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糖尿病性心肌病代谢紊乱相关研究进展

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摘　要

糖尿病性心肌病(diabetes cardiomyopathy, DCM)是一类与冠心病、高血压、瓣膜病等无关的特异性心肌病。DCM以心肌代谢紊乱、心肌纤维化及肥大、心肌细胞坏死等病理变化为主要特征，逐渐演变为收缩功能障碍，最终引发心力衰竭死亡。随着糖尿病的患病率的上升，DCM的高致死率受到越来越多的关注。糖脂代谢紊乱与DCM的发生、发展密切相关，目前关于DCM糖脂代谢紊乱方面的相关研究发现，葡萄糖转运体和脂质转运体的相互易位是糖尿病心肌病发病的重要基础。本文主要从糖脂代谢紊乱这一视角出发，对糖尿病性心肌病发病机制的最新研究进展进行系统性综述。

关键词

糖尿病性心肌病，糖脂代谢紊乱，发病机制

Research Progress on Metabolic Disorders Associated with Diabetic Cardiomyopathy

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Abstract

Diabetic cardiomyopathy (DCM) is a kind of specific cardiomyopathy that has nothing to do with coronary heart disease, hypertension and valvular disease. DCM is mainly characterized by

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pathological changes such as myocardial metabolism disorder, myocardial fibrosis and hypertrophy, and myocardial cell necrosis, which gradually evolves into systolic dysfunction and eventually leads to heart failure and death. With the increasing prevalence of diabetes mellitus, the high fatality rate of DCM has attracted more and more attention. The disorder of glucose and lipid metabolism plays an important role in the pathogenesis of DCM. Current studies on the disorder of glucose and lipid metabolism in DCM have found that the mutual translocation of glucose transporters and lipid transporters is an important basis for the pathogenesis of diabetic cardiomyopathy. In this paper, the latest research progress on the pathogenesis of diabetic cardiomyopathy was systematically reviewed from the perspective of the disorder of glucose and lipid metabolism.

Keywords

Diabetic Cardiomyopathy, Dysglycolipid Metabolic Disorders, Mechanism of Pathogenesis

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1. 流行病学

据国际糖尿病联盟(International Diabetes Federation, IDF)最新数据显示，截止至 2021 年，全球范围内 20~79 岁的成年人中糖尿病患者的数量已攀增至 5.37 亿，5.41 亿成年人患 2 型糖尿病的风险增加，将近二分之一(2.4 亿)的糖尿病成人未被诊断出来。预计到 2030 年，糖尿病患者总数将增至 6.43 亿，到 2045 年将增至 7.83 亿[1]。对于糖尿病相关的机制、表现和防治研究越来越被学界重视。研究表明，糖尿病合并心力衰竭相对于其它类型心力衰竭而言，其死亡率要高出 50%~90% [2]。射血分数降低的心力衰竭(Heart failure with reduced ejection fraction, HFrEF)患者中糖尿病的患病率为 10%~30%，与未患糖尿病的患者相比，糖尿病患者心衰住院的风险增加 33% [3]。在一项前瞻性队列研究中，40.2%的 HFrEF 患者患有 T2DM，而射血分数保留的心衰(Heart failure with preserved ejection fraction, HFpEF)患者中 T2DM 的患病率更是高达 45.0% [4]。在患有肥厚性心肌病患者的一项随访调研中，同时患有糖尿病的患者相较于未患糖尿病的患者，其患心力衰竭(Heart failure, HF)的风险比增加 15%，随着糖尿病的病程发展，发生 HF 的风险更高[5]。这些研究都强调糖尿病和心肌病之间具有明显的相关性。

2. 代谢紊乱

糖尿病心肌病期间的代谢紊乱的特征是脂质氧化增加、心肌内甘油三酯蓄积和葡萄糖利用率降低。心脏相对于身体其它器官而言，它所需要的能量是最大的，其中 ATP 主要由脂肪酸(60%~70%)，葡萄糖(20%)和乳酸(10%)三种底物的线粒体氧化快速产生以满足心肌需求[6]。

