过氧化物酶体增殖物激活受体α在代谢性心血管疾病中的研究进展

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摘要: 代谢性心血管疾病是一类由肥胖、高血压、代谢相关性脂肪性肝病 (metabolic-associated fatty liver disease, MAFLD) 和糖尿病等代谢危险因素共同驱动的心血管疾病, 其发生发展与代谢紊乱、炎症反应等病理过程密切相关。过氧化物酶体增殖物激活受体α (peroxisome proliferator-activated receptor α, PPARα) 作为核受体超家族成员, 对维持机体代谢稳态至关重要。近年研究表明, PPARα可通过调控机体脂质代谢、抑制炎症及氧化应激等, 在代谢性心血管疾病中发挥保护作用。本文系统综述PPARα的分子结构及其生物学功能, 重点讨论其在代谢性心血管疾病中的作用机制, 并对PPARα激动剂在临床前研究与临床试验中的疗效及面临的挑战进行总结, 以期为代谢性心血管疾病防治提供理论依据和策略方向。

关键词: 代谢性心血管疾病; 肥胖; 高血压; 糖尿病; 过氧化物酶体增殖物激活受体α

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The role of peroxisome proliferator-activated receptor α in metabolic cardiovascular diseases

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Abstract: Metabolic cardiovascular diseases are a category of cardiovascular conditions driven by metabolic risk factors, such as obesity, hypertension, metabolic-associated fatty liver disease (MAFLD), and diabetes, in which metabolism disturbance and inflammatory responses are key contributors. Peroxisome proliferator-activated receptor α (PPARα), a member of the nuclear receptor superfamily, plays a critical role in the maintenance of metabolic homeostasis. Recent studies have indicated that PPARα exerts beneficial effects on metabolic cardiovascular diseases *via* regulating lipid metabolism, inflammatory responses, and mitigating oxidative stress. This review summarized the molecular structure and biological functions of PPARα, with a focus on the underlying mechanisms in PPARα regulating metabolic cardiovascular diseases and translational significance of PPARα agonists in preclinical-clinical studies, aiming to establish novel therapeutic paradigms for these disorders.

Key words: metabolic cardiovascular disease; obesity; hypertension; diabetes; peroxisome proliferator-activated receptor α

代谢性心血管疾病是一类由肥胖、高血压、糖尿病等代谢危险因素共同驱动的心血管疾病[1]。流行病学显示, 我国成年人超重/肥胖患病率50.7%、高血压患病率31.6%、糖尿病患病率11.2%, 导致代谢性心血管

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疾病发生率显著升高[2]。因此, 深入研究代谢性心血管疾病的分子机制, 寻找有效的调控靶点并开发相应治疗药物, 具有重要临床意义。过氧化物酶体增殖物激活受体 α (peroxisome proliferator-activated receptors α, PPARα) 在调控机体脂质代谢、抑制炎症与氧化应激中发挥关键作用, 是代谢性心血管疾病领域一个具有重要开发潜力的治疗靶点[3]。本文系统综述PPARα在代谢性心血管疾病中的作用及机制, 以期为临床开发PPARα激动剂作为代谢性心血管疾病治疗药物提供更多科学依据。

1 PPARα概述

1.1 PPARα分子结构

PPARα属于核受体超家族成员, 其作为配体依赖的转录因子, 在与相应配体结合后, 进一步与靶基因启动子区的特定反应元件结合, 调控下游靶基因转录。PPARα包含4个特征性功能结构域[4]: ① A/B结构域是非配体依赖的转录激活功能域, 此区域含激活功能域-1 (activation function-1, AF-1), 其通过与转录共激活因子直接结合, 借助组蛋白乙酰转移酶介导染色质构象改变, 启动靶基因基础转录, AF-1磷酸化修饰与否可动态调控PPARα转录活性。② C结构域是DNA结合结构域 (DNA-binding domain, DBD), 此区域由70个氨基酸构成, 含有两段锌指结构基元, 该结构域与视黄醛X受体 (retinoid X receptor, RXR) 的DBD形成异源二聚体, 进而与靶基因启动子区的过氧化物酶体增殖物反应元件 (peroxisome proliferator responsive element, PPRE) 高效结合。③ D结构域是转录活性调节结构域, 此区域是连接DBD与配体结合域 (ligand-binding domain, LBD) 的铰链区, 受翻译后修饰调控构象变化, 动态调节核受体共抑制因子与共激活因子的结合−解离平衡, 实现PPARα的活性调控。④ E/F结构域作为LBD, 选择性结合内源性配体 (如脂肪酸衍生物二十碳五烯酸、白三烯B4) 或外源性配体 (如非诺贝特等), 引发配体依赖性激活功能并诱导AF-2基序构象重排, 暴露共激活因子并解除辅阻遏因子抑制作用, 最终形成活性PPARα转录激活复合物[4]。

