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综 述

转化生长因子-β与肾脏纤维化的研究进展

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摘 要：转化生长因子-β (transforming growth factor-β, TGF-β)是促进肾脏纤维化、促进慢性肾脏疾病进展，甚至进入终末期肾脏疾病的重要因子之一。TGF-β可通过激活下游Smad依赖或非依赖途径诱导胶原等细胞外基质的合成，并抑制胶原的降解。疾病状态下大量分泌的TGF-β1还可促进肾小管上皮细胞、内皮细胞、足细胞、巨噬细胞、成纤维细胞、周细胞等细胞的凋亡、增殖及纤维化反应，并诱导肌纤维母细胞的生成、激活与增殖。TGF-β通过与BMP-7、Wnt/β-catenin、MAPK等经典通路相互调控，共同介导了肾纤维化的发生和发展。Smad3被认为是TGF-β通路下游最关键的致纤维化分子，其相关的表观遗传学修饰(如非编码RNA、DNA和组蛋白的表观修饰等)是近来研究的热点。尽管TGF-β功能多样、作用机制复杂，导致靶向TGF-β的抗肾脏纤维化临床治疗难以获得理想效果，TGF-β下游相关靶点的寻找仍被视为重要的肾脏纤维化防治策略。

关键词：肾脏纤维化；TGF-β/Smads；表观遗传学修饰；肌纤维母细胞；巨噬细胞
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Transforming growth factor-β and renal fibrosis

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Abstract: Transforming growth factor-β (TGF-β) is a driving force of renal fibrosis, which may lead to chronic kidney diseases and even end stage renal diseases. By activating canonical and non-canonical signaling pathways, TGF-β promotes the synthesis of extracellular matrix while preventing their degradation. In the injured kidney, TGF-β induces apoptosis, proliferation and fibrotic response of renal cells including epithelial cells, endothelial cells, podocytes, fibroblasts, pericytes and macrophages, and it also promotes transdifferentiation, activation and proliferation of myofibroblasts. Additionally, TGF-β exerts profibrotic effects by interplaying with other signaling pathways like BMP-7, Wnt/β-catenin and MAP kinase. Smad3 is the central pathological gene in renal fibrosis, and epigenetic regulation of TGF-β/Smad3 is a hot topic in kidney field. Although direct targeting TGF-β may cause side effects including tumorigenesis and immune diseases, the therapeutic strategies targeting the balance of downstream Smad3 and Smad7 may prevent or delay the progression of fibrotic kidney disease.

Key words: renal fibrosis; TGF-β/Smads; epigenetic modifications; myofibroblast; macrophage

肾脏纤维化是慢性肾脏疾病 (chronic kidney disease, CKD) 的共有特征之一，以大量肌纤维母细胞的浸润和细胞外基质 (extracellular matrix, ECM) 的过度沉积为主要特征，常导致肾功能的持续恶化，最终

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可能进展为终末期肾脏疾病 (end-stage renal disease, ESRD)，而转化生长因子 -β (transforming growth factor-β, TGF-β) 及其下游信号分子是公认的肾脏纤维化的关键调控因素 [1]。

1 TGF-β家族

TGF-β 是一种多功细胞因子，参与了细胞生长、分化、凋亡、创面修复与纤维化等多种细胞过程的调控。TGF-β 超家族含有 38 个家族成员，如 TGF-β、骨形成蛋白 (bone morphogenetic proteins, BMP)、抑制素、激活素等，其中 TGF-β 在 CKD 的进展中具有最重要的作用 [2]。迄今为止，科学家在哺乳动物中发现了 TGF-β 的三种亚型 (TGF-β1、2 和 3)，它们在氨基酸序列上有 70% 以上的相似性，但功能却不尽相同，有待进一步研究 [3]。TGF-β 生成后以 latent TGF-β 形式存在，其与无活性相关肽 (latency-associated peptide, LAP) 及 latent TGF-β 结合蛋白 (latent TGF-β binding protein, LTBP) 组成复合体，该复合体可抑制 TGF-β 与下游受体结合，使之处于非激活状态。latent TGF-β 可被活性氧产物、酸、基质金属蛋白酶 (matrix metalloproteinases, MMPs) 等激活，进而与 TGF-β II 型受体结合，招募 I 型受体并激活下游通路，发挥生物学效应 [4]。

