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The association between Interleukins 6, 8, and 10 levels and response to treatment of the hepatitis C virus with direct-acting antiviral.

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ABSTRACT

This study seeks to investigate the clinical importance of interleukins 6, 8, and 10 in the therapy of HCV. It has been well-recognized that interleukins are essential agents in the immune response and have vital functions in controlling inflammation, antiviral defense systems, and tissue repair. Interleukins such as IL-6, IL-8, and IL-10 show a substantial role in the development and treatment response of HCV infection. The study analyzes a wide range of research findings to emphasize the potential predictive utility of these interleukins as biomarkers for forecasting treatment response and disease progression. Moreover, it investigates the influence of DAA therapies on the manifestation and fluctuations of these interleukins throughout treatment and post-treatment. The study also examined the possible therapeutic implications of targeting these interleukins to improve treatment effectiveness and minimize negative side effects. Ultimately, it is essential to comprehend the therapeutic importance of IL-6, IL-8, and IL-10 in HCV treatment to enhance patient care and progress customized medicine strategies. Additional investigation is necessary to clarify the exact processes that explain the functions of these interleukins and to develop standardized procedures for measuring them and applying them in therapeutic settings. ***Conclusion:*** IL-6, IL-8, and IL-10 hold promise as valuable markers for evaluating HCV therapy efficacy, predicting treatment outcomes, and identifying individuals who could benefit from tailored therapeutic approaches. The analysis also explores the potential therapeutic implications of targeting these interleukins to enhance treatment efficacy and reduce adverse effects. It is crucial to understand them.

Key Words: Hepatitis C virus, Interleukins 6, 8, and 10, direct-acting antiviral, liver diseases, viral infections, chronic state.

1. Hepatitis C virus

During the 1970s, cases of transfusion-associated hepatitis were observed, and it was believed that an unidentified virus was responsible. This condition was recognized as non-A, non-B hepatitis. It is interesting to illustrate that the hepatitis C virus (HCV) was discovered and named in 1989, and shortly after, the first diagnostic test for HCV antibodies was created. This development resulted in a significant

reduction in new infections. Currently, HCV infection continues to be a significant worldwide health problem and a primary contributor to liver cirrhosis, hepatocellular cancer, and liver transplantation. Nevertheless, significant progress had been achieved over the years, leading to the successful treatment of HCV, which was formerly considered an incurable, long-lasting viral infection. The advent of direct antiviral medications has brought about a significant transformation in the field of antiviral treatment, resulting in the complete elimination of HCV in over 98% of infected patients **[1]**. HCV was acknowledged as a substantial pathogen affecting humans and it primarily induces acute hepatitis. Nevertheless, this virus possesses the capacity to progress into chronic state of hepatitis, resulting in significant liver consequences like hepatocellular carcinoma and cirrhosis, which presents a significant worldwide public health issue. HCV is a RNA virus with a complex mechanism of infection and reproduction. This virus is a member of the Flaviviridae family. It entails avoiding the immunological response of the host, which contributes to the long-lasting nature of the infection in affected subjects. The genetic diversity of HCV is characterized by several subtypes and genotypes, hinders the development of vaccines and treatment options. In addition, it is noteworthy to clarify that early identification and effective antiviral therapy are crucial in preventing liver damage on the long-term and reducing the possibility of development of hepatic malignancy in individuals transitioning from HCV infection (acute) to chronic. Although there have been improvements in therapy, HCV nevertheless is still a prominent indication of hepatic transplantation on a global scale. This emphasizes the importance of ongoing studies and public health initiatives to address HCV **[2].**

It has been well-known that HCV is typically transmitted by direct contact between an infected subject's blood and a non-infected subject's blood. The practice of reusing or poorly sterilizing medical equipment, particularly needles and syringes, poses a substantial hazard in healthcare settings. Furthermore, the transmission of HCV might occur through the

transfer of blood or blood products without first undergoing stringent screenin. Another common method is sharing the equipments of injection among subjects who use injectable medicines [3]. This virus is categorized into seven genotypes, each with various subtypes. These genotypes and subtypes are not evenly distributed throughout different geographical regions and also exhibit different responses to therapy **[4]**.

