From renal development to pathology: An analysis of the multilevel role of insulin-like growth factor 2 (Review)

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Abstract. Insulin-like growth factor 2 (IGF2) is a multifunctional polypeptide hormone that serves important roles in embryonic development, metabolic regulation and disease pathogenesis. IGF2 expression is tightly regulated by genomic imprinting, which restricts transcription to the paternal allele. IGF2 modulates cellular processes, including proliferation, differentiation and metabolic homeostasis, by activating downstream signaling cascades via binding to IGF1 receptor, insulin receptor isoform A and IGF2 receptor. IGF2 is important for kidney development, promoting both nephron formation, and the functional maintenance of renal tubules and glomeruli. Aberrant IGF2 expression is associated with the pathogenesis of diverse renal diseases, including acute kidney injury, chronic kidney disease, diabetic nephropathy, renal cell carcinoma and Wilms' tumor. Under pathological conditions, IGF2 promotes renal fibrosis and promotes tumor expansion and progression by activating key signaling pathways such as the PI3K/Akt and TGF-β pathways. Due to these roles, IGF2 has attracted growing clinical interest as a potential therapeutic target. The present review presents a comprehensive analysis of the structure and function of IGF2, its roles in renal pathophysiology, and its therapeutic potential, while outlining future research directions.

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1. Introduction

Insulin-like growth factor 2 (IGF2) is a peptide hormone that is important for embryonic development and the regulation of metabolic processes (1,2). IGF2 expression is tightly regulated by genomic imprinting, which ensures spatially and temporally precise activity (3,4). Beyond its role in development, IGF2 is involved in kidney physiology by promoting cell proliferation, metabolic activity and tissue repair (5-7). Emerging evidence implicates IGF2 dysregulation in the pathogenesis of several kidney disorders, including acute kidney injury (AKI) (8), chronic kidney disease (CKD) (9) and renal malignancies (10). Through interactions with receptors such as IGF1 receptor (IGF1R), insulin receptor isoform A (IR-A) and IGF2 receptor (IGF2R), IGF2 activates signaling pathways, including the PI3K/Akt and MAPK pathways, that modulate inflammation, fibrosis and cell survival (11,12) (Fig. 1). The present review summarizes the structural characteristics and biological functions of IGF2, its regulatory mechanisms and its involvement in kidney diseases, highlighting its potential as both a diagnostic biomarker and a therapeutic target.

2. Structure and physiological function of IGF2

IGF2, a polypeptide hormone, has a similar action as insulin, yet its biological activity is low (approximately 14% of that of insulin) (13). The IGF2 gene is located on human chromosome 11p15.5 and spans ~30 kb of genomic DNA. It encodes a 7.5-kDa peptide comprising 67 amino acid residues and shares ~67% sequence homology with insulin-like growth factor 1 (IGF1) (14).

IGF2 is widely expressed in embryonic and fetal tissues, although transcript levels vary considerably across different organs (15). The gene is regulated by five distinct promoters (P0-P4) and consists of 10 exons, with only the final three exons encoding protein-coding sequences (15,16). These

promoters are differentially regulated in a tissue- and developmental stage-specific manner, giving rise to functionally distinct mRNA isoforms (16,17). Each promoter is functionally active at specific stages of development and in distinct tissue types. For example, the P0 promoter is predominantly active in the placenta and serves a role in determining placental size and composition. Loss of P0 promoter activity reduces passive diffusion across the placenta, resulting in fetal growth retardation, although systemic levels of fetal IGF2 remain unaffected. This observation suggests that placental IGF2 expression operates independently of circulating IGF2 levels (18).

The P1 promoter is primarily active in the adult liver and the choroid plexus of the brain and contains an internal ribosomal entry site (16). P2 is mainly active in the fetal liver, whereas P3 and P4 drive expression in non-hepatic fetal and adult tissues. Notably, P3 and P4 are epigenetically silenced after birth but may be reactivated in certain tumors [including Wilms' tumor (19) and rhabdomyosarcoma] (20,21). Both P3 and P4 contain canonical TATA and CCAAT boxes recognized by RNA polymerase II, while P2 lacks these elements (22). Transient transfection assays have demonstrated that the activity of P2, P3 and P4 varies by cell type and species. For example, P2 is minimally active in most cell lines, whereas P3 exhibits the highest transcriptional activity in hepatocyte-derived human cells (23). Overall, IGF2 transcription declines sharply in most tissues after birth (16).

IGF2 serves an important role in tissue development and growth, particularly during embryogenesis (24). The biological functions of IGF2 are primarily mediated through interactions with three specific receptors: IGF1R, IR-A and IGF2R (11,12). IGF1R is a transmembrane tyrosine kinase receptor structurally related to the insulin receptor (IR) (9,19,25). Upon binding IGF2, IGF1R activates the PI3K/Akt and MAPK signaling cascades, thereby promoting cell proliferation, differentiation and survival, which are processes that are important for embryonic tissue and organ formation (11,26). IGF1R signaling also serves a central role in tumor biology by enhancing cell survival via anti-apoptotic mechanisms, particularly in IGF1R-dependent malignancies (27).

Compared with IGF1R, IR-A has a higher binding affinity for IGF2 and is predominantly expressed in fetal tissues and specific cancer types, including colorectal cancer, osteosarcoma and thyroid cancer (23,28,29). Upon binding to IGF2, IR-A activates the PI3K/Akt and MAPK pathways, regulating cell metabolism, proliferation and survival, and contributing to tumor growth and adaptability (30-32). Under specific pathological conditions, such as tumors that excessively secrete IGF2, notably including mesenchymal tumors and hepatocellular carcinomas, IGF2 can induce hypoglycemia by activating the IR-A signaling pathway. The aforementioned tumor cells commonly highly express IGF2 mRNA (33-35). However, defective post-translational processing leads to the production of a high molecular weight precursor (15-25 kDa), referred to as pro-IGF2 or 'big IGF2', characterized by an uncleaved E-domain extension (36-38). Under physiological conditions, mature IGF2 circulates primarily as part of a 150-kDa ternary complex with IGF-binding protein (IGFBP)-3 and the acid-labile subunit (ALS). This large complex is unable to cross the capillary endothelium, thereby limiting its biological activity (36,38).

