NDUFB9-SCD1 pathway inhibits adipogenesis. J Physiol Biochem 2022; 78(2): 377-388.
92 Mutch DM, Lowry DE, Roth M, Sihag J, Hammad SS, Taylor CG, Zahradka P, Connelly PW, West SG, Bowen K, Kris-Etherton PM, Lamarche B, Couture P, Guay V, Jenkins DJA, Eck P, Jones PJH. Polymorphisms in the stearoyl-CoA desaturase gene modify blood glucose response to dietary oils varying in MUFA content in adults with obesity. Br J Nutr 2022; 127(4): 503-512.
93 Rudkowska I, Julien P, Couture P, Lemieux S, Tchernof A, Barbier O, Vohl MC. Cardiometabolic risk factors are influenced by stearoyl-CoA desaturase (SCD) -1 gene polymorphisms and n-3 polyunsaturated fatty acid supplementation. Mol Nutr Food Res 2014; 58(5): 1079-1086.
94 Stryjecki C, Roke K, Clarke S, Nielsen D, Badawi A, El-Sohemy A, Ma DW, Mutch DM. Enzymatic activity and genetic variation in SCD1 modulate the relationship between fatty acids and inflammation. Mol Genet Metab 2012; 105 (3): 421-427.
95 Warensjö E, Ingelsson E, Lundmark P, Lannfelt L, Syvänen AC, Vessby B, Risérus U. Polymorphisms in the SCD1 gene: associations with body fat distribution and insulin sensitivity. Obesity (Silver Spring) 2007; 15(7): 1732-1740.
96 Arregui M, Buijsse B, Stefan N, Corella D, Fisher E, di Giuseppe R, Coltell O, Knüppel S, Aleksandrova K, Joost HG, Boeing H, Weikert C. Heterogeneity of the Stearoyl-CoA desaturase-1 (SCD1) gene and metabolic risk factors in the EPIC-Potsdam study. PLoS One 2012; 7(11): e48338.
97 Gong J, Campos H, McGarvey S, Wu Z, Goldberg R, Baylin A. Genetic variation in stearoyl-CoA desaturase 1 is associated with metabolic syndrome prevalence in Costa Rican adults. J Nutr 2011; 141(12): 2211-2218.
98 Tibori K, Orosz G, Zámbó V, Szelényi P, Sarnyai F, Tamási V, Rónai Z, Mátyási J, Tóth B, Csala M, Kereszturi É. Molecular mechanisms underlying the elevated expression of a potentially type 2 diabetes mellitus associated SCD1 variant. Int J Mol Sci 2022; 23(11): 6221.
99 Attie AD, Flowers MT, Flowers JB, Groen AK, Kuipers F, Ntambi JM. Stearoyl-CoA desaturase deficiency, hypercholesterolemia, cholestasis, and diabetes. Nutr Rev 2007; 65(6 Pt 2): S35-S38.
100 Martín-Núñez GM, Cabrera-Mulero R, Rojo-Martínez G, Gómez-Zumaquero JM, Chaves FJ, de Marco G, Soriguer F, Castaño L, Morcillo S. Polymorphisms in the SCD1 gene are associated with indices of stearoyl CoA desaturase activity and obesity: a prospective study. Mol Nutr Food Res 2013; 57(12): 2177-2184.
101 Huang Q, Wang Q, Li D, Wei X, Jia Y, Zhang Z, Ai B, Cao X, Guo T, Liao Y. Co-administration of 20(S)-protopanaxatriol (g-PPT) and EGFR-TKI overcomes EGFR-TKI resistance by decreasing SCD1 induced lipid accumulation in non-small cell lung cancer. J Exp Clin Cancer Res 2019; 38 (1): 129.
102 Dobosz AM, Janikiewicz J, Borkowska AM, Dziewulska A, Lipiec E, Dobrzyn P, Kwiatek WM, Dobrzyn A. Stearoyl-CoA desaturase 1 activity determines the maintenance of DNMT1-mediated dna methylation patterns in pancreatic β-cells. Int J Mol Sci 2020; 21(18): 6844.
103 Ascenzi F, De Vitis C, Maugeri-Saccà M, Napoli C, Ciliberto G, Mancini R. SCD1, autophagy and cancer: implications for therapy. J Exp Clin Cancer Res 2021; 40(1): 265.
104 Jazurek-Ciesiolka M, Janikiewicz J, Dobrzyn P, Dziewulska A, Kozinski K, Dobrzyn A. Oleic acid increases the transcriptional activity of FoxO1 by promoting its nuclear translocation and β-catenin binding in pancreatic β-cells. Biochim Biophys Acta Mol Basis Dis 2019; 1865(10): 2753-2764.
105 Carobbio S, Hagen RM, Lelliott CJ, Slawik M, Medina-

