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Overview of Hepatitis B Virus, Clinical Features, and Host Immune Response

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Abstract:
Hepatitis B virus is a DNA virus that causes infection, often through exposure to infected blood, during sexual intercourse, and by vertical transmission of the virus from mother to child. After the incubation period of the virus, which lasts from 1 to 6 months, the prodrome stage appears in 10% - 20% of patients, which is characterized by fever, joint pain and the appearance of a rash. Then, at a later time, characteristic clinical and laboratory signs of acute hepatitis appear, which usually last from 1 month to 3 months. However, most of those infected are asymptomatically in the acute stage of disease, and the fact that they are carriers of the virus is discovered later, by chance. People with HBV infection may make a full recovery and their infection may be chronic, whether as carriers or as those with chronic hepatitis. Chronic infection appears in only 1% - 5% of adults who are exposed to HBV infection, while 95% of newborns develop chronic infection. About a third of people who suffer from chronic infection develop cirrhosis liver or liver cancer at a later time. And acute liver failure appears in less than 1% of patients. Infection with the HBV virus can manifest itself by the appearance of non-hepatic symptoms, such as arthritis, infection of the kidneys and vasculitis.
The aim of this reviewis to know the immune response against HBV and the ability of the virus to cause the damage in chronic cases.
Keyword: HBV, Cytokine, TNF, Cytokine Gene Polymorphism, IFN

Introduction:

Approximately, 280 million people have been estimated to have a chronic HBV infection, and most of them live in Asia, sub-Saharan Africa and other developing countries. The overall mortality rate was 800,000 people have died due to hepatocellular carcinoma and HBV-related cirrhosis and 130,000 deaths due to acute HBV infection [1].The infection is characterized by HBV, which is a tiny, incomplete double-stranded genus Orthohepadnavirus (Hepadna-viridae) DNA virus stated to have three different viral particles; small spherical HBs Ag particles, surface antigen tubular structures, and large spheroidal particles, and the complete particle virus [2]. A number of important features will be:

1- Virus Structure

Hepatitis B virus is an enveloped virus, measuring 42 nm in diameter, consisting of an outer lipid envelope and an icosahedral nucleocapsid core; the latter being composed of both protein and

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double-stranded relaxed-circular DNA genome covalently bound to the viral polymerase. The outer envelope contains embedded proteins which are involved in viral binding [3]. In general, Virion is spherical, but polymorphic forms, including filamentous forms, are also present. The DNA genome, comprising long and short segments that converge to form a closed loop, is partly double-stranded and non-segmented. The longer strand consists of long nucleotides 3020-3320 while the shorter strand is long nucleotides 700-2800 [4].

The infectious portion of the virus is the viral core, while the outer coat carries the virus' main antigenic determinants, HBs Ag [5], as shown in **figure 1.**