By contrast, pro-IGF2 binds to IGFBP-2 or IGFBP-3 to form a smaller (~50 kDa) binary complex. Steric hindrance from the uncleaved E-domain prevents ALS binding, thereby impeding the formation of the ternary complex. Due to its reduced molecular weight, the binary complex can freely diffuse across the capillary endothelium into the interstitial fluid (37). A clinical study demonstrated that serum concentrations of the 50-kDa complex in patients with tumors can be elevated >10-fold compared with normal levels, enhancing its tissue distribution (37). Additionally, pro-IGF2 promotes vascular leakage and tissue penetration by stimulating tumor secretion of VEGF and MMP-9. VEGF increases vascular permeability, while MMP-9 degrades the basement membrane and disrupts endothelial junctions (39,40). Furthermore, tumor-associated neovasculature is often characterized by incomplete basement membranes and loosely connected endothelial cells, creating a 'leaky' vascular phenotype that facilitates the extravasation of small molecular complexes (41).

Once within the interstitial fluid, pro-IGF2 retains receptor-binding affinities to both IR and IGF1R similar to mature IGF2 but exhibits 2- to 3-fold greater molar bioactivity, leading to prolonged receptor activation (36,37). Consequently, in patients with extra-pancreatic tumor-induced hypoglycemia, circulating pro-IGF2 levels are markedly elevated and typically normalize following successful tumor resection (42).

The biological effects of ligand binding are notably influenced by receptor subtype. For instance, in 32D clone 3 murine hematopoietic progenitor cells, IGF2 binding to IR-A induces pro-mitotic and anti-apoptotic signaling, whereas its binding to IR-B promotes differentiation (43). In mouse fibroblasts expressing exclusively IR-A, insulin binding elicits metabolic responses (44).

In contrast to IGF1R, IGF2R exhibits distinct structural and functional characteristics and has the highest binding affinity for IGF2. IGF2R is a single-chain transmembrane receptor that lacks intrinsic tyrosine kinase activity and primarily mediates IGF2 degradation via endocytosis, thereby suppressing cellular over-proliferation and reducing tumorigenic potential (45-47). Additionally, IGF2R facilitates lysosomal enzyme trafficking by recognizing mannose-6-phosphate residues and is therefore also referred to as the cation-independent mannose-6-phosphate receptor (46). This function is evolutionarily conserved, and mammalian IGF2R has further acquired the capacity to bind IGF2, thereby enhancing its role in limiting cell proliferation (48). IGF2R also modulates the TGF-β signaling pathway, which is involved in extracellular matrix (ECM) synthesis, immune regulation, and the control of cell proliferation, differentiation and development (49,50). Collectively, these properties allow IGF2R to maintain growth homeostasis under physiological conditions, and inhibit tumorigenesis and progression under pathological conditions (51).

Despite advances in deciphering the complex structure and regulatory mechanisms of IGF2, such as its genomic imprinting and the existence of multiple promoters and isoforms (52,53), the role of IGF2, particularly in renal physiology and pathology, remains to be fully elucidated. The present review focuses on the expression, regulation and function of IGF2 in the kidney, summarizing its contributions to renal development and its involvement in kidney disease.

