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综 述

骨骼肌脂肪异位沉积在高脂膳食诱导胰岛素抵抗中的作用

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摘 要：高脂膳食会引起机体摄入脂肪的增加，导致人体内过量的脂肪储存，甚至超过人体脂肪组织的储存能力，造成脂肪的异位沉积，即在肝脏和骨骼肌等糖代谢的重要组织积累。最近的研究表明，与肥胖相比，骨骼肌脂肪含量与胰岛素抵抗的发生相关性更高。骨骼肌是最大的糖代谢场所，约80%~90%的2型糖尿病的发病原因为骨骼肌胰岛素抵抗。因此，骨骼肌脂肪含量与胰岛素抵抗之间的关系成为最近研究的热点，本文综述了高脂膳食引起骨骼肌脂肪异位沉积，进而诱导产生骨骼肌胰岛素抵抗的主要机制的研究进展。

关键词：骨骼肌；脂肪异位沉积；胰岛素抵抗；脂肪细胞因子；脂质中间产物
中图分类号：R363；Q445；Q591.5

Role of skeletal muscle fat ectopic deposition in insulin resistance induced by high-fat diet

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Abstract: Consumption of high-fat diet leads to the increase of fat intake and consequent excess storage of fat in the body. When the regular adipose tissues reach their capacity to store fat, ectopic fat is stored around and within non-adipose tissues, such as the liver and skeletal muscle, which plays important roles in glucose metabolism. Hence ectopic fat accumulation in major insulin target tissues is a critical determinant of insulin resistance (IR) and various related metabolic syndromes. Recent studies have shown that skeletal muscle lipid accumulation is more closely related with IR than general obesity and accounts for approximately 80%–90% type 2 diabetes, since the skeletal muscle is the largest glucose disposal site. Therefore, the association between skeletal muscle lipid and IR has attracted more and more research interest. This review summarized the role of ectopic skeletal muscle lipid in IR induced by high-fat diet and its possible mechanisms.

Key words: skeletal muscle; ectopic fat; insulin resistance; adipokine; lipid intermediates

近年来，随着人们生活条件的改善，高脂膳食受到极大的欢迎，使得脂肪摄入量急剧增加，进而导致机体脂质沉积及脂肪代谢中间产物的增加[1]，并通过多种途径诱导产生胰岛素抵抗。机体内的脂肪组织主要分为皮下脂肪组织 (subcutaneous fatty tissue, SAT) 和内脏脂肪组织 (visceral adipose tissue, VAT)，而肝脏和肌肉等组织器官内的脂肪含量非常低，但是，由于摄入脂肪的增加、SAT 储存能力的下降、脂肪代谢障碍及衰老等因素的影响，这些器官、组织内的脂肪含量会发生异常增加，称为脂肪的异位沉积[2, 3]，从而损伤器官、组织正常生理功能。目前的研究表明脂肪的异位沉积与胰岛素抵抗有一定的相关性，不同部位的脂肪积累与胰岛素抵抗的相关性有所不同[4, 5]，对于其机制也有一定的研究。大量研究表明，骨骼肌脂肪过量累积与胰岛素抵抗及 2 型糖尿病的相关性高于整体性肥胖[2, 6]，这可

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能与骨骼肌是葡萄糖代谢的主要部位有关。但是由于机体内脂肪过度积累导致胰岛素抵抗的机制非常复杂，因此这方面的研究目前备受关注。本文综述了国内外相关领域研究进展，旨在促进对骨骼肌脂肪积累及代谢诱导胰岛素抵抗机制的理解，为运动及饮食控制治疗和改善胰岛素抵抗提供新的思路和方法。

