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STUDY OF FIBROSIS PATHWAYS (TGF-B AND WNT SIGNALING) AS THERAPEUTIC TARGETS IN CHRONIC KIDNEY DISEASE

[1]Karabaeva Gulchekhra Khudoyberdievna (Medicine) , [2]Samatov Dilshod Karimovich(Medicine) , [3] Avalov Fayzullo Olmosovich (Medicine) , [4] Gulomov Jakhongir Ibrokhimovich (Medicine)

[1] Assistant of department Internal diseases No. 3 of Samarkand State Medical University Samarkand, Uzbekistan , karabaeva9229@gmail.com , https://orcid.org/0009-0003-2362-9928

[2]PhD, Assistant of department Internal diseases No. 3 of Samarkand State Medical University , Samarkand,Uzbekistan , dr86@inbox.ru, ORCID:0009-0009-8595-114X

[3]Chief Physician, Samarkand City Medical Association, Ministry of Health of the Republic of Uzbekistan , Samarkand,Uzbekistan

[4] PhD , Head of the Admissions Department, Republican Specialized Scientific and Practical Medical Center of Cardiology Samarkand branch , Samarkand, Uzbekistan , gulomovjahongir609@gmail.com

Abstract

Chronic kidney disease (CKD) is a progressive disorder, which is related to irreversible renal failure, to a large degree, facilitated by renal fibrosis. Fibrosis refers to the excess deposition of an extracellular matrix (ECM) that damages the structure and deteriorates the functionality. The transforming growth factor-beta (TGF- 1) and Wnt/ -catenin signaling networks are among the major molecular mediators of epithelial-to-mesenchymal transition (EMT), inflammation and fibroblast stimulation of renal fibrosis. This review discusses molecular pathways of TGF-B and Wnt in CKD, cross-talk, and new treatment approaches of these pathways. Recent developments emphasize pharmacological inhibitors, natural products and traditional medicine methods that regulate such signaling cascades. Moreover, the idea of individual antifibrotic treatment is becoming more popular, which will have to personalize treatment according to the molecular profiles. The knowledge of these pathways provides good opportunities to decelerate or halt fibrosis of the kidneys and enhance the results of CKD.

Keywords: Chronic kidney disease, renal fibrosis, TGF-β signaling, Wnt/β-catenin pathway, therapeutic targets

1. Introduction

Chronic kidney disease (CKD) is an irreversible and progressive illness, which is a serious health problem worldwide, causing great morbidity and mortality to millions of people worldwide. Diabetes, hypertension, and glomerulonephritis are just some of the various etiologists of the disease but in either case, the evolution of CKD is always characterized by the presence of renal fibrosis. Renal fibrosis is a pathophysiological process, which consists of excessive extracellular matrix (ECM) formation in the kidney interstitium that eventually results in the structural disorder, loss of nephron, atrophy of tubules, and progressive impairment of renal functioning.

Notably fibrosis is not an inactive by-product of injury but an active and highly controlled biological reaction, which is comprised of complex interplay between different types of cells. These are tubular epithelial cells, interstitial fibroblasts, endothelial cells as well as infiltrating immune cells. As the disease develops, phenotypic and functional alterations take place in these cells, helping in the maintenance of inflammation and fibrogenesis. Epithelial-to-mesenchymal transition (EMT) is one of the processes that involve epithelial cells changing mesenchymal properties and improving the production of the matrix. These mechanisms are regulated at the molecular level by a number of signaling pathways, the transforming growth factor-beta (TGF-b) and Wnt/ 0-catenin signaling pathways of which are regarded as driving factors of renal fibrosis. TGF-B signaling is generally accepted to be a supreme controller of fibrogenesis, which induces ECM synthesis and inhibits its degradation. On the same note, the Wnt/ 2-catenin pathway has a major role in cell communication, cell proliferation and cell differentiation and chronic stimulation of the pathway is one contributor of fibrotic chronic reactions.

More recently there has been a more interest in aiming to target these molecular pathways as opposed to merely controlling symptoms. As Huang et al. (2023) and Reiss et al. (2024) note, further insights into such signaling mechanisms have potential benefits in the creation of new antifibrotic drugs to reduce or even stop the development of CKD.

