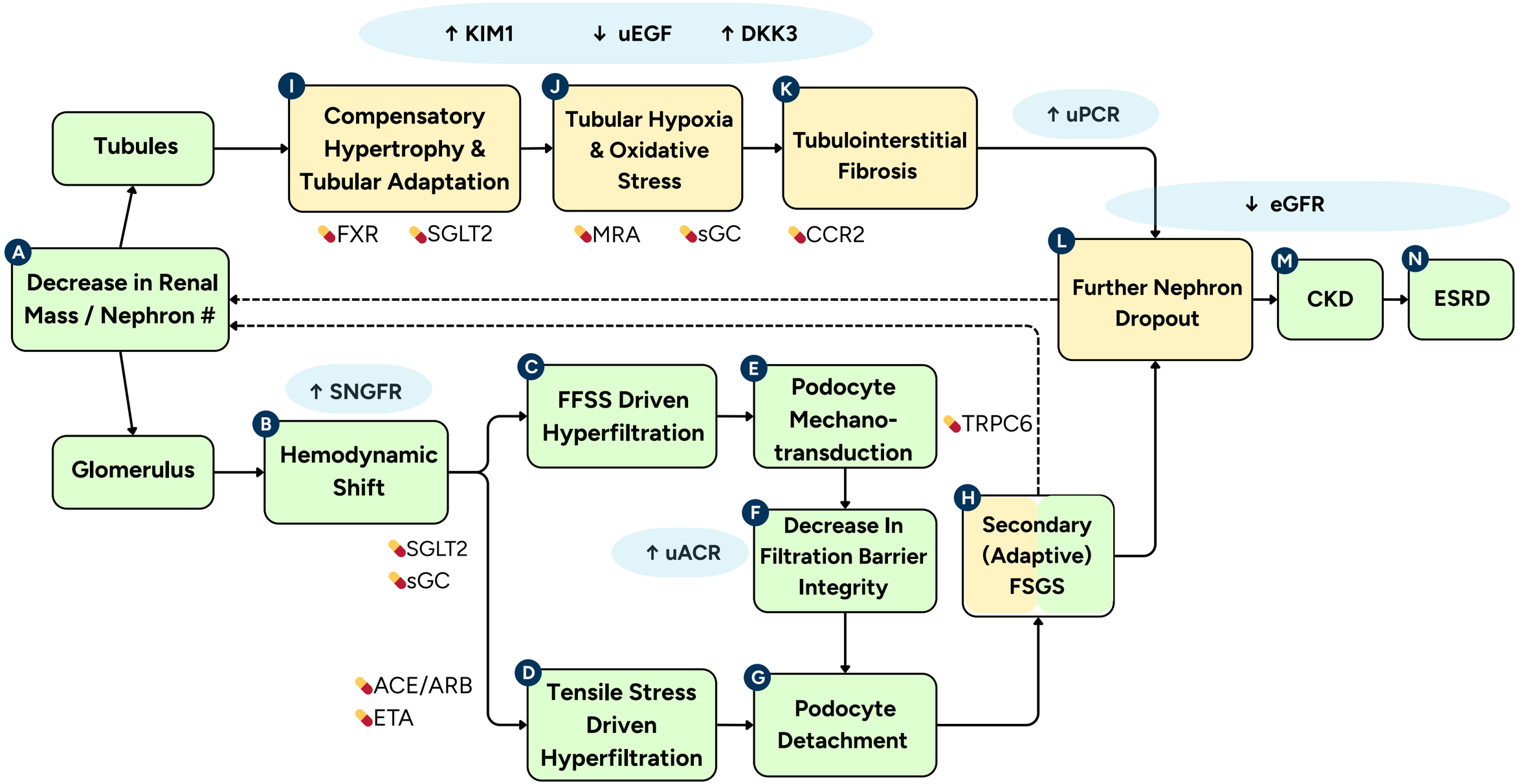
↑ KIM1
↓ uEGF
↑ DKK3
Tubules
I
Compensatory Hypertrophy & Tubular Adaptation
J
Tubular Hypoxia & Oxidative Stress
K
Tubulointerstitial Fibrosis
↑ uPCR
↓ eGFR
FXR
SGLT2
MRA
sGC
CCR2
A
Decrease in Renal Mass / Nephron #
L
Further Nephron Dropout
M
CKD
N
ESRD
↑ SNGFR
C
FFSS Driven Hyperfiltration
E
Podocyte Mechano-transduction
TRPC6
Glomerulus
B
Hemodynamic Shift
F
Decrease In Filtration Barrier Integrity
H
Secondary (Adaptive) FSGS
SGLT2
sGC
↑ uACR
ACE/ARB
ETA
D
Tensile Stress Driven Hyperfiltration
G
Podocyte Detachment

