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THE ROLE OF INTERLEUKIN 17A AND INTERLEUKIN 17E (IL25) IN THE PROGRESSION OF LIVER FIBROSIS IN PATIENTS WITH HEPATITIS C VIRUS INFECTION

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Abstract:

The chronic infection with the hepatitis C virus (HCV) is regarded as one of the main health problem. Globally, around 180 million people had an HCV infection. With a new evidence supporting the involvement of IL-17A and IL-17E (IL25) in the development of chronic HCV infection as the host immunity plays a significant role in this infection, since the high levels of these two types may raise the risk of developing liver fibrosis in the chronic HCV infection, so our goal was to estimate the involvement of interleukins in the liver fibrosis in patients with chronic HCV infection and this study estimated the fibrosis in liver by measuring the levels of IL-17A and IL-17E as c markers for fibrosis which contributes to the development of liver fibrosis.

Keywords: hepatitis C virus, liver fibrosis, IL17A, IL17E.

Introduction

Introduction

An infection with the hepatitis C virus (HCV) could damage the liver and causes cirrhosis of the liver associated with hepatocellular carcinoma [1]. The blood transfusions, dental and surgical process as wheel as dangerous contaminated injection techniques are the primary ways of different viruses spreading. Certain features of the hemodialysis environment, such as the likelihood of blood splattering on the surfaces make it easier for HCV to diffuse [2]. The HCV disrupts both the innate and adaptive immune responses, which lowers the viral clearance and causes immune-mediated liver damage [3]. An important organ for metabolism and immunity is the liver which is the primary organ that produces acute-phase proteins, it is essential for both immunosurveillance and systemic inflammatory responses [4]. The inflammation and immune cell homeostasis dysregulation are the

key characteristics of practically all liver disorders. Liver injury may result from interactions between the infiltrating immune cells and the liver cells [5]. Chronic liver inflammation could lead to cirrhosis, liver fibrosis, and ultimately hepatocellular cancer if left untreated [6]. Both the humoral and cellular immunity mediated the host's immunity to HCV infection. In the process of the immune response related to HCV, both CD4+ T and CD8+ T cells are essential [7]. The Th17 cells were identified as a new subset of specialized T helper (Th) cells that are the potent enhancers of tissue-related inflammation and release a number of cytokines, including IL17A, IL17F, IL21, and IL22 [8]. A class of cytokines known as IL17 is involved in a variety of inflammatory reactions and the development of certain inflammatory diseases. This family consists of six members: IL17A, IL17B, IL17C, IL17D, and IL17E (or IL25) [9]. The creation of IL17A could started the host defense and neutrophil buildup, but its pathological development could result in significant inflammation and tissue damage [10]. Through up the regulating of antiapoptotic molecules, the Th17 and interleukin 17 (IL17) may contribute to hepatic viral persistence in addition to their critical role in the pathophysiology of viral infections [11]. Our work aimed to elucidate the function of IL17E (or IL25) in the pathophysiology of chronic HCV infection [12]. In the lesions of individuals suffering from a variety of chronic inflammatory conditions, including rheumatoid arthritis, inflammatory bowel disease, and lung infections, it's interesting to note that during viral infection, the IL-17 may have an immunopathological function that damages the tissues [13]. The IL-17E was also known as interleukin-25 (IL-25), which encodes 161 amino acids [14]. It was first discovered by alignment using DNA data in 2001. The IL-25 binds to a particular receptors of IL-17 [15].

