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基于成纤维细胞生长因子1的药物治疗肥胖相关并发症*

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摘要　目前，超重和肥胖的发生率已在全球范围内达到流行病的程度，这对慢性代谢性疾病预防和控制造成了巨大挑战。肥胖是包括2型糖尿病、非酒精性脂肪性肝病、心血管病、神经退行性疾病、睡眠呼吸暂停和某些类型的癌症等在内的一系列代谢疾病的主要危险因素。然而，治疗肥胖及其相关并发症的药物选择仍然有限，大多数抗肥胖药物因严重不良反应而退出市场，迫切需要开发有效的长期治疗方法来应对肥胖相关并发症。成纤维细胞生长因子1（fibroblast growth factor 1，FGF1）是全身能量稳态、糖脂代谢和胰岛素敏感性的重要调节因子。FGF1对于肥胖及2型糖尿病、非酒精性脂肪性肝病、癌症、心脏病等肥胖相关并发症具有一定的治疗益处，但长期使用导致的肿瘤发生风险增加限制了其应用。本综述总结了基于FGF1治疗肥胖相关并发症的生物药物开发的最新进展，强调了临床实施中的主要挑战，并讨论了克服这些障碍的可能策略。

关键词　成纤维细胞生长因子1，肥胖，脂代谢，糖尿病，非酒精性脂肪性肝病，癌症
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久坐不动和营养过剩会导致超重和肥胖，其发生率已在全球范围内达到流行病的程度[1]。肥胖的流行是全球慢性代谢性疾病预防和控制的一大挑战[2]。肥胖是一系列代谢疾病的主要危险因素，包括2型糖尿病（diabetes mellitus type 2，T2DM）、非酒精性脂肪性肝病（non-alcoholic fatty liver disease，NAFLD）、心血管病、神经退行性疾病、睡眠呼吸暂停和某些类型的癌症[3]。然而，治疗肥胖及其相关并发症的药物选择仍然有限。大多数抗肥胖药物因严重不良反应而退出市场[4]。目前没有一种抗糖尿病药物可以治愈糖尿病，糖尿病患者需要终身服药[5]。NAFLD通常与肥胖和T2DM同时发生，目前还没有批准的NAFLD药物治疗方法[6]。因此，迫切需要开发有效的长期治疗方法来应对肥胖相关并发症。

成纤维细胞生长因子1（fibroblast growth factor 1，FGF1），是成纤维细胞生长因子家族中最早的成员，由于其等电点低，也称为酸性FGF（aFGF），它最初从大脑和垂体中分离出来，作为有丝分裂原普遍存在于器官或组织中，如心脏、大脑、肾上腺、垂体、神经组织、视网膜和骨骼，是一种公认的自分泌/旁分泌调节因子[7]。FGF1是一种由155个氨基酸组成的非糖基化多肽，由12个具有氨基和羧基末端的反向平行β链组成。N端的自由延伸没有典型的分泌信号序列，与其自身的生物活性密切相关[8]。因此，可以通过在N端进行取代或剪接修饰来设计具有不同活性的FGF1突变体或衍生物。

FGF1存在于一些细胞的细胞核中，对细胞外基质中的硫酸乙酰肝素蛋白多糖具有高亲和力，这阻碍了FGF1从起源组织释放到循环中[7]。在细胞外，FGF1需要通过以硫酸乙酰肝素（heparan sulfate，HS）/硫酸乙酰肝素蛋白多糖（heparan sulfate proteoglycans，HSPG）依赖性的方式与细胞表面的酪氨酸激酶受体/成纤维细胞生长因子受体（fibroblast growth factor receptor，FGFR）结合，使FGFR二聚化，随后细胞内酪氨酸激酶通过自身反式磷酸化激活，这些自磷酸化增加了FGFR的激酶活性，并为下游信号传导的效应器/衔接蛋白产生募集位点，以实现其不同的作用[7]。在哺乳动物

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中，有4个不同的*FGFR*基因（*FGFR1~4*）[7, 9]。FGF1可以结合所有FGFR（FGFR1~FGFR4）及其异构体[10]。但是只有FGFR1和FGFR4能够介导FGF1进入细胞，而FGFR2和FGFR3缺乏这种易位能力[11]。FGFR激活后可以触发多个下游信号通路，包括RAS-MAPK、PI3K-AKT、PLCγ和STAT通路，从而重新编程细胞转录，最终决定细胞命运/反应[12]（图1）。其中，RAS-MAPK和PI3K-AKT途径由FGF受体底物2（FRS2）、生长因子受体结合蛋白2（GRB2）和GRB2相关结合蛋白1（GAB1）组成的支架复合物激活，RAS-MAPK参与控制细胞增殖和分化、肿瘤侵袭和转移、心脏保护、神经发生和脂肪细胞分化，PI3K-AKT的激活调节细胞存活、增殖、迁移、代谢、发育和血管生成，PLCγ与FGFR1的Tyr766处的磷酸酪氨酸残基结合，从而实现PLCγ的磷酸化和激活，STAT3在FGFR1的Tyr677处磷酸化后被募集[12]。最近研究发现，FGF1与肥胖相关并发症密切相关，可参与脂肪分解、降血糖、组织再生、创伤修复、心脏重构等，有望成为治疗肥胖相关并发症的候选药物[13-17]。