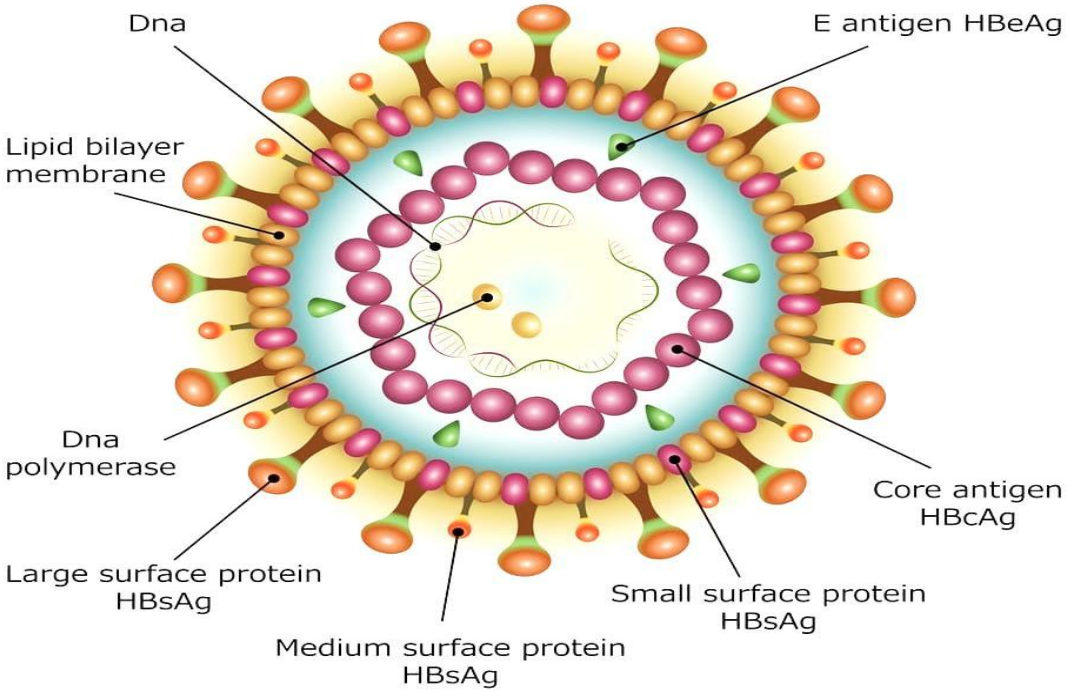

Figure 1: A simplified drawing of the HBV particle and surface antigen [6].

2- Virus Proteins

HBV proteins consist of a nucleus of the inner protein and an envelope of the outer protein. The outer envelope consists of many proteins; known as nucleocapsid-enclosing hepatitis B surface proteins (HBs) or inner protein shells consisting of hepatitis B core proteins (HBc) and a soluble nucleocapsid protein; hepatitis B e antigen protein; (HBe Ag) [7]. The HBV surface proteins, closely related envelope (surface) proteins, are classified into small (SHBs), middle (MHBs) and large (LHBs) proteins, with varying degrees of immunogenicity[8].

The capsid of HBV is formed by 180 copies of one major protein with a size of 22 kDa that is named hepatitis B core (HBc), which is assembled spontaneously into 27 nm core particles even in the absence of other viral proteins. The core particles are a potent immunogene and able to induce the production of high anti-HBV antibody titers during natural HBV infection and also in immunized animals[9]. The HBe Ag is found as a soluble protein and usually correlates with

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viremia [10]. It is a non-structural viral protein not necessary for HBV infectivity [7]. The final protein is polymerase, which is a basic protein rich in histidine with a molecular weight of 93kDa.It plays acritical role in the replication of the hepadnavirus genome, and its enzyme activity is catalyzing the RNA- and DNA-dependent DNA polymerase [11].

3- Replication Cycle

The main feature of the HBV replication cycle is replication of the DNA genome by reverse transcription of the RNA intermediate [12]. Cell-surface receptors are bound by incoming HBV virions, whose existence remains unclear. A series of genomic and subgenomic transcripts type this enzyme [13]. All viral RNA is passed to the cytoplasm, where even the proteins of the viral envelope, heart, and polymerase as well as the X protein are formed via their translation[12].

4- Mode of Transmission

Transmission of hepatitis B virus results through exposure to infected blood or body fluids containing blood and sexual contact is included in possible forms of transmission [14], blood transfusions and other human blood products, re-use of infected needles and syringes, and vertical mother-to-child transmission during delivery[15].HBV can live outside the body for at least 7 days and if a person who is not protected by the vaccine enters the body, the virus can still cause infection during this time. The incubation time for HBV is 75 days on average, but it can range from month to three months. The virus is observable 30 to 60 days after infection and survives over variable periods of time[16].

