HGF and BMP-7 : Potential as Anti-fibrotic Agents for Chronic Kidney Disease

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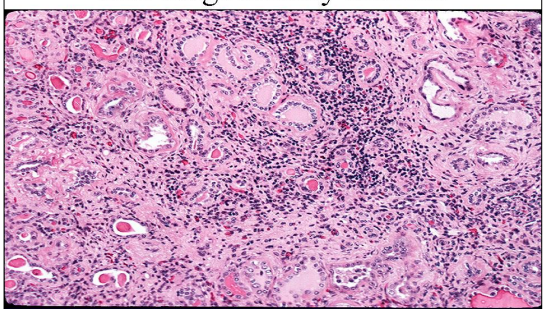
End Stage Kidney Disease



Chronic Allograft Nephropathy – tubular atrophy, interstitial fibrosis.

ESRD: Histopathology

- Interstitial fibrosis/cellular infiltration
- Tubular atrophy
- Glomerulosclerosis/podocyte depletion
- Vascular sclerosis/capillary loss
- Accumulation of extracellular matrix

ESRD: Uniqueness

- Cause of Injury:

  Final common pathway of all kidney diseases regardless of the nature of the injury

- Duration of Injury:

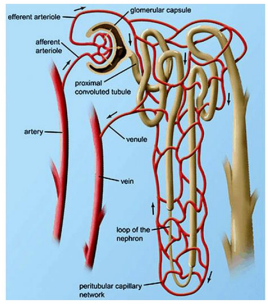
  Kidneys usually recover after an acute injury
  Chronic, protracted injuries can cause ESRD

Renal Fibrosis: Why Now?

- ❑ No specific Rx to reverse primary diseases
- ❑ Renal fibrosis is not a healing process. It is a major barrier to tissue repair.
- ❑ New findings in the pathogenesis of renal fibrosis
  - Cellular apoptosis
  - Epithelial-mesenchymal transition (EMT)
  - Mesenchymal-epithelial transition (MET)
  - Renoprotective cytokines

Pathogenesis of Renal Fibrosis

- Glomerular hyperfiltration and hypertension *(B. Brenner 1980)*
- Chronic hypoxia *(L. Fine, 2000)*
- Pro-fibrogenic/anti-fibrogenic cytokines



M. Nangaku J Am Soc Nehrol 17:17-25, 2006

Renin-Angiotensin System Blockages: Are They Really Working?

- **The Antihypertensive and Lipid-Lowering Treatment to prevent heart attack trial (ALLHAT)**
  JAMA 288:2981-2997, 2002
- **Renoprotective Specificity of R-A System Blockade**
  KA Griffin and AK Bidani; Clinical J Am Soc Nephrol 1:1054-1065, 2006
- **ACE inhibitor use and the long-term risk of renal failure in diabetes**. *S Suissa et al. KI 69:913-919, 2006*
- **R-A system blockade and nephropathy: Why is it being called into question and should it be?**
  NK Hollenberg and M Epstein. Clin J Am Soc Nephrol 1:1046-1048, 2006

Pathogenesis of Renal Fibrosis

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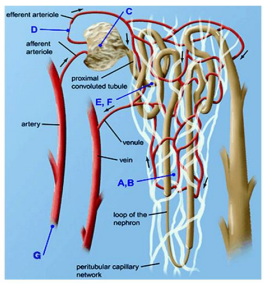
- Pro-fibrogenic/anti-fibrogenic cytokines

Chronic Hypoxia and Progression of Renal Disease



M. Nangaku J Am Soc Nephrol 17:17-25, 2006

VEGF and Angiopoietin

- Role of microvascular endothelium in progressive renal disease.
  DH Kang et al. J Am Soc Nephrol 13: 806-816, 2002
- Impaired angiogenesis in the remnant kidney model: II. Vascular endothelial growth factor administration reduces renal fibrosis and stabilizes renal function.
  DH Kang et al. J Am Soc Nephrol 12: 1448-1457, 2001
- COMP-angiopoietin-1 ameliorates renal fibrosis in unilateral ureteral obstruction model.
  W. Kim et al.J Am Soc Nephrol 17: 2474-2483, 2006

Pathogenesis of Renal Fibrosis

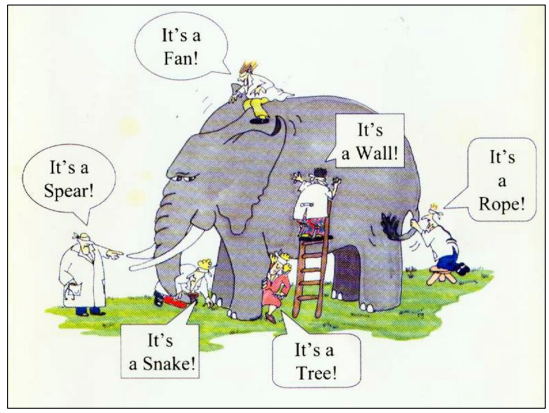
Balance of Profibrogenic

vs.

