•综述•

游离脂肪酸受体1在慢性炎症性疾病中的功能及药物研究进展

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摘要: 游离脂肪酸受体1 (free fatty acid receptor 1, FFAR1) 属于G蛋白受体家族 (G protein coupled-receptors, GPRs), 又称GPR40。研究发现FFAR1在多种组织器官中表达, 介导多种生物学功能, 不仅调控脂肪酸及葡萄糖等物质的代谢, 而且在免疫炎症反应中发挥重要作用, 可能成为多种慢性炎症性疾病的治疗靶点。本综述就FFAR1在病理生理过程的调控机制及药物研发对近年来取得的研究新进展作一总结, 并以多种化合物的发现为例, 展望FFAR1在慢性炎症性疾病中的应用前景。

关键词: 游离脂肪酸受体1; 慢性炎症性疾病; 作用机制; 药物研发; 代谢紊乱; 认知缺陷

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The function and drug development progress of free fatty acid receptor 1 in chronic inflammatory diseases

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Abstract: As a member of G protein coupled-receptors superfamily, free fatty acid receptor 1 (FFAR1), is also known as GPR40, has been shown to regulate numerous pathophysiological processes in a variety of tissues and organs. The activated FFAR1 has a variety of biological functions. For instance, it can not only regulate metabolism of fatty acids and glucose, but also play an important role in immune inflammatory response, it may be a potential drug target for the treatment of various chronic inflammatory diseases. In this review, we focus on the recent researches of FFAR1's action in the regulation of pathophysiological processes, its molecular mechanism and new agonists development. At the same time, this review will take the discovery of series FFAR1 agonists as examples, and display the applied prospects of FFAR1.

Key words: free fatty acid receptor 1; chronic inflammatory disease; mechanism of action; drug development; metabolic disorder; cognitive deficit

游离脂肪酸受体1 (free fatty acid receptor 1, FFAR1) 属于A类视紫红质样G蛋白偶联受体 (G protein coupled-receptors, GPRs), 能被中长链饱和或不饱和脂肪酸激活, 介导细胞内信号转导, 又称GPR40[1-3]。近年来, FFAR1 (GPR40)、FFAR2 (GPR43)、FFAR3 (GPR41) 和FFAR4 (GPR120) 相继发现并确证是脂肪酸的内源性受体, 被称为脂肪酸家族受体。脂肪酸受体可参与调节多种生理过程, 各受体的主要表达组织、生理作用及配体见表1。

炎症是一种机体应对感染、组织损伤或细胞应激的反应, 可通过修复机制恢复组织功能。其中, 慢性系统性低度炎症 (chronic systemic low-grade inflammation, CSLGI) 是指机体在特定免疫原的长期、低剂量刺激

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Table 1 Classification, physiological function and drug development of free fatty acid receptors (FFARs). PPI: Proton pump inhibitor; GPR: G protein coupled-receptor

Classification	FFAR1	FFAR2	FFAR3	FFAR4
Distribution	Pancreatic β cells, enteroendocrine cells, immune cells	Immune cells, enteroendocrine cells, enterocytes, adipocytes	Adipocytes, enteroendocrine cells, enterocytes, pancreatic β cells, immune cells	Adipocyte, enteroendocrine cells, macrophages, taste bud
Natural ligands	Palmitic acid, oleic acid, linolenic acid	Acetic acid, propionic acid, butyric acid	Acetic acid, propionic acid, butyric acid	α-Linolenic acid, docosahexaenoic acid
Physiological function	Secretion of insulin and incretin, anti-inflammation, improvement of cognitive deficits	Anti-inflammation, inhibition of lipolysis and lipogenesis, anti-tumor, maintenance of intestinal homeostasis	Secretion of insulin, incretin and leptin, protection of the intestinal epithelium	Anti-inflammation, secretion of insulin and incretin, taste preference, browning of adipose tissue
Synthetic agonists	GW9508, TAK875, AMG-837, TUG770, Medica-16, LY2881835	AMG-7703, TUG-1357	AR420626, 1-methylcyclopropane carboxylic acid	GW9508, NCG21, NCG46, GSK137647A, TUG-891
Antagonists	GW1100, DC261026, ANT-203	GLPG0974, CATPB	β-Hydroxybutyrate	Eicosapentaenoic acid
Drug development	Fasiglifam (TAK-875); phase III clinical trial	GLPG0974; phase II clinical trial	The effect of PPI therapy on expression of GPR41 and GPR43; phase I clinical trial	KDT501; phase I clinical trial

