INTRODUCTION

Interleukin-18 (IL-18), originally known as interferon-γ inducing factor (IGIF), is a cytokine that shares structural and functional properties with interleukin-1 (IL-1). This cytokine is mainly produced by activated macrophages, but may also be expressed by Kupffer cells, T-cells, B-cells, keratinocytes, astrocytes, and osteoblast *(Tangkijvanich et al., 2007)*.

IL-18 has multiple biological activities via its capacity to stimulate innate immunity and both Th1 and Th2 mediated response. It also exerts anti-tumor effects that are mediated by enhancement of NK cell activity, reduction of tumorigenesis, induction of apoptosis and inhibition of angiogenesis in tumor cells *(Tangkijvanich et al., 2007)*.

In addition, recent data have been suggested that inappropriate production of IL-18 contributes to the pathogenesis of cancers and may influence the clinical outcome of patients. Specifically, it has been demonstrated that serum IL-18 level may have prognostic significance in some types of cancer including colonic carcinoma, gastric carcinoma,

esophageal carcinoma, breast cancer, and hematologic malignancies *(Tangkijvanich et al., 2007)*.

Elevated levels of IL-18 were described previously for chronically hepatitis C (HCV) infected patients with different disease severities (chronic hepatitis C, liver cirrhosis and hepatocellular carcinoma) with an association between IL-18 plasma concentration with the outcome of chronic HCV infection *(Bouzgarrou et al., 2008)*.

AIM OF THE WORK

The aim of this study is to assess the role of IL-18 in the diagnosis of HCC in comparison to AFP.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is the most common form of liver cancer in adults. It accounts for about 75% of primary liver cancers *(Ikai et al., 2004)*. It is observed characteristically as a complication of chronic liver disease and cirrhosis, especially related to chronic viral infection with hepatitis B virus and hepatitis C virus. Because early detection of HCC is difficult, the prognosis remains poor *(Fallon, 2004)*.

Epidemiology:

Hepatocellular carcinoma ranks as the fifth most common cancer in the world and the second most common cancer of the digestive tract, after cancer of the stomach *(Colombo, 2003)*. Its incidence is increasing worldwide ranging between 3% and 9% annually *(Velazquez et al., 2003).*

The number of deaths per year from HCC exceeds 250,000, placing it sixth as the cause of death from cancer worldwide *(Steel et al., 2004)*. The frequency of HCC depends on the geographical area. The highest frequency is in the African and Oriental races in which there is nearly always associated

cirrhosis. It is the second commonest cancer encountered in South-East Asia *(Sherlock and Dooley, 2002)*. In Egypt, 4.7% of chronic liver disease patients suffer from HCC. The development of HCC is mainly due to high rates of hepatitis B and C infections among Egyptian patients *(El-Zayadi et al., 2001)*.

HCC occurs predominantly in males with a male : female ratio 4:1.The risk increases with age, and in Western countries HCC tends to appear in the fifth to seventh decades of life *(Fallon, 2004).* Cirrhotic patients older than 54 years are at four time greater risk to develop HCC *(Velazquez et al., 2003).* A rare fibrolamellar variant of HCC occur in young patients without underlying liver disease and has a favorable prognosis because it often can be successfully resected *(Fallon, 2004).*

Etiology:

Cirrhosis results in cell proliferation and increased DNA synthesis in regenerating nodules; these process may lead to aberrant dearrangements and altered regulatory protein function *(Fallon, 2004).* Cirrhosis of any origin is a risk factor for HCC; however, cirrhosis related to chronic viral hepatitis and genetic hemochromatosis carries an exceptionally

high risk of tumor development *(Hillebrand and Sandowski, 2000)*. The annual risk of developing HCC in patients with cirrhosis is between 1% and 6% *(Donato et al., 2001)*.

The prevailing hypothesis for how cirrhosis results in HCC is that dysplastic nodules (macro-regenerative nodules) develop within the cirrhotic liver. These are hepatocytic nodules greater than 1 cm in diameter and bounded by fibrosis, which are suspected of being the major premalignant lesion for HCC. Areas of cellular atypia develop within these large nodules, leading to dysplasia and then foci of well-differentiated HCC *(Theise, 1996)*.

