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论著

高血流性肺动脉高压大鼠肺组织中TGF-β1和CTGF的动态变化及意义

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摘要:

目的:观察转化生长因子-β1 (TGF-β1) 与结缔组织生长因子(CTGF) 在高血流性肺动脉高压大鼠肺组织的动态表达变化, 探讨TGF-β1 和CTGF 在高血流性肺动脉高压过程中的作用。方法:50 只成年雄性SD 大鼠随机分成假手术组(S 组) 、右肺切除1 周组(PE1 组)、2 周组(PE2 组)、4 周组(PE4 组) 和6 周组 (PE6 组), 每组10 只。测量各组大鼠平均肺动脉压(mPAP)、右室肥大指数(RVHI) 和血管形态学指标;免疫组织化学染色和Western 印迹检测肺组织TGF-β1 和CTGF 蛋白表达;RT-PCR 检测TGF-β1 和CTGF mRNA 的表达。结果:与S 组比较, 右肺切除各时间组大鼠mPAP 和RVHI 均显著升高 (P<0.05), PE1 和PE 2 组肌型动脉(MA) 和部分肌型动脉(PMA) 占肺中小血管总数的百分比[(MA+PMA)%]、MA 的相对中膜厚度(RMT) 和相对中膜面积(RMA) 与S 组比较无明显差异, PE4和PE6 组(MA+PMA)%、RMT 及RMA 明显增高(P<0.05);免疫组织化学染色显示, 右肺切除各时间组大鼠TGF-β1和CTGF 较S 组分布广泛, 表达增强。Western 印迹结果表明, 与S 组比较, 右肺切除各时间组TGF-β1 蛋白均显著上升(P<0.01), 峰值出现在PE2 组;CTGF 蛋白在PE1 组和PE2 组较S 组升高, 但差异无统计学意义, PE4 组和PE6组较S 组明显增高(P<0.05)。与S 组比较, 右肺切除各时间组TGF-β1mRNA 表达均显著升高(P<0.01), PE2 组达峰值, PE4 组和PE6 组维持在高水平。PE1 组CTGF mRNA 增高不明显, PE2 组、PE4 组和PE6 组明显上升(P<0.01)。相关分析表明, CTGF 蛋白和mRNA 表达与RMT 和RMA 呈正相关(P<0.05);TGF-β1 蛋白和mRNA 表达与RMT 和RMA无相关性;TGF-β1 mRNA 表达与CTGF mRNA 表达之间无明显相关性。结论:TGF-β1 和CTGF 参与了大鼠高血流性肺动脉高压的病理生理过程。

关键词: 转化生长因子-β1 结缔组织生长因子 高肺血流 肺动脉高压

Changes of TGF-β1 and CTGF in rats with increased blood flow-induced pulmonary artery hypertension

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Abstract:

Objective: To evaluate the role of transforming growth factor-β1 (TGF-β1) and connective tissuegrowth factor (CTGF) in the pathogenesis of pulmonary artery hypertension, we observed thedynamic expression of TGF-β1 and CTGF in rats with high blood flow.
Methods: Fifty adult male SD rats were randomly divided into 5 groups: a sham group (group S)and groups with right pneumonectomy for 1, 2, 4 and 6 weeks (PE1, PE2, PE4 and PE6 group),10 rats per group. The mean pulmonary arterial pressure (mPAP), vessel morphometry and rightventricle hypertrophy index (RVHI) were measured. TGF-β1 and CTGF protein expression in thelung tissues were determined with immunohistochemistry and Western blot. The expression ofTGF-β1 mRNA and CTGF mRNA in the lung tissues was evaluated by RT-PCR.
Results: Compared with group S, the mPAP and RVHI in the rats were significantlyincreased in group PE1, PE2, PE4, and PE6 (P<0.05); the indicators of vascular remodeling[(MA+PMA)%, RMT, and RMA] were markedly elevated in group PE4 and PE6 (P<0.05),but not in group PE1 and PE2. Immunohistochemical staining of TGF-β1 and CTGF weremore prominent in all of the right pneumonectomy groups than in the sham group. Westernblot showed that the level of TGF-β1 protein was significantly increased in all of the rightpneumonectomy groups (P<0.01), and the peak was observed in group PE2, whereas thelevel of CTGF protein was markedly elevated in group PE4 and PE6 (P<0.05), but no changewas noticed in group PE1 and PE2. Compare to group S, the mRNA level of TGF-β1 wasdramatically increased in all right pneumonectomy groups (P<0.01), peaked at group PE2, andremained high in group PE4 and PE6. In contrast, the elevation of mRNA level of CTGF wasnot significant in group PE1, but group PE2, PE4 and PE6 demonstrated significant mRNAlevel of CTGF (P<0.01). Correlation analysis showed that the protein and mRNA levels ofCTGF were positively correlated with RMT and RMA (r=0.743, r=0.906; P<0.05), while nocorrelation between the protein and

mRNA level of TGF-β1 with RMT or RMA. There was nocorrelation between the mRNA level of TGF-β1 and CTGF.
Conclusion: TGF-β1 and CTGF play a role in the pathogenesis of increased pulmonary bloodflow-induced pulmonary hypertension.

