

Role and Mechanism of Growth Differentiation Factor 15 in Chronic Kidney Disease

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Abstract: GDF-15 is an essential member of the transforming growth factor-beta superfamily. Its functions mainly involve in tissue injury, inflammation, fibrosis, regulation of appetite and weight, development of tumor, and cardiovascular disease. GDF-15 is involved in various signaling pathways, such as MAPK pathway, PI3K/AKT pathway, STAT3 pathway, RET pathway, and SMAD pathway. In addition, several factors such as p53, ROS, and TNF- α participate the regulation of GDF-15. However, the specific mechanism of these factors regulating GDF-15 is still unclear and more research is needed to explore them. GDF-15 mainly improves the function of kidneys in CKD and plays an important role in the prediction of CKD progression and cardiovascular complications. In addition, the role of GDF-15 in the kidney may be related to the SMAD and MAPK pathways. However, the specific mechanism of these pathways remains unclear. Accordingly, more research on the specific mechanism of GDF-15 affecting kidney disease is needed in the future. In conclusion, GDF-15 may be a therapeutic target for kidney disease.

Keywords: chronic kidney disease, GDF-15, biomarker, inflammation, renal protection

Introduction

Chronic kidney disease (CKD) has garnered global attention due to its prevalence, progressive nature, and irreversibility. The renal function of patients with CKD continues to decline and leads to end-stage renal disease (ESRD) or uremia.^{1,2} It is estimated that CKD causes over 35.8 million disabilities and 1.2 million deaths annually.^{3,4} It is reported that systemic inflammation and oxidation play a central role in CKD.⁵⁻⁷ Diabetic kidney disease (DKD) stands as one of the most prevalent causes of CKD. Elevated oxidative stress becomes apparent when vascular or glomerular cells are exposed to high glucose levels.⁸ Impaired mitochondrial function can contribute to DKD.⁹ It is elucidated that the escalation of oxidative stress levels during the progression of CKD is a pivotal pathological characteristic. Obesity, as a risk factor for diabetes, frequently manifests in diabetes-related conditions, including DKD.¹⁰ Following prolonged obesity, inflammation and oxidative stress levels escalate within the glomeruli, leading to proteinuria.^{10,11} Inflammation not only accelerates CKD but also triggers complications such as malnutrition, atherosclerosis, coronary artery calcification, heart failure, anemia, and bone diseases, which significantly increase the risk of mortality.¹²⁻¹⁷ Accordingly, it is crucial to explore the relationship between oxidation and inflammatory factors and CKD to prevent CKD and its complications.

It is well known that there are numerous inflammatory factors which trigger the onset or deterioration of diseases, such as TNF- α , IL-6, IL-1 β , chemokines, growth factors, and other regulatory factors.^{18,19} As an important inflammatory factor, growth differentiation factor 15 (GDF-15) has been the focus of increasing studies.^{20,21} GDF-15 is a member of

transforming growth factor-beta (TGF- β) superfamily and is expressed in various tissues, such as heart, pancreas, kidney, and so on.^{22–24} Levels of GDF-15 expression increases under the conditions of stress or disease.²⁵ Increasing evidence suggests that GDF-15 is associated with cardiovascular diseases, cancer, and diabetes.^{25–27} It is demonstrated that levels of GDF-15 are closely related to CKD and risk of cardiovascular complications in CKD.²⁸ Moreover, the increase of GDF-15 in CKD frequently causes inflammation, oxidative stress, fibrosis, and apoptosis, which suggest that GDF-15 play an important role in CKD.^{29,30} In this paper, we reviewed the role and mechanism of GDF-15 in CKD.

The Structure and Functions of GDF-15

The Structure of GDF-15

GDF15 is an essential member of the TGF- β superfamily, and its gene is located on human chromosome 19 and encodes a relatively large precursor protein with two distinct domains: the precursor domain and the mature domain. Most of the precursor domain is cleaved in cells, resulting in a biologically active C-terminal fragment which is known as the mature domain. Moreover, the mature domain not only forms a stable dimeric structure that enhances its stability in vitro but also possesses a core region composed of multiple β -folds in its three-dimensional conformation, which present similar functional properties to other members of the TGF- β superfamily. More importantly, GDF-15 undergoes various post-translational modifications such as glycosylation, phosphorylation, and lipid modification, which contribute to its increased stability and specific interactions with other biomolecules.^{31–34} For instance, GDF-15 binds to its receptors to exert its effects leading to specific cellular responses, such as cellular growth, differentiation, and apoptosis.^{26,29,35} Furthermore, GDF-15 can also block TGF- β receptors and downstream N-Myc signaling pathways, inhibiting apoptosis and collagen production in primary fibroblasts, thereby exerting anti-fibrotic effects on the kidneys.³⁶

