Structurally different RGTAs modulate collagen-type expression by cultured aortic smooth muscle cells via different pathways involving fibroblast growth factor-2 or transforming growth factor-beta1.

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Abstract

We have engineered polymers called ReGeneraTing Agents (RGTAs), which mimic the protecting and potentiating properties of heparan sulfates toward heparin-binding growth factors (HBGF). RGTAs have been shown to optimize cell growth and regulate collagen production in vitro. Here, we studied relationships between RGTA structure and collagen-type expression in aortic smooth muscle cells by using two RGTAs, the carboxylmethylsulfate dextran RG-1503 and the carboxylmethylsulfate dextran with added benzylamide RG-1192. RG-1192 specifically induced a fivefold decrease in collagen III synthesis. This effect was abolished by FGF-2 neutralizing antibody. RG-1192 and FGF-2 acted synergistically to decrease collagen III. RG-1192 was more effective than heparin in this process. RG-1192 increased the pericellular localization of FGF-2 and protected FGF-2 from proteolysis. Surface plasmon resonance analysis indicated a Kd of 15.7 nM for the RG-1192/FGF-2 interaction (10.6 nM for the heparin/FGF-2 interaction). The structurally different RG-1503 (without benzylamide) did not interact with FGF-2 and worked synergistically with TGF-beta1 to specifically induce a twofold increase in collagen V. RGTAs with different structures exert different modulating effects on the collagen phenotype. Selection of appropriate RGTAs, which had been shown to enhance in vivo tissue repair, may provide a mean of correcting collagen abnormalities in vascular disorders and more generally in fibrotic diseases.