Keywords: transforming growth factor-β1　connective tissue growth factor　high pulmonary blood flow　pulmonary artery hypertension
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参考文献：

1. Rabinovitch M. Molecular pathogenesis of pulmonary arterialhypertension［J］.J Clin Invest, 2008, 118(7):2372-2379.
2. Archer SL, Weir EK, Wilkins MR. Basic science of pulmonary arterialhypertension for clinicians: new concepts and experimental therapies［J］.Circulation, 2010, 121(18):2045-2066.
3. Tahira Y, Fukuda N, Endo M, et al. Transforming growth factor-betaexpression in cardiovascular organs in stroke-prone spontaneouslyhypertensive rats with the development of hypertension［J］.HypertensRes, 2002, 25(6):911-918.
4. Watari H, Xiong Y, Hassan MK, et al. Cyr61, a member of ccn(connective tissue growth factor/cysteine-rich 61/nephroblastoma overexpressed) family, predicts survival of patients with endometrialcancer of endometrioid subtype［J］.Gynecol Oncol, 2009, 112(1):229-234.
5. Okada K, Tanaka Y, Bernstein M, et al. Pulmonary hemodynamicsmodify the rat pulmonary artery response to injury. A neointimalmodel of pulmonar y hypertension［J］.Am J Pathol, 1997,151(4):1019-1025.
6. Gomez-Arroyo JG, Saleem SJ, Mizuno S, et al. A brief overview of mousemodels of pulmonary arterial hypertension: problems and prospects［J］.Am J Physiol Lung Cell Mol Physiol, 302(10): L977-L991.
7. Archer SL, Weir EK, Wilkins MR. Basic science of pulmonary arterialhypertension for clinicians: new concepts and experimental therapies［J］.Circulation, 2010, 121(18):2045-2066.
8. Humbert M, Morrell NW, Archer SL, et al. Cellular and molecularpathobiology of pulmonary arterial hypertension［J］.J Am CollCardiol, 2004, 43(12 Suppl S):13S-24S.
9. Mahmoud M, Upton PD, Arthur HM. Angiogenesis regulation by TGFbeta signalling: clues from an inherited vascular disease［J］.BiochemSoc Trans, 2011, 39(6):1659-1666.
10. Li MO, Flavell RA. Contextual regulation of in ammation: a duet bytransforming growth factor-beta and interleukin-10［J］.Immunity, 2008, 28(4):468-476.
11. Wang T, Han SX, Zhang SF, et al. Role of chymase in cigare e smokeinducedpulmonary artery remodeling and pulmonary hypertension inhamsters［J］.Respir Res, 2010,11:36.
12. Zaiman AL, Podowski M, Medicherla S, et al. Role of the TGFbeta/Alk5 signaling pathway in monocrotaline-induced pulmonaryhypertension［J］.Am J Respir Crit Care Med, 2008, 177(8):896-905.
13. Ma W, Han W, Greer PA, et al. Calpain mediates pulmonary vascularremodeling in rodent models of pulmonary hypertension, and itsinhibition a enuates pathologic features of disease［J］.J Clin Invest,2011, 121(11):4548-4566.
14. Morrell NW, Yang X, Upton PD, et al. Altered growth responses ofpulmonary artery smooth muscle cells from patients with primarypulmonary hypertension to transforming growth factor-beta(1) andbone morphogenetic proteins［J］.Circulation, 2001, 104(7):790-795.
15. Selimovic N, Bergh CH, Andersson B, et al. Growth factors andinterleukin-6 across the lung circulation in pulmonary hypertension［J］.Eur Respir J, 2009, 34(3): 662-668.
16. Liu B, Wang XM, Zhou TF, et al. Expression of connective tissuegrowth factor and its down-regulation by simvastatin administrationin pulmonary hypertensive rats［J］.Zhonghua Er Ke Za Zhi, 2008,46(5): 359-365.
17. Lee YS, Byun J, Kim JA, et al. Monocrotaline-induced pulmonaryhypertension correlates with upregulation of connective tissue growthfactor expression in the lung［J］.Exp Mol Med, 2005, 37(1): 27-35.
18. Alapati D, Rong M, Chen S, et al. Connective tissue growth factorantibody therapy a enuates hyperoxia-induced lung injury in neonatalrats［J］.Am J Respir Cell Mol Biol, 2011, 45(6): 1169-1177.
19. Leivonen SK, Hakkinen L, Liu D, et al. Smad3 and extracellular signalregulatedkinase 1/2