5- Clinical Manifestations of Infection

Clinical features of HBV infection vary considerably. Jaundice occurs in less than 10% of children younger than five years old; however, it has also been reported that jaundice is manifested in 50% of older children and adults. There have been no distinct clinical manifestations of acute HBV infection and their presence does not vary significantly from other causes of acute viral hepatitis[8]. Anorexia, nausea, vomiting, flu-like complaints, fatigue, and malaise are among the symptoms. Physical findings vary from minimal non-specific defects to jaundice and (sometimes tender) hepatomegaly and sometimes extend to extrahepatic features representing immune-complex phenomena such as vasculitis, nephritis of the immune complex, arthritis, serum disease, and nodosapolyarteritis [17]. Most adults with acute HBV have fully recovered and only 5 percent of adults, especially men, will develop a chronic, often asymptomatic, HBV infection [18]. A chronic HBV infection is characterized by the existence of HBs Ag in serum for at least six months or the presence of HBs Ag and the absence of anti-HBs immunoglobulin M (IgM) antibodies[19]. Over a period of several years, chronic HBV infection can be either asymptomatic or associated with chronic inflammation of the liver (chronic hepatitis), leading to cirrhosis. It has been found that this form of infection is significantly associated with an increase in hepatocellular carcinoma incidence [20].

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6- Immunological Response

6-1 Innate Immune Response

The innate immune response of the body to viruses is typically characterized by cytokine secretion and activation of natural killer (NK) cells. Cytokines that identify pathogen-associated molecular patterns [21].In HBV, a similar innate immune response occurs, but unlike most viruses, HBV does not immediately begin to replicate, and instead there is an initial lag period that usually lasts 4-7 weeks after infection. A logarithmic expansion process that infects most hepatocytes is followed by the lag phase [22]. Studies conducted on HBV-infected chimpanzees showed that during the lag time no genes were activated, indicating that during the initial HBV infection there was no innate immune response[17]. The onset of the logarithmic expansion process, however, triggers the release of infected interferon-alpha (IFN-alpha) and IFN-β hepatocytes, which are cytokines that are known to decrease the amount of viral capsids encoding pregenomic HBV RNA and stimulate double-stranded dependent kinase (PKR) activity, both of which inhibit HBV protein synthesis [23].

Antigen-presenting cells (APCs) comprising Kupffer cells and dendritic cells are also stimulated by these two cytokines, thereby stimulating the development of interleukin-18 (IL-18) and chemokine CCL3 by activated cells, which in turn activates NK and natural killer T (NKT) cell activity [24]. The latter cells (NKT cells) secrete a further cytokine called IFN-γ, which is one of the most powerful immune system mediators and is associated with viral replication inhibition[25]. In HBV transgenic mice stimulated by alpha-galactosylceramide injection, It was observed that NKT cells were involved in the competitive inhibitor of Viral replication without stimulation of CD4+ or CD8+ T cell activity[26].

6-2 Adaptive Immune Response

A. Humoral Immune Response

The human immune system has been well known to be important for long-term HBV clearance; it operates in combination with the cellular adaptive immune system in infection control[24]. The humoral immune response generates anti-envelope antibodies that are detectable in human serum after infection with HBV. Antibodies have been detected against each of the HBV proteins, although not all antibodies have been detected in each person exposed to HBV[17]. However, various stages of infection have been associated with the presence of different antibodies [27]. While HBV core protein (anti-HBc) antibodies may be present in chronic carriers of HBV, unlike anti-HB antibodies, they are persistent over the course of infection and do not play a role in neutralizing HBV infection. In addition, various HBV strains consist of different combinations of proteins, promoting the production of different subclasses of antibodies [25].In this regard, variations in the IgG antigen response subclasses have been shown to contribute to various stages of the disease and different forms of immune response, and individuals with chronic HBV infection had higher levels of total IgG and IgG1 than groups of individuals recovering from infection. Moreover, as compared with vaccinated or recovered persons, chronic carriers displayed varying ratios of different IgG subtypes. In the case of anti-HBc, the anti-HBcIgG

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subclass pattern of IgG1 > IgG3 > IgG4 was shown by chronic carriers, while recovered individuals showed a different pattern: IgG3 > IgG1 > IgG4 [28].