2 TGF-β1与肾脏纤维化

临床数据表明，在肾脏疾病患者的肾脏标本及尿液中，TGF-β1 含量明显上升，且与肾脏纤维化程度呈明显正相关，这种现象在多种肾脏疾病的动物模型中均被证实。小鼠肝脏过表达 TGF-β1 可引起肾脏的纤维化，而 TGF-β1 中和抗体、抑制剂、基因敲除等均可有效地减轻肾脏纤维化 [5]。TGF-β1 诱导肾脏纤维化的主要机制包括：(1) 从转录水平直接诱导胶原 I、纤连蛋白等 ECM 的合成 [6]；(2) 诱导 MMPs 和金属蛋白酶组织抑制物 (tissue inhibitor of metalloproteinase, TIMPs) 的失平衡，阻止 ECM 的降解；(3) 对肾脏固有细胞的直接作用：例如，可诱导系膜细胞增殖和胶原分泌；促进上皮细胞和足细胞损伤，加重炎症和继发纤维化等 [7]；(4) 促进周细胞、纤维细胞、上皮细胞、内皮细胞、巨噬细胞等多种来源的肌纤维化母细胞转分化和增殖，介导纤维化反应 [8] (图 1)。

值得注意的是，latent TGF-β 并无促纤维化作用，

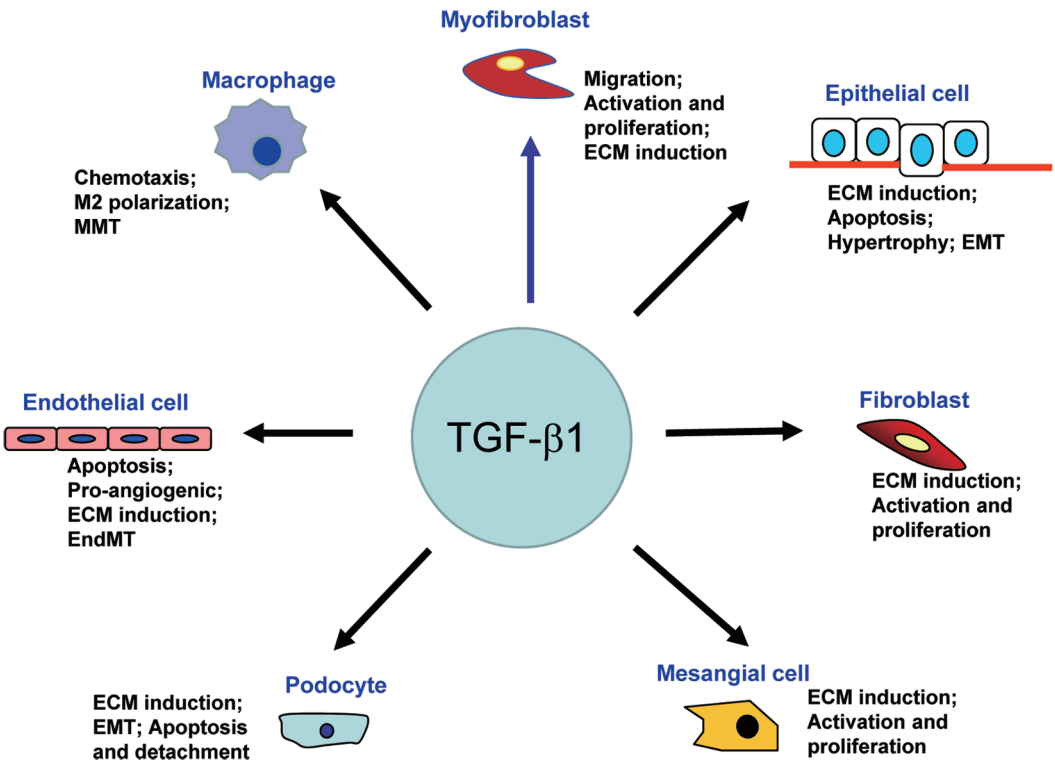

图 1. TGF-β1对各种肾脏细胞的调控作用

Fig. 1. Functional effects of TGF-β1 on renal cells. ECM: extracellular matrix; EMT: epithelial-mesenchymal transition; EndMT: endothelial-mesenchymal transition; MMT: macrophage-myofibroblast transition.

