Healthcare Innovations
How practice has changed

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MALADPTIVE REPAIR IN CHRONIC KIDNEY DISEASE (CKD)

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Introduction

- CKD is one of the most common chronic diseases in Australia.
- It is characterised by the repair response to injury of a key kidney cell population, the proximal tubular epithelial cell (PTEC).
- In response to injury, PTEC can (1) undergo adaptive/healthy repair, promoting regeneration and restore kidney function; or (2) initiate cellular senescence, a maladaptive process preventing healthy tubular regeneration and function [Fig 1].
- **This study aims to understand the roles of maladaptive repair in CKD and identify novel biomarkers for early diagnosis of kidney diseases.**

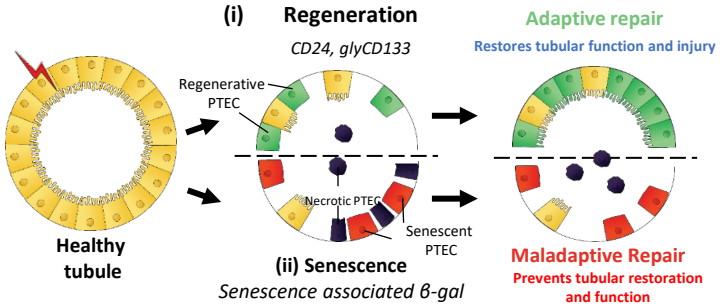

Fig 1: Healthy kidney tubule when subjected to damage can (i) give rise to new PTEC, called regenerative PTEC that restore the tubular damage via "Adaptive repair"; or (ii) lead to senescence, a form of permanent cell cycle arrest, that restricts tubular restoration via a process called "maladaptive" repair.

Methodology

Biopsy/Urine from patients | Single cell suspension | Flow cytometric identification, enumeration and phenotyping | Analyses using FlowJo -*Absolute cell number* -*Median Fluorescent Intensity (MFI)*

Fig 2: Live, single cell suspension from biopsy and urine of CKD patients are phenotyped using flow cytometry.

Results

1. PTEC loss in biopsy tissue is significantly associated with reduced kidney function and increased fibrosis

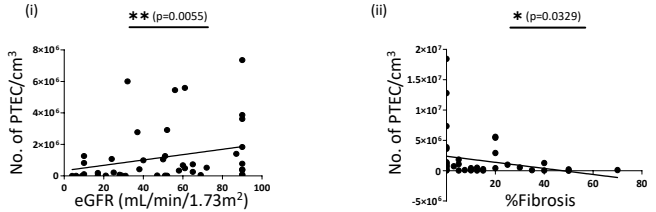

Fig 3: (i) Reduced kidney function and (ii) higher degree of fibrosis are associated with lower PTEC numbers in kidney biopsies. (Spearman's correlation, *p value= 0.0329 and **p value= 0.0055)

2. Urinary PTEC numbers are significantly associated with loss of kidney function and increased fibrosis

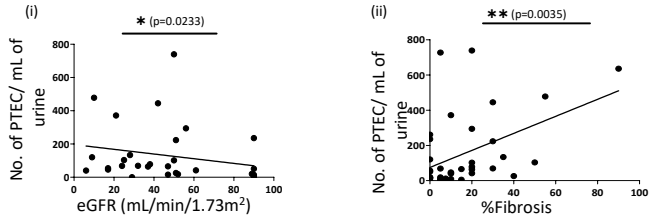

Fig 4: (i) Reduced kidney function and (ii) higher degree of fibrosis are associated with increased PTEC numbers in urine. (Spearman's correlation, *p value= 0.0233 and **p value= 0.0035)

3. Urinary PTEC express significantly reduced CD24 (regeneration) and elevated SA-β-gal (senescence) in CKD patients

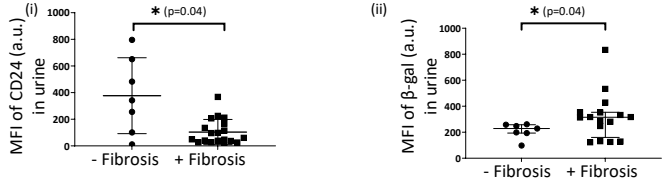

Fig 5: (i) Expression of regeneration marker CD24 is diminished and (ii) expression of senescence marker Spider β-galactosidase is upregulated in urinary PTEC. (Unpaired parametric t-test with Welch's correction, *p value= 0.04)

Summary and Conclusion

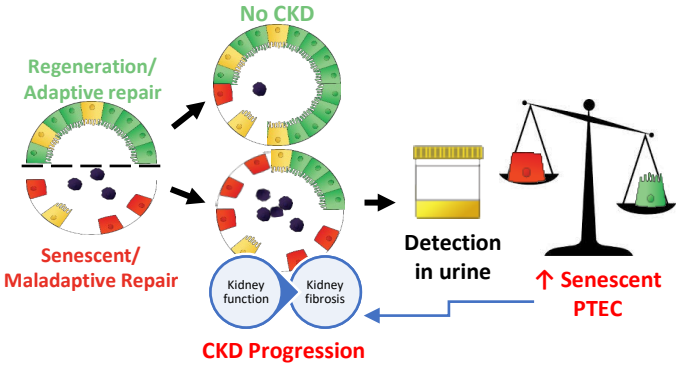

Fig 6: PTEC can undergo regenerative/adaptive repair or senescent/maladaptive repair post damage. We hypothesise that presence of a more senescent state will progress to CKD. Our data indicate a significant association of senescent urinary PTEC to kidney fibrosis, a hallmark of CKD.

Future Directions

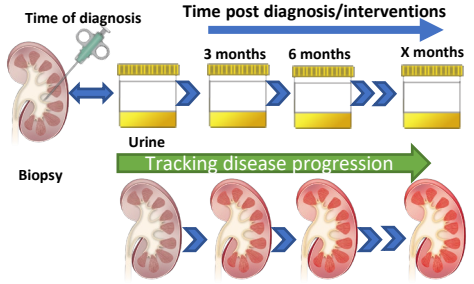

Fig 7: Develop a routine, "non-invasive" flow- cytometry based approach that complements the "gold-standard" biopsy method to predict CKD prognosis and disease progression, particularly after an intervention post first diagnosis.

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