OBJECTIVES
Mast cells (MC) may promote plaque vulnerability, via expressing various pro-inflammatory cytokines. Human mast cells (HMC-1) were pretreated with or without different concentrations of tranilast (30, 100, 300 μmol/L) for 1 h, and then incubated with 100 μmol/L ox-LDL for another 6 or 24 h. The real-time PCR and ELISA were used to detect the mRNA and protein expression of MCP-1, TGF-β, MMP2 and collagen. Protein expression of TLR4 was measured by real-time PCR and western-blot, respectively. The phosphorylations of MAPK (ERK1/2, p38 MAPK, JNK1/2) were measured by western-blot.

RESULTS Tranilast significantly attenuated ox-LDL-induced overexpression of MCP-1, TGF-β, IL-6 and NO in HMC-1 cells, in a concentration-dependent manner (P < 0.05). Moreover, tranilast remarkably dose-dependently inhibited ox-LDL-induced overexpression of TLR4 and iNOS expression (P < 0.05). Combination of TLR4-siRNA and tranilast synergistically strengthened the inhibitory effect, suggesting that the inhibitory effect of tranilast is possibly dependent on down-regulating the expression of TLR4 in HMC-1 cells. We also found that tranilast inhibited ox-LDL-induced phosphorylation of MAPK (ERK1/2, p38 MAPK, JNK1/2), with a concentration-dependent manner (P < 0.05). Pretreatment with ERK1/2 inhibitor PD98059, p38 MAPK inhibitor SB203580, or JNK1/2 inhibitor SP600125 partially attenuated ox-LDL-induced overexpression of pro-inflammatory factors in HMC-1 cells. In combination with tranilast, their inhibitory effect was synergistically strengthened.

CONCLUSIONS Tranilast could attenuate ox-LDL induced inflammatory response in HMC-1 cells via TLR4, ERK1/2, JNK1/2 and p38 MAPK pathway.

GW26-e2928
No Distinct Association Between COMT Val158Met Polymorphism and Blood Pressure and Serum Lipid Levels in the Oldest Olds From Guangxi Bama Area
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OBJECTIVES To see the possible relationship between COMT Val158Met polymorphism and blood pressure (BP) and serum lipid levels and its putative role in human longevity in the long-lived families inhabiting along Hongshuihe River Basin in Guangxi Province.

METHODS Genotyping of COMT Val158Met was conducted using PCR-RFLP for members from Bama long-lived families (BL, n = 1538), Bama non-long-lived families (BNL, n = 600), Pingguo (a county outside Bama region) long-lived families (PL, n = 538) and Pingguo non-long-lived families (PNL, n = 493) after anthropometric measures were collected and serum lipid levels were detected. Correlation analyses were then performed between genotypes and these variables.

RESULTS The distribution of genotypes and alleles among four families was significantly different (all P < 0.01), with GA/AA genotypic minor allele A presenting more frequently in Bama population than Pingguo Population (P < 0.01). The SBP, PP, TC, TG and LDL-C levels of GG genotype carriers were dramatically higher than non-GG carriers in BNL (P < 0.05); the SBP and PP levels of GG carriers were lower (P < 0.05) while TC, LDL-C level were higher (P < 0.01) than that of non-GG carriers in PL; no difference in blood pressure and lipids were observed between genotypes in BL and PNL (P > 0.05). Correlation analyses revealed that COMT Val158Met was positively correlated with BP in BL, negatively with SBP and DBP in BNL; TC level was negatively related to COMT polymorphism in BL, BNL and PL. LDL-C level was negatively associated with COMT polymorphism in total and Pingguo population and in BNL and PL.

CONCLUSIONS Although COMT Val158Met presented more frequently in Bama long-lived individuals, but it play limited role in BP and lipid modulation. The association between COMT Val158Met polymorphism and other phenotypes (e.g. cognition) thus warrant further investigation.

GW26-e3526
Effects of Renal Denervation on Left Atrial Fibrosis in Rats With Isoproterenol Induced Chronic Heart Failure
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OBJECTIVES To investigate effects of the renal denervation on left atrial fibrosis in rats with chronic heart failure.

METHODS 60 healthy male Sprague-Dawley rats were randomly assigned to control group (n=10) and isoproterenol induced chronic heart failure (IPiCHF) group (n=50). After 5 weeks, the 31 IPiCHF survivors were randomly divided into renal denervation (RDN) group (n=15) and sham group (n=16). Three group rats were sacrificed at 10 weeks. LVEF (left ventricular ejection fraction), IVSd (diastolic interventricular septal thickness) and LAD (left atrium dimension) were measured by echocardiogram at baseline, 5 and 10 weeks. After sacrificed, fibrosis expression of left atrial ejection tissue was detected by Masson staining, the protein expression of AngII, TGF-β1, MMP2 and collagen were determined by Western blots.

