Further, the two variants on SCAP and AGXT2 were introduced into H293T and EA. hy926 cell lines respectively utilizing CRISPR-Cas9 measure. Functional study revealed that the SCAP mutation impaired SCAP-SREBP feedback mechanism which may lead to a "consititutive activation" effect of cholesterol synthesis related genes, while the AGXT2 mutation caused a deficiency of its aminotransferase activity which would lead to a down-regulation of NO production by ADMA accumulation.

CONCLUSIONS SCAP and AGXT2 are potential causative genes for MI. Digenic mutation carriers may manifest a more severe phenotype, namely premature MI. In addition, the present results also hints the role of digenic (or polygenic) mutations in the molecular genetic mechanism of PMI.

GW27-e0471

Cardiac contractility modulation attenuate myocardial fibrosis by inhibiting TGF-β1/Smad3 signaling pathway in a rabbit model of chronic heart failure

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OBJECTIVES Cardiac Contractility Modulation(CCM) is an novel diviced-based therapy which delivery of non-excitatory electrical signals resulting in improved ventricular function. In our study, We investigated the effect of CCM on myocardial fibrosis in heart failure and investigate the underlying mechanism.

METHODS Thirty rabbits are divided into three groups: sham operated controls (C group, n=10), where the rabbits underwent thoracotomy only; HF with no CCM (HF group, n=10), where the rabbits underwent thoracotomy and ligate the ascending aortic from the distally of its root about 1.0cm, make sure the circumference of aortic at the constriction is 60% of its original circumference; HF with CCM (CCM group, n=10), where the rabbits underwent thoracotomy and legate the ascending aortic. The temporary pacing electrode used to delivery CCM was respectively sutured to left ventricular anterior wall in each group. After the formation of chronic heart failure only CCM group received CCM, CCM(R sensed delay 30ms, 7V, duration 2ms) lasting six hours everyday for 4weeks. Histology examination was carried out to evaluate the myocardial pathological changes. Protein levels of collagen I, collagen III, α-SMA, MMP2, MMP9, TIMP1, TGF-β1 and Smad3 were measured by western blot analysis. Expression of TGF-β1 and Smad3 mRNA were measure by real time polymerase chain reaction.

RESULTS Histology examination results showed that CCM therapy attenuated myocardial fibrosis and collagen deposition in chronic heart failure rabbits. The myocardial collagen volume fraction (CVF) of heart failure reduced 10.11% by CCM. Moreover protein levels of collagen I, collagen III, α-SMA, MMP2, MMP9 were down regulated by CCM ($p < 0.05$, respectively). Furthermore, CCM therapy decreases both protein and mRNA levels of TGF-β1 and Smad3 in heart failure rabbits ($p < 0.05$, respectively).

CONCLUSIONS CCM therapy exerted protective effects against myocardial fibrosis may by inhibiting TGF-β1/Smad3 signaling pathway in chronic heart failure rabbits.

GW27-e0475

Role of AMP-activated protein kinase (AMPK) in Resveratrol preconditioning against cardiomyocytes anoxia/reoxygenation injury

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OBJECTIVES To investigate the relationship between the cardioprotective effect of resveratrol from anoxia/reoxygenation injury and AMPK pathway.

METHODS H9c2 cardiomyocytes were divided into normal control group, A/R group and resveratrol pretreatment group. Expression of AMPK was determined by Western blot, and cell viability was measured by MTT method. LDH, SOD and GSH-Px activity were determined by chromometry.

RESULTS After 12h resveratrol precondition, the expression of AMPK was upregulated in cardiomyocytes ($P<0.01$). In the group pretreated with resveratrol before A/R, cell viability increased; the activity of LDH in culture medium decreased; the activity of intracellular SOD, GSH-Px increased ($P<0.01$).

CONCLUSIONS The effect of resveratrol against A/R injury in cardiomyocytes involves AMPK pathway, and at least partly depends on its effect of upregulating the expression of AMPK.

