

# Accumulation of Maladaptive Tubular Epithelial Cells (TECs) is Ubiquitous in Chronic Kidney Diseases and Represents a Common Initiating Mechanism of Disease Progression

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## Disclosures for Presenting Author

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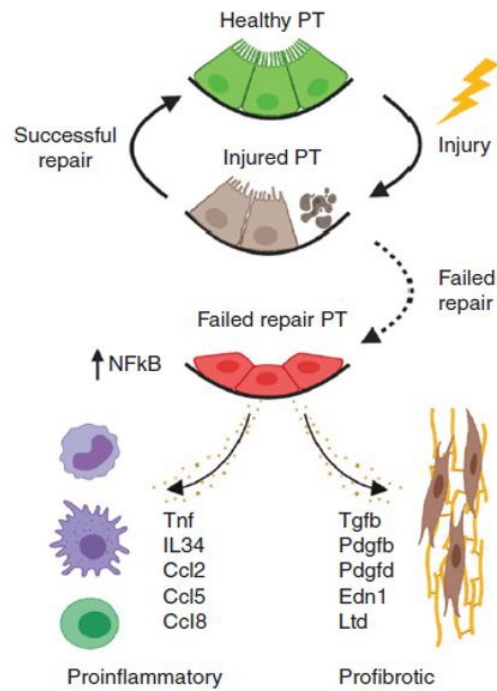


# Introduction – Maladaptive tubules and the NURTuRE dataset

Failed Repair Proximal Tubules (**FR-PT**) were first identified in mouse AKI models

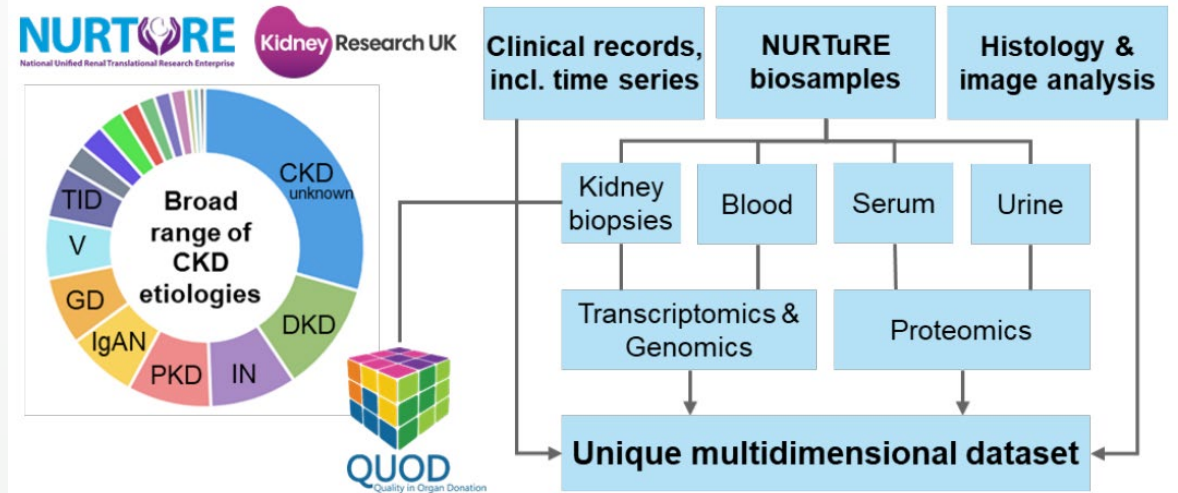
Derived from proximal tubules in response to ongoing injury

Key source of proinflammatory and profibrotic signals (Ccl2, Tnf, Tgfb, Edn1, etc.) in mouse AKI models



Regrow or Repair: An Update on Potential Regenerative Therapies for the Kidney; Little, MH, Humphreys, B; JASN 33(1):p 15-32

The **NURTuRE** consortium biobank comprises patient samples from a broad range of diagnoses and kidney functional states with rich clinical data from over **3,500** subjects