Gomez G, Tan CY, Sicard A, Atherton HJ, Barbarroja N, Bjursell M, Bohlooly YM, Virtue S, Tuthill A, Lefai E, Laville M, Wu T, Considine RV, Vidal H, Langin D, Oresic M, Tinahones FJ, Fernandez-Real JM, Griffin JL, Sethi JK, López M, Vidal-Puig A. Adaptive changes of the Insig1/SREBP1/SCD1 set point help adipose tissue to cope with increased storage demands of obesity. Diabetes 2013; 62(11): 3697-3708.

106 Yang S, Zhang R, Deng W, Chang S, Li Y, Li S. Pirfenidone ameliorates liver steatosis by targeting the STAT3-SCD1 axis. Inflamm Res 2023; 72(9): 1773-1787.

107 Wu M, Lo TH, Li L, Sun J, Deng C, Chan KY, Li X, Yeh ST, Lee JTH, Lui PPY, Xu A, Wong CM. Amelioration of non-alcoholic fatty liver disease by targeting adhesion G protein-coupled receptor F1 (Adgrf1). Elife 2023; 12: e85131.

108 Wang J, Zhang F, Yang W, Gao D, Yang L, Yu C, Chen C, Li X, Zhang JS. FGF1 ameliorates obesity-associated hepatic steatosis by reversing IGFBP2 hypermethylation. FASEB J 2023; 37(4): e22881.

109 Zhu X, Bian H, Wang L, Sun X, Xu X, Yan H, Xia M, Chang X, Lu Y, Li Y, Xia P, Li X, Gao X. Berberine attenuates nonalcoholic hepatic steatosis through the AMPK-SREBP-1c-SCD1 pathway. Free Radic Biol Med 2019; 141: 192-204.

110 Zou J, Song Q, Shaw PC, Zuo Z. Dendrobium officinale regulate lipid metabolism in diabetic mouse liver via PPAR-RXR signaling pathway: Evidence from an integrated multi-omics analysis. Biomed Pharmacother 2024; 173: 116395.

111 Chen M, Xu J, Wang Y, Wang Z, Guo L, Li X, Huang L. Arctium lappa L. polysaccharide can regulate lipid metabolism in type 2 diabetic rats through the SREBP-1/SCD-1 axis. Carbohydr Res 2020; 494: 108055.

112 Igal RA. Stearoyl CoA desaturase-1: New insights into a central regulator of cancer metabolism. Biochim Biophys Acta 2016; 1861(12 Pt A): 1865-1880.

113 Xu L, Wen B, Wu Q, Lu S, Liao J, Mo L, Li Q, Tong X, Yan H. Long non-coding RNA KB-1460A1.5 promotes ferroptosis by inhibiting mTOR/SREBP-1/SCD1-mediated polyunsaturated fatty acid desaturation in glioma. Carcinogenesis 2024; 45(7): 487-499.

114 Li Q, Wang Y, Meng X, Wang W, Duan F, Chen S, Zhang Y, Sheng Z, Gao Y, Zhou L. METTL16 inhibits papillary thyroid cancer tumorigenicity through m(6)A/YTHDC2/SCD1-regulated lipid metabolism. Cell Mol Life Sci 2024; 81(1): 81.

115 Luo Y, Huang S, Wei J, Zhou H, Wang W, Yang J, Deng Q, Wang H, Fu Z. Long noncoding RNA LINC01606 protects colon cancer cells from ferroptotic cell death and promotes stemness by SCD1-Wnt/β-catenin-TFE3 feedback loop signalling. Clin Transl Med 2022; 12(4): e752.

