Objectives: Increasing evidences show that OX40-OX40L interaction plays an important role in atherosclerosis. However, the mechanism of OX40 signaling pathway has not been clarified. The objective of this study was to investigate the effect of OX40-OX40L interaction on intracellular reactive oxygen species (ROS) level and the secretion of Cyclophilin A (CyPA) in C57BL/6J mice' atherogenesis.
Methods: Atherosclerotic plaque model was produced by rapid perivascular carotid collar placement plus western-type diet in C57BL/6J mice. In vivo, the expression of CyPA in mice plaque and lymphocytes was detected by immunohistochemical and Western blot, respectively. In vitro, the expression of CyPA protein in cultured lymphocytes of C57BL/6J mice was measured by Western blot. The level of ROS was detected by flow cytometry.
Results: We found that the expression of CyPA was significantly increased both in atherosclerotic lesion and in lymphocytes from C57BL/6J mice. In vitro and in vivo, the level of ROS in $OX40^{+}$lymphocytes was increased. In vitro, after stimulating OX40-OX40L interaction, the levels of ROS and CyPA in lymphocytes were obviously increased, while anti-OX40L mAb significantly down-regulated the anti-OX40 mAb-induced ROS generation and inhibited lymphocytes to secrete CyPA in lymphocytes.
Conclusions: This study suggested that OX40-OX40L interactions can up-regulate the intracellular level of ROS in C57BL/6J mice and increase the secretion of CyPA from lymphocytes, which might play a critical role in atherosclerotic plaque formation.

GW25-e4358

Lycopene ameliorates pressure overload-induced cardiac hypertrophy and fibrosis via increase in PPAR γ expression and inhibition of NF-κB nuclear binding

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Objectives: Lycopene plays a protective role in hypertension, atherosclerosis, and hyperlipidemia through scavenge free radicals and it's anti-inflammatory ability. The present study was designed to investigate the role of lycopene in cardiac hypertrophy and fibrosis in pressure overload model
Methods: C57BL/6 mice, 8 weeks of age, were subjected to transverse aortic constriction (TAC) surgery and randomly divided into TAC group, TAC+Lycopene group and TAC+Lycopene+GW9662 (PPAR γ inhibitor) group. In TAC+Lycopene group, the mice subjected to were fed with lycopene for four weeks. In TAC+Lycopene+GW9662 group, the mice were fed with lycopene and GW9662 at the same time for four weeks. While, in TAC group, the mice was just fed with corn oil. The characteristics of heart functions were evaluated by the methods of hemodynamics and echocardiography.Masson staining was employed to observe the pathological changes of myocardial tissues.Metalloproteinase (MMP) -2, MMP-9 and MMP-13 were detected through Western Blot. The expression of PPAR γ and the NF-κB activity were also detected.
Results: Dietary lycopene significantly attenuates pressure overload-induced increase in heart weight index, enlargement of ventricular volume, decrease in cardiac function, and worse in cardiac fibrosis. Additionally, lycopene attenuated pressure overload-induced over-expression of metalloproteinase (MMP) -2, MMP-9 and MMP-13. Moreover, the expression PPAR γ was significantly increased while the NF-κB activity was significantly decreased in the TAC+lycopene group. However, these protective effects were blunted by GW9662 (PPAR γ inhibitor), the expression of PPAR γ and the NF-κB activity was restored in the TAC+Lycopene+GW9662 group.
Conclusions: Our results suggest that dietary lycopene protects against cardiac hypertrophy and fibrosis in pressure overload mice via increase in PPAR γ expression and inhibition of NF-κB nuclear binding.

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Telmisartan protect broiler chickens from pulmonary arterial remodeling induced by low ambient temperature