1 高脂膳食增加骨骼肌间质祖细胞成脂分化及脂肪滴沉积

脂肪在骨骼肌中的异位沉积主要包括骨骼肌细胞外间质祖细胞在高脂条件下分化为骨骼肌肌束间脂肪组织及储存脂肪滴的增加。

1.1 骨骼肌间质祖细胞分化成为脂肪细胞

骨骼肌间质中的间质祖细胞 [包括间质干细胞、肌源性干细胞及骨骼肌卫星细胞 (satellite cell, SC)] 在肌肉疾病 [7]、衰老 [8, 9] 及静坐少动生活方式 [10] 等因素的影响下，可能会分化成为脂肪细胞 (图 1)[11, 12, 21]。其中 SC 是骨骼肌再生和重建最重要的干细胞，通常处于静息状态，但当骨骼肌运动、损伤或病变时，可被多种因素激活，开始增殖和分化。SC 的激活包含多种机制，但其基础均为微环境改变和肌细胞损伤导致胰岛素样生长因子 1 (insulin like growth factor 1, IGF-1) 和成纤维细胞生长因子 (fibroblast growth factor, FGF) 等生长因子表达增加，并通过激活相关信号通路，如肝细胞生长因子 (hepatocyte growth factor, HGF)/c-met、Notch 等，进而激活 SC，促进其增殖和分化以修复损伤的肌细胞 [13–16]。但是 SC 的分化方向取决于其所处的微环境，如将其在成脂培养基中培养，则会分化成为脂肪细胞，并表达特异性的成脂标志物，主要包括过氧化物酶体增生物激活受体 γ2 (peroxisome proliferator-activated receptor γ2, PPARγ2)、瘦素及脂联素 [17]；而在动物体内，若敲除小鼠卵磷脂胆固醇酰基转移酶 (lecithin cholesterol acyl transferase, LCAT) 和低密度脂蛋白受体基因 (降低血胆固醇)，则会降低 SC 的成脂分

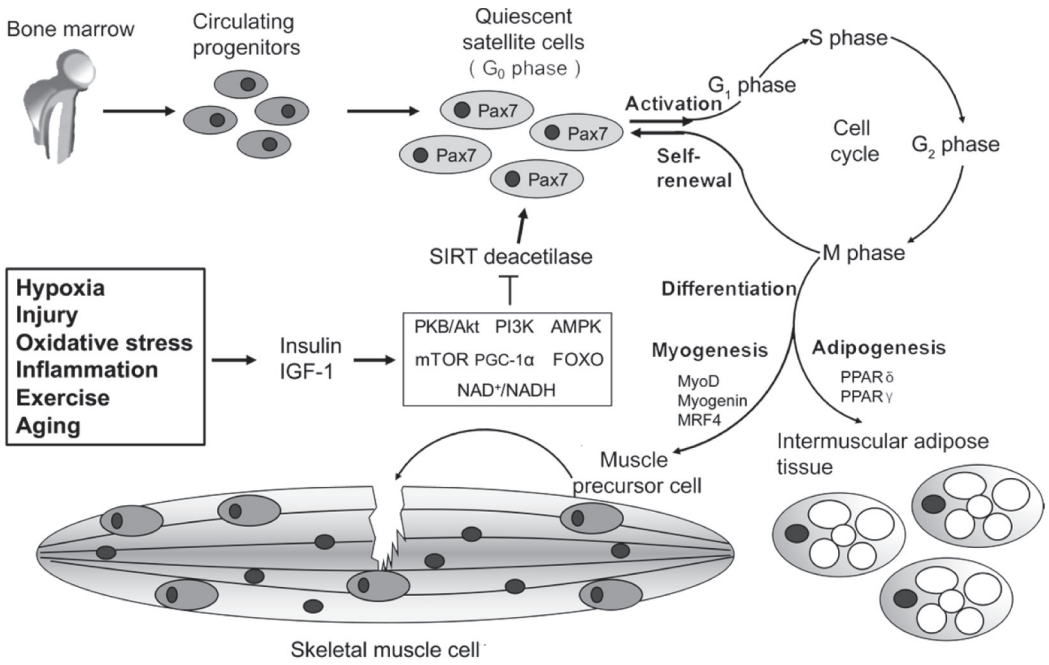

图 1. 骨骼肌卫星细胞的激活和分化示意图

Fig. 1. Diagram of activation and differentiation of skeletal muscle satellite cells. Circulating progenitors coming from bone marrow differentiate to quiescent satellite cells, and the quiescent satellite cells are activated by insulin and insulin-like growth factor 1 (IGF-1) related signal pathways, and eventually differentiate to muscle progenitor cells (myogenesis) or adipogenic cells (adipogenesis) [11, 21]. Pax7, paired homeobox transcription 7; PKB/Akt, protein kinase B; PI3K, phosphoinositol 3-kinase; AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; PGC-1α, peroxisome proliferator-activated receptor- γ coactivator-1α; FOXO, foxhead box proteins; NAD^+/NADH, nicotinamide adenine dinucleotide; MyoD, myogenic differentiation; MRF4, myogenic regulatory factor 4; PPARδ and -γ , peroxisome proliferator-activated receptor-δ and -γ; SIRT deacetilase, silent information regulator 2 homologue 1.