过表达 latent TGF-β 可能通过上调 Smad7 及 Foxp3 诱导的调节性 T 细胞水平，减轻单侧输尿管结扎、抗基底膜肾小球肾炎等疾病模型中的炎症和纤维化反应，提示了 TGF-β1 功能的多样性 [9–11]。

3 Smad依赖与非依赖的TGF-β通路

Smads 是 TGF-β 下游的主要效应蛋白，当 TGF-β 受体被激活时，磷酸化的 Smad2 和 Smad3 (R-Smads) 可与 Smad4 (Co-Smad) 结合，形成复合体转移入细胞核，调控下游基因转录 [4]。尽管 Smad2 和 Smad3 氨基酸序列具有 90% 以上的相似性，其功能却不尽相同：Smad3 是公认的致纤维化因子，它可直接结合胶原的启动子区域，参与 ECM 的生成和降解；同时 Smad3 也是调控肌纤维母细胞转分化的关键分子 [4, 12]。在梗阻性肾病、糖尿病肾病、高血压肾病等模型中，敲除 Smad3 明显减轻肾脏纤维化水平。与 Smad3 不同的是，Smad2 无法直接结合 DNA，条件性敲除肾小管 Smad2 增加了 Smad3 的磷酸化水平及其与胶原启动子的结合能力，提示 Smad2 在特定条件下发挥抗肾纤维化作用，这可能与 Smad2/3 在细胞中的比例平衡有关 [13]。Smad4 作为 TGF-β 和 BMP 信号通路共同的下游分子，在 Smad2/3 及 Smad1/5/8 的核转移过程中起到关键作用。本研究组研究表明，当肾小管上皮细胞 Smad4 缺失时，尽管 Smad2/3 磷酸化水平及核位移并未减少，其与胶原启动子的结合能力却受到了影响，导致肾脏纤维化减轻，这种现象也在 TGF-β1 刺激的系膜细胞中得到了证实 [14]。Smad6 和 Smad7 是 TGF-β/Smad 通路中的抑制性分子。TGF-β 可通过 Smad3 依赖性机制上调 Smad7 的合成，也可以诱导 Smurfs/arkadia 介导的泛素蛋白酶促进 Smad7 的降解，而 Smad7 可以与 R-Smads 竞争与 TGF-β 受体的结合，负反馈地调控 TGF-β/Smad3 的活性水平 [15]。本研究组及其他研究团队的结果一致证实，Smad7 在梗阻性肾病、糖尿病肾病、高血压肾病等模型中表达均降低，敲除 Smad7 加重肾脏损伤，而重新恢复 Smad7 水平可同时抑制 NF-κB 介导的炎症和 Smad3 介导的纤维化反应 [15–17]。

此外，TGF-β 可激活 Smad 非依赖途径，常见的下游分子包括 MKK3/p38、MKK4/JNK、ERK、Rho-GTPases、Rac、Cdc42、ILK 等，这些分子与 Smads 相互调控，介导了 TGF-β 的生物学效应，TGF-β 还可以与 Wnt/β-catenin、EGFR、mTOR、BMP-7 等经典信号通路产生交联 (crosstalk)，共同促进肾脏纤维化的发生、发展 [1]。

4 TGF-β与肾脏细胞

如图 1 所示，TGF-β 对肾脏固有细胞 (如上皮细胞、内皮细胞、足细胞、系膜细胞、成纤维细胞和周细胞) 和浸润的炎症细胞 (如巨噬细胞等) 均有着广泛和多样化的调控作用，共同介导了肾脏纤维化的进展。

