Selected Renal Cells Self-organize to Form Neo-nephrons and Attenuate Kidney Disease

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1. Introduction/Background

- Selected renal cells (SRC), a renal epithelial cell-enriched platform, are being advanced in a Phase 3 Global Registrational Trial for treatment of chronic kidney disease (CKD)\textsuperscript{1}.
- In CKD models, administration of SRC is associated with improved survival, preservation of renal microarchitecture, and reduced renal dysfunction\textsuperscript{2,3}.
- Preliminary data from a subset of diabetic kidney disease patients suggest randomization to SRC is associated with improvement in glomerular filtration rate\textsuperscript{1}.

2. Goal

To test the hypothesis that SRC organoids self-assemble into nephrons, and implantation of SRC into the diseased kidney induces repair and ameliorates organ dysfunction.

3. Methods

- Cells from rat renal cortex are expanded and subjected to buoyancy separation. Two bands, differentially expressing\textsuperscript{3} viz., nphs1, kdr, hes1, epo, pecam1, cdh1 and cubn, are selected and combined to produce rat SRC.
- Differentially expressed genes on rat SRC\textsuperscript{3} viz., nphs1, kdr, hes1, epo, pecam1, cdh1 and cubn, were sequenced into knowledgebases and queried for renal localization of their gene products and signaling interactome, and function.
- Rat SRC was placed in culture to evaluate formation of organoids and tubules and administered into the 5/6 nephrectomized rat kidney. Serum creatinine (Scr) was evaluated over 6 weeks following randomization and kidneys were examined on day five or month six following intervention with SRC.

Figure 1: Rat SRC Differentially Expresses Genes

Table 1: SRC Genes Participate in Kidney Development

<table>
<thead>
<tr>
<th>Biological Processes (BP)</th>
<th>SRC Gene Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>regulation of kidney development</td>
<td>epithelial cell differentiation</td>
</tr>
<tr>
<td>kidney epithelium development</td>
<td>kidney vasculature development</td>
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<tr>
<td>nephron development</td>
<td>glomerulus development</td>
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<tr>
<td>glomerulus vasculature development</td>
<td>renal filtration cell differentiation</td>
</tr>
<tr>
<td>glomerulus development</td>
<td>epithelial cell differentiation</td>
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</tbody>
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3. Results

- The SRC gene interactome is compartmentalized within the tubules and/or glomeruli (podocyte).
- SRC gene products (proteins) are compartmentalized within the tubules and/or glomeruli.
- SRC genes participate in kidney development.
- SRC cultures form organoids which self-assemble into tubules in the presence of a scaffold.
- In a CKD model, randomization to SRC is associated with preservation of renal function and tissue microarchitecture.

4. Discussion

- Activity of, and products of, differentially expressed SRC genes are compartmentalized within tubules and glomeruli (podocytes); these genes participate in (re)building the kidneys.
- Intervention with SRC in a model of CKD is associated with neo-nephrogenesis, mitigation of renal dysfunction and preservation of renal microarchitecture.

5. Conclusions

The nephrogenic potential of SRC may underlie its renal reparative and restorative effects in CKD.

References

1. Stavas et al. Kid Reports 2022; 7:1610-1629

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