The CD47/TSP1 axis in acute and chronic kidney injury

Natasha Rogers MD, PhD
Postdoctoral fellow
Vascular Medicine Institute and Starzl Transplant Institute
University of Pittsburgh
Thrombospondin-1 (TSP1)

- Trimeric structure
- EM rotary shadowing view
- Monomer

Diagram showing the structure of TSP1, including domains such as Coll, TSR, EGF, and Ca repeats.
TSP1 is only known soluble ligand and activator of CD47

Heterotrimeric G proteins
In vascular cells activated CD47 is a redundant and global inhibitor of NO.
CD47/TSP1 in acute kidney injury

- Model of renal IRI
  - bilateral clamping renal pedicles
    22mins duration,
  - body temp 37°C,
  - reperfusion assessed at 24h

- absent CD47 is protective in renal ischemia reperfusion injury

* \( p = 0.0018 \)
Absent CD47 reduces histologic injury in IRI

WT - Bilat IRI 24h reperfusion

CD47KO - Bilat IRI 24h reperfusion

* $p<0.001$
TSP1 is increased in renal IRI

Red = TSP1 expression
Yellow = Caspase-3 expression

Thakar et al JCI 2005
Absent CD47 reduces cell death and TLR activation
Absent CD47 reduces ROS production in IRI

\[
\begin{align*}
\text{O}_2^- & \quad \text{superoxide} & \quad \text{NO} & \quad \text{ONOO}^- & \quad \text{peroxynitrite} & \quad \text{Protein nitration} \\
\text{(3-nitrotyrosine)}
\end{align*}
\]

Amplex red assay
- Assess H2O2 production

\[
\begin{align*}
\text{WT, Sham (vehicle)} & \quad \text{WT, IRI (vehicle)} & \quad \text{CD47 null, Sham (vehicle)} & \quad \text{CD47 null, IRI (vehicle)}
\end{align*}
\]

Time (min)

45000
30000
15000
0

Relative density 3NT/beta actin

WT sham  CD47 null sham  WT IRI  CD47 null IRI
Ongoing research areas

• Role of CD47 in adaptive immunity
  – Dendritic cell function and allostimulatory capacity
  – ability of CD47 to regulate DC phagocytosis and promote subsequent allograft tolerance

• Effect of immunosuppressive agents and uraemic toxins on endothelial cell and renal mesangial cell expression of TSP1/CD47
  – potential relevance in pathogenesis of glomerulopathies (transplant related, vasculitis)
CD47/TSP1 and clinical disease

• Plasma TSP1 levels elevated in peripheral arterial disease
  – Smadja et al. *ATVB* 2011

• TSP1 is overexpressed in pulmonary arterial hypertension
CD47/TSP1 and kidney disease

What is known about TSP1 in patients with ESKD or CKD?

Nothing

Hypothesis

• TSP1 is elevated in patients with ESKD
• TSP1 levels are altered following haemodialysis and contribute to cardiovascular complications
• TSP1 levels rise as eGFR falls (correlation with stage of CKD)
Proposed pilot study

• Patients with ESKD (stable, outpatient treatment)
  – venous blood samples taken pre- and post-HD
  – TSP1 levels followed over 1 month
  – correlate with subsequent clinical outcomes

• Patients with stable CKD (non-deteriorating renal function, not on RRT)
  – correlate TSP1 level with serum creatinine
Acknowledgements

• Isenberg lab (VMI)
  Jeff Isenberg
  – Enrico Novelli
  – Molly Yao

• Thomson lab (STI)
  Angus Thomson

Pagano lab (VMI)
  Patrick Pagano
  - Gabor Csanyi

Grant support: K22 CA128616 (JSI)
  R01 HL-108954 (JSI)
  AHA 11BGIA7210001 (JSI)
  1P01HL103455-01A1 (JSI)
  Australian NHMRC Fellowship (NMR)