1.1. Epidemiology and Clinical Progression of HCV Infection

It has been reported that the incidence of infection with HCV has been decreasing during the latter half of the 20th century **[5]**. The reason for this is the enhancement of hygienic and dietary circumstances in emerging nations, as well as the implementation of vigilant monitoring in countries with high rates of occurrence. Collectively, these methods have been crucial in decreasing the worldwide impact of this virus, highlighting the significance of comprehensive initiatives of public health in addressing contagious illnesses. Estimating the global incidence of HCV is challenging because of factors such as decreased diagnosis, decreased reporting, and decreased regular surveillance in many countries **[6]**. In early 2020, the anticipated worldwide prevalence of viremia of HCV was found to be 0.7%, indicating that there were approximately 56.8 million individuals suffering from chronic infection with HCV. The data indicates a decline in prevalence in comparison with 2015, whereas there were 63.6 million cases suffering from chronic infections with HCV, accounting for 0.9% of people all over the world. The primary locations with the highest incidence rates in Europe are the Eastern Mediterranean countries, with a rate of 62.5/100,000, where it is linked to healthcare, and the Eastern European region, with a rate of 61.8 per 100,000, where it is related with the use of injectable drugs **[7]**.

1.2.Characteristics of the Hepatitis C Virus

It has been recognized that HCV is a virus molecule that has a diameter that falls between the range of 50 to 80 nanometers. The composition of this entity includes a genome made up of a single strand of ribonucleic acid (RNA), a nucleus, Glycoproteins E1 and E2 and type I trans-membrane proteins. Covalent bonds are formed by these proteins with infected hepatocytes **[8]**. They are strongly in

association with lipoproteins, resulting in a significant decrease in density **[9]**. The specific interactions between the virions of HCV and the various lipoproteins included are still required to be completely described **[10]**. Some believe that HCV virions are a mixture of viral components fused to lipoprotein encapsulation **[11]**. Another theory suggests that this association is established through interactions between apolipoproteins and the molecules of lipid forming the envelope of HCV **[12]**. Both scenarios involve the possibility of host lipoproteins playing a role in safeguarding and camouflaging the virion particles by enveloping their exterior. The presence of this glycoprotein coat is crucial for the incorporation of the particles of the virus in the target cells. This has an important function in the process of attachment and fusion of the viral envelope with the endosomal membrane of the host cell **[13].**

2. Direct-acting antivirals (DAAs):

The ongoing and thorough exploration of the life cycle of virus C has facilitated the emergence of a completely novel class of antiviral drugs, known as direct-acting antivirals (DAAs), for the treatment of the patients suffering from HCV infection. Unlike interferon (IFN) and ribavirin (RBV), which are rather unspecific, direct-acting antivirals (DAAs) preferentially target and damage the specific proteins of virus which are essential for replication of HCV. The 1st direct-acting antivirals (DAAs) were protease inhibitors. These inhibitors function by inhibiting HCV polyprotein cleavage at the NS3 and NS4A sites, which is carried out by the NS3 or NS4A protease of HCV. The chemical PI BILN 2061 was the 1st to exhibit antiviral activity in the patients suffering from HCV in 2003. On the other hand, clinical development of BILN 2061 was discontinued due to safety concerns regarding cardiotoxicity discovered in a mouse model **[14].**

2.1. DAAs HCV drug targets in the cell:

2.1.1. Protease inhibitors:

It has been recognized that the HCV genome's positive polarity allows the virus to promptly translate its genomic RNA into protein on entering the host cell, with the assistance of the cell's machinery. Nonetheless, the lengthy polyprotein must undergo cleavage into individual units to carry out its essential enzymatic functions, as each distinct protein plays a crucial role in the structural composition of viral progeny particles **[15].** The cleavage of the unprocessed polyprotein is mostly carried out by many proteases, with the NS3/4A serine protease being the main one **[16].** Protease inhibitors (PIs) disrupt the important function of NS3/4A in self-cleavage of HCV, which is necessary for replication of HCV. By targeting this protease, PIs have been proven to reestablish sensitivity to interferon-based treatment and in direct way hinder the reproduction of the virus **[17]**.

