What’s new in renal fibrosis?

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Causes of renal interstitial fibrosis

- Glomerulosclerosis
- Vascular intimal fibrosis
- Tubulointerstitial changes
- Glomerulosclerosis
Within the tubulointerstitial compartment

Accumulation of Myofibroblast is the culprit

Diverse origins of myofibroblasts in kidney fibrosis:

Lucas Falke et al., Nature Reviews Nephrology 2016
Novelties in traditional approach

Prevent accumulation and function of bad cells (myofibroblasts)

- Block inducers
- Block effectors

MAb (e.g. FG3019)
TKI (e.g. Nintedanib), Aptamer,
GLPG1690, Aptamer
Pirfenidone

TGF-β \(\rightarrow\) CTGF

PDGF

LPA

Autotaxin

IncRNAs (e.g. H19, “sponges miR-455” \(\Rightarrow\) CTGF↑)

Long noncoding RNAs in kidney and cardiovascular diseases

Novel approaches:

1. **Reverse the bad cells** (to their original state?)

2. **Eliminate the bad cells** and restore the stage for regeneration
Reverse the bad cells

A. BMP7 (Tampe et al., J Am Soc Nephrol. 2014)
   "TGFβ-antagonist"
   De-methylating RASAL1

B. Thrasos THR-V-123 (Sugomito et al., Nat Med 2012)
   BMPR activator
Reverse the bad cells

C. By low-dose hydralazine de-methylating RASAL1

(Tampe et al. EBioMedicine 2015)
Tubular epithelial cells

- G2/M arrest
  - Impaired proliferation
  - Altered secretome
- EMT
  - Impaired proliferation
  - Expression of transporters
  - Altered secretome
- Metabolic alterations
  - Lipotoxicity
  - Mitochondrial dysfunction
- Autophagy
  - Loss of TECs

/Apoptosis

Loss of functional parenchyma
Tubular atrophy
Inflammation
Preventing apoptosis (and AKI=>$CKD)$: p53-siRNA attenuates ischemic acute kidney injury in rats

Tubular epithelial cells (and endothelial cells) and G1/S arrest.

G2/M arrest leads to impaired proliferation and altered secretome.

EMT leads to impaired proliferation, decreased expression of transporters, altered secretome, FAO, lipotoxicity, mitochondrial dysfunction, and loss of TECs.

Metabolic alterations lead to lipotoxicity and mitochondrial dysfunction.

Autophagy leads to loss of TECs.

“Cellular Senescence”

Loss of functional parenchyma

Tubular atrophy

Inflammation
Cell cycle arrest at the G1/S or G2/M checkpoints
→ Senescent cells
Senescence in Cell Cycle Arrested Cells (Failure to resolve DNA damage) (Gire & Dolic, Cell Cycle 2015)
Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury

Yang L, Bonventre JV. Nat Med. 2010
Pushing cells through G2/M arrest by p53 inhibition inhibits CTGF expression and prevents fibrosis

Novel approaches:

1. **Reverse the bad cells** to their original state
   - BMP7/Thrasos THR-V-123 (ALK3-ligand)
   - De-methylating RASAL1 by low-dose hydralazine *(Tampe et al. EBioMedicine 2015)*

   • **Quark’s QPI-1002 (a p53 gene-targeting siRNA)**
     - Anti-apoptotic: (preventing AKI after major surgery!)
     - Overcoming G2M-arrest: (preventing DGF?)

2. **Eliminate the bad cells**
   - INK-ATTAC: a transgene for drug-dependent clearance of p16INK4a-positive senescent cells
   - FOXO4-DRI: a peptide for targeted apoptosis induction in senescent cells
What if reversal is *incomplete*?

- Persistence of dysfunctional cells
- Altered secretome (SASP)
  - Pro-inflammatory
  - Pro-fibrotic
- Frustration of regeneration
- Cancer risk?

**Alternatively: Could we afford to eliminate the bad cells?**
Acute Kidney Injury $\Rightarrow$ Massive exit from $G_0$

- Great Regenerative potential...

Ki-67 staining of AKI kidney
“Proliferation” and apoptosis in CKD (example: DN)

**Ki67**: Many non-\(G_0\) nuclei, mainly(!) in *atrophic* tubules

**Cl-Caspase3**: no apoptosis
FAN1 mutations cause karyomegalic interstitial nephritis, linking chronic kidney failure to defective DNA damage repair

γH2AX staining in human kidney transplant biopsies:

4 m post-transplantation, no evidence for injury

10 y post-transplantation, chronic damage

16 y post-transplantation, chronic damage
Novel approaches:

1. **Reverse the bad cells** to their original state (M-XT)
   - De-methylating RASAL1 by low-dose hydralazine (*Tampe et al. EBioMedicine* 2015)
   - BMP7/Thrasos THR-V-123 (ALK3-ligand)
   - Quark’s QPI-1002 (a p53 gene-targeting siRNA)
     - Anti-apoptotic: (preventing AKI after major surgery!)
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2. **Eliminate the bad cells**
   - INK-ATTAC: a transgene for drug-dependent clearance of p16INK4a-positive senescent cells
   - FOXO4-DRI: a peptide for targeted apoptosis induction in senescent cells
Clearance of p16^{\text{Ink4a}}-positive cells rescues kidney senescence in INK-ATTAC mice  


**Science: “2016 scientific breakthroughs of the year”**
Senescence leads to fibrosis

“SASP”: IL-1, IL-6, TGFβ, CTGF, ...

Modified from Sharfuddin, A. & Molitoris, B. Nat. Rev. Nephrol. 2011
If you do nothing

“SASP”: IL-1, IL-6, TGFβ, CTGF, ..
While killing senescent cells might halt fibrosis

“SASP”: IL-1, IL-6, TGFβ, CTGF, ..

Modified from Sharfuddin, A. & Molitoris, B.Nat. Rev. Nephrol. 2011
.. and enable regeneration
What’s new in renal fibrosis?

Out with the old! (or “out with Oates”)

On Scott’s doomed Antarctic expedition, Lawrence Oates sacrificed his life when his ill health began to compromise his companions’ chances of survival. Walking into a blizzard he said: “I am going outside and may be some time.” Scott said it was the “act of a brave man and an English gentleman.”

Still, the whole crew died...
Renal Pathologist will need to guide Senolytic Therapy

- Identify (developing better tools!)
- Validate
- Monitor

Timing is everything!

Early: Kill!

Too late: Don’t Kill!
What’s new in renal fibrosis”?

“To kill or not to kill, that is the question!

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