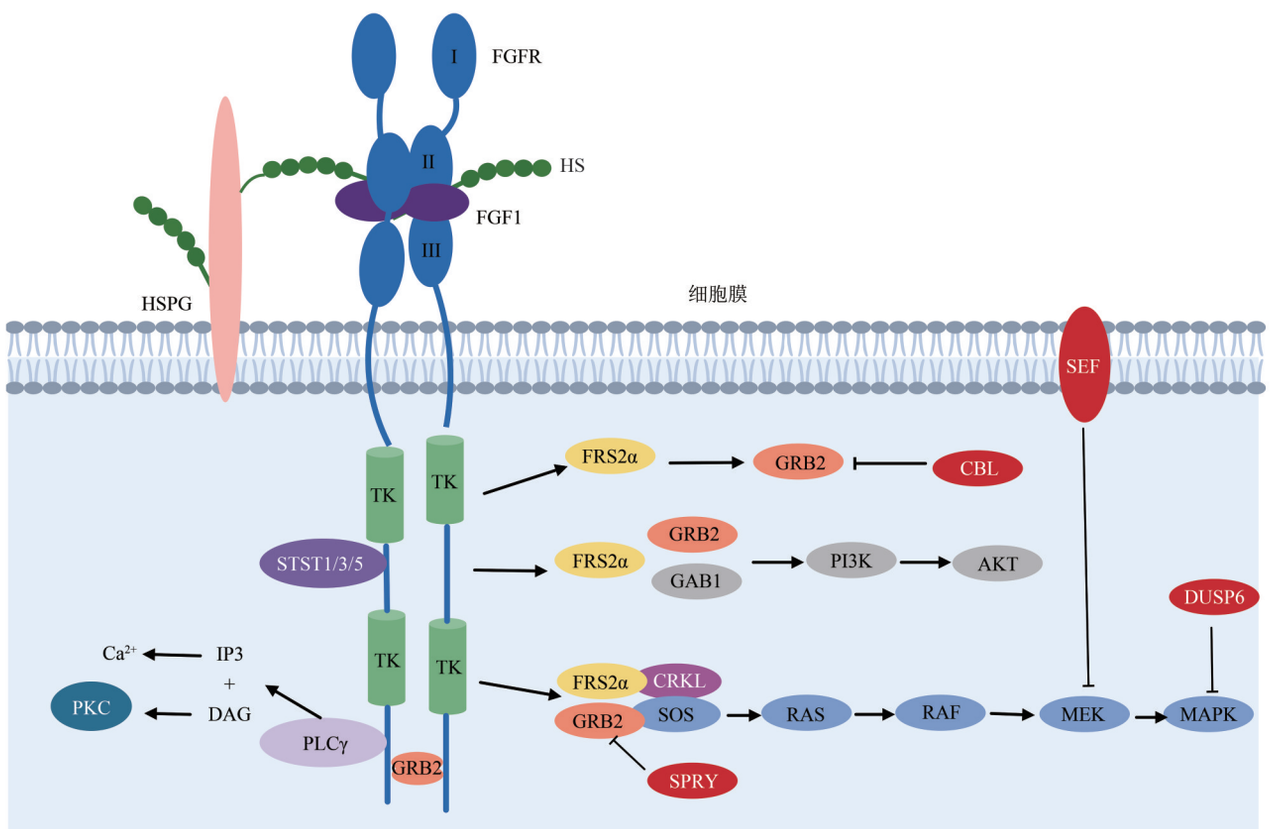

Fig. 1　The molecular action of FGF1

图1　FGF1的分子作用

以HS/HSPG为辅因子的FGF1与FGFR的结合诱导三元复合物FGF-FGFR-HS的形成。激活的受体与细胞内信号通路偶联，包括RAS-MAPK、PI3K-AKT、PLCγ和STAT通路。

1　FGF1与肥胖相关并发症

1.1　FGF1与脂肪调节

白色脂肪组织是脂肪储存和释放的主要部位。这一过程的失衡会导致肥胖及其相关并发症[18]。肥胖中的白色脂肪组织扩张是通过原有脂肪细胞的扩张（肥大）和新脂肪细胞的形成（增生）发生的[19]。肥胖期间脂肪细胞肥大和增生的平衡对包括T2DM在内的肥胖相关并发症有很大影响。

在过度营养条件下或禁食至进食的过渡过程中，脂肪组织会释放自分泌生长因子FGF1。高脂饮食喂养的肥胖小鼠脂肪中FGF1表达增加[20]。研究发现，FGF1与体重指数（body mass index，BMI）或肥胖指标之间的相关性存在矛盾。Wang等[21]报告了BMI和FGF1水平之间的正相关关系，而Zhu等[22]则显示了BMI与FGF1水平之间的负

相关关系。有研究显示，肥胖者皮下白色脂肪组织中FGF1的表达升高，而对循环水平没有影响[23]。尽管发现FGF1在多种组织中表达，但只有脂肪和脑来源的内源性FGF1参与代谢调节。FGF1对脂代谢的影响主要体现在脂肪重塑方面，包括血管中的多种组织病理学、加重的炎症反应、异常脂肪细胞大小分布和胰腺脂肪酶的异位表达[24]。

核受体过氧化物酶体增殖物激活受体γ（peroxisome proliferators-activated receptor γ，PPARγ）是肥胖相关代谢疾病的一个关键参与者，它是脂肪细胞分化和脂肪储存的脂质传感器与主要调节因子，也是噻唑烷二酮（TZD）类胰岛素增敏药物的分子靶点[25]。通过高脂饮食喂养或TZD处理激活PPARγ可诱导白色脂肪组织中FGF1的局部释放[24]。缺乏FGF1的小鼠在高脂饮食喂养后会产生严重的胰岛素抵抗，并表现出异常的白色脂肪结构，其特征是炎症和纤维化增加[24]。这意味着，在能量过剩期间，FGF1作为PPARγ的下游靶点，对白色脂肪组织扩张和血糖控制至关重要。

在高热量饮食条件下，位于脂肪细胞之间的基质血管组织中的未成熟间充质细胞即脂肪前体细胞迅速启动增殖活动，随后经历数周分化为成熟脂肪细胞[26]。白色脂肪的健康扩增需要前脂肪细胞的募集和成熟（即增生），这一过程得到了促血管生成环境、协调的炎症反应和最小细胞外基质沉积的支持；在病理条件下，则主要是预先存在的脂肪细胞扩大（即肥大），以保护其他组织在营养过剩期间免受脂毒性[24, 27]。最近有研究发现，机械敏感的阳离子通道Piezo1介导了饮食诱导的脂肪生成[28]。成熟脂肪细胞中缺乏Piezo1的小鼠在喂食高脂肪饮食时，表现出前脂肪细胞向成熟脂肪细胞的分化缺陷，导致脂肪细胞变大，白色脂肪炎症增加，胰岛素敏感性降低[28]。成熟脂肪细胞中Piezo1的开放会导致FGF1的释放，通过激活FGFR1诱导脂肪细胞前体分化[28]。在大型动物山羊体内，同样证实FGF1通过FGFR1促进肌内脂肪细胞的分化，而在皮下脂肪中则是通过FGFR2促进脂肪细胞分化[29]。可见，脂肪组织可通过FGF1/FGFR信号通路影响脂肪细胞的增殖分化介导肥胖脂肪的生成。

除了对脂肪生成的作用，FGF1还会对脂肪细胞的功能产生直接影响，而不依赖于与其他器官的相互作用。FGF1增加了3T3-L1脂肪细胞、附睾和腹股沟白色脂肪对葡萄糖的摄取[30]。从机制上讲，急性FGF1刺激通过激活胰岛素敏感的葡萄糖转运蛋白GLUT4增加脂肪细胞对葡萄糖摄取，这涉及MEK1/2和AKT信号蛋白之间的动态串扰，而慢性长期FGF1暴露则是通过基础葡萄糖转运蛋白GLUT1的MEK1/2依赖性转录上调介导的[30]。也就是说，FGF1可以依赖性自分泌途径实现对脂肪细胞的摄糖调控，该途径不同于胰岛素的降血糖作用。

综上，FGF1对脂肪的发育、沉积和功能发挥着不可替代的作用，高脂饮食可通过营养感应和机械感应两种独立的机制调节可用的FGF1，影响脂肪细胞功能，以参与肥胖及其并发症的调节（图2）。

