Mitochondrial tRNA-Thr Gene Mutation in Maternally Inherited Hypertension and the Regulatory Mechanism in Adiponectin Pathway

Lan yunfeng1,2, Yin Tong2, Zha Qingli2, Yang Jie2, Li Zonghui2, Liu Yu1, Qiu Yingxin1, Zha Chao1, Zhu Xiongting1, Li Yao2
1Department of Healthcare, Hainan Branch of Chinese PLA General Hospital, 2Cardiovascular Department of Chinese PLA General Hospital

Objectives: The offspring hypertension and mother hypertension has a significant correlation, and adipoctin mRNA expressions are related with elevated blood pressure, but the underlying mechanism is unclear. Based on a study with small sample size and two pedigrees maternal family members, we tried to reveal the related mechanisms how EH characterized with maternal inheritance is caused by mitochondrial mutations.

Methods: Totally 115 pedigrees were enrolled in this study. The subjects answered questionnaires and received full mitochondrial genome sequencing analysis. According to the incidence of hypertension in three-generations of Chinese family, they were divided into maternally-inherited EH pedigrees (group A, n=17), non-maternal inheritance pedigrees (group B, n=70), and normal control pedigrees (group C, n=33). In order to clarify the relationship between mtDNA C15910T and maternally inherited EH, all maternal family members' whole mitochondrial genome carrying mtDNA C15910T mutation from Zhaozhou and Inner Mongolia pedigrees were characterized by more viability and proliferation. The responsible mechanism through which mtDNA C15910T carries may be the reduced ATP production results in raised intracellular ROS. The mitochondrial dysfunction results in reduced APN levels secreted from adipose tissue, causing increased ATP production results in raised intracellular ROS. The responsible mechanism through which mtDNA C15910T carries may be the reduced ATP production results in raised intracellular ROS.

Conclusions: Mitochondrial tRNA-Thr gene mtDNA C15910T mutation from Zhuozhou and Inner Mongolia pedigrees were characterized by more viability and proliferation. The mitochondrial dysfunction results in reduced APN levels secreted from adipose tissue, causing increased ATP production results in raised intracellular ROS. The responsible mechanism through which mtDNA C15910T carries may be the reduced ATP production results in raised intracellular ROS.

Results: The results indicated that mitochondrial tRNA gene mutation was significantly correlated with EH. Mitochondrial tRNA gene mutation occurred more frequently in patients with EH. We found that the overall incidence rate of EH was 59.3% in Zhaozhou and Inner Mongolia pedigrees, and 90% in males, significantly higher than in the general population in China (33.5%); the age at onset of EH in members carrying mtDNA C15910T is earlier than in gender- and age-matched groups. The mtDNA C15910T, which is extraordinarily conserved from mollusc to human mitochondria, is located at D-loop of tRNA. The serum sodium and chloride levels were increased in members carrying mtDNA C15910T, while more significantly in maternally affected cases. In vitro, we found that PBMCs carrying mtDNA C15910T were characterized by more viability and proliferation. The increased ATP production results in raised intracellular ROS. The mitochondrial dysfunction results in reduced APN levels secreted from adipose tissue, causing increased ATP production results in raised intracellular ROS. The mitochondrial dysfunction results in reduced APN levels secreted from adipose tissue, causing increased ATP production results in raised intracellular ROS.

Conclusions: Mitochondrial tRNA-Thr gene mtDNA C15910T mutation may cause hypertension by changing APN, ADIPOQ, PGC-1a or APN, ERRα signal pathway to elevate blood pressure.

GW52-e2275

GW52-e2323

Effects and mechanisms of Angiotein (1-7) on the effects of cholesterol in macrophage foam cells

Wutao Zeng1, Xiang Wang1, Weiyun Chen1, Xiating Sun1, Meiling Liang1, Zhe Liang2
1Division of cardiology, Cardiovascular Medical Department, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, 2Division of Intensive Care Unit, the Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

Objectives: To explore if Angiotein (1-7) can modulate the content of cholesterol and the expression of ATP-binding cassette transporter A1 (ABCA1) in macrophage foam cells.