下, 呈现的一种非特异性的、可持续存在的低度炎症状态, 可由局部扩展到全身多个器官[4]。CSLGI是多种慢性疾病, 如糖尿病、非酒精性脂肪肝病 (nonalcoholic fatty liver disease, NAFLD)、肥胖、心血管疾病、阿尔茨海默病 (Alzheimer's disease, AD) 和癌症等共同的病理基础, 因此, 这些疾病也统称为慢性炎症性疾病。研究发现FFAR1在以上慢性炎症性疾病中扮演重要角色。本综述将总结近年来FFAR1在慢性炎症性疾病中的研究新进展, 并调研FFAR1新药研发情况, 展望其在以上疾病中的应用前景。

1 FFAR1概述

FFAR1最初于1997年由Sawzdargo等发现[5], 是由第19号染色体上的单外显子*FFAR1*基因编码的300个氨基酸的膜蛋白, 具有7个跨膜α螺旋结构, 在空间结构上可分为识别相应信号分子的胞外区 (N端)、充当蛋白分子骨架的跨膜区及与下游信号分子相结合的胞内区 (C端), 激活细胞内信号通路[6,7]。位于细胞内环2和跨膜螺旋3附近的精氨酸104 (R104) 对于维持FFAR1的正常功能至关重要, R104突变为脯氨酸 (R104P) 可导致FFAR1功能完全丧失[8]。FFAR1蛋白序列中第258位精氨酸突变为色氨酸使脂肪酸促胰岛素分泌能力消失[9], 第211位的精、组氨酸 (Arg211His) 多态性可能导致胰岛素分泌能力的变化[10]。已有许多研究证明[7,11,12], FFAR1在胰腺β细胞、肠内分泌K和L细胞、免疫细胞、味蕾、脾脏和中枢神经系统中高表达, 在胰腺α细胞、肠内分泌I细胞、成骨细胞、破骨细胞和肝细胞中亦有少量表达, 这提示FFAR1可能在多种生理和病理过程中扮演重要角色[13,14]。

2 FFAR1与糖尿病

随着人类生活方式的改变, 糖尿病在世界各地的发病率逐年上升, 预计在2030年, 全世界将有超过5.5亿患者[15]。胰岛素分泌障碍是2型糖尿病 (type 2 diabetes mellitus, T2DM) 的病因之一, 机体炎症反应与糖尿病病程密切相关[16,17]。FFAR1自2003年脱孤儿化以来[1], 首先作为促胰岛素分泌剂的新靶点受到广泛关注, 研究报道FFAR1激动剂不同于传统的磺酰脲类药物, 其促胰岛素分泌具有葡萄糖浓度依赖性, 能有效防止低血糖发生, 在临床应用方面有一定优势[18,19]。FFAR1的功能不仅局限于调节胰岛素分泌, 还可改善炎症, 可能通过抗炎作用改善糖尿病胰岛β细胞功能, 在糖尿病治疗方面具有广泛应用前景。

2.1 FFAR1活化发挥抗糖尿病作用的主要机制

2.1.1 促胰岛素分泌 在胰岛β细胞, FFAR1激活磷脂酶C (PLC) 通路, 开放L型Ca^{2+}通道, 细胞Ca^{2+}内流诱导胰岛素胞吐作用[20,21], 具体作用机制见图1; 也通过作用于胃肠道, 如肠道K、L细胞, 刺激抑胃肽 (gastric inhibitory peptide, GIP)、胰高血糖素样肽-1 (glucagon-like peptide-1, GLP-1) 等分泌, 而后者通过内分泌调节间接促进胰岛β细胞的胰岛素分泌[22,23]。