B. Cellular Immune Response

In most cases, control of HBV occurs by non-cytolytic down-regulation of viral replication, meaning viral removal results without the destruction of infected cells, usually occurring through the release of cytokines by lymphomonuclear virus-inactivated cells[28]. As a consequence, virus-specific CD8+ and CD4+ T cells are marked as having important antiviral immunity effector and regulatory functions, while CD8+ T cells are the key effector cells that induce viral clearance, CD4+ T cells are needed to promote the induction and maintenance of CD8+ T cells [29].Following the resolution of acute HBV infection, activated HBV specific CD4+ T cells are multi-specific, but strong helper T cell responses have been shown to be correlated with certain peptides in HBc Ag and HBe Ag; HBe Ag has been shown to induce immune response to Th2, while HBc Ag stimulates response to Th1. Furthermore, polymerase and X antigens have also been identified against CD4+ T cell responses[24]. CD8+ T cells, however, are the main effector cells in HBV viral clearance, and viral persistence was the result of loss of CD8+ T cells after HBV infection. These cells generate IFN-γ that, through viral capsid destabilization, viral protein degradation, and post-transcriptional degradation of HBV RNA, clears HBV. The overall effect, without unnecessary liver damage [23].

7- Cytokines

Cytokines are proteins that play a key role in immune system communication and in allowing information to be exchanged between the immune system and host tissue cells. In all aspects of innate and adaptive immune response, including differentiation and cell growth, inflammation, and repair, there are low molecular weight soluble protein messengers involved. These function in an antigen-non-specific manner and are involved in a broad variety of biological activities, from chemotaxis to cell-specific activation to significant physiological alterations. A great percentage of cytokines have been discovered and many are critical for controlling the development of lymphocytes and determining the types of immune responses evoked by specific responses [30].Cytokines can act locally either on the same cell that secreted it (autocrine) or on neighbouring cells (paracrine) or they can act systemically (endocrine) like hormones[31]. In fact, cytokines are similar to polypeptide hormones, as they promote cell-to-cell communication and function at very low concentrations. Each cytokine binds to a particular receptor on the surface, followed by subsequent intracellular signalling cascades that alter cell function. This involves the upregulation of many genes and their transcription factors, leading to an increase in the number of other molecular surface receptors, the development of other cytokines, or the suppression of their own effects through feedback inhibition[32].

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7-1 Role of Cytokines in Hepatitis

The cell-to-cell contact between mononuclear phagocytes and T lymphocytes during which one of the early events occurring during the host's response to viral infection such as HBV is the former current viral antigen. T cells therefore bind to mononuclear antigen-presenting cells, and cytokines are released shortly after immunological mediators [33]. Immunoregulatory cytokines of T-lymphocytes contribute significantly in the host's response to HBV infections. The immune response associated with the Th1 cytokine profile has been shown to indicate that cell-mediated immunity is associated with recovery, while the Th2 cytokine response is associated with persistent infection growth [34]. In the immune pathogenesis of HBV infections, the imbalance of pro-inflammatory Th1 and anti-inflammatory Th2 cytokine output can play an important role.It can be used for estimating the development, progression and outcome of chronic liver disease.Hepatotropic viruses like HBV continuously release particles of the viral into the blood stream while infecting the parenchyma of the liver. In the first row of protection viruses to be found, the liver-bound NK and NKT cells are included[35]. These cells are activated by Type-I IFNs (IFN-a and IFN-β) formed by infected liver cells. Infected cells can be destroyed by both NK and NKT cells, but they are also an important source of IFN-γ and TNF-alpha [29].These cytokines inhibit viral replication through non-cytolytic mechanisms, and can eliminate viruses without destroying liver cells. NK cells are activated by IL-12 released from dendritic cells (DCs), and thus become empowered to eliminate both infected cells and immature DCs with no Th1 cytokine profile, which would not result in appropriate stimulation of a specific response [36]. According to the balance between cytokines released by innate immune system cells resident in or recruited by the liver (IL-4/IFNα/IL-12), NK cells may induce partial or total DC maturation.Through class-I and class-II MHC molecules, dendritic cells can process viral antigens and present them to specific immune system cells. Through Toll-like receptors (TLRs), DCs capture viral particles and, upon activation, these cells secrete several types of cytokines (IL-12, TNF-a, IFN-a and IL-10) that are capable of regulating and polarizing the response of adjacent cells. Two types of DC have been described; myeloid DCs mainly produce IL-12 or TNF-α, whereas plasmacytoid DCs that release IFN-α [37].

