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INHIBITORY EFFECTS OF ADENOVIRUS-MEDIATED CYCLOOXYGENASE-1/PROSTACYCLIN SYNTHASE GENE TRANSFER ON RAT CARDIAC FIBROSIS

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BACKGROUND/AIMS: Cardiac fibrosis can proliferate and increase the deposition of extracellular matrix protein such as collagen, which leads to cardiac fibrosis and subsequent diastolic dysfunction, accounting for 30% to 50% of congestive heart failure. Recently, pharmacological interventions have demonstrated that angiotensin II (Ang II) plays an important role in the mediation of human hypertensive cardiac fibrosis or pressure overload-induced cardiac fibrosis in rats. Prostaglandins (PGs) have been shown to reduce collagen gene expression in cardiac fibroblasts. In this study, we determined whether the adenovirus-mediated COX-1/prostacyclin synthase (Ad-COPS) gene transfer, through enhanced prostacyclin (PGI_2) formation, can suppress cardiac fibroblast proliferation and collagen synthesis induced by Ang II.

METHODS: H^3-thymidine incorporation; Northern blotting; chloramphenicol acetyltransferase activity assay, Western blotting, gel shifting, tissue section and Masson's trichrome staining were performed.

RESULTS: Ad-COPS gene transfer increased arachidonic acid metabolite release and stimulated a dose- and time-dependent increase in PGI_2 and its stable metabolite 6-keto PGF_1. Ad-COPS gene transfer and iloprost (PGI_2 analog) reduced Ang II-induced fibroblast proliferation and collagen synthesis. Ang II induces endothelin-1 (ET-1) gene expression in cardiac fibroblasts, which serves as an autocrine growth factor. The ERK-mediated activator protein-1 (AP-1)-dependent transcription plays a crucial role in ET-1-induced proliferation and ET-1-stimulated ET-1 gene expression in cardiac fibroblasts. Ad-COPS also attenuated the Ang II-stimulated endothelin-1 gene expression and AP-1 binding activity. In vivo, continuous infusion of Ang II increased the collagen volume fraction in the ventricles, which was reduced significantly by simultaneous Ad-COPS gene transfer.

DISCUSSION/CONCLUSIONS: This enhancement of prostacyclin production via the Ad-COPS gene transfer attenuates the Ang II-induced fibroblast proliferation and collagen deposition. Our findings demonstrate the therapeutic potential of prostacyclin for treating cardiac fibrosis.

Keywords: Cardiac fibrosis, Adenovirus gene transfer, Prostacyclin