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Review

MCP-1: Function, regulation, and involvement in disease

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ABSTRACT

MCP-1 (Monocyte chemoattractant protein-1), also known as Chemokine (CC-motif) ligand 2 (CCL2), is from family of CC chemokines. It has a vital role in the process of inflammation, where it attracts or enhances the expression of other inflammatory factors/cells. It leads to the advancement of many disorders by this main mechanism of migration and infiltration of inflammatory cells like monocytes/macrophages and other cytokines at the site of inflammation. MCP-1 has been implicated in the pathogenesis of numerous disease conditions either directly or indirectly like novel corona virus, cancers, neuroinflammatory diseases, rheumatoid arthritis, cardiovascular diseases. The elevated MCP-1 level has been observed in COVID-19 patients and proven to be a biomarker associated with the extremity of disease along with IP-10. This review will focus on involvement and role of MCP-1 in various pathological conditions.

1. Introduction

Chemokines are a family of small, signaling proteins having small molecular weight of 8–14 kDa secreted by the cells of immune system [1]. These are chemotactic cytokines responsible for the regulation of movement of other cells in response to a chemical stimulus (chemotaxis) thus emanating their name as chemokines. The family of chemokines is characterized into four families with two main subgroups (CXC and CC) and two small subgroups (CX3C and C) [1]. This classification is broadly based on the presence of the cysteine amino acids nearby N-terminus. Monocyte chemoattractant protein-1(MCP-1)/CC chemokine ligand-2 (CCL2) belongs to the CC family which have cysteines adjoined closely to N-terminus (Fig. 1). The cysteine residues are linked by disulfide bridge between the first and third cysteine and between the second and fourth cysteine [2]. The other MCPs found in humans other than MCP-1 are MCP-2(CCL8), MCP-3(CCL7) and MCP-4(CCL13) sharing about ~ 60% homology [3].

CCL2 is the first purified and best characterized human CC chemokine, identified because of its monocyte chemotactic property *in-vitro* in human cell lines [4]. The location of MCP-1 gene in chromosome is at 17q11.2-q21.1 with three exons and two introns [3]. The MCP-1 precursor molecule consists of hydrophobic amino terminal signal peptide of 23 amino acids. The mature protein contains 76 amino acids after the cleavage of signal protein, forming monomeric polypeptide. The MCP-1

has been purified in different molecular mass forms which appear to be caused by O-glycosylation. The chemoattractant efficacy of MCP-1 has been seen to reduce slightly by glycosylation [2].

All chemokine receptors are seven transmembrane G-protein coupled receptors belonging to rhodopsin or serpentine receptor family. The MCP-1 can bind to several receptors but mainly enforces its biological effect by attaching to extracellular region of CCR2. The CCR2's amino terminal domain has been reported to be both necessary and adequate for MCP-1 binding. The mutation in the cysteine residues of N-terminal domain leads to the loss of MCP-1 binding affinity [5]. Site-directed mutational analysis of CCL2 has implied the importance of two regions of primary structure for biological activity. One region is amino acid 10–13, where mutation lowered the biological activity; the other region is amino acid 34–35 where mutation caused complete loss of MCP-1 activity [6].

The primary sources of monocyte chemoattractant protein-1 are epithelial cells, endothelial cells, smooth muscle cells, monocytes/macrophages, fibroblasts, astrocytes and microglial cells which are regulated by several other cytokines and factors [7–9]. They direct the migration and infiltration of monocytes, microglia, memory T lymphocytes at the place of injury and infection in various disorders. The role of MCP-1 has been implicated in pathogenesis of various diseases where it contributes by numerous mechanisms (Fig. 2). Here we have selected some pathological conditions where MCP-1 expression has been found

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more predominant and enumerate their involvement based on available literature.