116 Minville-Walz M, Pierre AS, Pichon L, Bellenger S, Fèvre C, Bellenger J, Tessier C, Narce M, Rialland M. Inhibition of stearoyl-CoA desaturase 1 expression induces CHOP-dependent cell death in human cancer cells. PLoS One 2010; 5(12): e14363.

117 Cruz-Color L, Hernández-Nazará ZH, Maldonado-González M, Navarro-Muñíz E, Domínguez-Rosales JA, Torres-Baranda JR, Ruelas-Cinco EDC, Ramírez-Meza SM, Ruíz-Madrigal B. Association of the PNPLA2, SCD1 and leptin expression with fat distribution in liver and adipose tissue from obese subjects. Exp Clin Endocrinol Diabetes 2020; 128(11): 715-722.

118 Ntambi JM, Miyazaki M, Stoehr JP, Lan H, Kendziorski CM, Yandell BS, Song Y, Cohen P, Friedman JM, Attie AD. Loss of stearoyl-CoA desaturase-1 function protects mice against adiposity. Proc Natl Acad Sci U S A 2002; 99(17): 11482-11486.

119 Cohen P, Miyazaki M, Socci ND, Hagge-Greenberg A, Liedtke W, Soukas AA, Sharma R, Hudgins LC, Ntambi JM, Friedman JM. Role for stearoyl-CoA desaturase-1 in leptin-mediated weight loss. Science 2002; 297(5579): 240-243.

120 Green CD, Olson LK. Modulation of palmitate-induced endoplasmic reticulum stress and apoptosis in pancreatic β-cells by stearoyl-CoA desaturase and Elovl6. Am J Physiol Endocrinol Metab 2011; 300(4): E640-E649.

121 Miyazaki M, Flowers MT, Sampath H, Chu K, Otzelberger C, Liu X, Ntambi JM. Hepatic stearoyl-CoA desaturase-1 deficiency protects mice from carbohydrate-induced adiposity and hepatic steatosis. Cell Metab 2007; 6(6): 484-496.

122 Schwenk RW, Jonas W, Ernst SB, Kammel A, Jähnert M, Schürmann A. Diet-dependent alterations of hepatic Scd1 expression are accompanied by differences in promoter methylation. Horm Metab Res 2013; 45(11): 786-794.

123 Wang W, Kong Y, Wang X, Wang Z, Tang C, Li J, Yang Q, Chen YQ, Zhu S. Identification of novel SCD1 inhibitor alleviates nonalcoholic fatty liver disease: critical role of liver-adipose axis. Cell Commun Signal 2023; 21(1): 268.

124 Mills SE, Foster DW, McGarry JD. Interaction of malonyl-CoA and related compounds with mitochondria from different rat tissues. Relationship between ligand binding and inhibition of carnitine palmitoyltransferase I. Biochem J 1983; 214(1): 83-91.

125 Powell EE, Wong VW-S, Rinella M. Non-alcoholic fatty liver disease. Lancet 2021; 397(10290): 2212-2224.

126 Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med 2018; 24(7): 908-922.