The Functions of GDF-15

GDF-15 is a cytokine that exhibits diverse biological functions (Figure 1). It is demonstrated that the expression of GDF-15 increases under the conditions of tissue injury, inflammation, and other pathological conditions to improve damaged tissues and further harm.^{37–39} It is reported that the GDF-15 inhibits cell apoptosis and consequently supports cell survival under conditions of ischemia, hypoxia, or toxic-induced damage.^{25,32,35} In addition, GDF-15 inhibits

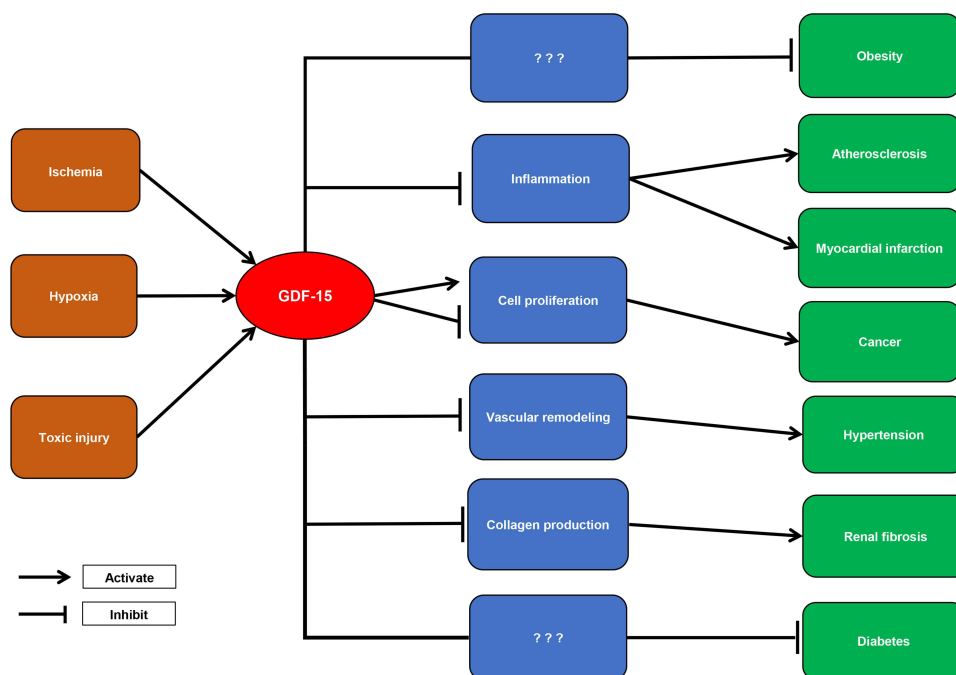


Figure 1 The functions of GDF-15.

Abbreviation: GDF-15, growth differentiation factor 15.

inflammation by reducing the infiltration of inflammatory cells, diminishing the secretion of cytokines and chemokines, and attenuating macrophage and T cell activity to suppress the release of $\text{TNF-}\alpha$, IL-6, and IL-1 β . Moreover, GDF-15 facilitates the transformation from these inflammatory cells to anti-inflammatory counterparts, which ultimately reduces the inflammatory response.^{35,40–43} Furthermore, GDF-15 plays a pivotal role in regulating appetite and weight. It is reported that increase of GDF-15 triggers a decrease in appetite by GDF-15 binding to its receptors of the hypothalamus, resulting in reduced food intake, which impacts body weight.^{44,45} Authors suggested that GDF-15 in the blood of obese patients presented higher concentrations, which means that a feedback regulatory mechanism responds to excessive energy intake and fat storage in GDF-15 regulating appetite and weight.^{27,41} Moreover, GDF-15 may contribute to the obesity-related diseases, such as diabetes and cardiovascular disease.^{26,46,47} Interestingly, GDF-15 demonstrates contradictory dual roles in tumor biology. On the one hand, the upregulation of GDF-15 following stress, inflammation, and tissue injury exerts a pro-apoptotic effect, countering the proliferation and survival of malignant cells.^{35,48} On the other hand, GDF-15 regulates the tumor microenvironment and promotes the proliferation, angiogenesis, and metastasis of tumor cells in the progression of cancers, such as breast cancer, stomach cancer, and colorectal cancer.^{40,49–52} In addition, studies suggest that GDF-15 increases rapidly with the occurrence of myocardial ischemia or reperfusion injury to reduce myocardial injury, inhibit inflammatory mediators such as $\text{TNF-}\alpha$ and IL-1 β , and combat atherosclerosis and myocardial infarction.^{53,54} GDF-15 regulates smooth muscle cells and inhibits vascular remodeling to maintain vascular health, especially in hypertensive diseases.^{55,56} Moreover, GDF-15 expression is associated with reduced cardiac function, which may also represent a protective mechanism in vivo.⁵⁷

