

ACE2/ApoE double KO mice. These changes were associated with exacerbation of renal tubule ultrastructure injury and greater activation of Akt and ERK1/2 phosphorylated signaling. Conversely, treatment with hrACE2 significantly attenuated renal oxidative stress levels and ultrastructure injury, and prevented the expression of NOX4 and phosphorylated level of Akt and ERK1/2 in ApoEKO mouse kidneys. However, there were no changes in renal expression of NOX2 among groups.

CONCLUSIONS Deletion of ACE2 triggers greater increases in renal oxidative stress and tubular ultrastructure injury in the ACE2/ApoE double mutant mice with greater activation of Akt-ERK1/2 phosphorylated signaling. While ACE2 overexpression alleviates renal tubular injury in ApoE-mutant mice with suppression of superoxide generation and downregulation of the Akt-ERK phosphorylated signaling. Strategies aimed at enhancing ACE2 action may have important therapeutic potential for atherosclerosis and renal diseases.

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Variants of Mitochondrial Genome in Patients with Subclinical Atherosclerosis

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OBJECTIVES Genetic predisposition plays an important role amidst the other risk factors in the development of atherosclerosis, a socially significant multifactorial disease. This study was aimed to identify the relationship between mitochondrial DNA (mtDNA) variants and the presence of subclinical atherosclerosis, which was defined ultrasonographically as the abnormal increase of intima-media thickness of common carotid arteries (cIMT).

METHODS For the accurate detection of mtDNA variants, high-throughput sequencing of the mitochondrial genome from blood leukocytes using the Roche 454 technology was carried out in 77 asymptomatic non-related subjects. To assess the state of the carotid artery wall, high-resolution B-mode ultrasonography was performed with ultrasound scanner SonoScape SSI-1000 (China) using a linear vascular 7.5 MHz probe. The borderline values for Russian population were used for detection of abnormal cIMT values.

RESULTS In patients with subclinical atherosclerosis, 70 mtDNA variants have been revealed that were characterized by the prevalence over 5% of the total sample or among patients or controls. Twenty-five of them occurred in coding region, and 5 were located in rRNA genes, 3 in tRNA genes, 5 were missense mutations. For 5 variants characterized by the increased frequency in healthy subjects there were significant differences from the patients with subclinical atherosclerosis. Three homoplasmic mtDNA variants were found only in patients with atherosclerosis. Six MtDNA variants were characterized by a more than 2-fold increased frequency in patients with subclinical atherosclerosis as compared to healthy subjects. As for 115 heteroplasmic mtDNA variants revealed, 15 were found both in healthy subjects and patients with subclinical carotid atherosclerosis. Three variants had higher frequency in healthy subjects, and two variants had higher frequency in patients with subclinical atherosclerosis.

CONCLUSIONS The data obtained in our study can be used to assess individual risk of atherosclerosis and for further studies on the role of mitochondrial genome mutations in the development of atherosclerosis and its clinical manifestations. The individual profile of certain mtDNA variants may partially explain atherosclerosis variability and genetic predisposition to atherosclerosis in population, which could be inherited by maternal line.

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Circulating lncRNA AC100865.1 from Monocytes as a Novel Biomarker for Coronary Artery Diseases

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OBJECTIVES Long non-coding RNAs (lncRNAs) have been found to be involved in coronary artery disease (CAD) development. Whether or

not circulating lncRNAs work as a CAD biomarker, needs to be established.

METHODS Using microarray-based lncRNA expression profiling to explore the lncRNA expression in the circulating peripheral blood monocyte (PBMCs) and plasma from 15 CAD patients and 15 control subjects. After criteria (average normalized intensity is more than 7 with significance less than 0.005) based selection, and confirmed by quantitative RT-PCR. Using the analysis of the area under the curve (AUC) of the receiver operating characteristic (ROC) in large amount of population. Functional enrichment analysis was performed by GO and pathway analysis. Further validation using the specific siRNA in the THP-1 cell line, and the concentrations of pro-inflammatory cytokines (IL-1 β , IL-6 and TNF α) in the culture media, were studied by ELISA.

