DCM, as evidenced by improved diabetes-induced cardiac dysfunction, hypertrophy and fibrosis, along with diminished cardiac oxidative stress, inflammation, and insulin resistance, not only in the mice sacrificed immediately or 3 months later following the three-month treatment. Furthermore, phosphorylated extracellular signal-regulated kinases (ERK) 1/2, a well-known initiator of cardiac hypertrophy, was significantly increased, while dual specificity phosphatase 5 (DUSP5), an ERK1/2 nuclear phosphatase, was substantially decreased in diabetic hearts. Both of these changes were prevented by RGFP966. Chromatin immunoprecipitation assay showed that HDAC3 inhibition elevated histone H3 acetylation on the *DUSP5* gene promoter at both two-time points.

CONCLUSIONS These findings suggest that diabetes-activated HDAC3 inhibits DUSP5 expression through deacetylating histone H3 on the primer region of *DUSP5* gene, leading to the derepression of ERK1/2 and the initiation of DCM. This study indicates the potential application of HDAC3 inhibitor for the prevention of DCM.

GW28-e1058

Trimetazidine Prevents Cardiac Rupture in Mice with Myocardial Infarction by Suppressing Oxidative Stress

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OBJECTIVES Cardiac rupture (CR) is a catastrophic complication of acute myocardial infarction (MI). At present, there are no effective pharmacological strategies for preventing post-MI rupture. Here we investigated the effect of trimetazidine (TMZ) on post-MI cardiac rupture and its underlying mechanisms of action.

METHODS MI models were induced by left coronary artery ligation in male C57BL/6 mice, with shams undergoing the same operation without coronary artery ligation. The operated mice were randomly divided into 4 groups: sham+saline, sham+TMZ, MI+saline and MI+TMZ (20mg/kg/day) treatment group. Animals allocated to the rupture incidence were closely monitored for 7 days; autopsy was performed once animals were found dead to determine the reason of death, and infarct size was determined. Heart function was detected by echocardiography. Oxidative stress markers were analyzed by Western blotting. Cultured neonatal cardiomyocytes and H9c2(2-1) were exposed to normoxia or anoxia and treated with TMZ.

RESULTS Since CR in mice mostly happen within the first week after MI, we observed the incidence of CR of MI mice for one week. We found that the CR rate of mice treated with TMZ was significantly lower than the saline-treated group (34.4% vs. 19.4%, $P<0.05$). To investigate the mechanism of the effect of TMZ on CR, we examined the expression of MMP2, MMP9 in the cardiac tissues of the sham-operated and MI groups of mice. The results showed that the MMP2, MMP9 expression in the TMZ-treated group was significantly lower than the saline-treated group. Further, we found that ROS and H_2O_2 level increased dramatically after MI, and TMZ treatment abolished level of ROS and H_2O_2. To further examine the action of TMZ on MMP2, MMP9 expression, we pretreated H9c2(2-1) and primary cardiomyocytes with anoxia and found that TMZ treatment increased expression of MMP2, MMP9. TMZ pretreatment markedly decreased the expression of MMP2, MMP9, and reduced level of ROS and H_2O_2 by anoxia.

CONCLUSIONS TMZ prevents cardiac rupture through inhibition of oxidative stress, which is attributable to the down-regulation of MMP2, MMP9 expression. Our findings suggested that early administration of TMZ to patients with acute MI is a potential preventive approach for CR.

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GW28-e1060

Involvement of histone methylation in macrophage apoptosis and unstable plaque formation in methionine induced hyperhomocysteinemic ApoE-/- mice

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OBJECTIVES Hyperhomocystinemia(Hhcy) is an independent risk factor of atherosclerosis and promotes the unstable plaque formation. Epigenetic mechanisms play an important role in the pathogenesis of atherosclerosis induced by Hhcy. However, the exact mechanism still undefined. The present study sought to determine the hypothesis whether histone methylation modification is involved in macrophage apoptosis and unstable plaque formation in the condition of Hhcy.