7-2 Cytokine Gene Polymorphism

Genetic polymorphism could be defined as the presence at a population locus of several forms of DNA sequences together, or a discontinuous genetic variation among members of a single species that results in different individual forms or types.Within a population, genetic polymorphism encourages diversity. For several centuries[38].Student outcomes of cytokine gene polymorphisms (CGPs) has shown variations between people that influence not only the expression of the cytokine gene, but also disease susceptibility, development, severity, and clinical outcomes. In population-level trends of CGPs, ethnic differences observed are mainly due to natural selection imposed by microbiota, environmental factors, and complex interactions between host and pathogen [39].

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As significant determinants of vulnerability and disease severity, genetic polymorphisms have emerged in recent years. DNA sequence variants that vary from gene mutations in that they occur and have a frequency of at least 1 percent in the normal healthy population are naturally occurring polymorphisms.Due to single base substitutions, approximately 90 percent of DNA polymorphisms are SNPs. Others include polymorphisms of insertion/deletion, mini-satellite and microsatellite polymorphisms [40]. While most polymorphisms are structurally neutral, certain of them have consequences for gene expression regulation or the coded protein's role. Despite the low penetrance, these functional polymorphisms may lead to differences in susceptibility to and severity of disease between individuals[41].

The association between certain polymorphisms of the cytokine gene, many other studies have examined in vitro expression of the cytokine gene and the vulnerability and clinical severity of diseases.[40]. In the study of genome structure and history, single nucleotide polymorphisms are an increasingly valuable method and one of their most common applications is in disease-association studies aimed at exploring statistically relevant associations of SNP alleles and diseases to classify candidate causative genes[42]. The outcomes of both HBV infections are recorded as distinctly heterogeneous, ranging from acute asymptomatic self-limiting infection to fulminant hepatic insufficiency to decompensated cirrhosis and hepatocellular carcinoma. At the time of infection, viral sequence and genotype variability, environmental factors, and age all lead to heterogeneity in the result, but all differences cannot be explained [43]. In this context, it has been observed that host genetics may influence the outcome of HBV infection. Studies showing evidence of clustering of related outcomes (e.g. chronicity of infection) in the same family support this point of view; the strongest evidence of host genetic impact is focused on twin studies in Taiwanese HBV-infected patients with higher concordance levels in monozygotic twins compared to dizygotic twins in the HBs Ag carriage [44].

Conclusion

More effective and less resistance-prone antiviral agents have recently become available for HBV infection therapy. The link between high-level replication of HBV and the late consequences of chronic HBV infection is confirmed by substantial data and there is growing evidence of the importance of deep, long-lasting therapeutic suppression of HBV DNA in slowing and reversing the progression of chronic HBV infection. In the future, without creating resistance, we should expect antiviral drug regimens to boost effectiveness and combination drug therapy can lead to this evolution. The challenge will be to establish shorter treatment regimens with longer-lasting clinical effects and therapies that are more effectively targeted at the time of infection with HBV, especially in patients with perinatal infection, when the most severe, injurious behavior of the disease occurs.

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Received 16 February 2021; Accepted 08 March 2021.

References:

1- WHO, (2015). Hepatitis.Retrieved 2015-3-22.

2- Liang, T.J. (2009). Hepatitis B: the virus and disease. *Hepatology*,**5**:13-21.

3- Kann, M. (2002). Structural and molecular virology. In: Hepatitis B Virus Guide. Lai, C.L., Locarnini, S., editors. London: International Medical Press, pp. 9–22.

4- Hoboken, A. (2013). Viral Hepatitis (4^{th}ed) Wiley. p:83.

5- Mast, E., Mahoney, F. and Kane, M. (2004). Hepatitis B vaccine. In: Plotkin, S. A., Orestein, W. A., Vaccines. Philadephia :Saunder, 299-337.

6- Trépo C, Chan HL, LokA.Lancet. 2014 Dec 6;384(9959):2053-63.