2.1. 糖代谢紊乱

细胞通过质膜中的葡萄糖转运蛋白(glucose transporters, GLUTs)来摄取葡萄糖，在心肌细胞中主要表达的为葡萄糖转运蛋白 1 (glucose transporter 1, GLUT1)和葡萄糖转运蛋白 4 (glucose transporter 4, GLUT4)，GLUT4 负责心肌收缩所需的葡萄糖摄取，GLUT1 主要摄取葡萄糖供应心肌细胞基础代谢[7]。相关研究表明，DCM 的糖代谢紊乱主要和 GLUT4 相关。GLUT4 由 12 个跨膜结构域组成，两个末端都在细胞质中，一个大的细胞内环和一个大的细胞外环[8]。GLUT4 接受胰岛素通过磷脂酰肌醇 3-激酶(PI3K)-RACα丝氨酸/苏氨酸蛋白激酶(AKT)途径调控[9]。在 AKT 激酶家族中，AKT2 负责参与胰岛素信号的传导[10]。

胰岛素通过作用于胰岛素受体 1 (insulin receptor substrate 1, IRS-1)激活 PI3K-Akt2 通路，Akt2 的激活可以使 GLUT4 由心肌细胞内体易位至心肌细胞膜上[11]。在糖尿病情况下，受胰岛素缺乏或胰岛素抵抗的影响，位于心肌细胞内的 GLUT4 易位到心肌膜的过程受损，使心肌摄取的葡萄糖数量下降。相关研究表明，机体内 AKT 的负向调节因子通过抑制 AKT2 的功能，加剧 DCM 患者心脏中的胰岛素抵抗。其中 AKT2 的主要负向调节因子有磷酸酶和张力素同系物 (Phosphoatase and tensin homolog, PTEN) [12]，蛋白酪氨酸磷酸酶 1B (ProteinTyrosine Phosphatase-1B, PTP-1B) [13]和 Tribbles 同源蛋白 3 (tribble homolog 3, TRB3) [14]，诱导其下调对改善胰岛素抵抗引起的 GLUT4 易位减少提供了潜在方向。相关研究也证实，金属硫蛋白通过抑制糖尿病心脏中的 TRB3 来保留 Akt2 活性改善了 GLUT4 的易位减少，保护了心脏的正常功能[15]。8-C-Ascorbyl-(−)-儿茶素(8-C-Ascorbyl-(−)-epigallocatechin, AE)通过抑制 PTP1B 的表达，以及轻微抑制 PTP1B 的活性，显着促进葡萄糖消耗[16]。香芹酚(Carvacrol)通过调节糖尿病小鼠的 PI3K/AKT 途径显著降低 PTEN 磷酸化的表达，改善了 GLUT4 的易位，从而减轻了糖尿病心肌病的发展[17]。神经酰胺(Ceramides, Cers)是由鞘氨醇和脂肪酸组成的一类酰胺化合物。Cers 通过抑制胰岛素诱导的 PI3K-Akt 信号途径，来减弱 GLUT4 易位和胰岛素刺激的葡萄糖摄取[18]。