127 Zeng C, Chen M. Progress in nonalcoholic fatty liver dis-

ease: SIRT family regulates mitochondrial biogenesis. Biomolecules 2022; 12(8): 1079.
128 Svegliati-Baroni G, Pierantonelli I, Torquato P, Marinelli R, Ferreri C, Chatgilialoglu C, Bartolini D, Galli F. Lipidomic biomarkers and mechanisms of lipotoxicity in non-alcoholic fatty liver disease. Free Radic Biol Med 2019; 144: 293-309.
129 Wei S, Wang L, Evans PC, Xu S. NAFLD and NASH: etiology, targets and emerging therapies. Drug Discov Today 2024; 29(3): 103910.
130 Cariou B, Byrne CD, Loomba R, Sanyal AJ. Nonalcoholic fatty liver disease as a metabolic disease in humans: A literature review. Diabetes Obes Metab 2021; 23(5): 1069-1083.
131 Armandi A, Schattenberg JM. NAFLD and NASH: The metabolically diseased liver. Handb Exp Pharmacol 2022; 274: 253-267.
132 Kanwal F, Kramer JR, Mapakshi S, Natarajan Y, Chayanupatkul M, Richardson PA, Li L, Desiderio R, Thrift AP, Asch SM, Chu J, El-Serag HB. Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. Gastroenterology 2018; 155(6): 1828-1837.e2.
133 Haber PK, Puigvehí M, Castet F, Lourdusamy V, Montal R, Tabrizian P, Buckstein M, Kim E, Villanueva A, Schwartz M, Llovet JM. Evidence-based management of hepatocellular carcinoma: systematic review and meta-analysis of randomized controlled trials (2002-2020). Gastroenterology 2021; 161(3): 879-898.
134 Young S, Sanghvi T, Rubin N, Hall D, Roller L, Charaf Y, Golzarian J. Transarterial chemoembolization of hepatocellular carcinoma: propensity score matching study comparing survival and complications in patients with nonalcoholic steatohepatitis versus other causes cirrhosis. Cardiovasc Intervent Radiol 2020; 43(1): 65-75.
135 Monga SP. β-Catenin signaling and roles in liver homeostasis, injury, and tumorigenesis. Gastroenterology 2015; 148 (7): 1294-1310.
136 Yin Y, Sichler A, Ecker J, Laschinger M, Liebisch G, Höring M, Basic M, Bleich A, Zhang XJ, Kübelsbeck L, Plagge J, Scherer E, Wohlleber D, Wang J, Wang Y, Steffani M, Stupakov P, Gärtner Y, Lohöfer F, Mogler C, Friess H, Hartmann D, Holzmann B, Hüser N, Janssen KP. Gut microbiota promote liver regeneration through hepatic membrane phospholipid biosynthesis. J Hepatol 2023; 78(4): 820-835.
137 de Souza CO, Vannice GK, Rosa Neto JC, Calder PC. Is palmitoleic acid a plausible nonpharmacological strategy to prevent or control chronic metabolic and inflammatory disorders? Mol Nutr Food Res 2018; 62(1). doi: 10.1002/mnfr.201700504.
138 Oballa RM, Belair L, Black WC, Bleasby K, Chan CC, Desroches C, Du X, Gordon R, Guay J, Guiral S, Hafey MJ, Hamelin E, Huang Z, Kennedy B, Lachance N, Landry F, Li CS, Mancini J, Normandin D, Pocai A, Powell DA, Ramtohul YK, Skorey K, Sørensen D, Sturkenboom W, Styhler A, Waddleton DM, Wang H, Wong S, Xu L, Zhang L. Development of a liver-targeted stearoyl-CoA desaturase (SCD) inhibitor (MK-8245) to establish a therapeutic window for the treatment of diabetes and dyslipidemia. J Med Chem 2011; 54(14): 5082-5096.
139 Chow LS, Li S, Eberly LE, Seaquist ER, Eckfeldt JH, Hoogeveen RC, Couper DJ, Steffen LM, Pankow JS. Estimated plasma stearoyl co-A desaturase-1 activity and risk of incident diabetes: the Atherosclerosis Risk in Communities (ARIC) study. Metabolism 2013; 62(1): 100-108.
140 Swisa A, Glaser B, Dor Y. Metabolic stress and compromised identity of pancreatic beta cells. Front Genet 2017; 8: 21.
141 Zámbó V, Simon-Szabó L, Sarnyai F, Mátyási J, Gór-Nagy Z, Somogyi A, Szelényi P, Kereszturi É, Tóth B, Csala M. Investigation of the putative rate-limiting role of electron transfer in fatty acid desaturation using transfected HEK293T cells. FEBS Lett 2020; 594(3): 530-539.
142 Plötz T, von Hanstein AS, Krümmel B, Laporte A, Mehmeti I, Lenzen S. Structure-toxicity relationships of saturated and unsaturated free fatty acids for elucidating the lipotoxic effects in human EndoC-βH1 beta-cells. Biochim Biophys Acta Mol Basis Dis 2019; 1865(11): 165525.
143 von Hanstein AS, Lenzen S, Plötz T. Toxicity of fatty acid profiles of popular edible oils in human EndoC-βH1 beta-cells. Nutr Diabetes 2020; 10(1): 5.
144 Janikiewicz J, Hanzelka K, Dziewulska A, Kozinski K, Dobrzyn P, Bernas T, Dobrzyn A. Inhibition of SCD1 impairs palmitate-derived autophagy at the step of autophagosome-lysosome fusion in pancreatic β-cells. J Lipid Res 2015; 56 (10): 1901-1911.
145 Cabrae R, Dubuquoy C, Caüzac M, Morzyglod L, Guilmeau S, Noblet B, Fève B, Postic C, Burnol AF, Moldes M. Insulin activates hepatic Wnt/β -catenin signaling through stearoyl-CoA desaturase 1 and Porcupine. Sci Rep 2020; 10(1): 5186.
146 Janikiewicz J, Dobosz AM, Majzner K, Bernas T, Dobrzyn A. Stearoyl-CoA desaturase 1 deficiency exacerbates palmitate-induced lipotoxicity by the formation of small lipid droplets in pancreatic β-cells. Biochim Biophys Acta Mol Basis Dis 2023; 1869(6): 166711.
147 Wang C, Shi M, Ji J, Cai Q, Zhao Q, Jiang J, Liu J, Zhang H, Zhu Z, Zhang J. Stearoyl-CoA desaturase 1 (SCD1) facilitates the growth and anti-ferroptosis of gastric cancer cells and predicts poor prognosis of gastric cancer. Aging (Albany NY) 2020; 12(15): 15374-15391.

