心房能量代谢重塑和 PPARγ 靶向干预在心房颤动中的研究进展

喜林强　孙华鑫　商鲁翔　汤宝鹏　周贤惠
（新疆医科大学第一附属医院心脏起搏与电生理科/新疆心电生理与心脏重塑重点实验室，新疆 乌鲁木齐 830054）

【摘要】心房颤动（房颤）是临床常见的心律失常，具有高死亡率和致残风险。心房重塑（电、结构重塑）与房颤发病密切相关。成熟心肌细胞向胎儿表型的转换、线粒体功能障碍和活性氧过载的细胞效应等生物学事件参与心房重塑。过氧化物酶体增殖物激活受体（PPAR）是心肌细胞能量代谢调控的关键开关。对房颤能量重塑、心房肌细胞代谢紊乱调控机制的研究，特别是针对 PPARγ 介导的糖脂代谢表型转换的干预，可能成为房颤治疗的新策略。

【关键词】心房颤动；心肌能量代谢；过氧化物酶体增殖物激活受体 γ；线粒体；吡格列酮
【DOI】10.16806/j.cnki.issn.1004-3934.2023.10.014

Atrial Energy Metabolism Remodeling and Targeted Intervention of PPARγ in Atrial Fibrillation

XI Linqiang, SUN Huaxin, SHANG Luxiang, TANG Baopeng, ZHOU Xianhui
(*Cardiac Pacing and Electrophysiology/Department of Cardiac Electrophysiology and Remodeling, The First Affiliated Hospital of Xinjiang Medical University, Urumqi* 830054, *Xinjiang, China*)

【**Abstract**】Atrial fibrillation is a common arrhythmia with high mortality and disability. Atrial remodeling (electrical and structural remodeling) is closely related to the pathogenesis of atrial fibrillation. Biological events such as the transition of mature cardiomyocytes to fetal phenotype, mitochondrial dysfunction and cellular effects of reactive oxygen species overload are involved in atrial remodeling. Peroxisome proliferator-activated receptor (PPAR) is a key switch in the regulation of energy metabolism in cardiomyocytes. The studies on the regulation mechanism of atrial fibrillation energy remodeling and atrial myocyte metabolic disorder, especially the intervention of glucose and lipid metabolism phenotype switching mediated by PPARγ, may become a new strategy for the treatment of atrial fibrillation.

【**Key words**】Atrial fibrillation; Myocardial energy metabolism; Peroxisome proliferator-activated receptor γ; Mitochondria; Pioglitazone

心房颤动（房颤）是最常见的心律失常，全球约 6 000万患者[1]。最新流行病学调查[2]显示中国成年人（年龄≥45 岁）的房颤患病率约为 1.8%，年龄 >75 岁的房颤患病率为 5.4%（男）和 4.9%（女）。房颤所致的脑卒中、心力衰竭和阿尔茨海默病等相关并发症严重危害着国民生命健康及影响生活质量，已成为中国公共卫生的沉重负担[3]。目前的研究[4]表明房颤的维持和进展与心房重塑密切相关。近年来心肌能量代谢重塑备受关注，人们逐渐认识到心脏代谢和线粒体功能的改变先于心脏功能的改变，这表明心肌能量代谢重塑是心脏疾病进展的早期事件[5]。由于房颤快速心房节律，心房肌细胞能量代谢也随之变化，长期能量代谢表型转换会导致心房肌细胞能量供需失衡，触发线粒体损伤，参与心房重塑进程。然而，过氧化物酶体增殖物激活受体（peroxisome proliferator-activated receptor，PPAR）被认为是微调节细胞能量代谢的开关，PPARγ 调节细胞精细代谢过程。因此，现拟对心房能量代谢表型及 PPARγ 靶向干预在房颤领域的相关研究进行综述，从心房能量代谢重塑角度为房颤防治整合积累研究证据。

1　结构重塑与电重塑

心房重塑和改变，通过介导心房肌细胞自律性变化、电生理特性变化、细胞间通信障碍、细胞间传导异常、心房间质改变等进一步参与触发活动和心房基质的形成[6]。结构重塑指心房肌实质和间质的超微结构改变，包括心房肌细胞、心房成纤维细胞等的变化。心房电重塑是指房颤引起心房肌有效不应期缩短、动作电位时程缩短和传导速度减慢等心房电生理学特