Appendix Pathophysiology Process

Number	Step	Description
A → B	A decrease in renal mass/functional nephrons leads to homeostatic compensation to maintain total GFR	
B	Hemodynamic Shift	• Rightward shift of TGF[1,2,3] • Dilation of Afferent Arteriole[4]
B → C	Hemodynamic shift drives an initial increase in SNGFR, contributing to early hyperfiltration	
B → D	Early Hyperfiltration due to increased tensile stress may vary and can contribute later in some models	
C	Fluid Flow Shear Stress (FFSS) Driven Hyperfiltration	• increase in Single Nephron GFR (SNGFR)[5,6] • FFSS increases 1.5-2x on podocytes[8,9] • increase in urinary PGE2[10,11]
D	Tensile Stress Driven Hyperfiltration	• increase in SNGFR[5,6] • increase in Pgc[7,8]
C → E	Increased FFSS induces podocyte mechanosignaling	
E	Podocyte Mechanotransduction	• COX-2 → PGE_2 → EP2 axis induced[10] • EP2 signaling remodels podocyte actin framework[12]
E → F	Actin remodeling creates weakened adhesion and increased permeability in the filtration barrier	
F	Decrease in Filtration Barrier Integrity	• Slit diaphragm & cytoskeleton become unstable[13,14] • albumin begins to leak[15]
F → G	An unstable cytoskeleton leads to an increased risk of podocyte detachment	
D → G	Capillary loss requires more pressure to maintain the same filtration rate	
G	Podocyte Detachment	• Podocytes detach from the GBM and are lost in the urine[16] • Adaptive hyperfiltration becomes irreversible[16]
G → H	Loss of podocytes exposes segments of the basement membrane	
H	Secondary (Adaptive) Focal Segmental Glomerulosclerosis	• increase in segmental scarring[17] • Adhesion of the glomerular tuft to the Bowman's Capsule (synechia)[18]
A → I	A decrease in renal mass/functional nephrons leads to an increased workload on remaining nephrons	
I	Compensatory Hypertrophy and Glomerulo-Tubular Adaptation	• increase in length and diameter of PCT and DCT[19,20] • increase in transporter density[21] • increased solute reabsorption[22,23]

I → J	Increased metabolic demand outpaces oxygen delivery	
J	Tubular Hypoxia and Oxidative Stress	• Albumin handling worsens stress (protein toxicity[24] • Mitochondrial dysfunction develops[25] • inflammatory signaling and hypoxia[26,27]
J → K	Oxidative stress and inflammatory signaling cause fibroblast activation	
K	Tubulointerstitial Fibrosis	• Extracellular matrix deposition causes tubular atrophy and capillary loss[28,29] • Irreversibly reduces functional nephron mass[30,31]
H → L	Segmental scarring leads to increased strain on remaining nephrons	
K → L	Fibrosis-mediated structural damage leads to increased strain on remaining nephrons	
L	Further Nephron Dropout	• leads to a positive feedback loop that decreases the remaining functional nephron mass and reduces overall kidney function
L → M	eGFR begins to decline	
M	Chronic Kidney Disease (CKD)	• Sustained eGFR decline[32] • persistent proteinuria[33] • systemic hypertension[33]
M → N	Functional nephron count reaches critical threshold	
N	End-Stage Renal Disease (ESRD)	• Kidney function is insufficient to maintain fluid, electrolyte, & metabolic homeostasis[34] • Requires dialysis or kidney transplantation for survival[34]

Appendix: Therapeutic Abbreviations and Full Terms

- **ACE**: Angiotensin-Converting Enzyme Inhibitor
- **ARB**: Angiotensin II Receptor Blocker
- **SGLT2**: Sodium-Glucose Cotransporter 2 Inhibitor
- **MRA**: Mineralocorticoid Receptor Antagonist2
- **ETA**: Endothelin A Receptor Antagonist
- **CCR2**: C-C Motif Chemokine Receptor 2 Antagonist
- **FXR**: Farnesoid X Receptor Agonist
- **sGC**: Soluble Guanylate Cyclase Stimulator
- **TRPC6**: Transient Receptor Potential Canonical 6 Inhibitor