GLUT4 的易位同时也接受心肌细胞收缩的调控，根据双信号输入假说，收缩信号通过肝激酶 B1 (Liver kinase B1, LKB1)——AMP 活化蛋白激酶(Adenosine 5’-monophosphate-activated protein kinase, AMPK)和死亡相关蛋白激酶(Death-associated protein kinase, DAPK)——蛋白激酶 D1 (Protein Kinase D1, PKD1)通路共同作用诱导 GLUT4 的易位[19]。基于收缩刺激独立于胰岛素刺激 GLUT4 易位的作用，通过增加收缩诱导的 GLUT4 易位可以改善糖尿病患者因胰岛素抵抗而导致的 GLIT4 易位减少。最新研究表明，磷脂酰肌醇-4-激酶-IIIβ (PI4KIIIβ)作为蛋白激酶 D1 (PKD1)下游的一种脂质激酶，可以介导心肌细胞中收缩诱导的 GLUT4 易位，同时不影响 CD36 易位或 LCFA 的摄取[20]。该发现有望使 PI4KIIIβ 成为糖尿病心肌病治疗的新靶标。胰岛素抵抗和心肌收缩均通过 AMPK 通路调控 GLUT4 易位，胰岛素抵抗时 AMPK 活性降低，影响 GLUT4 易位；而心肌收缩通过 AMPK 增加 GLUT4 易位，部分抵消胰岛素抵抗的影响[21]。胰岛素抵抗抑制 PI3K/Akt 通路，减少 GLUT4 易位，但心肌收缩通过 AMPK 和 Ca^{2+}信号通路部分补偿这一效应，增加 GLUT4 易位，改善胰岛素抵抗[20]。此外，研究显示，在糖尿性心肌病中葡萄糖利用率的下降会促进过氧化物酶体增殖物激活受体 α (Peroxisome Proliferator Activated Receptor alpha, PPARα)的表达上调，PPARα 诱导丙酮酸脱氢酶激酶 4 的表达，从而降低丙酮酸脱氢酶活性，更进一步抑制葡萄糖氧化[22]。

2.2. 脂代谢紊乱

心肌细胞对脂肪酸的摄取主要是由脂肪酸转位酶 CD36 介导[23]。CD36 是清道夫受体蛋白超家族(scavenger receptor, SR)的成员-B 类，被正式指定为 SR-B2 [24]，其本质是一种 88-kDa 跨膜蛋白，由 2 个跨膜结构域和一个包含 9 个糖基化位点和 2 个磷酸化位点的大细胞外环组成[25]。心肌细胞脂肪酸摄取速率由 CD36 从内体到心肌细胞膜的囊泡循环调节[26]。在糖尿病性心肌病患者的心肌细胞膜中 CD36 的表达明显上调[27]，在糖尿病早期阶段，胰岛素水平处于高水平状态[28]，胰岛素可以促进位于心肌细胞内的 CD36 向心肌细胞膜易位。在糖尿病晚期阶段，胰岛素的水平下降，心肌细胞对胰岛素产生抵抗，但 CD36 已经永久性地定位到心肌细胞膜上[29]，大量脂肪酸被转运到心肌细胞内，胰岛素水平的下降已无法改变这一事实。心脏脂肪酸的长期过量供应会引发 CD36 亚细胞循环的改变。在正常心脏中，CD36 的总细胞量大致均匀地分布在内体和肌层之间，但在慢性脂质供应过剩后，CD36 主要存在于肌膜上，而内体中的 CD36 则出现下降(即 CD36 从内体易位到肌层) [30]。慢性胰岛素刺激通过转录因子 FOX01 诱导 CD36 mRNA 转译增加 CD36 的表达[31]；相关研究显示，在高浓度葡萄糖作用下，由单核细胞分化的