148 Tesfay L, Paul BT, Konstorum A, Deng Z, Cox AO, Lee J, Furdui CM, Hegde P, Torti FM, Torti SV. Stearoyl-CoA desaturase 1 protects ovarian cancer cells from ferroptotic cell death. Cancer Res 2019; 79(20): 5355-5366.

149 Igal RA. Stearoyl-CoA desaturase-1: a novel key player in the mechanisms of cell proliferation, programmed cell death and transformation to cancer. Carcinogenesis 2010; 31 (9): 1509-1515.

150 Hess D, Chisholm JW, Igal RA. Inhibition of stearoylCoA desaturase activity blocks cell cycle progression and induces programmed cell death in lung cancer cells. PLoS One 2010; 5(6): e11394.

151 Zheng J, Conrad M. The Metabolic underpinnings of ferroptosis. Cell Metab 2020; 32(6): 920-937.

152 Hassannia B, Vandenabeele P, Vanden Berghe T. Targeting ferroptosis to iron out cancer. Cancer Cell 2019; 35(6): 830-849.

153 Madden E, Logue SE, Healy SJ, Manie S, Samali A. The role of the unfolded protein response in cancer progression: From oncogenesis to chemoresistance. Biol Cell 2019; 111 (1): 1-17.

154 Chen X, Cubillos-Ruiz JR. Endoplasmic reticulum stress signals in the tumour and its microenvironment. Nat Rev Cancer 2021; 21(2): 71-88.

155 Ben-David U, Gan QF, Golan-Lev T, Arora P, Yanuka O, Oren YS, Leikin-Frenkel A, Graf M, Garippa R, Boehringer M, Gromo G, Benvenisty N. Selective elimination of human pluripotent stem cells by an oleate synthesis inhibitor discovered in a high-throughput screen. Cell Stem Cell 2013; 12(2): 167-179.

156 Scaglia N, Igal RA. Stearoyl-CoA desaturase is involved in the control of proliferation, anchorage-independent growth, and survival in human transformed cells. J Biol Chem 2005; 280(27): 25339-25349.