4.1 TGF-β与上皮细胞

上皮细胞是 TGF-β 的重要来源之一。研究结果表明，当肾小管上皮细胞受到损伤并阻滞于 G2/M 细胞周期时，可以分泌大量的 TGF-β1，加重肾纤维化 [18]。条件性敲除肾小管上皮细胞的 TGF-β II 型受体或下游 Smad4 蛋白，均可改变纤维化进程 [14, 19, 20]。而当肾小管上皮细胞 Smad2 缺失时，Smad3 介导的肾脏纤维化反应明显加重 [13]，共同提示肾小管上皮细胞中的 TGF-β/Smad 通路在纤维化中扮演重要角色。

肌纤维母细胞的生成和激活是纤维化的中心事件，但其来源一直是学术争论的焦点。有证据表明其可能由上皮细胞、内皮细胞、骨髓来源的纤维细胞 (fibrocyte) 和巨噬细胞、周细胞 (pericyte) 转分化或成纤维细胞激活形成 [1, 21, 22]。1995 年，研究人员在上皮细胞中发现了成纤维细胞特异性蛋白 1 (fibroblast specific protein-1, FSP-1) 的异常表达，首次提出了“上皮细胞 - 间充质细胞转分化 (epithelial-mesenchymal transition, EMT)”的观点 [23]。大量证据表明，体外培养的上皮细胞在 TGF-β1 的刺激下大量表达 α-SMA 等肌纤维母细胞标志物，Smad3 及非经典通路中的 p38 MAPK、JNK、Wnt/β-catenin 信号均可能参与了此过程的调控 [24]。但是由于缺少足够的临床资料支持和在体影像学证据，EMT 概念近年来受到了质疑。细胞谱系追踪技术在单侧输尿管结扎引起的肾脏纤维化模型中也并未检测到 EMT 现象的存在 [25]，但值得注意的是，近期有研究表明在纤维化过程中，肾小管上皮细胞发生部分分化并开始表达纤维化基因，在未完全转化为 α-SMA 阳性肌纤维母细胞的情况下即可促进纤维化的进展 [26, 27]。此外，有研究结果还提示 TGF-β1 可促进足细胞的凋亡及其向肌纤维母细胞的转分化 [1]。

4.2 TGF-β与内皮细胞

TGF-β 可以调控内皮细胞的凋亡、增殖和迁移，

改变血管微环境。一方面，其可以直接诱导内皮细胞的凋亡，另一方面，TGF-β 可以刺激足细胞和肾小管上皮细胞分泌 VEGF，起到内皮细胞保护作用 [4]。TGF-β 还是内皮细胞 - 间充质细胞转分化 (endothelial-mesenchymal transition, EndMT) 的重要诱导剂 [28]。条件性敲除内皮细胞中的 TGF-β 受体或使用 Smad3 的抑制剂 SIS3，均可抑制 EndMT 水平，减轻肾间质纤维化，延缓链脲霉素诱导的糖尿病肾病进展 [29, 30]。此外，通过靶向 TGF-β/Smad3/miR-29 轴，抑制二肽基肽酶 -4 可减轻糖尿病肾病模型中的 EndMT 和纤维化水平 [31]。

4.3 TGF-β与巨噬细胞

尽管有证据表明巨噬细胞来源的 TGF-β1 缺失对单侧输尿管结扎和肾缺血再灌注损伤模型中肾脏纤维化的进展影响甚微，损伤肾脏中浸润的巨噬细胞仍被认为是 TGF-β1 的重要来源 [32]。本研究组近期研究表明，无论是在 IgA 肾病或移植后纤维化的人类标本，亦或是单侧输尿管结扎、肾脏移植后纤维化的小鼠模型中，骨髓来源的巨噬细胞均可能发生巨噬细胞 - 肌纤维母细胞转分化 (macrophage-myofibroblast transition, MMT)，形成具有强胶原分泌能力的 α-SMA 阳性肌纤维母细胞 [33]。此外，Smad3 野生型 / 敲除型小鼠骨髓移植实验及体外实验均证实，MMT 主要由 TGF-β/Smad3 依赖性机制所介导 [8, 34, 35]。