Antifibrogenic cytokines

TGF-β

HGF
BMP-7



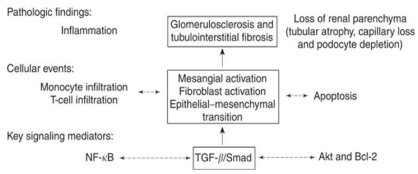
Transforming Growth Factor-β

- TGF-β is widely expressed and acts on virtually every cell line in kidney by engaging intracellular signal cascade (S-mad system)
- Renal source of TGF-β
  - Parenchymal cells
  - Infiltrating leucocytes
  - Circulating TGF-β
- Prime pro-fibrotic cytokine (ESRD, liver cirrhosis, pulmonary fibrosis, scleroderma, keloid)

TGF-β and Renal Fibrosis

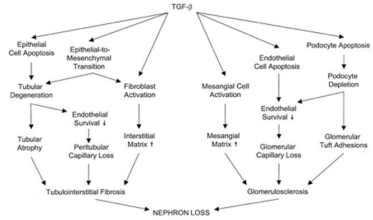
- Enhances renal tubular cell apoptosis
  Enhances EMT
  ⇒ **Tubular atrophy**
- Enhances fibroblast and mesangial cell proliferation
  Increases ECM deposition/decrease ECM degradation
  ⇒ **Fibrosis**
- Growth arrest for podocytes and gl. endothelial cells
  ⇒ **Glomerulosclerosis**
- Anti-inflammatory action via inhibition of NF-κB
- Reciprocal relationship in renal expression of TGF-β vs. HGF (and BMP-7); and functionally they are antagonistic to each other

TGF-β and Pathogenesis of Renal Fibrosis



Liu Y KI 69:213-217 2006

TGF-β & Progression of Renal Disease



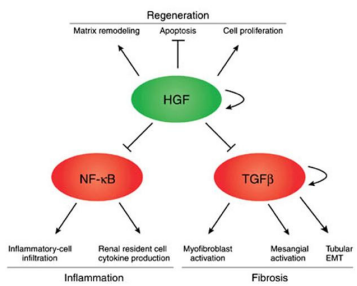
E.Boettinger et al. J Am Soc Nephrology 13:2600, 2002

Hepatocyte Growth Factor (HMP)

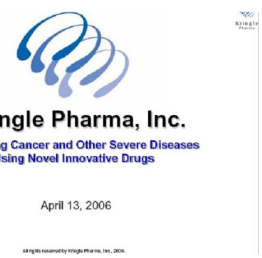
- Polypeptide; multifunctional cytokine
- Synthesized primarily by nonparenchymal cells of the kidney (fibroblasts; macrophages; endothelial cells)
  Receptor (c-met) is expresses primarily in parencymal cells
- Early stage of injury → Increased production
  Late stage of injury → Decreased production
- HGF expression is reciprocal with TGF-β, and functionally they are antagonistic to each other

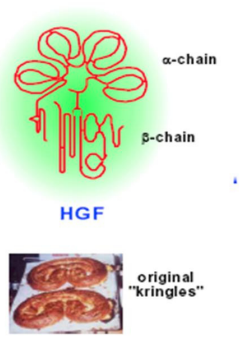
Renotropic Roles of HGF

Targets	Bioactivity
▪ **Glomeruli**	
• Mesengial cells	Anti-proliferation Suppress ECM depositions
• Podocytes	Anti-apoptosis Enhanced growth
• Endothelium	Proliferation
▪ **Tubules**	Proliferation Anti-apoptosis Suppress EMT (Tubulogenesis)
▪ **Interstitium**	
•Endotheilial cells	Anti-inflammation Proliferation (Angiogenesis)
• Fibroblasts	ECM degradation Promote MET



Liu Y, Yang J KI 70:238-240, 2006





Clinical Use of HGF

1. Too short half-life (∽15 minutes); Limited production
2. Antibody formation in animal experiments
3. Significance of mitogenic effect?

