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ROLE OF TRANSFORMING GROWTH FACTOR-B1 IN THE DEVELOPMENT OF CHRONIC KIDNEY DISEASE AND RENAL FIBROSIS

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Key words: transforming growth factor-β1 (TGF-β1), chronic kidney disease, renal fibrosis, Smad signaling, glomerulosclerosis, tubulointerstitial fibrosis, extracellular matrix (ECM) accumulation.
Tayanch so‘zlar: transformatsiyalovchi o‘sish omili beta-1 (TGF-β1), surunkali buyrak kasalligi, buyrak fibrozi, Smad signal yo‘li (yoki Smad signallanish tizimi), glomeruloskleroz, tubulointerstitsial fibroz, hujayradan tashqari matritsaning (ECM) to‘planishi.
Ключевые слова: трансформирующий фактор роста бета-1 (TGF-β1), хроническая болезнь почек, почечный фиброз, сигнальный путь Smad, гломерулосклероз, тубулоинтерстициальный фиброз, накопление внеклеточного матрикса (ECM).

Chronic kidney disease (CKD) is a progressive condition characterized by nephron loss, extracellular matrix (ECM) accumulation, and declining renal function. Transforming growth factor-β1 (TGF-β1) has been widely recognized as a master regulator of fibrosis and is strongly implicated in the pathogenesis of CKD. Elevated TGF-β1 expression promotes glomerulosclerosis and tubulointerstitial fibrosis by stimulating collagen and fibronectin production, thereby exacerbating structural damage and functional decline. Mechanistically, TGF-β1 activates the TβRII/TβRI receptor complex, triggering downstream Smad-dependent signaling pathways that regulate transcription of profibrotic genes. Inhibitory Smad7 counterbalances this pathway, but its suppression leads to uncontrolled fibrogenesis. Beyond fibrosis, TGF-β1 plays multifaceted roles in kidney physiology, participating in immune regulation, epithelial-to-mesenchymal transition, and tissue repair processes. Understanding these dual effects is essential for designing therapies that selectively block pathological TGF-β1 activity without disrupting its protective functions. This review summarizes current knowledge of TGF-β1 signaling in CKD and highlights potential therapeutic targets aimed at modulating its activity to prevent disease progression.

SURUNKALI BUYRAK KASALLIGI VA BUYRAK FIBROZINING RIVOJLANISHIDA TRANSFORMATSIYALOVCHI O‘SISH OMILI-B1 NING ROLI

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Surunkali buyrak kasalligi (SBK) — bu nefronlar yo‘qolishi, hujayralararo matritsa (ECM) to‘planishi va buyrak funksiyasining pasayishi bilan kechuvchi progressiv holatdir. Transformatsiyalovchi o‘sish omili-β1 (TGF-β1) fibrozning asosiy regulyatori sifatida tan olingan bo‘lib, SBK patogenezida muhim rol o‘ynaydi. TGF-β1 ning oshgan ekspressiyasi kollagen va fibronektin ishlab chiqarilishini rag‘batlantirish orqali glomeruloskleroz va tubulointerstitsial fibrozning rivojlanishiga sabab bo‘ladi, bu esa buyrak tuzilmasining shikastlanishini kuchaytiradi hamda funksional holatning yomonlashuviga olib keladi. Mexanizm nuqtai nazaridan, TGF-β1 TβRII/TβRI retseptor kompleksini faollashtiradi, bu esa profibrotik genlar transkripsiyasini boshqaradigan Smadga bog‘liq signallar yo‘llarini ishga tushiradi. Ingibirlangan Smad7 ushbu yo‘lga qarshi turadi, biroq uning susayishi fibrozning nazoratsiz rivojlanishiga olib keladi. Fibroz rivojlanishidan tashqari, TGF-β1 buyrak fiziologiyasida ko‘p qirrali funksiyalarni bajaradi: immun tartibga solishda, epiteliy-mezenximal o‘tishda hamda to‘qimalarning tiklanish jarayonlarida qatnashadi. Ushbu omilning ikki tomonlama (foydali va zararli) ta’sirini chuqur anglash, uning patologik faolligini to‘xtatib, himoya funksiyasini buzmaydigan terapevtik strategiyalarni ishlab chiqishda muhim ahamiyatga ega. Mazkur sharhda TGF-β1 ning SBKdagi signal mexanizmlariga doir zamonaviy ilmiy ma’lumotlar umumlashtirilgan hamda kasallikning progressiyasini oldini olish maqsadida uning faolligini modulyatsiya qiluvchi potentsial terapevtik nishonlar taqdim etilgan.