2. Pathophysiology of Renal Fibrosis

Renal fibrosis is universally acknowledged as the common end-stage in the development of chronic kidney disease (CKD), regardless of its cause. It is a pathophysiological mechanism of compensated wound healing after kidney damage and is typified by overload of extracellular matrix (ECM) protein (collagen, fibronectin and laminin). Such aberrant deposition disturbs the normal organisation of the kidney resulting in loss of the nephrons, tubular atrophy, as well as the gradual diminishing of renal functions.

Renal fibrosis has several important pathological characteristics. The activation of fibroblasts and their differentiation into myofibroblasts, which are the major effector cells in ECM production, are one of the most crucial ones. These myofibroblasts label α-smooth muscle actin (0 -SMA) and have stimulated contractile and secretory potentials. Moreover, tubular epithelial cells injury and apoptosis are also harmful factors leading to disaggregation and dysfunction of the kidney structure. Repeated damages to the epithelial cells cause the regenerative ability and even encourage fibrotic remodelling.

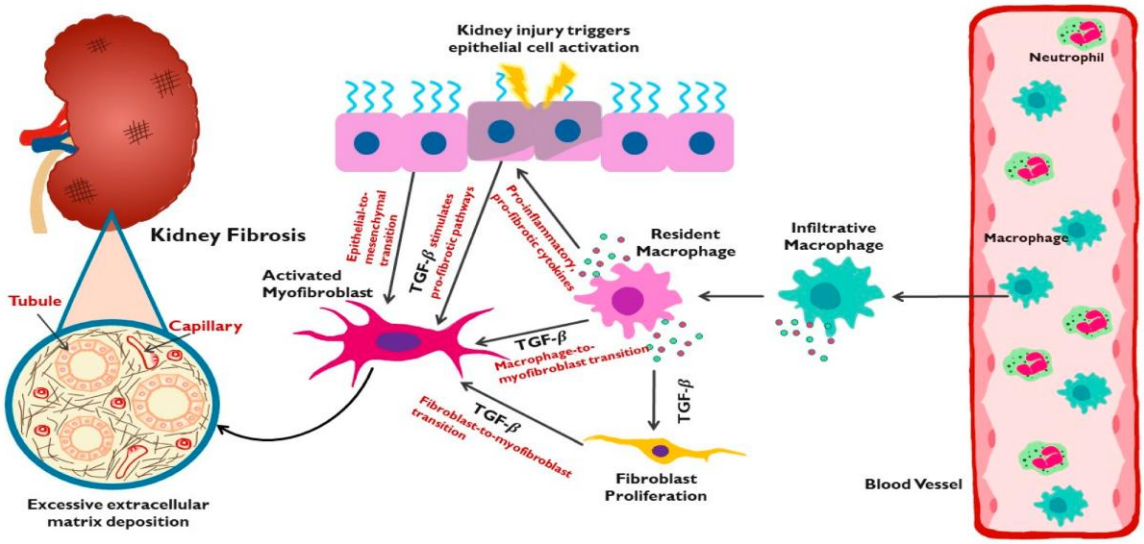

Figure 1: "Fibrosis in Chronic Kidney Disease"
(Source: Niculae et al. 2023)

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Fibrosis is also a primary cause of chronic inflammation. The immune response leading to the infiltration of immune cells, including macrophages and lymphocytes, leads to release of pro-inflammatory and pro-fibrotic cytokines, including TGF- β, which further enhances fibrogenesis. Niculae et al. (2023) remark that the development of renal fibrosis is frequently triggered by the acute kidney injury (AKI) when the incomplete or maladaptive repair pathways trigger the subsequent alteration in the pathology into the chronic. The conversion of AKI to CKD is characterized by the persistent stimulation of fibrogenic signalings, in particular, TGF- and Wnt/ -catenin.

The complexity of the disease is manifested by the fact that fibroblasts producing fibrosis can have many origins. These consist of resident interstitial fibroblasts, capillary detaching pericytes, bone marrow-derived fibrocytes, and epithelial cells that are in epithelial-to-mesenchymal transition (EMT). EMT is a vital procedure whereby the epithelial cells lose their polarity, adhesion capabilities and take on mesenchymal-like attributes so that they can generate ECM.