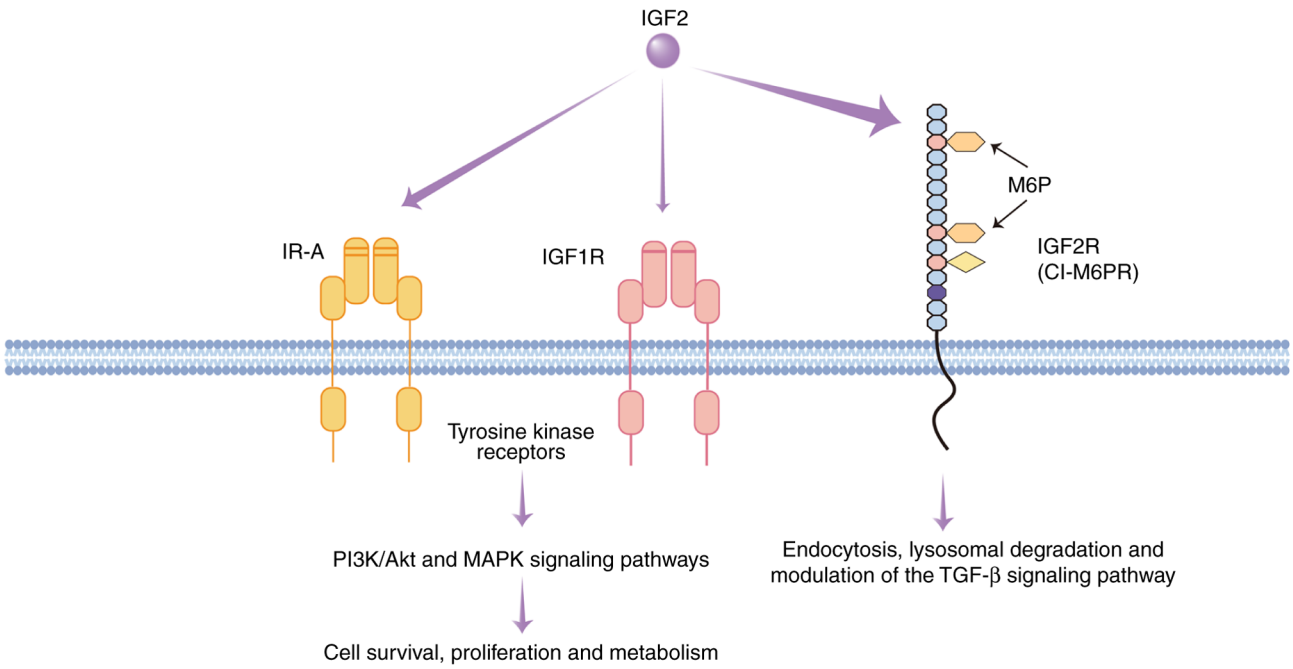

Figure 1. IGF2-mediated signaling pathways and the functional roles of IGF receptors. This schematic illustrates the interactions between IGF2 and its primary receptors: IR-A, IGF1R and IGF2R (CI-M6PR). The arrow thickness indicates the relative binding affinity. IR-A and IGF1R are tyrosine kinase receptors. Upon IGF2 binding, they activate the PI3K/Akt and MAPK signaling pathways, promoting cell survival, proliferation and metabolic regulation. By contrast, IGF2R lacks signaling capability and primarily functions to internalize and target IGF2 for lysosomal degradation, thus regulating its bioavailability. It also transports M6P-tagged proteins and modulates the TGF-β pathway, influencing extracellular matrix dynamics and tissue homeostasis. IGF, insulin-like growth factor; IGF1R/IGF2R, IGF1/2 receptor; CI-M6PR, cation-independent mannose-6-phosphate receptor; IR-A, insulin receptor isoform A.

3. Role of IGF2 in the development and functional maintenance of the kidney

IGF2 serves a notable role in renal development and the maintenance of kidney function by regulating cellular proliferation, differentiation and metabolic homeostasis (5). IGF2 expression exhibits a distinct spatiotemporal pattern aligned with specific physiological functions across developmental stages (23,54-56).

During embryogenesis, IGF2 is highly expressed and is important for normal renal morphogenesis (57,58). At this stage, IGF2 is primarily secreted by the placenta (6) and exhibits strong expression in renal structures, particularly the ureteric bud and metanephric mesenchyme (7). This elevated expression facilitates nephron formation by promoting the mesenchymal-to-epithelial transition of nephrogenic progenitors, driving the development of renal tubules and glomeruli, and directing mesodermal cell differentiation toward functionally specialized nephron segments (7,24,59). Animal studies have supported the important role of IGF2 during this period: Disruption of IGF2 signaling leads to notably reduced birth weight, whereas overexpression results in accelerated somatic growth (45,60,61). Furthermore, intrauterine growth restriction models have demonstrated that aberrant DNA methylation of the IGF2 promoter reduces its expression, lowers nephron endowment and increases the risk of CKD later in life (7), underscoring the importance of tightly regulated IGF2 expression during renal development.

As renal development reaches completion, IGF2 expression is downregulated (62). In the adult kidney, IGF2 is maintained at basal levels and is primarily localized to vascular structures and interstitial cells surrounding the glomeruli and renal tubules (57,63). IGF2 mRNA exhibits a spatially restricted pattern: It is enriched in the vascular components of the cortex, particularly within the endothelium and adventitia of afferent arterioles, while in the medulla, it is predominantly expressed in vascular and stromal compartments, with negligible expression in tubular epithelial cells (5). This distribution suggests a specialized role for IGF2 in regulating renal vasculature and glomerular function. Basal IGF2 also contributes to renal homeostasis by supporting cellular repair and metabolic balance (63-65). The transition from high embryonic IGF2 expression to adult basal levels appears to be epigenetically regulated, particularly via promoter methylation, ensuring structural and functional stability post-development (8). Notably, a study using IGF1-deficient transgenic mouse models showed that kidney-specific overexpression of IGF2 selectively increased both absolute and relative kidney weight, without altering body weight or the mass of other organs (66). These findings support a unique, organ-specific role for IGF2 in kidney growth, development and homeostatic maintenance, spanning from embryonic morphogenesis to adult physiological function.

The biological effects of IGF2 are primarily mediated via its interaction with IGF1R and IR (67). IGF1R, the primary signaling receptor for IGF2, is widely distributed in the kidney, with prominent expression in renal tubules, glomeruli and mesangial cells (68). The expression of IGF1R is particularly high in proximal and distal tubular segments, underscoring the role of IGF2 in regulating metabolic processes and ion transport in these structures (5). IGF2 promotes the proliferation and differentiation of renal precursor cells predominantly

through IGF1R activation, thus contributing to the formation of renal tubules and glomeruli (69). In a mouse model with P2 promoter deletion, resulting in reduced IGF2 expression, pronounced renal abnormalities were observed, manifesting as proteinuria, podocyte depletion, glomerulosclerosis, increased ECM deposition and glomerular basement membrane thickening at 18 months of age (70). These findings emphasize the importance of IGF2 in supporting renal architecture and maintaining nephron functionality, primarily through its role in podocyte health. The observed increase in ECM deposition is a secondary, dysregulated consequence of podocyte injury and loss, manifesting as mesangial expansion and glomerulosclerosis (70). Furthermore, IGF1R activation promotes ECM synthesis in renal tubules, thereby supporting the structural integrity and functionality of renal tissues (71).

IR is another important receptor for IGF2. Although IR primarily regulates glucose metabolism, it is also widely expressed in the kidney (72). In renal tubules and glomerular endothelial cells, IR expression is high and contributes to the regulation of renal blood flow and tubular reabsorption functions (73). Compared with IGF1R, IR displays a more uniform distribution across kidney regions, suggesting a broader role in maintaining renal metabolic homeostasis (74). Additionally, IGF2 may influence ionic transport and water-electrolyte balance in the kidney via IR signaling. An *in vitro* study has shown that IGF2 expression enhanced sodium uptake in proximal tubular brush border membrane vesicles (65).