化率 [18]。但事实上，成脂和成肌分化可能是由不同的 SC 亚型实现的，即同一肌纤维周围的 SC 分为“成肌亚型”和“非成肌亚型”，两种亚型以一定的比例存在，而仅有非成肌亚型 SC 能够积累脂肪，分化成为脂肪细胞 [19, 20]。

骨骼肌 SC 分化成为脂肪细胞涉及多种分子机制 [22]，主要包括 PPAR、WNT、肌源性因子 [白介素 -4 (interleukin-4, IL-4)、血管内皮生长因子 (vascular endothelial growth factor, VEGF)、IGF-1、myostatin、IL-6 等] 及 GEF-GAP-Rho 等多个信号通路。不同信号通路之间相互作用、相互影响，导致 SC 分化方向的改变，其确切的机制尚不完全清楚。除了上述分子机制外，线粒体生物发生减少导致肌细胞氧化能力降低，也会使骨骼肌干细胞向脂肪细胞的方向分化 [11]，其原因可能是脂肪细胞的主要功能是储存甘油三酯，为肌纤维中线粒体的氧化供能提供底物，因此脂肪细胞中则少有具有氧化功能的线粒体。而骨骼肌中脂肪细胞增加导致的线粒体生物发生的减少降低骨骼肌脂肪酸氧化代谢，进一步造成骨骼肌内脂肪积累增加。

1.2 骨骼肌脂肪滴储存

细胞内的脂肪滴由中性脂质核心和外层的磷脂和蛋白质构成，在脂肪储存、转运和代谢过程中具有重要的作用，此外，还与信号转导及为代谢过程提供适宜的微环境有关。因此，细胞内通常都含有一定量的脂肪滴。但是过量的脂肪摄入或脂肪细胞功能障碍，导致脂肪水解增加，释放过多的游离脂肪酸 (free fatty acid, FFA) 进入血液循环，与血清白蛋白相结合，随着血液循环进入骨骼肌，通过被动扩散、FAT/CD36 或质膜脂肪酸结合蛋白 (FABPpm) 进入骨骼肌细胞。另外，骨骼肌还可以通过 LPL 从乳糜微粒和极低密度脂蛋白 (very low density lipoprotein, VLDL) 中摄取脂肪酸。进入骨骼肌细胞后，FFA 会进入不同的代谢途径，包括在线粒体中被氧化、合成甘油三酯或以脂肪滴的形式储存起来 [23]。

2 骨骼肌脂肪含量增加导致胰岛素抵抗的机制

脂质异位沉积是导致胰岛素抵抗的重要因素之一 [24]，而骨骼肌是机体重要的能量代谢场所，糖和脂肪的氧化是该过程中必需的能源物质，因此骨骼肌脂肪积累增加及脂肪酸氧化代谢的中间产物都可能影响胰岛素信号通路，从而导致胰岛素抵抗；骨骼肌中脂肪组织和细胞还会分泌多种细胞因子，其中的一些因子抑制胰岛素信号转导，促使胰岛素抵抗的发生 [2, 25, 26]。而最近的研究表明过量脂肪酸氧化、线粒体过载及线粒体氧化应激也是肥胖引起胰岛素抵抗的重要机制 [27]。另外，FFA 含量升高也会降低骨骼肌细胞胰岛素介导的葡萄糖摄取 [28, 29]，从而导致甘油三酯积累及胰岛素敏感性降低。因此，骨骼肌脂肪异位沉积诱发胰岛素抵抗是多因素、多机制共同作用的结果。

2.1 脂肪细胞因子与胰岛素信号通路抑制及阻断

骨骼肌脂肪含量与 2 型糖尿病的发生呈正相关，而与体重、身体质量指数 (body mass index, BMI) 及腰围的相关性不显著，其主要机制可能是肌细胞外脂肪组织和细胞分泌的脂肪因子可改变细胞代谢，降低胰岛素敏感性 [2]。其中肿瘤坏死因子 -α (tumor necrosis factor-α, TNF-α)、脂源性 IL-6、视黄醇结合蛋白 4 (retinol binding protein 4, RBP4) 等主要通过调节胰岛素受体底物 1 (insulin receptor substrate 1, IRS1) 磷酸化及葡萄糖转运诱发胰岛素抵抗 (图 2)[25, 26]；而抵抗素和胎球蛋白 A 还通过激活细胞因子信号转导抑制蛋白 3 (suppressor of cytokine signaling 3, SOCS3) 及 Toll 样受体 4 (Toll like receptor 4, TLR4) 等信号通路诱发胰岛素抵抗。另外，脂联素、瘦素、鸢尾素 (irisin)、成纤维细胞生长因子 21 (fibroblast growth factor 21, FGF21) 及分泌型卷曲相关蛋白 5 (secreted frizzled-related protein 5, SFRP5) 等则与促进脂肪代谢、改善胰岛素抵抗有关，但这些因子在肥胖时分泌减少 [30]。因此，骨骼肌脂肪积累导致的脂肪因子分泌失衡是诱发胰岛素抵抗的重要因素之一。

