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FULLY VIRTUAL MEETING
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A mitochondrial cardiolipin targeting peptide ameliorates acute kidney oxidative damage

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Objectives: Mitochondria is a major organelle of adenosine triphosphate production and O2 consumption. Also, kidney is mitochondria abundant organ. In this respect, many mitochondria-targeting agents were developed, although there is no single agent approved in clinical practice. We investigate renoprotective effect of newly invented mitochondrial cardiolipin targeting peptide, the SNU-RD, in hypoxic condition.

Methods: Based on our experience that dimer formation by bisulfate bond of cell penetrating peptide accelerate cell permeability, we synthesized 15 candidate tetra-peptides which target inner mitochondrial membrane specific phospholipid, the cardiolipin. After cell viability, distribution and mitochondrial functional test, we selected best candidate and tentatively named as SNU-RD.
As hypoxic damage, bilateral ischemia-reperfusion injury (IRI) and primary cultured human proximal tubular epithelial cells (hPTECs) with H_2O_2 were chosen. Wild-type mice were divided into four groups: sham, IRI, IRI with low dose or high dose SNU-RD. After SNU-RD treatment with various concentration (10nM, 100nM, 1000nM), high dose H_2O_2 stress was done. Mitochondrial function was tested and mitochondrial oxygen consumption rate (OCR) was measured.

Results: In IRI, serum BUN and creatinine were significantly decreased without SNU-RD dose dependency. Pathologic findings (NGAL and cytochrome C expression) were improved. Also, mitochondrial anti-oxidative enzyme (NQO-1, SOD-1), ATP6 and IL-10 mRNAs were over-expressed after SNU-RD treatment.
Cell viability was increased and both early and late apoptosis were decreased dose-dependently. IL-1ß, IL-18, p16 and p21 mRNA were dramatically down-regulated. When traced by rhodamine, SNU-RD was intensively distributed to mitochondria then cytoplasm. In JC-1 assay, ratio of healthy mitochondria was increased with SNU-RD. Basal and maximal OCR were most recovered from SNU-RD 10nM.

Conclusions: Mitochondrial cardiolipin targeting peptide, SNU-RD can be a treatment choice of acute kidney injury by restoring mitochondrial function.

Figure 1. SNU-RD effect on mitochondria

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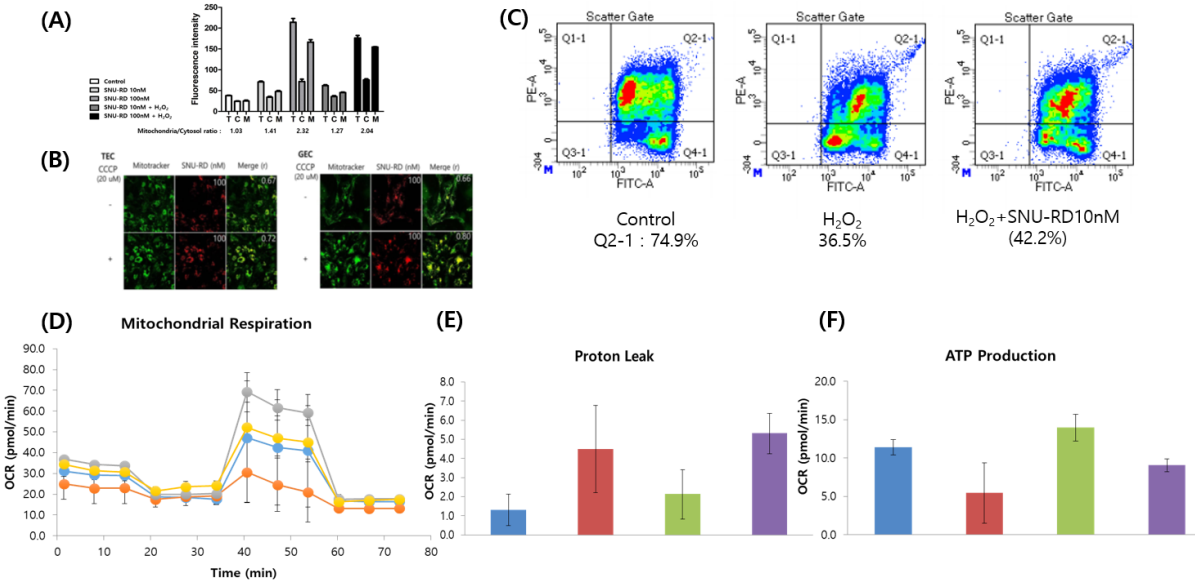

(A, B) Rhodamine tagged SNU-RD concentrated intensively to mitochondria, (C) In creased proportion of healthy mitochondria after SNU-RD treatment in JC-1 assay, (D-E) Treatment of SNU-RD 10nM effectively restore mitochondrial function from hypoxic injury