2.1.2 抗炎 糖尿病是一种慢性炎症疾病已成共识, 长期炎症造成机体胰岛素抵抗和β细胞功能受损[16]。研究报道FFAR1激活促进β细胞增殖, 减少细胞凋亡, 改善胰岛β细胞功能[24]。给予2型糖尿病*eNOS*$^{-/-}$*db/db*小鼠FFAR1激动剂PBI-4050, 可减少胰岛内免疫细胞浸润, 刺激胰岛细胞自噬增加, 细胞内质网应激降低, 胰岛功能恢复[25]。另一激动剂CNX-011-67能逆转慢性炎症导致的胰岛素瘤细胞 (NIT1) 功能受损、凋

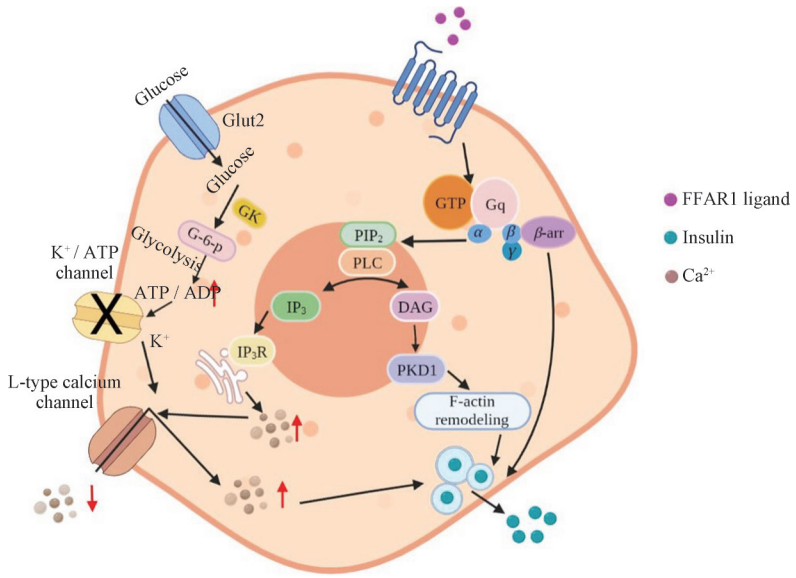

Figure 1 FFAR1 signaling in pancreatic β-cell. ADP: Adenosine diphosphate; ATP: Adenosine triphosphate; DAG: Diacyl glycerol; GK: Glucokinase; Glut2: Recombinant glucose transporter 2; GTP: Guanosine triphosphate; G-6-P: Glucose-6-phosphate; Gq: Gq subfamily; IP_3: Inositol-1,4,5-triphosphate; IP_3R: IP_3 receptor; PIP_2: Phosphatidylinositol-4,5-bisphosphate; PKD1: Protein kinase D1; PLC: Phospholipase C; β-arr: β-Arrestin

亡、细胞氧化和内质网应激及促炎细胞因子基因表达上调等[26,27]。联用二甲双胍和TAK875可通过FFAR1/PLC/IP3通路降低高脂饮食诱导肥胖SD大鼠血液炎症因子水平, 抑制Toll样受体4/核因子κB (Toll-like receptor 4/nuclear factor kappa-B, TLR4/NFκB)活化, 改善胰岛β细胞炎症损伤, 进而发挥胰岛保护作用[28,29]。以上研究提示, FFAR1激活主要改善内质网应激和氧化应激, 进而保护糖尿病胰岛β细胞功能, NFκB是其主要作用通路。

2.2 FFAR1激动剂作为抗糖尿病新药的研究

GW9508是第一个被报道的人工设计合成的FFAR1激动剂, 能在过表达FFAR1的293T细胞中促进钙离子释放[30]。Fasiglifam (TAK-875)是日本武田制药研发的选择性FFAR1激动剂, 可葡萄糖依赖性地刺激胰岛素分泌, 在禁食和餐后均能降低糖尿病大鼠的血糖, 已进入III期临床试验, 但由于肝脏毒性被终止[31,32]。Akros Pharma公司的glimepiride (JTT-851)进入II期临床试验 (NCT01699737), 但无进一步报道[33]。其他处于临床前或临床研究阶段的FFAR1小分子激动剂包括TUG-770[34]、DS-1558[35]、AM-1638、AM-5262[36]、AP1和AP3[37]、CPU025[38]、CPL207280[39]。现有FFAR1激动剂尚未成功通过临床研究, 除药物有效性需进一步提高外, 安全性可能是制约现有FFAR1激动剂作为抗糖尿病药物研发的重要因素, 如fasiglifam被报道由于结构的高亲脂性, 对肝脏胆汁酸转运蛋白有明显抑制, 可能是造成其肝毒性的主要原因[32,40], 未来的研究重点是设计和开发具有更好理化特性的FFAR1激动剂, 平衡药物的药效和安全性。