RESULTS Compared with control group, LVEF decreased (55.37±2.54 VS 75.95±2.61%, P<0.01), IVSd (1.96±0.05 VS 1.58±0.07mm, P<0.01) and LAD (5.18±0.41 VS 4.22±0.16mm, P<0.01) significantly increased in IPiCHF group at 5 weeks. Compared with sham group at 10 weeks, cardiac function significantly improved (LVEF 57.95±4.33 VS 49.31±4.35%, P<0.05), ventricular septa thickness not significantly decreased (IVSd 1.68±0.07 VS 1.56±0.08mm, P<0.05) and left atrium size reduced (LAD 4.91±0.69 VS 5.65±0.41mm) in RDN group. The Masson staining (CVF, collagen volume fraction) showed the fibrosis of left atrium tissue significantly decreased in RDN group than sham group (P<0.01). The western blots test demonstrated the expression of AngII, TGF-β1, MMP2 and collagen significantly down-regulated in RDN group but not in sham group (all P<0.05).

CONCLUSIONS RDN can effectively attenuate the left atrial fibrosis in IPiCHF rats. Our study demonstrated that RDN decreased left atrium size and tissue CVF. The attenuation of left atrium fibrosis by RDN may be attributed to cardiac function improvement and pro-fibrogenic factors (AngII, TGF-β1, MMP2 and Collagen) expression down-regulated in rats with CHF.

GW26-e3549
The Protective Effect of Aqueous Extracts of Tribulus Terrestris on Oxidized LDL-Induced Endothelial Injury
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OBJECTIVES To observe the efficacy of aqueous extracts of Tribulus terrestris (TET) on endothelial injury in obesity-related hypertensive rats and to investigate the protective effects of TET (30 μg/ml and
3 ug/ml) against oxidized low-density lipoprotein (ox-LDL)-induced Human umbilical vein endothelial cells (HUVECs) dysfunction in vitro.

**METHODS** In vivo, obesity-related hypertensive rat models were induced by high-fat diet for 25 weeks. The aqueous extract of TT and telmisartan was intragastrically administrated for 8 weeks. Body weight, blood pressure and heart rate were measured weekly to observe the slimming benefits and anti-hypertensive effects of the drugs. The endothelial morphology of the thoracic aorta was observed by HE staining and scanning electron microscope. The level of serum lipid was measured by biochemical methods, and serum leptin, AngII, ET-1, NPY and Hcy were measured. Reduced NO. arterial pressure and heart rate, and showed against weight gain effects.

**RESULTS** TT decreased systolic pressure, diastolic pressure, mean arterial pressure and heart rate, and showed against weight gain effects. TT improved endothelial integrity of thoracic aorta, decreased leptin, ET-1, NPY and Hcy, while increased NO. In vitro, TT suppressed ox-LDL-induced HUVEC proliferation and apoptosis rates significantly and TT prolonged the HUVEC survival time and postponed the cell’s decaying stage. TT improved the endothelial cytoskeletal network and increased cell migration. Additionally, TT regulated the synthesis of endothelial nitric oxide synthase and generation of intracellular reactive oxygen species. TT significantly decreased mRNA expression of PI3K and Socs3. It also increased mRNA expression of Akt1, AMPKα1, JAK2, LepR and STAT3 induced by ox-LDL. The results suggested that the JAK2/STAT3 and/or PI3K/AKT pathway might be a very important pathway which was involved in the pharmacological mechanism of TT as the vascular protective agent.

**CONCLUSIONS** TT demonstrated excellent slimming benefits, anti-hypertension and endothelial protective effects. It also suggested that the JAK2/STAT3 and/or PI3K/AKT pathway might be a very important pathway which was involved in the pharmacological mechanism of TT as the vascular protective agent.

**GW26-e3603**

**Cardiac Fibroblast Contributes to Myocardial Fibrosis in Mice With Diabetes Mellitus—Role of Cardiomyocyte-Fibroblast Interaction**

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**OBJECTIVES** The major cardiac cell type expressing HMGB1 is the cardiac myocyte (CM) while the primary IL-33 expressing cell is the cardiac fibroblast (CF). Here we delineated the extracellular communication pathway between cardiomyocyte and fibroblast that contributes to murine DiCM.