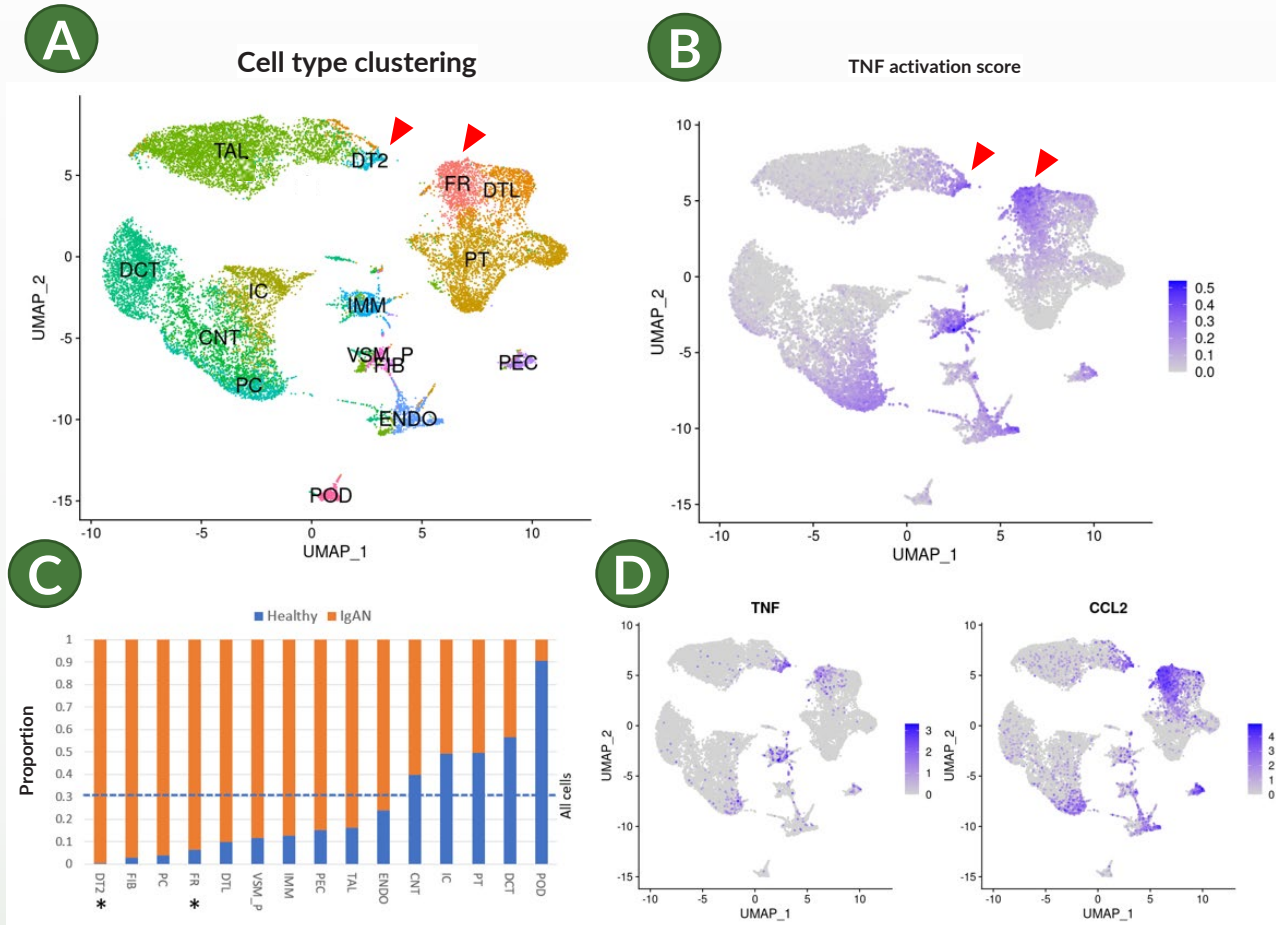


## Project Aims:

Explore the significance of maladaptive tubules and their association with disease progression in the NURTuRE CKD cohort, integrating clinical, histological, transcriptomic and biofluids proteomic data to gain insights into disease biology

