



• 代谢相关肾病 •

|| 文献综述 ||

TGF- β 1/SMAD在糖尿病肾病中的作用机制与研究进展*

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【摘要】 糖尿病肾病是糖尿病常见的并发症,也是导致终末期肾病的重要原因之一。转化生长因子- β 1(transforming growth factor- β 1, TGF- β 1)/SMAD信号活化是糖尿病肾病发病及进展的主要机制之一。研究表明,TGF- β 1(前体、本体、受体)及其下游信号蛋白(SMAD3、SMAD7等)的活化,在糖尿病肾脏损伤中起了关键的作用。此外,TGF- β 1/SMAD可通过多种miRNA和lncRNA等介导糖尿病肾病的发病及进展。TGF- β 1、SMAD3和SMAD7作为糖尿病肾脏损伤的主要蛋白,成为防治糖尿病肾病的关键靶点。近期临床试验显示TGF- β 1单克隆抗体治疗无法有效减缓糖尿病肾病。提示在TGF- β 1/SMAD信号上游抑制TGF- β 1/SMAD并无减轻临床症状的作用,可能与其具有多种生物效应有关。靶向抑制TGF- β 1下游信号分子(如SMAD3、SMAD7)可能是减轻糖尿病肾脏损伤的有效方法。本文总结了与TGF- β 1/SMAD相关的糖尿病肾病发病机制,并讨论抗TGF- β 1/SMAD信号防治糖尿病肾病的可能靶点。

【关键词】 糖尿病肾病 转化生长因子- β 1 SMAD 糖尿病 微RNA 长链非编码RNA 综述

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【Abstract】 Diabetic nephropathy (DN) is a common complication of diabetes and a leading cause of end-stage renal disease. Transforming growth factor- β 1 (TGF- β 1)/SMAD signaling activation plays an important role in the onset and progression of DN. Reported findings suggest that the activation of TGF- β 1 (including the latent form, the active form, and the receptors) and its downstream signaling proteins (SMAD3, SMAD7, etc.) plays a critical role in DN. In addition, TGF- β 1/SMAD signaling may mediate the pathogenesis and progression of DN via various microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). Emerging evidence shows that TGF- β 1, SMAD3, and SMAD7 are the main signaling proteins that contribute to the development of DN, and that they can be potential targets for the treatment of DN. However, recent clinical trials have shown that the anti-TGF- β 1 monoclonal antibody treatment fails to effectively alleviate DN, which suggests that upstream inhibition of TGF- β 1/SMAD signaling does not alleviate clinical symptoms and that this may be related to the fact that TGF- β 1/SMAD has multiple biological effects. Targeted inhibition of the downstream TGF- β 1 signaling (e.g., SMAD3 and SMAD7) may be an effective approach to attenuate DN. This article discussed the current understanding of the molecular mechanisms and potential targets for the treatment and prevention of DN by focusing on TGF- β 1/SMAD signaling.

【Key words】 Diabetic nephropathy TGF- β 1 SMAD Diabetes mellitus miRNA lncRNA
Review

糖尿病发病人数逐年升高。截至2021年,全球糖尿病患者总数超过5.3亿^[1],预计患者人数在2030年及2040年

分别达到6.4亿和7.8亿^[2]。仅在2021年,就有超过670万患者因糖尿病相关并发症而死亡^[2]。如今,糖尿病及其并发症已经成为全球公共卫生问题,前期研究结果表明,转化生长因子- β 1(transforming growth factor-beta 1, TGF- β 1)及其下游信号通路在糖尿病肾病的发病机制中扮演重要作用^[3]。本文总结了由TGF- β 1及其下游信号介导造成糖尿病肾病的分子机制及研究进展。

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1 糖尿病肾病与TGF- β

糖尿病肾病仍然是糖尿病人群中最常出现的并发症之一,也是发生终末期肾病的主要原因。糖尿病肾病主要由于肾脏长期暴露在糖代谢异常环境下,导致肾脏多种细胞损伤,进而出现蛋白尿、肌酐上升、肾小球滤过率降低的情况,严重者甚至会罹患肾性高血压及心血管疾病^[4]。糖尿病肾病的病理表现为肾小球中炎症细胞浸润、足细胞损伤死亡、系膜细胞增生、基底膜增厚、肾小球硬化以及肾小球和肾小管间质纤维化等^[5]。临床上虽可以通过控制血糖、血脂和血压等方法减缓糖尿病肾病的发生,但无法完全阻止疾病进程。