Table 1: Key Events in Renal Fibrosis

Component	Role in Fibrosis	Outcome
Fibroblasts/Myofibroblasts	ECM production	Tissue scarring
ECM accumulation	Structural disruption	Loss of kidney function
EMT	Generates fibroblast-like cells	Increased fibrosis
Inflammation	Cytokine release	Sustained injury
Apoptosis	Loss of epithelial cells	Reduced regeneration

3. TGF-β Signaling Pathway in CKD Fibrosis

3.1 Overview of TGF-β Signaling

Transforming growth factor-beta (TGF-8) is a versatile cytokine which takes center stage in the regulation of cell growth, differentiation, immune reactions, and tissue repair. TGF-B in CKD In the present case of CKD, TGF-b is commonly considered as the master of fibrosis because it has the strong capacity to stimulate the production and suppress the breakdown of the extracellular matrix.

TGF-b signaling takes place in two main pathways: the canonical (Smad-dependent) and non- canonical (Smad-independent) pathways. TGF-B interacts with type II receptors on the cell surface in the canonical pathway, which, in turn, recruit and phosphorylate type I receptors. In response to this activation, Smad proteins which are regulated by the receptor are phosphorylated, namely, Smad2 and Smad3. These proteins later on combine with Smad4 and move to the nucleus where they control the expression of fibrosis-related genes, such as those involved in the production of collagen and fibronectin.

Non-canonical pathway entails other signaling cascades like MAPK, PI3K/Akt and Rho-like GTPases. These pathways also help in cytoskeleton restructuring and cell movement as well as an inflammatory reaction and further promote fibrogenesis. Combining both the canonical and non-canonical pathways enables the canonical and non-canonical TGF-0 to have a wide-ranging and sustained effect on cellular behavior.

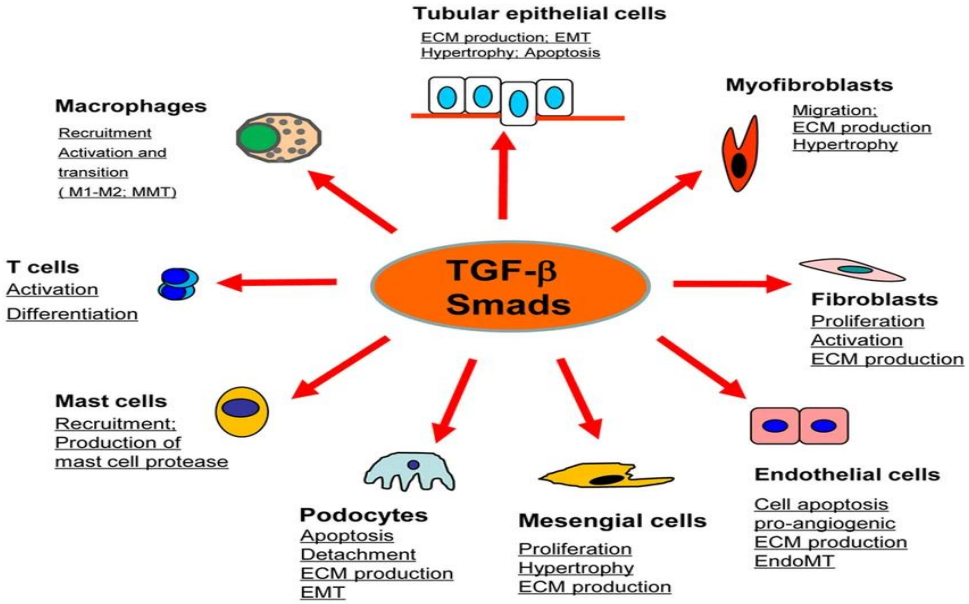

Figure 2: "Role of TGF-β/Smad signaling in kidney disease"
(Source: Zou et al. 2025)

Normal physiological conditions closely control the TGF-β signalling. But in CKD, chronic activation results in cellular homeostasis and encourages pathological fibrosis. Its effects are also widespread because the pathway is activated in various cells in the kidney such as tubular epithelial cells, fibroblasts, and endothelial cells. In general, the TGF-β signaling pathway is a central node in the fibrotic circle, integrating various mechanisms that lead to CKD development. Its complexity and prevalence as a widespread target make it an especially important target of therapeutic intervention.

