Deletion of Serum and Glucocorticoid-Regulated Kinase 1 (SGK1) in T cells Attenuates Hypertension and Renal/Vascular Dysfunction

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Pathophysiology of Hypertension
T helper Subsets

Virus/Intracellular Bacteria
Parasites
Extracellular Bacteria/Fungi
Virus/Intracellular Bacteria

Antigen Presenting Cell

Immune response

Initiation
IFNα/β IL-12
IL-4 + TGFβ

Amplification
Th1 Th2 Th9 Th17 CTL Tfh Treg
IFNγ TNFα IL-4 IL-9
IL-5 IL-13 IL-17

Exaggeration
Autoimmunity Asthma Allergy Autoimmunity Cytokine storm Tumor

Fibrosis

B cell costim IL-21

IL-10 TGFβ

IL17 is Required for the Maintenance of Ang II-induced Hypertension

Ang II: 490 ng/kg/min

(Madhur et al. *Hypertension* 2010)
Salt and Hypertension

- Numerous epidemiological, clinical, and experimental studies have demonstrated a link between dietary salt intake and hypertension.
**LETTER**

Sodium chloride drives autoimmune disease by the induction of pathogenic T\textsubscript{H}17 cells

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**LETTER**

Induction of pathogenic T\textsubscript{H}17 cells by inducible salt-sensing kinase SGK1

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Effect of Salt on T cells

Th0 → Th17 polarizing cytokines → Th17

SGK1 = serum and glucocorticoid-regulated kinase 1
Th17 polarizing cytokines: IL6, IL1β, IL23, TGFβ

IL17
Effect of Salt on T cells

SGK1 = serum and glucocorticoid-regulated kinase 1
Th17 polarizing cytokines: IL6, IL1β, IL23, TGFβ

Th0

Th17 polarizing cytokines

Th17

Th17 polarizing cytokines

Th17

IL17

IL17

Demonstrated as protective in a model of Experimental Autoimmune Encephalomyelitis
Hypothesis: The salt-sensing kinase SGK1 in T cells plays a role in the development of hypertension.

Structure of SGK1

(Zhao et al. Protein Science 2007)
Where would T cells see elevated salt concentrations?

Mouse Model of T cell SGK1 Deletion

Deletion of SGK1 in CD4+ and CD8+ T cells

Hypertensive Models Tested:
- Ang II
- DOCA-Salt
T cell SGK1 contributes to development of IL17A producing cells in the spleen
Tail cuff Blood Pressure Measurements:
Ang II: SGK1^{fl/fl} x tg^{CD4cre}
Telemetry Blood Pressure Measurements:
Ang II: SGK1^{fl/fl} x tg^{CD4cre}
Tail cuff Blood Pressure Measurements:

DOCA-salt: SGK1^{fl/fl} x tg^{CD4cre}

DOCA/salt model
T Cell SGK1 Modulates Vascular Inflammation (Ang II)
T Cell SGK1 Modulates Vascular Inflammation (Ang II)

SGK1^fl/fl^  SGK1^fl/fl^tgCD4cre

CD45^+ cells (10^3)/aorta

CD3^+ cells (10^3)/aorta

F4/80^+ cells (10^3)/aorta

Sham  Ang II
T cell SGK1 Modulates Vascular Inflammation (DOCA-salt)

Sham

DOCA-salt

CD45+ cells (10^3)/aorta

SGK1^fl/fl  SGK1^fl/fltg^CD4cre

CD3+ cells (10^3)/aorta

SGK1^fl/fl  SGK1^fl/fltg^CD4cre

F4/80+ cells (10^3)/aorta

SGK1^fl/fl  SGK1^fl/fltg^CD4cre
T Cell SGK1 Modulates Vascular Reactivity (Ang II)

Vascular Relaxation in Response to Acetylcholine

**SGK1^{fl/fl} Control**

**T cell SGK1 Deficient**
SGK1 Modulates Renal Inflammation

- SGK1<sup>fl/fl</sup>
  - Sham
- SGK1<sup>fl/fl</sup>
  - Ang II
- SGK1<sup>fl/fl</sup><sup>tg<sub>CD4cre</sub></sup>
  - Sham
- SGK1<sup>fl/fl</sup><sup>tg<sub>CD4cre</sub></sup>
  - Ang II

Flow cytometry plots showing changes in cell populations with different treatments.
T cell SGK1 Modulates Renal Inflammation (Ang II)

CD45+ cells (10³)/kidney

SGK1^fl/fl  SGK1^fl/tgCD4cre

CD3+ cells (10³)/kidney

SGK1^fl/fl  SGK1^fl/tgCD4cre

F4/80+ cells (10³)/kidney

SGK1^fl/fl  SGK1^fl/tgCD4cre

Sham

Ang II
T Cell SGK1 Contributes to Renal Injury (Ang II)
Sodium channel expression on CD3+ T Cells

- ENaC gamma
- Sodium/Chloride Cotransporter (NCC)
- Sodium/Calcium Exchanger 1 (NCX1)
- Sodium/Calcium Exchanger 2 (NCX2)
- Sodium/Hydrogen Exchanger 1 (NHE1)
- Sodium/Hydrogen Exchanger 6 (NHE6)
- Sodium/Potassium/Chloride Cotransporter 1 (NKCC1)
- Voltage-Gated Sodium Channel 5a (SCN5A)
Inhibition of NKCC1 prevents salt induced upregulation of SGK1 in CD4+ T cells

SGK1

Th17 polarizing cytokines: IL6, IL1β, IL23, TGFβ

Cytokines: - + + + + +
Salt: - - + + + +
Amiloride (ENaC): - - - + + +
Spironolactone (MR): - - - - + +
Furosemide (NKCC1): - - - - - +
Bumetamide (NKCC1): - - - - - +

Fold Change

p=ns p=ns
Working Model

Ang II, DOCA-salt

↑↑ SGK1

Th17

NKCC1

Na+

→ Renal/Vascular Dysfunction

→ Hypertension

Preserved Renal/Vascular Function
Clinical Implications

• Targeting T cell SGK1 may be a novel therapeutic strategy for the treatment of hypertension and its associated end-organ dysfunction.
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