巨噬细胞中 CD36 mRNA 翻译效率增加，其细胞表面 CD36 表达也相应增加，提示高糖刺激通过诱导 CD36 mRNA 的翻译增加 CD36 的表达[32]。而对大鼠心肌细胞进行免疫化学 CD36 抑制后，大鼠的基础葡萄糖摄取增加、三酰基甘油积累减少、收缩功能障碍得到明显改善[33]。PPARα 是心肌脂肪酸摄取和利用的关键调节因子[34]心肌细胞中过度表达 PPARα 是 DCM 发展的重要因素。有动物实验表明 PPARα 的过度表达导致小鼠发生严重心肌病，而抑制 PPARα 则阻止了小鼠 DCM 的发展。PPARα 负责调节脂肪酸代谢相关基因的表达[35]，研究表明 PPARα 调节脂肪酸代谢的途径之一是通过增加编码 CD36 的基因以增加 CD36 的表达[26]。脂肪酸诱导的 PPAR 激活也反受脂肪酸的诱导，从而使编码参与细胞脂肪酸利用的各种蛋白质和酶的基因表达上调[24]。研究表明，CD36 作为参与全身脂质稳态的关键膜蛋白，已然成为保护心肌细胞免受脂毒性的优选靶标，但是对其具体机制的了解尚且不足[25]。培马贝特(K-877, Parmodia™)是一种新型选择性 PPARα 调节剂，主要由肝脏代谢，激活 PPARα 的有效率是常规贝特类的 2500 倍[36]，其对甘油三酯摄取利用的降低具有良好疗效。在高糖状态下，心脏胰岛素信号传导缺陷使肌膜上 CD36 定位增加，心肌膜上 GLUT4 定位减少[37]。这种胰岛素信号传导的缺陷主要与细胞内甘油三酯积累后，脂肪酸代谢物水平的增加，特别是甘油二酯和神经酰胺这两种化合物的增多有关[38]。GLUT4 和 CD36 的相对易位使心肌摄取葡萄糖的量下降，摄取脂肪酸的量上升从而导致脂类物质在心肌细胞的积累并引发脂中毒[39]。糖尿病产生的脂毒性诱导内皮细胞生成活性氧(reactive oxygen species, ROS)和活性氮(reactive nitrogen species, RNS)，两者导致细胞对一氧化氮 NO 的利用度下降。这种 NO 的利用度下降使细胞内可溶性鸟苷酸环化酶(soluble guanylate cyclase, sGC)活性和环 GMP 水平降低，从而导致蛋白激酶 G 对心肌细胞的保护作用下降，导致血管舒张效应下降[40]。目前有相关的研究实验在探究 CD36 在内体和肌膜之间的囊泡循环机制，其中液泡质子泵(vacuolar H+-ATPase, v-ATP 酶)[41]和特异性囊泡相关膜蛋白(Vesicle-associated membrane protein, VAMP) VAMPs [42]在心肌 CD36 回收中的作用，为靶向 CD36 特异性囊泡运输以治疗脂质积累诱发的心肌损伤提供了思路。

3. 临床展望

糖尿病性心肌病的代谢紊乱研究为临床提供了多个潜在的治疗靶点和诊断标志物。GLUT4 和 CD36 的表达水平可作为 DCM 的诊断和预后生物标志物，通过检测心肌细胞中 GLUT4 和 CD36 的表达水平，来早期诊断 DCM，并评估疾病进展和治疗效果。通过调节 GLUT4 和 CD36 的相对易位，可恢复糖脂代谢平衡，通过开发能够同时调节 GLUT4 和 CD36 易位的药物，或通过饮食和运动干预，改善心肌能量代谢。通过增强心肌收缩或激活 AMPK 通路，可能改善胰岛素抵抗患者的葡萄糖摄取，从而缓解 DCM 的进展，药物开发可以针对 AMPK 或 PI3K/Akt 通路，促进 GLUT4 易位，改善心肌能量代谢。抑制 CD36 易位或减少其表达为治疗 DCM 提供新思路。例如，开发 CD36 抑制剂或调节其囊泡循环机制(如 v-ATP 酶和 VAMP 蛋白)的药物，可能减少心肌脂质积累，改善心脏功能；使用 PPARα 抑制剂或选择性调节剂(如培马贝特)可能有助于改善 DCM 患者的脂代谢紊乱。抗炎和抗氧化治疗可能成为 DCM 的辅助治疗手段，使用抗氧化剂或抗炎药物，减少活性氧(ROS)和活性氮(RNS)的产生，保护心肌细胞免受损伤。PI4KIIIβ 可能成为治疗 DCM 的新靶点。开发针对 PI4KIIIβ 的药物，可能通过促进 GLUT4 易位，改善葡萄糖摄取，而不影响脂肪酸代谢，从而避免脂毒性。

4. 讨论

糖尿病性心肌病作为一种独立的临床病理类型，其具体的相关机制相当复杂，在本综述中，我们在代谢层面对糖尿病性心肌病的相关机制进行了探讨，主要从葡萄糖的 GLUT4 和脂肪酸的 CD36 两种转运相关蛋白展开论述。糖尿病中糖代谢和脂代谢的紊乱是其引发心肌损伤的关键一环，对其具体机制的深

入了解，有助于今后对糖尿病性心肌病相关临床治疗的发展，为预防和延缓其发生发展提供方向。目前对其更深入的探索仍在继续，相信在不远的将来，从代谢层面的相关探索中，对认识、了解、诊断、防治糖尿性心肌病会带来更多进展。

参考文献

[1] Magliano, D.J. and Boyko, E.J. (2021) IDF Diabetes Atlas 10th Edition Scientific Committee. International Diabetes Federation.