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Objectives: Pulmonary hypertension syndrome, also known as ascites, is a common disease occurred in broiler chickens under conditions such as high altitude or low ambient temperatures. However, its mechanism is not clear. Studies show that dysregulated renin-Angiotensin system (RAS) contributes to increased pulmonary vascular remodeling and local RAS-upregulation was associated with increased pulmonary artery smooth muscle cell proliferation via enhanced angiotensin type 1 receptor (AT1-R) signaling in patients with idiopathic pulmonary arterial hypertension. Angiotensin (Ang) II, the main the major biologically active component of RAS, acts through AT1 receptor and AT2 receptor (AT2- R). AT1-R is responsible for mediating many of the well-known stimulatory pathological actions of Ang II including secretion of aldosterone, vasoconstriction, and renal sodium reabsorption. Telmisartan is the inhibitor of AT1-R. This study aims to explore the protective effect of Telmisartan, Angiotensin type 1 receptor blocker, on pulmonary arterial remodeling induced by low ambient temperature in broiler chickens.
Methods: Ninety chickens were randomly divided into 3 groups (n=30), including control group, low temperature group and telmisartan group. Chickens in low temperature group and telmisartan group were exposed to low ambient temperature from 14 days of age until 45 days of age; chickens in telmisartan group were gavaged with telmisartan 5 mg/kg once daily for thirty days. The pulmonary arterial systolic pressure was measured with Right Catheterization Method. Wet lung weight index and right ventricular hypertrophy index were evaluated. Small pulmonary artery wall thickness and elastic fibers was determined respectively by H-E staining and Weight staining. Proliferating cell nuclear antigen (PCNA) -positive cells were determined by Immunohistochemical staining.
Results: It showed that pulmonary arterial systolic pressure, wet lung weight index and right ventricular hypertrophy index, small pulmonary artery wall thickness, elastic fibers and PCNA expression increased significantly in Low temperature group compared with control group and telmisartan group.
Conclusions: Telmisartan can protect broiler chickens from pulmonary arterial remodeling induced by low ambient temperature.

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Mitofusin 2 decreases intracellular lipids in macrophages by regulating peroxisome proliferatoractivated receptor-γ

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Objectives: Previous studies found that overexpression of mitofusin 2 (Mfn2) inhibits atherosclerotic plaque formation. Mfn2 is also decreased in atherosclerotic arteries of apoE-/- mice but studies have not yet extended to the effects of Mfn2 on cholesterol transport in foam cell formation. The aim of this study was to determine whether Mfn2 was involved in cholesterol transport in foam cell formation.
Methods: Arteries of both mice and human were obtained to anlysis the Mfn2 mRNA and protein expression in atherosclerotic plaque. Using THP-1 as a macrophage model, we used oil red O staining and cellular cholesterol content analysis to determine the effect of overexpression of Mfn2 on macrophage-derived foam cell formation. Then, western blot and quantitative real-time polymerase chain reaction were used to detect the protein and mRNA expression in cells.
Results: This study showed that Mfn2 expression was significantly reduced in arterial atherosclerotic lesion in both mice and human compared to healthy counterparts. Then, cellular cholesterol content analysis and oil red O revealed that Mfn2 overexpression decreased the accumulation of cholesterol esters induced by exposure to oxidized low density lipoprotein (ox-LDL) in macrophages. Mfn2 promoted cholesterol transport by regulating expression of ABCA1, ABCG1 and SR-BI protein and mRNA in a titer-dependent manner in THP-1-derived foam cells. However, silencing Mfn2 gene with siRNA nearly reversed the upregulation of ABCA1, ABCG1 and SR-BI expression. In addition, peroxisome proliferator-activated receptor-γ (PPARγ) and liver X receptor-α (LXRα), which induced the activation of cellular cholesterol efflux pathway, were also activated by adenovirus-mediated Mfn2 (adv-Mfn2) transfection. Furthermore, the down- regulation of cholesterol transporters and PPARγ by siRNA-Mfn2 was rescued by the PPARγ agonist rosiglitazone and mitogen-activated protein kinase (MAPKs) inhibitors SB203580 and PD98059, indicating that MAPKs was involved in Mfn2-induced PPAR activation and cholesterol efflux.
Conclusions: Our studies provide new insights into potential mechanisms of Mfn2-mediated alterations in cellular cholesterol transport which may impact the development of atherosclerosis.

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Manipulating PHD2 to Promote the Therapeutic Effect of Stem Cell Transplantation for Myocardial Infarction

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Objectives: Stem cell transplantation has had modest success as a treatment for myocardial infarction (MI). One of the limitations is the poor stem cell survival and function in the diseased microenvironment. We studied whether and how prolyl hydroxylase domain protein 2 (PHD2), a cellular oxygen sensor, enhances stem cell cardioprotective effects after transplantation into infarcted hearts.
Methods: We first used adipose-derived stem cells (ADSCs), and then confirmed our findings in bone marrow mesenchymal stem cells (BM-MSCs). ADSCs were transduced with lentiviral short hairpin RNA to silence PHD2 (shPHD2) and intramyocardially injected into infarcted heart in mice.
Results: ADSCs reduced cardiomyocyte apoptosis, fibrosis, and infarct size (MI+ADSCs: 39.4±3.3%;MI+PBS: 48.4±4.5%) and improved cardiac function