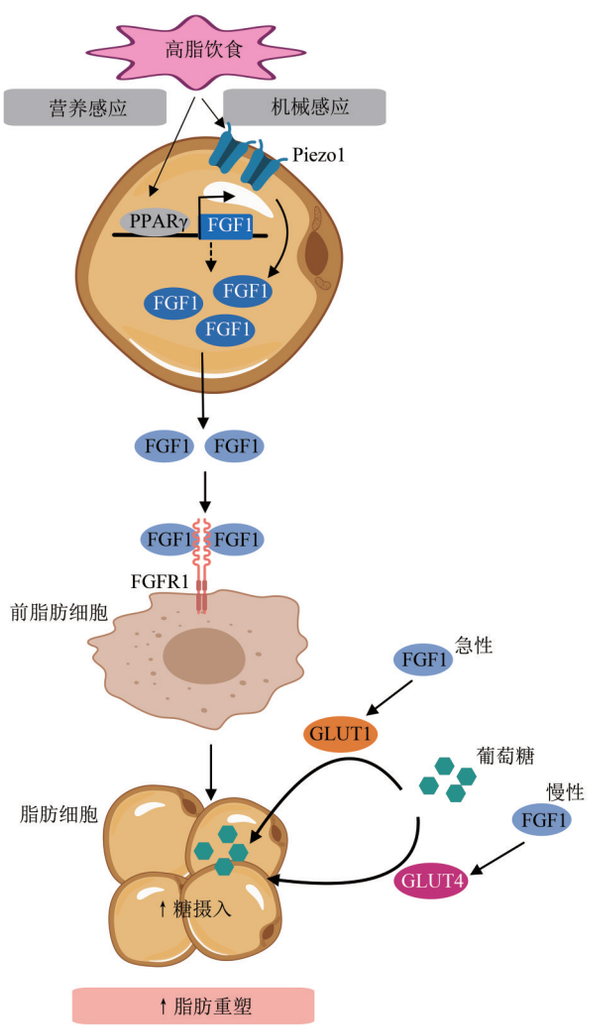

Fig. 2　The regulatory effect of FGF1 on fat

图2　FGF1对脂肪的调节作用

高脂饮食诱导的脂肪重塑依赖于PPARγ和Piezo1下游FGF1的作用。一方面，高脂饮食（HFD）提高了循环PPARγ配体的水平，导致FGF1表达增加（营养感应）。另一方面，HFD或Piezo1的药理学激活导致成熟脂肪细胞释放FGF1（机械感应）。FGF1通过GLUT1/4增加脂肪细胞对葡萄糖的摄取，调节脂肪细胞的功能。

1.2　FGF1与T2DM

由于不健康和久坐的生活方式，肥胖相关并发症T2DM已成为全球流行病，危害人体健康[12]。在被诊断为T2DM的患者中，一个典型的特征是胰岛素抵抗，胰岛素的疗效降低，使其无法发挥正常的生理功能，导致血糖水平升高。高血糖持续刺激胰岛素分泌，形成高胰岛素血症，长期高胰岛素会加重胰岛素抵抗，形成恶性循环[31]。胰岛素抵抗已成为医疗实践中常见的健康问题，与肥胖密切相关[32]。最近，FGF1被鉴定为一种代谢激素，通过外周和中枢作用，在调节胰岛素敏感性、血糖控制和营养压力方面发挥着关键作用（图3）[33-34]。

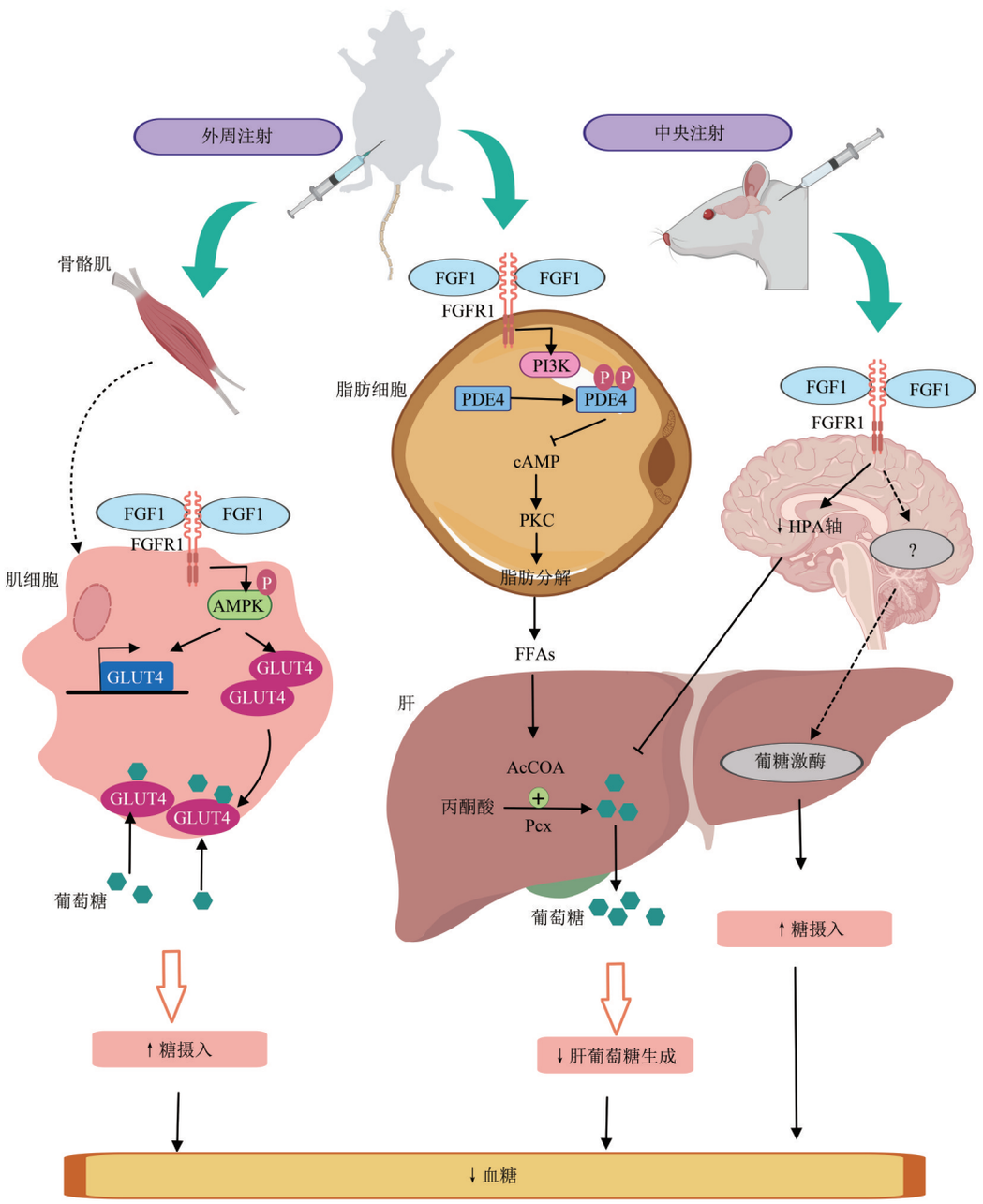

Fig. 3　The regulation effect of FGF1 on blood glucose

图3　FGF1对血糖的调节作用

FGF1通过中枢和外周发挥其血糖调节作用。外周注射FGF1通过激活成熟脂肪细胞中FGFR1/PI3K下游的PDE4D，随后抑制cAMP-PKA-HSL轴来抑制脂解，导致游离脂肪酸（free fatty acid，FFA）和丙酮酸羧化酶活性的下调，从而降低肝葡萄糖生成（hepatic glucose production，HGP），降低血糖。外周注射FGF1还可以通过促进骨骼肌FGFR1和AMPK介导的GLUT4的表达并增加GLUT4向质膜的易位，以降低肌肉对葡萄糖的摄取，降低血糖。中枢注射FGF1通过未知的脑-肝轴诱导肝葡萄糖激酶来增加肝葡萄糖摄取，并通过限制下丘脑-垂体-肾上腺（hypothalamic-pituitary-adrenal，HPA）轴的活性来减少HGP，从而降低葡萄糖水平。