[2] Park, J.J. (2021) Epidemiology, Pathophysiology, Diagnosis and Treatment of Heart Failure in Diabetes. *Diabetes & Metabolism Journal*, **45**, 146-157. https://doi.org/10.4093/dmj.2020.0282

[3] Siao, W.Z., Chen, Y.H., Tsai, C.F., Lee, C.M. and Jong, G.P. (2022) Diabetes Mellitus and Heart Failure. *Journal of Personalized Medicine*, **12**, Article 1698. https://doi.org/10.3390/jpm12101698

[4] Yap, J., Tay, W.T., Teng, T.K., Anand, I., Richards, A.M., Ling, L.H., MacDonald, M.R., Chandramouli, C., Tromp, J., Siswanto, B.B., *et al*. (2019) Association of Diabetes Mellitus on Cardiac Remodeling, Quality of Life, and Clinical Outcomes in Heart Failure with Reduced and Preserved Ejection Fraction. *Journal of the American Heart Association*, **8**, e013114. https://doi.org/10.1161/JAHA.119.013114

[5] Lee, H.J., Kim, H.K., Kim, B.S., Han, K.D., Rhee, T.M., Park, J.B., Lee, H., Lee, S.P. and Kim, Y.J. (2022) Impact of Diabetes Mellitus on the Outcomes of Subjects with Hypertrophic Cardiomyopathy: A Nationwide Cohort Study. *Diabetes Research and Clinical Practice*, **186**, Article 109838. https://doi.org/10.1016/j.diabres.2022.109838

[6] Bertrand, L., Horman, S., Beauloye, C. and Vanoverschelde, J.L. (2008) Insulin Signalling in the Heart. *Cardiovascular Research*, **79**, 238-248. https://doi.org/10.1093/cvr/cvn093

[7] Abel, E.D. (2004) Glucose Transport in the Heart. *Frontiers in Bioscience*, **9,** 201-215. https://doi.org/10.2741/1216

[8] Olson, A.L. and Pessin, J.E. (1996) Structure, Function, and Regulation of the Mammalian Facilitative Glucose Transporter Gene Family. *Annual Review of Nutrition*, **16**, 235-256. https://doi.org/10.1146/annurev.nu.16.070196.001315

[9] Fischer, Y., Thomas, J., Sevilla, L., Muñoz, P., Becker, C., Holman, G., Kozka, I.J., Palacín, M., Testar, X., Kammermeier, H. and Zorzano, A. (1997) Insulin-Induced Recruitment of Glucose Transporter 4 ($GLUT_4$) and $GLUT_1$ in Isolated Rat Cardiac Myocytes. Evidence of the Existence of Different Intracellular $GLUT_4$ Vesicle Populations. *Journal of Biological Chemistry*, **272**, 7085-7092. https://doi.org/10.1074/jbc.272.11.7085

[10] Calera, M.R., Martinez, C., Liu, H., *et al*. (1998) Insulin Increases the Association of Akt-2 with $Glut_4$-Containing Vesicles. *Journal of Biological Chemistry*, **273**, 7201-7204. https://doi.org/10.1074/jbc.273.13.7201

[11] Jia, G., DeMarco, V.G. and Sowers, J.R. (2016) Insulin Resistance and Hyperinsulinaemia in Diabetic Cardiomyopathy. *Nature Reviews Endocrinology*, **12**, 144-153. https://doi.org/10.1038/nrendo.2015.216

