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Research Article

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Genomic Organization of Hepatitis C Virus and Correlation with Hepatocellular Carcinoma

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Abstract

Hepatitis C virus is included in the Flaviviridae family. It is enveloped positive sense and member of Hepacivirus species. It's a worldwide issue and its prevalence varies around the globe while most of it was in the USA but now Egypt is the most affected one. Hepacivirus C accounts for around177.5 million chronic infections worldwide. Its genotype diversity is due to the recombination in RNA genomics Major transmission route is by contamination of the blood. It can cause fatigue, jaundice, and anorexia, etc. It also affects the liver if it's a chronic infection. Genotypes and subtypes are 8 and multiple (to be precise almost 126) respectively. These are present in different parts of the world. The genotype that has the highest percentage around the globe is genotype 1. It affects about 40%-80% of the population. The USA has the highest percentage of the 1a and 1b, while in other countries genotype 1a is not so common. Pakistan has the highest percentage of HCV genotypes. Hepacivirus C viruses are indirect such as chronic inflammation, cell deaths, and proliferation. Chronic liver disease is also responsible for HCC because it can cause fibrosis and then eventually cirrhosis. Host and the environment also play a pivotal role in cirrhosis progression. The viral proteins of HCV directly upon cells signaling pathway that promote the HCC by stopping tumor-suppressing genes or due to signal pathways activation that helps in the growth and division upregulation. The retinoblastoma protein and p53 tumor suppressor are specific genes that suppress tumors are repressed by the HCV core protein. Carcinogenesis is caused by the loss of above mention tumor-suppressing genes.

Keywords: Hepatitis c; Carcinoma; Liver; Cirrhosis; Hepatocellular; Genome

Introduction

Hepatitis C Virus (HCV) is global issue and very common infection, affecting 71 million people all over the world. It can cause liver cancer and other disorders of liver as well. Cirrhosis, fibrosis is also included in the issues that have been caused by HCV. These are present worldwide in patients suffering from chronic infection. Shortly it is responsible for increase in deaths due to liver cancer. Annually approximately 399,000 deaths occur due to HCC and fibrosis which are the result of HCV [1]. HCV is not only cause of liver related disorders that are said to be hepatic disorders, but it also causes many non hepatic manifestation affection various gland and organ of body such as skin, salivary gland, kidneys, nervous and immune system. These disorders presence is in 1/3 of HCV patients. So, it is responsible for enhancing worldwide burden as well as problems associated to health care system. Its prevalence varies worldwide and. The prevalence rate of this infection ranges in countries from less than 1% to greater than 10%. It is present in very high percentage in Africa and middle-east while the lowest percentage has been reported in Americas, Australia, and North and West Europe [2]. In 2015 newly infected patient that were reported were 1.75 million which was limited than HCV occurrence. It was due to the uncertain signs and features of acute and chronic infection while most of patients suffering with chronic HCV were unaware of infection. HCV is transmitted by blood, so is considered in the category of blood borne. The most common transmission pathway or route is skin percutaneous through IVDU, transfusion of blood that is not tested properly or its screening has not been done in HCV genotype 1 and 3 are quite prevalent in the world. With the help of DAA 90% patients can be treated it is an effective treatment to some extent for the HCV. It is basically spread due to the blood transfusion of infected blood or by injecting. It can as well be transmitted to the baby from mother as well so could be sexually transmitted [3]. HCV is the member of family Flaviviridae. Its properties include that it is covered with lipid membrane, small and round in size and shape. It is included in RNA viruses that are single positive stranded. Its diameter is 50 nm (Bostan and Mahmood, 2010). 9.6 kb is the length of its genome and it has one open reading frame and have two ends 5′ and 3′ Untranslated Regions (UTRs) are present [4]. 5′ UTRis the part of genome which is more conserved and helps in genotyping and evolutionary studies [5].