GDF-15 and Signaling Pathways

GDF-15 binds to its receptor to trigger a series of signal cascades inside the cell, which cause a profound impact on key processes such as cell growth, migration, survival, and apoptosis. There are several signaling pathways that GDF-15 is involved in (Figure 2).

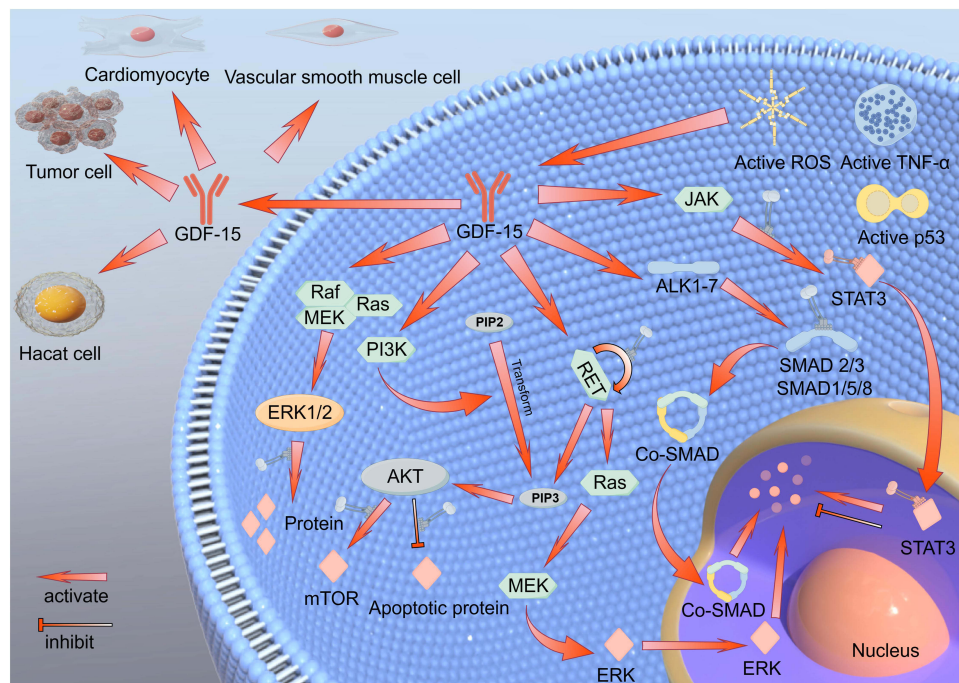


Figure 2 GDF-15 and signaling pathways.

Abbreviations: GDF-15, growth differentiation factor 15; JAK, janus kinase; STAT3, signal transduction and transcription-activating protein 3; RET, rearranged during transfection; MEK, mitogen-activated protein kinase kinase; ERK, extracellular regulated protein kinases; PIP3, phosphoinosine-triphosphate; AKT, protein kinase B; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide3-kinase; PIP2, phosphoinosine-diphosphate; ROS, reactive oxygen species; $\text{TNF-}\alpha$, tumor necrosis factor α ; SMAD, drosophila mothers against decapentaplegic; ALK 1–7, activin-like kinase type I receptors.

