ABSTRACTS

Abstracts for Posters:

P1.

FUNCTIONAL TRANSIENT RECEPTOR POTENTIAL CHANNELS AND ADIPOGENIC REGULATION IN HUMAN PREADIPOCYTES

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Background: Preadipocytes are extensively used as a type of proliferative cell culture model to investigate proliferation and differentiation of adipocytes and lipodystrophy (e.g. obesity)-related metabolic dysfunctions and disorders. However, cell biology is not well understood in human preadipocytes. The present study was to investigate the expression of transient receptor potential (TRP) channels in human preadipocytes, and their role in regulating adipogenesis.
Methods: Whole-cell patch voltage-clamp, RT-PCR, Western blot, and confocal microscopic approaches were used to determine functional expression of TRP channels in cultured human preadipocytes. ShRNA targeting TRP channels were constructed to silence the related TRP channels. Adipogenesis and oil red O staining were applied to observe the effect of the TRP channels on cell differentiation.
Results: A small background current was inhibited by the TRPC channel blocker La^{3+}. Removal of Mg^{2+} of pipette solution or bath solution induced a Mg^{2+}-sensitive current, and the current was suppressed by the TRP channel blocker 2-aminoethoxydiphenyl borate. In addition, an intracellular Ca^{2+}-activated current was inhibited by the TRPV channel blocker capsazepine. RT-PCR revealed significant mRNA expression of TRPC1, TRPC4, TRPV2, TRPV4, and TRPM7 channels in human preadipocytes. Western blot analysis confirmed the protein expression of these TRP channels. Interestingly, shRNAs targeting TRPV2, TRPV4 and TRPM7 suppressed the corresponding gene and protein expression and significantly reduced adipogenesis of human preadipocytes, which was revealed by the reduced oil red O staining and the decreased expression of peroxisome proliferator-activated receptor gamma (PPARγ, a marker of adipogenesis).
Conclusion: Our results demonstrate for the first time that multiple TRP channels, TPC1/4, TRPV1/2/4, and TRPM7, are present in human preadipocytes. TRPV2, TRPV4 and TRPM7 channels participate in regulating adipogenesis.

P2.

AGING, HYPERTENSION AND HEART ENLARGEMENT INCREASED THE RISK OF VENTRICULAR ARRTHYMIA IN GENERAL POPULATION

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Objectives: To investigate the risk factors of arrthymia in general population.
Methods: A total of 25788 subjects were enrolled from an annual health examination. Their average age was 45±11.1 years, each of them received ECG examination. Heart enlargement was determined by cardio-thoracic proportion >= 0.5 on chest X-ray.
Results: Prevalence of hypertension was 30.6%, and that of diabetes was 6.0%. The rate of all cause of ECG abnormalities was 20.8%, and that of ventricular premature was 0.6%. Logistic regression showed that age>=65 years (OR 2.65, 95% CI 1.68-4.17, P<0.001), hypertension (OR 1.56, 95% CI 1.11-2.20, P=0.01) and heart enlargement (OR 4.74, 95% CI 1.11- 20.3, P=0.36) were independent predictors for presence of ventricular premature, but other variables such as hypercholesterolemia and hyperglycerides were not.
Conclusions: This study showed that aging, hypertension and heart enlargement increased risk of ventricular arrthymia in general population.

Table. Logistic Regression Analysis for Predicting

	Ventricular Premature	
Variables	**OR (95% CI)**	**P-value**
Age >=65 years	2.65 (1.68-4.17)	<0.001**
Female gender	1.09 (0.78-1.51)	0.63
Hypertension	1.56 (1.11-2.20)	0.01*
Diabetes	1.26 (0.72-2.21)	0.42
Left ventricular hypertrophy	2.13 (0.66-6.89)	0.21
Heart enlargement	4.74 (1.11-20.3)	0.036*

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DRUG-INDUCED QT PROLONGATION IN GUINEA PIG IS AUTOMATICALLY ANALYZED BY MICRO-MAGNETOCARDIOGRAPHY SYSTEM WITH SUPERCONDUCTING QUANTUM INTERFERENCE DEVICE: COMPARISON WITH ECG