4.4 TGF-β与其他肾脏细胞

肾脏固有的成纤维样细胞包括肾小球系膜细胞、间质成纤维细胞和周细胞等，均可被诱导激活为肌纤维母细胞表型。其中 TGF-β1 是最重要的诱导因素，小剂量 TGF-β1 可诱导系膜细胞增殖、α-SMA 的表达和胶原蛋白生成 [36, 37]。阻断 TGF-β1 可延缓肾小球硬化的进程 [38]。TGF-β1 可以上调 Nox4 介导的活性氧产生，进而激活肾间质成纤维细胞，诱发纤维化 [39]。此外，研究表明，损伤小管上皮细胞来源的 TGF-β1 可以诱导相邻的周细胞转分化为肌纤维母细胞，TGF-β1 还会以旁分泌的方式刺激肾小管上皮细胞血小板衍生生长因子 (platelet derived growth factor, PDGF) 的产生，促进周细胞增殖 [40]。纤维细胞是表达 I 型胶原的 $CD45^+$ 细胞，衍生自骨髓中的单核细胞前体，并存在于循环或脾内 [41, 42]，被认为是肾纤维化模型中肌纤维母细胞的来源之一，研究显示 TGF-β1 通过激活 Smad2/3 和 JNK 途径来驱动纤维细胞向肌纤维母细胞的转分化 [41]。

5 TGF-β依赖性非编码RNA与纤维化

越来越多的证据表明，TGF-β 能够通过调控某些特定的 microRNA (miRNA)，促进肾纤维化的发生、发展。肾纤维化时，TGF-β1 上调 miR-21、miR-192、miR-377、miR-382、miR-433 和 miR-491-5p，而下调 miR-29 和 miR-200 的水平 [43–47]。在纤维化的肾脏中，miR-21 的水平明显升高 [48–53]，抑制 miR-21 减弱了 ECM 的沉积，延缓了肾纤维化的进程，其靶点包括 Smad7、Spry1、PTEN、PPARα、Cdc25a、Cdk6 等 [49, 50, 54]。miR-192 在纤维化中的作用仍有争议。研究表明在纤维化小鼠模型和 TGF-β1 刺激的小鼠细胞中，miR-192 显著上调 [55, 56]。沉默或敲除 miR-192 可通过诱导 ZEB1/2 的表达减轻肾纤维化。但是，最新证据表明在糖尿病肾病患者标本和 TGF-β 处理的人肾小管上皮细胞中，miR-192 的水平降低，而 miR-192 的缺乏加速了糖尿病肾病患者的肾脏纤维化 [57, 58]。miR-192 在肾脏纤维化中的复杂功能及种属特异性有待进一步研究。miR-29 和 miR-200 是 TGF-β1 依赖性的抗纤维化 miRNAs，在疾病肾脏中被明显抑制。值得注意的是，超过 20 种 ECM 相关的基因 (包括 I 型胶原) 都是 miR-29 的潜在靶点 [59]。过表达 miR-29 可减弱梗阻性肾病和糖尿病肾病模型中的纤维化反应，同时可以减轻 TGF-β1、高糖及盐等多种刺激因素诱导的纤维化基因表达水平上调 [59–63]。miR-200 家族包括 miR-200a、miR-200b、miR-200c、miR-429 及 miR-141[64]，在梗阻性肾病和糖尿病肾病模型的肾脏中，miR-200a 和 miR-141 的水平明显降低 [65, 66]。miR-200 在调控上皮分化的过程中非常重要，它可以通过抑制上皮细胞转录因子 ZEB1 和 ZEB2 显著减轻肾纤维化 [67, 68]。作为一种 Smad3 调控的 miRNA，miR-433 在肾纤维化时被上调，沉默 miR-433 可通过抑制 Azin1/TGF-β/Smad 轴减轻纤维化 [69]；最近研究表明，TGF-β1 还可通过抑制 miR-30a 和 miR-152，上调 DNA 甲基转移酶 DNMT1 和 DNMT3a 的表达进而下调 Klotho 水平，促进肾纤维化 [70]。