Materials and Methods

Materials

Types of Hepacivirus C: HCV is divided into two stages the chronic Hepatitis C and acute Hepatitis C. The Risk of acute HCV is higher in person that undergo blood transfusion, body piercing, tattoos or those who are more involved in sexual activities [6]. It's not as severe as the chronic one and is frequently diagnosed as compared to the latter. Its symptoms and physical discomfort include anorexia, jaundice or abdominal discomfort. Physical findings are only in one third of patients while in other these are most as obvious as in the latter [7]. As descried before that liver disease and HCC are associated with HCV in western countries. Gradually inflammation is caused due to HCV that further cause cirrhosis between the time period of 20-30 years of HCV infection. According to some research from last 22years its rate has been slow down to 2%-3% while increase to 51% [8]. Fibrosis progression is as well caused by it in 20 years of infection. Patients suffering. Rate of fibrosis is 41% that is 3 times more in patients suffering HCV from 30 years. [9]. Chronic hepatitis is also related with many other diseases which are non-hepatic manifestation including HCV associated nephropathy, Diabetes type 2, Cerebrovascular and Heart disorder. Combined HBV and HCV is prevalent due to their similar transmission mode. Prevalence of it in HBsAg positive and HCV patients are 5%-20% and 2%-10% respectively [10]. There are

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total of 8 genotypes and more than 120 subtypes of HCV. Genotype 1-3 are more prevalent worldwide and hence are said to be endemic. Genotyping plays pivotal role in the HCV treatment planning and cure of HCV infection [11].

Methods

Transmission

The main transmission routes are blood transfusions, IVDU and injection. Other routes include transfer to child from mother. Before the discovery of HCV, it was considered that most of the non-A, non-B hepatic infections spread due to the pathogen that has some viral characteristics or properties. HCV was considered to be the most vital source of blood borne infection. It was done after the HBV identification and HBsAg donor implementation screening in 1970s [12]. HCV transmission occurs by blood transfer but with also associated blood products. [13]. During 2002 the risk of post transfusion HCV was reduced to 1& from 7.7% in 276,000 donations in USA, while in Italy it was reduced to 1% from 3.5%. It was due to the use of the test for blood screening donors. [14]. Blood screening is not controlled in the low- income countries properly as compared to the developed or rich countries. [15]. According to WHO global database blood safety report in 2011, more than 25% blood supply that is collected or gained from volunteers that are blood donors, while blood donations in 39 countries, are tested regularly for infectious agents, including HCV. It was conducted in 40 countries altogether. Improper quality control procedures and use of assay testing rapidly results in lowering the sensitivity that detects the infections. In a multinational study that was conducted or collected from 17 African countries showed that HCV sensitivities are low as 80%, while for HIV and HBsAg it was 81.4% and 75.6% respectively [16]. After the 2nd world war, with the increasing no of person using injections and blood transfusion there was the terrible increase in HCV genotype 1b globally. Its occurrence was specifically in the drug users [17] from the past 5-year study it was observed that after outbreaks by endoscopy or myocardial perfusion syringes are the source of transmission, not the procedure [18]. Although in developed and industrialized countries the rate of HCV transmission through this route is decreased but balance must be created in the control of infection and hygiene otherwise it will take no time to reoccur [19]. Various steps, strategies or acts could be taken to avoid or reduce the HCV transmission from injection drug use. These steps are said to be health interventions. These include those that aim at change in behavior and disinfecting of syringes. Opiate-substitution programme lessen the usage of drugs that is hazardous to health and helps in promoting the safe methods. It reduced the HCV transmission up to30- 65% [20].