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Objectives: Drug-induced QT prolongation is a critical problem for drug development process. The guideline of International Conference on Harmonization requires to evaluate pre-clinical potential hazards of drug-induced QT prolongation. We have developed a micro-magnetocardiography (MCG) system for small animals comprised of ultrafine magnetometer array consisting of a 3×3 matrix of superconducting quantum interference device (SQUID) on a single silicon chip of 10 mm square.
Methods: Ten male Hartley guinea pigs (250 g) were anesthetized with pentobarbital. Platinum needle electrodes were attached to animals. Excessive quinidine (60 mg/kg) was administered intraperitoneally. MCG and ECG were recorded simultaneously at baseline, 3, 5, 7, 10, 15 min after injection. QT interval was automatically analyzed (PowerLab, ADInstruments Pty Ltd) and QTc was calculated by Bazett formula.
Results: QTc was prolonged from 284±10 to 299±11 msec in ECG (QTc-ECG). QTc was prolonged from 280±16 msec to 295±10 msec in MCG (QTc-MCG). QTc-MCG correlated well with QTc-ECG at baseline ($r2=0.944$, $p<0.0001$) and at 15 min after injection ($r2=0.780$, $p=0.0007$).
Conclusion: Micro-MCG successfully measured drug-induced QT prolongation with good correlation with ECG in guinea pig. Non-contact characteristics of MCG may enable high throughput screening test of drug-induced QT prolongation in the small animal.

P4.

PROTECTION AGAINST OXIDATIVE STRESS-INDUCED DAMAGE IN ENDOTHELIAL CELLS BY ERGOTHIONEINE

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Ergothioneine is abundantly found in mushroom. It possesses strong antioxidant effects by removing radical species or chelating metal ions. However, these antioxidant effects are mainly studied in simple cell-free systems but not in *in intro* or *in vivo* study. It is also not known whether ergothionine can enter the cells to exert antioxidant effect since ergothioneine is not permeable to cell membrane and a specific carrier noval organic cation transporter (OCTN)-1 is required for its cellular internalization. The objective of this study was to investigate whether or not ergothioneine can be taken up by endothelial cells, thereby protecting endothelial cells against oxidative stress-induced cellular damage.

Experimental results show that [^{3}H]ergothioneine could be taken up by human umbilical vein endothelial cells (HUVECs) through a sodium-dependent and transporter-dependent system. This ergothionine transport system was probably OCTN-1. In line with this notion, the results of RT-PCR demonstrated that OCTN-1 was expressed in HUVECs. Reactive oxygen species (ROS) generation of HUVECs was detected by the fluorescence intensity of DCF. The pyrogallol and xanthine/xanthine oxidase-induced production of ROS could be decreased by ergothionine. In addition. MTT assay was used to study the viability of HUVECs. The cytotoxic effects of hyperglycemia and hydrogen peroxide on HUVECs could be reduced by ergothionine.

In conclusion, our recent findings suggest that ergothioneine can be taken up by endothelial cells, probably through OCTN-1. Besides, ergothioneine is a potential agent that can protect endothelial cells against oxidative stress-induced cellular damage.

Acknowledgement: This study was financially supported by the RGC general research fund (project number: 771410).

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P5.

OVARIECTOMY PROMOTES THE ENHANCEMENT OF ENDOTHELIUM-DERIVED HYPERPOLARIZING FACTOR-MEDIATED RELAXATION IN MESENTERIC ARTERIES OF RATS WITH CHRONIC NITRIC OXIDE SYNTHASE INHIBITION