Unlike IGF1R and IR, IGF2R lacks intrinsic kinase activity, and is traditionally regarded as a decoy receptor involved in IGF2 internalization and degradation (75). However, a previous study has revealed that IGF2R may serve an active signaling role. IGF2R nuclear translocation has been linked to GSK3, which primes macrophages toward an anti-inflammatory phenotype. These findings reveal a novel immunomodulatory role for IGF2R in macrophages and suggest that IGF2 may influence immune responses within the kidney via IGF2R. Notably, activation of IGF1R, by either IGF1 or IGF2, can antagonize IGF2R signaling, thereby modulating macrophage polarization. The balance between IGF1R and IGF2R activation is important for maintaining macrophage-mediated immune homeostasis and appropriately shaping the immune response to infection or inflammation (76).

Understanding the regulatory mechanisms governing IGF2 expression is important for elucidating its roles in renal development and disease. IGF2 expression is controlled by genomic imprinting, with transcription occurring exclusively from the paternal allele while the maternal allele remains epigenetically silenced (77,78). This monoallelic expression pattern is maintained by DNA methylation at the H19/IGF2 imprinting control region (ICR) and its associated epigenetic regulatory elements (79,80). Specifically, paternal-specific methylation of the ICR, enhancer competition and CCCTC-binding factor-mediated boundary insulation ensure the spatial and temporal precision of IGF2 function during renal development (81).

Loss of genomic imprinting is associated with pathological growth abnormalities. For example, Beckwith-Wiedemann syndrome is caused by IGF2 upregulation and is characterized by somatic overgrowth of the body, including kidney overgrowth (61). Conversely, Silver-Russell syndrome involves IGF2 downregulation and presents with growth restriction of body and the kidneys are generally small in proportion to the overall body growth restriction (82). Experimental models further underscore the important role of imprinting in renal development. These include the model demonstrating that CTCF mediates methylation-sensitive enhancer-blocking activity at the H19/Igf2 locus, where it binds the unmethylated imprinting control region (ICR) on the maternal allele to insulate Igf2 from enhancers, thereby silencing it (79), and the model of aberrant establishment of paternal methylation imprint at the H19/Igf2 ICR, which disrupts the parent-of-origin-specific expression pattern (83,84). In both cases, enhancer deletion at the 3' end of the H19 gene and demethylation of ICR alter IGF2 expression and impair normal kidney development (85).

4. Role of IGF2 in kidney disease

Above studies suggest a potential pathogenic and therapeutic role for IGF2 in diverse renal disorders, and highlight the need for further investigation into IGF2 signaling pathways and receptor interactions in the kidney to advance early diagnosis, therapeutic strategies and targeted interventions for renal pathologies. The following section explores the effects of IGF2 administration or overexpression in experimental models of renal disease.

IGF2 modulates renal physiology and pathology via a complex receptor network, including IGF2R, IGF1R and IR-A, and downstream signaling pathways such as the PI3K/Akt, MAPK and GSK3 pathways, exhibiting a biphasic regulatory pattern (76,86). Under physiological conditions, IGF2 predominantly interacts with IGF2R, activating the GSK3 signaling pathway and inducing the epigenetic reprogramming of macrophages (8,76). This promotes a metabolic shift toward oxidative phosphorylation (OXPHOS), fosters a macrophagic anti-inflammatory phenotype (76,87). In parallel, IGF2 signaling supports the proliferation of renal tubular epithelial cells, thereby contributing to podocyte cytoskeletal integrity and renal tissue repair (70,88).

By contrast, under pathological conditions, including chronic inflammation, hyperglycemia or loss of genomic imprinting, IGF2 preferentially binds IGF1R and IR-A, leading to sustained activation of the PI3K/Akt-MAPK axis. This signaling cascade disrupts the integrity of the podocyte-slit diaphragm complex and, in synergy with TGF-β1, stimulates collagen deposition and promotes irreversible renal fibrosis (70,89). Furthermore, in contexts involving biallelic IGF2 expression, persistent pro-proliferative signaling may ensue, contributing to proteinuria, glomerulosclerosis and the malignant transformation of renal tissues (90). This receptor-dependent shift in IGF2 signaling cascades represents a central molecular mechanism that governs renal cell fate decisions under both homeostatic and pathological states.

Role of IGF2 in AKI. AKI is a heterogeneous clinical syndrome that is characterized by a sudden decline in the glomerular filtration rate (GFR), commonly indicated by elevated serum creatinine (SCr) levels and/or oliguria (91). The incidence of AKI among hospitalized patients is ~20% and is often associated with complications such as fluid retention, electrolyte imbalances, uremic symptoms and drug-induced nephrotoxicity (91).

Traditionally, ischemia-reperfusion injury, nephrotoxic insults and sepsis have been regarded as the primary causes of AKI (91). However, growing evidence suggests that modifiable lifestyle factors influence both the onset and progression of AKI. Chronic alcohol consumption exacerbates AKI, increases the vulnerability and severity of kidney (92,93). Cigarette smoking impairs renal perfusion by inducing systemic inflammation, oxidative stress and endothelial dysfunction (94). Diets high in sodium, saturated fats and processed foods are strongly linked to hypertension, diabetes and cardiovascular disease, which are chronic metabolic conditions that are established risk factors for AKI (95,96). These findings underscore the multifactorial pathogenesis of AKI and highlight the need for integrative prevention strategies addressing both clinical and lifestyle-related risk factors.

At the molecular level, IGF2 may emerge as a potential key modulator of immune response and tissue repair during acute kidney injury (AKI). Although direct evidence elucidating the role of IGF2 in AKI remains limited, the well-documented functions of its related family member IGF-1 and other growth factors, including FGF2, in renal repair processes have been established (97,98). Mechanistically, it is proposed that IGF2 binds to its receptor IGF2R on macrophages, activating the GSK3β/β-catenin pathway to suppress pro-inflammatory cytokines, such as TNF-α and IL-1β, and enhance anti-inflammatory markers, such as arginase-1 and IL-10, thereby reshaping the immune microenvironment to attenuate renal injury (76). Furthermore, following ischemia-reperfusion injury, IGF2 expression is transiently upregulated and contributes to tubular epithelial cell repair (99). Animal studies have further demonstrated that IGF2R agonist administration reduced tubular necrosis by 42% and macrophage infiltration by 57%, underscoring the protective role of IGF2 in AKI (8,76).

