Salt Activates Immune Cells to Promote Hypertension

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No Conflict of Interest to Disclose
Mechanism of T cell activation by isoketal formation

Dendritic cell

Hypertensive stimuli

ROS

Isoketals

Modified Proteins

T cell


$^{23}$Na magnetic resonance imaging of tissue sodium in healthy and hypertensive humans

Koop et al. Hypertension 2013, 61:635-640
High salt induces superoxide production in DCs and this is NADPH oxidase dependent.

Salt (mM) gp91dstat
- 150
+ 190

High salt induces superoxide production in DCs and this is NADPH oxidase dependent. The graph shows the percentage of normal salt with gp91ds-tat under normal salt (NS) and high salt (HS) conditions. The data points indicate a significant difference with p<0.05 and p<0.001.
High salt increases isoketal adducts in dendritic cells

% of Isoketal+ cells

Dendritic Cells

D11 (Isoketals)

NS  Man  HS
Mechanism of T cell activation by isoketal formation

Increased salt

ROS

Isoketals

Modified Proteins

Dendritic cell

CD86

CD28

T cell
High salt increases CD86 expression in dendritic cells

- NS
- Man
- HS

% of CD86+ cells

Dendritic Cells

CD86

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High salt treated DCs drive T cell proliferation

- DCs
- High salt/control media
- Co-culture with CFSE loaded T cells
  To determine T cell proliferation
High salt treated DCs drive T cell proliferation

CD4

CD8

DCs: NS  Man  HS

CFSE

Proliferated CD4^+ T cells

Proliferated CD8^+ T cells

DCs: NS  Man  HS

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Effect of elevated interstitial sodium on DC activation

Monocytes

Elevated interstitial NaCl

ROS/isoketal-activated DCs

T cell proliferation

Myeloid-derived DCs
Potential Role of SGK1 in DC NADPH oxidase activation

**Known Actions**
- Stabilization of eNAC in collecting duct (via NEDD4-2 phosphorylation)
- Activation of IL-17A production by T cells

**Hypothesized Action**
- Modulation of NADPH oxidase expression (via NEDD4-2?)
High salt increases all NOX2 subunits and this is SGK1-dependent.

SGK 1-Inhibitor: -  -  -  +  +
NEDD4-2 Inhibitor: -  -  -  +  +

SGK inhibitor
NEDD4-2 inhibitor

* ** ****
SGK1 mediates high salt-induced production of isoketals in dendritic cells

D11 (Isoketals) + SGK1 Inhibitor

% of D11+ cells

-NS  HS  HS + SGK1 Inhibitor

Graph showing the percentage of D11+ cells under different conditions.
Effect of elevated interstitial sodium on DC activation

Monocytes

Elevated interstitial NaCl

ROS/isoketal-activated DCs

NAPDH Oxidase

SGK-1

T cell proliferation

Myeloid-derived DCs