GW25-e1584

COL4A1 gene polymorphism is related to arterial pulse wave velocity in healthy Han Chinese subjects

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Objectives: Pulse wave velocity (PWV), which is dependent on the structural and functional characteristics of the arterial wall, is a noninvasive index of arterial stiffness and an independent predictor of cardiovascular outcomes. Type IV collagen is an important structural component of the vascular basement membrane, thus it is important for the integrity and functions of basement membrane. However, the relationship between genetic polymorphisms of COL4A1 gene and PWV value in healthy Han Chinese subjects remains unclear. We aimed to investigate the association between PWV value and COL4A1 gene polymorphisms in healthy Han Chinese subjects participating in the Cardiovascular Risk Survey (CRS) study.

Methods: A total of 905 healthy Han Chinese subjects (406 men, 524 women) were included in this study. Brachial-ankle pulse wave velocity (baPWV) was measured and used as markers of arterial stiffness. One SNP rs605143 was genotyped using the polymerase chain reaction-restriction fragment length polymorphism method (PCR-RFLP).

Results: The SNP rs605143 was associated with PWV by analyses of a recessive model (P=0.001) and additive model (P=0.028), and the difference remained significant after multivariate adjustment of sex and age (P=0.031, P=0.025, respectively). The AA genotype was associated with increased PWV value compared with the AG or GG genotype (1505.52±303.762 cm/s vs. 1450.84±308.989 cm/s and 1404.92±297.902 cm/s).

Conclusions: The SNP rs605143 of the COL4A1 gene is associated with PWV value in healthy Han Chinese subjects, indicating that carriers of the A allele of rs605143 have a high risk of Arterial stiffness.

GW25-e1641

The effect of testosterone on the angiotensinII induced proliferation and collagen synthesis in neonatal rat cardiac fibroblasts

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Objectives: To explore the effect and the mechanism of testosterone (T) on angiotensinII (Ang II) induced proliferation and collagen synthesis in neonatal rat cardiac fibroblasts (CF).

Methods: CF were cultured in vitro, and then divided into four groups: control group, AngII (10⁻⁸mol/l) group, testosterone (30nmol/l) group, testosterone (30nmol/l) and AngII (10⁻⁸mol/l) group. Cell synthesis was detected by V,G. staining. Flow cytometry analysis was used to detect cell cycle distribution. The expression of the phosphorylated extracellular signal-regulated kinase (P-ERK1/2) was detected by immunochemistry.

Results: (1) Compared to control group, the collagen synthesis, the percentage of S phase and the expression of P-ERK1/2 of CF were significantly increased in AngII group (P<0.01). The expression of P-ERK1/2 was increased in testosterone group (P<0.01). (2) Compared to AngII group, the collagen synthesis, the percentage of S phase and the expression of P-ERK1/2 of CF were reduced in testosterone and AngII group (P<0.01).

Conclusions: Testosterone can inhibit CF proliferation and collagen synthesis induced by AngII, and the mechanism may be related to the inhibition of ERK1/2’s activation.

GW25-e1667

Genome association study of human chromosome 16 and susceptibility to coronary artery disease in a Chinese population.

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Objectives: Coronary artery disease (CAD) is a complex disease influenced by modifiable risk factors as well as genetic susceptibility. Despite the considerable advances, it remains apparent that the underlying causes of CAD are multifactorial and involve a complex interplay between acquired and inherited risk factors. Previous genome-wide association studies (GWAS) in populations of European ancestry identified several genetic loci for CAD, but no such study has yet been reported in the Chinese population. To find the genetic loci associated with CAD in Chinese population, we performed a genome scan on chromosome 16 in CAD patients and healthy people from Shandong peninsula. This approach led to the identification of a CAD susceptibility locus on chromosome 16.

Methods: We performed an association study of coronary artery disease comprising 156 cases with coronary artery disease and 1000 controls. For this study, we selected 156 subjects based on their CAD status as previously used for genetic analysis. The control group consisted of 1000 healthy blood donors selected from the Blood Center of Shandong province. Genomic DNA was extracted from peripheral arterial blood by a modified phenol-chloroform method, and then DNA samples were diluted to 20ng/μl for working concentration. The SNP genotyping and data analysis were carried out using the CLUMP software which can analyze multimarker loci. The probability level accepted for significance was P<0.05.