2.1.1 诱发胰岛素抵抗的脂肪因子

TNF-α 是由脂肪组织中单核细胞和巨噬细胞产生的抗炎因子，主要通过降低脂肪组织和骨骼肌中胰岛素受体和 IRS1 中酪氨酸的磷酸化诱导胰岛素抵抗的产生。另外，TNF-α 还可能促使脂肪酸形成甘油二酯 (diglyceride, DAG)，诱导骨骼肌产生胰岛素抵抗 [31]。研究表明，肥胖和 2 型糖尿病患者和小鼠脂肪组织中的 TNF-α 表达增加 [32]；而在肥胖个体中，TNF-α 主要由 VAT 中的巨噬细胞分泌 [33, 34]，因此内脏脂肪积累与胰岛素敏感性降低和抗炎性因子增加显著相关。敲除 ob/ob 小鼠或饮食诱导肥胖小鼠体内的 TNF-α 及其受体基因能够提高胰岛素敏感性，降低血清 FFA，进而改善脂肪组织和骨骼肌

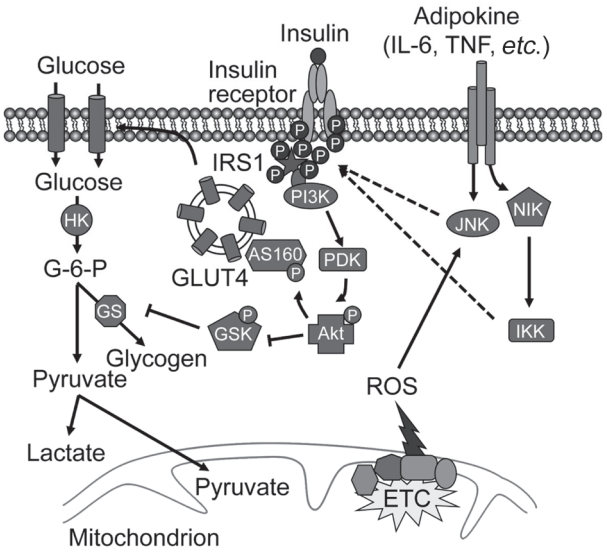

图 2. 促炎细胞因子抑制胰岛素信号通路的机制

Fig. 2. Mechanism of pro-inflammatory cytokines inhibiting insulin signaling pathway. Pro-inflammatory adipokines inhibit serine kinases through JNK and NIK/IKK pathways, and lead to inhibition of IRS1 phosphorylation, reduce the uptake of glucose, and eventually induce insulin resistance [26]. HK, hexokinase; GS, glycogen synthase; IRS1, insulin receptor substrate 1; PDK, phosphoinositide-dependent kinase; AS160, Akt substrate of 160 kDa; GLUT4, glucose transporter type 4; GSK, glycogen synthase kinase; IL-6, interleukin-6; TNF, tumor necrosis factor; JNK, c-Jun N-terminal kinase; NIK, nuclear factor κB inducible kinase; IKK, inducer of κ kinase; ROS, reactive oxygen species; ETC, electron transport chain.

胰岛素抵抗 [35]。

IL-6 既是具有促炎作用的脂肪因子 [36]，也是具有抗炎作用的肌肉因子 [37]，其原因可能是不同部位诱导产生 IL-6 的物质和信号不同。如运动后血清 IL-6 主要由骨骼肌分泌 [38]，能够改善糖脂代谢和胰岛素信号通路 [39]；而脂肪细胞产生的 IL-6 则与胰岛素抵抗和代谢失调有关 [40]。研究表明 2 型糖尿病、肥胖及胰岛素抵抗患者血清 IL-6 主要由 VAT 分泌 [41]，且与 BMI 呈正相关 [42]。IL-6 诱发胰岛素抵抗主要是通过抑制葡萄糖转移酶 4 (glucose transferase 4, GLUT4) 和 IRS1 的表达，进而抑制胰岛素信号转导，减少其胰岛素依赖的葡萄糖摄取 [25]。

