**e0061 THE MODULATION OF DILATED CARDIOMYOPATHY BY HEPC1 IN CTNTR141W TRANSGENIC MICE**

Zhang Li, Lv Dan, Dong Wei, Zhang Wei, Quan Xiongzi, Wang Shumei. Comparative Medical Center Peking Union Medical College

Objective Ionic regulatory hormone hepcidin is possible to be possibly involved in the physiological function of heart and pathogenesis of heart disease. The current paper reports the establishment of heart specific Hepc1 transgenic mice and analysis of the effect of Hepc1 on the development of dilated cardiomyopathy in the cTnTR141W transgenic mice.

Methods The heart specific Hepc1 transgenic mice were generated by the method of microinjection and the target gene was under the control of α-MHC promoter. The expression level of the gene Hepc1 was determined by RT-PCR and slot blotting. The H9c2 cell line, H9c2 cell line treated with desferrioxamine (50 μmol/l), and H9c2 cell lines expressing Hepc1 protein and H9c2 cell lines expressing Hepc1 protein treated with ferri ammonium citrate (100 μmol/l). Results 2 heart specific Hepc1 transgenic mice lines were established. Hepc1 transgenic mice demonstrated no signs of cardiomyopathy or lethality up to 7 months of age. The immature death rate was 18% before 7 months of age in the cTnTR141W mice, while Hepc1×cTnTR141W transgenic mice showed a lower immature death (10%). Hepc1×cTnTR141W transgenic mice showed a smaller ventricular chamber, improved left ventricular systolic function, and ameliorated interstitial fibrosis, compared with (to) cTnTR141W transgenic mice. ERK1/2 phosphorylation was strongly decreased in cTnTR141W transgenic mice compared with (to) WT mice, while it was significantly increased in the Hepc1×cTnTR141W transgenic mice compared with (to) cTnTR141W transgenic mice. Both desferrioxamine, an iron chelator and the gene Hepc1 significantly increased ERK1/2 phosphorylation in H9c2 cell line.

Conclusions Hepc1 showed a marked improved on (in) the pathologic phenotype of DCM in cTnTR141W transgenic mice, in which ERK1/2 signal pathway may play an important role. Hepc1 may be a new target in the treatment of human dilated cardiomyopathy.

**e0062 THE RELATIONSHIP BETWEEN TWO POLYMORPHISMS IN CHRNA3 GENE AND NONSMALL CELL LUNG CANCER EVIDENCE FROM A METAANALYSIS**

Niu Wenquan, Gu Mingliang, Zhang Xuezhi, Guo Shujie, Qi Yue. Shanghai Jiaotong University School of Medicine, Shanghai, China; 2Chinese Academy Sciences, Key Laboratory of Genome Science and Information Chinese Academy of Sciences, Chaoyang District, Beijing, China; 3Clinical Laboratory of Biochemistry, Central Hospital of Shengli Oil Field, China Petrochemical Corporation, Dongying, China; 4Capital Medical University, Affiliated Beijing Anzhen Hospital Beijing, Institute of Heart Lung & Blood Vessel Diseases, Chaoyang District, Beijing, China

Objective Lung cancer is the most common cause of cancer deaths worldwide; it is a complex disease that many genes involved (involves many genes) on chromosomes. Recently, several genome-wide association studies have identified chromosomal region 15q24-25.1 as a hotspot for lung cancer risk. We therefore aimed to explore the association of CHRNA3 gene rs1051750 and rs8034191 polymorphisms of this region with lung cancer via meta-analysis.

Methods Random-effects model was performed irrespective of the between-study heterogeneity. Data and study quality were assessed in duplicate. Publication bias was evaluated using the fail-safe number.

Results Overall, five studies involving nine populations were identified for both rs1051750 (cases/controls: 7594/8784) and rs8034191 (9553/7985) polymorphisms. Genotype frequencies of two polymorphisms satisfied the Hardy–Weinberg law in controls. Presence of rs1051750 A allele was significantly associated with 52% increased risk of lung cancer (95% CI 1.25 to 1.39; p<0.00001). Contrastingly, rs8034191 C allele only conferred a marginal association yielding 18% increased risk (95% CI 0.99 to 1.42; p=0.07). Under assumption of dominant and recessive modes, risk magnitude was strengthened for rs1051750 with an increased risk of 39% (95% CI 1.50 to 1.48; p<0.00001) and 48% (95% CI 1.25 to 1.76; p<0.00001) for lung cancer, respectively. As for rs8034191, there was marginal or null association for the dominant (pooled OR=1.28; p=0.06) and recessive (pooled OR=1.26; p=0.15) modes. The fail-safe number at the level of 0.05 supported these significant associations.

Conclusions Our results demonstrated that the rs1051750 A allele was significantly associated with an increased lung cancer risk and the effect of rs804191 polymorphism was moderate.

**e0063 CARDIOPROTECTION BY ISCHAEMIC PRECONDITIONING IS LOST IN ISOLATED DIABETIC HEARTS: ROLE OF TRANSIENT RECEPTOR POTENTIAL VANILLOID 1**

Song Jun-Xian, Chen Hong. Department of Cardiology, Peking University People’s Hospital

Objective Extensive studies demonstrated that diabetes abolished the effectiveness of cardioprotection by ischaemic preconditioning (IPC) during ischaemia/reperfusion. Transient receptor potential vanilloid type 1 (TRPV1) contributes to the cardioprotective effect of IPC against ischaemia/reperfusion injury through the release of calcitonin gene-related peptide (CGRP) and substance P (SP). Our previous study found that the expression of TRPV1 receptor and the level of CGRP and SP were decreased in diabetic hearts. However, whether the underlying mechanism of the loss of cardioprotection by IPC during diabetes is associated with the impairment of TRPV1 receptor remains largely unknown.

