Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Relation between Monocyte chemotactic protein -1 and Cirrhosis

Rashed Mohammed Hassen [1], Sahar Abdelshafy Elnemr [1], Heba Fouad Pasha [2], Akram Said Ali Khafagy 1
1 Department of Tropical Medicine, Zagazig University Hospital, Egypt
2 Department of Medical Biochemistry, Zagazig University Hospital, Egypt
Corresponding Author: Akram Said Ali Khafagy
Email: khafagyakram790@gmail.com

Abstract

Background: Cirrhosis is the final stage of several chronic hepatic diseases and characterized by fibrosis, morphological conversion from normal hepatic architecture into structural abnormal nodules and disturbed normal liver vasculature. Cirrhosis has two clinical types which are compensated, and decompensated Decompensation is defined as ascites, spontaneous bacterial peritonitis, variceal hemorrhage, hepatic encephalopathy and jaundice. Monocyte chemotactic protein-1 (MCP-1) is one of the most potent chemokines for monocytes/macrophages and activated lymphocytes during infections. In addition, several studies have shown that neutrophil infiltration is affected either directly or indirectly *via* MCP-1. Monocyte chemotactic protein-1 (MCP-1) gene encoding a potent activator of mononuclear phagocytes. Located on chromosome 17 (chr.17, q11.2), human MCP-1 is composed of 76 amino acids and is 13 kDa in size. A polymorphism -2518 G/A (rs 1024611) of MCP-1 was found to affect the transcriptional activity of the distal regulatory region and monocyte MCP-1 production.Hence,this polymorphism correlates with individual differences in monocyte MCP-1 production. Monocytes from individuals carrying a -2518 G allele produced more MCP-1 than monocytes from A/A homozygous individuals. The effect of the G allele appears to be dose dependent, as cells from individuals homozygous for G at -2518 produced more MCP-1 than cells from G/A heterozygotes.

Keywords: Monocyte chemotactic protein -1, Cirrhosis

Background

Patients with cirrhosis and ascites show higher susceptibility to bacterial infections, mainly because of the inadequate defence mechanisms. Factors influencing the development of spontaneous bacterial peritonitis (SBP) in patients with liver cirrhosis are poorly understood. Previous studies have indicated that peritoneal macrophages of cirrhotic patients might contribute to the control of SBP or influence its associated pathology in human cirrhosis by producing high quantities of angiogenic peptides and nitric oxide. **(1)**

Monocyte chemotactic protein -1 (MCP-1)

Chemokines include a large class of cytokine chemotaxis content, monocyte chemotactic protein-1 (MCP-1), also known as chemokine ligand 2 (CCL2), belonging to the chemokine family CC subclass. In the family, MCP-1 is a major chemotactic and activating factor of inflammation-associated cells such as monocytes/macrophages and is capable of inducing expression of chemokine receptor 2 (CCR2) in a variety of cells. When MCP-1 binds to CCR2, it directly activates monocytes and other immune cells, such as memory T lymphocytes and natural killer cells, to promote inflammation. **(2)**

MCP-1 also induces the expression of adhesion molecules and interleukin-1 (IL-1), IL-6, tumor necrosis factor-α (TNF-α) and other by activating various intracellular signal transduction pathways. The factor, which causes basophils and mast cells to release histamine, regulates the phagocytic function and pro-apoptotic effect of mononuclear macrophages, and participates in inflammatory diseases and neovascularization and damage repair. **(3)**

MCP-1 recruits and activates inflammatory cells, and activated macrophages secrete profibrotic factors such as transforming growth factor-β1 (TGF-β1), platelet-derived growth factor (PDGF), and plasma plasminogen activator inhibitors. 1 (PAI-1), matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinase-1 (TIMP-1), induce fibroblasts into differentiate myofibroblasts, which play a role in interstitial fibrosis. **(4)**