大量基础研究证实肾脏细胞中多种信号通路参与了糖尿病肾病的发生和进展,其中包括最重要的信号通路TGF- β 1及其下游信号的活化。糖尿病患者血清TGF- β 1含量显著升高,有学者认为TGF- β 1含量可作为诊断糖尿病肾病的重要临床指标之一^[5]。TGF- β 1细胞因子及相关信号活化对细胞增殖、细胞分化、细胞形态、内环境稳态和细胞再生均有重要的作用,其失调往往会导致各种疾病的产生^[6]。TGF- β 的信号传导受TGF- β 配体、受体及其下游蛋白等多种因素影响。

1.1 TGF- β 简介

TGF- β 包含TGF- β 1/2/3三种亚型,广泛表达于多种细胞和组织类型。TGF- β 1受体主要包含I型(TGF β R1)与II型(TGF β R2)两种受体,均为丝氨酸/苏氨酸激酶受体。TGF β R2为跨膜受体,胞外为配体结合区,胞内为丝氨酸/苏氨酸酶活性区,尾端有短尾结构可自我激活,并进一步激活TGF β R1^[6]。另外还有辅助性TGF β R3受体,也被称为betaglycan,由于缺乏蛋白激酶活性,通常认为不直接参与信号传递^[7]。

1.2 TGF- β 1信号通路的激活

TGF- β 1信号的激活与传递可分为两大类,分别是依赖SMAD蛋白的“经典”激活方式与不依赖SMAD蛋白的“非经典”激活方式。

经典激活过程中TGF- β 1首先与跨膜蛋白TGF β R2结合,使胞内TGF β R2尾端磷酸化,随后TGF β R2募集并磷酸化TGF β R1。磷酸化过程将TGF β R1中的一个区域从结合12 kDa-FK506结合蛋白(FKBP12)的沉默激酶活性位点转换为可结合并磷酸化SMAD蛋白的位点^[8]。在受到上游信号激活后,磷酸化的R-SMAD与SMAD4形成复合物,进入细胞核中与DNA结合并转录出效应蛋白,如SMAD2/3与SMAD4复合物入核后可以与效应蛋白基因的启动子序列结合,调节靶基因的识别与转录^[9]。

TGF- β 1信号传递还可通过非SMAD方式,如调控丝裂原激活的蛋白激酶(mitogen-activated protein kinase, MAPK)、Rho、PI3K/Akt等信号通路^[10]。SMAD依赖的经典通路与非经典通路之间并非独立,其中存在很多信号间对话。

2 TGF- β 1/SMAD信号与糖尿病肾病

2.1 TGF- β 1/SMAD

糖尿病肾病患者血清、尿液和肾脏中的TGF- β 1含量显著增加^[11]。研究认为TGF- β 1不仅促使肾小球系膜细胞增殖、系膜基质沉积及肾小球硬化,也导致肾脏小管间质纤维化^[12]。由于全身性过表达TGF- β 1往往导致胚胎在发育中死亡,目前尚未有用全身性TGF- β 1转基因鼠建立的糖尿病肾病模型来研究糖尿病发病机制^[13]。而利用小鼠皮肤高表达Latent TGF- β 1的转基因小鼠^[14],建立链脲佐菌素(streptozotocin, STZ)诱导的糖尿病肾病模型中,Latent TGF- β 1能显著减轻糖尿病肾病的炎症和纤维化。显示活化的TGF- β 1与前体Latent TGF- β 1有不同的生理功能。进一步研究表明Latent TGF- β 1可以通过Arkadia上调SMAD7来抑制TGF- β 1/SMAD活化介导的肾脏纤维化^[15]。

作为TGF- β 1通路下游,SMAD蛋白在糖尿病肾病中扮演重要角色,其中以SMAD2/3/4/7被广为研究。糖尿病肾病患者肾脏组织中SMAD2/3显著性激活。在STZ诱导的糖尿病肾病动物模型中,由成纤维细胞特异性蛋白(fibroblast-specific protein 1, FSP1)启动子驱动的成纤维细胞中条件性删除SMAD2可减少小鼠肾脏的纤维化^[16]。在STZ诱导的糖尿病肾病小鼠中,敲除SMAD3可以显著性减轻肾小球基底膜增厚、细胞外基质沉积和蛋白尿的情况^[17]。将db/m与SMAD3敲除的老鼠交配繁殖出db/db-SMAD3敲除的2型糖尿病肾脏病模型显示:敲除SMAD3后,可显著减轻db/db糖尿病肾病损伤(如肾脏炎症与纤维化)。同时,SMAD3可直接与溶酶体生成相关蛋白TFEB结合,抑制TFEB表达,导致糖尿病肾脏中自噬功能紊乱^[18]。