IGF2 signaling has also shown promise as a clinical biomarker. The combined urinary detection of IGFBP-7 and tissue inhibitor of metalloproteinases-2 exhibits high predictive accuracy for AKI (area under the curve, 0.80), supporting the translational potential of IGF2-related mechanisms (100). Mesenchymal stem and/or stromal cells mediate part of their renoprotective effects via IGF2. Under hypoxic or inflammatory conditions, MSCs exhibit a 3.5- to 5.2-fold increase in IGF2 secretion, promoting macrophage polarization toward the anti-inflammatory M2 phenotype (8). IGF2 also facilitates macrophage metabolic reprogramming from glycolysis to mitochondrial OXPHOS, enhancing ATP production and sustaining the anti-inflammatory activity of the macrophages (8). However, IGF2 is not the sole mediator of MSC-induced renal protection. Knockdown of IGF2 partially attenuates, but does not abolish, MSC-mediated protection, suggesting compensatory roles for other factors such as hepatocyte growth factor, VEGF and exosomal microRNAs (97,101). Furthermore, although hypoxia preconditioning enhances MSC-derived IGF2 expression in glycerol-induced AKI models, it does not significantly improve therapeutic efficacy compared with unconditioned MSCs, highlighting the importance of multifactorial synergy (8).

A specific subtype of AKI, aristolochic acid nephropathy (AAN), results primarily from aristolochic acid I (AAI) exposure, and is characterized by AKI, interstitial nephritis and metabolic dysfunction (102,103). AA forms covalent adducts with DNA or RNA, driving the progression of renal damage (104), with ischemic injury forming a central pathophysiological basis (105). It is therefore plausible that AA may interfere with IGF2 signaling through spatially specific mechanisms. Histological analyses have demonstrated that AA primarily targets the renal cortex, where it induces DNA adducts, such as 7-(deoxyadenosine-N6-yl) aristolactam (dA-AAI), in proximal tubular cells, leading to epigenetic silencing of IGF2 through aberrant DNA methylation and disruption of ICRs (106,107). Spatial transcriptomics analysis has revealed that AA exposure activates the TGF-β/SMAD pathway in cortex-localized injured tubular clusters. This process promotes the establishment of a pro-inflammatory microenvironment characterized by macrophage infiltration and CCL5/CCR5 axis activation (108) and may potentially represses IGF2 transcription via SMAD3/NF-κB co-regulation (107,109,110).

Although the intense oxidative stress induced by aristolochic acid (AA) has been established as a core mechanism of its nephrotoxicity, the upstream drivers of this process require further investigation (107,111-114). Based on the well-documented role of the xanthine oxidoreductase system as a key source of reactive oxygen species (ROS) in renal injury (115,116), a plausible scientific hypothesis may be proposed: AA may activate this pathway by triggering 'purine metabolic reprogramming' in the renal cortex. Specifically, it may be postulated that AA or its metabolites may upregulate the expression or activity of xanthine dehydrogenase, leading to the accumulation of its substrates (xanthine) and products (uric acid), which in turn results in a burst of ROS production and ATP depletion. This metabolic disruption may further suppress the expression of critical repair signals like IGF2 through epigenetic mechanisms, thereby forming a self-reinforcing 'vicious cycle' with persistent inflammation and fibrosis (8,76). Although this hypothesis still requires direct experimental validation, studies have suggested the protective efficacy of targeting this pathway, providing a theoretical foundation for exploring its therapeutic potential in aristolochic acid nephropathy (117,118).

Role of IGF2 in CKD. CKD is a progressive disorder that constitutes a notable global health burden, affecting >10% of the global population, ~800 million individuals (119). Over the past 2 decades, both its incidence and mortality have steadily increased, positioning CKD as one of the leading non-communicable causes of death worldwide (119). IGF2 serves an important role in renal development and functional maintenance, and its dysregulation is increasingly implicated in CKD pathogenesis, particularly in fibrotic remodeling and tubulointerstitial injury (53,70,89) (Fig. 2).

Primary CKD. In the context of primary CKD, IGF2 acts as an important modulator of disease progression by influencing ECM deposition, tubular dysfunction and fibrosis via activation of the PI3K/Akt and MAPK signaling pathways (71,89). Clinical data reveal that serum IGF2 levels are elevated in patients with chronic renal failure compared with healthy controls, a finding likely attributable to impaired renal clearance. Notably, serum IGF2 levels remain unchanged following hemodialysis, whereas urinary excretion of IGF2 increases,