Processes involved in life cycle: The life cycle of this virus is not completely acknowledged. There are problems in initiating the establishment of in vitro model of replication as well as the cells that mediate the viral entry that delays the molecular mechanism [21]. Circulation of its virion is either as free particle or lipoprotein surrounding the virion. Lipoprotein that surrounds the virion is low in density [22]. It attaches on the membrane of target cells by binding with the receptors and make entry by the process called Clathrin-mediated endocytosis. In endocytic compartment viral capsid is disrupted releasing the genome of HCV in the cytoplasm. Genome translation then takes place in rough endoplasmic reticulum. As a result of translation 3000 amino acid residue is constructed which is cleaved afterwards by protease into 10 mature products [23]. These proteins include structural core, E1 and E2, and the nonstructural proteins: nonstructural protein 2, nonstructural protein 3, nonstructural protein 4A, nonstructural protein 4B, nonstructural protein 5A, and nonstructural protein 5B. Assembly of generated virion is done in rough endoplasmic reticulum. These are release by the process of exocytosis. Next virus maturation takes place. It is surrounded by lipoprotein that help in immune escape.

Hepacivirus correlation with hepatocellular carcinoma

Hepatocellular Carcinoma (HCC) causes liver cancer for approximately 85%-90%. It is the liver cancer which is derived from hepatocytes it presents in both men and women worldwide. It is found to be at fifth position in common cancer in men, while among ladies it is at position 7 among the most common cancers. [24]. It is the at no 3 that cause death related to, lungs and stomach cancer are the remaining two that exceed it. It is not in the list of most frequent cancer in the world but the person suffering from it has less survival time, also have high mortality due to which it is considered to be the worldwide burden. Its mortality rate is 0.95% while survival rate is 6.9% for 5 years. The reason is that very less patients are diagnosed at early stage. Time period for the median survival is 330 days [25]. HCV and HBV both are responsible for HCC occurrence with the account of 10%-20% and 75%-80% respectively. Up to 70% of the patents of HCC shows the occurrence of anti- HCV antibody in their serum. This was in the areas where the incidence rate of HCC is quite low such as Western Europe and North America proving HCV as the major etiological factor [26]. Pathways for the major factor or causative agent of HCC Hepacivirus C virus are indirect such as: chronic inflammation, cell deaths, and proliferation. Chronic liver disease is also responsible for HCC because it can cause fibrosis and then eventually cirrhosis. Host and the environment also play pivotal role in the cirrhosis progression. In fact, these are more pivotal than the viral factors. These factors include older age, male sex, >50g intake of alcohol per day [27]. HCV causing HCC is associated with fibrosis formation with. 2%-6% is the occurrence among the patients of HCV cirrhosis causing HCC annually. Risk of HCC among HCV patients increase to 15-20 fold as compared with HCV negative patients. [28]. Chances of HCC in patients that suffer from HCV chronic infection for three years is 1%-3%. Combined infection of HBV HCV causing HCC rate is higher than developing infection due to alone HCV and HBV. Alcohol consumption is the major factor causing HCC in the western world [29]. Mostly o HCV- HCC is associated with cirrhosis and fibrosis of liver [30]. After the establishment of cirrhosis occurrence rate of liver cancer is 3.5% per year. Rate of HCC in HCV infected patients enhance up to 15%-20% folds, with the incidence rate of 15 to 20 folds yearly [31]. HCV was the major cause of 170000 new cancer cases in 2012 [32]. Death rate due to HCV causing HCC has been increase up to 21.1% [33]. HCV related HCC occurrence changes with geographical location as well as with culture. It's the major reason of HCC in the America, Europe, Japan and South America, while (HBV) is the reason of HCC in the Asia and Africa [34]. Almost 2.5% population around the world is affected with HCV [35]. It was very common in Japan and USA in 1920's and 1960's. People affected with HCV and HCV associated HCV in Japan are estimated to be 2.5% and 85% respectively [36]. On the contrary USA has less percentage of HCV and HCV associated HCC that ranges to 1.8% and 50%-60% respectively [37]. HCC risk in HCV patients increases due to combined infection of HBV and HIV dominantly. HBV plays the crucial role in HBV-HCV infection. Person that has undetected HBV DNA have equal chance of HCC in comparison with person suffering solely with HCV [38]. While patients with active HBV replication have double

HCC developing risk. There is as well 21% increase in death rate as well in comparison with latent HBV and HCV. Considerable increase in HCC prevalence in HIV-HCV patients compared to HCV patients has been observed. In such kind of population HCC occurs at the early age [39].