In addition to chemotactic mononuclear/macrophage-like inflammation-related cells, MCP-1 also affects T cell proliferation and immune function. MCP-1 activates

monocytes/macrophages, activated monocytes/macrophages and secrete IL-12, induces initial CD4+ T cells into differentiate Th1 cells, and Th1 cells produce IL-2, gamma interferon (IFN-γ) and TNFα, thus positive feedback enhances cellular immunity and macrophage function; Th2 cells produce IL-4 and IL-10, inhibit Th1 cell response, and inhibit macrophage activation. **(5)**

MCP-1 can directly activate IL-4 promoter, make IL-4 expressing cells increased, so that naive T cells differentiate into Th2 cells, thereby enhancing the type 2 immune response. In addition, MCP-1 can also affect the differentiation of neutrophils. Recent studies have found that MCP-1 plays an important role in autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, type 1 diabetes, multiple sclerosis and inflammatory bowel disease. **(3)**

Monocyte chemotactic protein-1 family:

Human mcp-1 gene is located on the long arm of chromosome 17 (17q11. 2-q21. 1), it consists of three exons and two introns. This gene encodes a MCP-1 precursor molecule containing 99 amino acids and is modified by shear to become a mature molecule containing 76 amino acids. Two intrachain disulfide bonds are formed between the four cysteines in the MCP-1 mature molecule, and these two adjacent highly conserved disulfide bonds may play an important role in the biological activity of MCP-1. **(5)**

The N-terminus of the MCP-1 molecule binds to the receptor and exerts biological activity, while the MCP-1 mutant the N-terminus can become an inhibitor of MCP-1, thereby blocking the downstream signalling pathway and completely inhibiting MCP-1, so the N-terminus may be its chemotactic functional region. In addition, mutations in certain amino acids such as Lys37, Lys38, Arg24, Tyr28, etc. in MCP-1 molecules may also affect their binding to receptors, causing changes in signalling pathways. **(4)**

Monocyte chemotactic protein-1 signalling pathway:

Monocyte chemotactic protein-1 signalling pathway cascade

MCP-1 can activate monocyte-injured renal parenchyma and induce the secretion of various cytokines and growth factor by binding to the receptor CCR2, allowing proliferation of epithelial cells, endothelial cells, and vascular smooth muscle cells, resulting in inflammation. The reaction changes to interstitial fibrosis, which ultimately leads to renal interstitial fibrosis. MCP-1 gene transcription require activation or binding of NF-κB and AP-1, thereby activating downstream signal transduction pathways. **(2)**

MCP-1 recruits mononuclear/macrophages and stimulates interstitial fibroblasts, which promote extracellular matrix protein deposition, leading to interstitial fibrosis. MCP-1 up-regulates TGF-β and matrix metalloenzyme inhibitors by increasing lymphocyte infiltration and interaction with fibroblast/fibroblasts (TIMP1), which ultimately leads to fibrosis of the intestinal wall. **(3)**

Pathway regulation:

The role of MCP-1 in ATH inflammatory response and the distribution and function of VSMCs in ET1-specific ETAR suggest that ET1 may also be another important stimulator of MCP-1 activation in VSMCs during ATH vascular inflammation. The experiment confirmed that ET1 can induce the expression of MCP-1 protein and mRNA in rat VSMCs. BQ123 ETAR inhibitor significantly inhibited this effect of ET1, and inhibition of BQ788 ETBR inhibitor is not obvious, suggesting ET1 induced MCP-1 in VSMCs produce primarily mediated by ETAR on VSMCs. **(2)**

Further, antioxidants NAC, ERK, p38MAPK and NF-κB inhibitors PD98059, SB203580 and PDTC also inhibited the expression of MCP-1 protein and mRNA in VSMCs under ET1 stimulation conditions, suggesting that ROS, ERK, p38MAPK and NF-κB may be involved in ET1-induction VSMCs produce MCP-1 signal transduction pathway. **(5)**