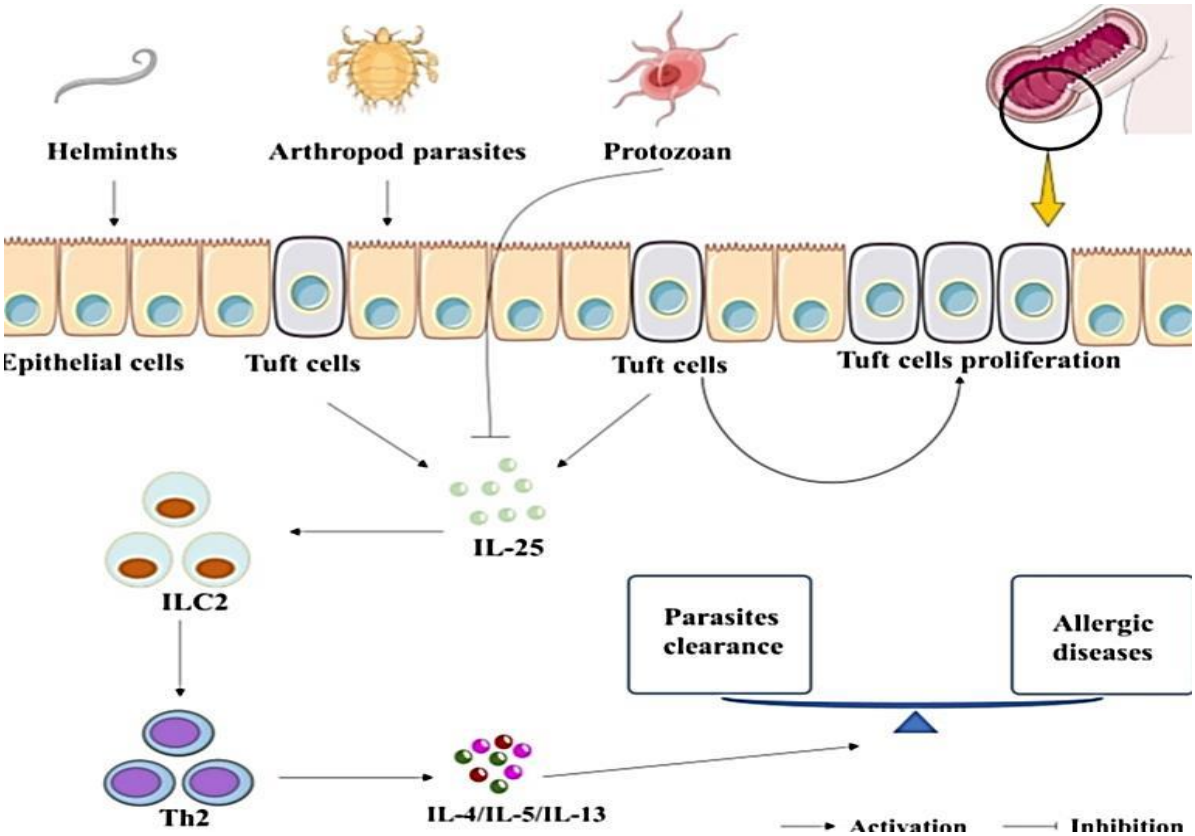

Figure 1 The role of IL-25 in inflammation [16]

Actually, IL-25 plays an important roles in controlling the immunological responses in various illnesses and a number of allergy disorders are influenced by IL-25 [17]. The Th2 immune responses are amplified by IL-25, which binds to its receptor, which is made up of IL-17 receptor A (IL17RA) [18]. The IL-25 stimulates the transcription factors to produce interleukin 4 (IL-4), which

promotes the Th2 cell development [19]. The activator B binds to IL-17RB in response to IL-25 stimulation. This subsequently contributes to the activating and recruiting eosinophils and promoting the production of immunoglobulin E (IgE) [20]. However, there are also positive benefits of IL-25 with the inflammation as there are three stages to a chronic HBV infection: an immune stage with elevated HBV DNA and little liver damage [21]. One of the main causes of liver illnesses is hepatitis C. Consequently, immunopathology is actually mediated by the host immune responses against the invasive viruses, which also lead to tissue damage and liver failure [22].

