Suppression of hepatitis B virus core promoter by the nuclear orphan receptor TR4

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摘要

Abstract

The TR4 orphan receptor is a member of the nuclear receptor superfamily that modulates gene expression via binding to the AGGTCA direct repeat hormone response element. Here we report a functional study of TR4 interaction with the core promoter of the hepatitis B virus (HBV). The electrophoretic mobility shift assay shows that TR4 can bind to the direct repeat 1 sequence element (AGGTTAAAGGTCT, nucleotide coordinates 1757-1769, TR4RE-HBV) on the HBV core promoter. TR4 also can enhance the activity of a synthetic luciferase reporter linked with four copies of TR4RE-HBV in either liver HepG2 or non-liver H1299 cells in a dose-dependent manner. Surprisingly, TR4 represses the activity of a luciferase reporter containing the entire HBV genome sequences. Moreover, mutation of this TR4RE-HBV site in the HBV core promoter diminishes the TR4 suppression effect. This TR4-induced suppression of HBV core promoter activity is further confirmed by primer extension analysis of the HBV core RNAs, showing that TR4 represses both pre-core and core mRNAs. Further dissection of this repressive mechanism indicates that TR4 may suppress the HBV core promoter activity via repressing HNF4alpha-mediated transactivation by protein-protein interactions without inhibition of HNF4alpha DNA binding. Furthermore, our results indicate that the N- and C-terminal regions of TR4 protein are required for TR4-HNF4alpha interaction. It is possible that TR4-HNF4alpha interaction may block the HNF4alpha function that results in the suppression of HBV gene expression. Together, these results demonstrate that TR4 can serve as a negative modulator in the transcriptional regulation of HBV core gene expression.