FFAR1多靶点化合物或FFAR1激动剂与其他药物联用也是抗糖尿病药物研发的思路之一, 与高选择性激动剂相比, FFAR1和PPARs或FFAR4的双重配体可能同时具有促胰岛素分泌和胰岛素增敏的治疗作用, 如FFAR1/PPARδ双靶点化合物HWL-088改善*ob/ob*小鼠糖脂代谢及肾纤维化[41]; FFAR1/PPARα、γ、δ四靶点激动剂RLA8-A、ZLY18改善高脂血症小鼠的糖脂代谢、非酒精性脂肪肝炎 (non-alcoholic steatohepatitis, NASH)和纤维化[42,43]。此外, FFAR1激动剂与艾塞那肽等降糖药联用对碳水化合物和脂类的分解代谢表现出较好的协同作用[44]; HWL-088与二甲双胍[41]、TAK875与二甲双胍联用[28]在改善*ob/ob*小鼠糖脂代谢及炎症方面展现出协同作用。但是, 无论是多靶点药物还是药物联用都需深入研究, 为临床试验进一步提供依据。

3 FFAR1与NAFLD

NAFLD是一种常见的代谢紊乱性疾病, 常与T2DM共存[45]。如果治疗不当, 可由单纯的肝脏脂质堆积进展为NASH甚至肝硬化[46]。目前NAFLD的病理机制仍不清楚, 多次打击学说认为肝细胞内甘油三酯 (TG)的聚积为第一次打击, 而胰岛素抵抗、氧化应激及随后的炎症为第二次打击, 细胞坏死和纤维化为第三次打击[47,48]。针对NAFLD治疗药物开发多以GLP-1受体、钠-葡萄糖共转运体2 (SGLT2)、法尼醇X

受体 (FXR)、PPAR 受体及乙酰辅酶 A 羧化酶 (ACC) 为靶点, 因不良反应、价格、患者依从性等, 目前尚未有批准针对 NAFLD 治疗的药物, 大分子药物的经济成本和患者依从性, 以及药物长期使用的潜在安全性问题需要重视[49,50]。

3.1 FFAR1 调节肝脏脂质代谢

FFAR1 活化可通过间接或直接的作用改善肝脂代谢紊乱, 具体作用总结为: ① 通过胰岛素作用。激活 FFAR1 增加胰岛素分泌, 而胰岛素通过磷脂酰肌醇 3- 激酶/丝/苏氨酸激酶/雷帕霉素靶蛋白 (phosphoinositide 3-kinase/serine/threonine-protein kinase/mammalian target of rapamycin, PI3K/Akt/mTOR) 信号通路促进载脂蛋白 B (apolipoprotein B, Apo B) 脂解调节肝脏脂质代谢[51]; ② 通过 GLP-1 作用。激活 FFAR1 增加 GLP-1 分泌, GLP-1 通过抑制食欲、减轻体重和改善肠道脂蛋白代谢改善肝脏脂质堆积[52,53]; ③ 通过胰高血糖素作用。现有报道[54], 某些 FFAR1 激动剂如 SCO-267, 可增加胰高血糖素分泌, 而胰高血糖素可促进肝脏脂质氧化, 减少脂质合成; ④ 肝细胞 FFAR1 直接参与细胞的脂质代谢调节。研究发现激活肝细胞 FFAR1 可通过 p38、腺苷酸活化蛋白激酶 (AMP-activated protein kinase, AMPK) 等通路下调胆固醇调节元件结合蛋白 1 (sterol-regulatory element binding protein 1, SREBP1) 的转录翻译, 下调脂质合成关键酶, 如脂肪酸合成酶 (fatty acid synthase, FAS)、乙酰辅酶 A 羧化酶 (acetyl-CoA carboxylase, ACC) 和硬脂酰辅酶 A 去饱和酶 1 (stearoyl-CoA desaturase-1, SCD-1) 的表达, 改善肝细胞脂肪变性[55,56]。另有研究报道 FFAR1 敲除小鼠诱发 NAFLD, 其机制与肝脏脂肪酸转位酶 (hepatic fatty acid translocase, FAT)/CD36 上调有关[13]。此外, FFAR1/PPARδ 的双靶点激动剂 CPU025、ZLY032、HWL-088 等可改善肝脏脂质异常堆积、NASH 及肝脏纤维化[57-59], 提示多靶点药物可能对治疗 NASH 更有效。上述研究提示, FFAR1 主要通过促进胰岛素、GLP-1、胰高血糖素分泌及 AMPK-SREBP1 信号通路抑制肝脏脂质合成, 促进肝脏脂质氧化, 改善肝脏脂质堆积。