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Background and objectives: Gender differences exist in the incidence and manifestation of vascular diseases, of which endothelial dysfunction is the underlying cause. Endothelial dysfunction is associated with a reduced bioavailability of nitric oxide. Therefore, the effects of ovariectomy with and without 17β-estradiol supplement on endothelial function were examined in rats following chronic inhibition of nitric oxide synthases with L-NAME.
Methods: Female Sprague Dawley rats were ovariectomized or sham-operated at 12 weeks old. Half of ovariectomized rats were supplemented with 17β-estradiol (25 $\mu gkg^{-1}day^{-1}$, intramuscularly) or its vehicle (olive oil) until they were sacrificed. At 18 weeks old, all rats were administered daily with L-NAME (60 $mgkg^{-1}$, by gavage) or its vehicle (drinking water) for 6 weeks. Rats were then anaesthetized for blood pressure measurement and for isolation of mesenteric arteries for isometric tension measurement in organ baths.
Results: Chronic L-NAME treatment did not increase blood pressure in all rats, but impaired endothelium-dependent relaxation in ovariectomized rats without 17β-estradiol supplement. This impairment was reversed in the presence of indomethacin (a cyclooxygenase inhibitor). Chronic L-NAME treatment improved endothelium-derived hyperpolarizing factor (EDHF)-mediated relaxation only in mesenteric arteries of ovariectomized rats without 17β-estradiol supplement, although ovariectomy alone reduced EDHF-mediated relaxation.
Conclusions: Inhibition of cyclooxygenase alone, but not 17β-estradiol supplement, improved endothelial function in ovariectomized rats with chronic nitric oxide synthase inhibition. This greater relaxation appears to be mediated by EDHF, the function of which is enhanced when there is the occurrence of cyclooxygenase-dependent contraction.

This study was supported by a General Research Fund of the Research Grant Council of HKSAR, and a Committee on Research and Conference Grant, The University of Hong Kong.

P6.

PURINERGIC RECEPTORS MEDIATE PROLIFERATION AND MIGRATION IN CULTURED HUMAN CARDIAC FIBROBLASTS

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Objectives: Physiological role of ATP in human cardiac fibroblasts is unknown, and the present study was to investigate whether ATP regulates proliferation and migration and purinergic receptors involvement in cultured human cardiac fibroblasts.
Methods and results: Cell proliferation and migration assay, RT-PCR, Western blot, siRNA gene silence, and flow cytometric analysis were used in cultured human cardiac fibroblasts. We found that ATP (1-100 μM) increased cell proliferation in a concentration-dependent manner. The P2X receptor agonist AMP-CPP and P2Y receptor agonist ATP-γS displayed a similar role in regulating cell proliferation. The P2 receptor antagonists suramin and reactive blue-2 countered the ATP-induced increase of proliferation. Silence of P2X4, P2X7 and P2Y2 with the corresponding siRNAs significantly inhibited proliferation of fibroblasts. In addition, ATP significantly promoted migration of human cardiac fibroblasts. Flowcytometry and Western blot analysis revealed that ATP promoting G0/G1 cells to S phase via increasing cyclin D1 and cyclin E protein expression, and phosphorylated Akt and ERK1/2 levels. Suramin, reactive blue-2, the PI3K inhibitor wortmannin, the Akt inhibitor API-2, and the MAPK inhibitors PD98059 reduced phosphorylated Akt and ERK1/2 levels antagonized ATP-induced increase of proliferation and migration in cultured human cardiac fibroblasts.
Conclusions: These results demonstrate the novel information that ATP stimulates proliferation and migration of human cardiac fibroblasts mediated by activating P2X4, P2X7 and P2Y2 receptors, increasing phsophorylated PI3K/Akt, MAPK/ERK1/2, and modulating cyclin D1 and cyclin E expression, which likely plays a role in cardiac remodeling of the injured heart.

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P7.