Common causes of cirrhosis in which HCC may arise include chronic viral hepatitis (hepatitis B, C, and B with D), alcohol abuse, obesity, hemochro-matosis, alpha 1-antitrypsin deficiency, and toxins. Primary biliary cirrhosis is a less common cause. At autopsy, 20% to 40% of patients who die with cirrhosis are found to have occult HCC *(Hillebrand and Sandowski, 2000).*

Viral infection:

Hepatitis B Virus (HBV) Infection:

HBV is considered as a major risk factor for the progression to liver cirrhosis and HCC *(Ohata et al., 2004)*. The relative risk of developing HCC for HBV carriers may be 100-200 folds higher than that for non-carriers *(Xiong et al., 2003).*

Chronic HBV infection may predispose to HCC by integration of HBV DNA at sites within the human genome responsible for the control of the cell cycle, and thus lead to disruption of tumor suppressor genes or activation of oncogenes. The HBV gene product may also result in transactivation of oncogenes *(Fallon, 2004).* However, the prevelances of HBV in Egypt has been declining over the last two decades; this may be due to vaccination program *(EL-Zayadi et al., 2001).*

Hepatitis D Virus (HDV) Infection:

Infection with HDV occurs exclusively among patients with HBV infection. Some studies suggest that HCC may develop more rapidly among patients with both HBV and HDV infection than among those infected with HBV alone by increasing the risk of development of cirrhosis *(Di Bisceglie, 1999).*

Hepatitis C Virus (HCV) Infection:

There is a strong association between chronic HCV infection and HCC. There is a four times higher incidence of liver cancer among anti-HCV positive patient than among HBsAg carriers *(Sherlock and Dooley, 2002)*.

As many as 20% of patients with cirrhosis related to hepatitis C develop HCC during 5 years of follow up, and nearly one half will harbor HCC if followed for 10 years *(Hillebrand and Sandowski, 2000)*.

The annual risk for the development of HCC was 0.4% for unselected HCV carriers with persistently high values of alanine aminotransferase (ALT), but it rose to 1.7% in patients with a histologic diagnosis of chronic active hepatitis and to 2.5% in those with compensated cirrhosis *(Colombo, 2003)*. The role of HCV in the pathogenesis of HCC is still poorly understood. Replicating HCV RNA and the expression of virus-specific protein have been demonstrated in HCC cells, but no reverse transcriptase activity has been detected in infected livers *(Ballardini et al., 1995 and Lau et al., 1996)*.

Concomitant alcohol abuse or HBV infection probably contributes to the worldwide epidemiologic and clinical heterogeneity of the tumor *(Colombo, 2003)*. There is a relationship between metal contents of the liver cells and the prevalence of HCC in patients with chronic hepatitis or hepatic cirrhosis caused by HCV infection especially, the copper level in liver parenchyma which is significantly raised with the coexistence of HCC in HCV-positive patients with chronic liver disease *(Ebara et al., 2003)*.

Regarding the HCV genotypes, it is found that genotype 1b was the most prevalent in patients with HCC followed by 2a then 2b *(Murakami et al., 1999).* Patients infected with type 1b developed a more aggressive liver disease than patients infected with other genotypes *(Ferray et al., 1995 and Gane et al., 1996).* The mechanisms responsible for the apparently greater pathogenicity of type 1b are unknown, although it has been speculated that this type may have a greater capacity to escape host immunity because of presence of one additional hyper-variable region within the envelope domain *(Choo et al., 1991).*

Hepatitis TT Virus Infection:

This virus is prevalent in blood donors and patients with acute and chronic liver diseases but has no clear disease association *(Naoumov, 2000)*.

Alcohol:

The hepatotoxic effect of alcohol is dose-dependent, and cirrhosis appears to be the basis for ethanol-associated cases of HCC *(Miyakawa et al., 1996)*. Moderate alcohol intake is not associated with an increased risk for HCC, whereas a daily intake of 40 gram in men and 20 gram in women can result in significant liver disease and an increased risk for HCC *(Colombo, 2003)*.

The risk for HCC development is 13 times greater in alcohol drinkers than in abstainers, but the abstinence from alcohol does not protect against HCC development *(Lee, 1996)*.

HBV appears to be an agent that promotes liver cancer in alcoholics; alcohol abusers with HBs Ag-related cirrhosis are 10 years younger than patients with HBs Ag -related cirrhosis who do not drink alcohol. The finding of integrated HBV DNA in the hepatocytes of HBsAg sero-negative alcoholics with HCC is also

thought to be a sign of occult HBV infection promoting liver carcinogenesis *(Colombo, 2003)*.