胰岛素抵抗、脂解和肝葡萄糖生成（hepatic glucose production，HGP）的不可逆增加是T2DM的标志。研究发现，高脂肪饮食喂养的FGF1敲除小鼠会出现严重的高血糖和胰岛素抵抗[24]。FGF1与T2DM患者的血糖控制能力密切相关[35]。外周注射FGF1可通过抑制脂解和减少HGP，部分逆转高血糖[16]。单剂量重组FGF1（rFGF1）的胃肠外给药可以使ob/ob、db/db和饮食肥胖小鼠的血糖水平正常化，而不会引发低血糖[36]。此外，rFGF1蛋白的慢性治疗通过促进骨骼肌中胰岛素依赖性葡萄糖摄取和抑制HGP来引起持续的葡萄糖降低，从而实现全身胰岛素增敏[36]。在aP2-Cre驱动的Fgfr1消融小鼠中，rFGF1的降血糖和胰岛素增敏作用被消除，这表明FGF1的抗糖尿病作用部分由脂肪组织中的FGFR1介导[36]。从机制上讲，FGF1通过诱导磷酸二酯酶4D（PDE4D）的Ser44位点磷酸化将其激活，随后抑制cAMP-PKA轴来抑制脂肪组织中的脂解，从而导致HGP的急性下调[16]。FGF1的这种降血糖作用不依赖于胰岛素通过抑制PDE3B发挥血糖调节功能。

除了其外围作用外，越来越多的证据表明，FGF1的抗糖尿病活性也与其中枢作用相关。FGF1可以穿过血脑屏障，提高脑内FGF1水平[37]。将FGF1输注到侧脑室中诱导了进食行为的减少，提示FGF1与进食抑制的中央调节有关[38]。在ob/ob和db/db小鼠以及瘦素受体缺乏的Zucker糖尿病脂肪大鼠中，以外周给药剂量的1/10的剂量单次侧脑室注射rFGF1蛋白可导致高血糖持续缓解数周[39]。侧脑室注射FGF1已被证明可以通过抑制下丘脑-垂体-肾上腺轴来逆转链脲佐菌素诱导的1型糖尿病大鼠的糖尿病，从而降低HGP、肝乙酰辅酶A水平和脂解作用[40]。下丘脑神经元和神经胶质细胞，如伸展细胞和星形胶质细胞，被认为是FGF1中枢作用的靶点[41]。在T2DM啮齿类动物模型中，FGF1可以诱导下丘脑MAPK/ERK信号的持续激活，增加下丘脑星形胶质细胞与神经元的相互作用，引发高血糖的持续缓解[42]。然而，赋予FGF1对抗高血糖的中枢作用的神经元和特定大脑区域的确切类型仍然难以捉摸。

有证据表明，FGF1还调节胰岛β细胞的功能。外周注射FGF1可增加糖尿病小鼠胰岛中的β细胞密度和离体胰岛素分泌[43]。中枢和外周FGF1给药增加了糖尿病小鼠离体胰岛的胰岛素分泌，外周FGF1增加了胰岛β细胞密度[43]。在斑马鱼中，营养过剩通过FGF1信号传导诱导β细胞的补偿性分化，FGF1的失活消除了补偿性β细胞分化。人FGF1在FGF1$^{-/-}$动物的β细胞中的表达挽救了补偿反应[44]。另一项研究表明，在糖尿病大鼠模型中，中央注射FGF1延缓了进行性β细胞损失的发生，FGF1的中枢作用诱导的高血糖持续缓解涉及胰岛β细胞功能的保护[45]。在新诊断为T2DM的患者和健康对照组中，FGF1水平较高的参与者的糖化血红蛋白较低[46]。胰岛素分泌低的个体的血清FGF1浓度显著升高[47]。这表明，FGF1与人类胰岛β细胞功能之间可能存在相互作用，FGF1可能诱导胰岛结构和功能的长期变化来实现对血糖的调节作用。

除了改善糖尿病患者的血糖调控能力和胰岛素抵抗，FGF1还对糖尿病诱导的并发症具有一定作用。由于持续暴露于高糖，糖尿病患者很容易发生足部溃疡、糖尿病肾病、糖尿病肝损伤、血管和周围神经病变等一系列并发症。FGF1与糖尿病患者伤口的愈合密切相关，可以通过提高细胞增殖能力、促进细胞外基质合成、促进血管生成、增殖和分化，显著增加溃疡组织中毛细血管和成纤维细胞的数量，并增强转化生长因子β和核抗原增殖蛋白的表达，从而改善糖尿病溃疡组织[48-49]。有研究报道，FGF1通过NF-κB和JNK途径，发挥抗炎和肾保护活性，抑制糖尿病小鼠肾小球和肾小管损伤，改善肾功能不全，进而改善糖尿病肾病[50-51]。FGF1可阻断细胞应激和自噬，减轻糖尿病介导的db/db小鼠的肝纤维化、肝细胞脂肪变性、细胞凋亡和其他病理特征，通过抑制晚期糖基化终产物受体（RAGE）的表达来改善糖尿病诱导的肝细胞凋亡和炎症[52-53]。Wu等[54]还发现，FGF1会触发脾脏中TLR4、MyD88和NF-κB p65蛋白以及下游促炎细胞因子（IL-6和TNF-α）的表达下调，逆转糖尿病诱导的脾肿大和功能障碍。aFGF通过Wnt/β-catenin介导的HXK2上调来降低氧化应激，从而减轻糖尿病内皮功能障碍[55]。此外，据报道，FGF1可以通过降低氧化应激和抑制脑源性神经营养因子的水平，减轻神经炎症水平，改善糖尿病诱导的认知能力下降[56-57]。作为aFGF，FGF1在T2DM发病过程中还可通过调控受损神经纤维的节段性脱髓鞘的病理变化，改善糖尿病周围神经病变[58]。

综上，FGF1作为一种代谢调节剂，在调节糖脂代谢中发挥着重要作用，可通过外周和中枢作用控血糖，增强胰岛素敏感性，改善胰岛素抵抗，并

对糖尿病并发症产生一定的作用，有望成为未来治疗T2DM的新靶点。

1.3 FGF1与NAFLD

NAFLD与肥胖相关代谢综合征密切相关，已成为近几十年来最常见的慢性肝病，其患病率正以惊人的速度增加[59-60]。肥胖是NAFLD进展的一个重要风险因素，在NAFLD中，过量的脂质以甘油三酯的形式储存在肝细胞中，导致脂肪变性[61]。NAFLD是一组疾病，从轻度脂肪变性到严重的非酒精性脂肪性肝炎（non-alcoholic steatohepatitis，NASH），其全球患病率约为30%，并在持续增加[62]。因NAFLD造成的经济负担也在逐渐加重，且因地理区域和种族而异[63]。最近，几个专家小组主张将代谢相关脂肪性肝病（metabolically associated fatty liver disease，MAFLD）作为反映NAFLD异质性的更好术语[64]。