SMAD4在糖尿病肾病中具有促纤维化的作用。SMAD4在糖尿病肾病的人和小鼠(高脂饲料与STZ诱导建模)的足细胞中过量表达,条件性敲除小鼠足细胞中的SMAD4后,尽管肾小球仍然明显肥大,但系膜基质扩张和肾小球硬化的情况则得到明显改善^[19]。在早期糖尿病肾病小鼠模型和高糖环境刺激的肾小球系膜细胞中发现,SMAD4的激活依赖于腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)信号通路^[20]。

SMAD7在糖尿病肾病中具有保护作用。SMAD7可

以同SMAD2/3竞争性结合TGFβR1, 并促进TGFβR1的降解, 从而抑制SMAD2/3的磷酸化^[21]。在STZ诱导的糖尿病肾病和db/db糖尿病肾病小鼠中, SMAD7敲除小鼠出现更严重的蛋白尿、肾纤维化和炎症的情况; 而通过超声波递送SMAD7高表达质粒至糖尿病大鼠和db/db小鼠的肾脏则可以减轻TGF-β1/SMAD活化导致的肾脏纤维化和NF-κB介导的炎症, 同时改善肾功能^[22]。

结合以上研究结果, TGF-β1/SMAD在糖尿病肾病的发病和进展中起重要作用。抑制SMAD3并激活SMAD7或许是减缓糖尿病肾病的有效手段。本课题组发现SMAD3抑制剂柚皮素与SMAD7激动剂积雪草酸可以帮助恢复糖尿病肾病小鼠体内SMAD3/7的平衡, 进而减缓病程发展^[23]。目前针对SMAD3/7的临床试验较少, 尚需后续研究。

2.2 TGF-β1/SMAD依赖微RNA (microRNA, miRNA)

miRNA是由长度为20 ~ 22个核苷酸组成的单链RNA, 具有调节翻译后修饰的作用。miRNA可通过与目标mRNA的3'端非翻译区(untranslated region, UTR), 或诱导mRNA降解结合来阻断蛋白质翻译。miRNA在糖尿病肾病中的相关作用机制总结见表1。

2.2.1 糖尿病肾病中上调的miRNAs

TGF-β1可通过其下游SMAD信号分子上调众多miRNAs, 包括miR-21、miR-135a-5p、miR-200b/c、miR-377和miR-1207-5p等。

在上调的miRNA中, miR-21与miR-1207-5p都可以与SMAD7 mRNA的3' UTR结合并诱导其降解, 进而抑制

SMAD7的肾脏保护作用^[24]。miR-21在db/db糖尿病肾病小鼠中的表达上调, miR-1207-5p是一种由浆细胞瘤变异异位基因1(plasmacytoma variant translocation 1, PVT1)衍生的miRNA, TGF-β1可以剂量依赖性提高系膜细胞中miR-1207-5p的含量, 加重细胞外基质的沉积^[25]。

miR-135a-5p表达含量在糖尿病肾病患者的肾脏组织和血清中明显升高, 高糖环境下用TGF-β1刺激HK-2和人肾小球系膜细胞同样发现miR-135a-5p的高表达; 体外机制研究发现, miR-135a-5p可以与Sirtuin 1(SIRT1)的3' UTR结合, 敲除miR-135a-5p可以抑制TGF-β1诱导的肾脏纤维化, 并可以通过SIRT1的上调抑制TGF-β1/SMAD3通路激活^[26]。

在2型糖尿病患者的血液样本中的miR-377的含量相比于健康人明显上调^[27], 但该研究仅呈现临床数据, 其分子机制仍需进一步研究。

高糖或TGF-β1刺激下, 小鼠肾小球系膜细胞中的miR-200b/c含量显著上调, 并造成肾小球系膜细胞的肥大; 同时, miR-200b/c也在STZ诱导的糖尿病小鼠和db/db小鼠的肾小球中高表达, miR-200b/c可以抑制FOG2, 从而加重TGF-β1诱导的锌指蛋白, FOG家族成员2(zinc finger protein, FOG family member 2, FOG2)下游PI3K-Akt-ERK信号通路的激活^[28]。

值得注意的是, 在糖尿病肾病的临床患者中发现了miR-21的高表达, 然而敲除miR-21却造成了肾小球疾病的恶化^[29]。miR-21功能的复杂性可能与TGF-β信号通路的复杂级联有关。单一阻断TGF-β信号通路的某个环节可能导致整体的信号通路稳态失调。因此结合上文通过柚

