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Full Record

Record 1 of 6 (Set #2) ▶ SUMMARY

Title: Insulin-like growth factor-1 mediates stretch-induced upregulation of myostatin expression in neonatal rat cardiomyocytes

Author(s): **Shyu KG**, Ko WH, Yang WS, Wang BW, Kuan P

Source: CARDIOVASCULAR RESEARCH 68 (3): 405-414 DEC 1 2005

Document Type: Article

Language: English

Cited References: 32 **Times Cited:** 1 FIND RELATED RECORDS

Abstract: Objectives: Myostatin, a negative regulator of muscle growth, is increased in hypertrophied and infarcted heart. However, the mechanism of regulation is not known. Mechanical stress is an important regulatory factor for cardiomyocyte growth. The aim of the study was to investigate the effect of cyclic stretch on the expression of myostatin gene in cardiomyocytes.

Methods: Neonatal Wistar rat cardiomyocytes grown on a flexible membrane base were stretched by vacuum to 20% of maximum elongation at 60 cycles/min. An in vivo model of aorta-caval shunt in adult rats was used to investigate the myostatin expression.

Results: Cyclic stretch significantly increased myostatin protein and mRNA expression after 6 to 18 11 of stretch. Addition of the p38 mitogen-activated protein (MAP) kinase inhibitor SB203580, insulin-like growth factor-1 (IGF-1) monoclonal antibody, and p38 siRNA 30 min before stretch inhibited the induction of myostatin protein. Cyclic stretch increased, while SB203580, IGF-1, and 1GF-1 receptor antibody abolished, the phosphorylated p38 protein. Gel shift assays showed significant increase of DNA-protein binding activity of myocyte enhancer factor 2 (MEF2) after stretch, and transfection with p38 siRNA abolished the DNA-protein binding activity induced by cyclic stretch. Cyclic stretch significantly increased the IGF-1 secretion from myocytes. Both conditioned media from stretched myocytes and exogenous administration of IGF-1 recombinant protein to the non-stretched myocytes increased myostatin protein expression similar to that seen after cyclic stretch. An in vivo model of aorta-caval shunt in adult rats also demonstrated the increased myostatin expression in the myocardium.

Conclusions: Cyclic mechanical stretch enhances myostatin expression in cultured rat neonatal cardiomyocytes. The stretch-induced myostatin is mediated by IGF-1 at least in part through a p38 MAP kinase and MEF2 pathway. (c) 2005 European Society of Cardiology. Published by Elsevier B.V. All rights reserved.

Author Keywords: myostatin; insulin-like growth factor-1; myocytes; cyclic stretch; p38 MAP kinase

KeyWords Plus: CYCLICAL MECHANICAL STRETCH; BETA SUPERFAMILY MEMBER; VEIN ENDOTHELIAL-CELLS; TRANSCRIPTION FACTORS; CARDIAC-HYPERTROPHY; GENE-EXPRESSION; MUSCLE-CELLS; INDUCTION; P38; HEART

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Full Record

Record 2 of 6 (Set #2) | SUMMARY

Title: Combined cord blood stem cells and gene therapy enhances angiogenesis and improves cardiac performance in mouse after acute myocardial infarction

Author(s): Chen HK, Hung HF, **Shyu KG**, Wang BW, Sheu JR, Liang YJ, Chang CC, Kuan P

Source: EUROPEAN JOURNAL OF CLINICAL INVESTIGATION 35 (11): 677-686 NOV 2005

Document Type: Article

Language: English

Cited References: 34 **Times Cited:** 0 FIND RELATED RECORDS

Abstract: Background Gene and stem cell therapies hold promise for the treatment of ischaemic cardiovascular disease. However, combined stem cell and angiogenic growth factor gene therapy for acute ischaemic myocardium has not been previously reported. This study hypothesized that combined stem cell and gene therapy would not only augment new vessels formation but also improve myocardial function in acute ischaemic myocardium.

Materials and methods Human angiopoietin-1 (Ang1) cDNA and VEGF(165) cDNA were ligated into AAV vector. The purified CD34 (+) cells were obtained from human umbilical cord blood samples. Cord blood CD34(+) cells were transduced with AAV vector encoding either the human Ang1 (AAV-Ang1) or VEGF(165) (AAV-VEGF) cDNA alone, or both (AAV-Ang1 plus VEGF). Immediately after ligation of the left anterior descending coronary artery in male SCID mice, culture-expanded CD34(+) cells transduced with AAV-Ang1, AAV-VEGF or AAV-Ang1 plus VEGF were injected intramyocardially at the left anterior free wall.

Result Western blot showed that Ang1 and VEGF protein expressions were enhanced in the CD34(+)cells transduced with AAV-Ang1 and AAV-VEGF, respectively. Infarct size significantly decreased and capillary density significantly increased after treatment with CD34(+)/AAV-Ang1 plus VEGF when compared with treatment by CD34(+) only. Combined therapy with CD34(+) and AAV-Ang1, CD34(+) and AAV-VEGF, CD34(+) and AAV-Ang1 plus VEGF, all showed significantly higher cardiac performance in echocardiography than the therapy with CD34(+) alone 4 weeks after myocardial infarction.