1.2 PPARα的生物学作用

PPARα广泛表达于机体各类代谢活跃的组织和细胞, 如肝脏、心脏、肾脏、骨骼肌等, 在生理功能调节中发挥关键作用[3]。

1.2.1 PPARα调控机体脂质代谢 在脂质代谢调控方面, PPARα的核心功能是促进脂肪酸转运、摄取及氧化利用, 以维持全身脂质稳态。PPARα通过上调脂肪酸转运蛋白 (fatty acid transport protein, FATP) (如分化簇36, cluster of differentiation 36, CD36) 与脂肪酸结合蛋白 (fatty acid-binding protein, FABP) [如脂肪酸结合蛋白1 (FABP1)] 水平, 增强心脏、肝脏等高代谢组织对游离脂肪酸的摄取[5]。同时, PPARα直接促进其靶基因肉碱棕榈酰转移酶1A (carnitine palmitoyltransferase 1A, CPT1A) 表达, 使长链脂肪酸通过肉碱穿梭系统进入线粒体, 并上调其另一靶基因过氧化物酶体限速酶乙酰辅酶A氧化酶1 (acyl-CoA oxidase 1, ACOX1) 表达, 从而驱动脂肪酸氧化 (fatty acid oxidation, FAO) 过程, 这是降低细胞内及循环中甘油三酯水平的核心机制[6]。此外, PPARα还通过诱导脂蛋白脂肪酶 (lipoprotein lipase, LPL) 表达, 抑制极低密度脂蛋白 (very low density lipoprotein, VLDL) 分泌等途径, 协同降低血清甘油三酯及脂肪酸水平, 减轻脂毒性, 进一步维持机体脂质代谢平衡[7]。

1.2.2 PPARα抑制炎症及氧化应激 在抑制炎症方面, PPARα的核心机制是反式抑制, 即通过蛋白−蛋白相互作用, 下调核因子-κB (nuclear factor κ-light-chain-enhancer of activated B cells, NF-κB)、激活蛋白-1 (activator protein-1, AP-1) 等促炎转录因子活性, 从而阻止肿瘤坏死因子 α (tumor necrosis factor α, TNFα)、白细胞介素1β (interleukin 1β, IL1β) 等促炎因子的转录, 降低其表达水平[8]。PPARα可与NF-κB的p65亚基直接结合, 阻止其与靶基因NF-κB的反应元件 (NF-κB-RE) 结合, 从而抑制IL6、TNFα、血管细胞黏附分子-1 (vascular cell adhesion molecule-1, VCAM-1) 等基因的表达; PPARα可与AP-1中的c-Jun结合, 干扰其DNA结合能力, 进而抑制环加氧酶-2 (cyclooxygenase-2, COX-2)、单核细胞趋化蛋白1等基因的转录[9]。PPARα也通过结合靶基因 [如NF-κB抑制蛋白α (inhibitor of NF-κB α, IκBα)、白细胞介素1受体拮抗剂 (interleukin 1 receptor antagonist, IL1RA)] 的PPRE, 直接上调抗炎相关基因表达, 抑制炎症[10,11]。此外, 炎症与氧化应激有复杂的相关性, PPARα抑制NF-κB信号通路, 并抑制炎症及其伴发的氧化应激。

2 PPARα与代谢性心血管疾病

2.1 PPARα与肥胖相关心血管疾病

肥胖是心血管疾病的重要独立危险因素。一项基于华人社区成年人群的队列研究表明, 肥胖与颈动脉粥样硬化风险呈显著正相关[12]。肥胖会诱导心包脂肪组织、心外膜脂肪组织和血管周围脂肪组织的异常沉积[13]。长期高糖高脂饮食喂养会导致小鼠患有代谢综合征, 心脏微血管内皮功能障碍, 导致血管内皮细胞脂质蓄积。蓄积的脂质通过小窝蛋白1 (caveolin 1) 的介导, 从血管内皮向心肌细胞转运并大量沉积, 造成心肌细胞中内质网和线粒体关联性膜损伤, 最终导致心脏

重构与功能异常[14]。同时, 脂质超载的脂肪细胞通过坏死等方式诱发慢性代谢应激, 激活核苷酸结合寡聚结构域样受体蛋白3 (nucleotide-binding oligomerization domain-like receptor protein 3, NLRP3) 炎症小体, 导致IL1β等促炎因子释放, 驱动血管炎症及心肌重构[15]。此外, 肥胖状态下交感神经功能激活、副交感神经功能减弱, 正常的心脏功能和血管张力被破坏, 加速心力衰竭等终末期心血管疾病的发生[16]。多项研究表明, PPARα可通过调控机体脂质代谢和抑制炎症及氧化应激作用干预肥胖发展。在高脂饮食诱导肥胖大鼠模型中, PPARα激动剂WY14643通过上调CPT1α的表达, 下调乙酰辅酶A羧化酶2 (acetyl-CoA carboxylase 2, ACC2) 的表达, 维持脂质代谢平衡, 减少心肌脂质蓄积、改善心肌线粒体功能, 从而保护左心室收缩功能[17]。环核苷酸磷酸二酯酶9的抑制剂通过阻断环磷酸鸟苷水解激活信号, 上调PPARα表达及活性, 促进脂肪分解与FAO、增强线粒体功能, 最终可降低肥胖相关心血管损伤[18]。此外, PPARα可上调CD36水平, 并诱导LPL活性增强, 加速循环中的脂肪酸清除[19]。对于抗炎抗氧化作用, 一项针对肥胖和糖尿病相关的心力衰竭的研究表明, PPARα下调TNF、IL1β等炎症因子表达, 减轻心肌炎症, 进而减轻炎症介导的心脏重塑; 同时, PPARα上调抗氧化酶 [如超氧化物歧化酶1 (superoxide dismutase 1, SOD1) 和SOD2] 表达, 清除活性氧, 增强心肌细胞抗氧化能力, 减少心肌细胞凋亡和坏死, 改善心肌细胞活力, 对心脏组织中的代谢应激起保护作用[20]。