长链非编码 RNA (long noncoding RNA, lncRNA) 参与了多种疾病的病理进程，但其在肾脏纤维化中的功能学研究尚属于起步阶段 [71]。本研究组在 Smad3 野生型 / 敲除型的小鼠上构建单侧输尿管结扎诱导的肾脏纤维化模型，RNA 测序结果显示至少 21 种 lncRNA 在肾纤维化过程中受到 TGF-β/Smad3 信号通路的调控。其中，lncRNA np_5318 和

np_17856 参与了 TGF-β1 介导的肾纤维化，并可能成为肾脏纤维化的潜在治疗靶点 [72]。在 TGF-β1 刺激的小管上皮细胞中，lncRNA MEG3 水平明显降低，过表达 lncRNA MEG3 可抑制 TGF-β1 诱导的 EMT 反应和细胞增殖 [73]。本研究组最新研究表明，在梗阻性肾病和糖尿病肾病模型中，作为 TGF-β/Smad3 通路下游的关键调控因子，抑制肾脏 lncRNA Erbb4-IR 可诱导 Smad7 表达，从而减轻 Smad3 介导的肾脏纤维化 [74, 75]。

6 靶向于TGF-β及下游通路的治疗策略

6.1 TGF-β信号的完全性阻断

抗 TGF-β 疗法的潜在治疗作用已经被广泛证实。研究表明 TGF-β 中和抗体、TGF-β 反义寡核苷酸、TGF-β 受体激酶抑制剂 (例如 GW788388，IN-1130) 等在多种纤维化疾病模型中均能有效减慢肾纤维化进程 [5]。研究表明 TGF-β 受体转录后核心岩藻糖基化的阻断可以减轻肾脏间质纤维化水平 [76]。Klotho 是一种主要在肾小管上皮细胞中表达的单向跨膜蛋白质，可直接结合 TGF-β II 型受体阻断 TGF-β 信号的启动，进而抑制肾纤维化 [77]。更为重要的是，某些 TGF-β 抑制剂的抗纤维化作用已在临床试验或临床前研究中得到证实 [78]。例如，小分子吡非尼酮可以抑制 TGF-β1 启动子活性水平，从而预防局灶节段性肾小球硬化 (focal segmental glomerular sclerosis, FSGS) 和糖尿病肾病患者估计肾小球滤过率 (estimated glomerular filtration rate, eGFR) 的减少 [79, 80]。此外 TGF-β1 活性抑制剂 Fresolimumad 和 LY2382770 在 FSGS 和糖尿病肾病患者中也取得了较理想的疗效 [78, 81, 82]。与之相反的是，近期临床研究表明，抗 TGF-β1 抗体治疗无法延缓糖尿病肾病进程 [83]，另一项研究也表明低剂量 TGF-β1 对糖尿病肾脏损害有一定的保护作用 [84]。此外，完全阻断 TGF-β 信号可能存在加重炎症反应和促进肿瘤发生的风险，阻碍了其在临床治疗中的广泛应用。

