Disclosures

• None
Dendritic cells mediate T cell activation in the kidney lymph node during hypertension

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Dendritic cells (DCs) and hypertension

- Dendritic cells are potent antigen presenting cells that mediate T cell activation
- Adoptive transfer of DCs from hypertensive mice increased susceptibility to hypertension
- Preventing interactions between antigen presenting cells and T cells attenuated hypertension
T lymphocytes and hypertension

• T cells are adaptive immune cells that infiltrate the kidney during hypertension

• Pharmacological or genetic inhibition of T cells:
  -- diminishes hypertension
  -- Preserves renal sodium excretion after a hypertensive stimulus

• Inflammatory cytokines produced by mononuclear cells that infiltrate the hypertensive kidney:
  -- Upregulate sodium transporter activity
  -- Promote sodium retention by the kidney

Hypothesis

Dendritic cells activate T cells in the kidney lymph node during hypertension
Hypertensive model – chronic angiotensin II infusion

- Weeks 0 1 2
- Implant Ang II pump 300 ng/kg/min
- Unilateral Nephrectomy
- Implant radiotelemeter
- Record Blood Pressure
- Weeks
- Tissue harvest
- C57BL/6
Kidney Lymph Node - Hypertension enhances CD44 expression on T cells

Control

Ang II

CD4 T cells

CD44-APC

CD3-PE

CD8 T cells

P = 0.009

P = 0.01
Model of dendritic cell deficiency (FLT3L-/- = “DC KO”)

• FMS-like tyrosine kinase 3 ligand (FLT3L) is a cytokine important in the development and steady state regulation of dendritic cells

• Widely used model of DC deficiency

• T cell compartment is undisturbed

DC KO mice have attenuated hypertension

MAP (mmHg)

WT
DC KO

Days of ANG II infusion

P = 0.04

n = 4-5/group
Kidney Lymph Node - DC deficiency blunts accumulation of CD44$^{\text{hi}}$ T cells during hypertension

CD4 T cells

CD44-APC

CD8 T cells

CD3-PE

WT

DC KO

P = 0.04

P = 0.08
Kidney - DC deficiency attenuates accumulation of CD44<sup>hi</sup> T cells in the hypertensive kidney

WT  DC KO

%CD44<sup>hi</sup> of CD4 T cells

%CD44<sup>hi</sup> of CD8 T cells

CD4 T cells

CD8 T cells

$P = 0.001$

$P = 0.05$
Kidney - DC deficiency attenuates accumulation of CD44$^{hi}$ Effector T cells in the hypertensive kidney.
Model of spontaneous dendritic cell activation

\( \text{CD11c-Cre A20}^{\text{flox/wt}} = \text{“DC ACT”} \)

- A20 is a ubiquitin-editing protein that prevents NF-κB-mediated DC maturation
- CD11c is a widely used Cre for dendritic cells
- Heterozygous deletion of A20 in DCs yields mice that:
  -- are phenotypically normal at baseline
  -- have enhanced T cell activation

DC ACT have augmented Ang II-induced hypertension

$P = 0.04$
Kidney Lymph Node - DC ACT have greater proportion CD44$^{\text{hi}}$ T cells during hypertension

CD4 T cells

CD8 T cells
Summary

• Dendritic cell deficiency attenuates hypertension and blunts T cell activation in the kidney and its draining lymph node during hypertension.

• Spontaneous dendritic cell activation augments blood pressure elevation and T cell activation in the kidney lymph node during hypertension.
• Dendritic cells make a key contribution to blood pressure elevation during renin-angiotensin system activation.

• Further analysis of activated T cells in the kidney and its draining lymph node should reveal mechanisms through which DCs exacerbate hypertension.

• Investigating proximal mechanisms of immune activation in hypertension should lead to novel immunomodulatory therapies to reduce blood pressure and target organ damage.
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