JOURNAL-BASED LEARNING EXERCISES

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DEADLINE WEDNESDAY 3 JULY 2019

Association of genetic polymorphisms of chemokines and their receptors with clearance or persistence of hepatitis C virus infection

El-Bendary M, Neamatallah M, Elalfy H. *Br J Biomed Sci* 2019; **76** (1): 11–6. Assessment No A101019

01	Approximately 20% of hepatitis C virus (HCV)-infected cases are able to clear the virus.
02	Chemokines are usually referred to as either homeostatic or pro-inflammatory, the latter initiating the signalling pathways by which leukocytes undergo migration and extrusion from blood into tissues.
03	Expression of CC chemokine receptor type 2 (CCR2) occurs on macrophages and monocytes, but not on dendritic cells (DCs) or T cells.
04	Understanding the pathogenesis of the disease is determined mainly by observational studies of HCV-infected patients and *in vivo* experiments.
05	In this study, the negative control group comprised 1460 healthy household contacts.
06	HCV-infected patients have significantly increased transcription levels of CCR2 and CCL2 mRNA in liver tissue.
07	Mean aspartate aminotransferase (AST) level in the control group was 45 IU/L.
08	Of all individuals infected with HCV, at least 70% develop chronic disease, with 20–50% advancing to cirrhosis.
09	Antibodies to HCV were determined by enzyme immunoassay, and qualitative PCR was used to measure HCV seropositive patients.
10	Results suggest that the A allele of rs1799864 G/A polymorphism is associated with higher risk for development of chronic hepatitis C (CHC).
11	Interferon (IFN)-inducible CCL2 is released by Kupffer cells early in the infection, resulting in stimulation of infiltrating monocytes including CCR2+ plasmacytoid DCs.
12	Heterozygosity of all the single nucleotide polymorphisms (SNPs) in the three groups studied ranged from 0.19 to 0.51.
13	Carriage of allele A of *CCR2* rs743660 G/A polymorphism was shown to be significantly higher in the CHC group compared to the other two groups.
14	Chemokines and chemokine receptors are not involved in leukocyte aggregation at immune response sites.
15	A previous study of haemodialysis patients with HCV reported that the frequency of the *CCR2* rs1799864 genotype was significantly reduced in an HCV-infected patient group.
16	Interaction of CCL5 with CCR5 has no significance during HCV infection.
17	Genetic analysis of subjects taking part in the current study demonstrated the contribution of *CCL2* and *CCR2*, but not *CCL5*, in the pathogenesis of HCV infection.
18	All samples were successfully genotyped for rs13900 while 100 samples from the SVC group failed to be genotyped for the other three SNPs.
19	There is compelling *in vitro* and *in vivo* evidence of the important role of *CCL5* as a mediator of experimental liver fibrosis.
20	Frequency of the CCR5Δ32 polymorphism decreases from northern to southern Europe and is completely missing in African and Asian cohorts.

TLR3 and *TLR4* SNP variants in the liver disease resulting from hepatitis B virus and hepatitis C virus infection.

Sghaier I, Zidi S, Mouelhi L *et al. Br J Biomed Sci* 2019; **76** (1): 35–41. Assessment No T101019

01	With almost one million new cases and approximately 600,000 deaths recorded per year, hepatocellular carcinoma (HCC) ranks as the fifth most common cancer worldwide.
02	TLR4 influences the chronicity of virus infection and thus subsequent pathological changes including liver cirrhosis and HCC.
03	Homogeneity in TLR3 and TLR4 expression and levels are due to specific intronic and exonic gene variants in both genes.
04	The study recruited 174 chronic HBV carriers and 100 chronic HCV carriers, plus 360 individuals seronegative for both HBV and HCV to serve as controls.
05	There was no difference in the sex ratios of the HBV patients, but age increased with liver disease stage.
06	No significant link was found between *TLR3* rs3775290 major allele genotype and HBV infection.
07	The rs4986790 minor G allele was more frequent among HBV-infected patients.
08	Both homozygous major (C/C) and heterozygote (C/T) *TLR3* rs3775290 genotypes were more frequent among patients with cirrhosis.
09	Thirty patients in the HBV group had hepatocellular carcinoma.
10	In both HBV and HCV cohorts, increased age and male sex were linked to disease severity.
11	*TLR3* (rs3775290) and *TLR4* (rs4986790) genotyping was performed by PCR-restriction fragment length polymorphism (PCR-RFLP) methodology.
12	Chronic viral infection may increase by 10- to 100-fold the risk of HCC.
13	Effective detection and control of viral replication depends on viral and host immunity.
14	The carriage of *TLR3* Asp299Gly variant results in poor responsiveness in TLR signalling, which in turn facilitates HCV escape from immune surveillance.
15	Results showed little differences in distribution of alternate alleles in earlier stages of infection.
16	Persistence of HBeAg seronegativity (>6 months) in HBV-infected patients results from mutations in precore and basal core promoter regions of HBV DNA.
17	Previous studies have shown that mutations in molecules involved in TLR4 signalling are associated with lymphoma.
18	Figure 1d plotted α-fetoprotein (AFP) level in HCV patients with the *TLR3* rs3775290 genotype according to disease stage.
19	In one study, almost three-quarters of HCC was attributed to HCV infection.
20	Genomic DNA was extracted from peripheral venous blood using the QIAamp DNA Blood Mini Kit.

REFLECTIVE LEARNING

01	Perform a literature search for the CCR5Δ32 polymorphism and then summarise its role in disease.
02	The authors previously published a paper on the association of SNPs of Toll-like receptor genes with susceptibility to HCV infection. Explain in detail why this work represents an advance in biomedical science.

01	Non-alcoholic fatty liver disease (NAFLD) has emerged as a health problem worldwide. Discuss the role that genetic factors such as single nucleotide polymorphisms play in the aetiology of this condition.
02	Explain the meaning of the term heterogeneity in relation to gene expression in patients with hepatitis.