肥胖通过脂毒性、炎症激活与神经内分泌失调等多种机制促进心血管病变。PPARα作为关键调控因子, 可通过多途径改善脂代谢、抑制炎症及保护心血管功能, 为肥胖相关心血管疾病的防治提供重要靶点。

2.2 PPARα与高血压相关心血管疾病

高血压增加心脏后负荷, 引发心肌肥厚与心力衰竭等心血管并发症[21]。PPARα可降低肾皮层基底外侧Na^+/K^+腺嘌呤核苷酸三磷酸 (adenosine triphosphate, ATP) 酶中α1亚基的蛋白表达和活性, 从而减轻血管紧张素II介导的血压升高[22]。压力超负荷会下调心肌细胞PPARα表达。PPARα缺失时, FAO相关基因 (*Cd36*、*Cpt1b*、*Acox1* 等) 下调, 糖酵解相关基因 [葡萄糖转运体 (glucose transporter type, *Glut*)、己糖激酶 (hexokinase, *Hk*)、丙酮酸激酶 (pyruvate kinase, *Pkm*) 等] 上调, 缺氧诱导因子蛋白水平升高, 心肌依赖葡萄糖供能, 能量产生不足。并且PPARα敲除后, ECM相关基因 (纤维化标志物I型胶原和III型胶原等) 显著上调, 导致心肌间质纤维化加重, 最终加剧心脏重塑与功能障碍[23]。PPARα激动剂氯贝酸, 可缓解血管紧张素II通过下调脂肪甘油三酯脂肪酶 (adipose triglyceride lipase, ATGL) 导致的心房颤动易感性增加[24]。PPARα激动剂非诺贝特对肾血管性高血压大鼠心脏肥大起保护作用。非诺贝特抑制蛋白激酶B (protein kinase B, PKB) 与哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) 磷酸化, 促进AMP依赖的蛋白激酶 (adenosine 5'-monophosphate-activated protein kinase, AMPK) 磷酸化, 直接抑制心肌细胞肥大; 同时, 非诺贝特上调解偶联蛋白2 (uncoupling protein 2, UCP2) 表达, 减少线粒体活性氧生成, 稳定线粒体膜电位, 缓解氧化应激对心肌细胞的损伤; 非诺贝特可显著下调线粒体融合蛋白2 (mitofusin 2, MFN2) 和动力相关蛋白1 (dynamin-related protein 1, DRP1) 的异常高表达, 恢复线粒体融合裂变稳态, 维持线粒体结构完整性, 最终减轻肾血管性高血压及其诱导的心脏肥大[25]。综上, PPARα与高血压形成和心脏重塑相关, 有助于治疗高血压相关心血管疾病。

2.3 PPARα与糖尿病相关心血管疾病

2.3.1 PPARα与糖尿病心肌病 糖尿病心肌病 (diabetic cardiomyopathy, DCM) 是糖尿病常见的心血管并发症, 诸多研究表明PPARα在其中起着重要作用[26]。PPARα通过参与肠道微生物群来源的支链氨基酸 (branched-chain amino acids, BCAA) 所介导的微生物群–肝–心轴, 在糖尿病心肌病中发挥调节作用[27]。1型糖尿病小鼠模型肠道微生物群的BCAA降解能力降低, 导致肠道向循环系统输送的BCAA增多, 过量BCAA会引发心肌细胞凋亡。同时, 过量的BCAA抑制肝脏中的PPARα信号通路, 减少肝脏成纤维细胞生长因子21 (fibroblast growth factor 21, FGF21) 产生, 使心脏中的转录因子含锌指和BTB结构域7C (zinc finger and BTB domain containing 7C, Zbtb7c) 的抑制被解除。Zbtb7c可直接结合L-型氨基酸转运体1 (L-type amino acid transporter 1, *LAT1*) 启动子并激活其转录, 最终使心脏LAT1的表达水平升高。升高的LAT1进一步增加心脏中BCAA的水平, 过量的BCAA激活mTOR信号通路, 导致线粒体损伤和心肌细胞凋亡, 诱发糖尿病小鼠心脏纤维化和功能障碍。既往研究发现, PPARα对DCM具有改善作用。中药思妙永安汤可用于糖尿病和心血管疾病的临床治疗, 体内外研究表明, 其主要活性成分绿原酸和阿魏酸通过上调PPARα水平, 减轻心脏脂毒性, 抑制DCM[28]。泛素特异性蛋白酶28 (ubiquitin specific peptidase 28, USP28) 过表达时, USP28的UCH结构域直接与PPARα的DBD片段结合, 从而促进PPARα在赖氨酸152位点的