7- Dienstag, J. L. (2010). Hepatitis B Virus Infection.*N Engl J Med*,**359**:14

8- Chu, C. J. and Lok, A. S. (2002). Clinical significance of hepatitis B virus genotypes.*Hepatology*,**35**:1274-1276.

9- Kenneth, W. L. and Jeffrey, T. K. (2004). Hepatitis B. *MicrobiolMolBiol Rev.*,**69**:61-78.

10- Goldstein, S. T. (2005). A mathematical model to estimate global hepatitis B disease burden and vaccination impact.*Int J Epidemiol.*,**34**:1329-1339.

11- Mason. A., Jeremy, T., Vince.B., Adams, E. and Perrillo, R. (2005).Hepatitis B virus Replication in Damaged Endothelial Tissues of Patients with Extrahepatic Disease.*Am J Gastroenterol.*,**100**:972.

12- Beck, J., Nassal, M. and Nassal, J. (2007). Hepatitis B virus replication. *World J Gastroenterol.*, **1**:48-64.

13- Klenerman, P. and Gupta, P.K. (2012). Hepatitis C virus: Current concepts and future challenges. *QJM.*,**105**:29-32.

14- Fairley, C. and Read, T. (2012). Vaccination against sexually transmitted infections. *Curr Opinion Inf Dis.*, **25**:66-72.

15- Shi, Z., Yang, Y., Wang, H., Ma, L., Schreiber, A., Li, X., Sun, W., Zhao, X., Yang, X., Zhang, L., Lu, W., Teng, J. and An, Y. (2011). Breastfeeding of Newborns by Mothers Carrying Hepatitis B Virus: A Meta-analysis and Systematic Review. *Arch PediatrAdolesc Med.,* **165**:837-846.

16- Chen, H., Lin, L. and Hu, F. (2012). Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV.*Gastroenterology*,**142**:773.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 1704 - 1714
Received 16 February 2021; Accepted 08 March 2021.

17- Kayser, F. H. ;Biens, K. A. ; Eckert, J. and Zinkernagel, R. M. (2005). Medical microbiology. Georg ThiemeVerlag, Germany.

18- Terrault, N., Roche, B. and Samuel, D. (2005). Management of the hepatitis B virus in the liver transplantation setting: a European and an American perspective. *Liver Transpl.*, **11**:716-732.

19- Wright, T. L. (2002). Clinical aspects of HBV infection.*Lancet.*,**342**:1340-1344.

20- El-Serag, H. (2011). Hepatocellular carcinoma. *N Engl J Med.*, **365**:1118-1127.

21- Heil, F., Hemmi, H., Hochrein, H., Ampenberger, F., Kirschning, C., Akira, S., Lipford, G., Wagner, H. and Bauer, S. (2004). Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. *Science*, **303**:1526-1529.

22- Lin, K. and Kirchner, J. T. (2004). Hepatitis B virus.*Am Fam Physician*., **69**:11-15.

23- Bertoletti, A. and Gehring, A. (2006). The immune response during hepatitis B virus infection. *J Gen Virol.*,**87**:1439-1449.

24- Chang, J. and Lewin, S. (2007). Immunopathogenesis of hepatitis B virus infection. *Immuno Cell Biol*., **85**:16-23.

25- Huang, C., Lin, S., Ho, Y., Chen, F., and Yang, C. (2006). The immune response induced by hepatitis B virus principal antigens. *CelMolImmunol.*, **3**:97-106.

26- Bocharov, G., Ludewig, B., Bertoletti, A., Klenerman, P., Junt, T., Krebs, P., Luzyanina, T., Fraser, C. and Anderson, R. M. (2004). Underwhelming the immune response: effect of slow virus growth on CD8+-T-lymphocyte responses. *J Virol*., **78**:2247–2254.

27- Geetanjali, R. K., Dimpy, P., S. and Lu, H., (2014). Immune response to hepatitis B vaccination in drug using populations: A systematic review and meta-regression analysis. *Vaccine*,**20**:2265-2274.