3.2 Role in Renal Fibrosis

TGF-β has a central role in the pathogenesis of renal fibrosis and exerts numerous interacting pathways. The induction of extra-cellular matrix (ECM) production is one of its main roles. As a result of TGF-β, structural proteins, including collagen type I, collagen type III, and fibronectin, are stimulated which results in excessive deposition of the matrix in the renal interstitium. Meanwhile, it inhibits the ECM degradation by inhibiting matrix metalloproteinases (MMPs) and stimulating tissue inhibitors of metalloproteinases (TIMPs), which thus stabilize the matrix. The other significant mechanism is that fibroblasts are activated to myofibroblasts. These are activated cells that can be referred to as the primary contributors to ECM production and are those that cause the fibrosis. TGF-b also induces epithelial-to-mesenchymal transition (EMT) where tubular epithelial cells lose their epithelial phenotype and take on a mesenchymal phenotype which also increases the number of matrix-producing cells.

Yu et al. (2022) have shown that tubulointerstitial fibrosis is oriented around TGF-b/Smad signaling, especially in the promotion of EMT and ECM deposition. The latter role of it in the development of AKI to CKD was also pointed out by Zou et al. (2025), who emphasized that the protracted and irreversible fibrotic alterations occurred due to the sustained activation of the TGF-B signaling.

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Moreover, TGF-β is involved in inflammation and immune regulation, making further enhancement of fibrosis. It enhances immigration and mobilization of immune cells, developing a pro-fibrotic microenvironment.

Table 2: Functions of TGF-β in Renal Fibrosis

Function	Mechanism	Outcome
ECM synthesis	Collagen, fibronectin production	Matrix accumulation
EMT induction	Epithelial cell transformation	Fibroblast expansion
Fibroblast activation	Myofibroblast formation	Increased fibrosis
ECM degradation inhibition	MMP suppression	Persistent ECM
Immune modulation	Cytokine release	Chronic inflammation

3.3 Cross-Talk with Other Pathways

TGF-β signaling is not a single-decomposing process because it exists under many forms of interaction with other molecular pathways, creating a highly intricate set of regulations that enhances fibrotic activities. The largest interaction is one that occurs with the Wnt/ -catenin signaling pathway. TGF-β may increase the stabilization of 7 -catenin and nuclear translocation, which induces pro-fibrotic gene transcription. Wnt signaling, on the other hand, has the capability to potentiate TGF-β activity to form a positive feedback mechanism increasing the rate of fibrosis. Besides the Wnt signaling, the TGF-B also interacts with the NF-KB signaling that is also vital in inflammation. NF- kB stimulates production of pro-inflammatory cytokine and enhances TGF-β production and action. This relationship connects both inflammation and fibrosis and this may be regarded as a multifaceted nature of the CKD progression.

Another signaling cascade, which interacts with TGF-b, is the MAPK pathway. It helps in cell proliferation, differentiation and stress responses, improving the process of fibrotic process. All these interactions give rise to a very complex signaling network that maintains and increases fibrogenesis.These interactions are very important in the formulation of effective therapeutic programs because it is likely that acting upon one of them will not be enough to prevent the progression of the disease.

3.4 Therapeutic Targeting of TGF-β

As fibrosis is a central process, TGF-β signaling has become a major treatment objective of CKD. A number of approaches have been devised to prevent or interfere with this pathway.

One of these is by using TGF-b inhibitors such as neutralizing antibodies and receptor kinase inhibitors. The objectives of these agents are to inhibit the interaction of the ligands to the receptors and inhibit the subsequent signaling. The other approach involves controlling the Smad pathway especially by suppressing Smad3 or increasing the activity of Smad7, an endogenous antagonist to TGF- beta signaling.

Natural products and traditional Chinese medicine (TCM) have also attracted attention because they have the capacity to regulate TGF- 2 signaling. Zhanga and Wub (2025) and Jiao et al. (2025) point out the prospects of herbal preparations inhibiting the activation of Smad and preventing fibrosis with fewer side effects.

Some of the new methods are gene therapy, RNA interference, and epigenetic modulation, which are explained by Hong et al. (2025). The intention behind these strategies is to inhibit particular elements of the TGF- - of the pathway in a very precise fashion.