HCV progression to HCC

Viral induced factors and immune response mediates HCV carcinogenesis. Observations show that core protein initiates the lipogenesis and metabolism of stress. Viral proteins of HCV directly upon cells signaling pathway that promote the HCC by stopping tumor suppressing genes or due to signal pathways activation that helps in the growth and division upregulation [40]. Retinoblastoma protein and p53 tumor suppressor are specific genes that suppress tumors are repressed by the HCV core protein. Carcinogenesis is caused by loss of above mention tumor suppressing genes. Loss of these two is a synergetic affect [41]. Development and promotion of HCC and fibrosis is the responsibility of HCV nonstructural proteins. Induction of transforming β factor and activation of Hepatic stellate cells [42]. IFNs, tumor necrosis factor and chronic inflammation helps in arbitration of immunologic response induced by host to HCV. Accumulation of various mutational changes cause repetition of cell cycles. These mutations accumulation also results in the transformation of hepatocytes to malignant cells [43]. (Figure 1)

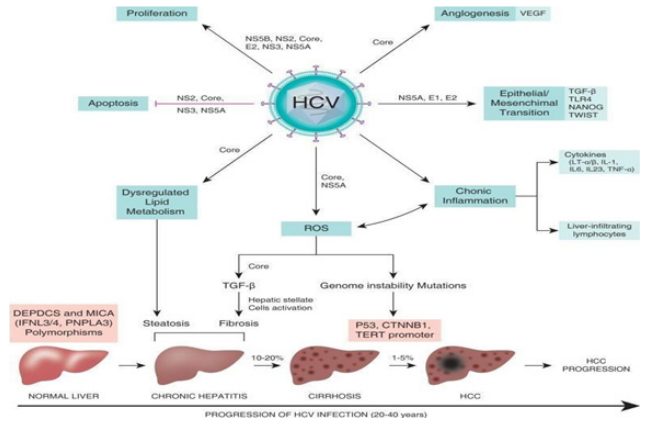

Figure 1: HCV progression to HCV

Discussion

Structural organization of HCV genome

It is an enveloped, circular and small in size RNA virus that belongs to Flaviviridae. It was discovered by the presence of its serum of non a non b hepatic patients by the [44]. HCV has genome length of 9.6Kb with single ORF and 5′ and 3 UTR region at both edge [45]. There are 10 proteins present in the open frame region E1, E2, P7, NS2, NS3, NS4A, NS4B, NS5A and NS5B these are called Core (c). From proteins present in core 3 are structural and 7 Nonstructural proteins [46]. It consists of protein core, enveloped protein and P7 protein. HCV protein core have 191 amino acids in their structure and are responsible for the assembly of nucleocapsid. Protein core is divided into three domains having following sequence of amino acids domain I have 1-117, domain II has 118-174, domain III has 175-191. The amino acids of these domain are highly hydrophobic in nature [47]. It plays vital role in interactions with pathways associated in viral life cycle and viral capsid formation [48]. E1 and E2 are the factors for the entrance in cell [49]. These identify the cell membrane receptors and then allow the cell entry [50]. E2 initiates the viral attachment process being responsible for causing infection [51]. HVR1 and HVR2 are the sites or regions on E2 protein and neutralizing antibodies are being targeted by the E2 protein. HVR1 allow the virus to enter Immune system and lead to chronic infection [52]. 63 amino acids are present in this which is present in middle of E2 and NS2. These play vital role in the virus infection because can easily form ion channels [53]. Ion channel and assembly of virus is the responsibility of the P7 protein [54]. (Figure 2)