157 Fernández-Ramos D, Lopitz-Otsoa F, Delacruz-Villar L, Bilbao J, Pagano M, Mosca L, Bizkarguenaga M, Serrano-Macia M, Azkargorta M, Iruarrizaga-Lejarreta M, Sot J, Tsvirkun D, van Liempd SM, Goni FM, Alonso C, Martínez-Chantar ML, Elortza F, Hayardeny L, Lu SC, Mato JM. Arachidyl amido cholanoic acid improves liver glucose and lipid homeostasis in nonalcoholic steatohepatitis via AMPK and mTOR regulation. World J Gastroenterol 2020; 26(34): 5101-5117.

158 Pivari F, Mingione A, Brasacchio C, Soldati L. Curcumin and type 2 diabetes mellitus: prevention and treatment. Nutrients 2019; 11(8): 1837.

159 Jabczyk M, Nowak J, Hudzik B, Zubelewicz-Szkodzińska B. Curcumin in metabolic health and disease. Nutrients 2021; 13(12): 4440.

160 Simos YV, Spyrou K, Patila M, Karouta N, Stamatis H, Gournis D, Dounousi E, Peschos D. Trends of nanotechnology in type 2 diabetes mellitus treatment. Asian J Pharm Sci 2021; 16(1): 62-76.

161 Zeng J, Acin-Perez R, Assali EA, Martin A, Brownstein AJ, Petcherski A, Fernández-Del-Rio L, Xiao R, Lo CH, Shum M, Liesa M, Han X, Shirihai OS, Grinstaff MW. Restoration of lysosomal acidification rescues autophagy and metabolic dysfunction in non-alcoholic fatty liver disease. Nat Commun 2023; 14(1): 2573.

162 Sibuyi NRS, Moabelo KL, Meyer M, Onani MO, Dube A, Madiehe AM. Nanotechnology advances towards development of targeted-treatment for obesity. J Nanobiotechnology 2019; 17(1): 122.

163 Vincent BM, Tardiff DF, Piotrowski JS, Aron R, Lucas MC, Chung CY, Bacherman H, Chen Y, Pires M, Subramaniam R, Doshi DB, Sadlish H, Raja WK, Solís EJ, Khurana V, Le Bourdonnec B, Scannevin RH, Rhodes KJ. Inhibiting stearoyl-CoA desaturase ameliorates α-synuclein cytotoxicity. Cell Rep 2018; 25(10): 2742-2754.e1.

164 Luo H, Wang X, Song S, Wang Y, Dan Q, Ge H. Targeting stearoyl-coa desaturase enhances radiation induced ferroptosis and immunogenic cell death in esophageal squamous cell carcinoma. Oncoimmunology 2022; 11(1): 2101769.

165 Xiao Q, Lan Z, Zhang S, Ren H, Wang S, Wang P, Feng L, Li D, Wang C, Bai X, Zhang J. Overexpression of ZNF488 supports pancreatic cancer cell proliferation and tumorigenesis through inhibition of ferroptosis via regulating SCD1-mediated unsaturated fatty acid metabolism. Biol Direct 2023; 18(1): 77.

166 Zhang Z, Dales NA, Winther MD. Opportunities and challenges in developing stearoyl-coenzyme A desaturase-1 inhibitors as novel therapeutics for human disease. J Med Chem 2014; 57(12): 5039-5056.

167 Hyun CK, Kim ED, Flowers MT, Liu X, Kim E, Strable M, Ntambi JM. Adipose-specific deletion of stearoyl-CoA desaturase 1 up-regulates the glucose transporter GLUT1 in adipose tissue. Biochem Biophys Res Commun 2010; 399 (4): 480-486.

168 Wohlhieter CA, Richards AL, Uddin F, Hulton CH, Quintanal-Villalonga À, Martin A, de Stanchina E, Bhanot U, Asher M, Shah NS, Hayatt O, Buonocore DJ, Rekhtman N, Shen R, Arbour KC, Donoghue M, Poirier JT, Sen T, Rudin CM. Concurrent mutations in STK11 and KEAP1 promote ferroptosis protection and SCD1 dependence in lung cancer. Cell Rep 2020; 33(9): 108444.

169 Guo Z, Huo X, Li X, Jiang C, Xue L. Advances in regulation and function of stearoyl-CoA desaturase 1 in cancer, from bench to bed. Sci China Life Sci 2023; 66(12): 2773-2785.