基金项目：国家自然科学基金（82100343，82260065，82260064，82060069）
通信作者：周贤惠，E-mail：zhouxhuiyf@163.com

性[7]的改变。同时,离子通道水平的重塑促使折返形成和房颤启动[8],Ca^{2+} 自发性释放事件、细胞内钙振荡、钙火花异常等诱发心房复极化的异质性,形成折返和房颤的发生[9]。

2 房颤中的心肌能量代谢重塑

心肌能量代谢稳定是维持心脏组织构造更新和内环境稳态的基础。心脏能量产生途径主要包括:(1)糖酵解;(2)葡萄糖氧化;(3)脂肪酸氧化;(4)三羧酸循环;(5)线粒体中电子传递链。线粒体氧化还原反应产生三磷酸腺苷(adenosine triphosphate, ATP),同时也产生副产物活性氧(reactive oxygen species, ROS)。正常情况下,心脏所需能量的 70% 来源于脂肪酸 β 氧化,10% ~30% 来源于葡萄糖代谢。为了满足能量需求,心脏通过转变底物代谢模式来产生 ATP。为了快速获能,糖酵解途径增强,丙酮酸-乳酸代谢轴激活,葡萄糖通过糖酵解途径转化为丙酮酸作为 ATP 合成的底物。一方面,随着糖酵解模式的逐渐减弱,短期内葡萄糖利用率将提高,但长期内会逐渐适应不良[10];另一方面,脂肪酸氧化模式的逐渐增强将会增加脂肪酸摄取,而线粒体氧化能力不足造成“脂毒性”心肌损伤。

房颤的代谢变化与氧、营养输送减少和/或能量需求增加有关。房颤相关代谢应激涉及增加代谢需求的变化(心脏做功和能量消耗增强)以及限制能量供应的变化(冠状动脉储备、能量底物供应和氧气输送的限制)。当能量供需失衡,心肌细胞代谢表型出现适应性改变。“代谢性重塑”是指在房颤发生后,短时间内即可出现能量代谢的异常,包括心肌细胞磷酸化低、葡萄糖氧化关键酶上调[11],可能是心房肌重塑的基础。虽然这种代谢模式的转化短期内提高了心肌细胞代谢效率,但随着时间的推移,长期线粒体功能不全会减少能量储备并恶化心脏电、机械功能,从而促进房颤底物的发展[12]。Warburg 效应是一种伴随乳酸生成的高速率有氧糖酵解途径。有研究[13]提示该效应参与了房颤时心房“胎儿代谢表型”的转化,此过程中糖的氧化磷酸化受到抑制。据此,Hu 等[14]提出 Warburg 效应参与了房颤的发生与发展,而抑制该效应可改善房颤犬的心房纤维化。

2.1 线粒体功能障碍和 ROS 过载参与房颤进程

线粒体是产生 ATP 的主要场所,也参与了 Ca^{2+} 稳态调节及细胞质内的 Ca^{2+} 缓冲,进而介导心脏兴奋-收缩耦联[15]。线粒体通过自身 DNA 编码线粒体蛋白,维持线粒体形态、功能和心脏生理功能[16]。房颤患者的心房肌细胞中,氧化应激和线粒体 DNA 损伤普遍存在,提示线粒体的生物能量功能受损和房颤发生、进展之间存在相关性。在起搏诱导的 HL-1 细胞房颤模型中,已观察到 ATP 水平降低、线粒体膜电位损失和线粒体网络断裂,易化房颤底物参与房颤进展[17]。此外,当线粒体功能受损,细胞内 ATP 浓度降低时,肌膜 K_{ATP} 开放,增加的 K_{ATP} 使膜超极化并缩短动作电位时程,促进房颤折返发生[18]。