ELECTROPHYSIOLOGICAL PROPERTIES OF ENDOTHELIAL PROGENITOR CELLS FROM RAT BONE MARROW MONONUCLEAR CELLS

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Objectives: Bone marrow endothelial progenitor cells (BMEPCs) are believed to be a promising cell source for regenerative medicine; however, their electrophysiology properties have not been fully clarified, which is important to the clinical application of BMEPCs. The current study was designed to determine the transmembrane ion currents and mRNA expression levels of related ion channel subunits in rat BMEPCs.
Methods: Bone marrow mononuclear cells were isolated by density gradient separation and cultured in EPC medium. The transmembrane ion currents were determined using whole cell patch-voltage clamp technique, the levels of mRNA expression of functional ionic channels were measured using reverse transcription polymerase chain reaction (RT-PCR).
Results: We observed two types of ionic currents in undifferentiated rat BMEPCs. One was Ca^{2+}-activated potassium current (I_{kca}), which was seen in approximate 90% of cells when 1 μM Ca^{2+} was employed in pipette solution, and it was predominantly inhibited by intermediate-conductance inhibitor clotrimazole. The other one was volume-sensitive chloride current (I_{cl}), which was detected in 85.7% of cells when BMEPCs were subjected to K^+-free hypotonic extracellular solution, whose currents could be inhibited by 5-nitro-2-(3-phenylpropylamino) benzoic acid (NPPB). The corresponding ion channel genes and proteins, KCNN4 for I_{kca} and Clcn3 for I_{cl}, were confirmed by RT-PCR and western immunoblotting analysis in BMEPCs.

P8.

ROLES OF TRPV1 AND TRPV2 CHANNELS IN THE DIFFERENTIATION OF MOUSE EMBRYONIC STEM CELLS TO CARDIOMYOCYTES

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The transient receptor potential vanilloid (TRPV) channels are Ca^{2+}-permeable non-selective cation channels, which can be activated by a variety of mechanisms, including thermo, low pH, osmolarity and stretch stress. However their roles in the differentiation of mouse embryonic stem cells (mESC) to ventricular cardiomyocytes are unknown. In this study, we tested the effects of capsaicin (an activator of TRPV1 channel, 1 μM), capsazepine (a TRPV1 antagonist, 10 μM), SB366791 (a potent and selective TRPV1 inhibitor, 10 μM), and probenecid (a TRPV2 agonist, 100 μM), on mESC differentiation. In mESC differentiation stage, the capsazepine and SB366791 suppressed the embryonic body formation. qPCR results also demonstrated capsazepine and SB366791 significantly inhibited the differentiation of mESC to cardiomyocytes. Treatment of capsazepine and SB366791 suppressed the expression level of cardiomyocyte marker genes (cardiac actin, c-TnT, c-TnI, -MHC and MLC2a) to only about one tenth of that in DMSO control group. However, capsaicin did not have any significant effect on mESC differentiation. Interestingly, as an activator of TRPV2, probenecid did not up-regulate the cardiomyocyte marker genes expression, on the contrary, it inhibited this process. The marker genes expression is less than half of the control group. Together these data suggest that TRPV1 and TRPV2 channels present important roles in the differentiation of mESC to cardiomyocytes. Further study may offer a new strategy to regulate the stem cells differentiation for therapeutic transplantation.

P9.

WY14643, THE DUAL PPAR ALPHA/GAMMA AGONIST, IMPROVES ENDOTHELIAL FUNCTION IN THE AORTA OF THE SPONTANEOUSLY HYPERTENSIVE RAT

