

FRS-005**Aldosterone Excretion Rate is Associated with Abdominal Subcutaneous Fat Area and with Diastolic Blood Pressure in Patients with Essential Hypertension**

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Background: Most obesity patients are accompanied by hypertension. Recently, aldosterone releasing factor is reported to be produced from fat cells. However, it is unclear what parameters of obesity predict the aldosterone production. Therefore, we aimed to clarify what parameters of obesity are associated with the aldosterone production using urinary aldosterone (U-aldo) excretion level. **Methods and Results:** Patients with essential hypertension were enrolled (n=51, Male/Female=28/23, Age 52 ± 12 years). Abdominal visceral fat area (AVFA), and abdominal subcutaneous fat area (ASFA) were measured by computed tomography as well as body mass index (BMI). All antihypertensive drugs had been stopped at least four days before the measurement of daily U-aldo excretion, blood sampling for serum potassium level (K) and plasma renin activity (PRA), and ambulatory blood pressure monitoring. Daily U-aldo excretion was $7.0 \pm 3.9 \mu\text{g/day}$. Among body weight, BMI, AVFA, ASFA, K, PRA, and age, by stepwise regression analysis, ASFA is independently associated with U-aldo excretion level ($\beta = 0.403$, $F = 8.323$, $P = 0.0061$). Furthermore, we clarified what blood pressure parameters are associated with U-aldo level. By stepwise regression analysis, among systolic blood pressure (SBP) and diastolic blood pressure (DBP) of day-time and night-time, day-time DBP is independently associated with U-aldo excretion level ($\beta = 0.490$, $F = 15.473$, $P = 0.0003$). **Conclusion:** It is suggested that aldosterone production level is predicted by ASFA, and is also associated with day-time DBP level in patients with essential hypertension.

Novel Pathophysiological Mechanisms of Heart Failure (M)**FRS02**

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Room 5 (Fukuoka International Congress Center 4F
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8 : 30 – 10 : 10

Keynote Lecture:**Cysteine Modulation of Class II HDAC Regulates Cardiac Hypertrophy**

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Thioredoxin1 (Trx1) reduces redox-sensitive proteins and regulates cell growth and death. Cardiac hypertrophy is suppressed in mice with cardiac specific overexpression of Trx1 (Tg-Trx1). The mechanism by which Trx1 suppresses cardiac hypertrophy remains to be elucidated. Using DNA microarray analyses, we identified DnaJb5, a heat shock protein, as a gene upregulated by Trx1. Trx1 and DnaJb5 were co-localized in the nucleus, where DnaJb5 interacted with Trx1 via TBP-2, a Trx1-binding protein. Both TBP-2 and DnaJb5 were required for the anti-hypertrophic action of Trx1. DnaJb5 interacted directly with histone deacetylase 4 (HDAC4), a class II HDAC. An HDAC4 mutant, which cannot interact with DnaJb5, was localized in the cytosol, suggesting the importance of the interaction with DnaJb5 for the nuclear localization of HDAC4. Overexpression of Trx1 suppressed hypertrophic stimuli-induced nuclear export of HDAC4 in myocytes. Using mass spectroscopy, we found that HDAC4 forms a disulfide bond between Cys-667 and -669, in the presence of hypertrophic stimuli, which was reduced by Trx1. An HDAC4 Cys667/669Ser mutant was localized in the cytosol, and its nuclear export was suppressed by leptomycin B, an inhibitor of exportin, suggesting that the cysteine modifica-

tion induces nuclear export of HDAC4. The Cys667/669Ser substitution abolished the suppressive effect of HDAC4 on cardiac hypertrophy. These results indicate that Trx1 upregulates DnaJb5, which recruits HDAC4 into the complex formed by Trx1-TBP-2-DnaJb5. Trx1 reduces HDAC4, thereby retaining its nuclear localization and suppressing cardiac hypertrophy through inhibition of hypertrophy master genes, such as NFAT. In conclusion, redox modulation of HDAC4 by Trx1 critically regulates cardiac hypertrophy.

FRS-006**Targeting p53 for therapy against myocardial infarction**

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Despite the significant therapeutic advances, heart failure remains one of the leading causes of death and it is necessary to develop more efficient treatment for this disease. We have recently reported that p53 plays a critical role in the development of heart failure and proposed that inhibition of p53 in the heart may be a novel therapeutic strategy for heart failure. To search the molecule(s) that suppress p53 activity in the heart, we performed expression screening of human heart cDNA library and identified 5 genes. One cDNA was a chaperone-interacting protein (CIP) that functions as a ubiquitin ligase and promotes the degradation of misfolded proteins. We here show a critical role of CIP in cardiac remodeling after myocardial infarction (MI). The in vitro experiments revealed that CIP negatively regulates p53 expression by inducing proteasome-mediated degradation. Abrogation of CIP increased p53 expression, whereas activation of CIP prevented hypoxia-induced p53 up-regulation and Bax-mediated apoptosis. Upon myocardial ischemia, expression of CIP was decreased, and p53 was up-regulated. Activation of CIP inhibited p53 accumulation in the MI heart and thereby reduced p53-mediated apoptosis and cardiac remodeling. These results indicate that CIP plays an important role in the pathophysiology of heart failure after MI. Activation of CIP may become a novel therapeutic strategy for heart failure.

FRS-007**Functional inhibition of p300 in the post-natal heart leads to mitochondrial dysfunction and cell death in mice**¹Yasuaki Nakagawa²Koichiro Kuwahara, ³Masaharu Akao, ⁴Masashi Katoh,⁵Genzou Takemura, ⁶Makoto Takano, ⁷Masaki Harada,⁸Masao Murakami, ⁹Michio Nakanishi, ¹⁰Satoru Usami,¹¹Shinji Yasuno, ¹²Hideyuki Kinoshita, ¹³Masataka Fujiwara,¹⁴Yoshihiro Kuwabara, ¹⁵Kenji Ueshima, ¹⁶Kazuwa Nakao

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To evaluate the physiological role of p300 in the adult heart, we analyzed the mice carrying cardiac specific overexpression of dominant-negative mutant of p300 (C/H3 domain deletion mutant of p300; DN-p300). DN-p300 transgenic mice (TG) showed the significantly reduced survival rate compared to non-transgenic mice (NTG) and mostly died by 20 weeks of age. At 12 weeks, TG showed a significant increase in the heart or lung weight-to-body weight ratio and a decrease in systolic function. Electron microscopic analysis revealed a marked increase in number and a decrease in size of mitochondria in TG hearts. The mRNA expression of mitochondrial fatty acid beta-oxidation genes was significantly reduced as well as that of PGC-1 α , a master regulator of mitochondrial gene expression, in TG. DN-p300 significantly suppressed the activity of PGC-1 α promoter. Tetramethylrhodamine-ethylesters staining demonstrated a diminished mitochondrial membranous potential in TG, suggesting the mitochondrial dysfunction leading to cell death contributes to the cardiac dysfunction. Indeed, in the electron microscopic analysis, several degenerative myocytes showing typical features of autophagosome were detected. In addition, Western blot analysis showed the increased expression of LC3 and cathepsin-D, a marker for autophagic cell death in TG ventricle. All these data demonstrate the critical role of p300 in the regulation of cardiac mitochondrial gene expression and function, and in the maintenance of cardiac muscle cell survival.