ROS 产生速率和清除机制决定着组织或细胞的健康状态[19]。当 ROS 产生过量或抗氧化系统清除活性降低时,ROS 的平衡随之紊乱,导致房颤发生[19]。ROS 过载所驱动的氧化应激反应会加剧线粒体损伤,自身 DNA 破坏、线粒体膜通透性转换孔开放、细胞色素 C 逃逸、代谢信号通路异常激活,甚至核 DNA 损伤及基因组不稳定,最终促进心房重塑和房颤进展[20]。同时 ROS 的蓄积还可以介导细胞膜上多种通道转运体功能和离子流的变化。在线粒体氧化应激情况下,Na^+ 电流构成的慢失活电流部分增加,延长动作电位时程。此外,ROS 可致细胞质 Ca^{2+} 超载,肌质网的 Ca^{2+} 减少,使动作电位及后除极延迟,导致收缩功能障碍及 Ca^{2+} 依赖的信号转导障碍等,进而引发异位激动产生和心肌细胞凋亡[21]。最后,ROS 同样可以作用于心脏成纤维细胞而促进心脏间质改变,研究证实 ROS 生成剂过氧亚硝酸盐诱导成纤维细胞核因子 κB 核转位,导致成纤维细胞活化和转化生长因子-β、纤维连接蛋白和Ⅰ型胶原的分泌。ROS 还通过激活转化生长因子-β1 下游靶点 Smad2/3 激活促纤维化信号,ROS 的促纤维化效应可能是心房结构重塑的基础。

2.2 核受体 PPARγ 介导的心房能量代谢表型转换

PPARγ 是一种复杂的转录因子,可调节精细的代谢、炎症和细胞增殖等生物学过程。PPARγ 促进脂肪酸摄取、甘油三酯形成并储存在脂滴中,从而增加胰岛素敏感性和葡萄糖代谢[22]。PPARγ 调控心房肌细胞的底物利用和能量产生[23],并影响细胞内线粒体的功能。

生理状况下,PPARα、PPARβ 和 PPARγ 共激活因子-1α(peroxisome proliferator-activated receptor γ coactivator-1α, PGC-1α)保持高活性,诱导心脏脂肪酸氧化为主要代谢模式,以产生能量并维持生理需求。在病理状态下,部分脂肪酸摄取和线粒体分解代谢的编码基因表达下调,而参与葡萄糖摄取、糖酵解、糖原和脂质储存相关分子的编码基因表达上调,说明存在糖脂代谢模式的切换。尤其在损伤的心肌细胞中,脂肪酸摄取和线粒体脂肪酸氧化则成比例地减少,导致线粒体毒性脂质的积累。病理代偿条件下,肾素-血管紧张素-醛固酮系统等激活,促进缺氧诱导因子(hypoxia inducible factor, HIF)、雷帕霉素靶向机制哺

乳动物雷帕霉素靶蛋白和核因子 κB 信号转导通路激活，下调 PPARα 和 PPARβ 的表达，而 PPARγ 转录活性激活。在 SU5416/缺氧大鼠肺动脉高压和右心室超载模型中，PPARγ 激活经 miRNA-197 和 miRNA-146b 的调节诱导脂肪酸氧化并维持线粒体功能，从而抑制心脏间质胶原的积累[24]。在糖尿病小鼠模型中，激活 PPARγ 通过抑制 ERK1/2 途径来降低心脏纤维化和间质上皮转化[25]。表明 PPARγ 的激活在抑制心肌结构重塑中的作用不可或缺。

2.3 HIF-1α 介导的心房能量代谢表型转换

HIF 是在低氧条件下作出反应的核心因子。生理条件下，HIF-1α 调控无氧糖酵解相关基因的表达，限制丙酮酸的氧化并维持缺氧条件下的乳酸水平[26]。在缺氧时 HIF-1α 进入细胞核，与 HIF-1β 二聚化后结合形成缺氧反应元件发挥转录因子的功能。HIF-1α 对于底物代谢稳态的调控依赖于其对线粒体功能的保护作用。Ambrose 等[27]证实 HIF-1α 失活导致线粒体丢失和脂质积累，以及氧化磷酸化和脂肪酸代谢降低。在房颤患者的心房组织中，细胞膜脂肪酸转运蛋白下调，而激活态的磷酸腺苷活化的蛋白激酶上调，这种细胞内脂肪酸摄取与氧化的不匹配进一步解释了房颤状态下心房过度的脂质积累[28]。而上调 HIF-1α 通过限制三羧酸循环活性，上调线粒体蛋白磷酸肌醇依赖性蛋白激酶-1 及促凋亡调节蛋白 3[29]降低线粒体质量可减轻心肌脂毒性。

