

ABSTRACT

Transcriptional Regulation of TGF- β Type II Receptor

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Transforming growth factor- β (TGF- β) is the prototypical multi-functional cytokine, participating in the regulation of vital cellular activities such as proliferation and differentiation as well as a number of basic physiological functions. The effects of TGF- β are critically dependent on the expression and distribution of a family of TGF- β receptors, TGF- β types I, II, and III. It is now known that a wide variety of human pathology can be caused by aberrant expression and function of these receptors. High levels of mutation in the TGF- β RII gene have been observed in a wide range of primarily epithelial malignancies.

In the previous study, several additional TGF- β resistant cell lines in which Southern analysis failed to show gross deletions or rearrangements were discovered with no TGF- β RII protein or no mRNA. This suggest that abnormalities in transcriptional regulation of the type II receptor might also be found to underlie certain instances of escape from TGF- β mediated growth inhibition.

The promoter region of the TGF- β RII gene was cloned, sequenced, and identified. Several positive (PRE1, PRE2) and negative (NRE) transcriptional regulatory elements were identified with the relevant target sequences.

To identify potential transcriptional activators of the TGF- β RII gene, yeast one-hybrid system was employed to find proteins that recognize the PRE2 of the TGF- β type II receptor gene. Screening a human placenta cDNA library fused to GAL4 activation domain resulted

in a cDNA clone that induced greater LacZ activity. DNA sequencing analysis of a corresponding plasmid, pACT2ERT, revealed that the encoded gene belongs to a novel member of the ets transcriptional factor family.

Comparison of the nucleotide sequence of ERT to the recently reported epithelial specific ets-family member, ESX/ESE-1 showed it to be identical, but the ERT cDNA revealed an additional 524 nucleotides in the 3'-UTR. It was demonstrated that the ERT protein specifically binds to the PRE2 region of the TGF- β RII gene and activates its transcription.

References

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