RBP4 是肝细胞分泌的细胞因子，主要功能是将视黄醇从肝脏转运至外周组织 [43]，但是最近研究显示脂肪细胞和巨噬细胞也可以分泌 RBP4[44]。脂肪细胞分泌的 RBP4 通常以自分泌或旁分泌的方式抑制胰岛素诱导的 IRS1 磷酸化 [45]。特异性敲除小鼠脂肪细胞 GLUT4 基因，其脂肪细胞的 RBP4 表达增加 [44]，导致葡萄糖不耐受和胰岛素抵抗。而在胰岛素抵抗的情况下，血清 RBP4 主要由 VAT 产生 [46]，与 BMI 升高有关 [47]。

抵抗素介导肥胖相关的胰岛素抵抗 [48]，其浓度与脂肪含量正相关。抵抗素有三聚体和六聚体两种亚型，其中三聚体对诱导胰岛素抵抗具有较强的作用，通过激活细胞因子 SOCS3 抑制胰岛素受体信号转导，调节糖代谢 [49]。在小鼠中仅脂肪细胞能够合成抵抗素，但在人体中抵抗素则是由单核细胞和巨噬细胞所分泌，因此，在小鼠体内抵抗素含量升高诱发胰岛素抵抗，但是在人体中的作用尚不明确 [25]。

胎球蛋白 A (fetuin-A，也称为 α2-HS- 糖蛋白) 是肝脏分泌的糖蛋白，能够刺激脂肪细胞和巨噬细胞产生炎性细胞因子 [50, 51]。最近，有报道显示 FFA 可以增加 fetuin-A 表达，而 FFA 诱导的 fetuin-A 可以激活脂肪组织中 TLR4 介导的炎症反应，进而导致胰岛素抵抗 [52]。另外，FFA 孵育脂肪细胞能够使其释放 fetuin-A，促进巨噬细胞迁移进入脂肪组织 [53]。有研究显示，与皮下脂肪相比，内脏脂肪分泌更多的 fetuin-A，并且 fetuin-A 过度分泌会抑制胰岛素信号转导 [54]。

2.1.2 改善胰岛素抵抗的脂肪因子

脂联素参与调节葡萄糖稳态、胰岛素敏感性及代谢平衡 [55]，与 2 型糖尿病和代谢综合征有关 [56, 57]。肥胖、2 型糖尿病和胰岛素抵抗受试者的血清脂联素浓度降低 [58–60]，与 BMI 呈负相关 [30]。脂联素的主要作用机制可能是激活 AMPK，增加骨骼肌葡萄糖摄取和脂肪酸氧化，抑制肝脏糖异生作用 [61, 62]，刺激体内胰岛素分泌；而低脂联素血症可导致 β-细胞功能障碍 [63, 64]。脂联素通过其受体 AdipoR1 和 AdipoR2 发挥作用 [65, 66]，其中 AdipoR1 可在不同组织中表达，激活 AMPK，减少葡萄糖生成，进而改善胰岛素抵抗；而 AdipoR2 主要在肝脏中表达，与 PPARα 激活有关，而 PPARα 与增加脂肪酸氧化、改善胰岛素抵抗有关。

瘦素主要由脂肪细胞分泌，主要功能是抑制下丘脑摄食中枢，使食欲减退，能量消耗增强，体重下降。瘦素缺陷小鼠表现为食物摄入增加、能量消耗降低、脂代谢异常、肥胖及胰岛素抵抗等；而瘦素可以改善 ob/ob 小鼠的脂代谢障碍 [67] 和胰岛素抵抗 [68]。但是，瘦素也可促进单核细胞分泌 TNF 和 IL-6[69]，同时增加 ROS 的产生 [70]。

FGF21 是最近新发现的脂肪因子[71–73]，以自分泌 / 旁分泌的方式增加脂肪组织中解耦联蛋白 1 (uncoupling protein 1, UCP1) 和其它产热基因的表达。FGF21 能够降低棕色脂肪的能量消耗，并且促进周围组织不依赖于胰岛素的葡萄糖摄取。脂源性 FGF21 促进白色脂肪组织和血液脂联素的表达[74]。但是，并未发现 FGF21 能够改善脂联素敲除小鼠的肝脏和骨骼肌胰岛素抵抗，提示脂联素是 FGF21 的下游效应分子。

