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THE GENETIC AND MOLECULAR STUDIES OF *HEPATITIS* C VIRUS: A REVIEW

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ABSTRACT
The role of Hepatitis viruses, particularly Hepatitis c virus (HCV) as human pathogen and their transmission have been of interest over the years. The virus is a small (55-65nm in size), included in Group IV, enveloped, positive sense, single stranded RNA virus, the family Flaviviridae, genus Hepacivirus, and Hepatitis c virus type species. Based on genetic differences between HCV isolates, the virus species is classified into six genotypes (1-6) with several subtypes within each genotype (represented by letters). Persistent infection with Hepatitis c virus (HCV) has emerged as one of the primary causes of chronic liver disease with an estimated 170 million people infected by HCV, more than 4 times the number of people living with HIV throughout the world. The present review looks at the genetic and molecular nature of this virus with the view to provide more information about its biology which may be useful to the present and feature researchers.

Key words: Hepatitis c virus, biology, genome, chronic, liver, disease

INTRODUCTION

Despite the rapid scientific progress in understanding the biology of viral illness, viral liver disease remains a common and challenging problem for physicians and their patients (Alter and Seeff, 2000). Persistent infection with *Hepatitis* c virus (HCV) has emerged as one of the primary causes of chronic liver disease with an estimated 170 million people infected by HCV, more than 4 times the number of people living with HIV throughout the world (WHO,2000). Of the typical hepatitis viruses, chronic infection with *Hepatitis* c virus remains one of the most important clinical and public health problems (El-Zayadi *et al.,* 2004). In the western world, chronic damage from *Hepatitis* c is the primary cause of the end stage liver disease requiring liver transplantation (Niederan *et al*., 1998). The discovery of HCV in 1989 was a major breakthrough. Before that point, it was clear that a major cause of acute hepatitis after a blood transfusion was neither related to *Hepatitis* A nor to *Hepatitis* B- hence the early names for this disease, non-A, non-B hepatitis (Simmonds *et al.,* 2005).

In the mid 1970's Harvey J. Alter and his research team demonstrated that most post-transfusion hepatitis cases were not due to hepatitis A or B viruses. Despite this discovery, international research efforts to identify the virus, initially called non-A, non-B hepatitis (NANBH), failed for the next decade. In 1987 Michael Houghton, Qui-Lim Choo, and George Kuo at Chiron Corporation, collaboration with Dr. D.W. Bradley from CDC, utilised a novel molecular cloning approach to identify the unknown organism (Sharma,2010). In 1988, the virus was confirmed by Alter by verifying its presence in a panel of NANAH specimens. In April of 1989, the discovery of the virus, re-named *Hepatitis* C virus (HCV), (Choo *et al.,* 1989; Kuo *et al*., 1989). The virus belongs to the family Flaviviridae and Hepacivirus genus (Jawezt *et al*., 2004).

Virology of Hepatitis C Virus Virion

Hepatitis C virus (HCV) is a member of the Hepacivirus genus, of the Flaviviridae family (Meir and Ramadori, 2009). It is a small (55-65nm in size), enveloped, positive sense polarity, single stranded RNA virus. The viral particle consist of a core of genetic material (RNA), surrounded by an icosahedral protective shell of protein, and further encased in a lipid (fatty) envelope of cellular origin. Two viral envelope glycoproteins, E1 and E2, are embedded in the lipid envelope (Op De Beeck and Dubuisson, 2003).

Genome Organisation of HCV

Hepatitis C virus has a positive sense RNA that consists of a single open reading frame of 9600 nucleoside bases (Kato, 2000). At the 5' and 3' ends of the RNA are the UTR regions that are not translated into proteins but are important to translation and replication of the viral RNA. The 5' UTR has a ribosome binding site (Jubin, 2001), (IRES-International Ribosome Entery Site) that starts the translation of a 3000 amino acid containing protein that is later cut by and viral proteases into active structural and non-structural smaller protein (Jawezt *et al*., 2004; Dubuisson, 2007).