据报道，FGF1与脂肪肝的发生发展密切相关[65]。在MAFLD动物模型中，FGF1治疗改善了肥胖相关的脂肪变性[36]。脂肪变性是NAFLD的早期阶段。新出现的证据表明，表观遗传学修饰，特别是DNA甲基化，在MAFLD的发病机制中发挥着关键作用[66-68]。基因甲基化是指DNA甲基转移酶将甲基共价连接到鸟嘌呤附近的胞嘧啶上，DNA甲基化在代谢性疾病中受到动态调节[69]。脱氧核糖核酸甲基转移酶3A（DNA methyltransferases 3A，DNMT3A）和脱氧核糖核酸甲酯转移酶3B（DNA methyltransferases 3B，DNMT3B）是哺乳动物胚胎发育所必需的两种关键的从头脱氧核糖核酸甲基转移酶[70]。胰岛素样生长因子结合蛋白2（insulin-like growth factor binding protein 2，IGFBP2）已被确定为肥胖相关代谢紊乱的关键调节因子[71]。肥胖小鼠内脏白色脂肪组织和肝脏中IGFBP2的表达显著减少，其过表达对肥胖小鼠中MAFLD的发展起保护作用[72]。最近发现，FGF1信号传导的下调可通过抑制DNMT3B导致体外受精相关的DNA甲基化缺陷[73]。在小鼠高脂肪饮食诱导的MAFLD模型中，用rFGF1进行慢性治疗可以有效降低胰岛素抵抗、高脂血症和炎症的严重程度。从机制上讲，rFGF1处理减少了DNMT3A向*IGFBP2*基因组位点的募集，导致*IGFBP2*基因甲基化减少，mRNA和蛋白质表达增加[74]。可见，FGF1通过IGFBP2表达的表观遗传学调控调节葡萄糖和脂质代谢，进而改善小鼠肥胖相关的肝脂肪变性。FGF1是一种特性良好的有丝分裂原，具有强大的抗氧化特性[75]。由于FGF1可以促进肝源性干细胞的分化和成熟，基于对氧化应激的抑制，其在肝脏疾病中的治疗益处已被广泛研究[76]。新出现的证据表明，FGF1抑制肝脏氧化应激的能力是通过激活腺苷酸活化蛋白激酶（AMP-activated protein kinase，AMPK）实现的，AMPK随后激活核因子红细胞2相关因子2介导的抗氧化途径[76]。非肌源性FGF1的系统给药已被证明可以通过激活肝脏中的AMPK来减轻肥胖诱导的NAFLD[76]。

NASH是NAFLD发展到晚期出现的一种侵袭性脂肪性肝炎，以肝细胞气球状突起和小叶炎症伴或不伴纤维化为特征[77]。40%的NASH患者会发生纤维化，纤维化的严重程度是NASH患者长期预后的关键指标[78-79]。在NASH小鼠模型中，单剂量的rFGF1的给药不影响胶原沉积，但改善了肝脏炎症和肝细胞损伤[80]。FGF1信号参与调解肝纤维化，对NASH的治疗可能具有积极作用[81]。此外，NASH的发生发展还与线粒体功能障碍密切相关[82-83]。有研究显示，FGF1信号还可参与调节肝细胞中的线粒体呼吸[84]，这意味着FGF1可能通过线粒体功能调节改善NASH。

综上，FGF1从轻度脂肪变性到严重的NASH都可参与调节，对NAFLD的治疗和预后可能具有重要作用。

1.4 FGF1与癌症

过去几十年来，肥胖和糖尿病的发病率显着增加，预计未来几年患病率将进一步上升。许多观察结果表明，肥胖和糖尿病与多种癌症的风险增加有关[85]。据估计，30%~40%的癌症可以通过改变可改变的生活方式和已知与癌症发病率相关的环境风险因素来预防。肥胖是13种不同部位癌症（子宫内膜癌、绝经后乳腺癌、结直肠癌、食管癌、肾癌、脑膜瘤、胰腺癌、贲门癌、肝癌、多发性骨髓瘤、卵巢癌、胆囊癌和甲状腺癌）的已知危险因素[86]。

成人体重增加是癌症风险的一个独立指标，肥胖是乳腺癌症发展和乳腺癌特异性死亡率的一个既定风险因素[87]。BMI被用来定义肥胖，但在个体水平上，它可能不是乳腺癌症风险或预后的最佳预测指标[88]。在体重增加的过程中，脂肪组织膨胀并产生许多生长因子，其中包括FGF1。在正能量平衡期间，FGF1刺激脂肪组织的增生生长对个体有益，因为它可以防止脂肪营养不良和异位脂质沉

积。然而，脂肪细胞产生的生长因子也可以刺激附近的癌症细胞，特别是在脂肪和上皮相互接近的乳房中[88]。研究发现，在卵巢切除后体重增加的过程中，肥胖雌性小鼠的乳腺脂肪中FGF1升高，并且与女性乳腺脂肪组织中的BMI直接相关[89]。在体外乳腺癌细胞中，FGF1以时间依赖的方式内化到细胞中[90]，提高癌症乳腺细胞的放射敏感性[91]。最近有研究显示，FGFR1和雌激素受体（estrogen receptor，ER）水平之间存在显著的负相关，ER阳性的乳腺癌患者FGFR1蛋白高表达与乳腺癌预后不良相关[92]。在体重增加的肥胖女性中，局部产生的FGF1可能激活ER，以促进癌症细胞代谢重编程和肿瘤进展，而不依赖于雌激素[93]。阻断FGF1与其受体FGFRD2的结合可抑制乳腺癌症细胞系的增殖活性[94]。此外，FGF1还与乳腺癌的恶性发展有关[95]。

肾细胞癌起源于肾小管上皮细胞，是一种常见的恶性肿瘤，在成人尿路恶性肿瘤中仅次于膀胱癌[96]。在肾细胞癌中，65%~70%为透明细胞肾细胞癌，其具有不同于其他肾细胞癌亚型的特定显微镜外观。肾细胞癌一般存在许多分子遗传异常，包括染色体数目或结构异常、染色体易位引起的基因突变、扩增或融合基因[97]。有研究显示，无论种族、年龄、癌症分级和分期，透明细胞肾细胞癌患者的肾组织*FGF1*基因表达均存在缺失，并与患者的总生存率显著相关，FGF1表达越高，生存率越高[98]。这表明，FGF1具有潜在的肾脏肿瘤抑制功能。

FGF1还参与其他多种癌症的发生发展。研究表明，细胞内FGF1与甲状腺癌的侵袭和迁移有关[99]。FGF1介导的PI3K-AKT信号通路参与卵巢癌细胞的增殖和迁移[100]。FGF1上调促进肝脏肿瘤生长和化疗药物的耐药性[101]。激活FGF1/FGFR轴可促进鼻咽癌的进展[102]。这些结果显示了，FGF1在多种肿瘤细胞的发生发展中的关键作用，预示着其潜在靶点治疗意义。