有趣的是，部分基础研究表明 HIF-1α 可能是 PPARγ 的上游调节分子。在肥厚型心肌病模型中证实 HIF-1α 的积累与 PPARγ 表达的增加相关[30]。其机制可能是 HIF-1α 直接激活 PPARγ 转录[31]。PPARγ 是甘油三酯合成代谢的主要媒介，通过其转录调控作用促进脂肪酸摄取、甘油-3-磷酸生成和下游酯化过程的转录。这些基因在患病心脏中以 HIF-1α 依赖的方式特异性上调[30]。然而，目前有关 HIF-1α 在心血管系统的保护作用仍存在争议和矛盾观点。多项研究[32]证实激活 HIF-1α 促进包括心脏、肾脏、脉管系统、脂肪组织炎症和纤维化。具体而言，HIF-1α 在转录水平调控炎症因子、促纤维化趋化因子和分泌性胶原分子的表达，但 HIF-1α 在房颤进展中的确切角色仍需进一步探究。

3 心肌能量代谢的干预措施

在发现钠-葡萄糖共转运蛋白 2 抑制剂，如卡格列净等具有抑制氧化应激、炎症、纤维化等作用使心血管获益，而胰高血糖素样肽 1 受体激动剂，如利拉鲁肽等直接作用心肌细胞，抑制心肌细胞凋亡而发挥心脏保护作用后，降血糖药的心脏保护作用备受关注。机制上，卡格列净上调腺苷酸活化蛋白激酶和人去乙酰化酶沉默信息调节因子 1，抑制哺乳动物雷帕霉素靶蛋白和胰岛素样生长因子 1，并调节 HIF-2α/HIF-1α 通路[33]，而腺苷酸活化蛋白依赖的蛋白激酶诱导的磷酸化人去乙酰化酶直接激活 PGC-1α，发挥能量调节效应。PPARγ 激动剂——噻唑烷二酮类药物已被广泛用于 2 型糖尿病的基础治疗。基础研究报告显示吡格列酮对心肌细胞电生理学、能量代谢、缺血再灌注损伤、心脏重塑、神经激素激活、肺循环和双心室收缩舒张功能均产生有益影响。因此，吡格列酮被视为心肌能量代谢相关疾病的潜在治疗药物。

2017 年，一项针对心血管疾病患者和非心血管疾病个体（n = 12 026）的 9 项随机对照荟萃分析[34]表明，吡格列酮降低了主要不良心血管事件的风险，糖尿病前期/胰岛素抵抗为 23%（*OR* = 0.77，95% *CI* 0.64 ~ 0.93），糖尿病为 17%（*OR* = 0.83，95% *CI* 0.72 ~ 0.97）。噻唑烷二酮类药物对体内的心脏代谢影响通常被认为是间接的，继发于降脂特性。在基础研究方面，研究表明尽管血浆游离脂肪酸浓度同时降低，吡格列酮仍可诱导大鼠心肌脂肪摄取增多，PPARγ 激动剂对心肌细胞有直接作用；组织特异性敲除 PPARγ 会诱导心肌细胞肥大，心功能下降并伴有线粒体氧化损伤，而不改变脂质控制和葡萄糖代谢的相关基因的表达[35]，说明 PPARγ 激活有改善心肌脂肪酸利用，恢复糖脂代谢平衡，缓解线粒体损伤等重要作用。

4 靶向药物吡格列酮对房颤的治疗作用

临床研究表明，吡格列酮能延缓 2 型糖尿病合并持续性房颤患者进展为永久性房颤。2017 年对超过 130 000 例糖尿病患者进行的一项荟萃分析[36]结果显示，接受吡格列酮治疗与房颤负荷的降低（*OR* = 0.73，*P* = 0.000 3），房颤发生的风险降低（*OR* = 0.77，*P* = 0.002）以及导管消融术后的复发风险降低（*OR* = 0.41，*P* = 0.002）有关。基础研究证实，吡格列酮通过抗氧化和抗炎作用减弱糖尿病诱导的心房结构重塑和电重塑。吡格列酮有效降低糖尿病心肌病中房颤的诱发率，其分子机制是吡格列酮正向激活 PPARγ/PGC-1α 信号轴，恢复线粒体生物合成、线粒体动力学稳态，逆转心房能量代谢重塑，从而显著缓解糖尿病心肌病模型的心房易感底物。Liu 等[37]明确了吡格列酮通过增加膜电位减轻电重塑来预防房颤，减少血管紧张素Ⅱ诱导的分离的非糖尿病动物心房肌细胞钾通道重塑和 L 型钙通道重塑。吡格列酮可降低人体血浆Ⅲ型胶原发挥抗纤维化作用。在非糖尿病缺血再灌注损伤模型中，吡格列酮通过 PPARγ 依赖性抑制核因子 κB 的途径[38]减少细胞外基质的合成，特别是Ⅰ型和Ⅲ型胶

