

PI3K/Akt/mTOR 通路与足细胞自噬在糖尿病肾病 肾功能修复中的研究

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摘要:糖尿病肾病(DKD)是机体长期糖、脂代谢紊乱引起的肾脏损伤。足细胞损伤是导致蛋白质漏出,肾脏纤维化的直接原因。自噬是足细胞的自我保护机制,可识别并清除受损、衰老的细胞器与生物大分子物质,调节细胞增殖与代谢。在DKD个体中,自噬相关蛋白表达减少,肾小球足细胞的稳态难以维持。现有研究表明,PI3K/Akt/mTOR信号通路通过自噬途径促进细胞自我修复。本文旨在对多种因子共同参与PI3K/Akt/mTOR通路调节自噬,延缓肾功能恶化做出归纳总结,以期对药物研发以及肾功能修复治疗提供参考。

关键词:糖尿病肾病;足细胞;自噬;PI3K/Akt/mTOR通路

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The study of PI3K/Akt/mTOR Pathway and Podocyte Autophagy in Renal Function Repair of Diabetic Nephropathy

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Abstract: Diabetic kidney disease (DKD) is a kidney injury caused by long-term glucose and lipid metabolism disorders. Podocyte injury is the direct cause of protein leakage and renal fibrosis. Autophagy is a self-protective mechanism of podocytes that recognizes and clears damaged and aging organelles and biological macromolecules and regulates cell proliferation and metabolism. In DKD individuals, the expression of autophagy-related proteins decreased, glomerular podocyte homeostasis is difficult to maintain. Studies have shown that the PI3K/Akt/mTOR signaling pathway promotes cell self-repair through autophagy. This article aims to summarize the multiple factors involved in the PI3K/Akt/mTOR pathway to regulate autophagy and delay the deterioration of renal function, and provide reference for drug development and renal function repair treatment.

Key words: Diabetic kidney disease; Podocyte; Autophagy; PI3K/Akt/mTOR pathway

随着肥胖、久坐以及高糖(hyperglycemia, HG)、高脂(hyperlipemia, HLP)等不良饮食习惯的改变及遗传因素的影响,糖尿病(diabetes mellitus, DM)患者群体不断扩大^[1,2]。DM及其并发症糖尿病肾病(diabetic kidney disease, DKD)的出现显著增加了全身多脏器功能障碍以及衰竭的风险^[3,4]。在营养物质代谢紊乱的环境下,PI3K/Akt/mTOR为轴的信号通路可显著激活自噬,促使足细胞为自身输送能量,延长寿命,减少蛋白尿的流失^[5]。本文对PI3K/Akt/mTOR信号通路下多种调节因子激活足细胞自噬的相关生化途径进行综述,为寻找未来治疗的潜在靶点提供参考。

1 DKD的概述

DKD是DM最为严重的并发症之一,是终末

期肾病的源头所在,是进入肾脏替代治疗的主要原因^[6,7]。DM病程、血糖控制情况、基础疾病和遗传因素是DKD的驱动因素^[8]。1型和2型糖尿病患者发生DKD风险及病理生理机制基本相似,均需要10~20年才能表现出来。近些年来,DM及DKD患病人数不断扩大,长期HG损害肾脏、心血管系统、神经、骨骼、眼等多个器官^[9-11]。根据2020年KDIGO指南所述,DKD的界定标准为尿蛋白排泄率持续升高 ≥ 30 mg/g,尿蛋白与尿肌酐的比值 ≥ 3 mg/mmol,或肾小球滤过率 $eGFR < 60$ ml/(min $\cdot 1.73$ m²),或两者兼有,持续3个月以上^[12]。近年来,DKD患者出现了一种非蛋白尿CKD表型,其特征是 $eGFR$ 逐渐降低,无蛋白尿的出现^[13,14]。有研究^[15,16]通过建立DKD发展为肾衰竭的预测模型,探究影响DKD预后的因素,结果显示较低的 $eGFR$ 与血红蛋白含量、高胱抑素C水平、中性粒细胞与淋巴细胞比率及24h尿蛋白显著增加了DKD患者接受肾脏替代治疗的风险。此外,肥胖、高血压、高尿酸与同型半胱氨酸血症、HG、HLP等代谢综合征(metabolic syndrome, MS)可