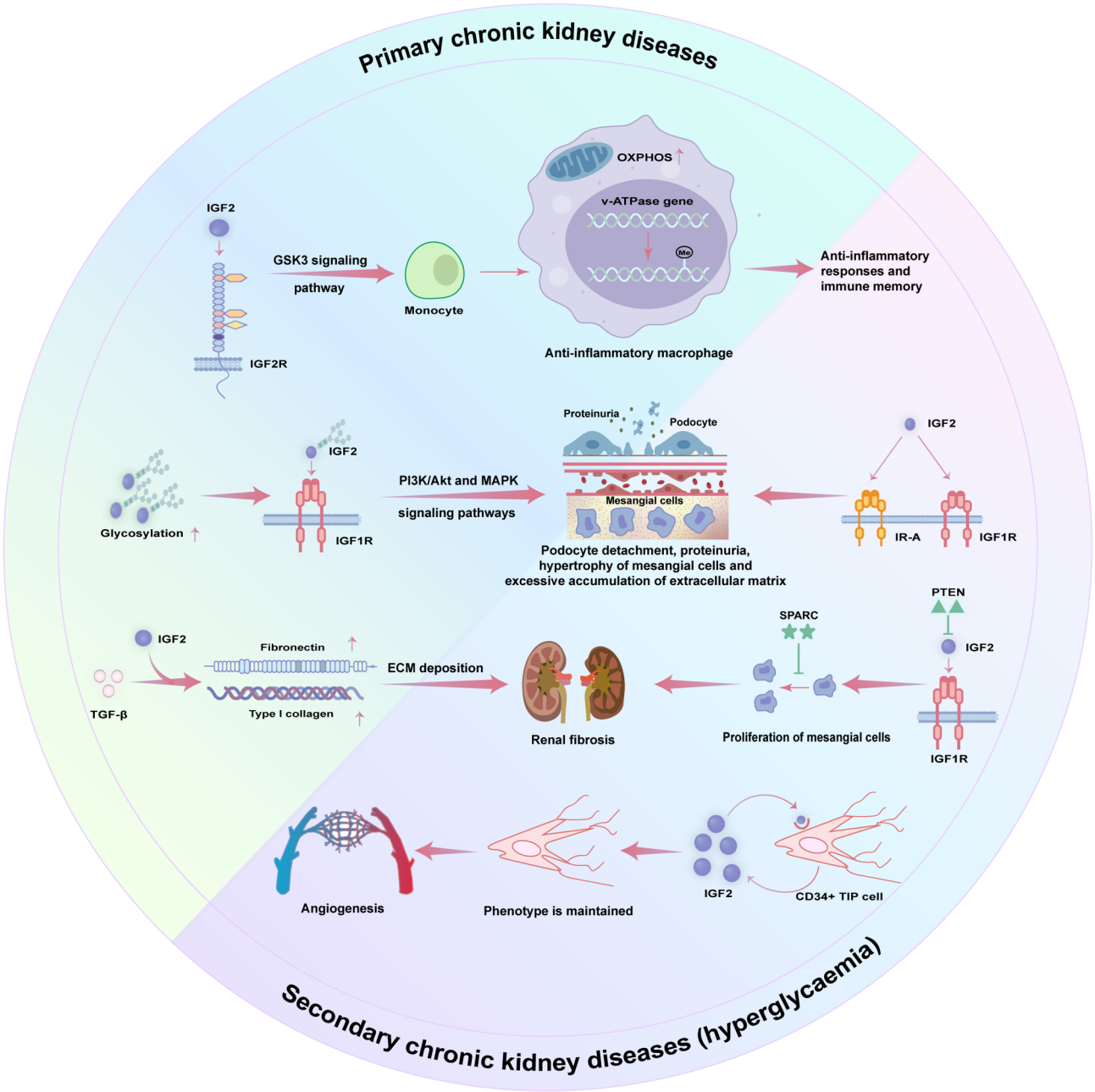

Figure 2. Role of IGF2-mediated signaling pathways in CKD. This figure delineates the dual roles of IGF2 signaling in CKD, encompassing both primary and hyperglycemia-induced secondary mechanisms. In primary CKD, IGF2 binding to IGF1R activates PI3K/Akt and MAPK pathways, promoting podocyte detachment, mesangial cell hypertrophy and excessive ECM accumulation, ultimately compromising glomerular filtration barrier integrity. Furthermore, IGF2 synergizes with TGF-β to upregulate fibronectin and type I collagen, accelerating renal fibrosis. Conversely, signaling through IGF2R activates the GSK3 pathway, inducing anti-inflammatory macrophage differentiation and modulating mitochondrial metabolism, which may confer protective effects. In hyperglycemia-induced CKD, IGF2 binding to IGF1R and IR-A drives pathological mesangial cell proliferation and ECM accumulation. This process is exacerbated by loss of PTEN-mediated negative feedback. Concurrently, SPARC is upregulated as a compensatory repair mechanism. Additionally, hyperglycemia enhances autocrine IGF2 secretion by CD34+ TIP cells, facilitating phenotype maintenance and angiogenesis. These findings underscore the multifaceted role of IGF2 in CKD pathophysiology, highlighting its potential as a therapeutic target. IGF, insulin-like growth factor; CKD, chronic kidney disease; IGF1R/IGF2R, IGF1/2 receptor; OXPHOS, oxidative phosphorylation; v-ATPase, vacuolar-type ATPase; TIP cell, tip endothelial cell; SPARC, secreted protein acidic and rich in cysteine; IR-A, insulin receptor isoform A; ECM, extracellular matrix; PTEN, phosphatase and tensin homolog on chromosome 10.

suggesting a compensatory clearance mechanism mediated by residual nephrons (120). Urinary proteomic analysis has further identified elevated levels of glycosylated IGF2 in patients with CKD, with this form exhibiting an inverse association with estimated GFR, highlighting its potential utility as a biomarker for disease progression and therapeutic monitoring (121).

Under physiological conditions, IGF2 supports podocyte survival and cytoskeletal integrity. However, aberrant IGF2 activation disrupts this homeostasis, leading to podocyte detachment and glomerular filtration barrier dysfunction. Podocyte injury thus becomes a central mechanism contributing to proteinuria and glomerulosclerosis (71,89). Additionally, IGF2 synergizes with TGF-β1 to enhance

expression of fibrogenic mediators such as type I collagen and fibronectin, thereby promoting irreversible glomerular and tubulointerstitial fibrosis (89).

IGF2 also facilitates tubular regeneration during the early stages of CKD by promoting epithelial cell proliferation and repair (9). This duality underscores its context-dependent effects and highlights the potential of IGF2 as a therapeutic target in CKD, although its precise roles in fibrotic vs. reparative processes warrant further exploration.