原、金属蛋白酶组织抑制剂 1 和心脏成纤维细胞中的基质金属蛋白酶-2，而 PPARγ 激动剂降低了动物再灌注心肌中促炎标志物的表达。多项实验[39]表明噻唑烷二酮类药物可抑制 ROS 的产生，抑制线粒体凋亡通路，改善线粒体的生物合成、动力学、结构和功能。

5 总结与展望

目前房颤的药物治疗主要集中于预防卒中、维持窦性心律和稳定心室率三大目标，药物治疗的靶标并非针对驱动房颤的潜在病理生理过程。线粒体功能障碍相关的能量代谢重塑已被确定为房颤的促成因素之一。当前，从线粒体功能障碍、心房能量代谢重塑角度入手，旨在明确心房能量重塑、代谢重塑在房颤发病机制中的地位，并努力识别更多关键的分子靶点。其中，HIF-1α/PPARγ 所介导的心肌糖脂代谢调控过程及其调控机制也需要详细阐释。作为 PPARγ 靶向激动剂，笔者在有限的初步证据中观察到了其靶向干预在改善心房重塑、房颤能量代谢底物中的潜力。未来需要更多的直接实验证据阐明心房能量代谢重塑与房颤的因果关系，并针对 PPARγ 靶点开展更多深入的机制探索研究。

参 考 文 献

[1] Essien UR, Kornej J, Johnson AE, et al. Social determinants of atrial fibrillation [J]. Nat Rev Cardiol, 2021, 18(11): 763-773.

[2] Du X, Guo L, Xia S, et al. Atrial fibrillation prevalence, awareness and management in a nationwide survey of adults in China [J]. Heart, 2021, 107(7): 535-541.

[3] Burdett P, Lip GYH. Atrial fibrillation in the UK: predicting costs of an emerging epidemic recognizing and forecasting the cost drivers of atrial fibrillation-related costs [J]. Eur Heart J Qual Care Clin Outcomes, 2022, 8(2): 187-194.

[4] Wijesurendra RS, Casadei B. Mechanisms of atrial fibrillation [J]. Heart, 2019, 105(24): 1860-1867.

[5] Xia W, Li X, Wu Q, et al. The importance of caveolin as a target in the prevention and treatment of diabetic cardiomyopathy [J]. Front Immunol, 2022, 13: 951381.

[6] Chen YC, Voskoboinik A, Gerche A, et al. Prevention of pathological atrial remodeling and atrial fibrillation: JACC state-of-the-art review [J]. J Am Coll Cardiol, 2021, 77(22): 2846-2864.

[7] Tribulova N, Egan Benova T, Szeiffova Bacova B, et al. New aspects of pathogenesis of atrial fibrillation: remodelling of intercalated discs [J]. J Physiol Pharmacol, 2015, 66(5): 625-634.

[8] Landstrom AP, Dobrev D, Wehrens XHT. Calcium signaling and cardiac arrhythmias [J]. Circ Res, 2017, 120(12): 1969-1993.

[9] Heijman J, Muna AP, Veleva T, et al. Atrial myocyte NLRP3/CaMK Ⅱ nexus forms a substrate for postoperative atrial fibrillation [J]. Circ Res, 2020, 127(8): 1036-1055.

[10] Zhou B, Caudal A, Tang X, et al. Upregulation of mitochondrial ATPase inhibitory factor 1 (ATPIF1) mediates increased glycolysis in mouse hearts [J]. J Clin Invest, 2022, 132(10): e155333.

[11] Guan D, Xiong Y, Borck PC, et al. Diet-induced circadian enhancer remodeling synchronizes opposing hepatic lipid metabolic processes [J]. Cell, 2018, 174(4): 831-842. e12.

[12] Emelyanova L, Ashary Z, Cosic M, et al. Selective downregulation of mitochondrial electron transport chain activity and increased oxidative stress in human atrial fibrillation [J]. Am J Physiol Heart Circ Physiol, 2016, 311(1): H54-H63.