Appendix References

1. (Celsi et al., 1989;1991): Micropuncture studies show ~2× SNGFR following nephrectomy; early maintenance relies heavily on ultrafiltration pressure; later maintenance adds increased filtering surface area.
2. (Müller-Suur 1980): UNx → TGF reset (right-shift)
3. (Brown 2011): TGF plasticity in prenatal/postnatal ovine kidney
4. (Monu 2018): Reset mediated by increased CTGF (ENaC) → afferent arteriole dilation
5. (Celsi et al., 1989;1991): Micropuncture studies show ~2× SNGFR following nephrectomy; early maintenance relies heavily on ultrafiltration pressure; later maintenance adds increased filtering surface area.
6. (Brenner et al., 1988): Increases in SNGFR facilitate adaptations compensating for loss of functioning nephrons
7. (Salmond & Seney 1991): higher flow needed to engage inhibition, permits ↑SNGFR & ↑P_GC
8. (Sharma et al. 2017): hyperfiltration-associated biomechanical forces include both pressure-induced tensile stress and FFSS. increased glomerular capillary pressure drives these mechanical forces in the context of congenital nephron reduction.
9. (Srivastava et al., 2014;2017)(NDT): animal models of solitary kidney has 1.5-2x increased FFSS
10. (Srivastava et al., 2014) (AJP Renal): FFSS makes podocytes upregulate COX-2, produce more PGE2, and increase EP2 receptor expression.
11. (Srivastava et al., 2020): shows urinary PGE2 is a biomarker of early adaptive hyperfiltration (prior to albuminuria)
12. (Friedrich et al. 2006): FFSS activates specific tyrosine kinases that play a role in actin cytoskeleton reorganization in podocytes
13. Hamano et al. 2002): defects in glomerular epithelial slit diaphragm proteins lead to precipitous plasma protein leak, distinguishing this mechanism from the more gradual leak caused by basement membrane defects.
14. (Yu et al. 2018): disruption of slit diaphragm proteins (nephrin, podocin, TRPC6/5) and cytoskeletal proteins (Rho/small GTPases, synaptopodin) participate in the pathogenesis of proteinuric kidney diseases.
15. (Benzing & Salant, 2021): When the cytoskeleton is disrupted, foot-process effacement occurs with loss of the buttressing force, reducing GBM compression and increasing albumin permeability.
16. (Kriz & Lemley, 2014): Detachment of viable podocytes from the glomerular basement membrane (GBM), rather than cell death, is the major mechanism of podocyte loss.
17. (D'Agati et al. 2011): following initial podocyte injury and detachment, denuded patches of glomerular basement membrane become covered by parietal cells, leading to synechia formation with Bowman's capsule and creating a nidus for segmental sclerosis development
18. (Kuppe et al. 2015): cellular adhesions (synechiae) between Bowman's capsule and the tuft are formed by cells expressing podocyte and/or parietal epithelial cell (PEC) markers. Cells expressing PEC markers were detected in all FSGS lesions and often stained positive for markers of activation (CD44 and cytokeratin-19)
19. (Hayslett et al. 1968): foundational micropuncture evidence demonstrating that Following uninephrectomy, tubular volume increased in both proximal and distal portions, with the volume increase twice as great in the proximal tubule as in the distal.
20. (Fine et al. 1978): fluid reabsorption per unit length was 60-70% greater in hypertrophied tubules, closely correlated with a twofold increase in dry weight per unit length.
21. (Pollock et al. 1992): demonstrated enhanced net tubular Na transport in established compensatory renal hypertrophy. Total Na reabsorption up to the late proximal site increased from 1.8 ± 0.2 to 2.7 ± 0.1 nmol/min following uninephrectomy
22. (Fong et al. 2014): synthesized current understanding, noting that hypertrophy of tubules (predominantly the proximal tubule) is accompanied by increased single nephron glomerular filtration rate and tubular reabsorption of sodium
23. (Layton et al. 2017): computational modeling to quantify the extent of these adaptations, demonstrating that nephrectomy-induced SNGFR increase and tubular hypertrophy alone are insufficient to fully maintain salt balance. The model identified necessary increases in protein density of Na-K-ATPase, Na-K-2Cl cotransporter, Na-Cl cotransporter, and epithelial Na channel
24. (Morigi et al. 2002): foundational evidence that protein overload induces toxicity through reactive oxygen species generation. In human proximal tubular cells (HK-2), both albumin and IgG (1-30 mg/ml) induced rapid and significant increases in hydrogen peroxide (H_2O_2) production at 5 minutes, persisting at 60 minutes in a dose-dependent manner.