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Wy14643 is an agonist at peroxisome proliferator-activated receptors (PPAR) α and γ. PPAR α and ψ agonists are currently used in the treatment of dyslipidemia and insulin-resistance, respectively. The present study aimed to determine whether or not Wy14643 improves endothelial dysfunction in hypertension, and if so, to determine the mechanism involved. Isometric tension was measured in isolated thoracic aortic rings of spontaneously hypertensive rats (SHR). Wy14643 caused more pronounced relaxations than fenofibrate (PPARα agonist) or rosiglitazone (PPARγ agonist). MK886 (PPARα antagonist) nearly abolished the Wy14643-induced relaxation while GW9662 (PPARγ antagonist) caused a modest inhibition of the response. L-NAME (nitric oxide synthase inhibitor) and ODQ (soluble guanylyl cyclase inhibitor), given alone or in combination, inhibited these relaxations to the same extent. Compound C [adenosine monophosphate-activated protein kinase (AMPK) inhibitor] reduced Wy14643-induced relaxations to the same extent as L-NAME. Wy14643 and fenofibrate, but not rosiglitazone, significantly increased the protein expression (determined by Western blotting) of phosphorylated endothelial nitric oxide synthase and AMPK and their ratio to the total forms of the enzymes in aortae of SHR but not in those of WKY. Compound C but not L-NAME abolished the above effect. Endothelium-dependent contractions evoked by acetylcholine in the presence of L-NAME were reduced by Wy14643 and fenofibrate but not by rosiglitazone. MK886, but not GW9662, prevented the Wy14643-induced inhibition. Wy14643 and fenofibrate inhibited acetylcholine-induced prostanoid release to the same extent. Cyclooxygenase-1 expression and activity were reduced after administration of Wy14643 and fenofibrate in the aorta of SHR. The present data suggest that the PPARα agonists induce nitric oxide-mediated relaxation through activation of AMPK. This relaxing effect is more prominent with Wy14643. Together with the ability to reduce the release of endothelium-dependent contracting factors, it appears that dual PPAR agonists such as Wy14643 provide better protection against the endothelial dysfunction of spontaneous (essential) hypertension.

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P10.

UPREGULATED TRPM2 AND ITS POTENTIAL ROLE IN NEOINTIMAL HYPERPLASIA

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A hallmark in atherosclerosis is progressive intimal thickening, which leads to occlusive vascular disease such as myocardial infarction and stroke. A causation of neointimal hyperplasia is the migration and proliferation of smooth muscle cells, in which reactive oxygen species (ROS) play an important role. This study was designed to investigate the involvement of TRPM2, a member of the transient receptor potential superfamily, in neointimal hyperplasia. Neointimal hyperplasia of rat femoral artery was induced by cuff placement. The TRPM2 expression and ROS generation were detected. The effect of TRPM2 inhibitors on hydrogen peroxide-induced proliferation of primary rat aortic smooth muscle cells was further examined. It was found that arteries with cuff placement for 14 days showed distinct intimal thickening. The neointima has enhanced cell cycle activity and upregulated TRPM2 expression. ROS generation was dramatically increased in the neointima and media layer of arteries after cuff placement. *In vitro*, exposure to hydrogen peroxide at low concentration promoted the proliferation of smooth muscle cells. This effect was abolished by both TM2E3, a specific blocking antibody to TRPM2, and 2-aminoethoxydiphenyl borate, a chemical blocker. These results suggest that TRPM2 is involved in neointimal hyperplasia and is a potential therapeutic target of ROS-induced hyperplasia of vascular smooth muscle cells.

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P11.

THE FUNCTIONAL ROLE OF TRPM2 CHANNELS IN H_2O_2-INDUCED CA^{2+} RISES AND CELL APOPTOSIS IN ENDOTHELIAL CELLS

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Objectives: Melastatin-like transient receptor potential channel 2 (TRPM2) is an oxidant-sensitive, non-selective cation channel which has been shown to be widely expressed in mammalian tissues, including the vascular endothelium. Here we investigated the functional role of TRPM2 channels in hydrogen peroxide (H_2O_2)-induced endothelial Ca^{2+} responses and cell apoptosis in microvessel endothelial cells (H5V).

Methods: With the use of Cytosolic Ca^{2+} measurement, DNA ladder formation assay, DAPI Staining, western blotting, MTT assay, TRPM2 shRNA and transfection methods, it was found that TRPM2 play a key role in H_2O_2-induced endothelial Ca^{2+} responses and cell apoptosis. Application of H_2O_2 caused a significant increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]i$), which was inhibited by TM2E3, a TRPM2 specific blocking antibody, or by TRPM2 shRNA. In addition, the data of DNA ladder formation assay showed that pretreatment of TM2E3 successfully protected the cells from H_2O_2-induced apoptosis, which was also confirmed by TRPM2 shRNA. Moreover, over-expression of TRPM2 in H5V cells significantly increased cell sensitivity to Ca^{2+} overload and cell apoptosis under H_2O_2 treatment.