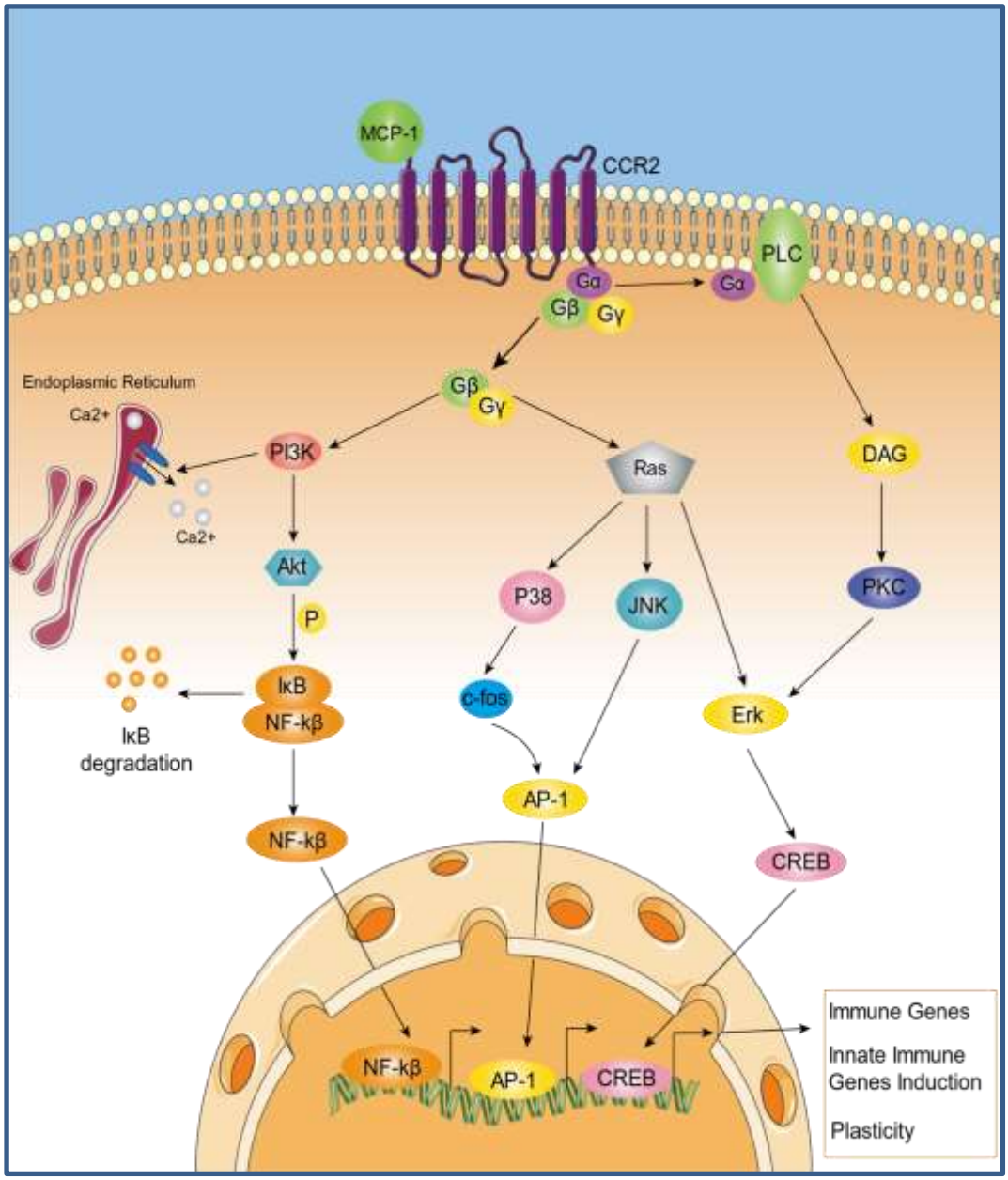

Figure (1): Monocyte Chemotactic Protein-1 Signalling Pathway **(5)**

Meanwhile, BQ123 NAC and PD98059 or SB203580 can respectively inhibit the phosphorylation of ERK and p38MAPK in the cytoplasm of VSMCs under ET1 stimulation, further proving that ETAR ROS and MAPK signal molecules (ERK p38MAPK) are important signal molecules in the MCP-1 signal pathway induced by ET1. **(3)**