6.2 下游Smad蛋白的靶向治疗

为了避免完全阻断 TGF-β1 信号通路产生的不良后果，靶向于下游效应分子 Smad3、Smad7 等的治疗策略愈发受到关注。研究显示，BMP-7 作为 TGF-β/Smad3 的天然拮抗剂，在多种肾脏纤维化模型中具有保护作用 [4, 85–89]。抑制调节蛋白 Kindlin-2，可以减少 Smad3 与 TGF-β I 型受体的结合，减轻肾间质纤维化 [90]。Ski 及 SnoN 作为 Smad 重要的转录共抑制因子，可拮抗 Smad 调节的基因转录，进而发挥抗纤维化作用 [91]。Smad3 磷酸化抑制剂 SIS3 可通过减少 EndMT，减缓糖尿病肾病的纤维化水平 [30]。以 Smad 为靶点的中药抗肾纤维化治疗也逐渐得到了重视。GQ5 是一种从漆树树脂中提取的小分子酚醛化合物，其通过干预 Smad3 和 SARA 的结合，抑制 TGF-β I 型受体和 Smad3 的相互作用，从而减少 Smad3 的磷酸化，显著下调体内、外模型中 I 型胶原、α-SMA 及纤维连接蛋白等纤维化指标水平 [92]。汉黄芩素明显抑制 Smad3 活性及纤维化反应，而在 Smad3 缺失的肾小管上皮细胞上，汉黄芩素不能进一步抑制 TGF-β 诱导的纤维化反应，提示 Smad3 可能是汉黄芩素抗纤维化的重要靶点 [93]。研究显示在多种肾脏损伤模型中，恢复 Smad7 的表达水平有助于抑制炎症和纤维化 [16, 94–97]，但值得注意的是，过度表达 Smad7 可能会阻断 NF-κB 的生理学功能，诱导足细胞等发生凋亡，因此剂量的控制是 Smad7 治疗的重要注意事项 [98]。此外，鉴于 Smad3 与 Smad7 信号的失衡是肾纤维化发生的重要机制，本研究组联用柚皮素 (Smad3 抑制剂) 和积雪草酸 (Smad7 激动剂) 再平衡 Smad3/Smad7 信号，在不增加毒性的前提下，小剂量联用即取得了更佳的治疗效果 [99] (图 2)。

6.3 表观遗传学相关的TGF-β/Smad靶向治疗

表观遗传学修饰 (特别是 miRNA) 在肾脏纤维化的治疗价值近来得到了充分的关注。如图 3 所示，在 Smad 依赖性的 miRNA 中，过表达 miR-29、miR-200 或抑制 miR-21、miR-192、miR-433 均可有效减缓肾纤维化的进程 [49, 50, 55, 59, 63, 68]。此外，一系列 miRNAs 可靶向调控 TGF-β 及下游信号分子，改变

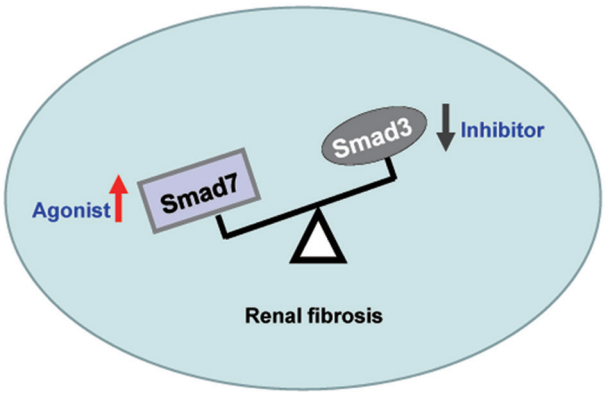

图 2. 再平衡TGF-β/Smads 信号防治纤维化

Fig. 2. Anti-fibrotic strategy by rebalancing TGF-β/Smads.