表 1 小分子RNA在TGF-β1/SMAD介导的糖尿病肾病中的作用
Table 1 Role of miRNAs in TGF-β1/SMAD-mediated diabetic nephropathy

miRNA	Diabetic nephropathy model	Target and reference
Up-regulated		
miR-21	db/db mice	SMAD7 ^[24]
miR-135a-5p	HK-2, HMC	SMAD3, Sirtuin 1 ^[26]
miR-200b/c	db/db mice, STZ induced C57BL/6 mice, MMC	FOG2 ^[28]
miR-377	Diabetic nephropathy patient sample	Patients' clinical symptoms ^[27]
miR-1207-5p	HMC	SMAD7 ^[25]
Down-regulated		
miR-10a/b	STZ and high fat diet induced C57BL/6Jmice, human podocyte	NLRP3 ^[30] , TGFβR1
miR-26a	Human podocyte	CTGF ^[32]
miR-29a/b/c	Human podocyte, MMC, NRK52E, HK-2, RMC, db/db mice	Col1a1 ^[33] , Col4a1 ^[33, 35] , Col4a2 ^[35] , Col4a3 ^[33] , CB1R ^[34] , SMAD3 ^[36] , SP1 ^[36] , Tbx21 ^[36]
miR-93	HK-2	Orail ^[37]
miR-200a	NRK52E	TGFβR2 ^[31]
miR-let-7b	db/db mice, STZ induced C57BL/6 mice, MMC	TGFβR1 ^[38] , Col1a2 ^[38] , Col4a1 ^[38] , Lin28b ^[38]
miR-346	db/db mice	SMAD3/4 ^[39]
Expression of indeterminacy*		
miR-192	HK-2, MMC, db/db mice, STZ induced C57BL/6 mice	ZEB1 ^[43] , ZEB2 ^[42-43] , SIP1 ^[41] , P53 ^[42]

HK-2: human kidney 2 cells (human renal proximal tubular cells); HMC: human mesangial cells; MMC: mice mesangial cells; STZ: streptozotocin; RMC: rat mesangial cells; FOG2: zinc finger protein, FOG family member 2; NLRP3: NOD-, LRR-, and pyrin domain-containing protein 3; TGFβR1/2: transforming growth factor β receptor 1/2; CTGF: connective tissue growth factor; Col1a1/2: collagen type I alpha 1/2 chain; Col4a1/2/3: collagen type IV alpha 1/2/3 chain; ZEB1/2: zinc finger E-box binding homeobox 1/2. * Different miRNA expression levels depending on disease staging or animal models.

皮素与积雪草酸维持SMAD3/7平衡的治疗手段,如以miRNAs为治疗靶点,单一调节其表达可能导致TGF- β 信号传导失调,而恢复SMAD信号通路平衡可能是治疗的更优解。

2.2.2 糖尿病肾病中下调的miRNAs

糖尿病肾病中,下调的miRNA包括miR-10a/b、miR-26a、miR-29a/b/c、miR-93、miR-200a、miR-let-7b及miR-346等。

miR-10a/b和miR-200a都可以与TGF- β 受体的mRNA的3' UTR结合以诱导其降解,miR-10a/b作用在TGF β R1 mRNA,miR-200a则作用在TGF β R2 mRNA。miR-10a/b在人体和C57BL/6J小鼠中主要在肾脏中表达,其可以与核苷酸结合寡聚化结构域样受体蛋白3(NOD-, LRR-, and pyrin domain-containing protein 3, NLRP3) mRNA的3' UTR结合以诱导其降解,在STZ诱导的1型糖尿病小鼠和db/db小鼠肾脏中miR-10a/b表达含量明显降低,从而导致NLRP3诱导的炎症反应加剧^[30]。miR-200a在STZ诱导的糖尿病肾病小鼠中低表达,在大鼠NRK52E细胞中过表达miR-200a能够抑制纤维化,此机制为miR-200a能够结合在TGF β R2 mRNA的3' UTR来诱导其降解^[31]。

结缔组织生长因子(connective tissue growth factor, CTGF)在成纤维细胞的增殖中发挥重要作用,CTGF在糖尿病肾病患者的尿液中含量显著升高,并与糖尿病肾病的严重程度正相关。在对TGF- β 1刺激的人足细胞进行的miRNA阵列分析发现,共有46个miRNA的表达水平发生大于1.5倍的变化,其中仅miR-26a与CTGF相关;糖尿病肾病患者肾小球中的miR-26a含量和肾小球滤过率下降,miR-26a可以通过与CTGF mRNA的3' UTR结合来抑制TGF- β /SMAD3通路的激活^[32]。