3.2 FFAR1 活化改善肝脏炎症

FFAR1 在肝细胞和巨噬细胞中表达, 激活 FFAR1 能减轻 NASH 的氧化应激和炎症反应, 改善肝纤维化。研究发现 FFAR1 全身敲除导致高脂饮食诱导及低脂饲料喂养小鼠的肝脏巨噬细胞标志物 F4/80 升高及胶原蛋白含量增加, 提示 FFAR1 敲除会导致肝脏炎症及纤维化[13]。而 FFAR1 激动剂 EPA 和 DHA 通过下调巨噬细胞中关键炎症介质 (TLRs、CD14 和 NFκB), 减少肝细胞对血浆炎症因子的反应, 改善肝脏炎症[60]。Park 等[61]发现, FFAR1 选择性激动剂如 TAK875 和 AMG1638 抑制骨髓源巨噬细胞中 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) 炎性小体的活化, 在巨噬细胞 RAW264.7 及肝脏 Kuppfer 细胞中也有类似的研究结果[62], 提示 FFAR1 激动剂可通过 NLRP3 炎症小体抑制巨噬细胞活化, 发挥抗炎作用。在 NAFLD 小鼠模型中, RLA8、CPU025、HWL-088 及 ZLY032 等 FFAR1 激动剂可减少肿瘤坏死因子 α (tumor necrosis factor α, TNF-α)、白细胞介素 6 (IL-6) 等炎症因子的分泌, 在改善肝脏脂质堆积同时, 还能改善 NASH 的多种常见症状如炎症、氧化应激、纤维化等[42,57-59]。此外, 激活 FFAR1 后可增加高脂喂养小鼠肝组织内抗炎因子 IL-10 的表达, 进而改善肝脏炎症[63]。根据目前的研究结果, FFAR1 激动剂改善 NASH 的作用是独立于改善肝脏脂质代谢之外的抗炎机制, 主要通过抑制炎症细胞 (巨噬细胞为主) 的炎症通路, 调节促炎/抗炎因子分泌来实现。因此 FFAR1 是 NASH 的一个潜在药物靶点, 虽然 fasiglifam 因肝毒性被停止开发, 但其他 FFAR1 激动剂的研发依旧值得关注。

4 FFAR1 与中枢神经系统疾病

FFAR1 在神经细胞中广泛表达, 包括大脑皮层、海马、杏仁核、下丘脑、小脑和脊髓等神经元, 其可能在慢性炎症密切相关的内源性疼痛控制系统、认知功能改善、情绪功能调节及癫痫中发挥关键作用[30,64,65]。