Aflatoxin:

Aflatoxin is a toxin produced by Aspergillus flavus and Aspergillus parasiticus which are molds that grow in poorly stored foods, especially peanuts (*Hillebrand and Sandowski, 2000)*. Aflatoxin B1 is a toxic product produced during aflatoxin metabolism which is normally handled by two enzymes that are known to have impaired activity in Africa and China. The toxic intermediate has been demonstrated to bind to genomic structures *(Aguayo and Patt, 2001*), inducing a G to T mutation of the p 53 gene at codon 249 *(Bressac et al., 1991).* This in turn has been shown to up-regulate insulin-like growth factor II and lead to a reduction in apoptosis and formation of HCC *(Lee, 2000).*

Human can be exposed to aflatoxin by ingesting contaminated foodstuffs (i.e., peanuts, wheat, soybeans, ground nuts, corn, and rice) or products of animals fed cereals contaminated with aflatoxin. Aflatoxin B1 is a frequent contaminant of grains and legumes, particularly in tropical and subtropical regions (i.e., Asia and sub-Saharan Africa), where a

hot climate and methods of food storage cause high quantities of aflatoxins in the food supply *(Koike and Shiratori, 2004)*.

Metabolic Liver Diseases:

Several inherited metabolism diseases have been associated with the development of HCC *(Ishak, 1991)*. They can be grouped into diseases that occur against a background of cirrhosis and those that do not. Those that occur with cirrhosis include hemochromatosis, alpha-1-antitrypsin (AAT) deficiency, porphyria cutanea tarda, Wilson's disease, and tyrosinemia; those that occur without cirrhosis include glycogen storage disease, acute intermittent and variegate porphyria, hypercitrullinemia, and hereditary fructose intolerance, the latter being very rare overall *(Di Bisceglie, 1999)*.

Vascular cause:

Membranous obstruction of the inferior vena cava:

Membranous obstruction of the inferior vena cava (MOIVC) is a rare developmental abnormality of the upper end of the inferior vena cava, which obstructs venous drainage and result in cirrhosis. HCC has been found as many of 46% of patients with MOIVC *(Kew and Fisher, 1986).*

Autoimmune Liver Diseases:

The incidence of HCC in patients with autoimmune hepatitis is low (0.2% per year), but the relative pathogenic role of coexisting chronic hepatitis C has not been established *(Ryder, 2003)*. patients with primary biliary cirrhosis are also at increased risk for the development of HCC, with an estimated yearly incidence of 0.7%, but the incidence is higher in men and in patients with established cirrhosis; in those with stage III or IV disease, the incidence of HCC was approximately 6% *(Colombo, 2003)*.

Obesity:

A recent study was done to determine whether obesity is an independent risk factor for HCC in patients with cirrhosis. They concluded that obesity is not an independent predictor in patients with hepatitis C, hepatitis B, primary biliary cirrhosis, and autoimmune hepatitis. The higher risk of HCC in obese patients is confined to alcoholic liver disease and cryptogenic cirrhosis. They concluded that, more frequent surveillance for HCC may be warranted in obese patients with alcoholic and cryptogenic cirrhosis *(Nair et al., 2002).*

HCC is a known possible complication of nonalcoholic fatty liver disease, although whether this occurs through cirrhosis or from obesity-induced metabolic derangements remains unclear *(Yang et al., 2001a).*

Drugs:

Oral Contraceptives:

The association between oral contraceptives and HCC is controversial *(Stanford et al., 1999)*. A statistically significant association has been demonstrated between the use of oral contraceptive drugs and the occurrence of hepatocellular carcinoma in countries where the incidence of the tumor is low and no overriding risk factor for HCC is known *(Austin, 1991)*. However, a World Health Organization study found no increased risk for HCC in persons taking oral contraceptives *(Stanford et al., 1999)*.

Anabolic Steroids:

Anabolic steroids are male hormones that are used by some athletes to increase their strength. Long-term anabolic steroid use can slightly increase the risk of hepatocellular cancer. Cortisone-like steroids, such as hydrocortisone and dexamethasone, do not carry this same risk *(Koike and Shiratori, 2004)*.

Tobacco:

The association between tobacco smoking and human HCC is biologically significant because the liver is a natural target of the many potential carcinogens in tobacco, and experimental data suggest hepatic carcinogenesis *(Mant and Vessey, 1995)*. However, the epidemiologic evidence for a pathogenic role of tobacco smoking in human HCC is controversial *(Howel et al., 1991)* and its effect may be difficult to distinguish from that of alcohol and other associated lifestyle diseases, such as viral hepatitis *(Di Bisceglie, 1999)*.

Chemical Compounds:

Thorotrast, a colloidal solution of thorium dioxide prepared with a radioactive isotope of thorium, was formerly used as an intravenous contrast agent in radiology for a short period after the second world war *(Doll and Peto, 1988)*. The isotope has a long half-life, as the radioactive particles are taken up by Kupffer cells within the liver and remain there for decades, eventually resulting in some form of malignancy, including HCC, cholangiocarcinoma, or angiosarcoma, which usually develop after a latent period of about 20 years following the intravascular administration of thorotrast *(Ito et al.,*