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加速肾脏超微结构发生改变^[17-19]。

由内皮细胞和足细胞产生的细胞外基质(extracellular matrix, ECM)异常周转与修饰所致的肾小球基底膜(glomerular basement membrane, GBM)增厚是 DKD 的早期病理改变;损伤的内皮细胞表面产生促凝、促血管收缩因子以及抗血管生成因子,粘附分子、血管生成因子及其受体减少,内皮祖细胞减少,内皮细胞大量凋亡与血管平滑肌细胞增殖引起进行性肾微血管性缺血,上述多种病理改变通常被认为是 DKD 中足细胞激活的早期信号^[20,21]。若上述过程未能给予早期干预,将发生不可逆转的肾损害。Balmer LA 等^[22]仅在 HG 数天观察到肾小管肥大,小管间质改变,随着 DKD 的进展,肾小管发生萎缩,小管间质纤维化改变,管周毛细血管稀疏。长期在 HG 环境下,缺血缺氧促使足细胞发生代偿性肥大,ECM 产生过多,系膜基质中的蛋白质发生非酶糖基化导致系膜基质扩张,肾小球毛细血管袢被粉红色透明物质包围形成肾小球内微动脉瘤,又称 Kimmelstiel Wilson(KW)结节,肾脏功能逐渐退化^[17]。

2 足细胞损伤

肾小球滤过屏障是最复杂的生物膜,允许水分子通过,中小分子不能完全通过,白蛋白和大分子营养物质完全不能通过。足细胞是通过足突锚定在 GBM 的外层的终末分化上皮细胞,参与构成滤过屏障,是减少蛋白尿产生的关键环节,一旦损伤,不可再生^[23]。生理情况下,足细胞作为胰岛素敏感细胞,可通过细胞膜表面的葡萄糖转运体(glucose transporter, GLUTs)将葡萄糖转移至细胞内。DKD 患者体内存在着广泛的胰岛素抵抗, HG 使 GLUTs 数量难以代偿性增加,葡萄糖向胞外转运率降低,如多元醇通路通量、晚期糖基化终末产物(advanced glycation end products, AGEs)大量蓄积、AGEs 受体及其活化配体表达升高、细胞内信号转导递质 PKC 亚型的刺激和氨基己糖信号通路激活使得细胞内葡萄糖水平持续升高^[24]。HG 与 HPL 引起活性氧、糖化蛋白和氧化脂质等多种有害生化因子大量产生可直接激活补体系统,启动促炎信号传导^[25,26]。血管内皮细胞对氧化应激的易感性增加,肾素-血管紧张素系统(renin-angiotensin system, RAS)激活、哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)、TGF- β /SMAD 通路等多种机制诱导促炎因子释放^[25]。线粒体稳态难以维持,细胞器的工作信号

相互串扰,传入与传出小动脉玻璃样变,肾小球血流动力学改变导致灌注不足,自我调节功能受损,肾小球微循环受阻,系膜基质、小管间质中的胶原蛋白、纤维连接蛋白等细胞外基质蛋白沉积,致使营养信号传递及摄取中断,能量代谢的平衡状态被严重打破,足细胞发生凋亡^[26,27]。Matsusaka T 等^[28]通过体外试验对足细胞损伤特点进行挖掘,结果显示毒素蓄积导致的足细胞损伤,损伤的足细胞可释放转化生长因子、内皮素-1、趋化因子等多种有毒物质波及周围的细胞,肾单位大量丢失。

3 足细胞自我保护机制

自噬是细胞对氧化应激、炎症反应、营养缺乏等恶劣条件下作出的应激反应,分为巨噬、伴侣蛋白介导的自噬与微自噬三种模式,包括自噬诱导与自噬小体的形成等多个过程^[29,30]。自噬程序的启动可将胞内衰老受损的细胞器以及异常的大分子物质、病原体转入溶酶体内降解,降解产物可作为能源物质被回收利用。这种自我清洁与能量循环的过程有利于节约外界能量供给,促进细胞生长发育,提高细胞生存适应性,保持细胞活力^[31-33]。自噬周转的相对速率反映自噬活性的高低,又被称为自噬通量^[34]。

mTOR 是自噬重要的调节因子,是一种丝氨酸/苏氨酸磷酸化酶,共分为两种:mTOR 复合物 1(mTORC1)和复合物 2(mTORC2)^[35]。mTORC1 是一种对 RAPA 敏感的蛋白激酶复合物,由 mTOR 调控相关蛋白(RAPTOR)、G 蛋白 β -亚基样蛋白(G β l)等多种成分组成,通过感知葡萄糖、氨基酸、氧的水平,磷酸化 p70、S6K1、4EBP1 等多种调节因子参与细胞周期与自噬进程,维持营养物质平衡^[32]。mTORC2 对 RAPA 的敏感性远低于 mTORC1,由 mTOR、G β 、对 mTOR 的 RAPA 不敏感的伴侣蛋白 RICTOR 等成分组成,对生长因子敏感,负责细胞骨架的搭建^[36]。