4.1 镇痛

研究表明, FFAR1 是疼痛的重要调节因子, FFAR1 全身性敲除可能导致小鼠内源性疼痛控制系统功能障碍, 疼痛行为加剧[66]。FFAR1 内源性配体 DHA 和外源性激动剂 GW9508 能在不同实验性疼痛模型中起镇痛作用, 如环磷酰胺诱导内脏性疼痛、癌症性神经痛、福尔马林诱导炎症疼痛及术后异常机械疼痛等[67,68]。GW9508 可促进福尔马林诱导炎症性疼痛小鼠和脊髓结扎诱导神经疼痛小鼠脊髓中 β 内啡肽、5 羟色胺及去甲肾上腺素释放, 这可能是激活 FFAR1 发挥镇痛作用的机制之一[67]; 此外, FFAR1 表达于去甲肾上腺素能及血清素能神经元, 提示 FFAR1 信号可能参与了疼痛控制下行系统的调节, 介导损伤后内源性下行疼痛抑制系统的激活[69]。在外周神经损伤后, FFAR1 的表达上调, 另外在足底切口疼痛实验早期阶段, DHA 及其代谢产物在小鼠下丘脑和中脑均有增加, 提示 DHA 激活 FFAR1 也许是疼痛的代偿反应[66,68]。Harada 等[70]评估了 FFAR1 在中枢卒中后疼痛实验模型中的作用, 脑室内注射 GW9508 或 DHA 能缓解双侧颈动脉闭塞

(bCAO) 的雄性ddY小鼠机械痛觉过敏模型的伤害性作用。以上研究均提示, FFAR1可能是调节内源性疼痛控制系统的关键因素。

4.2 改善AD

最近研究发现, AD与慢性神经炎症密切相关, 激活FFAR1除了减少Aβ淀粉样蛋白沉积、改善AD模型小鼠空间定位及认知记忆, 也可通过改善神经炎症进一步改善AD[71]。目前认为, FFAR1活化改善AD的作用机制主要包括: ① 间接改善中枢神经系统炎症, 改善中枢神经元功能。Aβ的沉积与脑组织中炎症介质和黏附分子增加有关, 且Aβ表达增多可激活小胶质细胞和巨噬细胞, 进一步诱导炎症介质及趋化因子分泌, 导致认知受损加重[71]。激活FFAR1通过增加下丘脑中α黑素细胞刺激素、改善AD小鼠神经元自噬功能异常和增强α分泌酶ADAM10的活性, 使脑内异常沉积的Aβ和Tau蛋白清除、减少β样淀粉蛋白形成, 进而改善神经炎症、记忆及认知功能[72]。此外, 激活下丘脑和人神经母细胞瘤中FFAR1可通过诱导环磷腺苷效应元件结合蛋白 (cAMP-response element binding protein, CREB) 和细胞外调节蛋白激酶1/2 (ERK1/2) 的磷酸化及丝裂原活化蛋白激酶 (P38) 的活化, 增加脑源性神经营养因子, 间接发挥改善中枢神经系统炎症, 促进成人下丘脑和海马神经形成和生长[73,74]; ② 直接改善中枢神经系统炎症。给予GW9508能显著改善啮齿类动物的神经炎症状态, 这一作用在不同的研究中得到验证。GW9508通过NLRP3/IL-1β及CREB/P21活化激酶4 (p21-activated kinases 4, PKA4)/组蛋白去甲基化酶 (histone H3 lysine demethylase, KDM6B) 信号通路诱导小胶质细胞由M1型转变为M2型, 改善脂多糖 (lipopolysaccharide, LPS) 诱导的小胶质细胞中枢神经系统炎症[75]; 激活FFAR1可募集非视觉抑制蛋白ARRB2 (β-arrestin-2), 使NLRP3直接失活, 抑制中枢炎症进程从而发挥神经保护功能[76]; ③ 通过肠脑肽的作用。FFAR1活化在外周可促进肠脑肽 (如GLP-1、GIP、胰岛素等) 分泌, 后者可透过血脑屏障, 缓解神经元自噬功能异常, 改善神经炎症, 发挥神经保护作用[71]。以上有力证明了FFAR1激动剂可通过直接和间接作用抑制神经炎症的病理过程, 发挥保护神经系统、改善认知缺陷的作用。

4.3 其他中枢神经系统疾病

此外, FFAR1在抑郁[77,78]、癫痫[79]、急性脑梗死诱发的炎症[80]中也发挥有益作用, 已成为治疗神经系统疾病及神经炎症的热门靶点, 但目前的FFAR1激动剂需脑室内注射给药, 限制了其应用。针对FFAR1在中枢神经系统功能的研究尚需深入。