癌症耐药性是一种常见的、不可预测的现象，在多种类型的肿瘤中都会发生，导致当前抗癌疗法疗效不佳。除了直接作用于肿瘤，FGF1还可作用于肿瘤细胞的耐药性，影响患者的生存和化疗反应，间接抗肿瘤[103]。具有表皮生长因子受体（epidermal growth factor receptor，EGFR）激活突变的非小细胞肺癌患者对EGFR酪氨酸激酶抑制剂TKI的治疗敏感，但存活的药物耐受细胞会充当可能出现耐药性肿瘤的储库，EGFR-丝氨酸/苏氨酸/酪氨酸激酶1（STYK1）-FGF1轴可以维持对EGFR抑制剂的功能性药物耐受[104]。FGF1信号通路介导的高保真同源重组DNA损伤修复促进卵巢癌的耐药性[105]。这些充分说明FGF1在癌症耐药性中的重要作用。

综上，FGF1与多种癌症的发生发展均密切相关，可能作为癌症的有效治疗靶点，提高抗癌药物的疗效，发挥直接和间接抗癌作用。

1.5　FGF1与心脏病

心血管系统是我们身体中最重要的系统之一。它可以将氧气和营养物质输送到组织和器官，也可以将组织和器官的废物输送到排泄器官，以维持身体的稳态并支持正常的生命活动，一旦其功能受到影响，其结果可能是灾难性的。超重和肥胖成年人中心血管疾病的患病率较高，其危险因素与BMI密切相关[106-107]。

FGF1 mRNA在多种组织中高度表达，FGF1蛋白在心脏和肾脏中富集[108]。在体内，内源性FGF1及其受体在胎儿心脏发育过程中表达显著[109]。研究显示，转基因小鼠心肌中FGF1的过表达可以增加出生后小鼠的冠状动脉和支干密度[110]。在体外，FGF1已被证明可通过受体FGFR1刺激新生儿心肌细胞重新进入细胞周期[111]。FGF1可通过FGF1/FGFR/PKC信号轴调节小鼠胚胎干细胞向心肌细胞分化[112]。此外，FGF1还与主动脉血管平滑肌细胞的增殖和迁移有关[113]。这表明FGF1可能在心血管系统的发育和再生中具有关键的调节作用。

FGF1具有提高心肌细胞存活率，保护心脏功能的作用[114]。动物和细胞研究表明，FGF1在缺血/再灌注条件下发挥心脏保护作用[115-116]。FGF1的过表达可以通过FGFR介导的信号传导和蛋白激酶C（protein kinase C，PKC）依赖性途径保护心脏免受损伤[117]。FGF1可以通过调节氧化应激和钠/钙稳态降低肺静脉和心房心律失常的发生[118]。在小鼠心肌梗死模型中，纳米颗粒介导的FGF1心肌纤维递送可增强心肌细胞的再生能力，通过改善心肌代谢来保护心脏免受缺血性损伤[119-120]。除了缺血性心脏保护作用外，rFGF1还可通过增强线粒体氧化磷酸化能力和PGC-1α/β的表达，达到防止心脏肥大模型动物的病理性心脏重塑的功能[14]。最近，有研究显示，FGF1的这种心脏保护作用，会在其受体FGFR1甲基化的过程中消失，FGFR1

甲基化通过破坏脂质代谢导致心脏功能障碍[121]。这意味着，FGF1在心脏功能发挥中的作用至关重要，可以通过抑制氧化应激、心脏纤维化、细胞凋亡和下调炎症反应，来改善心脏功能和提高细胞存活率。

FGF1保护心脏的作用还体现在减轻药物诱导的心脏毒性方面。阿霉素作为蒽环类药物，是抗癌化疗的常用药。以蒽环素为基础的化疗可导致累积性和渐进性心肌病的发展，从而导致患者心力衰竭甚至死亡[122]。研究发现，阿霉素处理的小鼠心脏和心肌细胞中FGF1的mRNA和蛋白质水平降低[123]。添加外源性FGF1能够在体外增强胚胎小鼠心室细胞的迁移，减轻阿霉素引起的心肌损伤[124]。从机制上讲，细胞内FGF1可以通过与p53直接相互作用来保护细胞免于凋亡[125]，FGF1突变体通过Sirt1介导的p53去乙酰化，促进MDM2介导的p53泛素化和蛋白酶体依赖性降解，从而逆转心脏氧化损伤和细胞凋亡，达到保护心肌重塑和功能障碍免受化疗影响的作用[123]。这些结果表明，FGF1对阿霉素诱导的心脏毒性具有潜在的保护作用。

综上，FGF1在心血系统的发生发展及改善心血管疾病如缺血/再灌注损伤、心肌梗死、病理性心脏重塑和心脏毒性等中发挥着重要作用。

2 FGF1类似物/模拟物的生物制药开发

作为一种经典的有丝分裂原，尽管FGF1参与脂肪重塑，具有强大的降血糖和胰岛素增敏作用，可缓解脂肪肝、抵抗癌症和保护心脏，其代谢调节活性的发现拓宽了其功能多样性，并为代谢性疾病治疗（如MAFLD和T2DM）带来了新的希望。前文已述，FGF1可与特定的细胞表面酪氨酸激酶受体结合并激活细胞内信号转导，会导致多种细胞类型的增殖和分化。因为FGF1具有较强的有丝分裂活性，长期使用会导致肿瘤发生的风险增加，故其体内使用受限，并抑制了开发其治疗肥胖相关并发症的热情。然而，有研究发现，FGF1主要通过FGFR3和FGFR4诱导细胞增殖，但其代谢活性主要由FGFR1介导[36, 126-127]。也就是说，FGF1的促有丝分裂和抗肥胖相关并发症活性似乎是可分离的。目前，已经开发出很多工程化的FGF1变体，如$FGF1^{\Delta HBS}$、$MT\text{-}FGF1^{\Delta HBS}$、$FGF1^{\Delta NT}$、ΔnFGF1、$FGF1^{R50E}$等（图4），它们的代谢活性有待进一步研究。