Methods: THP-1 cells were induced into macrophages by 130mg/L phorbol myristate acetate (PMA) for 48h. The THP-1-derived macrophages were co-cultured with Angiotein (1-7) with different concentrations or A-779 in combination with 50ng/L oxidized low-density lipoprotein. The contents of cholesterol in foam cells were determined by using enzyme fluorescence. The expression levels of ABCA1 mRNA and protein were determined by using real time-polymerase chain reaction (RT-PCR).

Conclusions: Angiotein (1-7) can modulate the content of cholesterol and the expression of ATP-binding cassette transporter A1 (ABCA1) in macrophage foam cells.

Results: Compared with control group, Angiotein (1-7) reduced the expression of inflammatory cytokines TNF-α, IL-6 and IL-1β mRNA and protein secreted from THP-1-derived macrophages in a dose-dependent manner (P<0.05). The inhibition induced by Angiotein (1-7) was partly disappeared after the pretreatment of selective Angiotein (1-7) antagonist A-779. While TLR4 was blocked by TLR4 monoclonal antibody, the effects of Angiotein (1-7) were partly prevented. Angiotein (1-7) reduced the expression of TLR4 mRNA and protein (1.450 ± 0.182x2s. 2.467 ± 0.153 and 0.313 ± 0.010x2s. 0.880 ± 0.080x2s < P<0.05), inhibited phosphorylation of IκB protein (1.15 (Control) vs. 0.617 ± 0.057 < P<0.05), and the translocation of NF-κB protein from cytoplasm to nucleus (0.177 ± 0.025 vs. 0.503 ± 0.025 < P<0.05). The inhibition induced by Angiotein (1-7) was partly disappeared after the pretreatment of the selective Angiotein (1-7) antagonist A-779. Angiotein (1-7) may be associated with the inhibition of the TLR4/NF-κB signaling pathway.

GW52-e2319

GW52-c2509

Hyperglycemia and oxidative stress stimulate abnormal proliferation of atrial fibroblast through NADPH oxidase/MAPK/MPM9 signal pathway

Liu Tong, Zhang Qiong, Wang Xinghua, Liang Xue, Li Guangying
Department of Cardiology, Second Hospital of Tianjin Medical University

Objectives: Atrial fibrosis is one of the fundamental pathophysiological mechanisms in the development of atrial fibrillation, and the abnormal proliferation and polarization of atrial fibroblast stimulated by some pathological factors participate in this process. Several epidemiological studies have indicated that diabetes mellitus is an independent risk factor of the onset and perpetuation of atrial fibrillation. Previous studies found that oxidative stress is a significant trigger of the abnormal proliferation and polarization of atrial fibroblast by up-regulation of the activity of nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase) and mitogen-activated protein kinases (MAPK) signaling transduction. However, the variation of atrial fibroblast in hyperglycemic and oxidative stress state needs more exploration.

Methods: Atrial fibroblast isolated from adult rabbits' left atrium is cultured and stimulated respectively by high levels of glucose, hydrogen peroxide (H2O2) and their combination and the NADPH oxidase inhibitor apocynin. We test the variation of proliferation activity of the fibroblast by MTS colorimetric method and the alteration of protein expressions of NADPH oxidase, MAPK signal pathway and matrix metalloproteinases 9 (MMP9).

Results: High levels of glucose and H2O2 promote the proliferation of atrial fibroblast and H2O2+H2O2 have the similar ability of acceleration compared with hyperglycemia. However, the combined stimulus of hyperglycemia and H2O2 reveals even more remarkable enhancement of proliferation of fibroblast (P<0.01). And all the promotion by these agents can be depressed by apocynin (P<0.01). The expression of Rac1, the regulatory subunit of NADPH oxidase is up-regulated by activation of high concentration of glucose, H2O2 and the combined stimulus (P<0.01). And this