miR-29家族包含miR-29a/b/c。miR-29的表达受TGF- β 1的负调节,在人足细胞和小鼠肾小球系膜细胞中发现miR-29可以通过与Col1a1、Col4a1和Col4a3 mRNA的3' UTR结合来调控胶原的表达^[33]。早期糖尿病肾病小鼠中发现miR-29a/b/c均呈现低表达,其中miR-29a/c的下降差异有统计学意义;晚期糖尿病肾病小鼠接受 ρ 相关激酶抑制剂法舒地尔(fasudil)或血管紧张素受体阻滞剂氯沙坦(losartan)治疗后,miR-29a/c的含量回调上升^[33]。在STZ诱导的糖尿病肾病小鼠模型中,过表达miR-29a可以通过与大麻素受体1(cannabinoid receptor 1, CB1R)mRNA结合来减轻糖尿病肾小球损伤(纤维化和炎症)^[34]。同时HK-2细胞在高糖环境中miR-29a表达下调,呈现更严重的纤维化情况,其机制与miR-29a可以结合Col4a1和Col4a2 mRNA的3' UTR抑制其表达有关^[35]。miR-29b的表达在

db/db小鼠肾脏中和晚期糖基化终末产物(advanced glycation end-products, AGEs)刺激的系膜细胞中均显著性降低,而高表达miR-29b可以减缓蛋白尿、肾脏炎症及纤维化的情况,其机制可能与miR-29b调控SP1和Tbx21相关^[36]。

2型糖尿病肾病患者中miR-93的表达含量显著下调,而Orai1的表达含量则显著升高;HK-2细胞中发现,miR-93可以通过与Orai1 mRNA的3' UTR结合来抑制TGF- β 1诱导的纤连蛋白和胶原蛋白IV的表达,并能抑制TGF- β 1介导的SMAD3磷酸化^[37]。

miR-let-7b在STZ诱导的糖尿病肾病小鼠和在TGF- β 1刺激的系膜细胞中表达量降低,过量表达miR-let-7b也可以通过与TGF β R1、Col1a2和Col4a1 mRNA的3' UTR结合来减缓糖尿病肾病;同时,糖尿病肾病患者情况下miR-let-7b的低表达也与TGF- β 1/SMAD诱导的Lin28b表达上调有关^[38]。

在一项针对db/db小鼠肾脏皮质的miRNA阵列研究分析中发现,miR-346与SMAD3/4有明显关联,miR-346的表达含量在db/db小鼠中明显降低;过表达miR-346可以改善蛋白尿的情况,并使db/db小鼠的肾小球形态恢复正常^[39]。

miR-192在糖尿病肾病的不同阶段可能起不同作用,在糖尿病早期miR-192表达降低,而在晚期则显著升高^[40]。2型糖尿病患者的血液样本中miR-192的含量相比于健康人明显上调^[27]。同时,在1型和2型糖尿病小鼠模型中,miR-192的表达含量都显著性升高,并靶向于TGF- β 1介导的SMAD相互作用蛋白(SMAD-interacting protein 1, SIP1)^[41]。在STZ诱导的糖尿病小鼠肾小球中,TGF- β 1上调,导致miR-192升高,进而导致抑制P53蛋白翻译的Zeb2下调,从而加重了肾脏损伤^[42]。然而,在糖尿病肾病患者肾脏活检样本中,miR-192的表达含量显著性降低;过表达miR-192能够抑制ZEB1和ZEB2的表达,从而对抗TGF- β 介导的E-钙黏蛋白下调^[43]。糖尿病肾病患者活检结果与小鼠模型结果不一致,可能提示miR-192在疾病过程中起不同作用,同时不同的疾病背景也会造成表达含量的差异。同上述维持SMAD3/7稳态的思路相同,针对miR-192为靶点的治疗方案可能也要从维持TGF- β 信号通路稳态着手,具体机制还需进一步研究。

2.3 TGF- β 1/SMAD依赖长链非编码RNAs

长链非编码RNA(long non-coding RNA, lncRNA)是指一组长度大于200个核苷酸的非蛋白质编码转录本^[44],大量研究表明lncRNA可通过SMAD3介导发挥重要作用,在糖尿病肾病中与lncRNA的相关作用机制见表2。