5 FFAR1与慢性肾病

FFAR1在肾脏中表达, 在缺血、单侧输尿管梗阻 (UUO) 小鼠模型肾脏中FFAR1表达降低[81,82]。小鼠FFAR1缺失增加肾间质纤维化[25], 而FFAR1激动剂GW9508可减弱顺铂诱导的人肾近端小管上皮细胞凋亡[83], 提示FFAR1在肾脏疾病中的关键作用。在慢性肾脏炎症过程中, 激活FFAR1可通过PLC、钙离子−钙调蛋白依赖性蛋白激酶II (CaMKII)、钙调磷酸酶 (CaN) 和环磷酸腺苷cAMP信号传导降低氧化和内质网应激的压力, 促进细胞存活[27]。在嘌呤诱导的慢性肾脏损伤模型及*eNOS*$^{-/-}$ *db/db*小鼠, FFAR1激动剂PBI-4050可通过MAPK信号通路减少肾脏内质网应激及未折叠蛋白反应介导的凋亡, 发挥肾脏保护作用[25,84], 缓解糖尿病肾病的进展, 减少肾小球损伤和蛋白尿[25]。以上研究提示FFAR1可能是治疗肾损伤的新靶点, 主要机制与抗氧化和内质网应激、抗凋亡有关。

6 FFAR1与心血管系统疾病

6.1 动脉粥样硬化

炎症和氧化应激破坏内皮功能, 增加免疫细胞的黏附和浸润, 增加血管平滑肌细胞向血管壁增殖, 可导致斑块形成和心血管疾病 (cardiovascular diseases, CVD)。在人脐静脉内皮细胞 (HUVECs) 中, FFAR1激动剂LY2922470抑制LPS介导的黏附分子的表达及细胞间的黏附作用, 抑制NFκB的核转位及磷酸化, 下调炎症细胞的浸润及减少动脉硬化斑块的形成, FFAR1活化可抑制内皮细胞向动脉粥样硬化转化的过程[85]。

6.2 心肌细胞保护

FFAR1在啮齿类动物心脏中表达[86], 并参与对缺血再灌注损伤的心脏保护。在培养的原代心肌细胞和大鼠心脏上进行棕榈酸甲酯 (methyl palmitate, MP) 的体外、离体和体内抗缺血再灌注损伤实验, 发现MP通过激活FFAR1/PI3K/Akt信号通路减少心肌细胞的死亡[87]。此外, 激活FFAR1可增加细胞内Ca^{2+}水平, 增强心肌正性肌力作用, 保护心功能[88]。上述研究提示, 以GPR40作为治疗靶点研发在防治心血管系统疾病及心肌细胞保护中具有潜在前景。

7 FFAR1与其他炎性疾病

7.1 FFAR1与癌症

在癌症中, FFAR1激活或阻断的效果会因肿瘤类型而不同, 如胰腺癌细胞中FFAR1敲除会导致基质金属蛋白酶2增加促进细胞侵袭迁移[89]; FFAR1激活促进黑色素瘤[90]和前列腺癌[91]的侵袭迁移及抑制胸腺癌[92]、肺癌[93]的细胞活力和细胞侵袭。FFAR1在不同的癌症中发挥不同的作用, 研究报道也存在矛盾和争议, 可能是由于癌症组织特异性、FFAR1靶标化合物

不同, 导致不同的细胞行为和生物效应, 目前的研究尚未定论。

7.2 FFAR1与其他慢性炎症性疾病

FFAR1激动剂如GW9508、TAK875对外源性糖基化终末产物 (advanced glycation end products, AGEs) 诱导的软骨细胞损伤有保护作用[94], 并可抑制破骨细胞生成, 对骨质疏松有预防作用[95]。在炎性肠病中, FFAR1激动剂通过抑制TNF-α和NFκB信号通路及刺激GLP-2分泌发挥改善肠道炎症的作用[58,96]。在*L*-精氨酸注射诱导的急性胰腺炎模型, 从牛乳中提炼的酥油 (ghee butter from bovine colostrum, GBBC) 通过FFAR1改善急性胰腺炎的炎症反应[97]。此外, FFAR1激动剂可提高表皮干细胞 (ESCs) 及皮肤组织抵抗UV-B损伤的能力[98]。

