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

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Objective Iron 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 $cTnT^{R141W}$ 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 Hepc1×$cTnT^{R141W}$ double transgenic mice were generated by breeding the Hepc1 transgenic mice with $cTnT^{R141W}$ transgenic mice. The structural and functional changes of the transgenic heart were analysed with M-mode echocardiography. Survival data were recorded from 1 month to 7 months (the 1st to the 7th month) postnatally. The histological and subcellular changes were observed under light microscope and transmission electronic microscope. The accumulation of phos-ERK1/2 and ERK1/2 in wild type, Hepc1, $cTnT^{R141W}$ and Hepc1×$cTnT^{R141W}$ transgenic mice were determined by western blotting. Phos-ERK1/2 expression was also detected in H9c2 cell line, H9c2 cell line treated with desferrioxamine (50 μmol/l), H9c2 cell lines expressing Hepc1 protein and H9c2 cell lines expressing Hepc1 protein treated with ferric 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 $cTnT^{R141W}$ mice, while Hepc1×$cTnT^{R141W}$ transgenic mice showed a lower immature death (10%). Hepc1×$cTnT^{R141W}$ transgenic mice showed a smaller ventricular chamber, improved left ventricular systolic function, and ameliorated interstitial fibrosis, compared with (to) $cTnT^{R141W}$ transgenic mice. ERK1/2 phosphorylation was strongly decreased in $cTnT^{R141W}$ transgenic mice compared with (to) WT mice, while it was significantly increased in the Hepc1×$cTnT^{R141W}$ transgenic mice compared with (to) $cTnT^{R141W}$ 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 improvement on (in) the pathologic phenotype of DCM in $cTnT^{R141W}$ 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

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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 rs1051730 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 rs1051730 (cases/controls: 7394/8784) and rs8034191 (9553/7953) polymorphisms. Genotype frequencies of two polymorphisms satisfied the Hardy–Weinberg law in controls. Presence of rs1051730 A allele was significantly associated with 32% 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 rs1051730 with an increased risk of 39% (95% CI 1.30 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=1.23; 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 rs1051730 A allele was significantly associated with an increased lung cancer risk and the effect of rs8034191 polymorphism was moderate.

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

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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