coordinately mediate transforming growth factorbeta-induced expression of connective tissue growth factor in human broblasts［J］.J Invest Dermatol, 2005, 124(6): 1162-1169.
20. Xu SW, Howat SL, Renzoni EA, et al. Endothelin-1 induces expressionof matrix-associated genes in lung broblasts through MEK/ERK［J］.JBiol Chem, 2004, 279(22): 23098-23103.
21. Qi W, Twigg S, Chen X, et al. Integrated actions of transforming growthfactor-beta1 and connective tissue growth factor in renal brosis［J］.Am J Physiol Renal Physiol, 2005, 288(4): F800-F809.
22. Chen Y, Abraham DJ, Shi-Wen X, et al. CCN2 (connective tissuegrowth factor) promotes fibroblast adhesion to fibronectin［J］.MolBiol Cell, 2004,15(12):5635-5646.

本刊中的类似文章

1．杜巍； 胡建国； 周新民； 刘锋； .30岁以上动脉导管未闭患者的手术治疗[J]. 中南大学学报(医学版), 2003,28(1): 90-
2．黄健； 丁依玲； 朱付凡； 皮丕湘； 夏晓梦；.足月妊娠合并原发性肺动脉高压一例[J]. 中南大学学报(医学版), 2003,28(2): 140-
3．王琳娜， 宁旺斌， 陶立坚， 王菱， 彭张哲.动态观察依那普利对单侧输尿管梗阻大鼠TGF-β1,CTGF,Smad7和α-SMA的影响[J]. 中南大学学报(医学版), 2009,34(03): 252-258
4．许辉1， 刘惺2， 宁旺斌1， 陶立坚1.HIF-1α在5/6肾切除大鼠慢性肾纤维化模型中的表达[J]. 中南大学学报(医学版), 2009,34(04): 308-312
5．籍雪颖, 张金嵩, 王艳婷, 孙宏亮, 贾沛生.Smad3信号通路及结缔组织生长因子在哌仑西平抑制形觉剥夺性近视中的作用机制[J]. 中南大学学报(医学版), 2009,34(04): 349-355
6． 张赛丹， 周小雄， 余国龙.肺动脉高压上腔静脉多普勒血流频谱特点[J]. 中南大学学报(医学版), 2009,34(06): 543-540
7． 段绍斌, 刘伏友, 陈愔音, 刘芳, 李莹, 凌光辉, 肖力, 刘虹, 彭佑铭.转化生长因子&bgr;1短发夹RNA对白蛋白致人肾小管上皮细胞细胞因子过表达的抑制作用[J]. 中南大学学报(医学版), 2009,34(10): 949-956
8．袁运长1， 夏振坤1， 章庆春2， 尹邦良1 .结缔组织生长因子在大鼠移植心脏急性排斥反应期的表达[J]. 中南大学学报(医学版), 2008,33(05): 425-431
9．许军英1，陶立坚1，王菱1，宁旺斌1，刘纪实2.氯沙坦对糖尿病肾病大鼠肾小球硬化的影响[J]. 中南大学学报(医学版), 2008,33(09): 836-840
10．王琳娜， 陶立坚， 宁旺斌.依那普利对单侧输尿管梗阻大鼠肾间质纤维化的防治作用[J]. 中南大学学报(医学版), 2008,33(09): 841-848
11．袁运长，王电军，尹邦良.结缔组织生长因子与大鼠移植肺纤维化的关系[J]. 中南大学学报(医学版), 2007,32(05): 873-876
12．龚启华*，杨一峰，胡建国，尹邦良，赵天力，吴忠仕，杨进福 .102例室间隔缺损合并动脉导管未闭的诊治体会[J]. 中南大学学报(医学版), 2005,30(2): 221-223
13．刘虹1，2， 刘伏友1，2，*， 彭佑铭1，2， 袁芳1，2， 刘映红1，2.pcDU6质粒载体介导的TGFβ1 shRNA抑制TGFβ1在人腹膜间皮细胞中的表达[J]. 中南大学学报(医学版), 2004,29(5): 552-557
14．王小红1, 2， 张瑞娟1， 谢辉1， 伍贤平1.女性血清卵泡刺激素水平与护骨素、瘦素、TGF-β1及TGF-β2之间的关系[J]. 中南大学学报(医学版), 2010,35(12): 1266-
15．宋逢林； 罗会昭； 刘峰； 喻杰锋； 李炎升； .先天性心脏病合并肺动脉高压患者体外循环围术期血浆内皮素水平的动态观察[J]. 中南大学学报(医学版), 2001,26(4): 379-