РОЛЬ ТРАНСФОРМИРУЮЩЕГО ФАКТОРА РОСТА-B1 В РАЗВИТИИ ХРОНИЧЕСКОЙ БОЛЕЗНИ ПОЧЕК И ПОЧЕЧНОГО ФИБРОЗА

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Хроническая болезнь почек (ХБП) — это прогрессирующее состояние, характеризующееся потерей нефронов, накоплением внеклеточного матрикса (ВКМ) и снижением функции почек. «Фактор трансформирующего роста» -β1 (TGF-β1) широко признан ключевым регулятором фиброза и играет важную роль в патогенезе ХБП. Повышенная экспрессия TGF-β1 способствует развитию гломерулосклероза и тубулоинтерстициального фиброза за счёт стимуляции продукции коллагена и фибронектина, что усиливает структурные повреждения и ухудшает функциональное состояние почек. Механистически TGF-β1 активирует рецепторный комплекс TβRII/TβRI, запускающий Smad-зависимые сигнальные пути, регулирующие транскрипцию профибротических генов. Ингибирующий Smad7 противодействует этому пути, однако его подавление приводит к не-

контролируемому развитию фиброза. Помимо развития фибротических изменений, TGF-β1 выполняет многогранные функции в физиологии почек, участвуя в иммунной регуляции, эпителиально-мезенхимальном переходе и процессах регенерации тканей. Понимание этих двойственных эффектов имеет важное значение для разработки терапевтических стратегий, направленных на селективную блокаду патологической активности TGF-β1 без нарушения его защитных функций. В данном обзоре суммированы современные данные о сигнальных механизмах TGF-β1 при ХБП и представлены потенциальные терапевтические мишени, позволяющие модулировать его активность с целью предотвращения прогрессирования заболевания.

Introduction. Chronic kidney disease (CKD) is a major global health burden, affecting more than 850 million people worldwide and ranking among the top 10 causes of death (Bikbov et al., 2020). CKD is characterized by gradual loss of renal function over months or years, often progressing to end-stage renal disease (ESRD), which requires dialysis or kidney transplantation. A defining feature of CKD is renal fibrosis, marked by excessive deposition of extracellular matrix (ECM) proteins such as collagens and fibronectin. This fibrotic remodeling distorts normal renal structure, reduces glomerular filtration rate (GFR), and drives irreversible organ damage (Gu et al., 2020).

Among numerous profibrotic cytokines, transforming growth factor-β1 (TGF-β1) is considered the “master regulator” of fibrosis. TGF-β1 levels are elevated in CKD, where they activate glomerular and tubular cells to produce ECM components, leading to glomerulosclerosis and tubulointerstitial fibrosis (Loeffler & Wolf, 2014). Apart from these effects, TGF-β1 also exerts several protective functions. For example, it has anti-inflammatory properties, promotes immune tolerance by inhibiting excessive T-cell activation, supports tissue repair and regeneration, and helps maintain extracellular matrix homeostasis. Understanding the molecular mechanisms underlying TGF-β1 signaling is essential for developing therapeutic strategies that prevent CKD progression while preserving its physiological functions.

Molecular Biology of TGF-β1.

Gene and Protein.

Structure TGF-β1 is encoded by the TGFB1 gene, located on chromosome 19q13.1–13.3. This gene encodes a 390-amino acid precursor protein that undergoes multiple post-translational modifications. It is first synthesized as a latent precursor, consisting of a signal peptide, latency-associated peptide (LAP), and the mature TGF-β1 domain. Proteolytic cleavage by furin-like convertases separates LAP from the mature peptide, although the two remain non-covalently associated in a latent complex. The mature TGF-β1 protein functions as a disulfide-linked homodimer and belongs to the TGF-β superfamily, a group of multifunctional cytokines that regulate cell proliferation, differentiation, immune homeostasis, angiogenesis, and extracellular matrix (ECM) turnover (Massagué, 2012). Dysregulation of TGFB1 expression or signaling has been implicated in a wide range of pathological conditions, including fibrosis, cancer progression, and autoimmune disease, highlighting its dual role as both a homeostatic regulator and a potential driver of disease.

Activation and Signaling.

The activation of TGF-β1 is tightly regulated, as uncontrolled activation can result in pathological tissue remodeling. Latent TGF-β1 is stored in the ECM in association with latent TGF-β binding proteins (LTBPs). It is activated by several mechanisms, including proteolytic cleavage by matrix metalloproteinases (MMPs), mechanical force exerted by integrins (such as αvβ6 and αvβ8), and changes in pH. Once activated, TGF-β1 binds to the type II TGF-β receptor (TβRII), a constitutively active serine/threonine kinase, which subsequently recruits and phosphorylates the type I receptor (TβRI/ALK5). This receptor heterotetramer phosphorylates receptor-regulated Smads (Smad2 and Smad3), which then form heteromeric complexes with the common-mediator Smad4. The Smad complex translocates into the nucleus, where it associates with co-activators or co-repressors to regulate transcription of target genes involved in ECM production, such as COL1A1 (collagen I), fibronectin, and plasminogen activator inhibitor-1 (PAI-1) (Gu et al., 2020).