2.1.2. NS5A inhibitors:

The NS5A polymerase plays a crucial part in replicating and assembly of the virus, although its specific function in the life cycle of HCV is still not fully understood. The utilization of NS5A inhibitors, even at extremely low doses (picomolar), has been linked to substantial decreases in HCV RNA levels in models based on cell culture. These inhibitors have demonstrated the fastest decline in viral load compared to any other category of antiviral drugs in clinical trials focused on monotherapy **[18].**

2.1.3. NS5B inhibitors:

NS5B inhibitors show two categories: nucleoside inhibitors and non-nucleoside inhibitors. RNA-based nucleotide inhibitors work by actively binding to their targets. These inhibitors show a great barrier to resistance and have been found active against multiple HCV genotypes. On the other hand, non-nucleoside allosteric RNA polymerase inhibitors show a decreased level of resistance and are only active against selected HCV strains. Sofosbuvir is a specific form of nucleotide analogues, whereas beclabuvir and dasabuvir belong to the existing family of non-nucleoside analogues. **[19].**

2.1.4. Ribavirin:

It has been reported that various categories of DAAs were administered in conjunction with the synthesized analog, ribavirin. Ribavirin, a guanosine analogue, was initially synthesized in 1970 as a novel treatment for RNA and DNA viruses. Despite being discovered and developed over four decades ago, ribavirin continues to demonstrate its efficacy in HCV therapy. Despite being widely used in clinical practice for a long time, the specific way in which ribavirin produces its antiviral properties has remained a scientific puzzle **[20].**

2.1.5. Interferon antiviral treatment (INF):

2.1.5.1. IFNα monotherapy:

The initial endeavors to develop antiviral therapy for non-A, non-B hepatitis (NANBH) were initiated in 1986, a significant milestone that occurred three years before the identification of HCV. Recombinant IFNα, also referred to as IFN alfa, became accessible in the 1980s for cancer treatment before the publication of encouraging outcomes in the context of hepatitis B virus (HBV) infection. Due to suspicions of an unidentified viral pathogen being the root cause of NANBH, Hoofnagle and his colleagues opted to test the effectiveness of recombinant IFNα as a treatment for this condition, which is currently not well recognized. Additionally, it is important to illustrate that they conducted preliminary research where they administered recombinant IFNα2b to ten individuals with NANBH for a maximum duration of 12 months. The researchers recorded a significant reduction in the levels of serum transaminase. This discovery marked the beginning of the age of IFN in HCV treatment. Based on these findings, larger randomized studies were started, which validated the impact of IFNα in a significant number of patients with HCV infection. This led to the adoption of IFNα single-agent therapy as the standard treatment for some time, but its effectiveness appeared to be restricted to less than 40% **[21].**

2.1.5.2. Pegylated interferons:

It has been documented that the administration of extended release pegylated interferons (IFNs) marked an important improvement of the therapy of virus c infection. The Peg-IFNs that were altered exhibited a beneficial and extended pharmacokinetic profile, resulting in two significant results. Initially, the dosing schedule might be streamlined to a frequency of once per week, ensuring enhanced treatment adherence, a factor that has been demonstrated to be vital for the effectiveness of treatment. Furthermore, the antiviral effectiveness exhibited a greater magnitude. Unaltered traditional recombinant IFN had a duration of 3–8 h until it was reduced to negligible levels in the bloodstream within 24 h **[22]**. Therefore, the frequently used schedule of three times per week appeared inadequate while striving for a lasting antiviral impact. With this method, it was possible to identify an elevation in HCV RNA levels before to the next IFN injection, which was not observed with Peg-IFN. The FDA and the European Medicines Agency (EMA) approved two distinct forms of Peg-IFN, namely Peg-IFNα2a (with a 40 kDa Peg chain) and Peg-IFNα2b (with a 12 kDa Peg chain) **[23].**

The conventional therapeutic choices for HCV encompass peginterferon, ribavirin, and harvoni, which are linked to the reversal of liver fibrosis. Recently, the FDA has approved a couple of new HCV medicines, namely Epclusa® (sofosbuvir) and OLYSIO® (simeprevir). DAAs demonstrate a high rate of sustained virologic response (SVR), suggesting that HCV is no longer detectable in blood plasma up to 24 weeks after the conclusion of antiviral therapy. Nevertheless, around 30% of patients exhibit no amelioration in fibrosis during sustained virologic response (SVR) **[24].**

3. Cytokines

Cytokines are small proteins with molecular weights below 40 kDa that are secreted by many immune cells, including Th-cells, dendritic cells, neutrophils, macrophages, B-lymphocytes, and others **[25].** They have a crucial function in enabling communication and coordination between immune cells to control the development and nature of the immune response, as well as to preserve immune equilibrium and surveillance.