GW27-e0481

mRNA expression profile analysis of WenxinKeli treated rabbits with myocardial infarction

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OBJECTIVES There is little evidence proving the molecular mechanism of WenxinKeli (WXKL). This study tried to explore the gene expression profile and pathology alteration of WXKL treated rabbits with myocardial infarction.

METHODS Twenty male adult rabbits were randomly divided into 4 groups: sham, model, WXKL and captopril groups. Model, WXKL and captopril groups underwent the ligation of the left anterior descending coronary artery while sham group went through an identical procedure without ligation. WXKL (817mg/kg/d), captopril (8mg/kg/d) and distilled water (model and sham) were administered orally to the rabbits. 4 weeks later, hearts were taken out for expression chip and pathological staining (HE, Masson and Tunel) after echocardiography.

RESULTS WXKL could down-regulate genes associated with inflammation (CX3CR1, MRC1, and FPR1), apoptosis (Cathepsin C and TTC5), neuro-humoral system (ACE and EDN1) and up-regulate angiogenesis promoting gene like RSPO3, which explained why WXKL group represented with better cardiac function, less histopathological injury and slighter apoptosis.

CONCLUSIONS The present study showed that WXKL had played an important role in suppressing inflammation, inhibiting renin-angiotensin system, alleviating apoptosis and might be a promising Chinese medicine in treating patients with myocardial infarction.

GW27-e0513

Inhibition of mammalian target of rapamycin complex 1 protects against reperfusion injury in heart through STAT3 signaling

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OBJECTIVES Patients suffer alleviated severity of ischemia-reperfusion with the use of rapamycin. Excessive activation of the mammalian target of rapamycin (mTOR) and decreased activation of STAT3 are implicated in infarction and repferfusion injury. Considering the potent cardioprotective effect of mTOR inhibitor, rapamycin, we hypothesized that reperfusion therapy with rapamycin would reduce infarct size in hearts through STAT3 signaling.

METHODS Eight week-old wild type mice (WT) inoculated intraperitoneally to low dose(50nM) and high dose(100nM) rapamycin were subjected to 30 min of ischemia followed by 24h reperfusion. Echocardiogram was performed for analysis of cardiac function. I/R injury was evaluated by IS(infarcted size)/AAR(Area at Risk) using TTC staining. The expressions of mTOR, Raptor, Rictor, p-AKT, p70s6k, STAT3 were analyzed by Western blot. WT and Cardiac conditional Raptor (component of mTORC1 complex) knockout (Raptor KO) mice were subjected to 30 min of ischemia followed by 24h reperfusion, respectively, To determine the cause and effect relationship of STAT3 in cardioprotection, a STAT3 inhibitor (5, 15-DPP) was given to both WT and Raptor (KO) mice at reperfusion. Cardiomyocytes isolated from Raptor (KO) mice were treated during reoxygenation following simulated ischemia. Necrosis and apoptosis of the cardiomyocytes were determined by Trypan blue staining and TUNEL assay.

RESULTS IS/AAR was significantly reduced in low dose(LD) rapamycin(Rapa) treated group. LD Rapa+ I/R mice (45.3 ± 2.4%) compared to I/R mice (63.9 ± 0.9%) or HD (high dose) Rapa+ I/R mice (57.7 ± 1.1%). Left ventricular ejection fraction (LVEF) was prominently preserved in LD Rapa treated mice(65.6±1.54%) compared to I/R mice (53.44±2.25%) or HD (high dose) Rapa+ I/R mice (55.80±1.76%); LD Rapa treatment restored phosphorylation of STAT3 and enhanced AKT phosphorylation (target of mTORC2), but significantly reduced ribosomal protein S6 phosphorylation (target of mTORC1) in the I/R heart. Inhibition (5, 15-DPP) of STAT3 in both WT and Raptor (KO) mice at reperfusion, the cardioprotection was diminished during I/R in Raptor (KO) group. Necrosis and apoptosis analysis showed such protection of Raptor (KO) was also absent in cardiomyocytes treated with 5, 15-DPP.

CONCLUSIONS Inhibition of mTORC1 reducing IS/AAR and attenuates cardiomyocyte death following reperfusion via STAT3 signaling pathway.