去泛素化, 进而促进 *MFN2* 转录, 导致线粒体融合增加, 改善 DCM 病理进程[29]。PR 结构域蛋白 16 (PR domain-containing 16, PRDM16) 是 DCM 的一个保护因子。有研究表明, PPARα 过表达可逆转 2 型糖尿病模型中 PRDM16 心脏特异性缺失引起的细胞功能障碍, 在糖尿病的心肌脂质代谢和线粒体功能中发挥保护作用[30]。糖尿病作为代谢性疾病, 与其他代谢性疾病间存在交互作用。2 型糖尿病与高血压共存时, 过量的脂肪酸激活心肌细胞 mTORC1 下游的 p70 核糖体蛋白 S6 激酶 (70 kDa ribosomal protein S6 kinase, p70S6K) 磷酸化, 抑制过氧化物酶体增殖活化受体 γ 辅助活化因子 1α (peroxisome proliferator-activated receptor-γ coactivator 1α, PGC1α) 表达, 进而下调 PPARα 及其下游靶基因 (如 FAO 关键酶−酰基辅酶 A 脱氢酶、线粒体复合物 II 亚基等) 表达, 导致 FAO 受抑制、ATP 生成不足, 心肌能量稳态失衡, 诱发心力衰竭和 DCM[31]。

然而另有一些研究表明, 在糖尿病小鼠中 PPARα 表达异常升高会促进 DCM 发生发展。糖尿病状态下, PPARα 抑制生长分化因子 11 (growth differentiation factor 11, GDF11) 表达, 从而 GDF11 与含 CARD 结构域的凋亡相关斑点样蛋白的结合减弱, 炎性小体组装激活, 进而造成心肌细胞焦亡、心肌纤维化和心功能损伤[32]。糖尿病状态下, 心肌细胞中 USP7 表达显著升高, 升高的 USP7 作为去泛素化酶, 可直接结合并稳定 PGC1β, 减少 PGC1β 的泛素化降解, 进而增强其对 PPARα 的共激活作用。过度激活的 PPARα 通过上调 CD36、CPT1 等基因, 导致心肌细胞过度摄取和氧化脂肪酸, 使得心肌细胞能量底物从葡萄糖转向脂肪酸, ATP 生成减少, 能量供应不足; PPARα 过度激活还会促进线粒体裂变相关蛋白 [DRP1、线粒体分裂蛋白 1 (mitochondrial fission protein 1, FIS1)] 表达, 抑制融合相关蛋白 [MFN2、视神经萎缩蛋白 1 (optic atrophy type 1, OPA1)], 导致线粒体裂变融合失衡[33]。造成这一现象的原因, 可能与不同研究使用的动物模型处于疾病的不同阶段有关。因此, 未来进一步探索在 DCM 进展中 PPARα 水平的动态变化存在一定价值。

2.3.2 PPARα 与糖尿病血管损伤 研究发现, 糖尿病患者出现血管内皮细胞功能受损, 血管平滑肌细胞 (vascular smooth muscle cells, VSMCs) 增殖与迁移异常, 从而导致大血管、微血管狭窄和硬化[34]。在血管内皮细胞中, PPARα 通过上调转录因子 Kruppel 样因子 11 (Kruppel-like factor 11, KLF11) 表达并促进其与内皮素-1 (endothelin-1, *ET-1*) 基因启动子结合, 从而抑制 *ET-1* 表达改善微血管功能[35]。糖尿病状态下, 微小 RNA-21 通过下调 PGC1α 下调 PPARα, 进而 PGC1α 与 PPARα 协同促进的内皮型一氧化氮合酶 (endothelial nitric oxide synthase, eNOS) 活性受抑制, 一氧化氮 (nitric oxide, NO) 的生成减少[36]。此外, PPARα 抑制转化生长因子-β (transforming growth factor-β, TGF-β) 诱导的 β5 整合素转录, 阻断血小板源生长因子诱导的 VSMCs 迁移[37]。另外, 激活 PPARα 还可下调 VCAM-1、细胞间黏附分子-1 (intercellular adhesion molecule-1, ICAM-1) 表达, 显著抑制 TNFα 诱导的 NF-κB p65 亚基核转位与细胞迁移以及 IL1β 诱导的人视网膜色素上皮细胞中血管内皮生长因子 (vascular endothelial growth factor, VEGF) 产生, 从而抑制糖尿病视网膜微血管病变[38]。研究表明, 非诺贝特能改善糖尿病小鼠的血管内皮功能和收缩力。非诺贝特通过激活 PPARα, 诱导肝脏激酶 B1 (liver kinase B1, LKB1) 从细胞核转移至细胞质, 并促进其磷酸化。细胞质中活化的 LKB1 进一步催化 AMPKα 的 Thr172 位点磷酸化。激活的 AMPKα 直接磷酸化 eNOS 的 Ser1177 位点, 增强 eNOS 活性, 促进 NO 生成; 同时, 非诺贝特治疗后, 可降低主动脉中异常的 NF-κB 的 p65 亚基核定位和 COX-2 表达, 减少血栓素和前列腺素的血清水平, 抑制异常血管收缩[39]。此外, 目前研究发现, 一些传统中药通过 PPARα 改善糖尿病血管系统的内皮功能障碍, 如薏苡附子散通过激活 PPARα/PGC-1α/sirtuin3 信号通路, 促进线粒体能量代谢[40]; 淫羊藿苷通过调节 PPARα/sirtuin1/AMPKα 通路减轻内质网应激, 进而缓解内皮功能障碍[41]。