METHODS $ApoE^{-/-}$mice were supplemented with high-methionine (HM) diet for 20 weeks to induce Hhcy. Macrophage Raw 264.7 cells were challenged with homocysteine and histone inhibitor BIX 01294.

RESULTS The hallmark of unstable plaque, lesion apoptotic cells are increased in $ApoE^{-/-}$mice supplemented with high-methionine (HM), accompanied with a decrease expression of histone H3 lysine 9 dimethylation. Hcy increases the apoptosis of macrophage and inhibits the histone H3 lysine 9 dimethylation and the expression of histone methyltransferase G9a in vitro. Inhibition of histone methylation by BIX01294 enhances the macrophage apoptosis and foam cell formation in vitro.

CONCLUSIONS Our data suggests that Hhcy promotes the progression of atherosclerosis via macrophage apoptosis. Histone methylation might involve in macrophage apoptosis and unstable plaque formation in methionine induced hyperhomocysteinemic $ApoE^{-/-}$ mice.

GW28-e1061

The role of LXRα in homocysteine induced foam cell formation

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OBJECTIVES To investigate the role of Liver X α (LXRα) in homocysteine(Hcy) induced foam cells formation.

METHODS THP-1 monocytes were cultured and induced by ox-LDL to become to foam cell. Then cells were intervened by different concentrations of homocysteine(Hcy) and LXRα agonist T0901317 for 24 hours. Oil red O staining was performed for identification and qualitative analysis. The protein expression of LXRα and its target gene ABCG1 as well as ABCA1 was detected by cyto-immunofluorescence and Western blot.

RESULTS Oil red staining showed that Hcy facilitate foam cell formation. The immunofluorescence and Western blot result suggest that the protein expression of LXRα, ABCG1 and ABCA1 were decreased after the intervention of Hcy and T0901317 could reverse this effect.

CONCLUSIONS Our results suggesting that LXRα might be one of the key role of macrophage lipid metabolism interrupted by Hcy.

GW28-e1062

WWC3 inhibits intimal proliferation after vascular injury through Hippo signaling pathway

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OBJECTIVES To investigate the effect of WWC3 on vascular smooth muscle cells (VSMCs) after injury and its possible mechanism.

METHODS We used platelet-derived growth factor BB (PDGF-BB) as cell injury, rats with balloon injury to make model of rat carotid artery intima injury. Detect the expression of WWC3 in A10 cells (VSMCs) and arteries after injury, and the influence on the proliferation and migration of VSMCs by MTT, Transwell, Western blot, immunohistochemical, and other methods. By regulating WWC3 expression, with luciferase activity assay, immunoprecipitation and other methods, to investigate the molecular mechanism of WWC3 on Hippo signaling pathway.

RESULTS After injury, the expression of WWC3 decreased in A10 cells and rat carotid artery, Hippo signaling pathway activity down-regulated significantly, the expression of YAP (main effector of Hippo signaling pathway), and its main negative downstream target genes such as CTGF increased, enhancing the proliferation WWC3. Over-expressing WWC3, meanwhile stimulating with PDGF-BB, the proliferation and migration of VSMCs were significantly weakened, compared with stimulating with PDGF-BB alone. It is confirmed that WWC3 could interact with LATS1 by co-immunoprecipitation, induce phosphorylation of LATS1, inhibit the nuclear import of YAP with phosphorylation of YAP, thereby upregulate Hippo pathway activity. However, transfecting WWC3-ΔWW, this effect disappeared.

CONCLUSIONS WWC3 expression is down-regulated in VSMCs and the neointimal hyperplasia after the injury (with PDGF-BB or balloon injury), inhibiting the activity of Hippo signaling pathway, enhancing the ability of proliferation and migration of VSMCs. WWC3 can interact with LATS1, to promote the phosphorylation of YAP and reduce its nuclear transference, upregulating Hippo signaling