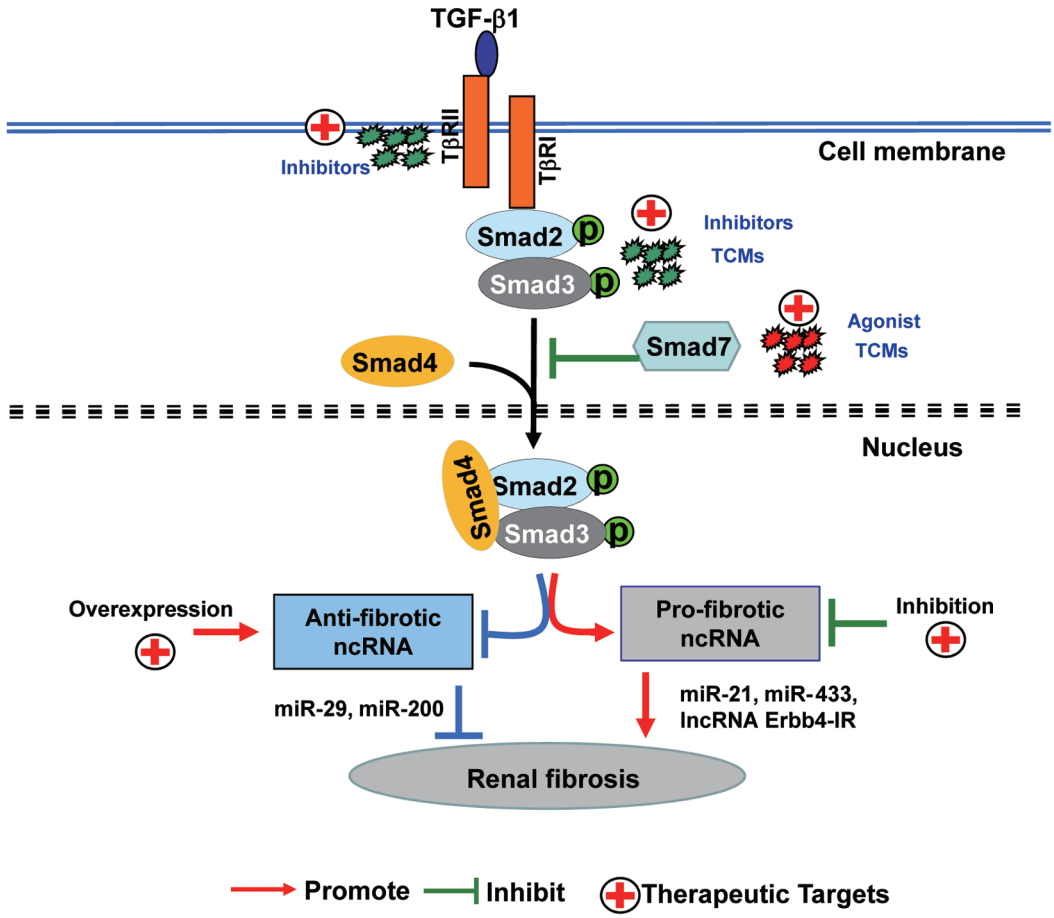

图 3. TGF-β/Smad通路中的肾脏纤维化防治靶点

Fig. 3. Potential therapeutic targets in TGF-β/Smad signaling in treatment of renal fibrosis. TCM: Traditional Chinese Medicine; lncRNA: long noncoding RNA; miR: microRNA.

肾纤维化的进程。例如 let-7b 可靶向性抑制 TGF-β I 型受体，进而阻断 TGF-β 经典 / 非经典通路介导的肾脏纤维化 [100]。但值得注意的是，miRNA 靶点众多，且同一靶点又常受到多个 miRNAs 调控，因此“脱靶效应”的存在限制了其广泛应用。其他表观遗传学方式亦可通过调控 TGF-β/Smad 影响肾纤维化进程。例如，I 类组蛋白去乙酰化酶 (histone deacetylase, HDAC) 抑制剂 MS-275 和 HDAC6 抑制剂通过阻断 TGF-β/Smad3 及其与胶原启动子的结合，分别减轻梗阻性肾病模型和血管紧张素 II 诱导的肾脏纤维化 [101, 102]；甲基转移酶 EZH2 可以通过下调 Smad7 表达水平促进纤维化发生，也被视为肾纤维化新的治疗靶点 [103]。

7 结论与展望

综上所述，大量证据表明 TGF-β 及下游经典 / 非经典通路的激活是肾脏纤维化发生、发展的重要驱动因素。作为 TGF-β 致纤维化发生的关键分子，Smad3 及其表观遗传学修饰的变化均与纤维化发生有关，Smad3 有可能成为干预肾脏纤维化较为理想的靶点，而调整疾病状态下 Smad3/Smad7 的再平衡可能是治疗纤维化的关键。因此，进一步探索并发现 TGF-β/Smad 相关的、更具特异性的纤维化调节分子和转录因子，及将实验室研究成果逐步推广至临床试验，均是未来抗肾脏纤维化的重要研究方向。

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