根据全基因组单核苷酸多态性关联研究,lncR-PVT1是首个被确定与1型和2型糖尿病引发的终末期肾

表 2 长链非编码RNA在TGF-β1/SMAD介导的糖尿病肾病中的作用
Table 2 Role of lncRNAs in TGF-β1/SMAD-mediated diabetic nephropathy

lncRNA	Diabetic nephropathy model	Target and reference
lncR-PVT1	MPC5, high fat diet induced C57BL/6 mice	FOXA1 ^[47]
lncR-H19	HMVEC, STZ induced CD1 mice	SMAD3 ^[48] , FSP1 ^[48]
lncR-9884	db/db mice, MTEC	MCP-1 ^[50]
lncR-ErbB4-IR	db/db mice, MTEC, MMC	SMAD7 ^[52]
lncR-CYP4B1-PS1-001	db/db mice, MMC, HEK293T	Fibrosis ^[53]
lncR-ENSMUST00000147869	db/db mice, MMC, HEK293T	HSPA9 ^[54]
lncR-MEG3	STZ induced Wistar rat, HK-2	SMAD3 ^[56]

MPC5: mouse podocyte-5; FOXA1: forkhead box A1; FSP1: ferroptosis suppressor protein 1; MCP-1: monocyte chemoattractant protein-1; HSPA9: heat shock protein family A member 9; HMVEC: human microvascular endothelial cells; HEK293T: human embryonic kidney 293T; HK-2, HMC, and MMC denote the same as those in Table 1.

病相关的lncRNA^[45]。高糖环境可以诱导人肾小球系膜细胞中lncR-PVT1、纤连蛋白-1(fibronectin-1, FN1)、Col4a1和骨形成蛋白-7(bone morphogenetic protein 7, BMP7)的表达^[46], 敲低lncR-PVT1则会抑制此病理过程^[47]。亦有研究表明抑制lncR-PVT1可以通过上调FOXA1, 减少糖尿病肾病中足细胞损伤与凋亡^[48]。

在STZ诱导的糖尿病小鼠肾脏中及TGF-β2刺激的人真皮内血管内皮细胞中发现lncR-H19表达的显著上调; 敲低lncR-H19不但可以通过抑制内皮-间质转化相关基因FSP-1来抑制肾脏炎症, 还能显著抑制TGF-β/SMAD3信号通路^[49]。

体外实验在AGEs的刺激下, 系膜细胞中的lncR-ErbB4-IR和肾小管细胞中的lncR-9884呈现高表达的情况^[50], 这是由于lncR-9884通过与单核细胞趋化蛋白-1(monocyte chemoattractant protein-1, MCP-1)启动子结合以激活其转录^[51], lncR-ErbB4-IR则通过与SMAD7 mRNA 3' UTR结合来抑制其表达^[52]。

糖尿病肾病中, lncR-CYP4B1-PS1-001可以调节系膜细胞的增殖与纤维化。在db/db小鼠模型中lncR-CYP4B1-PS1-001呈下降趋势; 体外实验表明, lncR-CYP4B1-PS1-001特异性表达于系膜细胞中, 过表达lncR-CYP4B1-PS1-001能够减轻系膜细胞的纤维化^[53]。除此之外, lncR-ENSMUST00000147869也可能通过调节热休克蛋白家族A成员9(heat shock protein family A member 9, HSPA9)减轻高糖环境下系膜细胞中的细胞增殖与纤维化^[54]。

糖肾方是一种中药复方, 具有改善糖尿病肾病的作用^[55]。在STZ诱导的糖尿病肾病大鼠中发现lncR-MEG3的表达含量显著上调, 糖肾方可以降低TGF-β1/SMAD3通路的激活并下调lncR-MEG3的表达^[56]。

2.4 TGF-β1/SMAD相关的其他通路

在糖尿病小鼠模型中, ERK/P38 MAPK通路被显著激活, 伴随着p-SMAD2/3活化和TGF-β1的表达含量升高。本课题组前期研究发现, C反应蛋白(C-reactive protein, CRP)不仅直接激活TGF-β1/SAMD信号来加重

STZ诱导1型糖尿病小鼠肾脏的炎症与纤维化^[57], 还通过ERK/p38 MAPK串扰途径直接激活SMAD3信号传导, 并通过TGF-β1依赖性机制间接激活SMAD3信号传导^[58]。CRP通过CD32b-NF-κB信号通路加剧肾脏炎症, 通过CD32b-SMAD3-mTOR信号通路加重肾脏纤维化^[58]。另外, 本课题组还发现CRP可以促进CD32b-NF-κB与激活二肽基肽酶-4(dipeptidyl peptidase-4, DPP4)启动子区域结合而激活DPP4, 同时CRP还促进DPP4与CD32b二聚化, 形成DPP4/CD32b/NF-κB, 加重CRP引起的糖尿病肾脏损伤^[59]。