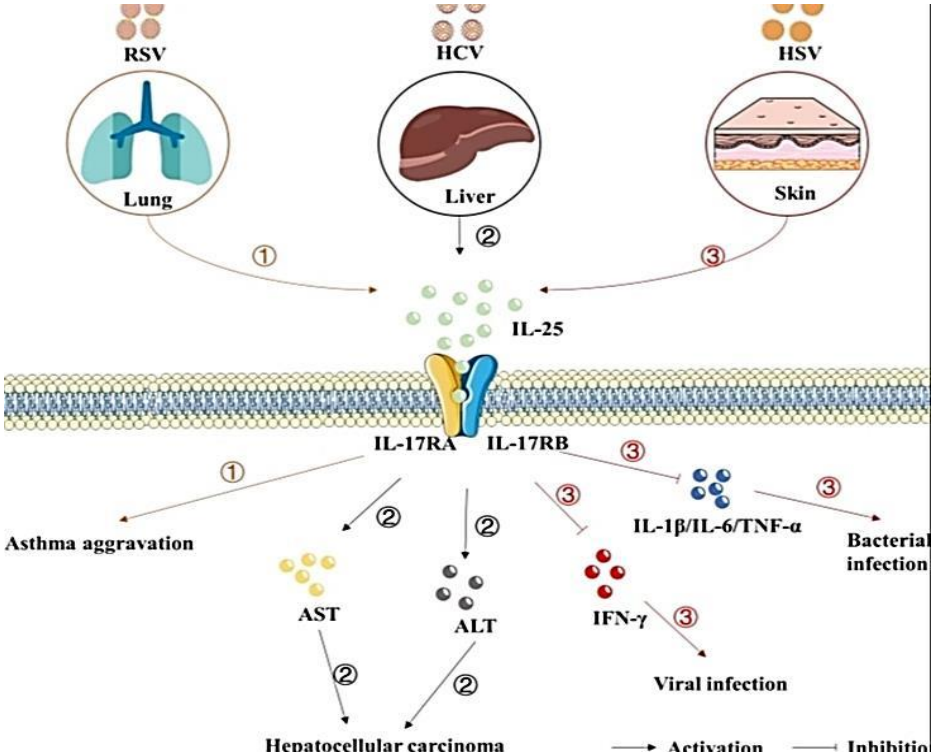

Figure 2 The role of IL-25 in viral infection

2. Materials and Methods

Seventy participants with long-term HCV patients who visited the Medical City in Baghdad were included in this study compared with about 70 healthy controls who tested negative for HCV RNA for more than six months. Both groups were matched in the terms of age and sex. Those with a history of HCV therapy were not allowed to participate.

2.1 Measurement of serum liver tests

Total bilirubin (TBIL), albumin, globulin and alanine aminotransferase (ALT) were all tested using an automated biochemical analyzer.

2.2 measurement of cytokine by ELISA

measurement of IL17 A by eBioscience→Human IL17 A Platinum ELISA and measure the IL17E (IL-25) using the eBioscience→Human IL17E Platinum ELISA for the patient and control groups. Following the skin sterilization, 3 mm of fresh blood were drawn into a disposable plastic tube free of anticoagulants, The serum was collected in tubes and kept in a deep freeze at -20°C to uses by ELISA kits [23].

2.3 Immunohistochemistry for liver fibrosis

All liver tissues were preserved in 10% formalin. Condensed IL-17 cells expressing fields were chosen, and cell counts were performed at high magnification (400×). IL-17 cells were identified by

brown-stained cell clusters in liver tissue corresponding adjacent normal tissues with low IL-17 cells [24].

2.4 Statistics

The statistical software SPSS version 11.5 (SPSS) was used to analyze all of the data.

3. The Results

This study shows that the level of IL-17A was higher in the patient compared with the healthy group, the P value was less than 0.0001, as well the levels of IL-17E indicating a highly significant different between the two groups, the P value was less than 0.25. and the ratio of albumin, globulin and alanine aminotransferase were positively associated with IL-17 A and IL-17 E ratio (Tables 1 and 2).

Table1: Demographic and laboratory data of the study groups

Parameter	Chronic HCV (*N* = 70) Mean ± SD	Healthy control (*N* = 30) Mean ± SD	P value
Age \ years	45.2 ± 3.5	43.2 ± 3.5	0.58
BMI	23.7±0.83	22.5±0.83	0.26
Gender(M\F)	40\30	40\30	0.62
Albumin (gm\dl)	5.7± 52	4.2± 62	0.001<
Bilirubin (mg\dl)	1.50±34	0.80±14	0.0001<
ALT (U\L)	91.5 ± 5.5	42.5 ± 5.5	0.001<

Table 2: The different in serum levels of IL-17 and IL-25 between patients and controls

Parameter	Patient Group	Controls Group	P-value
IL-17	53.8116	19.1665	<0.0001
IL-25	19.7804	16.2963	<0.25