**METHODS** DM was induced in 6-week-old, male C57BL/6 mice by intraperitoneal (i.p.) injection of streptozotocin (STZ). The sex matched littermates were injected with an equal volume of citrate buffer as controls (pH = 4.5). CMs or CFs cultured individually or in co-culture were challenged with 30 mM mannitol in M199. Immunofluorescence staining and Western blot were used for assessment of protein expression of HMGB1, IL-33 and collagen I and III. A mouse pressure-volume loop analyzer was used for assessment of myocardial function.

**RESULTS** 1) myocardial expression of HMGB1 and IL-33 were detected by immunofluorescence staining and Western blot in the murine STZ model of DM. Myocardial expression of HMGB1 was increased, while that of IL-33 was decreased at 2 and 4 weeks after achieving a hyperglycemic state. HMGB1 was primarily localized to the myocytes, while IL-33 was localized to the interstitial fibroblasts. 2) Mice developed cardiomyopathy six weeks after the induction of DM as indicated by increased myocardial fibrosis and dysfunction. The myocardial collagen deposition and improvement of myocardial function were substantially attenuated by inhibition of HMGB1 or exogenous IL-33.

3) Although challenge of isolated CFs with HG increased HMGB1 production, the effects were minimal compared to those noted in CM. In vitro HG model, cardiac myocytes can potentiate the down-regulation of IL-33 in CFs; an effect mediated by myocyte-derived HMGB1.

4) HG challenge of CFs alone slightly increased collagen I expression. The effect was significantly enhanced when CFs were co-cultured with CMs; the potentiating effect was abrogated by the HMGB1 inhibitor, A-born. Further, increase in collagen I expression by isolated CFs in response to HG, was potentiated by exogenous administration of HMGB1.

5) When TLR4<sup>−/−</sup> CFs were co-cultured with wild type CMs, the CM-induced potentiation effect on down-regulation of CF IL-33 and increase in CF collagen production was negated. Two weeks after the induction of the STZ model, the expected decrease in IL-33 was noted in WT mice, but it was not evident in TLR4<sup>−/−</sup> mice. Further, in TLR4<sup>−/−</sup> mice, the STZ-induced myocardial fibrosis and dysfunction were blunted.

**CONCLUSIONS** Our data support that cardiac myocyte-fibroblast interaction plays a key role in diabetic myocardial fibrosis. Specifically, our study indicates myocyte HMGB1-fibroblast TLR4/IL-33 axis contributes to the development of myocardial fibrosis and dysfunction in mice with diabetes.

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**GW26-e3847**

**Postinfarction Gene Therapy With Hepatocyte Growth Factor Mitigates Cardiac Remodeling and Dysfunction**

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**OBJECTIVES** To investigated beneficial effects and its mechanisms of naked plasmid expressing recombinant human hepatocyte growth factor on left ventricular remodeling and dysfunction.

**METHODS** Acute myocardial infarction was induced male SD rats by ligating anterior descending of left coronary artery. These rats were randomly assigned to HGF group (n=8); a single myocardial injection of naked plasmid expressing HGF (250 ug/injection) immediately after left coronary artery ligation. Control group (n=8);myocardial injection of same dose naked plasmid without HGF, normal group (n=10); the suture was passed but not tied treated. After four or eight weeks, cardiac function was evaluated by echocardiography respectively, the cardiac specimens at eight-week time point were subjected to Masson staining and immunohistochemical analysis.

**RESULTS** Four weeks later, left ventricular remodeling and dysfunction were apparent, and LV anterior wall thickness (LVWVT) were significantly reduced (P<0.001) in the control group. However, left ventricular remodeling and dysfunction were significantly relieved (P<0.05) and LVWVT were thicker (P<0.378) in the HGF group. Eight weeks later, HGF-treated rats showed that left ventricular remodeling and dysfunction were still significantly improved (P<0.05, furthermore significant mitigation of LVWVT was seen in HGF-treated rats (P<0.05). Eight weeks later, the infarct size significantly reduced and the infarct wall was thicker in the HGF-treated group (P<0.05). Myocardial fibrosis was significantly reduced and the density of blood capillary was significantly increased in the myocardial infarced area in HGF group (P<0.001).

**CONCLUSIONS** Recombinant human hepatocyte growth factor improves postinfarction cardiac remodeling and dysfunction by reducing infarct size and myocardial fibrosis and increasing by density of blood capillary.

**GW26-e3875**

**Diabetes Blunt the Compensatory Enhancement of SUMOylation Intensity of Sarco(Plasm)atic Reticulum Calcium-transporting ATPase After Myocardial Infarction**

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**OBJECTIVES** Diabetes is an independent risk factor of heart failure and mortality after myocardial infarction(MI). The activity and