自噬程序的启动受多种信号通路的调控,高度进化保守的自噬相关基因(autophagy-related gene, ATG)的表达决定了自噬通量的大小与底物降解的高度选择性^[37]。Audzeyenka I 等^[36]通过实验发现,长期暴露于 HG 环境下,由于细胞对胰岛素的敏感性被抑制,大鼠原代足细胞自噬相关基因 Atg12-Atg5 表达减少,LC3-II、Beclin1 等自噬相关蛋白表达大幅度降低,自噬通量下调。mTORC1 抑制剂雷帕霉素(RAPA)是防止器官移植后临床排斥反应的常用药物,可特异性结合 mTOR 激酶,抑

制 mTOR 活性^[38,39]。Li Q 等^[40]研究表明,AGEs 的积累抑制了足细胞对纤维连接蛋白的粘附与迁移,降低足细胞活力,提升凋亡水平。RAPA 的应用减少了 HG 对足细胞的不利影响,而 mTORC1 和 mTORC2 双抑制剂 KU0063794 的应用进一步增加了 HG 环境足细胞存活的可能性。Fang L 等^[41]使用自噬增强剂低剂量 RAP(1 ng/ml)恢复自噬,双免疫荧光染色显示足细胞素表达减少,分布模式得到明显改善,缺陷性自噬得以修复,滤过屏障功能受损得到缓解,因此恢复自噬活性可能是缓解足细胞损伤的新靶点。Yu S 等^[42]也得出同样的结论。

4 PI3K/Akt/mTOR 通路与足细胞自噬调节

生理状态下,足细胞膜表面镶嵌着大量生长因子受体与营养物质转运通道蛋白。当机体血糖水平升高时,胰岛素的分泌促进葡萄糖向细胞内转运,推进氨基酸、脂质等营养素的生物合成,抑制糖异生,足细胞内外环境处于稳定状态,以 PI3K/Akt/mTOR 通路为主轴的自噬机制往往不被激活而处于休眠状态^[43,44]。在 DKD 患者体内,在足细胞长期处于 HG、HLP 环境时,使抗氧化能力大大受限^[45],活性氧的诱导与内质网应激信号的表达、胰岛素抵抗、营养物质代谢紊乱、毒素蓄积及激素的异常分泌、HG、HLP 刺激胰岛素样生长因子 1(IGF-1)、胰高血糖素、一氧化氮(NO)、血管内皮生长因子(VEGF)和前列腺素等血管活性介质的释放^[21]。DKD 前期肾小球内部灌注不足,足细胞长期处于饥饿状态,极易发生程序性死亡^[40]。此时,能量感知因子与生长因子激活脑 Ras 同源蛋白(Rheb)开关,并与 G 蛋白偶联受体(GPCRs)、酪氨酸激酶受体(TKRs)结合,触发磷脂酰肌醇激酶(PI3K)、PI3K 下游的蛋白激酶 B(Akt)的磷酸化,进而激活 mTORC1 的组成成分 4EBP1 与 S6K1 诱导自噬^[46],胞内有益成分的继续保留,异常免疫复合物及衰老损伤的细胞器及大分子物质降解,部分排出体外,部分合成核酸及其前体、蛋白质、脂质、ATP 和 NADPH 等能源物质平衡细胞合成代谢与分解代谢^[47]。mTORC2 位于 Akt 的下游,磷酸化的 Akt 启动 mTORC2 参与细胞骨架的搭建,与此同时,mTORC1 也得到了最大程度的激活,mTORC1 与 mTORC2 二者相辅相成,共同减少胰岛素抵抗诱导的细胞毒作用,实现细胞内营养物质的循环使用,细胞外源源不断的能量供应与足细胞的自我修复^[43]。

有研究显示^[48],用正常培养液和无氨基酸培养液对足细胞进行体外培养,Western blot 检测到 LC3

II 和 beclin1 水平增加,逆转录-定量聚合酶链反应结果显示 LC3 II 对应的 mRNA 水平呈现上升趋势,透射电镜观察自噬小体大量产生,由此可知:氨基酸饥饿(amino acid starvation,AAS)可促进核转位,提高转录因子 EB(TFEB)的活性,高活性的 TFEB 可抑制 mTOR,促进自噬体、自噬溶酶体的形成和底物降解。糖原合成酶激酶 3 β (GSK3 β)作为糖原代谢的重要组成部分,已被证实为 PI3K/Akt 通路的下游靶点,其活性与自噬呈负相关。