25. (Zhuang et al. 2015): mechanistic detail on the mitochondrial dysfunction pathway. In albumin-overload mouse models, marked changes in mitochondrial morphology were accompanied by mitochondrial cytochrome c release and copy number reduction of mitochondrial DNA. Treatment with MnTBAP, a mitochondrial SOD2 mimic, robustly blocked tubular structure damage, cell apoptosis, and phenotypic alterations, demonstrating a key role for mitochondria-derived oxidative stress. Demonstrated that the NLRP3/caspase-1/cytokine cascade was activated in kidneys by albumin overload and entirely abolished by MnTBAP treatment, establishing the mitochondrial dysfunction/NLRP3 inflammasome axis as central to proteinuria-induced tubular injury.
26. (Zhuang et al. 2018): identified the COX-2/mPGES-1/PGE_2 cascade as an additional inflammatory pathway activated by mitochondrial oxidative stress. Albumin overload-induced upregulation of COX-2 and mPGES-1 at mRNA and protein levels, along with increased urinary PGE_2 excretion, was largely abolished by MnTBAP treatment.
27. (Fontecha-Barriuso et al. 2022): synthesize current understanding, noting that increased oxygen consumption is closely linked to increased oxidative stress, which increases mitochondrial oxygen usage and reduces tubular transport efficiency, creating a vicious cycle where tubulointerstitial hypoxia stimulates fibrogenesis and aggravates chronic kidney disease progression.
28. (Meguid El Nahas & Bello, 2005): tubulointerstitial scarring and fibrosis are closely associated with impairment of renal function. The study demonstrates that activation and proliferation of fibroblasts and myofibroblasts with associated excessive synthesis of ECM culminates in interstitial fibrosis. Critically, injured tubules undergo programmed cell death (apoptosis) leading to tubular atrophy and the formation of atubular glomeruli, with the outcome depending on the capacity of inflammation to regress, tubules to regenerate, fibroblasts to die, and ECM to be broken down—continuing injury leads to irreversible fibrosis.
29. (Webster et al. 2017): connected capillary loss to functional decline, demonstrating that a progressive decline in the surface area of interstitial capillaries leads to hypoxia within the kidney and affects the function of cells usually involved in degradation of collagen.
30. (Li et al. 2022): introduced the concept of the fibrogenic niche, demonstrating that renal fibrotic lesions initiate at focal sites where a unique tissue microenvironment is orchestrated by a specialized ECM network. Studies using decellularized ECM scaffolds from fibrotic kidneys show that the fibrogenic niche autonomously promotes fibroblast proliferation, tubular injury, macrophage activation, and endothelial cell depletion—pathological features that recapitulate key events in CKD pathogenesis.
31. (Liu et al. 2011): Liu (2011, PMID: 22009250) provided comprehensive mechanistic detail, demonstrating that renal fibrogenesis consists of four overlapping phases: priming, activation, execution, and progression. The study shows that multiple cellular and molecular events, such as tubular atrophy, microvascular rarefaction, and tissue hypoxia, promote scar formation and ensure vicious progression to end-stage kidney failure.
32. (Veterans Affairs, 2025): five-stage classification of chronic kidney disease based on sustained decline in GFR is the 2002 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) clinical practice guidelines
33. (Ruggenenti, 2001): Observational studies have shown that proteinuria independently predicts the risk of end-stage renal disease and mortality. The correlation between urinary protein excretion and rate of GFR decline has been documented in both diabetic and non-diabetic chronic nephropathy
34. (Wouk, 2021): End-stage renal disease is defined as the stage when kidney function is insufficient to sustain life long-term without kidney replacement therapy, occurring when GFR falls below 15 mL/min per 1.73 m^2 (CKD stage G5). At this point, the kidneys can no longer maintain fluid, electrolyte, and metabolic homeostasis, necessitating dialysis or kidney transplantation for survival.

Three Frameworks: A Toolkit for Therapeutic Development

No single framework serves all contexts — a toolkit approach provides regulatory-grade flexibility

1 Anatomical / Developmental Phenotype

Primary Grouping

- A. Renal Parenchymal Disorders (SFK, hypodysplasia, cystic dysplasia)
- B. Congenital Obstructive Uropathies (UPJO, megaureter)
- C. PUV & Bladder-Mediated (PUV, spina bifida, prune belly)
- Modifier: VUR, UTI, bladder function

2 Mechanistic Injury Pathway

The Biological Unifier

- A. Hemodynamic load (hyperfiltration)
- B. Shear stress & glomerular hypertension
- C. Podocyte stress and depletion
- D. Tubular stress and maladaptation fibrosis, nephron loss
- E. Interstitial fibrosis / nephron loss

3 Risk Stratification

Enrichment for Trials

- Severity of nephron deficit at baseline (kidney volume, eGFR)
- Rate of progression (eGFR slope, proteinuria)
- Genetic risk modifiers (PAX2, HNF1B, others)
- Compounding exposures (prematurity, AKI history)