28- Rehermann, B. (2013). Pathogenesis of chronic viral hepatitis: differential roles of T-cells and NK cells. *Nat Med.*,**19**:859-868.

29- Guiotti, L. and Chisari, F. (2006). Immunobiology and pathogenesis of viral hepatitis.*Annu Rev Pathol*., **1**:23-61.

30- Chokkalingam, V., Tel, J., Wimmers, F., Liu, X., Semenov, S., Thiele, J., Figdor, C. and Huck, W. T. (2013). Probing cellular heterogeneity in cytokine-secreting immune cells using droplet-based microfluidics. *Lab Chip*, **24**:4740-4744.

31- Zygmunt, B. and Veldhoen, M. (2011). T- helper cell differentiation: more than just cytokines. *AdvImmunol.*,**109**:159-196.

32- Horacek, J.M., Kupsa, T., Vasatova, M., Jebavy, L. and Zak, P. (2014). Biochip array technology and evaluation of serum levels of multiple cytokines and adhesion molecules in patients with newly diagnosed acute myeloid leukemia.*ExpOncol.,* **36**:50-51.

33- Dimitropoulou, D., Marina, K., Georgios, L. Theodorou, L., Stelios, F., Athanasia, M. and Charalambos, A. (2013). Serum cytokine profile in patients with hepatitis B e-antigen-negative chronic active hepatitis B and inactive hepatitis B virus carriers. *World J GastrointestPathophysiol.,***4**:24-27.

34- Fan, X. G., Liu, W. E., Li, C. Z., Wang, Z. C., Luo, L. X. and Tan, D.M. (1998). Circulating Th1 and Th2 cytokines in patients with hepatitis C virus infection. *Mediators Inflamm.,***7**:295-297.

35- Su, A., Pezacki, J., Wodicka, L., Brideau, A., Supekova, L. and Thimme, R. (2002). Genomic analysis of the host response to hepatitis C virus infection. Proc. Natl. Acad. Sci. **99**:15669-15674.

36- Moretta, A. (2002). Natural killer cells and dendritic cells: rendezvous in abused tissues. *Nat Rev Immunol.,***12**:957-964.

37- Shortman, K., and Liu, Y. (2002). Mouse and human dendritic cell subtypes. *Nat Rev Immunol.,***2**:151-161.

38- Dai, C., Chuang, W. and Lee, L. (2008). Association between transforming growth factor–beta 1 polymorphism and virologic characteristics of chronic hepatitis C. *Transplant Res.,***152**:151-156.

39- Fareed, M., Afzal, M. (2013). Single nucleotide polymorphism in genome-wide association of human population: A tool for broad spectrum service. *Egypt J Med Hum Genet.,* **14**:123-134.

40- Ulger, M., Emekdas, G., Aslan, G., Tas, D., Ilvan, A., Tezcan, S., Calıkoglu, M., Erdal, M. and Kartaloglu, Z. (2014). Determination of the cytokine gene polymorphism and genetic susceptibility in tuberculosis patients.*Mikrobiyol Bul*. **47**:250-264.

41- Conde, S. R., Feitosa, R. N., Freitas, F. B., Hermes, R. B., Demachki, S., Araujo, M. T., Soares, M. C., Ishak, R. and Vallinoto, A. C. (2013). Association of cytokine gene polymorphisms and serum concentrations with the outcome of chronic hepatitis B. *Cytokine*, **61**:940-944

42- Ning, S., Zhao, Z., Ye, J., Wang, P., Zhi, H., Li, R., Wang, T. and Li, X. (2014). Link SNP: a database of linking disease-associated SNPs to human large intergenic non-coding RNAs.BMC.*Bioinformatics.,***15**:152.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 1704 - 1714
Received 16 February 2021; Accepted 08 March 2021.

43- Mohd, H., Groeger, J., Flaxman, A. and Wiersma, S. (2013). Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV sero-prevalence. *Hepatology*, **57**:1333-1342.

44- Zhao, Z., Aizhen, L., Xiaomin, X., (2014). Risk factors for intrauterine infection with hepatitis B virus.*Int J Gynaecol Obstet.*,**2**:158-161.