題名:The molecular regulation of GADD153 in apoptosis of cultured vascular smooth muscle cells by cyclic mechanical stretch.

作者:徐國基

Cheng WP; Hung HF; Wang BW; Shyu KG

貢獻者:臨床醫學研究所

上傳時間:2009-08-21T08:59:02Z

摘要:AIMS: The expression of GADD153 (growth arrest and DNA damage-inducible gene 153), an apoptosis-regulated gene, increases during endoplasmic reticulum (ER) stress. How mechanical stretch affects the regulation of GADD153 in vascular smooth muscle cells (VSMCs) during apoptosis is not fully understood. We aimed to test the hypothesis that mechanical stretch induces GADD153 expression in VSMCs undergoing apoptosis. METHODS AND RESULTS: Rat VSMCs 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 GADD153 expression. Cyclic stretch significantly increased GADD153 protein and mRNA expression after 18 h of stretch. Addition of c-jun N-terminal kinase (JNK) inhibitor SP600125, JNK siRNA, tumour necrosis factor-alpha (TNF-alpha) and TNF-alpha receptor antibody 30 min before stretch inhibited the induction of GADD153 protein. Gel shift assay showed that DNA-binding activity of activating factor 1 (AP-1) increased after stretch. SP600125, JNK siRNA and TNF-alpha antibody abolished the binding activity induced by stretch. Stretch increased while GADD153-Mut plasmid, SP600125, and c-jun antibody abolished the promoter activity. Both conditioned media from stretched VSMCs and exogenous administration of TNF-alpha recombinant protein to the non-stretched VSMCs increased GADD153 protein expression similar to that seen after stretch. An in vivo model of aorta-caval shunt in adult rats also demonstrated the increased GADD153 protein expression in the aorta. CONCLUSION: Cyclic stretch enhanced GADD153

expression in cultured rat VSMCs. The stretch-induced GADD153 is mediated by TNF-alpha, at least in part, through the JNK and AP-1 pathway. These findings suggest that GADD153 plays a role in stretch-induced VSMC apoptosis.