In summary, vasoactive peptide ET1 can induce MCP-1 production in VSMCs via ROS and MAPK signalling pathways, suggesting that ET1→ETAR→ROS→MAPK→NF-κB→MCP-1 may be involved in the activation of VSMCs during ATH. This will provide

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

a new theoretical basis and therapeutic target for the clinical prevention and treatment of ATH. **(3)**

However, the detailed signal transduction mechanism of this pathway and its relationship with other inflammatory need further study. In the demyelinating lesions of patients with multiple sclerosis, there are many monocyte-derived macrophages, which secrete inflammatory mediators and promote the progression of MS. **(4)**

As a monocyte chemotactic protein, MCP-1 can up-regulate the expression of monocytes, microglia, and T cells in the brain, cerebrospinal fluid, and blood of MS patients, and induce mononuclear macrophage infiltration of CNS, EAE. Symptoms and degree of inflammation were positively correlated with MCP-1 expression. **(5)**

Experimental studies have shown that electroacupuncture can inhibit the expression of MCP-1 in rat cervical spinal cord, possibly by down-regulating the chemotaxis of MCP-1 on monocytes and interfering with the exudation of activated macrophages and autoreactive T cells. The mononuclear macrophages and T cells infiltrated in the CNS were significantly reduced, thereby alleviating the symptoms of EAE rats and inhibiting the progression of the disease. **(2)**

Relationship with diseases:

Genetic variations of MCP-1 have been reported to influence the serum levels of MCP-1 and the incidence of myocardial infarction. Two SNPs of MCP-1, namely, G-927C and A-2578G, were found to be associated with carotid intima-media thickness, which reflects generalized atherosclerosis and is predictive of future vascular events. **(6)**

Further studies examined the distribution of SNPs in the MCP-1 gene in tuberculosis. The authors found that the probability of developing tuberculosis was 2.3- and 5.4-fold higher in carriers of MCP-1 genotypes AG and GG, respectively, than in homozygous AA. These findings suggest that persons bearing the MCP-1 genotype GG produce higher concentrations of MCP-1, which inhibits the production of IL-12 p40 in response to Mycobacterium tuberculosis and increases the likelihood that M. tuberculosis infection will progress to active pulmonary tuberculosis. **(7)**

In addition, the influence of genetic variation in MCP-1 on HIV-1 pathogenesis has been examined using large cohorts of HIV-1-infected adults and children. Results showed that in adults, homozygosity for the MCP-1 −2578G (alternatively designated −2518) allele was associated with a 50% reduction in the risk of acquiring HIV-1. However, once HIV-1 infection was established, this same MCP-1 genotype was associated with accelerated disease progression and a 4.5-fold increased risk of HIV-associated dementia (HAD). Finally, HIV-patients with a mutated MCP-1 allele have an undetectable viral load after treatment with protease inhibitor–based antiretroviral therapy. **(8)**

Many studies have shown that the content of MCP-1 is significantly increased in systemic lupus erythematosus lesions. The specific mechanism has been described above. The clinical use of MCP-1 inhibitors or other methods to reduce MCP-1 content can effectively alleviate systemic lupus erythematosus. **(6)**

T1DM is an organ-specific autoimmune disease, mainly characterized by dysfunction of glucose metabolism caused by destruction of islet β cells, which is genetically predisposed and can be associated with various acute and chronic complications. High levels of MCP-1 observed during islet inflammation. ***(2)***

Several studies have linked MCP-1 to cardiovascular disease. Using MCP-1- or CCR2-deficient mice to examine atherosclerosis, it was demonstrated that, in the absence of MCP-1 or its receptor, CCR2, there was a substantial reduction in arterial lipid deposition. Further, amelioration from the disease was associated with diminished numbers of macrophages in the arterial wall consistent with a model in which MCP-1 contributes to atherosclerosis by attracting monocytes into the subendothelium via MCP-1 activation. **(6)**

Increased plasma levels of MCP-1 following balloon angioplasty of coronary arteries predicts early restenosis, which may represent an accelerated form of atherosclerosis. Finally, at a population level, a polymorphism in the MCP-1 promoter has been demonstrated to be associated with an increased risk of an individual to suffer from coronary artery disease. **(6)**