Conclusions Combined therapy with human umbilical cord blood CD34(+) cells and both Ang1 and VEGF genes reduced infarct size, attenuated the progression of cardiac dysfunction and increased capillary density in acute myocardial infarction in mice.

Author Keywords: acute myocardial infarction; angiogenesis; angiopoietin-1; cell therapy; vascular endothelial growth factor; vasculogenesis

KeyWords Plus: ENDOTHELIAL GROWTH-FACTOR; PROGENITOR CELLS; ANGIOPOIETIN-1; ISCHEMIA; REGENERATION; MODEL; RAT; TRANSPLANTATION; CARDIOMYOCYTES; EXPRESSION

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Full Record

Record 3 of 6 (Set #2) | SUMMARY

Title: Regulation of discoidin domain receptor 2 by cyclic mechanical stretch in cultured rat vascular smooth muscle cells

Author(s): **Shyu KG**, Chao YM, Wang BW, Kuan PL

Source: HYPERTENSION 46 (3): 614-621 SEP 2005

Document Type: Article

Language: English

Cited References: 34 **Times Cited:** 0 FIND RELATED RECORDS

Abstract: Discoidin domain receptor 2 (DDR2) plays potential roles in the regulation of collagen turnover mediated by smooth muscle cells in atherosclerosis. How mechanical stretch affects the regulation of DDR2 in smooth muscle cells is not fully understood. We sought to investigate the cellular and molecular mechanisms of regulation of DDR2 by cyclic stretch in smooth muscle cells. Rat vascular smooth muscle cells grown on a flexible membrane base were stretched by vacuum to 20% of maximum elongation, at 60 cycles/ min. Cyclic stretch significantly increased DDR2 protein and mRNA expression after stretch. Cyclic stretch also significantly increased DNA - protein binding activity of Myc- Max. Addition of SB203580, transforming growth factor-beta 1 (TGF-beta 1) monoclonal antibody, p38 small interfering RNA (siRNA), and c-myc siRNA 30 minutes before stretch inhibited the induction of DDR2 protein and abolished the DNA - protein binding activity induced by cyclic stretch. Cyclic stretch increased, whereas SB203580 abolished the phosphorylated p38 protein. Conditioned medium from stretched smooth muscle cells and exogenous administration of angiotensin II and TGF-beta 1 recombinant proteins to the nonstretched cells increased DDR2 protein expression similar to that seen after stretch. In conclusion, cyclic mechanical stretch enhances DDR2 expression in cultured rat smooth muscle cells. The stretch- induced DDR2 is mediated by angiotensin II and TGF-beta 1, at least in part, through p38 mitogen- activated protein kinase and Myc pathway.

Author Keywords: muscle, smooth, vascular; protein kinases; angiotensin II; transforming growth factors

KeyWords Plus: GROWTH-FACTOR-BETA; DISCOIDIN DOMAIN RECEPTOR-1; TYROSINE KINASE; ANGIOTENSIN-II; PROLIFERATION; COLLAGEN; EXPRESSION; MIGRATION; STRESS; MYC

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Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST,

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ISSN: 0194-911X

Record 3 of 6 (Set #2) SUMMARY

Full Record

Title: Carvedilol prevents cardiac hypertrophy and overexpression of hypoxia-inducible factor-1 alpha and vascular endothelial growth factor in pressure-overloaded rat heart

