REGULATION OF THE HEPATITIS B VIRUS X GENE PROMOTERS

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ABSTRACT

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The X gene product of hepatitis B virus (HBV) is absolutely necessary for establishment of virus infection *in vivo*. In chronic HBV infections, the X protein has been implicated in the development of hepatocellular carcinoma due to its oncogenic potential, such as its ability to function as a non-specific transactivator and to bind and inactivate p53, a tumor suppressor gene product. The X protein is encoded by the X open reading frame (ORF) whose expression is governed by a transcriptional unit consisting of the HBV enhancerI and a promoter. Although the exact location of the X promoter is somewhat controversial, this promoter is shown to be one of the strongest HBV promoters. Moreover, the X promoter appears to be strictly regulated since it is relatively difficult to detect the X transcript in natural infections. The nature of this regulation has yet to be elucidated.

Data presented in this study indicate that the HBV core antigen inhibits the activity of the X transcriptional regulatory unit. Yet, it has no effect on the activity of the enhancerI. Due to the uncertainty of the location of the X promoter, the DNA sequence driving the expression of the X gene was identified. Functional analyses as well as RNase protection assays showed that two distinct promoters modulate the expression of the X gene. Both promoters are suppressed by the core antigen. The effect of the X protein on its own promoters was also investigated. The upstream

promoter appears to be more responsive to transactivation by the X protein than is the downstream promoter. Surprisingly, an additional promoter was detected in the non-coding DNA strand. RNA transcripts generated from this "antisense" promoter were also observed. The biological significance of this promoter remains to be determined.

In summary, there are two distinct promoters for the HBV X gene. Both promoters are regulated positively by the X protein and negatively by the core antigen.

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