前期研究发现,肝细胞生长因子(HGF)通过抑制 GSK3 β HG 还原 Ser9 磷酸化而增加自噬通量,因此 Ser9 磷酸化是 GSK3 β 活化的指标。Hou B 等^[49]评估 HGF 在 DKD 中足细胞稳态中的作用并进一步阐明其机制:对自噬相关蛋白和足细胞骨架蛋白——突触素(Synapt)进行免疫荧光双染色发现 DKD 患者足细胞自噬通量受损。与未接受 HGF 治疗的 DM 小鼠相比,接受 HGF 治疗的 DM 小鼠的尿白蛋白排泄率、足细胞损失量显著降低,LC3 II/LC3 I 比例增加。HGF 的这些有益作用可被其抑制剂克唑替尼或 PI3K 抑制剂 LY294002 阻断,与对照组相比,DKD 小鼠组 p-Akt(ser473)/Akt 和 pGSK3 β (ser9)/GSK3 β 比值降低。上述实验证实 HGF 在足细胞中通过 PI3K/Akt-GSK3 β -TFEB 轴改善溶酶体功能和自噬。表皮生长因子(EGF)已被认为是慢性肾脏疾病进展的潜在生物标志物,是典型的表皮生长因子受体(EGFR)配体,主要来源于肾脏。Sun Y 等^[50]使用 EGF 处理 HG 刺激后的足细胞,DNA 甲基化表达谱分析显示,与 HG 组相比,HG+EGF 组有 9309 个 CpG 高甲基化位点(5220 个基因)和 3111 个 CpG 低甲基化位点(2511 个基因),差异甲基化基因在 PI3K/AKT/mTOR 信号通路中显著富集,提示 EGF 介导的保护作用通过 PI3K/AKT/mTOR 信号通路中的相关 DNA 甲基化参与肾足细胞的修复。

当 HG 诱导的脂质蓄积超过细胞的代偿能力时,对足细胞产生不可逆转的损伤^[51]。既往研究表明^[52-54],硫氧还蛋白互作蛋白(thioredoxin-interacting protein, TXNIP)参与调节细胞的糖、脂代谢。Du C 等^[55]研究了 TXNIP 对 DKD 中脂质积累的影响,与 DM 野生型小鼠相比,敲除 TXNIP 相关基因后,乙酰辅酶 a 羧化酶、肉碱棕榈酰转移酶 I 等脂代谢相关酶以及 Akt、mTOR 的表达减弱,小鼠体内脂质积聚增加。使用 PI3K 特异性抑制剂 LY294002 阻断 Akt/mTOR 信号通路,可以复制 TXNIP 沉默的效果。因

此, TXNIP 的存在可通过抑制 Akt/mTOR 通路抑制自噬, 加重脂质在肾脏中积聚。抑制 TXNIP 的产生与释放可能为足细胞损伤相关肾病患者提供新的希望。HG 可诱导足细胞中精子相关抗原 5 (SPAG5) 的 mRNA 和相应蛋白表达上调, 沉默 SPAG5 可逆转 HG 处理的足细胞凋亡小体与自噬小体减少的状况^[56-58]。Xu J 等^[59]发现 SPAG5-as1 作为 SPAG5 的邻居基因, 与泛素特异性肽酶 14 (USP14) 相互作用, 使 SPAG5 蛋白去泛素化并趋于稳定状态。因此, 当 SPAG5-as1 作用于 SPAG5/AKT/mTOR 通路时, 对足细胞自噬具有抑制作用, 加剧足细胞凋亡。靶向调节 SPAG5-as1/SPAG5 激活自噬为缓解足细胞损伤提供一种新的治疗选择。

含 SH2 结构域的肌醇 5'-磷酸酶 (SHIP) 被称为 PI3K/Akt 通路的负调控因子^[60]。Li F 等^[61]研究发现, 在 DKD 小鼠体内, HG 以时间依赖性的方式降低了 SHIP 的表达, 同时激活了 PI3K/Akt 信号通路导致 ECM 的产生, 而转染 M90-SHIP 载体可以显著阻止这一过程; 在 DM 小鼠体内腹腔注射 SHIP 表达载体促使 SHIP 高表达后发现, Akt 与结缔组织生长因子 (CTGF) 的表达明显降低, 肾小管细胞的 ECM 积累减少。可见, 过表达 SHIP 可能是一种通过失活 PI3K/Akt 通路和抑制 DKD 中 CTGF 的产生来减少 ECM 积聚的有效方法^[62-64]。

5 总结

自噬广泛存在于足细胞内, 感知细胞内外能量变化并激活相应通路作出应答。生理情况下, PI3K/AKT/mTOR 通路往往不被激活; 在 DKD 初期, 细胞处于饥饿环境下并具有一定的代偿能力, 以 PI3K/AKT/mTOR 通路为轴, HGF、EGF、GSK3 β -TFEB 等多种调节因子共同参与自噬, 线粒体的生化反应以及细胞的大分子营养物质的生物合成得以顺利进行。然而, 在 DKD 终末期, MS 是其常见的并发症, TXNIP、SPAG5-AS1 等相关因子产生增多, SHIP 含量降低, 抑制自噬, 加速足细胞凋亡。上述多项研究结果多基于体外试验, 为推进靶向治疗的进一步发展, 今后还应加大药物研发力度, 提高药物疗效。

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