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Homology Modeling of NS3 Protease of Hepatitis C Virus Genotype 4a

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ABSTRACT

The amino acid sequence of the NS3 protease of hepatitis C virus genotype 4a was obtained from the SWISS-PROT database. The tertiary structure of NS3 protease of hepatitis C virus genotype 4a was modeled using Swiss-model server (i.e. Automatic homology modeling server). The percentage identity was > 86%. The model was validated using the Procheck program. The results indicated that at least 89% of the amino acid residues are in the core region and 0% in the disallowed region.

Keywords: 3D structure, drug design, liver cirrhosis, positive-stranded RNA virus, Swiss model

INTRODUCTION

Hepatitis C virus (HCV) was identified in 1989 as the etiological agent for non-A, non-B hepatitis, which is a lethal single positive-stranded RNA virus (Hussein *et al.* 2000). An estimated 200 million cases of HCV infection exist worldwide (Patel *et al.* 2008). Of those infected, over 85% will develop chronic hepatitis, and 20% of the chronic infections progress to liver cirrhosis and hepatocellular carcinoma. Presently, there is no vaccine for HCV. The HCV genome consists of a single-stranded, positive sense RNA molecule of approximately 9600 nucleotides. Translation of the viral RNA generates a polyprotein that is proteolytically cleaved into 10 viral proteins of different function: the structural proteins C, E1 and E2, p7, and the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B (Appel *et al.* 2006).

The NS3 protein is a bi-functional enzyme with a helicase/NTPase domain and a protease domain. The NS3 protease, in complex with its co-factor NS4A, is a key factor in the processing of the HCV polyprotein. Moreover, it has been suggested that the NS3 protease interferes with cellular mechanisms involved in the host immune response to an HCV infection. Thus, inhibition of the protease is an attractive antiviral approach that will block viral replication as well as potentially restore the host immune response (Bartenschlager and Lohmann 2000).

MATERIALS AND METHODS

The amino acid sequence of the NS3 protease of hepatitis C virus genotype 4a was obtained from the SWISS-PROT database (Boeckmann *et al.* 2003) included in the Expasy serve (Gasteiger *et al.* 2003). Homology modeling requests were sent to Swiss-model server (Kopp and Schwede 2004).

The results were reported by e-mail after only one day of sending requests. The Swiss-pdbviewer tool was used to plot the models and to calculate their free energy using the implemented *Gromos 96*. The validation of model was examined by the Procheck program (Laskowski *et al.* 1993).

RESULTS

The sequence of the NS3 protease of hepatitis C virus genotype 4a, as derived from SWISS-PROT database, is given by:

ITAYAQQTRGLFSTIVTSLTGRDTNENCGEVQVLSTAT
QSFLGTAVNGVMWTVYHGAGAKTISGPKGPVNQMY
TNVDQDLVGWPAPPGVRSLAPCTCGSADLYLVTRHA
DVIPVRRRGDTRGALLSPRPISILKGSSGGPLLCPMGH
RAGIFRAAVCTRGVAKAVDFVPVESLETTMRSPVFTD
NSTPPAVPQTYQVAHLHAPTGSGKSTKVPAAHAAQG
YKVLVLNPSVAATLGFGVYMSKAYGIDPNIRSGVRTI
TTGAPITYSTYGKFLADGGCSGGAYDIIICDECYSTDS
TTILGIGTVLDQAETAGVRLTVLATATPPGSVTTPHSNI
EEVALPTTGEIPFYGKAIPLELIKGGRHLIFCHSKKKC
DELARQLTSLGLNAVAYYRGLDVSVIPTSGDVVVCAT
DALMTGFTGDFDSVIDCNTSVIQTVDFSLDPTFSIEITT
VPQDAVSRSQRRGRTGRGRLGTYRYVTPGERPSGMF
DTAELCECYDAGCAWYELTPAETTTRLKAYFDTPGLP
VCQDHLEFWESVFTGLTHIDGHFLSQTKQSGENFPYL
VAYQATVSAKVWLAPPSWDTMWKCLIRLKPTLHGPT
PLLYRLGSVQNEVVLTHPITKYIMACMSADLEVVT.

The sequence aliment results are summarized in **Table 1**.

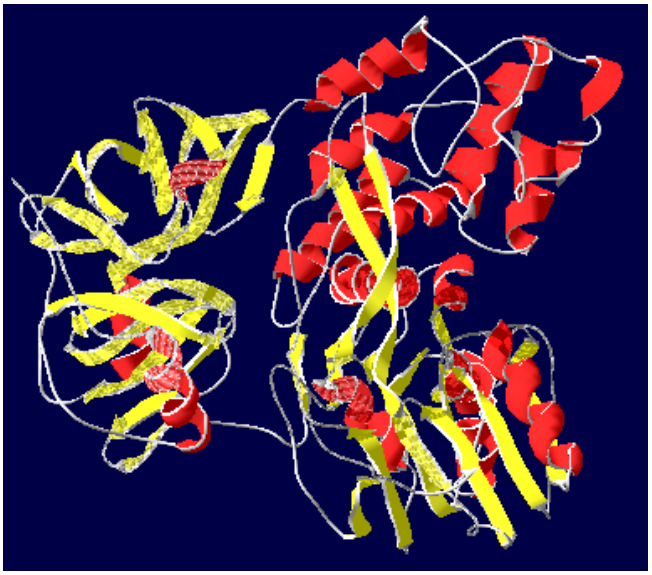

Fig. 1 The model of the NS3 protease of hepatitis C virus genotype 4a as plotted by Swiss-pdbviewer Version 4.0

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Research Note

Table 1 The sequence alignment results.

Modelled residue range	Template	Sequence Identity [%]	E-value
1029 to 1657	**1cu1A** (2.50 Å)	86.804	0.00e-1

Table 2 The results of the procheck validation program.

Core	Allowed	Generous	Disallowed
89.7 %	8.8 %	1.5 %	0 %

The results show that the percentage sequence identity of the sequence alignment was > 86%.

The model of the NS3 protease of hepatitis C virus genotype 4a as plotted by Swiss-pdbviewer (http://www.expasy.org/spdbv) ver. 4.0 (Guex and Peitch 1997) appears in **Fig. 1**. The free energy of the model as calculated by Gromos 96 43B1 implemented in the Swiss-pdbviewer equals -21861.

The results of the procheck validation program (Ramachandran plot) are summarized in **Table 2**. The results of the Ramachandran (Ramachandran *et al.* 1963) plot indicated that at least 89% of the amino acid residues are in the core region and 0% in the disallowed region.

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