MAPK Pathway

The mitogen-activated protein kinase (MAPK) pathway is one of the key signal transduction pathways in cells and is widely involved in many physiological and pathological processes such as cell growth, differentiation, migration, apoptosis, and stress response. It is reported that GDF-15 activates MAPK pathways.^{58,59} GDF-15 activates ERK1/2, a core component of the MAPK family, by binding to its receptor to regulate various upstream kinases, such as Ras, Raf, and MEK. Activation of ERK1/2 further regulates the phosphorylation of a variety of downstream target proteins, thereby affecting cell growth, differentiation, and survival.^{25,60,61} GDF-15 may exert its specific effects by modulating specific branches or regulatory points of the MAPK pathway. For example, GDF-15 may promote cell survival and proliferation by enhancing the sustained activation of ERK1/2 in vascular smooth muscle cells, while GDF-15 may regulate cellular stress response and apoptosis by regulating JNK or p38 MAPK in HaCaT cells.^{25,62,63}

PI3K/AKT Pathway

The phosphoinositide3-kinase/protein kinase B (PI3K/AKT) pathway plays a central role in cell growth, metabolism, survival, and apoptosis.^{64–67} PI3K is the primary promoter of PI3K/AKT pathway and is activated by various stimuli such as growth factors and insulin. Activated PI3K converts phosphoinosine-diphosphate (PIP2) to phosphoinosine-triphosphate (PIP3). As a powerful secondary messenger, PIP3 activates AKT which is also known as protein kinase B. Activated AKT subsequently inhibits the function of the pro-apoptotic protein Bcl-2 family, thereby inhibiting apoptosis.⁶⁸ In addition, AKT activates mammalian target of rapamycin (mTOR) protein to stimulate cell growth and protein synthesis.⁶⁹ It is reported that the GDF-15 is an important activator of the PI3K/AKT pathway. GDF-15 increases the activity of PI3K to activate AKT in certain stressful environments and pathological states, which is closely related to cell survival and proliferation. It is suggested that GDF-15 significantly reduces cardiomyocyte apoptosis in a myocardial ischemia/reperfusion injury by activating the PI3K/AKT pathway to protect the effect of the heart.^{70,71} In addition, GDF-15 promotes the survival, migration, and invasion of cancer cells by activating the PI3K/AKT pathway.^{25,35}

STAT3 Pathway

The signal transduction and transcription-activating protein 3 (STAT3) pathway plays a central role in cell growth, differentiation, survival, and immune response and abnormal activation of STAT3 is implicated in various cancers, immune diseases, and inflammation-related diseases.^{72,73} Biologically, STAT3 is activated by a variety of signals such as growth factors, cytokines, and hormones. These stimuli first bind to their receptors to activate the janus kinase (JAK). Subsequently, JAK phosphorylates STAT3, causing it to form a dimer and transfer to the nucleus, which in turn regulates the target genes.^{74,75} It is reported that GDF-15 promotes the phosphorylation of STAT3 in the context of inflammation and tumor, thereby affecting cell survival, proliferation, and differentiation.⁷⁶ Moreover, GDF-15 increases the survival and proliferation ability of breast tumor cells and promotes tumor progression by activating STAT3 pathway.⁷⁷ In addition, the GDF-15 activates the STAT3 pathway to inhibit inflammation. It is suggested that GDF-15 inhibits the production of inflammatory factors by regulating STAT3 activity in the recruitment of inflammatory cells after myocardial infarction, which present anti-inflammatory effect of GDF-15.⁷⁸

RET Pathway

Rearranged during transfection (RET) is a transmembrane receptor tyrosine kinase, which is mainly involved in the regulation of neuron growth, differentiation, and migration.^{79,80} GDF-15 binds to RET co-receptor to promote the activation and self-phosphorylation of RET. Activated RET further activates a variety of downstream signal molecules or pathways, such as Ras/MAPK, PI3K/AKT, or PLC γ pathways to mediate biological effects.^{81,82} It is reported that high expression of GDF-15 enhances RET activation in tumor cells, thereby promoting tumor cell proliferation and survival.⁸¹ In addition, GDF-15 activating RET pathway enhances cell migration and invasion in a variety of tumor models.⁸³ Accordingly, GDF-15 is involved in the RET pathway to regulate cell growth, survival, migration, and invasion.