综上, 糖尿病引发血管细胞功能异常导致血管病变, 而 PPARα 在血管内皮细胞与 VSMCs 中, 通过抑制细胞增殖迁移、调节黏附分子表达等机制, 维持血管正常功能。PPARα 激动剂有望成为糖尿病血管病变临床治疗药物, 推动糖尿病血管并发症防治策略的发展。

2.4 PPARα 与动脉粥样硬化

动脉粥样硬化是一种慢性炎症性疾病, 其已知危险因素包括高胆固醇血症、高血压、糖尿病和吸烟等[42]。PPARα 已被许多研究证实可发挥抗动脉粥样硬化作用。PPARα 激活可抑制血管内皮细胞的 VCAM-1 表达从而减少单核细胞黏附, 抑制巨噬细胞基质金属蛋白酶 (matrix metalloproteinase, MMP) 表达从而增强斑块稳定性[43]。此外, 近期有研究表明, 中药活性成分汉黄芩素 (wogonin) 能通过直接结合并激活 PPARα, 进而与 KLF11、Yes 相关蛋白 1 (Yes-associated protein 1, YAP1) 形成转录复合物, 在抑制 YAP1 介导的糖酵解的同时增强 PPARα-CPT1α 驱动的脂肪酸氧化和 KLF11-ATP 结合盒蛋白 A1/G1 (ATP-binding cassette

transporter A1/G1, ABCA1/G1) 介导的胆固醇外流, 从而重编程巨噬细胞代谢, 减轻炎症与泡沫细胞形成, 最终减缓动脉粥样硬化进展[44]。一组涉及1 388名受试者的随机试验表明, 贝特类药物降低血浆脂蛋白a (动脉粥样硬化的独立致病危险因素) 的效果优于他汀类药物[45]。上述研究表明, PPARα可发挥抗动脉粥样硬化作用。

2.5 PPARα与其他代谢性心血管疾病

2.5.1 PPARα与高尿酸血症相关心血管疾病 高尿酸血症通过激活NLRP3炎症小体等途径损伤心肌, 是多种心血管疾病重要危险因素[46]。队列研究表明, 高尿酸血症或痛风的患者更易患心血管疾病 (如心力衰竭), 且更易发生全因死亡[47]。车前草预防和治疗高尿酸血症有着悠久历史, 研究发现其可通过激活PPARα, 上调*Lpl*、*Atgl*等脂解相关基因, 改善高尿酸血症常伴随的脂质代谢紊乱, 同时为尿酸排泄创造有利的代谢环境[48]。然而另有研究表明, PPARα在高尿酸血症相关心血管疾病中的作用有待进一步探索。桑黄是一种食用和药用真菌, 在传统中医学中有广泛应用, 桑黄通过抑制PPARα, 抑制黄嘌呤氧化酶 (xanthine oxidase, XOD) 的表达和活性, 降低血清尿酸和总胆固醇水平, 改善高尿酸血症, 同时可调节肠肝胆汁酸代谢[49]。胆汁酸通过抑制PPARα/RXRα复合物与*XOD*启动子的结合, 降低肝脏XOD表达, 从而缓解高尿酸血症[50]。因此, 目前关于PPARα与高尿酸血症相关心血管疾病的直接研究较少, 但上述研究提示PPARα可能成为治疗高尿酸血症相关心血管疾病的关键靶点。

2.5.2 PPARα与多囊卵巢综合征相关心血管疾病 多囊卵巢综合征 (polycystic ovary syndrome, PCOS) 常合并心血管炎症并加重缺血性心脏损伤, 造成多囊卵巢综合征相关心血管疾病[51]。动物研究显示, PCOS大鼠模型经非诺贝特治疗3周后, 通过激活PPARα、调控TNFα/CD95通路, 发挥抗氧化、抗炎及抗凋亡作用, 从而改善大鼠PCOS[52]。此外, 最近的遗传研究表明, 肝内脂质积累在PCOS和心血管疾病的发病机制中起着积极作用, 表明多囊卵巢综合征相关心血管疾病与代谢功能障碍相关脂肪性肝病存在交叉作用[53]。综上, PPARα与PCOS患者的心血管疾病之间存在相关性, 深入探究PPARα在PCOS患者的心血管疾病中的作用及机制为临床防治相关疾病提供新方向。