In addition to the canonical Smad-dependent pathway, TGF-β1 activates multiple non-Smad signaling cascades, including MAPK (ERK, JNK, p38), PI3K/AKT, and Rho-like GTPase pathways. These alternative routes amplify TGF-β1’s cellular effects, particularly in promoting epithelial-to-mesenchymal transition (EMT), cytoskeletal remodeling, cell motility, and further ECM deposition (Derynck & Zhang, 2003). The integration of canonical and non-canonical pathways allows TGF-β1 to exert context-dependent effects, such as tumor suppression in early carcinogenesis and tumor promotion in advanced cancers.

Physiological and Protective Functions.

Although often discussed in the context of fibrosis and pathological remodeling, TGF-β1 also plays critical protective roles. It is a potent immunoregulatory cytokine that suppresses pro-inflammatory responses by inhibiting the production of TNF-α, IL-1β, and IFN-γ, while promoting the differentiation of regulatory T cells (Tregs) through upregulation of the transcription factor Foxp3. This helps maintain peripheral immune tolerance and prevents autoimmunity. Additionally, TGF-β1 contributes to wound healing by stimulating fibroblast proliferation, angiogenesis, and deposition of provisional ECM, which collectively facilitate tissue repair. By maintaining epithelial barrier integrity and controlling immune cell infiltration, TGF-β1 limits excessive tissue injury and promotes resolution of inflammation (Li et al., 2019).

Role of TGF-β1 in CKD Pathogenesis.

Glomerular Effects.

Within the glomerulus, TGF-β1 is a central mediator of structural remodeling and functional decline. It stimulates mesangial cell proliferation and excessive synthesis of extracellular matrix (ECM) components, including collagen IV, laminin, and fibronectin, leading to mesangial expansion and glomerulosclerosis (Loeffler & Wolf, 2014). Overproduction of these ECM proteins thickens the glomerular basement membrane (GBM), disrupts the charge- and size-selective filtration barrier, and contributes to proteinuria—an early clinical manifestation of CKD. Persistent activation of TGF-β1 in the glomerulus also increases expression of connective tissue growth factor (CTGF), a downstream profibrotic mediator that further amplifies matrix accumulation.

Tubulointerstitial Effects.

TGF-β1 plays a crucial role in tubulointerstitial fibrosis, a hallmark of CKD progression and a strong predictor of renal function decline. Through canonical Smad2/3 signaling, TGF-β1 induces epithelial-to-mesenchymal transition (EMT) in tubular epithelial cells, causing them to lose epithelial markers such as E-cadherin and gain mesenchymal markers including α-smooth muscle actin (α-SMA) and vimentin. These transformed cells acquire a myofibroblast-like phenotype and secrete abundant ECM proteins, thereby promoting interstitial fibrosis and tubular atrophy (Sureshbabu et al., 2016).

Additionally, TGF-β1 enhances the recruitment and activation of interstitial macrophages and fibroblasts, both of which act as major sources of further TGF-β1 production. This creates a self-perpetuating positive feedback loop, often referred to as the "fibrotic vicious cycle," which maintains chronic inflammation and tissue scarring. Non-canonical signaling pathways, such as PI3K/AKT and p38 MAPK, further amplify these effects by increasing fibroblast survival, proliferation, and resistance to apoptosis (Meng et al., 2016).

TGF-β1 also reduces matrix degradation by suppressing matrix metalloproteinases (MMPs) and upregulating tissue inhibitors of metalloproteinases (TIMPs), thereby skewing the balance toward net ECM accumulation. This maladaptive response ultimately leads to nephron dropout, irreversible loss of renal function, and progression to end-stage kidney disease (ESKD).

Challenges in Maintaining TGF-β1 Homeostasis.

TGF-β plays a crucial role in immune cell development, homeostasis, differentiation, and tolerance. When TGF-β1 levels are reduced, immune cells become overactivated, leading to autoimmune disease, as shown in mouse models lacking TGF-β1 or its receptors. These animals display severe inflammatory responses, marked by extensive lymphocyte and macrophage infiltration across multiple organs, particularly the heart and lungs (Jianchun Li et al., 2024).

Regulation of TGF-β1 Activity.

The TGF-β1 pathway is tightly regulated by inhibitory Smad7, which prevents excessive signaling by blocking receptor-Smad phosphorylation. In CKD, Smad7 expression is reduced, resulting in unchecked TGF-β1 activity (Lan, 2011). MicroRNAs such as miR-29 suppress collagen synthesis, but TGF-β1 downregulates miR-29 expression, promoting fibrosis (Huang et al., 2023). Epigenetic changes, including DNA methylation and histone modifications, also enhance TGFB1 gene expression and sustain fibrogenesis.