SMAD Pathway

Drosophila mothers against decapentaplegic (SMAD) proteins constitute a crucial class of signaling transducers, participating in the regulation of various biological processes such as cell proliferation, differentiation, and growth. The SMAD signaling pathway primarily involves transforming growth factor- β (TGF- β), bone morphogenetic protein (BMP), and activin-like kinase (ALK). It has been reported that in pressure-induced cardiac hypertrophy models, GDF-15 inhibits myocardial hypertrophy via the SMAD2/3 pathway.⁸⁴ Similarly, it also reported that GDF-15 protects the heart from adrenergic-induced hypertrophy through a SMAD-independent pathway.⁸⁴ GDF-15 exerts cardioprotective effects by activating ALK type 1 receptors (ALK 1–7) and phosphorylating SMAD2/3 and SMAD1/5/8. Phosphorylated SMAD proteins form heteromeric complexes with SMAD4, which are then translocated to the nucleus, activating anti-hypertrophic and anti-apoptotic pathways.³⁰

Other Factors

Although the expression and secretion of GDF-15 is regulated by a variety of physiological and pathological conditions, the exact upstream regulatory factors and mechanisms are still being investigated. It is known that p53, ROS, and TNF- α up-regulate the expression of GDF-15.

As a well-known tumor suppressor protein, p53 is activated and stabilized with the damage of DNA. It is reported that activated p53 directly enhances the transcriptional activity of GDF-15 gene, resulting in an increase of GDF-15.^{85,86}

Reactive oxygen species (ROS) plays a vital role in cells and is involved in many important biological processes, such as signal transduction, gene expression regulation, and cell growth.^{87,88} Excess ROS frequently leads to cell damage, leading to a variety of diseases, such as cancer, cardiovascular disease, neurodegenerative diseases, and premature aging.^{89–91} It is presented that high ROS induced by oxidative stress significantly elevates the expression and accumulation of GDF-15.⁹² Moreover, the upregulation of GDF-15 modulates antioxidant expression or activates antioxidant pathways to reduce the cell damage caused by ROS.⁴⁸ However, persistent GDF-15 overexpression often means continuous oxidative stress, which contributes to cellular dysfunction and disease progression.

Tumor necrosis factor α (TNF- α) is a multifunctional cytokine, which plays a key role in inflammation, immune response, cell proliferation, and apoptosis.^{93,94} TNF- α binding to its receptor activates multiple signal transduction pathways, especially the classical NF- κ B and MAPK pathways, thereby enhancing the transcriptional activity of GDF-15.³⁰ In addition, TNF- α affects the stability of GDF-15 mRNA or interacts with microRNAs, such as miR-20a and miR-221.^{95,96}

The Role of GDF-15 in the Kidney Diseases

Renal Protection Provided by GDF-15

The role of GDF-15 presents potential renal protective effects in kidney disease and injury, especially during inflammation, injury, and recovery.⁹⁷ It is shown that the loss of GDF-15 enhances the inflammatory response, which is harmful for lipopolysaccharide-induced (LPS-induced) kidney and heart damage, while overexpression of GDF-15 improves LPS-induced organ dysfunction.⁹⁸ In addition, GDF-15 is related to early renal protective injury responses by altering the behavior of immune cells, such as T cells.⁸¹ It is reported that the mice deficient in GDF-15 exhibited more severe symptoms, including increased proteinuria, crescent formation, and mesangial dilation in a model of anti-glomerular basement membrane glomerulonephritis,³⁵ which means the critical role of GDF-15 in regulating T cells, particularly their chemotaxis within the kidney.⁹⁹ In addition, GDF-15 protects the renal interstitial and tubule compartments, and deletion or absence of this GDF-15 gene results in increased damage of tubule and interstitial in diabetes, though the glomerular damage is not impaired.^{26,100} Moreover, renal injury causes a notable upregulation of GDF-15 at the proximal renal tubule site, which induces up-expression of Klotho protein to improve kidney injury.¹⁰¹ Accordingly, GDF-15 presents the renal protection.

Chronic Kidney Disease

CKD is a global health issue due to its association with multiple complications and adverse outcomes.¹⁰² In recent years, the research mainly focuses on the predictive value of GDF-15 for the progression of CKD, especially for diabetic

nephropathy. In addition, another focus is the role of GDF-15 in the occurrence of complications of CKD, such as cardiovascular risk, renal fibrosis, mineral bone disease, and anemia.