# Identification of human maladaptive tubule gene signatures

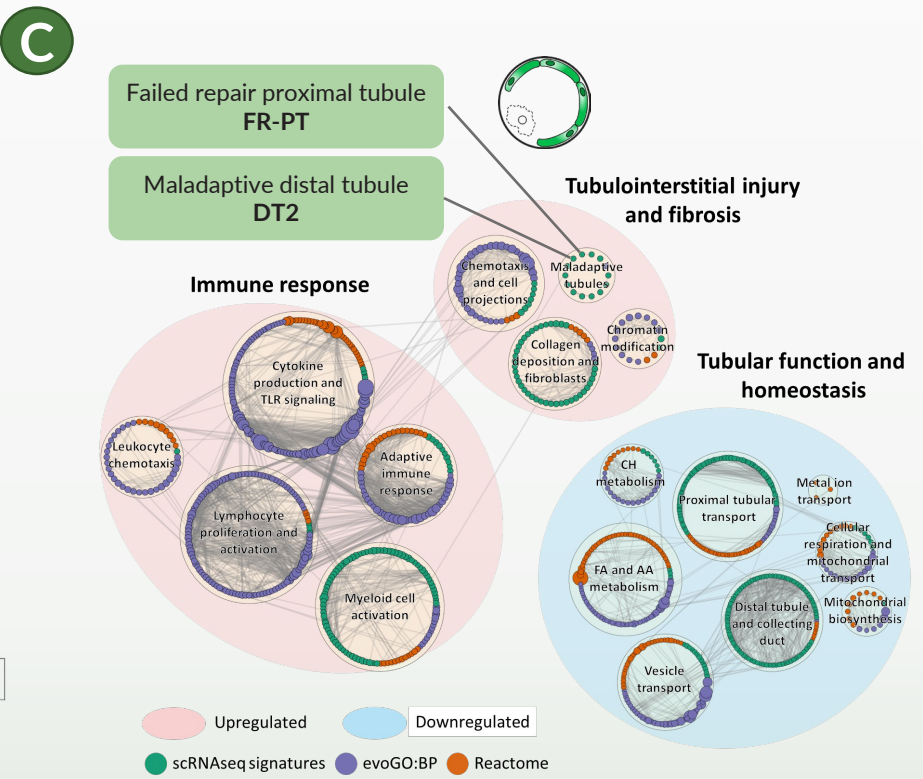
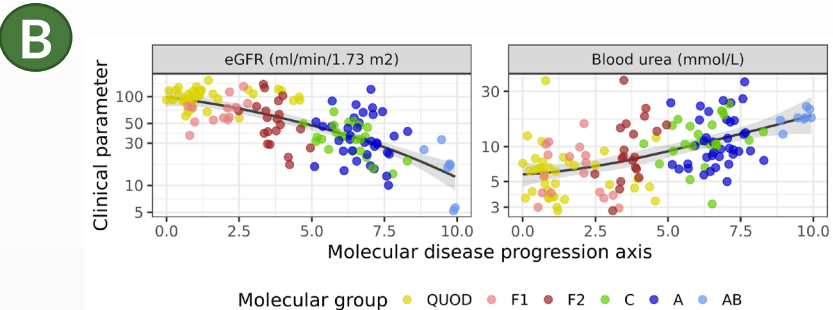
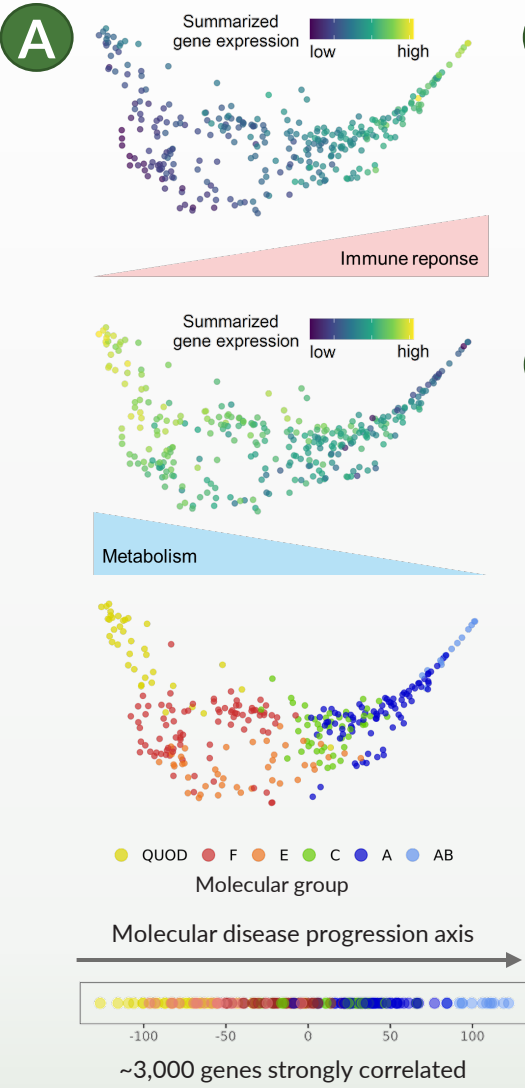
## Identification of TNF-responsive proximal (FR-PT) and distal (DT2) maladaptive TECs in an IgAN scRNA-seq dataset