[13] Davogustto G, Dillon W, Salazar R, et al. The Warburg effect in the heart: increased glucose metabolism drives car-diomyocyte hypertrophy in response to adrenergic stimulation [J]. J Am Coll Cardiol, 2018, 71(11): A802-A812. 14.

[14] Hu HJ, Zhang C, Tang ZH, et al. Regulating the Warburg effect on metabolic stress and myocardial fibrosis remodeling and atrial intracardiac waveform activity induced by atrial fibrillation [J]. Biochem Biophys Res Commun, 2019, 516(3): 653-660.

[15] Garbincius JF, Elrod JW. Mitochondrial calcium exchange in physiology and disease [J]. Physiol Rev, 2022, 102(2): 893-992.

[16] Kummer E, Ban N. Mechanisms and regulation of protein synthesis in mitochondria [J]. Nat Rev Mol Cell Biol, 2021, 22(5): 307-325.

[17] Wiersma M, van Marion DMS, Wüst RCI, et al. Mitochondrial dysfunction underlies cardiomyocyte remodeling in experimental and clinical atrial fibrillation [J]. Cells, 2019, 8(10): 1202.

[18] Foster MN, Coetzee WA. K_{ATP} channels in the cardiovascular system [J]. Physiol Rev, 2016, 96(1): 177-252.

[19] Brown SM, Larsen NK, Thankam FG, et al. Fetal cardiomyocyte phenotype, ketone body metabolism, and mitochondrial dysfunction in the pathology of atrial fibrillation [J]. Mol Cell Biochem, 2021, 476(2): 1165-1178.

[20] Zhang D, Wu CT, Qi X, et al. Activation of histone deacetylase-6 induces contractile dysfunction through derailment of α-tubulin proteostasis in experimental and human atrial fibrillation [J]. Circulation, 2014, 129(3): 346-358.

[21] Boyman L, Karbowski M, Lederer WJ. Regulation of mitochondrial ATP production: Ca^{2+} signaling and quality control [J]. Trends Mol Med, 2020, 26(1): 21-39.

[22] Montaigne D, Butruille L, Staels B. PPAR control of metabolism and cardiovascular functions [J]. Nat Rev Cardiol, 2021, 18(12): 809-823.

[23] Pol CJ, Lieu M, Drosatos K. PPARs: protectors or opponents of myocardial function? [J]. PPAR Res, 2015, 2015: 835985.

[24] Legchenko E, Chouvarine P, Borchert P, et al. PPARγ agonist pioglitazone reverses pulmonary hypertension and prevents right heart failure via fatty acid oxidation [J]. Sci Transl Med, 2018, 10(438): eaao0303.

[25] Yan XL, Wang YY, Yu ZF, et al. Peroxisome proliferator-activated receptor-gamma activation attenuates diabetic cardiomyopathy via regulation of the TGF-β/ERK pathway and epithelial-to-mesenchymal transition [J]. Life Sci, 2018, 213: 269-278.

[26] Taylor CT, Scholz CC. The effect of HIF on metabolism and immunity [J]. Nat Rev Nephrol, 2022, 18(9): 573-587.

[27] Ambrose LJA, Abd-Jamil AH, Gomes RSM, et al. Investigating mitochondrial metabolism in contracting HL-1 cardiomyocytes following hypoxia and pharmacological HIF activation identifies HIF-dependent and independent mechanisms of regulation [J]. J Cardiovasc Pharmacol Ther, 2014, 19(6): 574-585.

[28] Suffee N, Baptista E, Piquereau J, et al. Impacts of a high-fat diet on the metabolic profile and the phenotype of atrial myocardium in mice [J]. Cardiovasc Res, 2022, 118(15): 3126-3139.

[29] Lim SA, Moon Y, Shin MH, et al. Hypoxia-driven HIF-1α activation reprograms pre-activated NK cells towards highly potent effector phenotypes via ERK/STAT3 pathways [J]. Cancers (Basel), 2021, 13(8): 1904.

[30] Krishnan J, Suter M, Windak R, et al. Activation of a HIF1α-PPARγ axis underlies the integration of glycolytic and lipid anabolic pathways in pathologic cardiac hypertrophy [J]. Cell Metab, 2009, 9(6): 512-524.

