

## YIA-5

### **An innovative cell therapy using mitochondrial drug delivery system for doxorubicin cardiomyopathy**

*Abe J.(1), Yamada Y.(2), Takeda A.(1), Harashima H.(2)*

*Department of Pediatrics, Faculty of Medicine, Hokkaido University, Sapporo, Japan(1);*

*Laboratory for molecular design of pharmaceuticals, Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan(2)*

**Objectives:** Recent molecular researches have revealed that doxorubicin(DOX)-induced cardiomyopathy happens mainly due to poor mitochondrial biogenesis and exaggerated oxidative stress. Resveratrol has a potent of anti-oxidative ability mediated through multiple functions in mitochondria. Here, we investigated mitochondrial therapeutic effect in stem cell antigen-1 positive cardiac progenitor cells (Sca1-CPCs) after mitochondrial delivery of resveratrol.

**Methods:** A MITO-Porter system, mitochondrial drug delivery system, was used to deliver resveratrol into mitochondria in Sca1-CPCs. We encapsulated resveratrol in MITO-Porter, and observed the intracellular trafficking after transfection into Sca1-CPCs. We next investigated the therapeutic effects using DOX-exposure cells by measuring the mitochondrial enzymatic activity and membrane potential. Moreover, we validated the therapeutic effects using DOX-induced cardiomyopathy model mice to assess survival rate and tissue pathology. We conducted a randomized study wherein 24 mice received an intramyocardial injection of placebo-medium, naked Sca1-CPCs, or Sca1-CPCs with MITO-Porter before DOX treatment. The survival rate was assessed by Kaplan-Meier curve, and the assessment of the left ventricular shortening fraction (LVFS) was followed 4 weeks after injection. To investigate mitochondrial function in the host heart, the mitochondrial protein expression levels, and mitochondria related gene expression levels were measured 3 days after the DOX treatment.

**Results:** Intracellular observation showed that MITO-Porter could accumulate in mitochondria of Sca1-CPCs. We confirmed that mitochondrial delivery of resveratrol protected Sca1-CPCs from DOX-induced toxicity due to the preservation of the mitochondrial enzymatic activity and membrane potential in vitro. In Sca1-CPCs with MITO-Porter-injected mice at 4 weeks, the values of LVFS were kept within the normal range, and these were associated with the better survival rate (log-rank test;  $P < 0.05$ ). In the myocardium of Sca1-CPCs with MITO-Porter-injected mice, mitochondrial electron transport complex proteins were partially preserved ( $P < 0.05$ ), and the OXPHOS and mitochondrial biogenesis related genes expression levels were also higher than naked Sca1-CPCs ( $P < 0.05$ ).

**Conclusions:** The transplant of Sca1-CPCs with MITO-Porter loading resveratrol, which possess activated mitochondria and reduce oxidative stress, would have more efficiency rather than the conventional CPCs transplant in doxorubicin-induced cardiomyopathy.