Meanwhile, elevation of GDF-15 is related to adverse outcomes of kidney disease, which suggest GDF-15 may be an early warning biomarker for CKD.¹⁰³ It is reported that circulating levels of GDF-15 are correlated with renal expression of GDF-15, which is significantly associated with the risk of CKD progression,²⁹ which suggests that circulating GDF-15 can independently predict CKD progression and poor prognosis.⁹⁸ Moreover, high levels of GDF-15 are significantly associated with increased all-cause and cardiovascular mortality and morbidity in patients with diabetic kidney disease. Notably, this association appears to reflect a more rapid deterioration of renal function than being directly related to the development of ESRD.¹⁰⁴ Accordingly, GDF-15 may play an important role in early prediction of kidney function decline. In addition, it is confirmed that high circulating levels of GDF-15 are associated with type 2 diabetic nephropathy, which means GDF-15 may be a potential biomarker for type 2 diabetic nephropathy.¹⁰⁵ It is reported that the GDF-15 is an important activator of the PI3K/AKT pathway. The PI3K/AKT signaling pathway attenuates cellular apoptosis in CKD. Glucagon-like peptide-1 (GLP-1) receptor agonists, commonly utilized as fundamental therapeutic agents in CKD,¹⁰⁶ inhibit protein kinase C (PKC) β activation,¹⁰⁷ promote insulin/IRS1 signaling, and via the PI3K/Akt pathway, mediate increased production of nitric oxide (NO), inducing vasodilation and inhibiting podocyte apoptosis.¹⁰⁸ Consequently, GDF-15 can suppress CKD cellular apoptosis via the PI3K/AKT signaling pathway, exerting renal protective effects.

GDF-15 is also involved in the occurrence of complications in CKD.^{109–111} It is reported that GDF-15 is independently associated with cardiovascular risk in patients with diabetic nephropathy.¹⁰⁴ GDF-15 is more closely associated with microvascular complications, especially diabetic nephropathy, than with macrovascular complications.⁸¹ In addition, GDF-15 is more closely associated with heart failure, especially heart failure with preserved ejection fraction in CKD.^{112,113} Moreover, GDF-15 is related with the complications such as renal fibrosis.²⁹ It is suggested that GDF-15 plays a role in the development of mineral bone disorders due to its association with vitamin D synthesis and phosphorus metabolism.¹¹⁴ Additionally, elevated levels of GDF-15 are correlated with reduced erythropoiesis and impaired iron utilization, which may lead to anemia in CKD.^{115,116}

Kidney Transplantation

GDF-15 plays an important role in post-transplant outcomes. The prevalence of anemia among kidney transplant recipients is notably high, primarily attributed to long-term uremia or the nephrotoxicity of immunosuppressive drugs.¹¹⁷ It is suggested that there is a plausible link between GDF-15 and anemia in patients with kidney transplantation. Intriguingly, GDF-15 levels reduce in kidney transplantation, while increases in single nephrectomy.¹¹⁸ It seems that elevated levels of GDF-15 may reflect the presence of chronic kidney disease rather than being solely attributable to transplantation itself. Notably, there is an intriguing correlation between GDF-15 and mortality following kidney transplantation,¹¹⁹ which suggest that GDF-15 may be a predictive indicator for early mortality after surgery. Remarkably, this predictive power even enhances the accuracy of the EPTS score which is a scoring model used to assess expected post-transplant survival among candidates for kidney transplantation.¹¹⁹ Apart from its prognostic value regarding mortality rates, GDF-15 also serves as a key predictor for cardiovascular events.¹¹⁸

Conclusions and Prospects

GDF-15 plays a crucial role in tissue injury, inflammation, fibrosis, regulation of appetite and weight, tumor development, cardiovascular disease, and other biological functions following the processes of glycosylation and phosphorylation. GDF-15 is involved in various signaling pathways such as MAPK pathway, PI3K/AKT pathway, STAT3 pathway, RET pathway, and SMAD pathway. In addition, GDF-15 is regulated by several factors such as p53, ROS, and TNF- α . In CKD, GDF-15 are strongly associated with CKD survival rate, disease progression rate, cardiovascular complications risk, and complications such as renal fibrosis and anemia. Particularly, GDF-15 are linked to both decreased kidney function and higher risk for cardiovascular diseases in diabetic nephropathy patients. Moreover, GDF-15 has shown potential value in predicting post-transplantation outcomes, such as anemia occurrence, cardiovascular events, and mortality rates. However, the specific mechanism that GDF-15 affects kidneys remains unclear. In addition, more

research is needed to explore the role of GDF-15 in common CKD, such as IgA nephropathy, membranous nephropathy, and lupus nephritis. In conclusion, GDF-15 may be a therapeutic target.

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Disclosure

The authors report no conflicts of interest in this work.

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