肾小管间质纤维化是糖尿病肾病的常见表现, KCa3.1在糖尿病肾病患者和小鼠中的表达含量明显升高^[60], 并同时参与纤维化及炎症进程。在纤维化方面, 使用KCa3.1抑制剂TRAM34可以显著降低在TGF-β1刺激下的人肾间质成纤维细胞的细胞外基质、Col1A和Col4a1的表达, 其调控TGF-β1通路则通过SMAD或ERK1/2; 值得注意的是, TRAM34并不会作用在P38/JNK MAPK信号通路上^[61]。在STZ诱导的糖尿病肾病小鼠中, 敲除KCa3.1可以通过MMP2/MMP9基因减少肾小管间质纤维化、蛋白尿和细胞外基质蛋白表达来保护肾脏^[61]。在炎症方面, 敲除KCa3.1可以减轻糖尿病肾病小鼠的肾损伤和肾脏炎症, 降低1型纤溶酶原激活剂抑制剂(plasminogen activator inhibitor type 1, PAI-1)含量、降低TGF-β1和TGFβR2的表达, 还能下调SMAD2/3的磷酸化水平^[60]。

3 抗TGF-β治疗糖尿病肾病在临床上的实践

在临床上已有很多治疗方法用于改善糖尿病肾病。在已经上市的药物中, 恩格列净(empagliflozin)与卡格列净(canagliflozin)是钠-葡萄糖协同转运蛋白2(sodium-dependent glucose transporters 2, SGLT-2)的抑制剂。利格列汀(linagliptin)则是二肽基肽酶-4(dipeptidyl peptidase-4, DPP4)的抑制剂。此外, 针对与糖尿病肾病相关的风险因素防控, 例如使用血管紧张素转换酶抑制剂(angiotensin-converting enzyme inhibitors, ACEis)和血

管紧张素 II 受体阻滞剂 (angiotensin II receptor antagonist, ARB) 治疗高血压, 以及使用他汀类药物治疗高脂血症也可显著延缓糖尿病肾病的进展^[62]。

大量研究证明 TGF- β 1 及其下游蛋白 (SMAD3、SMAD7) 在糖尿病肾病的发病及恶化中起重要作用, 那么抑制 TGF- β 1 的表达是否可以作为治疗糖尿病肾病的方法呢? 在小鼠糖尿病肾病造模后, 采用 TGF- β 中和抗体治疗, 发现可显著减轻 STZ 诱导的糖尿病肾脏肥大和纤维化^[63]。但是, 近期的一项 II 期随机对照双盲试验证明, 对糖尿病肾病患者使用 TGF- β 1 单克隆抗体治疗 12 个月, 无法延缓糖尿病肾病的发展^[64]。该研究的受试者中, 有接近一半的受试者由于缺乏疗效而未完成全程实验。同时, 尽管并未产生明显副作用, 但该临床试验仍在委员会的建议下以安全性为由提前 4 个月终止。此研究是一项开创性的针对 TGF- β 1 为靶点的研究, 并且设置了多种单克隆抗体剂量组和安慰剂对照, 虽然不同剂量的单克隆抗体均未体现良好的治疗效果, 但也是一种突破性的尝试。LAN 等^[9]提议: 更强化的 TGF- β 1 单克隆抗体治疗方

案 (更高剂量或更密频次给药), 或使用广谱的 TGF- β 1 抑制剂可能是更优的方案。但由于 TGF- β 1 的生理作用广泛, TGF- β 1 除了促进纤维化外, 也具有抑制炎症的作用, 长期和持续抑制 TGF- β 1 可能会对患者有促进炎症, 加重肾脏损害, 甚至可能造成肾脏毒性的副作用^[65]。因此如上文提到, 调控通路中更多的环节并维持 TGF- β 1 整体的稳态可能是更优方案。

而干预 TGF- β 1 通路下游的重要靶点 SMAD3 和 SMAD7, 可能是抑制糖尿病肾脏的炎症与纤维化的可行方案。既往研究发现 SMAD3 活化是肾脏纤维化的主要靶点, 并且导致肾脏小管上皮细胞自噬紊乱。SMAD3 抑制剂 SIS3 在一些肾脏疾病模型中有较好的抑制纤维化的作用^[66]。另外恢复糖尿病肾病中下调的 SMAD7 表达亦能减轻糖尿病肾脏的炎症与纤维化, 改善肾功能^[67]。