Chemokines and their receptors have been detected in most tumors. However, to date no susceptibility gene in any cancer has been mapped on to a chemokine or chemokine

receptor. Chemokines are involved in a broad array of normal host activities that impact cancer; therefore, it is possible that they will be found to have important effects on cancer pathogenesis. **(9)**

For this reason, chemokines might be expected to have either growth-promoting or growth-inhibiting influences on cancer cells depending on the particular setting in which they are expressed. Further, because of their ability to attract and activate lymphocytes, some chemokines might be expected to stimulate host antitumor responses. **(9)**

On the other hand, some of the chemokines are known to possess angiogenic activities, which could potentially contribute to tumor growth and progression. Some of the tumor-associated molecular alterations that increase macrophage infiltration and macrophage-mediated angiogenesis include increased expression of MCP-1 and VEGF, both of which are highly expressed in breast cancer cells. MCP-1 expression in tumor cells is significantly correlated with the extent of tumor-associated-macrophage (TAM) infiltration, and in particular both MCP-1 and VEGF expressions have been positively correlated with TAM infiltration, angiogenesis, and poor survival in breast cancer. **(2)**

Monocytes are critical for the initiation of tumor arteriogenesis because they adhere to and invade endothelium activated by the increased shear stress that results from large pressure differences between perfused areas. MCP-1 is once again implicated in this process because it not only attracts monocytes, but also promotes their adhesion by inducing them to upregulate MAC-1, the receptor for intracellular adhesion molecule-1 (ICAM-1) that is expressed in activated endothelium. **(2)**

Finally, note that MCP-1 has antitumor activity. This was demonstrated by its ability to augment cytostatic activity against tumor cells upon addition to macrophages in tissue culture and by its ability to induce FAS ligand protein expression in cultured endometrial stromal cells, thus driving cells to apoptosis. **(9)**

Both MCP-1 and its receptor MCP-1 have been found to be elevated and to play a pivotal role in the development of atherosclerosis. Moreover, differentiation of intestinal macrophages was disturbed by MCP-1, suggesting that MCP-1 could play a role in the

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

disturbed intestinal differentiation that occurs in the mucosa of patients suffering from inflammatory bowel disease. **(2)**

Further studies linked the induction of MCP-1 by IL-4 and IL-13 in human bronchial epithelial cells to its potential involvement in allergic asthma. Further, MCP-1 levels were significantly raised in individuals with rheumatoid arthritis. In addition, using a transgenic mouse model system, it has been shown that circulating MCP-1 may contribute to insulin resistance in diabetic patients. Finally, MCP-1 was also shown to be involved in neurological disorders such as ischemia-related neuronal death, where MCP-1 levels were elevated in astrocytes leading to neuronal death. **(2)**

The importance of MCP-1 and its receptor MCP-1 is not limited to the manifestation of coronary artery disease but can be expected to play equally important roles in other inflammatory diseases. For example, similar results have been obtained in experimental allergic encephalitis, which is a rodent model for multiple sclerosis. In these studies, it was found that MCP-1- or MCP-1-deficient mice recruited many fewer monocytes into the CNS and the severity of disease was greatly reduced. Note that the mechanisms of recruitment of MCP-1 in these diseases are not fully understood and, in some cases, remain to be identified. **(10)**

MCP-1 polymorphism and spontaneous bacterial peritonitis in cirrhotic patients:

Patients with cirrhosis and ascites show higher susceptibility to bacterial infections, mainly because of the inadequate defence mechanisms. Factors influencing the development of spontaneous bacterial peritonitis (SBP) in patients with liver cirrhosis are poorly understood. Previous studies have indicated that peritoneal macrophages of cirrhotic patients might contribute to the control of SBP or influence its associated pathology in human cirrhosis by producing high quantities of angiogenic peptides and nitric oxide. **(1)**

SBP can be caused by many reasons due to the alterations of the immune system that are very common in patients with end-stage liver disease and associated with an increased risk of infection and death. Consequently, elevated concentrations of pro-inflammatory cytokines are found in ascitic fluid of these patients. In addition, hepatitis C virus (HCV)

infection is associated with increased hepatic expression of monocyte chemotactic protein-1 (MCP-1). **(10)**