Author(s): **Shyu KG**, Liou JY, Wang BW, Fang WJ, Chang H

Source: JOURNAL OF BIOMEDICAL SCIENCE 12 (2): 409-420 2005

Document Type: Article

Language: English

Cited References: 26 **Times Cited:** 0 FIND RELATED RECORDS

Abstract: The use of beta-blockers has emerged as a beneficial treatment for cardiac hypertrophy. Hypoxia-inducible factor-1 alpha (HIF-1 alpha) is tightly regulated in the ventricular myocardium. However, the expression of HIF-1 alpha in cardiac hypertrophy due to pressure overload and after treatment with beta-blocker is little known. To evaluate the effect of carvedilol on both myocardial HIF-1 alpha expression and cardiac hypertrophy, infrarenal aortic banding was performed for 4 weeks in adult Sprague-Dawley rats to induce cardiac hypertrophy. Carvedilol at 50 mg/kg body weight per day after surgery was given. Heart weight and the ratio of heart weight and body weight increased significantly after aortic banding for 4 weeks in the absence of drug treatment. Mean arterial pressure increased from 80 +/- 9 mmHg in the sham group to 94 +/- 5 mmHg ($p < 0.001$) in the banding group. Echocardiography showed concentric hypertrophy after aortic banding. Mean arterial pressure decreased after treatment with carvedilol. The increased wall thickness and heart weight was reversed to normal by carvedilol. Western blot showed that HIF-1 alpha, vascular endothelial growth factor (VEGF) and brain natriuretic peptide (BNP) proteins were up-regulated and nerve growth factor-beta (NGF-beta) down-regulated in the banding group. Treatment with valsartan, doxazosin, or N-acetylcysteine did not significantly affect HIF-1 alpha and VEGF proteins expression in the banding groups. Real-time polymerase chain reaction showed that mRNA of HIF-1 alpha, VEGF and BNP increased and mRNA of NGF-beta decreased in the banding group. Treatment with carvedilol reversed both protein and mRNA of HIF-1 alpha, VEGF, BNP, and NGF-beta to the baseline values. Increased immunohistochemical labeling of HIF-1 alpha, VEGF, and BNP in the ventricular myocardium was observed in the banding group and carvedilol again normalized the labeling. In conclusion, HIF-1 alpha. VEGF, and BNP mRNA and protein expression were up-regulated, while NGF-beta mRNA and protein was downregulated in the rat model of pressure-overloaded cardiac hypertrophy. Treatment with carvedilol is associated with a reversal of abnormal regulation of HIF-1 alpha,VEGF, BNP, and NGF-beta in the hypertrophic myocardium.

Author Keywords: aortic banding; cardiac hypertrophy; HIF-1 alpha; pressure overload; VEGF

KeyWords Plus: LEFT-VENTRICULAR HYPERTROPHY; MYOCARDIAL GENE-EXPRESSION; SMOOTH-MUSCLE-CELLS; DILATED CARDIOMYOPATHY; TRANSCRIPTIONAL REGULATION; FACTOR-I; FAILURE; MODEL

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Subject Category: MEDICINE, RESEARCH & EXPERIMENTAL

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Record 4 of 6 (Set #2) SUMMARY

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Full Record

Record 6 of 6 (Set #2) SUMMARY

Title: Carvedilol modulates the expression of hypoxia-inducible factor-1 alpha and vascular endothelial growth factor in a rat model of volume-overload heart failure

Author(s): **Shyu KG**, Lu MJ, Chang H, Sun HY, Wang BW, Kuan PL

Source: JOURNAL OF CARDIAC FAILURE 11 (2): 152-159 MAR 2005

Document Type: Article

Language: English

Cited References: 26 **Times Cited:** 0 FIND RELATED RECORDS

Abstract: Background: The use of beta-blockers has emerged as a beneficial treatment for congestive heart failure. Hypoxia-inducible factor-1 alpha (HIF-1 alpha) is tightly regulated in the ventricular myocardium. However, the expression of HIF-1 alpha in chronic heart failure resulting from volume overload and after treatment with beta-blocker is little known.

Methods and Results: To test the hypothesis that HIF-1 alpha plays a role in the failing myocardium because of volume overload, an aorta-caval shunt was created for 4 weeks in adult Sprague-Dawley rats to induce volume-overload heart failure. Carvedilol at 50 mg/kg body weight per day after surgery was given. The heart weight and body weight ratio increased from 2.6 +/- 0.3 in the sham group to 3.9 +/- 0.7 (P < .001) in the shunt group. Left ventricular end-diastolic dimension increased from 6.5 +/- 0.5 mm to 8.7 +/- 0.6 mm (P < .001). Treatment with carvedilol in the shunt group reversed the heart weight and ventricular dimension to the baseline values. Western blot showed that HIF-1 alpha, vascular endothelial growth factor (VEGF), and brain natriuretic peptide (BNP) proteins were upregulated and nerve growth factor-beta (NGF-beta) downregulated in the shunt group. Real-time polymerase chain reaction showed that mRNA of HIF-1 alpha, VEGF, and BNP increased and mRNA of NGF-beta decreased in the shunt group. Treatment with carvedilol reversed both protein and mRNA of HIF-1 alpha, VEGF, BNP, and NGF-beta to the baseline values. Increased immunohistochemical labeling of HIF-1 alpha, VEGF, and BNP in the ventricular myocardium was observed in the shunt group and carvedilol again normalized the labeling.

Conclusion: HIF-1 alpha and VEGF mRNA and protein expression were upregulated in the rat model of volume-overload heart failure. Treatment with carvedilol is associated with a reversal of abnormal regulation of HIF-1 alpha and VEGF in the failing ventricular myocardium.

Author Keywords: beta-blocker; congestive heart failure; gene expression; growth factor

KeyWords Plus: MYOCARDIAL GENE-EXPRESSION; SMOOTH-MUSCLE-CELLS; DILATED CARDIOMYOPATHY; TRANSCRIPTIONAL REGULATION; FAILING HEART; ANGIOGENESIS; METABOLISM;

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Record 6 of 6 (Set #2) SUMMARY