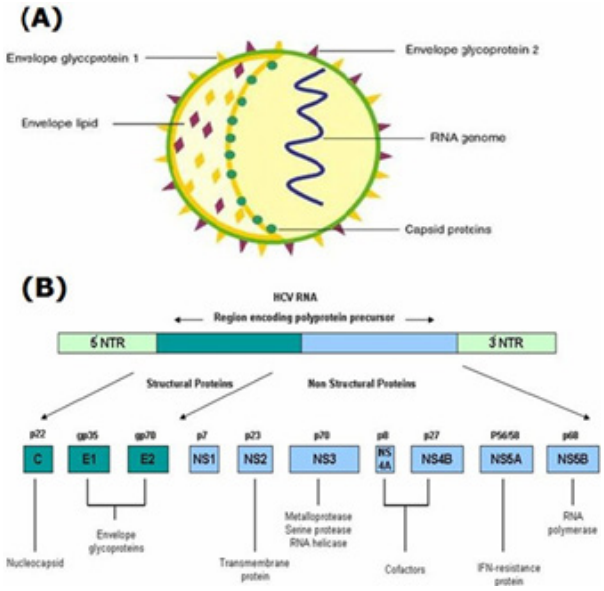

Figure 2: The HCV genome with a single-stranded positive-sense RNA of 9.6 kb with three structural proteins (core, E1 and E2) and seven nonstructural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B).

Conclusion

Hepacivirus C is the worldwide burden. It has been affecting the world from past 30 years. The prevalence of this has been decreasing in the developed countries because of their resources for the treatment therapies, while in under developed and developing countries the ratio of the HCV is expanding with each day. There are 8 subtypes and more than 100 subtypes. These are due to the genomic recombination. The prevalence of HCV genotypes varies because of geographical region, mutations, infection route around the globe all over the world. Genotyping also plays vital part in the diagnose and treatment of chronic infection. Also responsible for to study evolution affects the 2.5% population of world. The most abundant one is genotype 3 and genotype 3. Its prevalence has been increasing in the developing countries while its rate has been reduced in developed countries such as America is also the responsible for various liver problems such as fibrosis and cirrhosis etc. Hepatocellular carcinoma is also associated with HCV. The occurrence rate of HCC-HCV is higher than the normal HCC. The reason of its high prevalence is that in serum of HCC infected patients there are anti-HCV antibodies are present. HCV occurrence all over the world is 2.5 percent that means 177.5 million peoples are affected with it genotype 1 is about 46.2% that accounts for 83.4 million and is the most abundant one in the

world. It's distribution on the basis of location include North and West Europe, Asia, North and South America, and Australia [55]. HCV genotype 2 is likely to be occur in West and Central Africa, [56]. HCV genotype 3 is most prevalent one after genotype 1 and account for 54.3 million which is 30.1% around the globe. From the cases globally, South Asia have 75% of this genotype. Genotype 4 is present in the middle east specifically Egypt. Genotypes 2, 4, and 6 are the genotypes that account for majority of the remaining cases estimated to be 16.5 million that account for 9.1%.

15.0 million that account for 8%-3% and 9.8 million that account for 5.4% cases, respectively. Genotype 7 was only in one patient who was present in Canada and was immigrant. Innate immunity is a first line of defense for HCV infection and it restores acquired immune system. Binding of HCV RNA to retinoic acid-inducible gene I, activates the mitochondrial antiviral signaling (MAVS) proteins; double-stranded RNA than binds to toll-like receptor-3 urge signaling through TRIF. These than activates NFkB and IRF3 translocation to the nucleus. Then at nucleus they encourage expressing IFNs and ISGs so that these can stop the viral replication. HCV replication and spread could only be limited by the innate antiviral response but could not be completely removed or abolished without the action mechanism of adaptive immune response. Hepatocyte cell death occurs due to the boost in transaminase levels resulting in the decline of viral load. Chronic infection usually last for approximately more than six months. The clearance or removal of virus spontaneously is no rare but it also does not reappear after this. For controlling or clearance of infection adaptive immunity rapidly start supporting the mount cells to target multiple HCV epitopes, broadly-reactive neutralizing antibodies. The T lymphocytes does not let the virus to escape immune response by targeting the multiple epitopes and reducing the chances of escape.

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