[31] Liu Y, Zhang Q, Yang L, et al. Viametformin attenuates cardiac hypertrophy the HIF-1α/PPAR-γ signaling pathway in high-fat diet rats [J]. Front Pharmacol, 2022, 13: 919202.

（下转第 938 页）

[14] Ajima R, Sakakibara Y, Sakurai-Yamatani N, et al. Formal proof of the requirement of MESP1 and MESP2 in mesoderm specification and their transcriptional control via specific enhancers in mice[J]. Development, 2021, 148(20): dev194613.

[15] Wang H, Yang Y, Liu J, et al. Direct cell reprogramming: approaches, mechanisms and progress[J]. Nat Rev Mol Cell Biol, 2021, 22(6): 410-424.

[16] Garry GA, Bassel-Duby R, Olson EN. Direct reprogramming as a route to cardiac repair[J]. Semin Cell Dev Biol, 2022, 122: 3-13.

[17] Xie Y, Liu J, Qian L. Direct cardiac reprogramming comes of age: recent advance and remaining challenges[J]. Semin Cell Dev Biol, 2022, 122: 37-43.

[18] Isomi M, Sadahiro T, Yamakawa H, et al. Overexpression of Gata4, Mef2c, and Tbx5 generates induced cardiomyocytes via direct reprogramming and rare fusion in the heart[J]. Circulation, 2021, 143(21): 2123-2125.

[19] Tang Y, Aryal S, Geng X, et al. Tbx20 improves contractility and mitochondrial function during direct human cardiac reprogramming[J]. Circulation, 2022, 146(20): 1518-1536.

[20] Wang L, Liu Z, Yin C, et al. Stoichiometry of Gata4, Mef2c, and Tbx5 influences the efficiency and quality of induced cardiac myocyte reprogramming[J]. Circ Res, 2015, 116(2): 237-244.

[21] Stone NR, Gifford CA, Thomas R, et al. Context-specific transcription factor functions regulate epigenomic and transcriptional dynamics during cardiac reprogramming[J]. Cell Stem Cell, 2019, 25(1): 87-102. e9.

[22] Paoletti C, Divieto C, Tarricone G, et al. Microrna-mediated direct reprogramming of human adult fibroblasts toward cardiac phenotype[J]. Front Bioeng Biotechnol, 2020, 8: 529.

[23] Zhong Z, Hou J, Zhang Q, et al. Circulating microRNA expression profiling and bioinformatics analysis of dysregulated microRNAs of patients with coronary artery disease[J]. Medicine (Baltimore), 2018, 97(27): e11428.

[24] Baksh SS, Hodgkinson CP. Conservation of miR combo based direct cardiac reprogramming[J]. Biochem Biophys Rep, 2022, 31: 101310.

[25] Garbutt TA, Zhou Y, Keepers B, et al. An optimized protocol for human direct cardiac reprogramming[J]. STAR Protoc, 2020, 1(1): 100010.

[26] Jiang L, Liang J, Huang W, et al. Strategies and challenges to improve cellular programming-based approaches for heart regeneration therapy[J]. Int J Mol Sci, 2020, 21(20): 7662.

[27] Wang H, Cao N, Spencer CI, et al. Small molecules enable cardiac reprogramming of mouse fibroblasts with a single factor, Oct4[J]. Cell Rep, 2014, 6(5): 951-960.

[28] Werner JH, Rosenberg Jh, UM JY, et al. Molecular discoveries and treatment strategies by direct reprogramming in cardiac regeneration[J]. Transl Res, 2019, 203: 73-87.

[29] Yamakawa H, Ieda M. Cardiac regeneration by direct reprogramming in this decade and beyond[J]. Inflamm Regen, 2021, 41(1): 20.

[30] Abad M, Hashimoto H, Zhou H, et al. Notch inhibition enhances cardiac reprogramming by increasing Mef2C transcriptional activity[J]. Stem Cell Reports, 2017, 8(3): 548-560.

[31] Bektik E, Sun Y, Dennis AT, et al. Inhibition of CREB-CBP signaling improves fibroblast plasticity for direct cardiac reprogramming[J]. Cells, 2021, 10(7): 1572.

[32] Kurotsu S, Sadahiro T, Fujita R, et al. Soft matrix promotes cardiac reprogramming via inhibition of YAP/TAZ and suppression of fibroblast signatures[J]. Stem Cell Reports, 2020, 15(3): 612-628.

