

# Inflammatory Cytokines as a Predictor Markers for Hepatocellular Carcinoma

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## ABSTRACT

Hepatocellular carcinoma (HCC) is an important clinical problem, as it is the second major cause of cancer deaths worldwide and one of the most common causes of cancer-related mortality in the U.S.

**Keywords:** HCC; IL; cytokines

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## INTRODUCTION

The chronic inflammation is characterized by the expression of cytokines and recruitment of immune cells to the liver [1]. Activated inflammatory cells release free radicals, such as reactive oxygen species (ROS) and nitric oxide (NO) reactive species, these free radicals can cause DNA damage and result in gene mutations, and also neoplastic transformation. Also, hepatic oxidative stress is also strongly associated with increased risk for HCC in patients with chronic HCV and HBV infections [2].

### **Tumor-associated macrophages (TAMs) and HCC:**

Tumor-associated macrophages (TAMs) are key role of cancer-related inflammation, representing the main type of inflammatory cells infiltrating tumors [3]. Macrophages are able to exert both anti- and pro-tumor activities through the expression of different functional Programs in response to many micro-environmental signals. Activation state of Macrophage can be classified accordingly with the phenotypic polarization, as M1 (or classical activated) or M2 (or alternatively activated) [4]. Macrophages when exposed to microbe, lipopolysaccharide (LPS) and Interferon gamma (INF- $\gamma$ ); classical activation of macrophages (M1 polarization) is characterized by high ability to present antigen and high expression of Interleukin 12 (IL-12) and other proinflammatory cytokines, lead to T helper 1 (Th1) immune response stimulation [5].

They have cytotoxic activity towards ingested microorganisms and cancer cells as they produce high amounts of toxic substances, such as NO and ROS [6]. On the other hand, when monocytes are exposed to Interleukin 4 (IL-4), Interleukin 13 (IL-13), Interleukin 10 (IL-10), glucocorticoids, VEGF, and immune complexes/Toll-like Receptor (TLR) ligands, they lead to M2 phenotype polarization, characterized by cytokines and chemokines expression, such as IL-10, Transforming Growth Factor  $\beta$  (TGF- $\beta$ ) Chemokine (C-C motif) Ligand 17 (CCL17), Chemokine (C-C motif) Ligand 22 (CCL22), and Chemokine (C-C motif) Ligand 24 (CCL24). M2 macrophages stimulate T helper 2 (Th2) immune response activation and promote angiogenesis, tissue repair [3].

### **Tumor-associated macrophages-derived cytokines:**

Tumor-associated macrophages are involved in cancer cells, and TAM-released cytokines and chemokines play an important role in the progression and initiation of HCC, regulating cancer growth, invasion, and metastasis,

the expression of IL-6 and TNF- $\alpha$  genes, in peritumoral liver tissue was reported to predict late HCC recurrence [7].

### **Interleukin -4:**

The interleukin 4 (IL-4) is a cytokine that induces differentiation of naive helper T cells (Th0 cells) to Th2 cells. The resulting Th2 cells produce additional IL-4 in a positive feedback loop. The cell that initially produces IL-4, thus inducing Th2 differentiation, has not been identified, but recent studies suggest that basophils may be the effector cell [8]. The presence of IL-4 in extravascular tissues promotes activation of macrophages into M2 cells and inhibits activation of macrophages into M1 cells [8].

### **Interleukin -6:**

Increased serum levels of IL-6 have been associated with high risk to develop HCC in patients with chronic hepatitis B and C; accordingly, high serum IL-6 has been frequently observed in patients with HCC and it was associated with a poor prognosis. IL-6 also favor the epithelial-mesenchymal transition of HCC, which has an important role in tumor progression [9].

### **Interleukin -10:**

Interleukin -10 (IL-10) is one of the most important immunosuppressive cytokines. Several studies have found high IL-10 levels in HCC patients. IL-10, and TNF- $\alpha$  stimulate the expression of B7-H1 on macrophage surface, inhibiting CD8+ T cell activity and stimulate tumor immune escape [10].

### **Interlukin-17:**

Several reports demonstrated an association between high infiltration of Interlukin-17 (IL-17) producing cells in the peritumoral stroma and the progression of HCC [11].

### **Tumor necrosis factor :**

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is mainly produced by macrophages and is fundamental for liver regeneration following liver injury or partial hepatectomy. TNF- $\alpha$  is strongly involved in the pathogenesis of HCC, enhancing invasion, angiogenesis, and metastasis [12].

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