Persistent low-grade inflammation is a hallmark of CKD, with macrophage activation and functional plasticity serving a central role in disease progression (53). A previous study has demonstrated that IGF2 activates GSK3 signaling through IGF2R, triggering epigenetic reprogramming of macrophages toward an anti-inflammatory phenotype (8,76). Specifically, IGF2 suppresses lysosomal acidification by enhancing DNA methylation of the vacuolar-type H-ATPase gene, thereby altering macrophage energy metabolism. This reprogramming favors OXPHOS over glycolysis as the dominant energy source, which contrasts with the classical Warburg effect observed in inflammatory macrophages and tumor cells (122-124). Additionally, this reprogramming enables macrophages to exert anti-inflammatory responses and develop immune memory. These findings reinforce the importance of IGF2 as both a metabolic and immunological regulator in CKD.

Patients with CKD frequently exhibit persistent low-grade immune activation, involving macrophage immunological memory and phenotypic plasticity (125-127). IGF2 has been shown to enhance this form of 'trained immunity', enabling macrophages to respond more effectively to subsequent inflammatory stimuli with an anti-inflammatory profile (8). This process is especially relevant in CKD, where it helps attenuate disease progression by maintaining immune homeostasis and preventing excessive chronic inflammation (128,129).

Secondary CKD. Diabetic nephropathy (DN) is one of the most common complications of diabetes mellitus and a notable cause of CKD worldwide (130). Hallmark pathological features of DN include renal hypertrophy, mesangial expansion, excessive accumulation of ECM, tubular atrophy and interstitial fibrosis (131). A clinical study has demonstrated that serum levels of IGF2 are elevated in the early stages of DN, including the microalbuminuria phase, ~30% higher than in patients with diabetes alone, and are positively associated with cystatin C and 24-h urinary protein excretion (132). In advanced stages marked by overt proteinuria, IGF2 levels further increase ≤1.5-fold compared with those of healthy controls, and show positive associations with SCr and blood urea nitrogen levels, indicating a potential role of IGF2 in the development of glomerulosclerosis and interstitial fibrosis (132,133). While IGF2 serves a physiological role in angiogenesis and tissue repair, its upregulation under hyperglycemic conditions contributes to the pathogenesis of DN (99,132).

IGF2 expression is markedly upregulated in diabetic kidneys (134). Through activation of IGF1R and IR-A, IGF2 induces abnormal glomerular cell proliferation and promotes ECM deposition, resulting in glomerulosclerosis and compromising glomerular filtration barrier integrity (135). These changes not only impair renal structure and function but also accelerate DN progression (136,137).

In addition to its effects on glomerular cells, IGF2 regulates the balance between renal injury and repair by interacting with key signaling pathways, notably the phosphatase and tensin homolog on chromosome 10 (PTEN) and secreted protein acidic and rich in cysteine (SPARC) pathways. PTEN functions as a negative regulator of the insulin/IGF signaling pathway and serves an important role in DN, particularly in the hyperglycemic microenvironment (137,138). A study has demonstrated that IGF2, PTEN and SPARC are all upregulated in renal biopsies from patients with early-stage DN (137). When PTEN-mediated negative feedback is impaired, IGF2 activity increases, exacerbating pathological mesangial cell proliferation, ECM accumulation and renal fibrosis (136). This mechanism has been corroborated in streptozotocin-induced diabetic rat models (139,140).

SPARC, a matricellular protein involved in tissue remodeling and repair, is also modulated in DN. In DN, SPARC inhibits mesangial cell hypertrophy. While its upregulation may reflect a compensatory response to hyperglycemic injury, decreased SPARC expression is associated with impaired renal repair mechanisms, thereby worsening disease progression (141,142). Thus, in DN, IGF2 modulates renal injury and repair via interactions with PTEN and SPARC, highlighting a dual regulatory axis in disease pathophysiology.

IGF2 serves an important role in angiogenesis. *In a vitro* study using $CD34^+$ tip endothelial cell (TIP cell) models has revealed a strong association between IGF2 expression and both the number and angiogenic capacity of these cells. IGF2 knockdown reduces $CD34^+$ TIP cell numbers and inhibits vascular sprouting, supporting its role in angiogenic regulation. These findings also suggest that IGF2 may sustain the TIP cell phenotype via autocrine signaling (143). Therefore, targeted inhibition of IGF2 signaling may offer a promising therapeutic strategy for delaying DN progression by disrupting aberrant angiogenesis and fibrotic remodeling.

Role of IGF2 in renal tumors

Renal cell carcinoma (RCC). RCC is a prevalent renal malignancy characterized by complex genetic and epigenetic alterations. One of the notable molecular changes implicated in RCC is the upregulation of IGF2, particularly through loss of imprinting (LOI), which results in biallelic expression of the IGF2 gene. This aberrant expression contributes to tumor initiation and progression by activating multiple oncogenic signaling pathways (10).

A key regulatory mechanism involves the long non-coding RNA HOXA transcript at the distal tip, which acts as a competing endogenous RNA by sponging microRNA-615, thereby relieving repression of IGF2 and leading to its upregulation. This promotes renal cancer cell proliferation, migration and invasion (144). Within the tumor microenvironment, IGF2 interacts with IGF1R and IR-A to activate the PI3K/Akt and MAPK pathways, which enhance tumor cell survival, proliferation and motility (26,27). The oncogenic potential of IGF2 is markedly enhanced in tumors with high IR-A expression, underscoring the importance of receptor context in determining tumor behavior (17).

Preclinical models further support the role of IGF2 in RCC progression. In mouse models, IGF2 overexpression has been shown to accelerate tumor cell proliferation and metastasis,

suggesting that therapeutic strategies aimed at inhibiting IGF2 signaling or blocking receptor interactions may hold promise for targeted antitumor therapy in RCC (145-148).

Wilms' tumor. Wilms' tumor, or nephroblastoma, is a pediatric embryonal renal neoplasm arising from undifferentiated renal precursor cells. It is associated with epigenetic dysregulation of the IGF2 gene, particularly the loss of maternal imprinting, which leads to biallelic IGF2 expression and abnormal cellular proliferation (149).

