Presenter Disclosure Information

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Cytokine-Angiotensin II Interplay in Cyclophilin D-Mediated Vascular Oxidative Stress and Hypertension

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No relevant financial relationship exists
Cytokine-Angiotensin II Interplay in Cyclophilin D-Mediated Vascular Oxidative Stress and Hypertension

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Clinical data show that **26% of adult population has hypertension**. Despite treatment with multiple drugs, **37% of hypertensive patients remain hypertensive**, likely due to the mechanisms contributing to blood pressure elevation that are not affected by current treatments.

**Inflammation** is commonly associated with hypertension and contributes to pathogenesis of this disease. TNFα and IL-17 are increased in hypertensive subjects by 4-fold and TNFα is an independent risk factor for hypertension.

**We propose that angiotensin II and cytokines co-operatively induce mitochondrial ROS production leading to vascular impairment and hypertension, and that mitochondria-targeted therapy will decrease mitochondrial oxidative stress and reduce hypertension.**
Inflammation and mitochondrial oxidative stress in hypertension

Angiotensin II, Stress, High Salt → Brain → Circumventricular organs (CVOs) → Sympathetic Activity → Blood Vessels → Kidney → T cell activation

Cytokines (IL-17; TNF-α) → Pro-oxidant milieu


Angiotensin II and cytokines co-operatively induce hypertension

A: Blood pressure

B: MitoSOX HPLC

C: Blood pressure

AngII → IL-17A → TNFα → Etanercept

O₂ → SOD2

Vascular Oxidative Stress

Hypertension

WT TgSOD2
Angiotensin II and cytokines co-operatively induce mitochondrial $\text{O}_2^{-}$ and endothelial oxidative stress.
SOD2 overexpression inhibits cytokine-induced aortic oxidative stress and prevents NO inactivation

We have previously reported that inhibition of cyclophilin D (CypD) in isolated mitochondria reduced mitochondrial O$_2^•$.

We have tested potential role of mitochondrial CypD in vascular responses to AngII, TNFα and IL17A.
CypD depletion prevents cytokine-induced impairment of vasodilatation

CypD depletion preserve aortic vasodilatation (A) and attenuates production of mitochondrial $O_2^{•−}$ (B) in vessels treated for 24 hours with combination of AngII, TNFα and IL17A.
Mitochondrial O$_2^*$ • Cyclophilin D

HYPOTHESIS

Angiotensin II → Inflammation

IL17A  TNFα

Mitochondria

↑ Cyclophilin D

mPTP

↑ Mitochondrial O$_2^*$

SOD2

Vascular Oxidative Stress

Hypertension

CypD Blocker
Angiotensin II and cytokines co-operatively induce complex I S-glutathionylation

Human aortic endothelial cells (HAECs) were treated 24 hours prior analysis.
Angiotensin II and cytokines co-operatively induce CypD-dependent mitochondrial $O_2^•$.
Mitochondrial antioxidants and CypD inhibition prevent cytokine-induced impairment of vasodilatation

Effects of SOD2, mitochondria-targeted catalase (mCAT) and CypD inhibitor Sanglifehrin A (1 µM) on vasodilatation of aortic vessels treated with AngII (10 nM), IL-17A (10 ng/ml) and TNFα (1 ng/ml) for 24 hours.
We propose that mitochondrial H$_2$O$_2$ activates CypD by S-glutathionylation and this induces overproduction of mitochondrial O$_2^•$ in the electron transport chain.
Mitochondria targeted catalase inhibits AngII-induced hypertension (A), CypD S-glutathionylation (B) and mitochondrial $O_2^\cdot$ (C) in mCAT mice

These data implicate mitochondrial $H_2O_2$ in CypD activation by S-glutathionylation which induces overproduction of mitochondrial $O_2^\cdot$ in the electron transport chain.
Targeting Cyclophilin D in Hypertension with CypD Blocker Sanglifehrin A

Treatment with CypD inhibitor Sanglifehrin A (i.p. 10 mg/kg/day) after onset of angiotensin II-induced hypertension improves vasodilatation and reduces blood pressure.
CONCLUSION

Angiotensin II  \[ \rightarrow \] Inflammation
\[ \rightarrow \] IL17A  TNFα

\[ \rightarrow \] mCAT  \[ \uparrow \] Cyclophilin D  \[ \downarrow \] Sanglifehrin A

Mitochondria  \[ \uparrow \] Complex I-SG

\[ \rightarrow \] Mitochondrial \[ \uparrow \] O₂⁻

\[ \rightarrow \] SOD2  \[ \downarrow \] mitoTEMPO

\[ \rightarrow \] Vascular Oxidative Stress

\[ \rightarrow \] Hypertension
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Thank you!
Question?