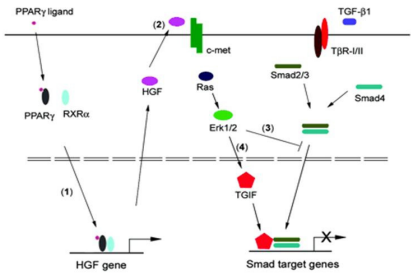
- ❖ Human clinical experience is limited to local use only
- ❖ Short term use to prevent or treat ARF
- ❖ Intramuscular HGF gene electrotransfer
- ❖ Ex vivo therapy

Peroxisome Proliferator-Activator Receptors-ɣ (PPAR-ɣ)

- Members of ligand-dependent transcription factors
- PPAR-α and β/δ: Lipid metabolism and control of cell proliferation and differentiation
- PPAR-γ: regulation of adipogenesis, immune response, insulin sensitivity, and glucose homeostasis

PPAR-ɣ Agonists

- Thiazolidinedione (TZD)
  - Rosiglitazone (Avandia)
  - Pioglitazone (Actos)
  - Troglitazone (Rezulin)
- PPAR-ɣ has renal anti-fibrotic action by enhancing HGF expression and suppressing TGF-β activation in renal fibroblasts and mesengial cells
- Remnant kidneys; Diabetic nephropathy (Type I and II); anti-GBM GN; Obstructive uropathy

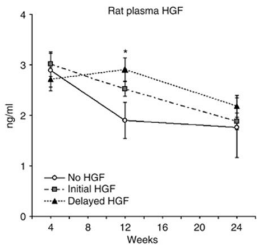


Yi et al. J Am Soc Nephrol 17:54, 2006

HGF Gene Therapy Attenuates Renal Allograft Scarring by Preventing the Pro-fibrotic Inflammatory-Induced Mechanism

Herrero-Fresneda et al. KI (2006) 70,265, Barcelona, Spain

- Lewis rats transplanted with Fischer kidneys
- Immunosuppression; cyclosporine (5 mg./kg./d), P.O.
- I.M. injection of plasmid DNA encoding HGF plus electroporation either 3 days before (Early) or 8/10 weeks (Delayed) after transplantation

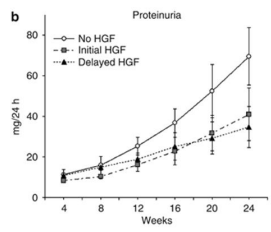


Herrero-Fresneda et al KI 70:265, 2006

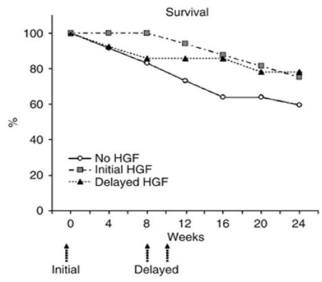
a

	ProtO (cv)	sCr (cv)	CrCl (cv)
No HGF	34.3±3.7	99±6	716±36
Initial HGF	21.7±3.1[a]	83±5[a]	808±38
Delayed HGF	20.2±2.2[a]	77±2[a]	821±28[a]
P	0.0019	0.0023	0.0500

b



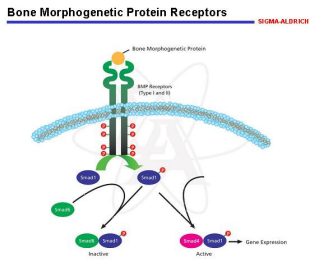
Herrero-Fresneda et al KI 70:265, 2006



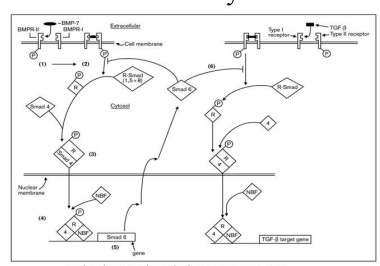
Herrero-Fresneda et al KI 70:265, 2006

Bone Morphogenic Protein-7 (BMP-7) (Osteogenic Protein-1)

- A polypeptide, one of the TGF-β superfamily; multifunctional cytokine
- Abundantly expressed in the adult kidney
- Production primarily from distal tubules and collective ducts
- Receptors (RI and RII) expressed primarily in distal tubules and collective ducts
- Counteracts against TGF- β
- Anti-fibrotic via multiple mechanisms
- ↑Bone and cartilage formation and Ca/P deposition
  ↓Bone resorption and peritrabecular fibrosis
  (Restore normal rate of bone formation)



BMP-7 and TGF-β Signaling Pathway



Lund et al. Curr Opin Nephrol Hypertens 11:31, 2002

BMP-7 and Renal Fibrosis

- **Glomeruli**: Preserves glomerular integrity

  Tubules:
  - Inhibits EMT/Enhance MET
  - Suppresses inflammatory chemokine (CMP-7) and cytokine release (IL-6 and TNF-2)
  - Less impact on apoptosis

  Mesengial and fibroblasts: Inhibit proliferation and production of ECM
- BMP-7 can prevent or reverse various forms of experimental kidney diseases (Remnant kidneys; Nephrotoxic nephritis; Diabetic nephropathy; Obstructive nephropathy; ATN; Transplant rejection)

Clinical Use of BMP-7

- FDA approved BMP-7 for adjunctive treatment for non-union in long-bone fractures
- Renal osteodystrophy
  Prevention of vascular calcification in uremia
  Osteoporosis
- Regression of CKD?
- Ex vivo therapy
- Use of USAG-1 antagonists?