[12] Chen, C.Y., Chen, J., He, L. and Stiles, B.L. (2018) PTEN: Tumor Suppressor and Metabolic Regulator. *Frontiers in Endocrinology*, **9**, Article 338. https://doi.org/10.3389/fendo.2018.00338

[13] Gum, R.J., Gaede, L.L., Sandra, L., *et al*. (2003) Reduction of Protein Tyrosine Phosphatase 1B Increases Insulin-Dependent Signaling in *ob*/*ob* Mice. *Diabetes*, **52**, 21-28. https://doi.org/10.2337/diabetes.52.1.21

[14] Koh, H.J., Toyoda, T., Didesch, M.M., *et al*. (2013) Tribbles 3 Mediates Endoplasmic Reticulum Stress-Induced Insulin Resistance in Skeletal Muscle. *Nature Communications*, **4**, Article 1871. https://doi.org/10.1038/ncomms2851

[15] Gu, J., Yan, X., Dai, X., *et al*. (2018) Metallothionein Preserves Akt2 Activity and Cardiac Function via Inhibiting TRB3 in Diabetic Hearts. *Diabetes*, **67**, 507-517. https://doi.org/10.2337/db17-0219

[16] Zhang, Y., Chen, M., Tao, Y., Chu, B., Ma, Y., Lu, K. and Sun, H. (2022) Natural 8-C-Ascorbyl-(−)-Epigallocatechin as Antidiabetic Agent: α-Glucosidase and PTP-1B Signaling Pathway dual Regulators. *Fitoterapia*, **162**, Article 105263. https://doi.org/10.1016/j.fitote.2022.105263

[17] Lopaschuk, G.D., Karwi, Q.G., Tian, R., Wende, A.R. and Abel, E.D. (2021) Cardiac Energy Metabolism in Heart Failure. *Circulation Research*, **128**, 1487-1513. https://doi.org/10.1161/CIRCRESAHA.121.318241

[18] Atkinson, L.L., Kozak, R., Kelly, S.E., Onay Besikci, A., Russell, J.C. and Lopaschuk, G.D. (2003) Potential Mechanisms and Consequences of Cardiac Triacylglycerol Accumulation in Insulin-Resistant Rats. *American Journal of Physiology-Endocrinology and Metabolism*, **284**, E923-E930. https://doi.org/10.1152/ajpendo.00360.2002

[19] Luiken, J.J., Glatz, J.F. and Neumann, D. (2015) Cardiac Contraction-Induced GLUT4 Translocation Requires Dual Signaling Input. *Trends in Endocrinology & Metabolism*, **26**, 404-410. https://doi.org/10.1016/j.tem.2015.06.002

[20] Sun, A., Simsek Papur, O., Dirkx, E., Wong, L., Sips, T., Wang, S., Strzelecka, A., Nabben, M., Glatz, J.F.C., Neumann, D. and Luiken, J.J.F.P. (2021) Phosphatidylinositol 4-Kinase IIIβ Mediates Contraction-Induced GLUT4 Translocation and Shows Its Anti-Diabetic Action in Cardiomyocytes. *Cellular and Molecular Life Sciences*, **78**, 2839-2856.

https://doi.org/10.1007/s00018-020-03669-7

[21] Luiken, J.J., Glatz, J.F. and Neumann, D. (2015) Cardiac Contraction-Induced GLUT4 Translocation Requires Dual Signaling Input. *Trends in Endocrinology & Metabolism*, **26**, 404-410. https://doi.org/10.1016/j.tem.2015.06.002

[22] Buchanan, J., Mazumder, P.K., Hu, P., Chakrabarti, G., Roberts, M.W., Yun, U.J., Cooksey, R.C., Litwin, SE. and Abel, E.D. (2005) Reduced Cardiac Efficiency and Altered Substrate Metabolism Precedes the Onset of Hyperglycemia and Contractile Dysfunction in Two Mouse Models of Insulin Resistance and Obesity. *Endocrinology*, **146**, 5341-5349. https://doi.org/10.1210/en.2005-0938