Table 3: Therapeutic Strategies Targeting TGF-β

Strategy	Mechanism	Advantage
TGF-β inhibitors	Block receptor signaling	Direct antifibrotic effect
Smad modulation	Regulate transcription	Target specificity
Natural compounds	Multi-target action	Lower toxicity
Gene therapy	Pathway suppression	Precision treatment
RNA interference	Gene silencing	High specificity

Nevertheless, TGF-β inhibition in all forms can have detrimental effects because of its involvement in immune control and the healing process, thus requiring selective and controlled forms of therapy.

4. Wnt/β-Catenin Signaling in Kidney Fibrosis

4.1 Overview of Wnt Signaling : The Wnt/Beta-catenin signaling pathway is a molecular system with high conservation that controls cell proliferation, differentiation and homeostasis of tissues in the embryo, as well as cellular development. This pathway is normally suppressed in the normal physiological state of the kidney, but it is activated upon injury.The canonical Wnt pathway has Frizzled receptors and co-receptors (LRP5/6) which are bound by Wnt ligands, resulting in the suppression of the β-catenin destruction complex. This leads to accumulation of β-catenin in the cytoplasm and after that, translocation of β-catenin into the nucleus occurs. In the nucleus 2 -catenin then binds to transcription factors to regulate gene transcription.

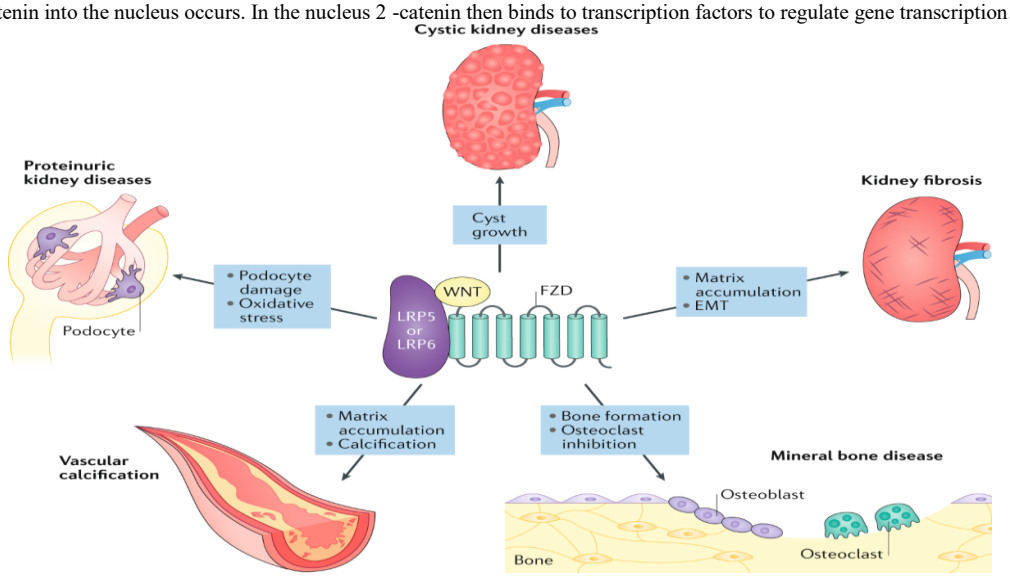

Figure 3: "WNT–β-catenin signalling"
(Source: Hu et al. 2022)

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This pathway is significant in the repair of tissues but its persistent stimulation is involved in the pathological fibrosis. It is the balance between activation of Wnt signaling and inhibition that is important to renal homeostasis.

4.2 Role in CKD: In normal kidneys, Wnt/β-catenin signaling is largely silent, but gets highly activated during injury and CKD progression. By showing that the activation of this pathway enhances EMT, fibroblast activation, and the production of ECM that participate in fibrosis, Hu et al. (2022) supported this assumption.

The role of the Wnt signal in communication between the different renal cells is also highlighted in Chen and Xue (2025) and combines the fibrotic response and the progressive progression of the disease.

4.3 Dual Role of Wnt Signaling : The Wnt signaling influences kidney disease twofold. The acute tissue repair and regeneration is promoted due to the short-term activation during acute injury. However, in chronic activation, fibrosis and further development of the disease takes place. This two-sided nature of diabetic kidney disease is particularly relevant to diabetic kidney disease.

4.4 Mechanisms of Fibrosis Induction : Fibrosis Wnt signaling triggers EMT and fibroblast activation, ECM synthesis, and inflammation. It also colludes with the TGF- β signal that forms a positive feedback loop that fills fibrogenesis.