Results: These data strongly suggest that TRPM2 channels are involved in important intrinsic mechanisms, which mediate H_2O_2-induced Ca^{2+} overload and cell apoptosis in H5V cells. Inhibition of endogenous ROS-sensitive TRPM2 channels with TM2E3 or their specific shRNA significantly protects the vascular cells from apoptotic cell death.

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P12.

ACTIVE TRANSPORT FOR CARDIOVASCULAR HEALTH

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Background: Active transport is the travel by walking, cycling, and other non-motorized modes from a place to destinations. Research suggested that walking or cycling in about 30 minutes daily is a kind of moderate physical activity to prevent ill health. Nevertheless, it is recognized that active transport offers health gain for cardiovascular health. The objective of this study is to identify the benefits of active transport to cardiovascular health from current literature.
Methods: A review of literature published between 2005 and 2011 was conducted. Results focusing on the benefits of active transport to cardiovascular health were summarized.
Results: The review of literature showed beneficial results of active transport to cardiovascular health. Active transport could modulate heart rate and maximize blood flow to contracting muscle during exercise, at the same time, minimize the energy cost of contraction of cardiac muscle. People who walk more could have a improved systolic and diastolic blood pressure and body mass index, thus, improve the heart workload. Also, people who did less active transport reported higher risk of cardiovascular death. Nevertheless, it could improve cardiorespiratory fitness for ill-health patients.
Conclusions: It is concluded that active transport benefits cardiovascular health in a number of ways. Thus, it is recommended that participating in active transport should be encouraged and be integrated into individual's daily life in order to promote cardiovascular health.

P13.

BONE MORPHOGENIC PROTEIN-4 IMPAIRS THE ENDOTHELIAL FUNCTION THROUGH INCREASING OF OXIDATIVE STRESS IN TYPE 2 DIABETIC MICE

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Objectives: Bone morphogenic protein (BMP4) stimulates superoxide production and exerts proinflammatory effects in the endothelium. BMP4 also mediates endothelial dysfunction in hypertension. However, the role of BMP4 in endothelial dysfunction of type 2 diabetes remains unknown. The present study aims to investigate whether inhibition of BMP4 can improve the endothelial function of type 2 diabetic mice, and to study the mechanism underlying BMP4-induced oxidative stress in diabetes.
Methods: *db/db* mice were infused with BMP4 inhibitor noggin (0.4 mg/kg/day) or vehicle through osmotic pump for two weeks, and vasoreactivities of mouse aortae and mesenteric arteries were measured. Isolated aortae of *db/db* mice were treated with BMP4 inhibitors including noggin, chordin, and follistatin for 24 hours. Reactive oxidative species (ROS) in both aortic endothelium and cultured endothelial cells were measured by DHE and CM-H_2DCFDA fluorescence.
Results: Noggin infusion in *db/db* mice reduced systolic blood pressure without affecting the insulin and glucose tolerance. Endothelium-dependent relaxations (EDRs) in both aortae and resistance mesenteric arteries improved after noggin infusion in *db/db* mice. Treatment with noggin, chordin, or follistatin for 24 hours improved EDRs in *db/db* mouse aortae. ROS production was reduced by BMP4 inhibitors in *en face* endothelium of *db/db* mouse aorta. BMP4 treatment also increased ROS production in both *en face* endothelium of C57BL/6J mice and HUVECs, which was inhibited by BMP4 inhibitors, diphenyleneiodonium, and tempol. In addition, p38 inhibitor SB202190 or JNK inhibitor SP600125 also improved EDRs in *db/db* mouse aortae, and EDRs in C57BL/6J mice aortae impaired by BMP4.
Conclusions: The present study showed that inhibition of BMP4 *in vivo* reduces blood pressure and improves endothelial function of *db/db* mice. Oxidative stress, p38 and JNK activation contribute to BMP4-induced endothelial dysfunction in diabetes. BMP4 could be a potential therapeutic target in the treatment of diabetic vascular dysfunction.