- A. Two clusters representing proximal (FR) and distal (DT2) tubule maladaptive cells were identified in an IgAN scRNA-seq dataset (GSE171314)
- B. Both cell clusters showed increased scores for expression of a TNF activation gene signature
- C. Both cell clusters were significantly enriched in cells from IgAN patients compared to healthy controls
- D. The FR and DT2 cells showed increased expression of *TNF* and *CCL2* as well as other proinflammatory and profibrotic genes

*These cell types were also identified in a MN scRNA-seq dataset (GSE171458)*

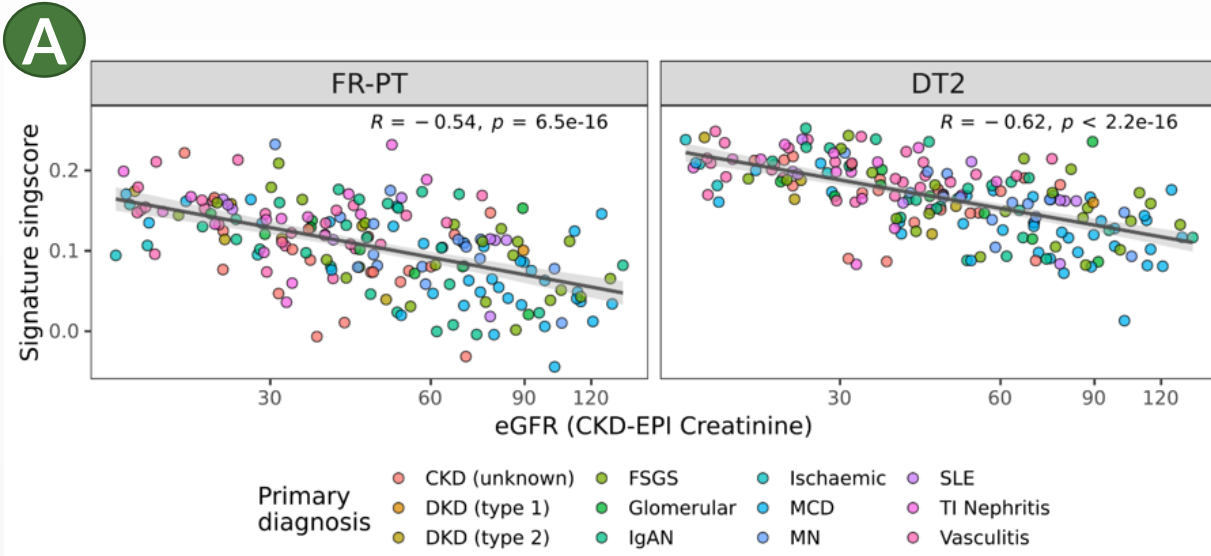
# Maladaptive tubules are a dominant feature correlated with disease progression in CKDs