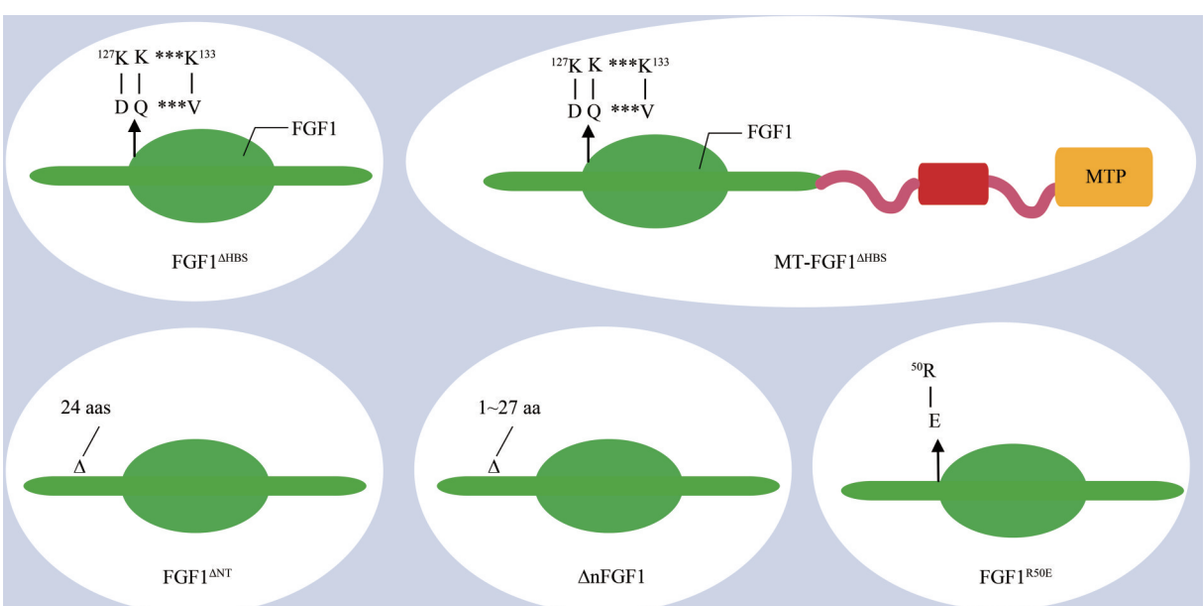

Fig. 4 FGF1 mutant structure

图4 FGF1突变体

$FGF1^{\Delta HBS}$通过HBS中3个赖氨酸残基（K127D、K128Q和K133V）的突变产生；$MT\text{-}FGF1^{\Delta HBS}$通过将$FGF1^{\Delta HBS}$与骨骼肌靶向肽MT相连而成；$FGF1^{\Delta NT}$通过其N末端结构域上24个氨基酸（aa）的缺失产生；ΔnFGF1通过其N末端结构域上1~27位氨基酸的缺失产生；$FGF1^{R50E}$通过整联蛋白结合位点中Arg50突变为Glu产生。

FGF1$^{\Delta HBS}$是通过三点突变抑制FGF1-FGFR二聚体的稳定性，以降低对肝素的亲和力，从而使有丝分裂和代谢活性解耦联，在降低其促有丝分裂潜能同时充分保留其代谢调节活性来最大限度地降低其癌症风险[128]。研究发现，肝素结合减少的FGF1$^{\Delta HBS}$配体即使在肝素联合给药的情况下也能保护心脏免受缺血再灌注损伤[129]。FGF1$^{\Delta HBS}$可通过维持线粒体稳态和减少氧化应激来预防糖尿病心肌病[130]，通过抑制足细胞上皮-间充质转化、耗竭、肾纤维化，保护肾功能免受糖尿病肾病的影响[131]，并延缓晚期T2DM小鼠的糖尿病肾病进展[132]。此外，FGF1$^{\Delta HBS}$还可以通过激活AMPK抑制肝脏炎症、氧化应激和脂质失调，在T2DM晚期逆转NAFLD[76]。

然而，长期服用FGF1$^{\Delta HBS}$会导致食欲急剧下降，随后体重大幅减轻。在一项使用食蟹猴的临床前安全性评估中，一只服用过量FGF1$^{\Delta HBS}$的猴子在第18天死亡[133]。FGF1$^{\Delta HBS}$由于缺乏组织选择性，可以在许多组织中不加选择地激活其信号通路，这可能导致毒副作用的发生率增加。Zhou等[134]将骨骼肌靶向肽（MT）与FGF1$^{\Delta HBS}$融合（MT-FGF1$^{\Delta HBS}$），在全身给药后特异性地定位于骨骼肌组织，通过激活AMPK以恢复骨骼肌细胞中受损的肌肉GLUT4表达和易位，并在db/db小鼠中发挥强大的降血糖作用。最重要的是，MT-FGF1$^{\Delta HBS}$的慢性治疗对食物摄入、体重或膀胱增生风险没有不良影响，这表明MT-FGF1$^{\Delta HBS}$可能是治疗T2DM的一种有前途的药物。

FGF1$^{\Delta NT}$是FGF1的一种变体，它缺乏N端的前24个氨基酸残基。这种变体降低了配体对FGFR的结合亲和力，降低了增殖特性，同时保持了代谢调节活性[36]。在体外，FGF1$^{\Delta NT}$激活FGFR下游细胞内信号的能力有所减弱，但有丝分裂活性严重降低。遗传和饮食诱导的糖尿病小鼠模型中，FGF1$^{\Delta NT}$的胃肠外给药剂量依赖性地降低了血糖水平，但不会影响脂肪组织Fgfr1特异性敲除小鼠的血糖[36]。更有甚者，FGF1$^{\Delta NT2}$（FGF1 L29~D155）突变体在体外可严重减弱FGFR介导的信号转导，对糖尿病小鼠的血糖也不会产生显著影响[36]。这进一步支持了FGFR1介导的信号传导是胃肠外FGF1的葡萄糖降低作用所必需的观点，同时，也提示FGF1$^{\Delta NT}$可能具有糖尿病治疗的前景。

ΔnFGF1是FGF1的非有丝分裂变体，缺乏N端1~27氨基酸残基，该变体不促进细胞增殖，但仍保留FGF1的代谢活性[135]。ΔnFGF1处理的db/db小鼠的胰岛素分泌和胰岛β细胞凋亡显著改善，ΔnFGF1处理显著抑制糖脂毒性诱导的胰岛β细胞凋亡[135]。从机制上讲，ΔnFGF1通过激活AMPK/SIRT1/PGC-1α信号通路对β细胞发挥保护作用。这些发现表明，ΔnFGF1保护胰岛β细胞免受糖脂毒性诱导的功能障碍和细胞凋亡的影响，可能对胰岛素抵抗和糖尿病具有治疗作用。

FGF1^{R50E}，即FGF1突变体（Arg-50 to Glu，R50E），整合素结合缺陷的FGF1突变体。整合素（αvβ3）通过串扰参与FGF信号传导，FGF1的整合素结合位点与肝素结合位点重叠，但与FGFR结合位点不同。R50E的整合素结合功能有缺陷，但仍与肝素和FGFR结合，在诱导FGFR1-FGF1-αvβ3三元复合物形成、细胞增殖和细胞迁移方面存在缺陷，并在体外抑制野生FGF1诱导的FGF1信号传导[136]。也就是说，R50E可以作为FGFR1的拮抗剂。研究发现，R50E可以抑制由FGF1或FGF2诱导的血管生成，从而间接抑制肿瘤发生，此外它可能对体内肿瘤细胞增殖产生直接影响[137]。最近，有研究证明，侧脑室注射FGF1^{R50E}仅能诱导短暂下丘脑MAPK/ERK信号转导，未能模拟FGF1诱导的持续葡萄糖降低[42]。因此，我们认为R50E具有作为抗癌和抗血管生成治疗剂（“FGF1诱饵”）的潜力，但其降血糖等代谢活力仍有待确定。

此外，在许多类型的癌症中，各种天然产物已被证明可以抑制肿瘤的发生和转移，而不会引起任何毒性或不良副作用。因此，天然产物可能降低FGF1的促有丝分裂功能，包括天然产物与FGF1的联合治疗可能能够促进FGF1的临床应用，同时将癌症的风险降至最低。如白藜芦醇和FGF1联合治疗可通过激活SIRT1-NRF2途径协同改善阿霉素诱导的心脏毒性[138]，可通过AMPK/NRF2途径保护阿霉素治疗后的急性肝毒性[139]。

3　FGF1类似物/模拟物的临床挑战

目前，FGF1类似物/模拟物的临床研究主要集中在肢体缺血、神经损伤、黏膜愈合等方面。FGF1作为一种治疗肥胖相关并发症的新型临床药物的开发正在不断推进，尽管FGF1对肥胖相关并发症的作用已在啮齿类动物的许多研究中得到复制，但相关临床应用的研究结果较少。一项临床研究对40例冠心病患者进行了一项双盲实验，将患者随机分为实验组和对照组，所有患者均因其冠状