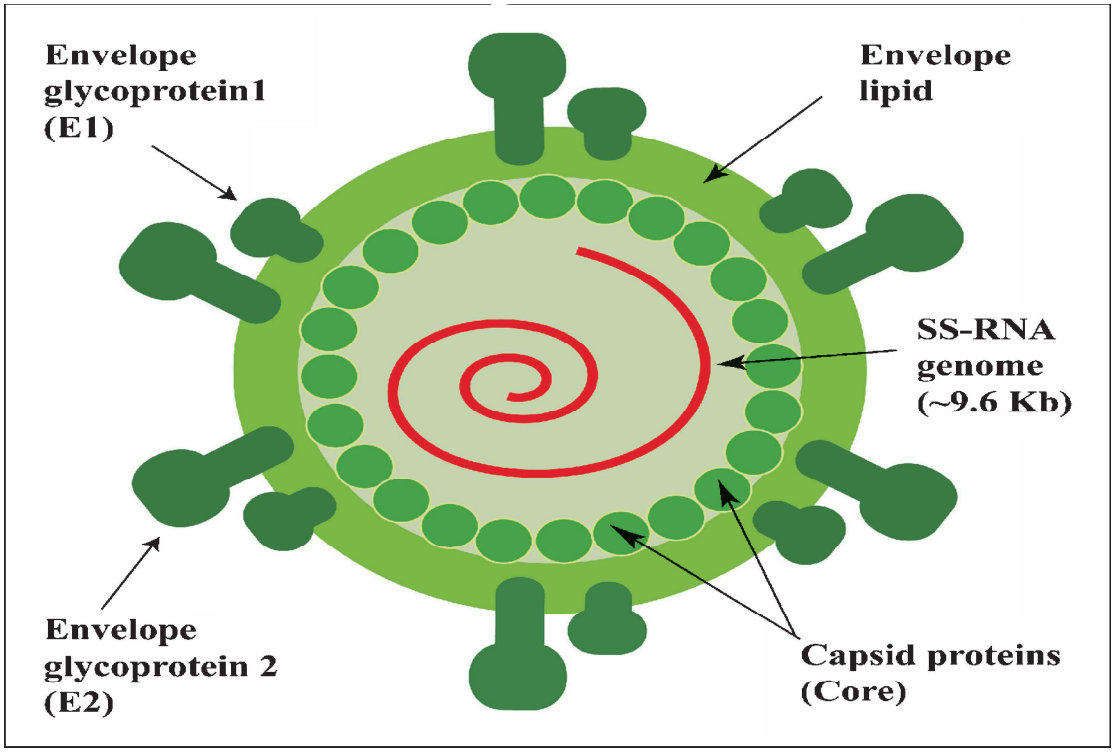

Figure 1. Hepatitis C virus particle structure: The HCV core protein interacts with viral genomic RNA to form the nucleocapsid. Two membrane-associated envelope glycoproteins, E1 and E2 are embedded in a lipid envelope which is derived from the host.

The 5'- and the 3'-NTRs of the genome are highly conserved and contain control elements for translation of the viral polyprotein and replication. The 5′ UTR (+) is ~341 nucleotides in length and contains an internal ribosomal entry site (IRES). The HCV IRES is folded into four stem-loop motifs which are called as I, II, III and IV. The IRES is required for cap-independent translation of viral RNA, which is carried out by host cell ribosome. The domain IIId of the IRES constitutes the key anchoring site for the 40S subunit (Lukavsky *et al.*, 2000). The IRES domains III-IV have also been shown to be an activator of protein kinase R (PKR) (Shimoike *et al.*, 2009). However, this activation does not interfere with cap-independent translation of HCV viral proteins. HCV core protein was reported to interact with the 5′-NTR of plus-strand RNA (Fan *et al.,* 1999). However, recent work with JHF1 viral RNA suggested that its 5′-NTR (+) does not contain RNA packaging signals (Friebe and Bartenschlager, 2009) and other authors further speculate that it may reside in the RNA region encoding the replicase. The 3'-UTR (+) is around ~200nt and is involved in RNA replication. Three different domains can be recognized in this U TR: (*i*) a poly (U/UC) tract with an average length of 80 nucleotides (nt), (*ii*) a variable region, and (*iii*) a virtually invariant 98-nt X-tail region made up of 3 stem-loops (3′SLI, 3′SLII and 3′SLIII). The 3'-UTR can robustly stimulate IRES dependent translation in human hepatoma cell lines (Song *et al.*, 2006). Recent studies have recognized that various stemloop structures exist in the negative strand 3′-NTR. This region is recognized by the viral polymerase as the initiation site for plus-strand synthesis of the HCV genome (*Ye et al.,* 2005). A recent study identified a cellular factor called Far-upstream element (FUSE) binding protein (FBP) which binds to 3'NTR by interacting with the poly (U) tract (Zhang *et al.,* 2008*)*. The importance of long-range RNARNA interactions in the modulation of HCV lifecycle has been well documented. Within the 3′-end of the non-structural protein 5B (NS5B) coding sequence, a cis-acting replication element (CRE) was discovered (You *et al.,* 2004). This CRE is called as SL9266 (or 5BSL3.2) and its disruption blocks RNA replication (Friebe *et al.,* 2005). Mutual long range binding with both 5' and 3' sequences is suggested to stabilize the CRE at the core of a complex pseudoknot (Deviney *et al.,* 2008). Non coding RNA molecules or microRNAs (miR) are important in the control of gene expression and regulation. MicroRNA, miR-122 is specifically expressed and is found to be abundant in the human liver (Jopling, 2008). A recent discovery showed binding of a miRNA (miR-122) to the 5′-UTR of HCV. Sequestration of miR-122 in liver cell lines strongly reduced HCV translation, whereas its addition stimulated translation via direct interaction of miR-122 with two sites in the 5'-UTR (Kruger *et al.,* 2001). These studies have generated a lot of interest in the role of miR-122 in HCV multiplication and its potential as a therapeutic target. A role for proteasome alpha-subunit PSMA7 in regulating HCV IRES mediated translation has also been demonstrated (Kruger *et al.*, 2001). These host factors require further scrutiny to be considered as candidates for drug targets.

The single open reading frame is expressed s a polyprotein that gets processed; the positions of structural and non-structural domains. HVR-1 represents the highly variable region of an envelope glycoprotein. The genome organisation as shown in figure 2 below is 5'^{UTR} C-E1-E2-NS2-NS3-NS4A-NS4B-NS5A-NS5B-3'^{URT} (Jawezt *et al*., 2004; Lindenbach and Rice, 2005).

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