DEPLETION OF THE CEREBLON GENE ENHANCES CARDIAC CONTRACTILITY, CA^{2+} TRANSIENT AND MITOCHONDRIAL ENERGY METABOLISM IN MICE.

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Background and Purpose: Cereblon (CRBN) is a interacting protein with large-conductance calcium-activated potassium channels. A mutation of CRBN causes a mild type of mental retardation in humans. While, recent study suggested its novel function as AMPK inhibitor via direct interaction with AMPK a1 subunit. Disruption of CRBN gene enhanced hepatic AMPK activity and prevents high-fat diet induced obesity and insulin resistance in mice. The aim of study is to figure out the effect of CRBN KO in heart and its mitochondrial function.

Method and Results: Eight weeks of Control ($CRBN^{+/+}$) and CRBN KO ($CRBN^{-/-}$) models were examined their body weight, heart rate and heart/body ratio. In vivo cardiac functions of animals were assessed by echocardiography. To evaluate mitochondrial function of those animals, cardiac mitochondria of $CRBN^{+/+}$ and $CRBN^{-/-}$ were isolated then examined their ATP contents and ATP production rate, ROS production rate, oxygen consumption rate (OCR) and membrane potential ($\Delta\Psi m$).

As results, the body weight, heart weight and heart/body ration were not significantly different between $CRBN^{+/+}$ and $CRBN^{-/-}$ mice. Echocardiography showed enhanced cardiac contractility in $CRBN^{-/-}$ mice based on increased ejection fraction (%) and fractional shortening (%).CRBN KO enhance single cardiac myocyte cell contraction with intracellular Ca^{2+} transient.

In their mitochondria, CRBN KO enhances Mitochondria Oxidative phosphorylation which lead to increase of basal ATP contents and substrate/ADP stimulated ATP production rate in $CRBN^{-/-}$ mice than $CRBN^{+/+}$. In addition, basal H2O2 level and rotenone induced ROS production rates were significantly lower in $CRBN^{-/-}$ mice than $CRBN^{+/+}$.

Conclusion: Our results suggested that CRBN is an important mitochondrial functional regulator which link cytosol to mitochondrial energy metabolism and Ca^{2+} signaling.

Keyword: Cereblon, cardiac contractility, mitochondrial energy metabolism. Ca^{2+} transient