Results: The genotypes of all 13 microsatellite markers on chromosome 16 were polymorphic in cases and controls, and the numbers of alleles at these loci ranged from 4 to 11. Statistical analysis was performed using CLUMP software to compare the differences in allele frequency between each locus of the two pooled samples. We found significant statistical differences at marker D16S3046 between allele frequencies in patients and those in controls (X²=14.9896, P=0.000490). There were 6 alleles at D16S3046 (80, 94, 96, 98, 100 and 102bp), and the frequency of the 80 bp allele in cases was significantly lower than that in controls.

Conclusions: The data suggest that the D16S3046 locus (16p12.2) is significantly associated with susceptibility to coronary artery disease in this population. We have identified a region on chromosome 16p12.2 that is linked to CAD, as well as additional regions of interest that will require further analysis. These data provide areas of the human genome where further investigation may reveal susceptibility genes for CAD. Understanding the genetic etiology of CAD may lead to novel preventative and/or therapeutic strategies.

GW25-e1704

Fructose Diet Elevates Circulating PCSK9 and LDL-cholesterol Levels and Reduces Liver LDLL Receptor Protein Abundance in Hamsters through a Novel Mechanism

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Objectives: High fructose diet (HFD) induces dyslipidemia and insulin resistance in animals and humans; however, whether PCSK9 has a causal role in the development of dyslipidemia by high fructose consumption remains elusive. In this study, we examined the effect of HFD on serum PCSK9 level and lipid homeostasis using hamsters as a model.

Methods: Hamsters were fed HFD or normal diet (ND) for 4 weeks. Serum PCSK9 and lipid levels were measured. Animals were sacrificed and liver tissues were collected and analyzed for LDL receptor (LDLR) and PCSK9 mRNA and protein expression.

Results: We showed that serum levels of LDL-C were elevated in hamsters fed HFD as compared to animals fed ND. The increase in circulating LDL-C was accompanied by a 50% reduction of liver LDLR protein abundance in HFD group without changes in liver LDLR mRNA. Examination of serum PCSK9 levels and liver PCSK9 expressions revealed that hepatic PCSK9 mRNA and protein expressions were reduced by HFD, however, surprisingly, serum PCSK9 levels in HFD group was 2.2-fold higher than ND group. We further conducted ultracentrifugation to separate serum lipoproteins and separately detected PCSK9 in each lipoprotein fractions. We found that hamster serum PCSK9 was predominantly associated with VLDL fraction with trace amount detected in LDL fraction. PCSK9 was not detected at all in HDL fraction.

Conclusions: Our new findings suggest that high fructose diet reduces liver LDLR mediated uptake of serum LDL-C through a novel mechanism that elevates circulating PCSK9 concentration without increasing its hepatic synthesis.

GW25-e1728

Anti-inflammatory Effect of B-Type Natriuretic Peptide Postconditioning During Myocardial Ischemia-Reperfusion: Involvement of PI3K/Akt Signaling Pathway

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Objectives: High mobility group box 1 protein (HMGB1) plays an important role in myocardial ischemia-reperfusion (IR) injury. B-type natriuretic peptide (BNP) postconditioning has been reported to reduce myocardial IR injury. The present study investigated whether postconditioning of BNP could reduce myocardial IR injury by inhibiting HMGB1 expression and the potential mechanisms in rats.

Methods: The left anterior descending coronary arteries of rats were occluded to induce ischemia for 30 min and reopened to imitate reperfusion for 4 h. The rats were treated with BNP (0.03 μg/kg, min, i.v.) 15 min before reperfusion until the end of the procedure, or without treatment of LY294002 (an inhibitor of phosphoinositide 3-kinase (PI3K)), 0.3 mg/kg, i.v., 3 min before reperfusion. Lactate dehydrogenase (LDH), creatine kinase (CK), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and infarct size were measured. Phospho-Akt, total Akt, and HMGB1 expression were assessed by immunoblotting.