Cytokines play a crucial role in controlling the development, growth, multiplication, and activity of different cell types. They are essential for the activation of immune responses that protect the body and contribute to the development of immune-mediated or autoimmune diseases, infections, cancer, and trauma **[25].** Cytokines are a group of different proteins that can be divided into many subgroups based on the structure of their receptors. These subgroups include transforming growth factors (TGF), interleukins (IL), interferons (IFN), colony stimulating factors (CSF), tumor necrosis factor (TNF), and many chemokines **[26]**. When they bind to specific receptors alone or in pairs, they stimulate the receptor domains inside the cell, which are responsible for intracellular signaling through specific kinases. As a result of this intracellular communication, some transcription factors are activated and enter the cell nucleus, affecting the expression of certain genes **[27].** Several IL and IFN receptors interact with Janus kinases (JAKs), which subsequently stimulate transcription factors that are part of the signal transducer and activator of transcription (STAT) protein family **[28]**. When TNF binds to its particular receptor, it triggers the activation of AP-1 and nuclear factor κB (NF-κB), initiating another signaling cascade **[29].**
Cytokines are proteins that are released or bound to the cell membrane. They play a vital role in controlling the growth, specialization, and stimulation of immune cells. They are a constituent of the immune system that aids in the host's defense against invading pathogens. Cellular stresses, such as infection, inflammation, and damage caused by carcinogens, stimulate the secretion of cytokines. Cytokines, mostly produced by CD4+ Th cells, are categorized into two groups: Th1 and Th2. Th1 cytokines mostly consist of interleukins (ILs). Cytokines, including IL-1, IL-2, IL-12p35, IL-12p40, IL-15, as well as non-ILs like interferons (IFN) and tumor necrosis factor (TNF), induce inflammation. Conversely, Th2 cytokines elicit anti-inflammatory reactions **[30].**

4. Interleukins

Interleukins (ILs) are a class of cytokines that were initially thought to be expressed only by white blood cells, but subsequent studies have shown that they are produced by several different cells in the body. They have crucial functions in the stimulation and specialization of immune cells, as well as in growth, development, motility, and attachment. In addition, they have both inflammatory and anti-inflammatory properties. Interleukins primarily serve to regulate growth, differentiation, and activation in the context of inflammatory and immunological responses. Interleukins are a diverse set of proteins that can induce various cellular and tissue responses by attaching to receptors with a strong affinity on the surface of cells. They possess both paracrine and autocrine activities**.** Interleukins are used in animal experiments to study clinically and medically relevant characteristics **[31].**

4.1. Interleukin-6 (IL-6)

Interleukin-6 is a cytokine that enhances the inflammatory response and was first identified as a stimulant for B-cells. The mature protein consists of 184 amino acids organized in a four-helix bundle, displaying a common up-up-down-down pattern observed in the majority of cytokines. After analyzing the cDNA sequence, it was clear that IL-6 was identical to hepatocyte-stimulating factor, hybridoma/plasmacytoma growth factor, interferon-β2, and a 26-kDa protein of unknown function. Although the initial observation provided some indications of the pleiotropic nature of IL-6, it is now recognized that IL-6 has multiple functions in the control and synchronization of the immune system, metabolism, and neurological system **[32].** T and B cells, fibroblasts, and macrophages produce interleukin-6 (IL-6). The primary targets of the virus are B lymphocytes and hepatocytes. The principal actions of IL-6 include the differentiation of B-cells and the activation of acute-phase proteins **[33].**

4.1.1. Regulation of IL6 synthesis:

IL-6 functions as a mediator to relay information about certain emergent events. IL-6 is synthesized locally in an infected region and releases a signal of distress that spreads throughout the entire body. Immune cells such as monocytes and macrophages identify pathogen-associated molecular patterns, which are distinct features of external pathogens, in the affected area using pathogen-recognition receptors (PRRs). The PRRs comprise Toll-like receptors (TLRs), retinoic acid-inducible gene-1-like receptors, nucleotide-binding oligomerization domain-like receptors, and DNA receptors. They stimulate multiple signaling pathways, including NF-κB, and enhance the synthesis of mRNA for inflammatory cytokines such as IL-6, tumor necrosis factor (TNF)-α, and IL-1β. Tumor necrosis factor alpha (TNF-α) and Interleukin-1 beta (IL-1β) activate transcription factors that trigger the synthesis of IL-6 **[34].**

