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مقدمه من

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Association of Genetic Polymorphism of TNF-α and TGF- β1 with Hepatocellular Carcinoma in Chronic Hepatitis C Egyptian Patients

Thesis

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List of Contents

List of abbreviation

AFP	Alpha-fetoprotein.
ALT	Alanine transaminase.
AST	Aspartate transaminase.
ER	Endoplasmic reticulum.
HBV	Hepatitis B virus.
HCV	Hepatitis C virus.
HCC	Hepatocellular carcinoma.
HIV	Human immunodeficiency virus.
HSCs	Hepatic satellite cells.
HVR	Hyper variable region.
IFN	Interferone.
IRES	Internal ribosomal entry site.
LDL	Low density Lipoprotein.
MAPK	Mitogen activated protein kinases.
RNA	Ribonucleic acid.
mRNA	Messenger Ribonucleic acid.
NK	Natural Killer.
NS	Non structural.
ORF	Open Reading Frame.
PCR	Polymerase Chain Reaction.
ROS	Reactive oxygen species.
RFLP	Restriction Fragment Lenghth Polymorphism.
SNPs	Single nucleotide polymorphisms.
TNF	Tumer necrosis factor.
TGF	Transforming growth factor.
UTRs	Untranslated regions.
VLDL	Very low density Lipoprotein.
WHO	World Health Organization.

List of Tables

List of Figures

Introduction

Hepatitis C virus (HCV) infection is a major public health problem, 150 million people are chronically infected worldwide and are at risk of developing liver cirrhosis and/or liver cancer while more than 350 000 people die every year from HCV related liver diseases ***(WHO, 2013).***

Egypt has the highest prevalence of HCV worldwide (15%) and the highest prevalence of HCV-4, which is responsible for 90% of the total HCV infections, with a predominance of the subtype 4a (HCV-4a)***(Abdel-Aziz et al., 2000, Lehman and Wilson, 2009).***

Part of the natural course of HCV infection is the progression to fibrosis and cirrhosis, and subsequently to hepatocellular carcinoma (HCC) in a significant proportion of HCV infected patients***(Banerjee et al.,2010, Miura et al., 2011).*** Thus, beside its role in the cause of chronic infection that is mostly associated with the development of fibrosis and cirrhosis, HCV may play an integral role in the development of HCC *via* mechanisms mediated by viral proteins-host cell interactions***(Chen et al., 2012).***

Whatever the etiology of HCC, the disease shares a common pathogenetic mechanism which is linked to chronic inflammatory reaction***(Alison et al.,2011).***

The development and resolution of an inflammatory process is regulated by a complex interplay among cytokines that have pro- and anti-inflammatory effects. Genetic polymorphism in particular regulatory regions or signal sequences of cytokine genes have been shown to affect the overall expression and secretion of cytokines as genetic polymorphism may directly or indirectly affect the binding of transcriptional factors, consequently increasing or decreasing the production of mRNA, thus regulating cytokine production***(Dogra et al.,2011, Yuan et al.,2013).***

Up-regulation and over expression of growth factors and cytokineshas been correlated to many processes related to cancer, including uncontrolled cellular proliferation, autocrine stimulation of tumors producing their own growth factors and prevention of apoptosis. This also appears to protect cancer cells from the toxic actions of chemotherapy and radiotherapy, rendering these treatment modalities less effective ***(Shi et al., 2012).***

Cytokines astumor necrosis factor (TNF-α)andtransforming growth factor (TGF-β1)have been shown to be involved in growth, differentiation and epithelial transformation in the

multistep processes of tumorgenesis ***(Luca et al., 2008, Miyake and Parsons, 2012).*** It has been hypothesized that certain polymorphisms for these factors result in functional changes in expression which may influence susceptibility to hepatocellular carcinoma ***(Shi et al.,2012, Capece et al., 2013).***

Studying correlation between TNF-α-308 andTGF-β1-509 gene polymorphisms with HCC among Egyptian patients will help in detecting patients with an increased risk to develop hepatocellular carcinoma which could then be subjected to a more careful or earlier routine screening for hepatocellular carcinoma. This also may help to identify targets for the development of alternative therapeutic strategies.

Aim of the Work

The aim of this study is to find out the association between TNF-α-308 and TGF-β1-509 gene polymorphisms with hepatocellular carcinoma in chronic HCV infected patients.

Hepatitis C Virus Infection

Hepatitis C virus (HCV) infection is a major health problem. It appears that nearly 170million people worldwide (about 2% of world population) are chronically infected , and more than 350,000 people die every year from HCVrelated liver diseases ***(WHO,2013).***It is estimated that about 3 to 4 million new cases are added each year. In Africa the prevalence is the highest and in some countries like Egypt about 15% of the people are infected ***(Sievert, 2011).*** Initially HCV does not cause any serious disease but in about 80% of the infected people the virus establishes a chronic infection that leads to severe forms of liver diseases primarily cirrhosis and hepatocellular carcinoma (HCC). A large proportion of these chronic carriers (10 to 20%)may end up with cirrhosis and/or HCC over a period of 10 to 20 years after infection. In the USA alone, more than 165,000 HCV-infected people die of liver diseases or HCCin this decade ***(Gellad et al., 2012.).***

Egypt has the highest HCV prevalence in the world (14.7%) ***(Cuadros et al., 2014).***HCV genotype 4 is responsible for almost 90% of infectionsin Egypt .The Egyptian HCV isolates belong to a single subtype, 4a, which responds less successfully to interferon therapy than other subtypes ***(Kamal and Nasser, 2008).***