Parenchymal CD47 Promotes Renal IRI via Multiple Mechanisms

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Thrombospondin-1 (TSP1) and CD47

- Widely expressed
- TSP1 only known ligand
- Secreted by many cells
- Upregulated by injury/stress
- Inhibits cell survival
- Promotes cell death pathways
NO-mediates autocrine and paracrine responses in vascular and inflammatory cells

- Anti-inflammatory
- Inhibits platelet aggregation
- Angiogenesis, permeability
- Vasorelaxation

TSP1 interaction with CD47 redundantly inhibits VEGFR2 and NO/cGMP signaling

Adapted from Isenberg et al, *Nature Reviews Cancer*, 2009
Renal Ischemia Reperfusion

- an important cause of acute organ injury
- dual mechanism of injury
  - Sham kidney: ischemia: hypoxic cell death
  - Ischemic kidney: reperfusion: ROS & cytokine production, leukocyte infiltration
- IRI in transplantation:
  - clamp: promotes delayed graft function & poorer graft outcomes (Hetzel et al. 2002)
  - decreases: increases graft immunogenicity & rejection (Halloran et al. 1997)
- Nothing known about TSP1-CD47 in renal IRI
TSP1 and CD47 are increased in renal IRI

Rogers et al, J Amer Society Nephrology, 2012
Renal tubular epithelial cells express CD47 and upregulate TSP1 in response to hypoxia

RTEC

CD47

DAPI

Isotype control

FiO₂ 1% for 30 min
Cells analyzed after 24h reoxygenation

Mean ± SD
n=4

Rogers et al, J Amer Society Nephrology, 2012
CD47 promotes death from renal IRI

Absence of activated CD47 confers survival to fatal renal IRI

Activated CD47 impairs blood flow following IRI

Rogers et al, J Amer Society Nephrology, 2012
Activated CD47 promotes histologic and functional damage following renal IRI

WT IRI 24h reperfusion

CD47^{-/-} IRI 24h reperfusion

magnification x400

Absent CD47 reduces inflammation in renal IRI

WT IRI 24h reperfusion  CD47^{-/-} IRI 24h reperfusion

Rogers et al, J Amer Society Nephrology, 2012
CD47 promotes IRI-associated cell death and apoptosis

WT IRI 24h reperfusion    CD47<sup>−/−</sup> IRI 24h reperfusion

Rogers et al, J Amer Society Nephrology, 2012
CD47 stimulates reactive oxygen species (ROS) production post renal reperfusion.
CD47 upregulates iNOS to promote renal IRI-mediated ROS production.

[Graph showing fold change in iNOS mRNA levels across different conditions: WT Sham, CD47−/− Sham, WT IRI 24h, CD47−/− IRI 24h, with a significant increase in the WT IRI 24h group marked by an asterisk.]

[Graph showing ROS production over time for different groups: WT-SHAM (vehicle), WT-IR (vehicle), CD47 null-IR (vehicle), CD47 null-SHAM (vehicle).]

Rogers et al, unpublished
CD47 blockade inhibits IRI mediated iNOS induction *in vitro* and *in vivo*

Rogers et al, unpublished
Parenchymal cell CD47 promotes renal IRI

Rogers et al, J Amer Society Nephrology, 2012
Blockade of CD47 abrogates renal IRI

CD47 mAb given 90 mins prior to renal IRI
- renal function and histology assessed at 24 h reperfusion

Rogers et al, J Amer Society Nephrology, 2012
Blocking CD47 activation post I/R injury is tissue protective

CD47 blocking Ab given 2 hours post reperfusion

Maxhimer et al, Plastic and Reconstructive Surgery, 2009
Renal IRI activates parenchymal CD47 to induce iNOS mediated ROS and tissue injury

Health

Renal TEC “parenchymal” CD47 is expressed but not activated

Renal IRI

Renal IRI upregulates TSP1

TSP1 binds cell surface CD47 on renal TEC

Activated CD47 induces iNOS-based superoxide production

Protein modifications
RTEC apoptosis
Renal failure
Thank you

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Absence of activated CD47 results in accelerated restoration of renal function post-IRI

Rogers et al, unpublished
Parenchymal CD47 is a global cell regulator

**Thrombospondin-1**

**CD47**

- **NO/cGMP signaling**
  - **Physiological**
    - angiogenesis
    - tissue perfusion
    - blood pressure
    - hemostasis
    - mitochondria
  - **Pathological (elevated TSP1)**
    - acute ischemia
    - ischemia/reperfusion
    - chronic diseases of aging
  - **Other signaling pathways**
    - adaptive responses to stress
    - innate immunity
    - adaptive immunity
    - cell motility
    - cell survival
    - radioresistance

**Other TSP1 receptors**