IL-6 also serves as an alarm signal in case of damage to tissues. DAMPs, or damage-associated molecular patterns, are molecules that are generated from cells that have been injured or are dying in non-infectious inflammatory conditions like burns or trauma. These molecules directly or indirectly stimulate inflammation. Before the rise in temperature in the body and acute stage protein concentration, there is a rise in serum IL-6 levels during sterile surgical procedures. Danger-associated molecular patterns (DAMPs) derived from damaged cells consist of a diverse array of components, including mitochondrial (mt) DNA, high mobility group box 1 (HMGB1), and S100 proteins. The concentrations of mtDNA in trauma patients' serum are significantly higher than in control subjects, with a difference of several thousand times. This increase in mtDNA levels triggers the stimulation of TLR9 and the activation of NF-κB. Additionally, the binding of HMGB1 to TLR2, TLR4, and the receptor of advanced glycation end products (RAGE) can contribute to the promotion of inflammation. The S100 protein family consists of over 25 members, some of which can interact with RAGE and trigger sterility **[35].**
Various triggers elicit the generation of IL-6 not only from immune-mediated cells, but also from mesenchymal cells, endothelial cells, fibroblasts, and other cell types. The rigorous management of IL-6 synthesis, both at the gene transcriptional and post-transcriptional levels, is due to IL-6's ability to deliver a warning signal indicating the existence of a medical emergency. Several transcription factors have been demonstrated to control the transcription of the IL-6 gene. The 5′ flanking region of the human IL-6 gene contains functional cis-regulator elements that serve as binding sites for NF-κB, specificity protein 1 (SP1), nuclear factor IL-6 (NF-IL-6) (also known as CAAT/enhancer-binding protein β), activator protein 1 (AP-1), and interferon regulatory factor 1. Stimulation by IL-1, TNF, TLR-mediated signal, and forskolin activates the IL-6 promoters through the stimulation of cis-regulatory components **[36].**

4.1.2. Clinical significance:

IL-6 is synthesized by several cell types and has diverse impacts on multiple biological processes. Specifically, IL-6 is crucial in facilitating both innate and adaptive immune reactions. Neutrophils are cells and monocytes/macrophages, which are types of immune cells that are naturally present in the body, both create and react to a substance called IL-6. This can lead to an increase in inflammation and a transition from a short-term to a long-term state of inflammation. IL-6 plays a role in facilitating the T and B cells' activation, which are the primary instigators of adaptive immune responses and crucial cells in the development of several autoimmune disorders. IL-6 has been linked to the development of fibrotic illnesses, such as SSc. Thus, focusing on IL-6 signaling could be a logical therapeutic approach for treating individuals with these disorders **[32].**

4.1.3. Role in liver disease:

IL-6 is a crucial cytokine in liver diseases related with inflammation. Current data indicates that IL-6 has dual effects on inflammation, acting both as a pro-inflammatory and anti-inflammatory agent. IL-6 released from adipose tissue can contribute to inflammation, whereas IL-6 produced by muscles can help reduce inflammation. In addition, prolonged interaction with elevated levels of IL-6 can lead to an increase in the production of glucose by the liver and a disruption in the metabolism of lipids. However,

IL-6 exerts protective effects on the liver during instances of sudden liver damage. Furthermore, a recent study has indicated that the IL-6 receptor (IL-6R) has the potential to decrease inflammation associated with non-alcoholic fatty liver disease (NAFLD) **[37].**

4.1.4. Role of IL 6 in the regeneration of the liver tissue:

IL-6 and subsequent STAT3 signaling act as key regulators that coordinate the transcriptional response to facilitate liver regeneration. The direct effect of IL-6 on hepatocytes leads to the formation of dimers and the movement of STAT3 into the nucleus. Once in the nucleus, STAT3 activates early genes that are involved in the processes of regeneration and mitosis, working together with ERK. IL-6 regulates approximately 40% of the immediate early genes involved in liver regeneration. The APP response and liver regeneration are impaired in animals lacking STAT3 **[38]**.