4.5 Therapeutic Targeting of Wnt Pathway : Therapeutic strategies include Wnt inhibitors, natural compounds, and EMT targeting. These approaches aim at inactivating the activity of 0 -catenin and fibrosis.

Table 4: Therapeutic Approaches Targeting Wnt Pathway

Strategy	Mechanism	Outcome
β-catenin inhibitors	Block transcription	Reduced fibrosis
Porcupine inhibitors	Prevent Wnt secretion	Pathway suppression
Natural compounds	Multi-pathway modulation	Safer therapy
EMT targeting	Prevent fibroblast formation	Reduced ECM

5. Cross-Talk Between TGF-β and Wnt Pathways : The Wnt/&-catenin Wnt/B-catenin and TGF- beta interacting signaling in the pathogenesis of renal fibrosis in chronic kidney disease (CKD) is significant. These pathways do not exist separately; they are tightly linked to one another to cooperate with each other as a regulatory system that augments fibrogenic reactions. This cross- talk intensifies the extracellular matrix (ECM) accretion, fibroblast activation, and epithelial-to-mesenchymal transition (EMT), which ultimately accelerates kidney damage.

5.1 Mechanisms of Interaction: The molecular mechanisms via which TGF- β induces beta-catenin signaling are ensuring that the beta-catenin remains stable and by moving to the nucleus it induces transcription of the pro-fibrotic genes. At the same time, Wnt signaling stabilizes Smad complexes, prolonging their activity, and enhancing the impact of transcription caused by TGF- β. These two pathways also control the key fibrotic genes such as collagen and fibronectin, and have a synergistic effect. Another point that Yuan et al. (2022) made is that such a two-way communication creates a positive feedback loop that causes sustained stimulation of fibrogenic activities and the emergence of chronic diseases.

5.2 Implications for Therapy: This interconnection richness between the TGF- β -impeded and the Wnt is an indication that the two can be targeted at the same time yielding enhanced effects of treatment. Compensatory activation can be mitigated by using dual inhibition techniques; this may help in eliminating the limitation of the single-pathway therapy as it usually has in practice. Integrative strategies could enhance effectiveness, reduce the development of fibrosis, and increase clinical outcomes. Therefore, there is a growing interest in existing studies to devise multi-target therapies with the ability to balance the two pathways to obtain stronger and long lasting antifibrotic responses.

6. Emerging Therapeutic Strategies : Recent breakthroughs in the knowledge about renal fibrosis have resulted in the generation of new treatment approaches that are based on underlying molecular pathways in addition to the symptoms.

6.1 Pharmacological Agents: Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are traditional pharmacological treatments which remain popular in CKD management. These agents indirectly decrease fibrosis through decreasing intraglomerular pressure and controlling inflammatory reactions as reviewed by Ruiz-Ortega et al. (2022). Moreover, more recent antifibrotic agents are undergoing development to target the response specifically with TGF-β and Wnt signaling pathways.

6.2 Natural Products and Phytotherapy: The natural compounds have been of interest owing to the multi-targeting effects and low toxicity. Li et al. (2025) have stated that some phytochemicals are able to modulate ubiquitination of fibrosis related processes. Conventional medicines, especially those in Chinese herbal therapy were shown to be able to modulate both TGF-β and Wnt signaling pathways, which is an effective complementary option.

6.3 Personalized Medicine: Individualized antifibrotic treatment is an area of emerging research in CKD management. Delrue et al. (2024) highlighted that biomarkers and genetic profiling could be utilized to personalize therapies based on the specifics of the patient. This will lead to a more effective and precise intervention, minimizing the negative outcomes and maximizing the results of treatment.

6.4 Gene and RNA-Based Therapies: Recent molecular therapeutics utilizing siRNA, CRISPR based gene editing and microRNA control aim to directly regulate fibrotic genes and signaling responses. The approaches are highly precise and can lead to sustained therapeutic effects, which is a positive future of CKD treatment.

7. Challenges and Limitations

Despite numerous achievements in understanding and therapy of renal fibrosis, there are various constraints that limit the outcomes of such researches to provide constructive clinical medication.