SFRP5 是具有抗炎效应的脂肪因子[75]，在白色脂肪组织中高表达，具有抗炎和促进胰岛素敏感性的作用。*SFRP5* 基因敲除小鼠的血糖浓度正常，但仍会出现胰岛素抵抗和脂肪肝[25]。研究表明 SFRP5 可与 Wnt5α 结合并抑制其活性，从而抑制 Wnt5α-JNK1 信号通路。而 JNK1 的激活会引起 IRS1 丝氨酸磷酸化，阻断胰岛素信号通路，从而导致胰岛素抵抗。因此，SFRP5 可能通过抑制 JNK1 信号通路提高胰岛素敏感性，改善胰岛素抵抗。

鸢尾素主要在脂肪组织与骨骼肌中产生和分泌[76]，能够作用于线粒体 UCP1，促进脂肪组织氧化耗能，使白色脂肪棕色化[77]。血清鸢尾素含量升高能够显著改善人体的葡萄糖耐量，而随着胰岛素抵抗指数的升高逐渐降低[78]。有研究表明，鸢尾素可以改善棕榈酸诱导的胰岛素抵抗，提示鸢尾素可调节骨骼肌细胞胰岛素信号通路关键蛋白的表达，改善胰岛素抵抗[79]。但是也有研究表明肥胖患者鸢尾素水平升高，且与体脂含量呈正相关[80]，提示白色脂肪组织分泌的鸢尾素可能在与肥胖和胰岛素抵抗有关的代谢性疾病中有重要作用。

2.2 骨骼肌细胞内脂肪代谢中间产物与胰岛素抵抗

甘油三酯是细胞内脂肪储存的主要形式，因此，它是细胞内脂肪积累的重要标记物，其中间代谢产物，如 DAG、长链脂酰 CoA (long-chain acyl-CoA, LCACoA) 和神经酰胺 (ceramide, CER) 及脂肪酸氧化的中间产物与胰岛素信号通路相互影响，导致胰岛素抵抗 (图 3)[26, 81, 82]。其主要机制是这些中间产物减少了信号通路中的磷酸化反应，从而导致 GLUT4 不能转移至细胞膜，抑制了葡萄糖转运，进而抑制细胞依赖胰岛素的葡糖糖摄入[83]。已有研究显示葡萄糖转运 / 磷酸化和糖原合成缺陷是脂肪诱导胰岛素抵抗的主要机制，因此，目前关于脂肪过度积累诱导胰岛素抵抗的研究主要集中在过量脂肪与胰岛素信号通路和葡萄糖转运缺陷之间的关系。

骨骼肌细胞内甘油三酯 (intramuscular triglyceride, IMTG) 通常以脂肪滴的形式存在，因此，一般认为 IMTG 的存在本身不会影响胰岛素信号通路[84]，但是，同样的，IMTG 的代谢也可能在胰岛素抵抗发生的过程中起中介作用。从这个方面来讲，甘油三酯代谢过程中产生的生物活性物质，包括 DAG 和 CER 可能在胰岛素抵抗的发生过程中发挥了主要作用[85–87](图 3)，可能通过激活丝氨酸 / 苏氨酸蛋白激酶级联反应诱导胰岛素抵抗[88–90]。其中 DAG 可以抑制 PKC，进而抑制胰岛素信号转导中的 IRS1 介导的葡萄糖转运[90, 91]；而 CER 则会影响 Akt 水平的胰岛素信号转导，另外，CER 还是多种炎性因子的激活剂，包括 JNK[92]、NFκB/IKK[93] 等。然而，也有研究表明，炎性因子并不促进脂肪诱导的胰岛素抵抗产生，而是维持或加快胰岛素抵抗的发展[94, 95]。尽管有大量的证据显示 DAG 和 CER 与胰岛素抵抗具有显著的相关性，但同时也有证据表明长期进行耐力训练的运动员 DAG 水平有所升高，同时其胰岛素敏感性增强[84, 96]；另外，也有研究表明，CER 可能与胰岛素敏感性呈正相关[97]。这些研究结果提示 DAG 和 CER 在调节胰岛素作用方面具有一定的复杂性，因此，在研究中应强调考察特定的异构体及其在细胞内的定位。

另外，细胞内过量的脂肪酸堆积也可能增加线粒体脂肪酸氧化，导致该过程中副产物的积累，包括脂肪酸不完全氧化的产物、细胞内脂酰肉碱及 ROS[98] 等，这些中间产物与胰岛素抵抗的发生呈正相关。如脂酰肉碱的含量在高脂膳食受试者体内有所上升[99]，但其在胰岛素抵抗发生过程中的作用并不确定；而 ROS 可能造成细胞的氧化应激、脂质过氧化及胰岛 β- 细胞损伤等[100]。总之，脂肪酸升高诱导胰岛素抵抗的机制是其活性代谢产物作用于胰岛素信号通路中的多种丝氨酸激酶，从而阻断胰岛素在细胞中的信号转导，降低细胞对葡萄糖的吸收，增加脂肪代谢，产生更多的活性代谢产物，形成恶性循环，进一步加重胰岛素抵抗。