[33] Herum KM, Choppe J, Kumar A, et al. Mechanical regulation of cardiac fibroblast profibrotic phenotypes[J]. Mol Biol Cell, 2017, 28(14): 1871-1882.

[34] Song SY, Yoo J, Go S, et al. Cardiac-mimetic cell-culture system for direct cardiac reprogramming[J]. Theranostics, 2019, 9(23): 6734-6744.

[35] Li Y, Dal-Pra S, Mirotsou M, et al. Tissue-engineered 3-dimensional (3D) microenvironment enhances the direct reprogramming of fibroblasts into cardiomyocytes by microRNAs[J]. Sci Rep, 2016, 6: 38815.

[36] Paoletti C, Marcello E, Melis ML, et al. Cardiac tissue-like 3D microenvironment enhances route towards human fibroblast direct reprogramming into induced cardiomyocytes by microRNAs[J]. Cells, 2022, 11(5): 800.

[37] Kim H, Song BW, Park SJ, et al. Ultraefficient extracellular vesicle-guided direct reprogramming of fibroblasts into functional cardiomyocytes[J]. Sci Adv, 2022, 8(8): eabj6621.

[38] Chang Y, Lee E, Kim J, et al. Efficient in vivo direct conversion of fibroblasts into cardiomyocytes using a nanoparticle-based gene carrier[J]. Biomaterials, 2019, 192: 500-509.

[39] Wang Q, Song Y, Chen J, et al. Direct in vivo reprogramming with non-viral sequential targeting nanoparticles promotes cardiac regeneration[J]. Biomaterials, 2021, 276: 121028.

[40] Vaseghi H, Liu J, Qian L. Molecular barriers to direct cardiac reprogramming[J]. Protein Cell, 2017, 8(10): 724-734.

[41] Chen Y, Yang Z, Zhao ZA, et al. Direct reprogramming of fibroblasts into cardiomyocytes[J]. Stem Cell Res Ther, 2017, 8(1): 118.

[42] Sauls K, Greco TM, Wang L, et al. Initiating events in direct cardiomyocyte reprogramming[J]. Cell Rep, 2018, 22(7): 1913-1922.

收稿日期：2022-09-16

（上接第 929 页）

[32] Ban JJ, Ruthenborg RJ, Cho KW, et al. Regulation of obesity and insulin resistance by hypoxia-inducible factors[J]. Hypoxia (Auckl), 2014, 2: 171-183.

[33] Hoong CWS, Chua MWJ. SGLT2 inhibitors as calorie restriction mimetics: insights on longevity pathways and age-related diseases[J]. Endocrinology, 2021, 162(8): bqab079.

[34] Liao HW, Saver JL, Wu YL, et al. Pioglitazone and cardiovascular outcomes in patients with insulin resistance, pre-diabetes and type 2 diabetes: a systematic review and meta-analysis[J]. BMJ Open, 2017, 7(1): e013927.

[35] Zhang Z, Zhang X, Meng L, et al. Pioglitazone inhibits diabetes-induced atrial mitochondrial oxidative stress and improves mitochondrial biogenesis, dynamics, and function through the PPAR-γ/PGC-1α signaling pathway[J]. Front Pharmacol, 2021, 12: 658362.

[36] Zhang Z, Zhang X, Korantzopoulos P, et al. Thiazolidinedione use and atrial fibrillation in diabetic patients: a meta-analysis[J]. BMC Cardiovasc Disord, 2017, 17(1): 96.

[37] Liu C, Liu R, Fu H, et al. Pioglitazone attenuates atrial remodeling and vulnerability to atrial fibrillation in alloxan-induced diabetic rabbits[J]. Cardiovasc Ther, 2017, 35(5). DOI: 10.1111/1755-5922.12284.

[38] Ploeg MC, Munts C, Prinzen FW, et al. Piezo1 mechanosensitive ion channel mediates stretch-induced Nppb expression in adult rat cardiac fibroblasts[J]. Cells, 2021, 10(7): 1745.

[39] Fernandez-Boyanapalli RF, Frasch SC, Thomas SM, et al. Pioglitazone restores phagocyte mitochondrial oxidants and bactericidal capacity in chronic granulomatous disease[J]. J Allergy Clin Immunol, 2015, 135(2): 517-527. e12.

收稿日期：2023-01-12