2.5.3 PPARα与肠道菌群相关心血管疾病 肠道菌群及其代谢产物可导致心血管疾病的发生发展, 这主要与菌落组成的失调、宿主免疫反应的紊乱和慢性炎症的诱导相关, 肠道菌群有望成为治疗心血管疾病潜在的新靶点[54]。一项研究表明, *Akkermansia muciniphila*作为解决代谢紊乱的潜在有益微生物, 通过维持内源性大麻素相关脂质 (单棕榈酰甘油) 的循环水平, 激活PPARα, 调控脂质代谢、抑制炎症, 提示PPARα可能介导肠道菌群在代谢综合征中所发挥的有益作用[55,56]。在诱导心肌梗死后, 与拥有年轻肠道菌群的小鼠相比, 移植了衰老肠道菌群的小鼠心脏组织中PPARα和PGC-1α蛋白表达降低。这破坏了心脏能量代谢平衡, 使心脏甘油三酯合成增加, FAO能力下降, 而激活PPARα可挽救其心脏损伤[57]。另外, 肠道菌群失调可导致短链脂肪酸丁酸盐等代谢产物缺失, 这种代谢产物的改变会引发PPARα减少, 进而下调细胞色素P450家族4亚家族X成员1 (cytochrome P450 family 4 subfamily X member 1, CYP4X1), 促进结肠巨噬细胞向NF-κB介导的M1型极化和促炎因子TNFα、IL1β的产生, 进而导致由免疫检查点抑制剂带来的心脏毒性, 反过来则可通过肠道丁酸盐-PPARα-CTP4X1轴减轻免疫检查点抑制剂带来的心脏毒性[8]。因此, 深入探究肠道菌群通过PPARα及相关信号通路调控宿主代谢和心血管健康的作用机制, 不仅为理解心血管疾病的发生发展提供新视角, 更为开发新的干预策略提供理论依据。

2.5.4 PPARα与非酒精性脂肪性肝病相关心血管疾病 非酒精性脂肪性肝病 (non-alcoholic fatty liver disease, NAFLD) 是心血管疾病的独立危险因素, 同时心血管疾病是NAFLD患者死亡的主要原因[58]。NAFLD与不同类型的心血管疾病间存在很强的相关性。最近的一项荟萃分析报告显示, NAFLD与心肌梗死、缺血性卒中、心房颤动和心力衰竭风险增加相关[59]。另外, NAFLD与肥胖、糖尿病、高血压等多种代谢性疾病存在复杂关联, 可协同导致代谢性心血管疾病[60]。PPARα与肝脏相关心血管疾病发生发展相关。研究表明, PPARα可通过激活下游靶基因 (如*Fgf21*), 促进肝脏脂肪酸β-氧化, 减少甘油三酯在肝细胞内的沉积, 降低肝脂含量, 抑制高脂饮食喂养小鼠肝脏炎症和NAFLD的发展[61,62]。肝细胞特异性*Pparα*敲除小鼠在常规饮食下易出现NAFLD表型, 进而诱导高血压等心血管疾病, 其机制与主动脉中原肌球蛋白受体激酶和p70S6K激酶活性降低相关, 提示肝脏PPARα可能具有保护心血管系统的作用[63]。FAT非典型钙粘蛋白1 (FAT atypical cadherin 1, FAT1) 可将体内*n*-6多不饱和脂肪酸转化为*n*-3多不饱和脂肪酸。*n*-3多不饱和脂肪酸作为PPARα的天然配体, 与PPARα结合后促进其进入细胞核, 进而PPARα激活下游脂质运输相关靶基因 (*Cyp4a10*、*Acox1*、*Fgf21*等) 以及参与脂质转运的青霉素结合蛋白-1的mRNA, 促进脂肪酸运输到线粒

体, 进而增强FAO; FAT1通过PPARα抑制p38丝裂原活化蛋白激酶/细胞质型磷脂酶A2信号通路的磷酸化, 减少IL6、TNFα等炎症因子表达, 缓解肝脏和血管的炎症反应, 表现为减轻MAFLD的肝纤维化, 同时减少动脉粥样硬化斑块中的脂质沉积和炎症细胞浸润[64]。近期研究表明, 肝细胞中的PPARα可独立于其降脂特性, 通过下调*Nlrp3*、*Casp1*等炎症基因, 减轻全身炎症反应, 抑制动脉粥样硬化的发展[65]。总之, PPARα具有治疗NAFLD及其相关心血管疾病的潜力, 但仍需进一步开展动物及大规模临床试验, 以期为临床实际应用提供更多有力支撑。

综上, PPARα在多种代谢性心血管疾病的发生和发展中发挥关键作用。PPARα通过调控脂质代谢、抑制炎症及氧化应激等多种机制改善代谢性心血管疾病, 提示PPARα激动剂有望成为治疗多种代谢性心血管疾病的新型药物, 为相关疾病的临床治疗提供了新的策略和方向 (图1)。

3 PPARα激动剂在临床代谢性心血管疾病中的作用

如前所述, PPARα在调控脂质代谢、抑制炎症及氧化应激中具有重要作用[66]。目前, PPARα激动剂已被用于多种代谢和心血管疾病 (表1), 可见其对于代谢性心血管疾病治疗的潜力。

在肥胖相关心血管疾病中, 一项20名超重和肥胖受试者参加的双盲交叉干预试验表明, 非诺贝特可显著减少循环中饱和甘油三酯, 并降低总胆固醇和总溶血磷脂酰胆碱, 从而有助于降低患肥胖相关

