題名:Characterization of novel transforming growth factor-beta type I

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摘要:BackgroundTumors expressing a transforming growth factor-beta type I receptor (TβRI) mutant with sequence deletions in a nine-alanine (9A) stretch of the signal peptide are reported to be highly associated with disease progression. Expression of this mutant could interfere with endogenous TGFβ signaling in the cell. However, little is known about the importance of the remaining part of the signal peptide on the cellular function of TβRI.ResultsWe cloned and identified four new in-frame deletion variants of TβRI, designated DM1 to DM4, in pleural effusion-derived tumor cells. Intriguingly, DM1 and DM2, with a small region truncated in the putative signal peptide of TβRI, had a serious defect in their protein expression compared with that of the wild-type receptor. Using serial deletion mutagenesis, we characterized a region encoded by nucleotides 16–51 as a key element controlling TβRI protein expression. Consistently, both DM1 and DM2 have this peptide deleted. Experiments using cycloheximde and MG132 further confirmed its indispensable role for the protein stability of TβRI. In contrast, truncation of the 9A-stretch itself or a region downstream to the stretch barely affected TβRI expression. However, variants lacking a region C-terminal to the stretch completely lost their capability to conduct TGFβ-induced transcriptional activation. Intriguingly, expression of DM3 in a cell sensitive to TGFβ made it significantly refractory to TGFβ-mediated growth inhibition. The effect of DM3 was to ablate the apoptotic event induced by TGFβ.ConclusionWe identified

four new transcript variants of TβRI in malignant effusion tumor cells and characterized two key elements controlling its protein stability and transcriptional activation. Expression of one of variants bestowed cancer cells with a growth advantage in the presence of TGFβ. These results highlight the potential roles of some naturally occurring TβRI variants on the promotion of tumor malignancy.