MCP-1 acts as a chemotactic factor for monocytes/macrophages, activated lymphocytes and neutrophils during infections; thus, these cells migrate to the ascitic fluid. Monocytes and macrophages release TNF-α and other cytokines, which in turn induce the expression of adhesion molecules on endothelial cells, thereby mediating a systemic reaction to the infection. **(11)**

TNF-α has been shown to be elevated in the ascitic fluid of SBP patients, stimulating the release of interleukin-8 (IL-8), growth-related oncogene-α (GRO-α), and MCP-1 by mononuclear cells or endothelial cells. This release propagates the inflammatory reaction. MCP-1 secretion is up-regulated during chronic hepatitis and correlates with the severity of hepatic inflammation. Furthermore, a previous study showed elevated MCP-1 levels in ascitic fluid of cirrhotic patients with SBP compared to patients without SBP. **(1)**

References.

1. **Salama, M. K., Sabry, D., Al-Ghussein, M. A., Ahmed, R., AbdAllah, S., Taha, F. M., & Darwish, T. (2014).** Molecular detection of monocyte chemotactic protein-1 polymorphism in spontaneous bacterial peritonitis patients. World Journal of Gastroenterology: WJG, 20(33), 11793.

2. **Jura, J., Skalniak, L., & Koj, A. (2012).** Monocyte chemotactic protein-1-induced protein-1 (MCPIP1) is a novel multifunctional modulator of inflammatory reactions. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1823(10), 1905-1913.

3. **Li, M., Cao, W., Liu, H., Zhang, W., Liu, X., Cai, Z., & Wang, L. (2012).** MCPIP1 down-regulates IL-2 expression through an ARE-independent pathway. PLoS One, 7(11), e49841.

4. **Liang, J., Saad, Y., Lei, T., Wang, J., Qi, D., Yang, Q., & Fu, M. (2010).** MCP-induced protein 1 deubiquitinates TRAF proteins and negatively regulates JNK and NF-κB signaling. Journal of Experimental Medicine, 207(13), 2959-2973.

5. **Xu, J., Fu, S., Peng, W., & Rao, Z. (2012).** MCP-1-induced protein-1, an immune regulator. Protein & cell, 3(12), 903-910.

6. **Park, Y. J., Shin, Y. J., Kim, W. U., & Cho, C. S. (2014).** Prediction of subclinical atherosclerosis by serum osteoprotegerin in premenopausal women with systemic lupus erythematous: correlation of osteoprotegerin with monocyte chemotactic protein 1. Lupus, 23(3), 236-244.

7. **Guo, X. H., Bai, Z., Qiang, B., Bu, F. H., & Zhao, N. (2017).** Roles of monocyte chemotactic protein 1 and nuclear factor-κB in immune response to spinal tuberculosis in a New Zealand white rabbit model. Brazilian Journal of Medical and Biological Research, 50.

8. **Takeuchi, O. (2018).** Endonuclease Regnase-1/Monocyte chemotactic protein-1-induced protein-1 (MCPIP1) in controlling immune responses and beyond. Wiley Interdisciplinary Reviews: RNA, 9(1), e1449.

9. **Zollo, M., Di Dato, V., Spano, D., De Martino, D., Liguori, L., Marino, N., & Guglielmotti, A. (2012).** Targeting monocyte chemotactic protein-1 synthesis with bindarit induces tumor regression in prostate and breast cancer animal models. Clinical & experimental metastasis, 29(6), 585-601.

10. **Mantovani, A., Sozzani, S., Proost, P., & Van Damme, J. (2020).** The monocyte chemoattractant protein family. In Chemoattractant ligands and their receptors (pp. 169-192). CRC Press.

11. **Kolattukudy, P. E., & Niu, J. (2012).** Inflammation, endoplasmic reticulum stress, autophagy, and the monocyte chemoattractant protein 1/CCR2 pathway. Circulation research, 110(1), 174-189.