4 总结与展望

TGF- β 1/SMAD 共同介导的纤维化是糖尿病肾病发病的关键机制。见图 1, 目前除了 TGF- β 1/SMAD 直接激

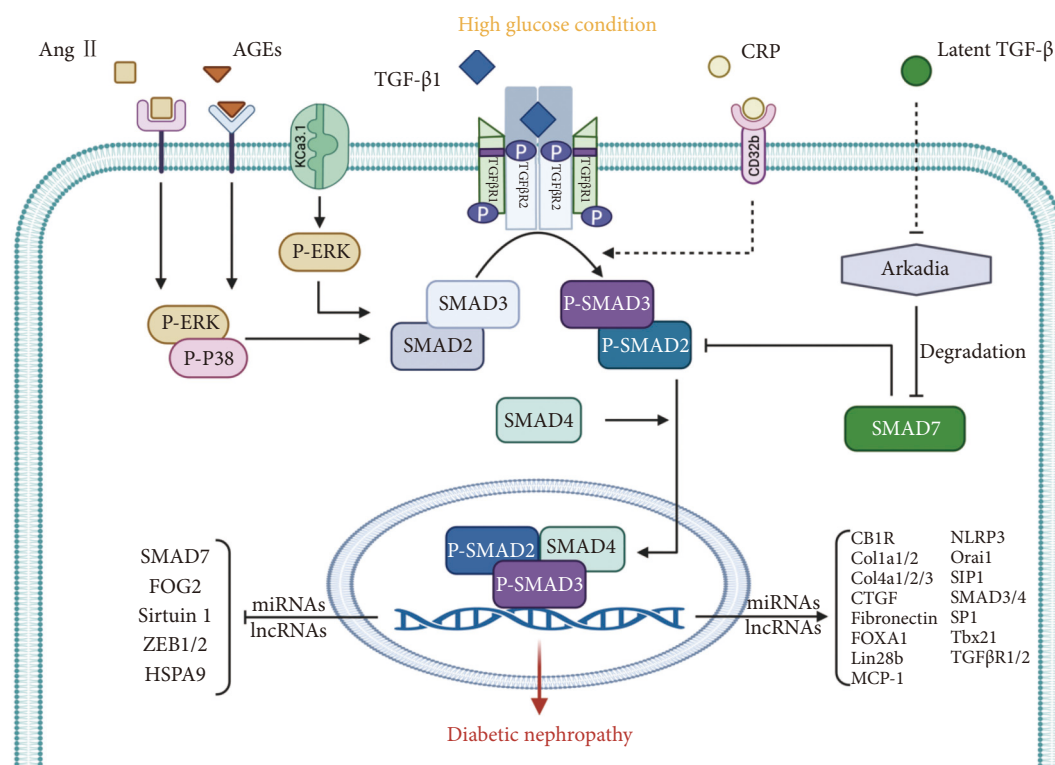


图 1 TGF- β 1/SMAD 介导糖尿病肾病的发病机制

Fig 1 Schematic illustration of the pathogenic mechanisms of TGF- β 1/SMAD-mediated diabetic nephropathy

Ang II: angiotensin II; CRP: C-reactive protein; TGF- β 1: transforming growth factor- β 1; P-ERK: phosphorylated extracellular signal-regulated kinases; miRNAs: micro-RNA; lncRNAs: long non-coding RNA; FOG2, ZEB1/2, HSPA9, CB1R, Col1a1/2, Col4a1/2/3, CTGF, FOXA1, MCP-1, NLRP3, SIP1, and TGF β R1/2 denote the same as those in Table 1 and Table 2. After TGF- β 1 binds to the receptor on the cell membrane surface, it activates the phosphorylation of SMAD2/3, recruits SMAD4 to form a complex, and enters the nucleus to stimulate gene expression. Ang II and advanced glycation end products (AGEs) can promote the phosphorylation of SMAD2/3 through ERK/P38. Latent TGF- β 1 can inhibit SMAD2/3 phosphorylation through Arkadia/SMAD7. Diabetic nephropathy can be inhibited or enhanced by miRNAs and lncRNAs through different mechanisms. Created with BioRender.com.

活引起糖尿病肾脏损伤外, TGF- β 1/SMAD信号也可通过调节miRNA和lncRNA以及其他信号通路介导糖尿病肾病。结合上文所述, 由于TGF- β 1信号通路与众多信号通路存在级联与对话, 并具有广泛的生理作用, 单一抑制其中某个环节可能无法达到理想的治疗效果, 这从临床上单纯抑制TGF- β 1并不能减缓肾脏损伤可见一斑。因此, 调控其下游关键蛋白, 可能是防治糖尿病肾脏损伤的可行方案。前期研究通过SMAD3抑制剂与SMAD7激动剂相结合, 恢复SMAD3/7的平衡, 进而帮助恢复TGF- β 1通路的整体稳态的方案, 为我们在临床上治疗由TGF- β 1/SMAD介导的糖尿病肾病提供了新的思路, 其临床疗效, 尚需进一步验证。

* * *

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