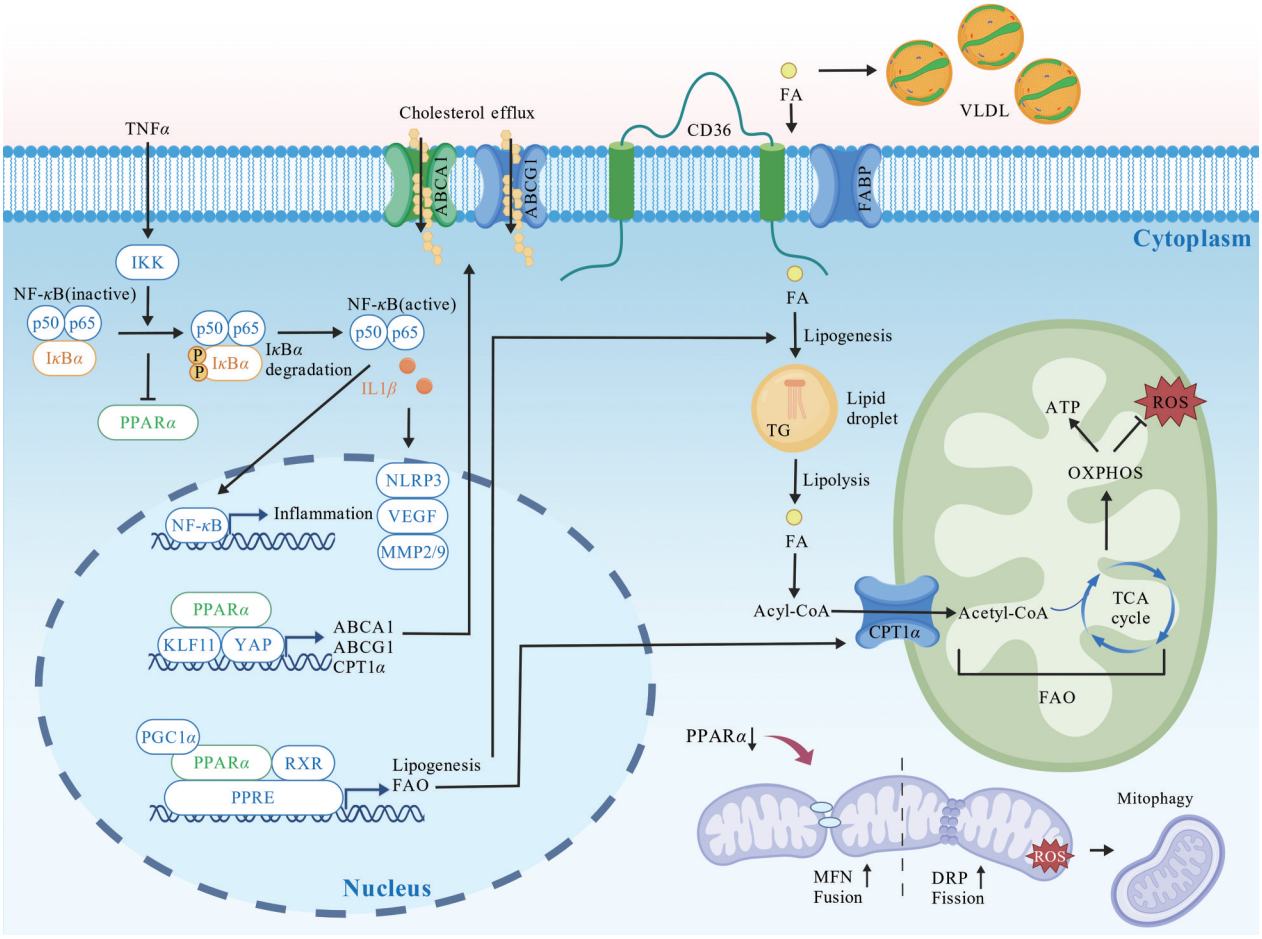


Figure 1 The role of PPARα in metabolic cardiovascular diseases. TNFα: Tumor necrosis factor α; IKK: Inhibitor of nuclear factor κ-B kinase; IκBα: Inhibitor of nuclear factor κB α; NF-κB: Nuclear factor κ-light-chain-enhancer of activated B cells; IL1β: Interleukin 1β; NLRP3: Nucleotide-binding oligomerization domain-like receptor protein 3; MMP2/9: Matrix metalloproteinase 2/9; VEGF: Vascular endothelial growth factor; PPARα: Peroxisome proliferator-activated receptor α; KLF11: Kruppel-like factor 11; YAP: Yes-associated protein; ABCA1: ATP-binding cassette transporter A1; ABCG1: ATP-binding cassette transporter G1; CPT1α: Carnitine palmitoyltransferase 1α; PGC1α: Peroxisome proliferator-activated receptor γ coactivator 1α; RXR: Retinoid X receptor; PPRE: Peroxisome proliferator response element; FAO: Fatty acid oxidation; MFN: Mitofusin; DRP: Dynamin-related protein; TG: Triglyceride; CD36: Cluster of differentiation 36; FABP: Fatty acid-binding protein; FA: Fatty acid; TCA cycle: Tricarboxylic acid cycle; OXPHOS: Oxidative phosphorylation; ATP: Adenosine triphosphate; ROS: Reactive oxygen species; VLDL: Very low density lipoprotein cholesterol