8 总结与展望

近20年来, 随着对FFAR1研究的深入, 发现了其调控炎症信号通路的作用机制, FFAR1可成为多种慢性炎症性疾病的药物靶点, 具体见图2。

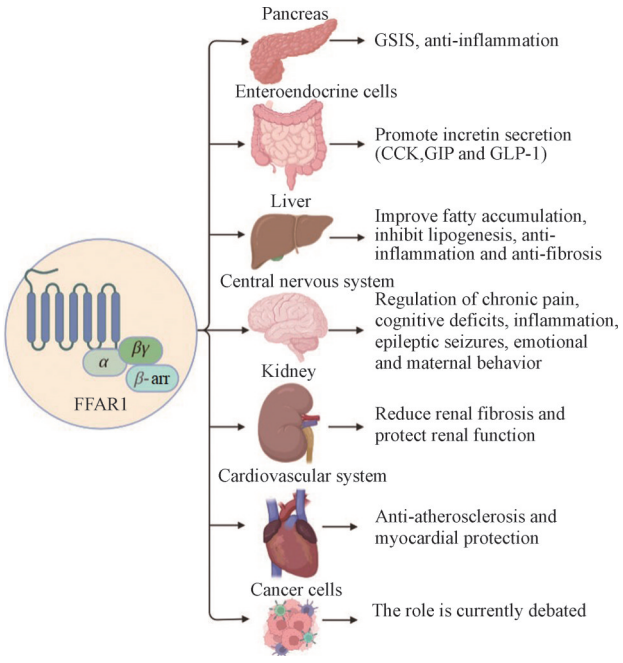

Figure 2 Schematic illustration of associated biological outcomes for FFAR1. FFAR1 is reported to be expressed in pancreatic β-cells, enteroendocrine cells, liver, the central nervous system, kidney and cancer cells. FFAR1 mediates various biological processes in each cell as illustrated. CCK: Cholecystokinin; GIP: Gastric inhibitory polypeptide; GLP-1: Glucagon-like peptide-1; GSIS: Glucose stimulated insulin secretion

尽管目前对FFAR1调节炎症的机制尚不完全清楚, 有的研究结果可能存在矛盾和争议, 在对FFAR1调节癌症的研究中, 并不是所有结果都指向FFAR1治疗癌症的潜力, 有研究报道FFAR1激动剂会促进黑色素瘤和前列腺癌等发生发展。此外, 在新药研发方面, 针对糖尿病、高脂血症和非酒精性脂肪肝的FFAR1激动剂研发进展相对较快。尽管许多医药公司和科研机构开展了针对FFAR1靶点的新药研发, 除高选择性FFAR1激动剂, 多靶点化合物也取得了突破性进展, 但目前尚无FFAR1激动剂成功获批用于疾病治疗。但相信随着技术进步和研究深入, 有望进一步阐明FFAR1介导的生理病理机制, 并开发安全有效的FFAR1靶向药物应用于慢性炎症性疾病的治疗。

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作者更正

耿晶、杨跃梅和李新颖发表在《药学学报》2022年57卷第3期695-699页，题目为“新型靶向HER2抗体MIL40偶联药物的抗肿瘤活性研究”的论文，参考了李新颖在军事医学科学院军事认知与脑科学研究所工作期间的工作基础，由耿晶在杨跃梅的研究基础上进行了相应深入研究。鉴于李新颖已于2019年调离军事医学科学院军事认知与脑科学研究所，经过与李新颖本人沟通后获得其同意，现申请将本文署名作者更改为“耿晶[1,2*]，杨跃梅[3]（1. 中国医学科学院医药生物技术研究所，北京 100050；2. 军事医学科学院军事认知与脑科学研究所，北京 100850；3. 北京瑷格干细胞科技有限公司，北京 102604）”。并对由此给编辑部和读者带来的不便表示诚挚歉意。