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Controlling *flk-1/KDR*gene expression and angiogenesis

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Keywords

Angiogenesis, *flk-1/KDR*, TGF-?, transcription regulation, VEGF

Context

Vasculogenesis and angiogenesis depend on binding between vascular endothelial growth factor (VEGF) and VEGF receptor-2, which is expressed by the *flk-1/KDR* gene, only on the endothelium in these contexts. Transforming growth factor (TGF)-? is a central modulator of inflammation and its resolution. At low concentrations, TGF-? enhances VEGF-induced angiogenesis. At high concentrations, TGF-? downregulates *flk-1/KDR* mRNA synthesis, inhibiting angiogenesis. This paper examined whether TGF-? influences *flk-1/KDR* expression by changing the binding of transcription factors to DNA in the *flk-1/KDR* promoter.

Significant findings

TGF-? suppressed activation of a *flk-1/KDR* promoter fragment spanning base pairs -115 to +296, which region contains a palindromic GATA site in the 5' untranslated region (UTR). Mutation of this GATA site abolished TGF-?-induced suppression of *flk-1/KDR*. Electrophoretic mobility shift assay (EMSA) confirmed at least one GATA protein, GATA-2, binds to this site, and TGF-? attenuated this binding. GATA-2 transactivated the *flk-1/KDR* promoter construct more than GATA-1, and TGF-? attenuated this activation. Therefore, TGF-? negatively regulates *flk-1/KDR* promoter activity by attenuating GATA-2 binding in the 5' UTR.

Comments

This study is the first step in characterization of the *flk-1/KDR* gene promoter as an integrator of pro-angiogenic and anti-angiogenic stimuli. The authors did not identify all proteins that bind to the 5' UTR GATA site of the *flk-1/KDR* promoter, hence other GATA members may be components of the protein-DNA complex. The signaling mechanisms downstream of the TGF-? receptor leading to inhibition of GATA binding to its cognate site in the *flk-1/KDR* promoter, remain unclear. A TGF-?-induced change in the phosphorylation or acetylation state of GATA may modify its binding activity. As angiogenesis either occurs (solid tumor growth, diabetic retinopathy) or fails to occur (arteriosclerotic ischemia, nonhealing wounds) in different pathological conditions, the ability to manipulate angiogenesis *in vivo* is a therapeutic goal. Understanding the mechanism of activation of *flk-1/KDR* gene expression represents progress in this direction. Determination of the protein factors and binding specificities in the signal transduction systems regulating *flk-1/KDR*transcription may enable small molecule therapeutics or therapeutic proteins or gene transfer to be designed to this end.

Methods

Cell culture, transient transfection with luciferase reporter gene, PCR cloning and mutagenesis, RNA isolation and RNase protection assay, EMSA

Additional information

References

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