RESULTS According to the array in the PBMCs and plasma, we found 86 lncRNAs that were differentially expressed in both PBMCs and plasma from 15 CAD patients and 15 control subjects. After criteria and confirmed by quantitative RT-PCR, only three lncRNAs (CoroMarker, BAT5 and IL21R-AS1) remained in the select candidate list. By ROC analysis, CoroMarker was found to be the best candidate biomarker for CAD with an AUC of 0.920, 95% CI 0.892-0.947. CoroMarker was independent from CAD risk factors and other cardiovascular diseases. In a prospective study, we found the sensitivity and specificity of CoroMarker were 76% and 92.5%, respectively. Functional enrichment analysis showed CoroMarker being clustered with small molecule metabolic process and the signal transduction signaling pathway. Further validation using the specific siRNA in the THP-1 cell line, the concentrations of pro-inflammatory cytokines (IL-1 β , IL-6 and TNF α) in the culture media, were reduced significantly.

CONCLUSIONS The present study suggests that CoroMarker have an unanticipated role in inflammatory response to finally impact in the risk of CAD, and be a novel and specific functional biomarker for the diagnosis of CAD.

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Captopril negatively regulated apamin sensitive SK channels in volume-overload rats

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OBJECTIVES Our previous study confirmed that in heart failure the expression and function of SK channels upregulated significantly and participated in electrical remodeling of cardiocytes, but the regulation of SK channels was poorly understood in this process. Studies indicated that the sensitivity of SK channels to [Ca²⁺]_i is positively regulated by PP2A, which is activated by angiotensin II in many biological response paths. In the present study, we explored the effect of angiotensin converting enzyme inhibitor captopril on apamin sensitive SK channels in HF.

METHODS We used volume-overload induced heart failure rat model by aortocaval fistulas (HF group), and captopril was administrated by gavage (CAF group). Whole-cell patch clamp was performed to recording I_{KAS} (Apamin sensitive current), and I-V curve was applied to determine the effect of captopril on I_{KAS}. We also explored the effect of captopril on the sensitivity of SK channels to [Ca²⁺]_i by setting various [Ca²⁺]_i (10, 100, 500, 900, 10,000 nM) at single isolated cells, and the Hill equation ($y=1/[1+(EC50/x)^n]$) was employed to fitted currents data (EC50 represents the [Ca²⁺]_i concentration at halfmaximal activation of I_{KAS}, n represents the Hill coefficient). And immunofluorescent staining, real time PCR, western blot were also carried out to furtherly investigate the underlying molecular mechanism of the regulation.

RESULTS Captopril significantly decreased the mean I_{KAS} density at 0 mV (CAF 5.40 ± 1.11 pA/pF, n = 6 cells from 5 rats vs HF 8.90 ± 1.79 pA/pF, n = 5 cells from 6 rats P<0.05) when [Ca²⁺]_i at 900 nM comparing with HF group, and obviously shifted down the I-V curve. Similarly, the I_{KAS} density was markedly downregulated by captopril when [Ca²⁺]_i at 500, 1000, 10000nM (500 nM: CAF 4.21 ± 0.16 pA/pF, n = 6 cells from 4 rats vs HF 7.98 ± 0.43 pA/pF, n = 6 cells from 6 rats P<0.05; 1000nM: CAF 5.51 ± 0.71 pA/pF, n = 6 cells from 6 rats vs HF 8.96 ± 0.51 pA/pF, n = 6 cells from 5 rats P<0.05; 10000nM: CAF 5.80 ± 0.52 pA/pF, n = 5 cells from 3 rats vs HF 9.02 ± 0.57 pA/pF, n = 5 cells from 4 rats P<0.05), the data of the Hill fitting showed the significant difference in EC50 values and the Hill coefficients among the three group cells (EC50 CAF 313 ± 17 nM, HF 231 ± 11 nM, P<0.05;