动脉多发性疾病而接受主动脉-冠状动脉搭桥术，在手术过程中将FGF1注入实验组患者心肌。手术3个月后以及3年后，在应用FGF1的实验组患者中发现从冠状动脉引发的毛细血管网络。FGF1诱导新血管生成可能成为一种治疗方法，尤其是在弥漫性冠状动脉疾病患者中[140]。然而，必须进行进一步的研究，以证明FGF1治疗的长期临床效果。目前，关于FGF1治疗肥胖相关并发症的临床研究少，这主要是因为：一方面，FGF1在大型动物和人类中的安全性和治疗效果需要进一步评估；另一方面，对肿瘤发生的担忧是将FGF1开发为终身治疗药物的另一个主要障碍。进一步深入研究，精确定义FGF1的靶组织、亚型和赋予FGF1代谢益处的细胞内信号通路，可能有助于开发基于FGF1的药物疗法，提高其治疗肥胖相关并发症的特异性、安全性和有效性。

4 结　　语

本综述总结了FGF1代谢功能的最新临床前和临床发现，强调FGF1类似物和激动剂用于治疗肥胖相关并发症的生物制药开发的最新进展，讨论目前将基于FGF1的药物治疗从试验台转化为临床的挑战，并提出解决这些障碍的可能策略。

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FGF1−based Drugs for The Treatment of Obesity−related Complications*

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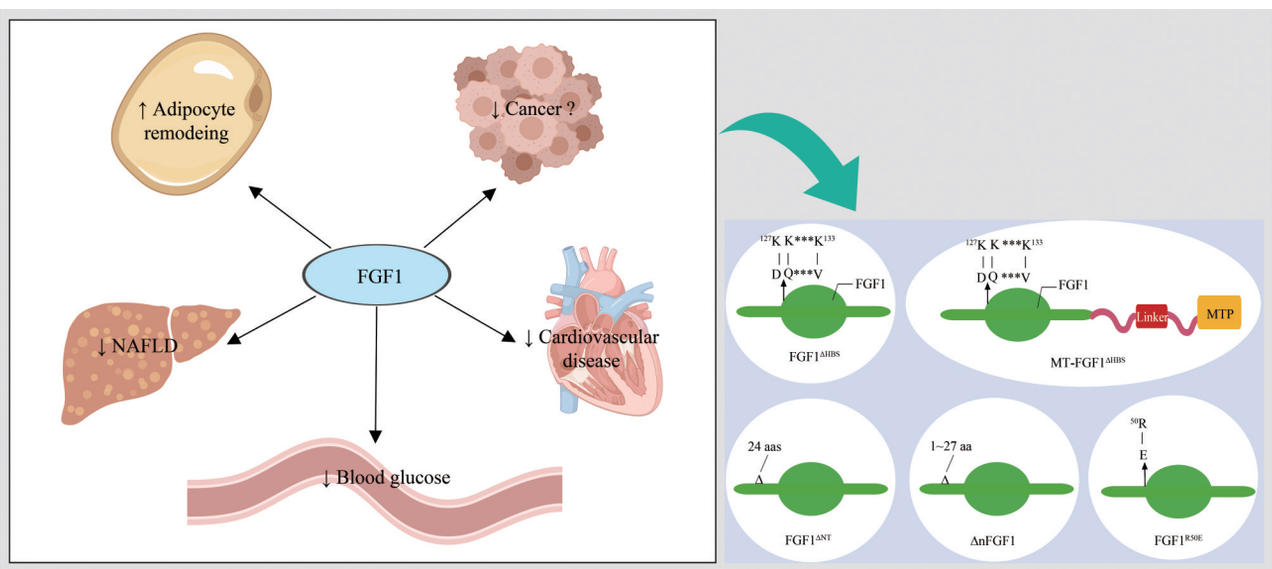
Graphical abstract



Abstract　At present, the incidence of overweight and obesity has reached epidemic levels worldwide, which call a challenge to the prevention and control of chronic metabolic diseases. Because obesity is a major risk factor for a range of metabolic diseases, including type 2 diabetes (T2DM), non-alcoholic fatty liver disease (NAFLD), cardiovascular and neurodegenerative diseases, sleep apnea, and some types of cancer. However, the drugs remain limited. Therefore, there is an urgent need to develop effective long-term treatments to address obesity-related complications. Fibroblast growth factor 1 (FGF1) is an important regulator of systemic energy homeostasis, glycolipid metabolism and insulin sensitivity. FGF1 is a non-glycosylated polypeptide consisting of 155 amino acids, consisting of 12 inverted parallel β chains with amino and carboxyl terminus, and N-terminus extending freely without the typical secretory signaling sequence, closely related to its own biological activity. Thus, FGF1 mutants or derivatives with different activities can be designed by substitution or splicing modification at the N-terminal. FGF1 plays an irreplaceable role in the development, deposition and function of fat. High-fat diet can regulate available FGF1 through two independent mechanisms of nutritional perception and mechanical perception, and influence the function of fat cells. FGF1 controls blood glucose through peripheral and central

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effects, enhances insulin sensitivity, improves insulin resistance, and plays a role in diabetic complications, which is expected to become a new target for the treatment of T2DM in the future. FGF1 may be involved in the regulation of NAFLD from mild steatosis to severe non-alcoholic steatohepatitis. FGF1 is closely related to the occurrence and development of a variety of cancers, improve the efficacy of anti-cancer drugs, and play a direct and indirect anti-cancer role. In addition, FGF1 plays an important role in the occurrence and development of the cardiovascular system and the improvement of cardiovascular diseases such as ischemia/reperfusion injury, myocardial infarction, pathological cardiac remodeling, cardiotoxicity. Therefore, FGF1 shows a number of therapeutic benefits in the treatment of obesity and obesity-related complications. But because FGF1 has strong mitotic activity and long-term use has been associated with an increased risk of tumorigenesis, its use *in vivo* has been limited and enthusiasm for developing it to treat obesity-related complications has been dampened. However, FGF1 was found to induce cell proliferation primarily through FGFR3 and FGFR4, but its metabolic activity was mainly mediated by FGFR1. That is, FGF1 activity that promotes mitosis and anti-obesity-related complications appears to be separable. Currently, many engineered FGF1 variants have been developed, such as $FGF1^{\Delta HBS}$, MT-$FGF1^{\Delta HBS}$, $FGF1^{\Delta NT}$, ΔnFGF1, $FGF1^{R50E}$. Although the effect of FGF1 or its analogues on obesity-related complications has been demonstrated in many rodent studies, there are no relevant clinical results. This may be due to the unknown safety and therapeutic efficacy of FGF1 in large animals and humans, as well as concerns about tumorigenesis that hinder its development into a lifelong therapeutic agent. This review summarizes recent advances in the development of FGF1-based biologic drugs for the treatment of obesity-related complications, highlights major challenges in clinical implementation, and discusses possible strategies to overcome these obstacles.

Key words FGF1, obesity, lipid metabolism, diabetes, non-alcoholic fatty liver disease, cancer
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