RESEARCH COMMUNICATION

Weak Linkage in Hepatitis C PePHD: Identification of Mutation Prone Point that can Lead to Failure of Antiviral Therapy for Prevention of Hepatocellular Carcinoma

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Abstract

Hepatitis C is an important blood borne infection caused by hepatitis C virus (HCV). Chronic inflammation induced by this viral infection and its role in carcinogenesis are well recognized. The treatment of HCV infection has developed enormously over recent years and is believed to be a good way for stopping of carcinogenesis process. Howevr, mutation of the virus is an important factor that can bring drug resistance. Presently, prediction of protein nanostructure and function is a great challenge in the proteomics and structural genomics era. To identify points which are vulnerable to mutation is a new trend to expand the knowledge at the genomic and proteomic levels Here, the author performed a bioinformatic analysis to determine positions that trend to comply with peptide motifs in the amino acid sequence of HCV protein kinase -eIF2-alpha phosphorylation homology domain (PePHD). To identify weak linkage in HCV PePHD, a new bioinformatic tool, GlobPlot, was used. Positions 2-7, 29-39, 53-57, 90-98, 123-133, 202-227, 324-355, 439-448 were identified as positions resistant to mutation. Some are already known and others are newly discovered. Based on this study, weak linkages in HCV PePHD could be identified and can be good information for expectation of possible new mutations that can lead to failure of HCV therapy. In addition, the results from this study can be good information for further research on the diagnosis for mutants HCV and vaccine development.

Key words: Hepatitis C -structure - weak linkage - mutation

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Introduction

Hepatitis C is an important blood borne infection caused by hepatitis C virus (HCV). Chronic inflammation induced by this viral infection and its role in carcinogenesis are well recognized (Kulik, 2006). The treatment of HCV infection has developed enormously over recent years and is believed to be a good way for stopping of carcinogenesis process (Cornberg et al., 2006). Early treatment of acute HCV infection with interferon-alpha can prevent chronicity and a significant proportion of patients with chronic HCV can be cured with the current standard therapy consisting of pegylated interferon-alpha and ribavirin (Cornberg et al., 2006). Treatment is accepted as a good prevention for hepatocellular carcinoma. Only 50-60% of the patients chronically infected with the HCV achieve a sustained virologic response to the current standard antiviral therapy consisting of pegylated interferon alpha in combination with ribavirin (Hofmann et al., 2005). Mutation within protein kinase -eIF2-alpha phosphorylation homology domain (PePHD) protein is a main mutation in HCV corresponding to drug resistance (Saito et al., 2003).

Presently, prediction of protein nanostructure and function is a great challenge in the proteomics and structural genomics era. To identify the point vulnerable to mutate is a new trend to expand the knowledge on disorders in genomic and proteomic level of diseases (Levin et al., 2002; Lee and Wang, 2005). Generally, disordered regions in proteins often contain short linear peptide motifs that are important for protein function. Identification of peptide motifs in the amino acid sequence can give a good prediction for the weak linkages in a protein (Levin et al., 2002; Lee and Wang, 2005). Here, the author performed a bioinformatic analysis to study the determine such positions in the amino acid sequence of HCV PePHD.

Material and Methods

A. Getting the sequence

The database ExPASY (Gasteiger et al., 2003) was used to search for the amino acid sequence of HCV PePHD. Then the derived sequence was used for further study on weak linkage.

B. Identification of weak linkage in HCV PePHD

For this purpose, a new bioinformatic tool namely GlobPlot (Linding et al., 2003) was used. GlobPlot is a web service that allows the user to plot the tendency within the query protein for order/globularity and disorder. It successfully identifies inter-domain segments containing

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Table 1. Identified Positions (in Capitals) in the Amino Acid Sequence of HCV PePHD

m**AGDLSA**gff meelntyrqk qgvvlkyq**EL PNSGPPHD**Rr ftfqviidgr ef**PEGEG**rsk keaknaaakl aveilnkekk avsplltt **TNSSEGLS**Mgn yiglinriaq kkrltvnyeq ca**SGVHGPEG FHY**kckmgqk eysigtgstk qeakqlaakl aylqilseet svksdylssg sfattcesqs nslvtstlas e**SSSEGDFSA DTSEINSNSD SLNSSSL**lmn glrnnqrkak rslaprfdlp dmketkytvd krfgmdfkei eligsggfgq vfkakhridg ktyvikrvky nnekaerevk alakldhvni vhy**NGCWDGF DYDPETSDDS LESSDYDPEN SKNSS** rsktk clfiqmefcd kgtleqwiek rrgekldkvl alelfeqitk gvdyihskkl ihrdlkpsni flvdtkqvki gdfglvts**LKNDGKRTRS**kg tlrymspeqi ssqdygkevd lyalglilae llhvcdtafe tskfftdlrd giisdifdkk ektllqklls kkpedrpnts eilrtltvwk kspeknerht c

linear motifs, and also apparently ordered regions that do not contain any recognised domain.

Results

In this work, HCV PePHD (P19525) was used for further study. The identified positions are presented in Table 1. The positions 2-7, 29-39, 53-57, 90-98, 123-133, 202-227, 324-355, 439-448 are identified as positions resistant to mutation.

Discussion

HCV is pathogenetically involved in many cases of hepatocellular carcinoma worldwide (Colombo, 1999), causing carcinogenesis by a mechanism related to chronic inflammation, taking viral, immunologic, cytokine and apoptotic responses into consideration (Hayashi et al., 1999). HCV-related HCC is on the rise in many developed countries as a consequence of past infections with HCV (Colombo, 1999) since the time lag between HCV infection and cancer development is several decades. Prevention for cancer development is the goal of HCV management at present. Antiviral therapy can be the good tool for prevention of cancer development (Hofmannn et al., 2005). However, the main problem in failure of treatment is mutation of HCV.

In many infectious diseases, a structural aberration is believed to be the main underlying pathogenesis. Some disorders are mentioned as a single substitution with other effects on the sequence frame, the others are mentioned as a frameshift. The mutation in HCV is believed to be the possible starting point for failure in HCV antiretroviral therapy. Ukai et al said that PePHD correlates with both response to IFN monotherapy and viral load (Ukai et al., 2006). Yang et al proposed that genetic heterogeneity in PePHD regions of the HCV genome may not serve as a predictor for treatment outcome with combination therapy in the patients with chronic HCV genotype 1b infection (Yang et al., 2003). Here, the author used an algorithm to identify the position in the amino acid sequences of HCV PEPHD that can be mutated.

Many positions were found in the present stduy. Some are known positions and the others are newly discovered. Based on this study, the weak linkages in the HCV PEPHD could be identified, providing information for expectation of possible new mutations that can lead to failure of HCV therapy. In addition, the results point to further research on the diagnosis of mutant HCV and vaccine development.

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