Methods Isolated hearts from streptozotocin-induced diabetic rats and normal control rats were subjected to 30 min of global ischaemia followed by 40 min of reperfusion. IPC was initiated by 3 cycles of 5 min of global ischaemia and 5 min of reperfusion before prolonged ischaemia in the presence or absence of CGRP or SP receptor inhibitor. Diabetic and normal control hearts were also pre-treated with CGRP or SP before prolonged ischaemia. Cardiac function parameters including left ventricular end-diastolic pressure, left ventricular developed pressure, maximum rise/fall rate of LV pressure, coronary flow and rate-pressure product and myocardial injury markers including creatine kinase (CK) and cardiac troponin I (cTnI) in coronary effluent were monitored during the experiment. In addition, CGRP and SP release in coronary effluent during IPC were measured in the presence or absence of TRPV1 receptor inhibitors. Results IPC effectively protected the hearts against ischaemia/reperfusion injury by improving the recovery of cardiac function and lowering CK and cTnI release in coronary effluent in normal control rats, but not in diabetic rats. Pre-treatment with CGRP or SP significantly increased the recovery of cardiac function and decreased CK and cTnI release during ischaemia/reperfusion in both normal control and diabetic rats, and these cardioprotection of
pre-treatment with CGRP or SP in normal control rats were comparable to those of IPC. In addition, inhibition of CGRP or SP receptor essentially abolished the cardiac protective effects of IPC in normal control rats, but not in diabetic rats. IPC resulted in significant increase of CGRP and SP release in coronary effluent of normal control hearts, and which were effectively inhibited by TRPV1 receptor inhibitor, capsazepine or ruthenium red. However, IPC had no effects on CGRP and SP release in coronary effluent of diabetic hearts in the presence or absence of capsazepine or ruthenium red.

**Conclusions** Cardioprotection by IPC against ischaemia/reperfusion injury is lost during diabetes, and their underlying mechanism is partly associated with the decreased CGRP and SP release due to the impairment of TRPV1 receptor in diabetic hearts.

**Objective** To investigate the relationship between the single nucleotide polymorphisms (SNP) of matrix metallo proteases (MMP-2 -735C/T; MMP-3 -1171 5A/6A) and the carotid atherosclerosis (CAS) in Chinese Han and Uygur populations with EH.

**Methods** The study comprised 276 Han nationality and 212 Uygur participants, who were divided into two groups: CAS (n = 293) and NS (n = 195). Genotypes were detected by PCR-RFLP and their frequencies were determined.

**Results** (1) The frequencies of MMP-2 TT genotype and T allele in CAS were higher than in NS (Han: X² = 11.441, p = 0.003; Uygur: X² = 28.255, p = 0.000). In NS, the frequencies of TT genotype and T allele in Han were higher than in Uygur (X² = 12.809, p = 0.001)). (2) The frequencies of MMP-3 6A/6A genotype and 6A allele in CAS were higher than in NS (Han: X² = 7.523, p = 0.024; Uygur: X² = 6.474, p = 0.039). The frequencies of MMP-3 6A/6A genotype and 6A allele in Han were higher than Uygur (CAS: X² = 26.230, p = 0.000; NS: X² = 18.809, p = 0.000). (3) The single gene analysis showed Han individuals with CT or TT genotypes had 2.25-fold risk and Han individuals with 6A/6A genotypes had 1.85-fold risk suffering from CAS. Han individuals with both T allele and 6A/6A genotypes had 3.17-fold risk suffering from CAS. The single gene analysis showed that Uygur individuals with CT or TT genotypes had 5.04-fold risk suffering from CAS. Uygur individuals with 6A/6A genotypes had 2.20-fold risk suffering from CAS. Uygur individuals with both T allele and 6A/6A genotypes had 3.20-fold risk suffering from CAS. (4) According to MMP-2 genotypes, Han individuals with MMP-2 CT+TT genotypes had higher LDL and lower HDL levels than CC genotype in CAS (LDL: 2.9 mmol/l vs 2.6 mmol/l; HDL: 1.2 mmol/l vs 1.0 mmol/l). Uygur individuals with CT+TT genotypes had higher TG levels than CC genotype (CAS: 2.5 mmol/l vs 1.6 mmol/l; NS: 3.9 mmol/l vs 2.0 mmol/l). According to MMP-3, Han individuals with 6A/6A genotype had higher T-CHOL and LDL levels than 5A/5A +5A/6A genotypes in NS group (T-CHOL : 4.6 mmol/l vs 4.2 mmol/l; LDL: 2.3 mmol/l vs 2.2 mmol/l). (5) The binary logistic regression analysis showed MMP-2 CT+TT genotypes were the risk factors for CAS in individuals with EH (Uygur: OR = 9.65; Han: OR = 2.076). MMP-3 6A homogenes were the risk factors for CAS in individuals with EH (OR = 1.802). MMP-2 CT+TT and MMP-3 6A homogenes had a combined influence on the incidence of CAS in Han individuals with EH.

**Conclusions** (1) Han and Uygur individuals had differential distribution of MMPs. (2) The SNP of MMP-2 -735C/T is associated with CAS in individuals with EH. The MMP-2 T allele may be a risk factors on CAS in individuals with EH. The SNP of MMP-3 -1171 5A/6A is associated with CAS in Han individuals with EH. The 6A allele may be a risk factors on CAS in Han individuals with EH.