The involvement of IL-6/STAT3 signaling in liver regeneration can be recognized in conjunction with other anti-inflammatory agents. For instance, A20 functions as an inhibitor of NF-κB, which is a well-known mechanism associated with inflammation. A study demonstrated that A20 enhances the regeneration of hepatocytes by augmenting the phosphorylation of STAT3 via IL-6 signaling. Additionally, it is important to mention that A20 can also stimulate the activation of cyclin dependent kinases, thereby facilitating cell proliferation. Consequently, the regenerative effect seen may be attributed to the impact of A20 on the progression of cell division and/or its ability to block the pro-inflammatory NF-κB pathway, leading to increased production of IL-6. The increase in activity of the IL-6/STAT3 pathway was further confirmed by the suppression of SOCS3, most likely through the influence of miRNA **[39].**

Liver regrowth progresses through three distinct phases: initial priming, proliferation, and termination. The IL-6 signaling pathway facilitates the transformation of inactive hepatocytes from the resting phase (G0) to the phases of cell division (G1 and S) by promoting DNA synthesis. This is achieved by increasing the expression of many genes involved in transcription**.** Proteins associated with the cell cycle, specifically c-myc and cyclin-D1, are not properly activated in animals lacking IL-6. Although these proteins are not necessary for liver regeneration, they are crucial for the most efficient growth of hepatocytes **[40].**

4.2. Interleukin 8 (IL-8)

IL-8 is a chemotactic cytokine that specifically attracts neutrophils, basophils, and T-cells to the site of inflammation. It does not exhibit chemotactic properties for monocytes. IL-8 has a role in activating neutrophils and is secreted by several cell types in response to inflammation, such as monocytes, macrophages, neutrophils, as well as cells in the intestine, kidney, placenta, and bone marrow. It belongs to the beta-thromboglobulin class and has a similar structure to platelet factor 4. IL-8 plays a role in promoting cell division, preventing the growth of new blood vessels, causing inflammation, attracting immune cells, releasing substances from neutrophils, activating white blood cells, and maintaining calcium balance **[41].** Monocytes and fibroblasts produce interleukin-8 (IL-8). The primary targets of this substance consist of keratinocytes, mast cells, basophils, neutrophils, and macrophages. It triggers the release of granules, superoxide, angiogenesis, and neutrophil chemotaxis **[42]**.

4.2.1. Interleukin-8 structure:

Interleukin-8 belongs to the CXC class of chemokines, some of which have a remarkably conserved glutamic acid-leucine-arginine (ELR) sequence motif that is critical for their biological function. The presence of common structural features suggests that observations about the composition, motion, and relationships of a particular chemokine may apply to a broad range of chemokine receptor configurations and activities. Interleukin-8 (IL-8, CXCL8) was the first chemokine to be identified **[43]**. The most common form of the protein consists of 72 residues. At high concentrations, it exists as a homo-dimer, At low concentrations, the substance exists as a monomer and interacts with its receptor in this

form. The arrangement of the IL-8 dimer in its natural form was initially established by the use of solution NMR and X-ray crystallography techniques. Afterward, the structure of it has been analyzed under various conditions and with several mutations **[44]**.

4.2.2. Signaling pathways of IL-8:

Interleukin-8 (IL-8), also referred to as CXCL8, is a chemokine of the CXC family that promotes inflammation. The IL-8 gene transcription produces a protein consisting of 99 amino acids. This protein is then processed to form a functional signaling protein, which has either 77 amino acids in non-immune cells or 72 amino acids in monocytes and macrophages. The transcriptional process mediated by activator protein and/or nuclear factor-κB is the main regulatory mechanism for the expression of IL-8.Three The physiological impacts of IL-8 are facilitated by the interaction between IL-8 and two receptors linked to G proteins on the surface of cells, known as CXCR1 and CXCR2.Four It activates Akt/PKB, MAPK, and Protein Kinase C (PKC), leading to the development of inflammatory **[45].**

4.2.3. Clinical significance:

IL-8 is a powerful factor that promotes the formation of blood vessels, inflammation, and the development of cells. It may have similar capabilities to other chemokines. IL-8 also attracts neutrophils and causes the production of various cell adhesion molecules. Additionally, it results in the proliferation of neutrophils, perhaps contributing to the development of inflammatory disorders. IL-8 selectively binds various types of cells, serving as the underlying mechanism for inflammation. Neovascularization plays a vital role in the progression of tumors and their spread to other parts of the body. The control of IL8 production is a crucial factor in the process of inflammatory processes, which is facilitated by NF-κB. IL-8 receptors are present in both normal cells and different types of malignant cells. IL-8 triggers inflammatory, chemotactic, and matrix-degradative reactions in many diseases **[46].**