- A. Unbiased analysis of biopsy gene expression identified 5 molecular subgroups across a wide range of CKDs
- B. Pseudotemporal ordering of samples reflected a molecular disease progression axis that was correlated with clinical features
- C. Functional enrichment analysis and mechanistic interpretation of molecular disease progression was performed for gene ontologies, pathways and over 600 cell signatures

*Maladaptive tubule signatures were found to be among the most highly associated with disease progression in the NURTuRE cohort*

# FR and DT2 signature scores predict renal event-free survival in CKDs

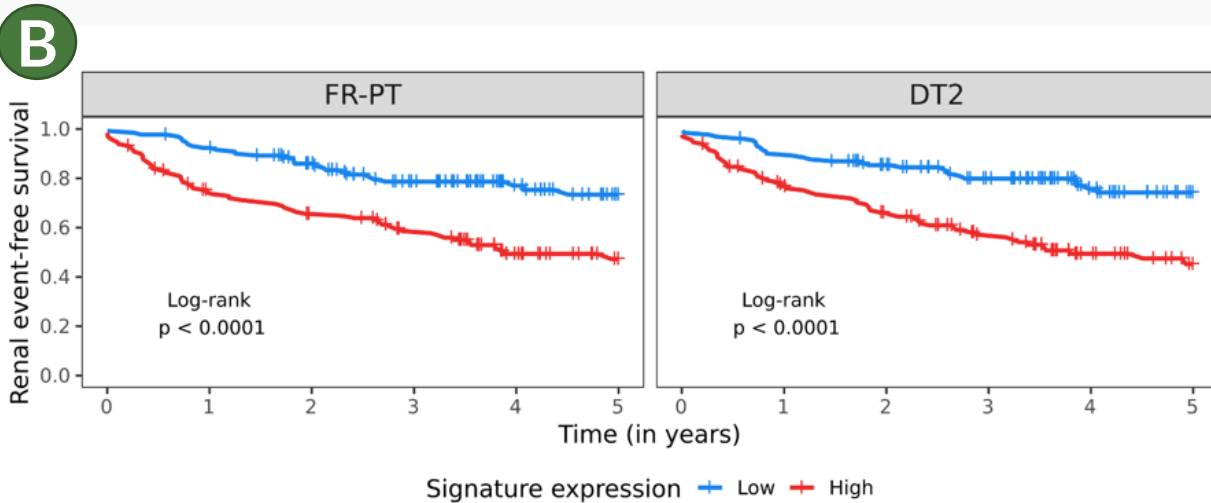


## Maladaptive TEC signature scores are inversely correlated with eGFR in the NURTuRE CKD Cohort

- Pearson correlation of log-transformed eGFR and FR-PT and DT2 signature in 190 kidney biopsy transcriptomes

## Maladaptive TEC signature scores predict shorter renal event-free survival

- Kaplan-Meier survival analysis with log-rank test comparing low and high expression of FR-PT and DT2 signatures in 310 NURTuRE kidney biopsy transcriptome from 304 patients over 5 years ( $p < 0.0001$ )
- Renal events were defined as 40% decrease in eGFR or incident ESRD
- Signatures were grouped in low and high representing 50% quantiles



# Summary and future plans

## Key observations

- Human gene signatures for two maladaptive tubule subtypes were identified in human CKD scRNA-Seq datasets
- Based on unbiased analysis, maladaptive tubule signatures were found to be among the most highly associated with disease stage in the NURTuRE cohort
- A high maladaptive tubule gene signature score at time of biopsy is significantly associated with shorter renal event-free survival in the NURTuRE cohort
- The emergence of maladaptive tubules is associated with disease progression across multiple CKDs as well as Chronic Allograft Nephropathy (data not shown)

## Future steps

- Identify and test which targets enriched in maladaptive tubules are drivers of disease
- Conduct urine and serum proteomic analysis on matched biofluid samples from the NURTuRE cohort to identify biomarkers of maladaptive tubules

## Goals

- **To assess role of maladaptive tubules in CKD progression and evaluate druggability across multiple etiologies of CKD**
- **To validate non-invasive surrogate biomarkers to identify and potentially stratify patients based on maladaptive tubule signatures**

# Thank You!

To all members of the  
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