[23] Coort, S.L., Bonen, A., van der Vusse, G.J., Glatz, J.F. and Luiken, J.J. (2007) Cardiac Substrate Uptake and Metabolism in Obesity and Type-2 Diabetes: Role of Sarcolemmal Substrate Transporters. *Molecular and Cellular Biochemistry*, **299**, 5-18. https://doi.org/10.1007/s11010-005-9030-5

[24] Prabhudas, M., Bowdish, D., Drickamer, K., Febbraio, M., Herz, J., Kobzik, L., Krieger, M., Loike, J., Means, T.K., Moestrup, S.K., Post, S., Sawamura, T., Silverstein, S., Wang, X.Y. and El Khoury, J. (2014) Standardizing Scavenger Receptor Nomenclature. *The Journal of Immunology*, **192**, 1997-2006. https://doi.org/10.4049/jimmunol.1490003

[25] Glatz, J.F.C. and Luiken, J.J.F.P. (2018) Dynamic Role of the Transmembrane Glycoprotein CD36 (SR-B2) in Cellular Fatty Acid Uptake and Utilization. *Journal of Lipid Research*, **59**, 1084-1093. https://doi.org/10.1194/jlr.R082933

[26] Glatz, J.F. and Luiken, J.J. (2017) From Fat to FAT (CD36/SR-B2): Understanding the Regulation of Cellular Fatty Acid Uptake. *Biochimie*, **136,** 21-26. https://doi.org/10.1016/j.biochi.2016.12.007

[27] García-Rúa, V., Otero, M.F., Lear, P.V., Rodríguez-Penas, D., Feijóo-Bandín, S., Noguera-Moreno, T., Calaza, M., Álvarez-Barredo, M., Mosquera-Leal, A., Parrington, J., Brugada, J., Portolés, M., Rivera, M., González-Juanatey, J.R. and Lago, F. (2012) Increased Expression of Fatty-Acid and Calcium Metabolism Genes in Failing Human Heart. *PLOS One*, **7**, e37505. https://doi.org/10.1371/journal.pone.0037505

[28] Paolillo, S., Marsico, F., Prastaro, M., Renga, F., Esposito, L., De Martino, F., Di Napoli, P., Esposito, I., Ambrosio, A., Ianniruberto, M., Mennella, R., Paolillo, R. and Gargiulo, P. (2019) Diabetic Cardiomyopathy: Definition, Diagnosis, and Therapeutic Implications. *Heart Failure Clinics*, **15**, 341-347. https://doi.org/10.1016/j.hfc.2019.02.003

[29] Steinbusch, L.K., Schwenk, R.W., Ouwens, D.M., Diamant, M., Glatz, J.F. and Luiken, J.J. (2011) Subcellular Trafficking of the Substrate Transporters GLUT4 and CD36 in Cardiomyocytes. *Cellular and Molecular Life Sciences*, **68**, 2525-2538. https://doi.org/10.1007/s00018-011-0690-x

[30] Glatz, J.F.C., Luiken, J.J.F.P. and Nabben, M. (2020) CD36 (SR-B2) As a Target to Treat Lipid Overload-Induced Cardiac Dysfunction. *Journal of Lipid and Atherosclerosis*, **9**, 66-78. https://doi.org/10.12997/jla.2020.9.1.66

[31] Chistiakov, D.A., Orekhov, A.N. and Bobryshev, Y.V. (2017) The Impact of FOXO-1 to Cardiac Pathology in Diabetes Mellitus and Diabetes-Related Metabolic Abnormalities. *International Journal of Cardiology*, **245,** 236-244. https://doi.org/10.1016/j.ijcard.2017.07.096

[32] Griffin, E., Re, A., Hamel, N., Fu, C., Bush, H., McCaffrey, T. and Asch, A.S. (2001) A Link between Diabetes and Atherosclerosis: Glucose Regulates Expression of CD36 at the Level of Translation. *Nature Medicine*, **7**, 840-846. https://doi.org/10.1038/89969