Therapeutic Implications.

Given its central role in fibrosis, TGF-β1 is an attractive therapeutic target. Approaches under investigation include neutralizing antibodies against TGF-β1, receptor kinase inhibitors, and antisense oligonucleotides to block TGFB1 expression. Standard CKD treatments such as renin–

TGF-β1 expression	Overexpression	Underexpression
Immune response	↓Decreases	↑Increases
Extra cellular matrix (ECM) production	↑Increases	↓Decreases (less fibrosis)
Cell proliferation	↓Epithelial cells decrease ↑fibroblasts increase	↑Epithelial cells increase ↓fibroblasts decrease
Inflammation	↓Decreases	↑Increases
Lymphocyte and macrophage infiltration	↓Decreases	↑Increases

angiotensin system inhibitors (ACE inhibitors, ARBs) indirectly suppress TGF-β1 activity and have shown benefit in slowing CKD progression (Ziyadeh et al., 2000). Novel agents such as BMP -7 analogs, microRNA-based therapies, and SGLT2 inhibitors offer additional antifibrotic potential. The main challenge remains to selectively inhibit pathological TGF-β1 signaling without impairing its protective roles in immune regulation and tissue repair.

Conclusion. TGF-β1 is a key mediator in the development of glomerular and tubulointerstitial fibrosis in CKD. Its overactivation promotes ECM deposition, EMT, and progressive nephron loss. Tight regulation of this pathway is essential for renal homeostasis, and its dysregulation represents a major driver of CKD progression. Therapeutic strategies targeting TGF-β1 or its downstream signaling components hold promise in halting fibrosis and preserving kidney function. Future research should focus on selective inhibitors that block pathogenic signaling while maintaining physiological tissue-repair mechanisms.

References:

1. Bikbov, B., et al. (2020). Global, regional, and national burden of chronic kidney disease, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. The Lancet, 395(10225), 709–733. https://doi.org/10.1016/S0140-6736(20)30045-3
2. Derynck, R., & Zhang, Y. E. (2003). Smad-dependent and Smad-independent pathways in TGF-β family signalling. Nature, 425(6958), 577–584. https://doi.org/10.1038/nature02006
3. Fuad N. Ziyadeh, Brenda B. Hoffman, Dong Cheol Han, M. Carmen Iglesias-de la Cruz, Soon Won Hong, Motohide Isono, Sheldon Chen, Tracy A. McGowan, Kumar Sharma (2000). Long-term prevention of renal insufficiency, excess matrix gene expression, and glomerular mesangial matrix expansion by treatment with monoclonal anti-TGF-β antibody in db/db diabetic mice. Proceedings of the National Academy of Sciences, 97 (14), 8015–8020. https://doi.org/10.1073/pnas.120055097
4. Gu, Y. Y., Liu, X. S., Huang, X. R., Yu, X. Q., & Lan, H. Y. (2020). Diverse role of TGF-β in kidney disease. Frontiers in Cell and Developmental Biology, 8, 123. https://doi.org/10.3389/fcell.2020.00123
5. Jianchun L., Yuanxia Z., Jiraporn K., Hongwei S., Li W., Nathupakorn D. (2024). TGF-β/Smad signaling in chronic kidney disease: Exploring post-translational regulatory perspectives (Review), 2024: Molecular Medicine Reports, 143, 3. https://www.spandidos-publications.com/10.3892/mmr.2024.13267
6. Lan, H. Y. (2011). Diverse roles of TGF-β/Smads in renal fibrosis and inflammation. International Journal of Biological Sciences, 7(7), 1056–1067. https://doi.org/10.7150/ijbs.7.1056
7. Loeffler, I., & Wolf, G. (2014). Transforming growth factor-β and the progression of renal disease. Nephrology Dialysis Transplantation, 29(suppl_1), i37–i45. https://doi.org/10.1093/ndt/gft267
8. Massagué, J. (2012). TGFβ signalling in context. Nature Reviews Molecular Cell Biology, 13(10), 616–630. https://doi.org/10.1038/nrm3434
9. Rongshuang Huang, Ping Fu, Liang Ma (2023). Kidney fibrosis: From mechanisms to therapeutic medicines. Signal Transduction and Targeted Therapy, 8, 107. https://doi.org/10.1038/s41392-023-01379-7
10. Sureshbabu, A., Muhsin, S. A., & Choi, M. E. (2016). TGF-β signaling in the kidney: Profibrotic and protective effects. American Journal of Physiology-Renal Physiology, 310(7), F593–F606. https://doi.org/10.1152/ajprenal.00365.2015
11. Xiao-Ming Meng, David J Nikolic-Paterson, Hui Yao Lan (2016). TGF-β: the master regulator of fibrosis. Nature Reviews Nephrology, 12(6), 325–338. https://www.nature.com/articles/nrneph.2016.48