2.3 线粒体生物发生及功能障碍与胰岛素抵抗

脂肪积累导致胰岛素抵抗的另一种主要机制为引发线粒体功能障碍，有研究表明在肥胖、胰岛素抵抗或 2 型糖尿病患者的骨骼肌细胞内线粒体基因 mRNA 和蛋白质表达减少[102–105]、mtDNA 水平降低[106, 107]、氧化酶活性降低[103, 106, 108] 及线粒体含量减少[102, 106, 109]，提示受试者线粒体功能衰退及生物

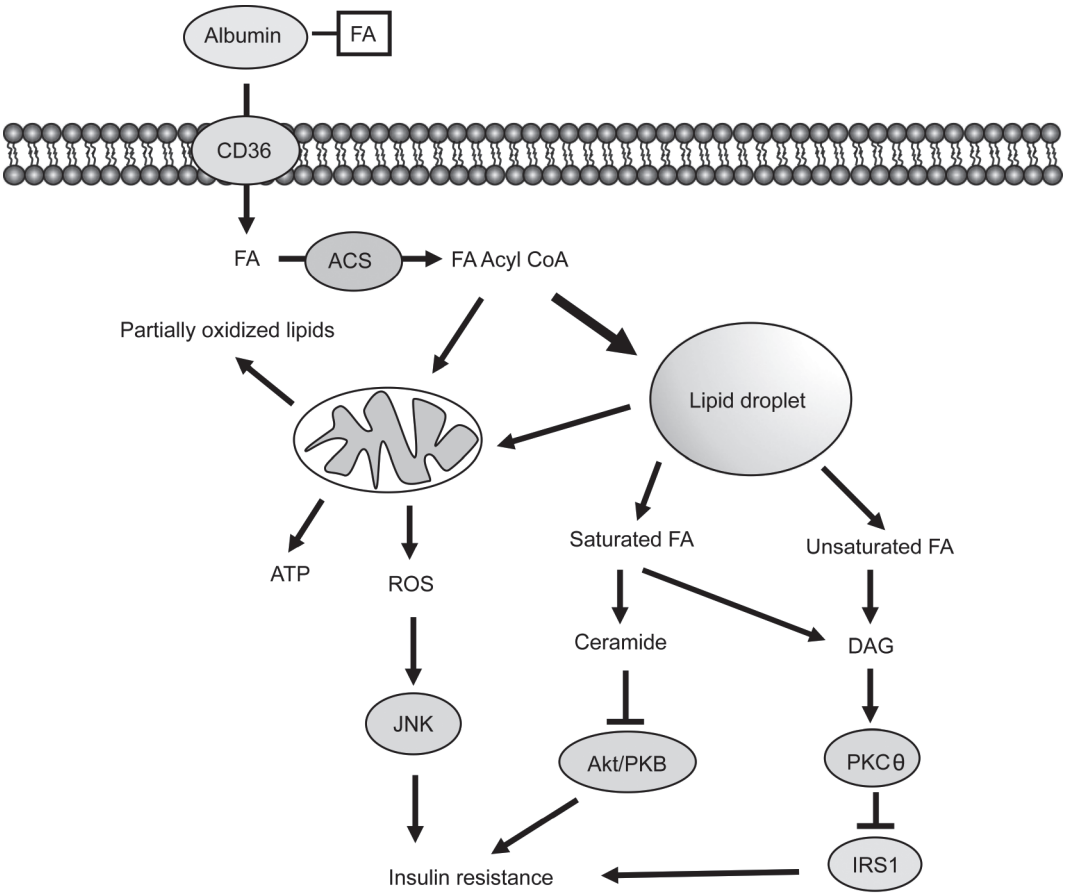

图 3. 骨骼肌细胞内脂肪沉积诱发胰岛素抵抗的可能机制

Fig. 3. Possible mechanisms of insulin resistance induced by lipid deposition in skeletal muscle cells. Most of the oversupplied fatty acids (FAs) are stored in the muscle cells as lipid droplets; overload of the FA-CoA to mitochondria results in incomplete β-oxidation and ROS production; Saturated FA may result in accumulation of ceramide, which inhibits phosphorylation and activation of Akt/PKB; Saturated and unsaturated FAs may induce DAG accumulation and subsequent activation of PKCθ, leading to serine phosphorylation of IRS1[101]. FA, fatty acid; CD36, cluster of differentiation 36; ACS, acyl coenzyme A synthase; DAG, diglyceride; PKCθ, protein kinase Cθ.