[33] Angin, Y., Steinbusch, L.K., Simons, P.J., Greulich, S., Hoebers, N.T., Douma, K., van Zandvoort, M.A., Coumans, W.A., Wijnen, W., Diamant, M., Ouwens, D.M., Glatz, J.F. and Luiken, J.J. (2012) CD36 Inhibition Prevents Lipid Accumulation and Contractile Dysfunction in Rat Cardiomyocytes. *Biochemical Journal*, **448**, 43-53. https://doi.org/10.1042/BJ20120060

[34] Finck, B.N., Lehman, J.J., Leone, T.C., Welch, M.J., Bennett, M.J., Kovacs, A., Han, X., Gross, R.W., Kozak, R., Lopaschuk, G.D. and Kelly, D.P. (2002) The Cardiac Phenotype Induced by PPARα Overexpression mimics that Caused by Diabetes Mellitus. *Journal of Clinical Investigation*, **109**, 121-130. https://doi.org/10.1172/JCI0214080

[35] Steinmetz, M., Quentin, T., Poppe, A., Paul, T. and Jux, C. (2005) Changes in Expression Levels of Genes Involved in Fatty Acid Metabolism: Upregulation of All Three Members of the PPAR Family (α, γ, δ) and the Newly Described Adiponectin Receptor 2, But Not Adiponectin Receptor 1 during Neonatal Cardiac Development of the Rat. *Basic Research in Cardiology*, **100**, 263-269. https://doi.org/10.1007/s00395-005-0520-0

[36] Yamashita, S., Masuda, D. and Matsuzawa, Y. (2020) Pemafibrate, a New Selective PPARα Modulator: Drug Concept and Its Clinical Applications for Dyslipidemia and Metabolic Diseases. *Current Atherosclerosis Reports*, **22**, Article No. 5. https://doi.org/10.1007/s11883-020-0823-5

[37] Ramírez, E., Picatoste, B., González-Bris, A., Oteo, M., Cruz, F., Caro-Vadillo, A., Egido, J., Tuñón, J., Morcillo, M.A. and Lorenzo, Ó. (2018) Sitagliptin Improved Glucose Assimilation in Detriment of Fatty-Acid Utilization in Experimental Type-II Diabetes: Role of GLP-1 Isoforms in Glut4 Receptor Trafficking. *Cardiovascular Diabetology*, **17**, Article No. 12. https://doi.org/10.1186/s12933-017-0643-2

[38] Shulman, G.I. (2000) Cellular Mechanisms of Insulin Resistance. *Journal of Clinical Investigation*, **106**, 171-176. https://doi.org/10.1172/JCI10583

[39] 陈艳艳, 周洁, 卢作维, 李梦颖, 马溪悦, 李晓苗. 糖尿病心肌病发病机制及治疗研究进展[J]. 解放军医学杂志, 2023, 48(8): 957-964.

[40] Franssen, C., Chen, S., Unger, A., *et al*. (2016) Myocardial Microvascular Inflammatory Endothelial Activation in Heart Failure with Preserved Ejection Fraction. *JACC*: *Heart Failure*, 4, 312-324. https://doi.org/10.1016/j.jchf.2015.10.007

[41] Liu, Y., Steinbusch, L.K.M., Nabben, M., Kapsokalyvas, D., van Zandvoort, M., Schönleitner, P., Antoons, G., Simons, P.J., Coumans, W.A., Geomini, A., Chanda, D., Glatz, J.F.C., Neumann, D. and Luiken, J.J.F.P. (2017) Palmitate-Induced Vacuolar-Type H^+-ATPase Inhibition Feeds Forward into Insulin Resistance and Contractile Dysfunction. *Diabetes*, **66**, 1521-1534. https://doi.org/10.2337/db16-0727

[42] Luiken, J.J.F.P., Nabben, M., Neumann, D. and Glatz, J.F.C. (2020) Understanding the Distinct Subcellular Trafficking of CD36 and GLUT4 during the Development of Myocardial Insulin Resistance. *Biochimica et Biophysica Acta* (*BBA*)-*Molecular Basis of Disease*, **1866**, Article 165775. https://doi.org/10.1016/j.bbadis.2020.165775