4.3. Interleukin 10

IL-10 is produced by a variety of cell types, including myeloid cells (such as dendritic cells, macrophages, eosinophils, neutrophils, and mast cells) and lymphoid cells (such as NK cells, B cells, and T cells). It has significant anti-inflammatory effects. Macrophages and myeloid dendritic cells secrete IL-10 in response to activation of MyD88- and TRIF-dependent TLR signaling pathways (particularly TLR3 and TLR4) by dsDNA and LPS stimulation, respectively. Furthermore, when exposed to LPS, tolerogenic dendritic cells (CD11clowCD45RBhigh) release substantial amounts of IL-10, which results in the development of T regulatory cells. Natural regulatory cells (nTreg) release IL-10 in response to IL-2 activation, which is essential for preserving immunological equilibrium **[47].** Th2 cells secrete IL-10. The main focus of this is on Th1 cells. It leads to the suppression of IL-2 and interferon-gamma. It reduces the display of antigens and the expression of MHC class II on cells called dendritic cells, as well as the presence of co-stimulatory substances on macrophages. Additionally, it suppresses the immune responses of pathogenic Th17 cells. The macrophages' production of IL-12 is suppressed by it **[48].**

4.3.1. Structure:

Interleukin-10 (IL-10) was initially identified as a factor that inhibits the production of cytokines by T lymphocytes, namely those produced by T helper 2 (Th2) cell clones. It can suppress the synthesis of interferon (IFN)-γ in Th1 cell clones. The IL-10 gene in humans is a homodimer with a molecular mass of 37 kilodaltons. It is situated on chromosome 1 and contains 5 exons. Every monomer is composed of 160 amino acids. The X-ray crystallography research revealed that the two equivalent polypeptide chains, each consisting of 160 amino acids, are intertwined and rotated by 180° relative to each other. This arrangement results in the formation of a V-shaped structure with two distinct domains, each composed of six helices. The number 52 is enclosed in square brackets **[49].**

4.3.2. Regulation:

The regulation of IL-10 transcription is highly precise to prevent disorders associated with either excessive or insufficient levels of this cytokine. Various regulatory mechanisms, common and unique to cells, ensure the proper synthesis of IL-10. These mechanisms involve the activation of certain signaling pathways, the expression and activation of specific transcription variables, and the regulation of gene expression after transcription and through epigenetic modifications **[50].**

4.3.3. Clinical significance:

IL-10 is a cytokine that has strong anti-inflammatory properties and is crucial in controlling the immune system's reaction to infections. Its major function is to protect the host from injury and maintain the natural balance of tissues. The dysregulation of IL-10 is linked to heightened immune pathology during infection and an elevated susceptibility to several autoimmune disorders. Increased concentrations of IL-10 can impede the host's ability to respond to pathogeneses of microorganisms and hamper the healing of tissue damage and changes in blood flow. Conversely, insufficient amounts of IL-10 can result in the emergence of autoimmune illness and increased susceptibility to developing tumors **[51].**

4.3.4. Role in Liver Disease:

IL-10 has demonstrated a prophylactic function in two types of developed hepatitis caused by Concavalin A or galactosamine and lipopolysaccharide.Seventy-five Prior injection of an anti-IL-10 antibody before ConA therapy results in the exacerbation of hepatitis and increased levels of IL-12, TNFα, and IFNγ in the bloodstream.The number is 75. IL-10-deficient animals have shown comparable findings **[52].**

5. CONCLUSION

IL-6, IL-8, and IL-10 hold promise as valuable markers for evaluating HCV therapy efficacy, predicting treatment outcomes, and identifying individuals who could benefit from tailored therapeutic approaches. The analysis also explores the potential therapeutic implications of targeting these interleukins to enhance treatment efficacy and reduce adverse effects. It is crucial to understand the therapeutic significance of IL-6, IL-8, and IL-10 in HCV treatment to improve patient care and advance personalized medicine techniques.

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