Table 1 PPARα agonists for metabolism and cardiovascular diseases. HL: Hyperlipidemia; HCL: Hypercholesterolemia; HTG: Hypertriglyceridemia; DL: Dyslipidemia; HLP: Hyperlipoproteinemia; T2D: Type 2 diabetes; NASH: Nonalcoholic steatohepatitis; NAFLD: Nonalcoholic fatty liver disease; MASLD: Metabolic dysfunction-associated steatotic liver disease. "Year (Country)" [e.g., 1974 (France)]: Indicates the year when the corresponding drug was first approved for marketing in the specified country/region, and the drug is already on the market; "None": No information on the marketing status or clinical phase of the drug has been retrieved so far. Additionally, the table above also references data from https://www.fda.gov/, https://www.clinicaltrials.gov/

Target	Drug	Clinical status	Indication
PPARα	Fenofibrate	1974 (France)	Treatment of HL, HCL, and HTG
	Ciprofibrate	1985 (France)	
	Ronifibrate	1985 (Italy)	
	Icosapent ethyl	1994 (Japan)	
	Aluminum clofibrate	1995 (China)	
	Choline fenofibrate	2008 (USA)	
	Pemafibrate	2017 (Japan)	
	WY14643 (pirinixic acid)	None	Improving mitochondrial function, insulin resistance and NAFLD
	GW7647	Preclinical	Improving asthma and myocardial reperfusion injury
	BMS-687453	None	Improving atherosclerosis and DL
PPARα/δ	Elafibranor	2024 (USA)	Treatment of primary biliary cholangitis
PPARα/γ	Clofibrate	1967 (USA)	Treatment of HL and HTG
	Gemfibrozil	1981 (USA)	Treatment of HL, HLP, and coronary heart disease
	Lobeglitazone	2013 (Korea)	Treatment of T2D
	Saroglitazar	2013 (India)	Treatment of HTG, DL, T2D, and NASH
	Tesaglitazar	Clinical phase III-terminated	Improving obesity and glucose metabolism
Pan-PPAR (PPARα, PPARδ and PPARγ)	Bezafibrate	1978 (Japan)	Treatment of HL and HCL
	Fenofibric acid	2009 (USA)	Treatment of DL and HL
	Chiglitazar	2021 (China)	Treatment of T2D and familial HDL deficiency
	Lanifibranor	Clinical phase III	Improving T2D and MASLD

心血管疾病的风险[67]。在糖尿病相关心血管疾病中, 临床研究显示, 非诺贝特对糖尿病相关心血管疾病的结局有益[68]。在肝脏相关心血管疾病中, 一项针对106例NAFLD/非酒精性脂肪性肝炎 (non-alcoholic steatohepatitis, NASH) 患者的随机对照临床试验表明, 双重PPARα/γ激动剂saroglitazar可显著改善NAFLD/NASH患者的胰岛素抵抗和与动脉粥样硬化相关的血脂异常[69]。一项纳入247名患者的研究表明, 泛PPAR激动剂lanifibranor可改善代谢相关脂肪性肝炎患者的心脏代谢健康[70]。然而, PPARα激动剂在临床应用上的表现并不稳定。有随机对照试验表明, 在2型糖尿病、轻度至中度高甘油三酯血症以及低HDL胆固醇水平患者中, 尽管PPARα激动剂佩玛贝特 (pemafibrate) 降低了甘油三酯、VLDL胆固醇、残余胆固醇和载脂蛋白C-III水平, 但接受pemafibrate的患者心血管事件的发生率与接受安慰剂的患者无明显差异[71]。

尽管PPARα激动剂具有治疗潜力, 但其临床应用受限于不良反应。研究显示, 在中国人群中贝特类药物的不良反应略高于他汀类, 使用时需监测肝肾功能[72,73]。具体而言, 非诺贝特常见胃肠道反应 (恶心和呕吐)、肝损伤、肌痉挛及横纹肌溶解症, 且中国人群中胃肠道症状为其最常见不良反应, 其次是肝脏和神经系统症状[73,74]; 苯扎贝特在中国人群中的主要不良反应同样为胃肠道反应[75]。相比之下, 新型激动剂安全性更好。随机对照试验的荟萃分析表明, 佩玛贝特治疗血脂异常的疗效优于安慰剂, 与非诺贝特相当 (且可改善肝胆酶活性), 总不良事件显著少于非诺贝特[76]。在中国开展的多中心双盲试验 (纳入344例高甘油三酯、低高密度脂蛋白胆固醇患者) 也显示, 佩玛贝特改善甘油三酯水平的效果更优于非诺贝特, 且能保障肝肾安全性[77]。

综上, PPARα激动剂在临床实际应用的过程中, 存在个体间差异和药物潜在不良反应风险, 但可干预代谢性心血管疾病的病理进程, 对代谢性心血管疾病具有潜在的治疗作用。

4 小结与展望

PPARα作为核受体超家族的重要成员, 在脂质代谢、炎症反应及氧化应激等方面发挥着关键作用。在多种代谢性心血管疾病中, PPARα通过调控机体脂质代谢、抑制炎症及氧化应激等机制, 对心血管系统起到保护作用。未来仍需进一步探究PPARα在不同代谢性心血管疾病中的具体作用机制, 同时结合人工智能药物开发等新兴领域的研究, 开发更加安全有效的PPARα激动剂, 为代谢性心血管疾病的防治提供新的

策略和方法。

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