Mechanisms of progressive renal injury and renal fibrosis

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Renal disease progression

- Mechanisms of kidney injury
- Mechanisms of kidney disease progression
- Glomerular hypertension and Ang II
- Proteinuria and tubulointerstitial fibrosis
Functions of the kidney

- Selectively filters blood to allow waste excretion but prevent protein into urine
- Modify fluid and salt composition of urine
- Synthesis of hormones eg erythropoietin
Compartments of the kidney

- Glomerulus: podocytes, mesangial cells, endothelial cells
- Tubules
- Interstitium
- Blood vessels

Requires precise arrangement to function
Glomerulus is a complex capillary that functions as a selective filter.
Foot process fusion/effacement in proteinuric kidney disease

Normal

Nephrotic
Causes and stages of CKD by Glomerular filtration rate (GFR)
Susceptibility factors in Thai subjects: EGAT study

- Cohort (n= 2067) followed for 12 years
- New CKD (GFR <60ml/min/1.73 m²) 6.3%

Risk factors

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Folds increase</th>
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<tbody>
<tr>
<td>High BS (&gt;110)</td>
<td>2.7</td>
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<tr>
<td>High BS + BP&gt;130/85 + High TG</td>
<td>6.3</td>
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<tr>
<td>High BS + high TG + Obese</td>
<td>7.3</td>
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Kittyakara C, Yamwong S, Sritara P. Kidney Int (in press)
Renal disease progression

- Once established: renal failure is often progressive even after original cause is treated

- Steps to prevent progression essential
Rate of progression depend on disease, genetics, treatment
Primary renal disease

Chronic renal failure
GFR < 60ml/1.73 M²

Cell Signals

ESRD

CV Mortality

Modulating Factors
- Proteinuria
- Hypertension
- Diabetes
- Obesity
- Smoking
- Dyslipemia
- Gender
- Ethnicity
- Birth weight
- Genetic factors
- Age
- Metabolic factors (Ca, phos, uric acid)
- Nephrotoxins

Cellular Pathways
- Inflammation
- Tubular epithelia activation/transition
- Fibroblasts/myofibroblasts stimulation
- Interstitial capillaries activation/rarefaction
- Interstitial scarring
- Nephron loss

Molecular Pathways
Pro-fibrotic
- Renin-angiotensin system
- Oxidant stress
- Growth factors (TGF-β, CTGF PDGF, FGF)
- PAI-1
- Endothelin-1
- Proteases
- Chemokines
- Adhesion molecules

Anti-fibrotic
- HGF
- BMP-7
- VEGF
- Angiopoietin

Recovery

Regression

?
Factors contributing to progressive renal disease

Primary renal disease:- extent of initial injury

Secondary factors

- Systemic hypertension
- Glomerular hypertension
- Renin-Angiotensin II-Aldosterone
- Proteinuria
- High protein intake
- Hyperlipidemia, obesity
- Smoking
- Anemia
- Race, male gender, genetics, decreased nephron endowment
Cellular pathways of progression

- Persistent glomerular injury and glomerular hypertension
- Heavy glomerular proteinuria
- Immune response and cytokines
- Fibroblast formation and recruitment
- Collagen matrix deposition
- Acellular scar, ischemia, tubular atrophy and interstitial fibrosis
Glomerular sclerosis and glomerular hypertension
Podocytes

Platelets

Mesangial cell

Chemokine and cytokine release

Endothelial cell injury

Inflammatory cells

Inflammation

Foot processes effacement

Activated transformed mesangial cells/myofibroblast

Monocyte

Foam cell

Proliferation

Fibrosis

Stretching of podocytes

Extra cellular matrix
Glomerular hypertension

- Hyperfiltration hypothesis - Brenner et al

- Decreased nephron mass leads to compensation by other remaining nephrons

- This is mediated by increased glomerular pressure and increased blood pressure and angiotensin II

- Decreasing intraglomerular pressure (eg by ACEi) or protein restriction decreases damage
\[ \Delta P = P_{Gc} - P_T \]
Nephron loss

Hyperfiltration, Hypertrophy, Glomerular hypertension

Increased Glomerular Membrane permeability

Glomerular Tubulointerstitial fibrosis

HTN

ANG II

ALDOSTERONE

growth factors

Proteinuria
Angiotensinogen

Renin

Ang I (1-10)

ACE

Ang II (1-8)

AT1

AT2

Ace inhibitors

ARBs

Negative feedback

Bradykinin

Inactive fragments

ACE

Angiotensinogen

Chymase

Cathepsin

ACE inhibitors

Angiotensinogen

Glomerular hypertension
Vasoconstriction
TGF β stimulation
Fibrosis

Vasodilation
Tubolulointertistial injury and fibrosis
Interstitial fibrosis predicts ESRD
Progression of interstitial fibrosis

Susceptibility
- Genetic
- Race
- Gender
- Glomerular injury

Initiation
- PTC
  - Immune
  - Haemodynamic
  - Metabolic
  - Proteinuria

Progression
- Fibroblasts
  - Activation
  - Proliferation
  - Fibrosis

Inflammation
Glomerular disease

Vascular damage

Tubular ischemia

Altered filtration

Reabsorption of noxious macromolecules

Chronic tubular cell injury

Release of cytokines, proteinases, adhesion molecules, growth factors

$\text{NH}_3 \rightarrow \text{C}_a, \text{b} \rightarrow \text{C}_3, \text{g}$

$\Delta$Cell balance

Fibroblast proliferation

Matrix deposition

$\uparrow$Recruitment of antigenically activated cells

Tubular atrophy

Interstitial fibrosis

Interstitial infiltrates

Tubular dysfunction

$\downarrow$Capillary perfusion

Progressive loss of renal function
Transforming growth factor beta

- Cytokine that is anti-inflammatory and stimulates fibrosis
- Increased in fibrogenic diseases
- Natural inhibitors (e.g. Bone morphometric protein 7-BMP7) which may decrease kidney disease progression
Relative expression of TGF-beta in disease and normal kidneys.
Conclusions:
Chronic kidney disease progression

• Occurs even if the primary disease is treated at an individually determined rate

• Injury and scarring of glomeruli, tubulo-intersitium and loss of blood vessels mediated by cells in the kidney, circulating cells and secreted factors

• Strategies to minimize these processes may prevent continued loss of kidney function
Can Chronic kidney disease be reversed?

Baseline
Reversal of diabetic nephropathy after pancreas transplantation

Fioretto et al NEJM 1998
THANK YOU