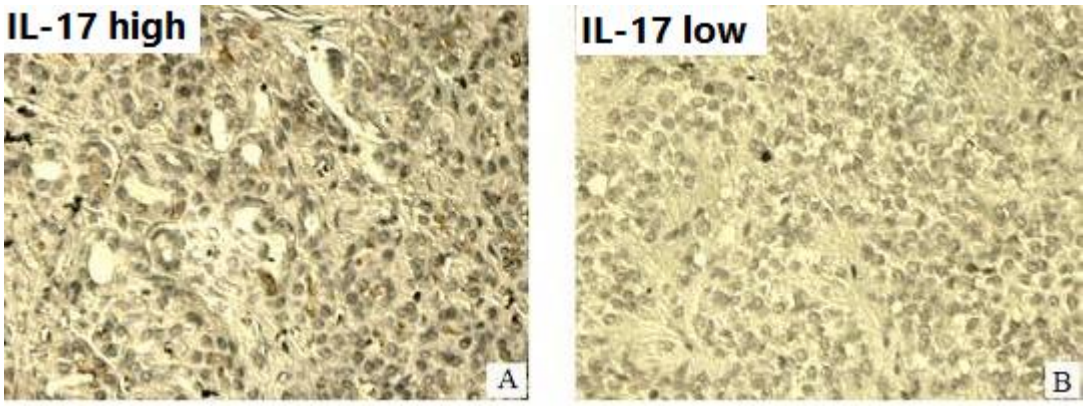

Figure 1 The express of IL-17 in liver fibeosia. IL-17+ cells with brown stain and were found in liver fibrosis tissues (A). The low concentration of IL-17+ cells is present in normal liver tissues (B).

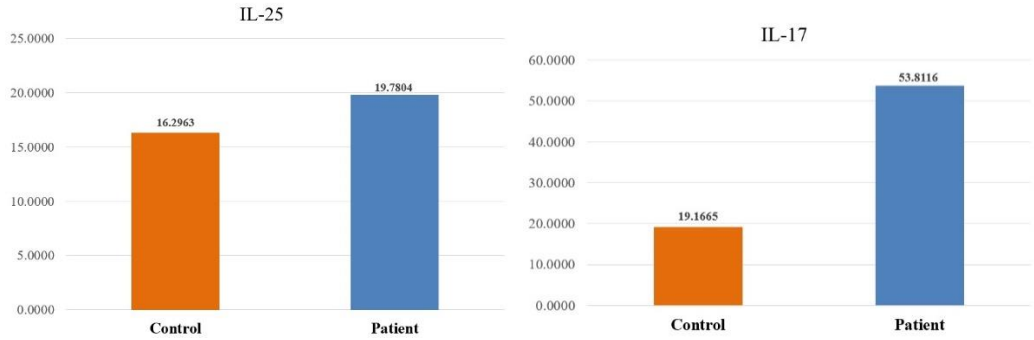

Figure 2 shows the differences in IL-17 A and IL-17E levels between controls and patients.

4. Discussion

This study is consistent with other research showing the liver samples or liver tissue with high fibrosis had greater levels of IL-17A and IL-17E consequently, the IL-17 types can affect the pathophysiology of inflammatory diseases or mediate the protective innate immunity against the infections [25]. The serum IL-17 levels types were significantly higher in HCV patients in the current study than in the control group [26]. However, the development of HCV in individuals are related with the increase in IL-17A and IL-17E in HCV infections with liver fibrosis [27]. These results raise the possibility that IL-17 types plays a part in the pathophysiology of HCV as these interleukins participate in the induction and effector phases of all inflammatory and immunological responses, it could impact on antiviral inflammation [28]. This study's indicated a positive relationship between the IL-17 types and HCV viral load, which made sense that greater HCV viral loads are associated with stronger immune responses and increased the IL-17 secretion which consider as an inflammatory mediators [29]. However, the IL-17 two type's levels release increases as the HCV infection became longer because additional regulatory mediators that regulate the IL-17 release [30]. This implies that the degree of fibrosis may be determined by the proliferation of fibroblasts which may be triggered by IL-17A and IL-17E [31]. It might also be a useful predictor of the course and outcome of the disease. A function for IL-17 in the infection is further supported by increased the expression of IL-17 in HCV-infected patients; however, when the IL-17A cytokine release by pure immune in different tissue [32]. Also the non-immune cells in the liver could producing the same interleukin. Nonetheless, the degree of fibrosis was correlated with the IL-7A and the IL-17E concentration in tissue lysates [33].

5. Conclusion:

Patients with Hepatitis C virus (HCV) had significantly higher IL-17A and IL-17E concentrations, and there was a positive connection between these types and HCV viral load. Furthermore, the blood levels of these interleukin were higher in older HCV patients. Nevertheless, there were a positive correlation between the HCV viral load and both types' measurements which participate in the etiology and development of liver fibrosis. Therefore, the estimation of IL-17 both type's levels could be an important medical approach to stop the progression of liver disorders.

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