7.1 Complexity of Signaling Networks: One of the principal challenges is the complexity of signaling during fibrosis. TGF- β and Wnt interact with a large number of other cascades, including NF-k B and MAPK, forming an extremely complex network. This complexity means that targeting particular pathways is challenging, without impacting others, which may have unintended consequences.

7.2 Side Effects: The inhibition of the major pathways that include TGF-β can have undesirable effects because of their crucial functions in the normal body activities, such as immune regulation and repairing tissue damages. Full suppression may thus hamper wound healing and predispose one to infections.

7.3 Dual Role of Pathways: Another limitation is the duality of Wnt signaling. Although it enhances the repairing of tissues in the acute case of injury, the chronic activation of it results in fibrosis. This type of behavior is context-specific and therefore presents challenges to the therapeutic targeting because it requires strict time and control in terms of inhibition.

7.4 Lack of Clinical Translation: Despite numerous good therapies that have been discovered during preclinical trials, their implementation in clinical trials is limited. Some of the challenges faced are the lack of clinical trials, patient variability, and the issue of long-term safety and efficacy. These problems need to be addressed in order to pursue the antifibrotic treatments.

8. Future Perspectives

The future studies of CKD fibrosis are predicted to be aimed at developing the further molecular knowledge and the conversion of research observations into clinical practice. One of the priorities is the discovery of useful biomarkers to identify early fibrosis and disease evolution. This would help make timely intervention possible by using these biomarkers and have a better outcome on a patient.

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The creation of selective pathway modulators that interfere with a particular part of TGF-β and Wnt signaling without interfering with physiological activity is also another crucial direction. The purpose of such an approach is to reduce side effects and still have therapeutic efficacy. Multipath way combination therapies are also taking part. The multidimensional network of signaling interactions can be treated with more advantageous and effective antifibrotics using these approaches. Besides, improved accuracy and effectiveness of medicine can be obtained, and that is the development of new drug delivery models like nanoparticle-based carriers.

Yin et al. (2025) also stated that the integration of molecular biology and clinical research is also crucial in accelerating the development of a new form of therapy. These include mass clinical trials, improved patient stratification and custom-made medicine.

Overall, the future of CKD treatment lies in a multidisciplinary approach to the disease therapy, where molecular understanding may be combined with revolutionary treatment and clinical validation. Research in the field has a lot of potential to be explored to manage renal fibrosis and prevent the onset of chronic kidney disease more effectively.

9. Conclusion

Renal fibrosis is the underlying pathophysiology of chronic kidney disease (CKD) progression, resulting in incurable renal dysfunction. Transforming growth factor-beta (TGF-by), Wnt/ -catenin signaling are two of the number of molecular mechanisms that have been found to control fibrogenesis. TGF-β is the master in its mediating role as it causes extracellular matrix (ECM) deposition, epithelial-to-mesenchymal transition (EMT), and conversion of fibroblasts to matrix-producing myofibroblasts. Concurrently, the Wnt signaling plays a role in intercellular communication and augmentation of fibrotic response by acting on cell proliferation, differentiation and inflammation. Notably, the cross-talk of these two pathways generates a synergistic and self-amplifying loop of disease pathogenesis, and propagates the chronic fibrotic activation. Developments have over recent years been made in determining therapeutic methods of targeting these pathways. There is an indirect antifibrotic effect of pharmacological agents, including ACE-inhibitors and angiotensin receptor blockers, and the recent compounds tend to inhibit TGF-) and Wnt signaling directly. Also, traditional medicine methods and natural products have proven to be promising as they have multi-target effects and reduced toxicity rates. New gene- and RNA-targeted therapies such as siRNA and microRNA regulation are a highly specific and innovative option to control fibrotic signaling at the molecular scale.

Even though these new developments have occurred, there are still a number of challenges. Signaling networks and the possible side effects of pathway inhibition are complicated and slow down progress as well as limited clinical translation of experimental therapies. Furthermore, the bifid nature of the roles played by the same pathways, such as Wnt signaling, requires that the therapeutic modulation should be done carefully. In the future, it is possible to have a great prospect of personalized medicine and combination therapies, which will achieve better treatment outcomes. Further studies that combine molecular understanding with clinical implementation are necessary in order to come up with safe, effective and targeted antifibrotic treatments. Finally, the further development of these pathways is going to become essential in reducing renal fibrosis and enhancing the prognosis of CKD patients.

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