During normal fetal kidney development, IGF2 is expressed exclusively from the paternal allele. All four known IGF2 promoters (P1-P4) maintain monoallelic expression in early development; however, imprinting at the P1 promoter begins to relax between gestational weeks 15-17 (150). In Wilms' tumor, this relaxation is exacerbated, ultimately resulting in LOI at all promoters and widespread upregulation of IGF2 (150).

In addition to LOI, mutations in tripartite motif containing 28 (TRIM28), a transcriptional co-repressor and epigenetic regulator, have been implicated in IGF2 dysregulation. Inactivating mutations in TRIM28 are frequently associated with biallelic IGF2 expression, especially in tumors lacking other common genetic alterations, suggesting that TRIM28 may drive tumorigenesis via an independent IGF2-related mechanism (151).

Ethnic differences have been observed in the prevalence of IGF2 imprinting abnormalities. For example, a study has shown that LOI of IGF2 is more frequent in Wilms' tumor cases among white children of Europe, North and South America and Oceania compared with Japanese children, potentially reflecting population-specific genetic or epigenetic susceptibility (152).

Collectively, the loss of IGF2 imprinting and TRIM28 mutations represent important events in the pathogenesis of Wilms' tumor. These insights provide a compelling theoretical framework for the development of IGF2-targeted therapies in pediatric renal malignancies.

5. Therapeutic potential and treatments targeting IGF2

As an important regulator of cell proliferation, metabolic reprogramming and angiogenesis, IGF2 has emerged as a promising therapeutic target, with encouraging progress reported in both preclinical and clinical studies (153-155).

In a preclinical model, the natural compound curcumin has demonstrated potent antitumor effects in bladder cancer by transcriptionally suppressing IGF2, blocking IGF1R/IR substrate 1 phosphorylation and inhibiting the downstream AKT/mTOR signaling cascade. These inhibitory effects are reversed by exogenous IGF2 administration or IGF1R overexpression, highlighting the notable role of IGF2 signaling in tumor progression and validating its therapeutic relevance (156).

Clinically, monoclonal antibodies targeting IGF1R, such as dalotuzumab, and tyrosine kinase inhibitors, such as linsitinib, have shown therapeutic efficacy in select sarcoma subtypes (153). However, these agents have shown limited benefit in breast cancer and non-small cell lung cancer, reflecting the context-dependent nature of IGF signaling and the heterogeneity of downstream pathway activation (157). To overcome compensatory mechanisms, dual-ligand neutralizing antibodies, neutralizing antibodies with different targets have been developed. These include dusigitumab (154), which targets the IGF-1 receptor to block signaling from both IGF-1 and IGF-2, and xentuzumab (155), a dual-IGF-1/IGF-2 ligand-neutralizing antibody that directly binds the ligands themselves. While conceptually promising, their clinical utility has been constrained by the absence of robust predictive biomarkers, which remains a notable barrier to broader application (158).

In pediatric oncology, Wilms' tumor represents a paradigm for IGF2-driven tumorigenesis (159). Using genetically engineered mouse models harboring Wilms' tumor protein deletion and IGF2 overexpression, researchers have successfully recapitulated key features of human WT, including impaired mesenchymal differentiation and persistent ERK1/2 activation. These models provide a robust platform for exploring therapeutic interventions targeting the IGF axis (160).

With respect to angiogenesis, truncated IGF2 variants such as Des(1-6)IGF2 have been shown to promote endothelial cell migration, tube formation and intra-ovarian neovascularization by upregulating IL-6, urokinase plasminogen activator surface receptor and CCL2. Notably, Des(1-6)IGF2 evades inhibition by IGFBP-6, unlike Leu27IGF2, which preferentially binds IGF2R and exhibits minimal angiogenic activity. These findings implicate IGF1R and IR-A as dominant mediators of the pro-angiogenic effects of IGF2 in pathological neovascularization (161).

Despite these promising advances from above experimental and mechanistic studies, several key challenges persist. Ligand redundancy, tissue-specific pathway activation and the lack of reliable biomarkers continue to impede precision targeting of the IGF2 axis (76,162). Future research should focus on developing IGF2-specific inhibitors, optimizing rational combination therapies and identifying context-specific biomarkers, particularly in diseases such as Wilms' tumor and epigenetically-deregulated renal disorders, where IGF2 signaling is pathologically upregulated.

6. Concluding remarks and future perspectives

In previous years, with in-depth studies on the biological role of IGF2 and its regulatory mechanisms, the multiple roles of IGF2 in renal development and disease have been revealed. Under normal physiological conditions, IGF2 serves an important role in renal tubular and glomerular formation through precise gene imprinting regulation (24,70). However, under pathological conditions, aberrant expression of IGF2 accelerates the progression of renal fibrosis, DN and renal tumors by activating specific signaling pathways (2,51,136).

Although IGF2 has been validated as a potential biomarker and therapeutic target in renal diseases, a number of mechanistic questions remain unresolved. Future investigations should examine: i) The molecular interplay between IGF2 and regulatory factors such as IGFBPs, TGF-β and VEGF; ii) the spatial and temporal dynamics of receptor activation; and iii) the differential roles of IGF2 in various pathological states. Additionally, the design of IGF2-specific therapies is expected to provide novel strategies for the treatment of kidney disease and associated metabolic disorders.

In conclusion, IGF2 serves an increasingly recognized role in renal biology and pathogenesis. A deeper understanding of its regulatory mechanisms will facilitate the development of precise diagnostic tools and targeted interventions for renal diseases.

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Authors' contributions

YS was responsible for conceptualization, investigation, methodology, visualization, writing the original draft, and reviewing and editing the manuscript. WHa acquired funding, and contributed to the methodology, supervision, and reviewing and editing of the manuscript. WL contributed to the methodology and supervision, and reviewed and edited the manuscript. WHu was responsible for conceptualization, the acquisition of funding and resources, and contributed to supervision, validation, writing the original draft, and reviewing and editing the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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