THE MODULATION OF DILATED CARDIOMYOPATHY BY HEPC1 IN CTNTR141W TRANSGENIC MICE

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Objective
Iron regulatory hormone hepcin 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 z-MHC promoter. The expression level of the gene Hepc1 was determined by RT-PCR and western blotting. Phos-ERK1/2 expression was also detected in the control and diabetic rats, and these cardioprotection of IPC against ischaemia/reperfusion injury through the release of endogenous CGRP and SP, which ERK1/2 signal pathway may play an important role. Hepc1 significantly increased the recovery of cardiac function and decreased the effect of rs8034191 polymorphism was moderate.

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 improvement on 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.

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 (includes 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: 7594/7874) and rs8034191 (9553/7953) polymorphisms. Genotype frequencies of two polymorphisms satisfied the Hardy–Weinberg law in controls. Presence of rs1051750 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 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 rs8034191 polymorphism was moderate.

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 ischemic preconditioning (IPC) during ischemia/reperfusion. Transient receptor potential vanilloid type 1 (TRPV1) contributes to the cardioprotective effect of IPC against ischemia/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 ischemia followed by 40 min of reperfusion. IPC was initiated by 3 cycles of 5 min of global ischemia and 5 min of reperfusion before prolonged ischemia 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 ischemia. 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. IPC effectively protected the hearts against ischemia/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 ischemia/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.