发生减少，受试者骨骼肌不能有效利用能源物质提供能量。但是，关于线粒体功能与胰岛素抵抗相关性的研究结果并不一致。一些研究结果显示，高脂膳食会导致实验动物胰岛素抵抗，但其线粒体蛋白质合成及氧化能力增强[110–113]；而另一些研究则显示通过转基因技术降低小鼠线粒体功能，并未发生胰岛素抵抗[114–117]，可以推测线粒体功能障碍可能并非骨骼肌脂肪积累及胰岛素抵抗的必要条件。

2.4 脂肪含量影响骨骼肌血流并导致胰岛素受体减少

骨骼肌脂肪含量诱导胰岛素抵抗的机制除了上述胰岛素信号通路的抑制和线粒体功能障碍外，肥胖人群胰岛素的作用还受到毛细血管密度、与肌细胞的距离以及肌纤维类型等因素的影响[118]，可能是由于骨骼肌细胞周围脂肪会阻断骨骼肌细胞的营养性血流，减少胰岛素与其受体的结合(图4)。另外，还可能是由于脂肪组织的胰岛素受体较少，因此骨骼肌脂肪含量的增加导致胰岛素受体减少，从而引起胰岛素抵抗。

3 总结

高脂膳食增加了机体脂肪的摄入，并以脂肪细胞或脂肪滴的形式储存在骨骼肌中，从而增加了骨骼肌中脂肪含量及脂肪酸氧化代谢。而脂肪细胞的增加促进了多种脂肪因子的分泌，同时脂肪酸的过量氧化会产生多种不完全氧化的活性中间产物，这些脂肪因子和中间产物与胰岛素信号通路中的信号分子相互作用，抑制或阻断胰岛素信号转导，诱导产生胰岛素抵抗。另外，脂肪含量的增加还会导致

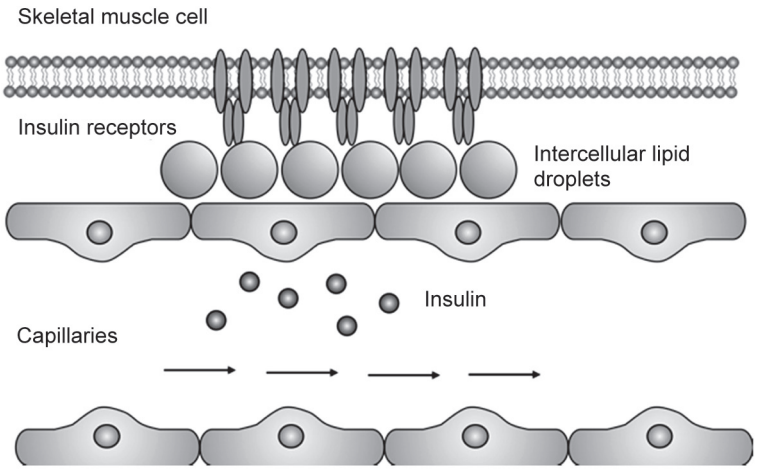

图 4. 骨骼肌细胞外脂肪滴增加诱发胰岛素抵抗的机制

Fig. 4. Mechanism of insulin resistance induced by increased extracellular lipoid droplets in skeletal muscle. Lipid droplets surrounding skeletal muscle cells impair, modulate nutritive blood flow to skeletal muscle, and reduce the binding of insulin with insulin receptors.

骨骼肌内线粒体数量减少，脂肪酸的过量氧化也会导致线粒体功能损伤，促进了骨骼肌胰岛素抵抗的发生。脂肪含量增加还减少了骨骼肌营养性血流，从而阻断了胰岛素与其受体的结合，发生胰岛素抵抗。但是，骨骼肌脂肪异位沉积在诱导胰岛素抵抗的发生过程中的作用极其复杂，不同分子诱导胰岛素抵抗的机制尚不明确，仍需进一步研究以明确不同脂肪因子和代谢产物在骨骼肌胰岛素抵抗中的作用机制，以便更有针对性地采取营养及运动干预减轻甚至逆转胰岛素抵抗。

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