2. MCP-1 in monocyte chemotaxis

MCP-1 prompts the concurrent initiation of different sign falls, their effect on monocyte chemotaxis could be extraordinary. In this manner, the migration of monocytic cells is presumably reliant on p38 MAPK and Src-kinases, while the transitory reaction is basically connected with PI3K and p42/44ERK1/2 MAPKs. The distinctions in the information concerning the MCP-1-instigated MAPKs signaling pathways and their role in chemotaxis could be clarified by the way that cell reactions coming about because of the given chemokine can change significantly relying upon the cell type in which they formed. This might be because of the distinctive accessibility of certain G-protein subunits or other downstream substance between in various cell types. A few reports demonstrate the p38 MAPK involved in MCP-1-mediated relocation of monocytes. MCP-1-intervened chemotaxis was exhibited to be repressed by the p38 inhibitor, while the restraint of p42/44ERK1/2 MAPKs actuation was incapable. Applying a monocytic cell line MonoMac6 it has been demonstrated that MCP-1 activated, with distinct time courses, p42/44ERK1/2, p38 MAPKs and JNK1. p38 MAPK initiation was repressed by PP2, uncovering an upstream guideline by Src-like kinases (Fig. 3) [10].

3. MCP-1 in oxidative stress

MCP-1 has been associated with oxidative stress in several studies. MCP-1 deficient mice have shown to produce less oxidative stress related molecules (intrahepatic ROS and HNE) and thus safeguarding from damage and advancement of oxidative stress in severe acute liver injury model [11]. The treatment of HK-2 cells and human peripheral blood mononuclear cells (HPBMC) with H₂O₂ for induction of oxidative stress, enhanced the expression of MCP-1 and other proinflammatory cytokines [12,13]. In study for age-related macular degeneration (AMD), it has been reported that the oxidative damage increases concentration of oxidized phospholipids and it up regulates secretion of MCP-1 in retinal cells [14]. The contribution of MCP-1 in ROS production has been confirmed in ovariectomy induced metabolic disturbance in mice, where the deficiency of MCP-1 attenuated the elevated levels of ROS and oxidative stress [15]. The escalated MCP-1 expression

mediated by NF- κ B activation and oxidative stress has been demonstrated in rat kidney during ischemia/reperfusion injury [16]. Another study with indoxyl sulfate (risk factor for CVD and CKD) has shown that it upregulates MCP-1 expression via oxidative stress induced NF- κ B activation in vascular endothelial cells [17]. Oxidative stress and MCP-1 have been correlated in the studies for diabetic nephropathy in both Type 1 and Type 2. Induction of MCP-1 expression via increased oxidative stress due to prolonged hyperglycemia may result in renal complications in type 1 diabetes [18]. In type 2 diabetes patients, close relation between MCP-1 and oxidative stress has been implied based on the urinary MCP-1 levels [19]. Even in *in-vitro* study done on adipocytes has shown that secretion of leptin, MCP-1, IL-6 by adipocytes increases due to oxidative stress [20]. The enhanced ROS generation by MCP-1 in monocytes elevates oxidative stress in patients of unstable angina [21]. The increase of oxidative stress marker F2-IsoPs in COPD patients is positively associated with inflammatory markers including MCP-1 [22].

4. Genetic variation in MCP-1

The genetic variation in MCP-1 has been seen in multiple diseases which varies with ethnicity. A certain MCP-1 polymorphism may affect a particular ethnic group but not act in the same manner in another. MCP-1 -2518G > A polymorphism is linked with greater risk of polycystic ovary syndrome (PCOS) as reported in a study on Korean population [23]. This polymorphism enhances the level of MCP-1 expression by influencing its gene transcriptional activity. The MCP-1 polymorphisms have been correlated with the increased risk of ovarian cancer and oral squamous cell carcinoma (OSCC) [24]. In ovarian cancer, the two genotypes of MCP-1, -2158GG and -362GG have been associated with higher susceptibility to the disease while in OSCC the MCP-1G and CCR2-64I were the risk factors [24,25]. In a *meta-analysis*, it was found that there is no significant correlation between asthma risk and MCP-1 -2518A4G polymorphism. Although it has been shown to be a risk factor for asthma in Caucasian population but in African population it has a protective association which represents the effect of genetic variation differs with ethnicities [26]. In Tunisian population, the protection against schizophrenia is mediated by MCP-1 haplotype combination -2581G/-362G/int1del554-567 in which more prominent protection is mediated by -2518G allele with -362G variants [27]. In Asian countries, especially China, MCP-1 A2518G genetic polymorphism has been linked with the increased susceptibility to Parkinson's disease as suggested by a

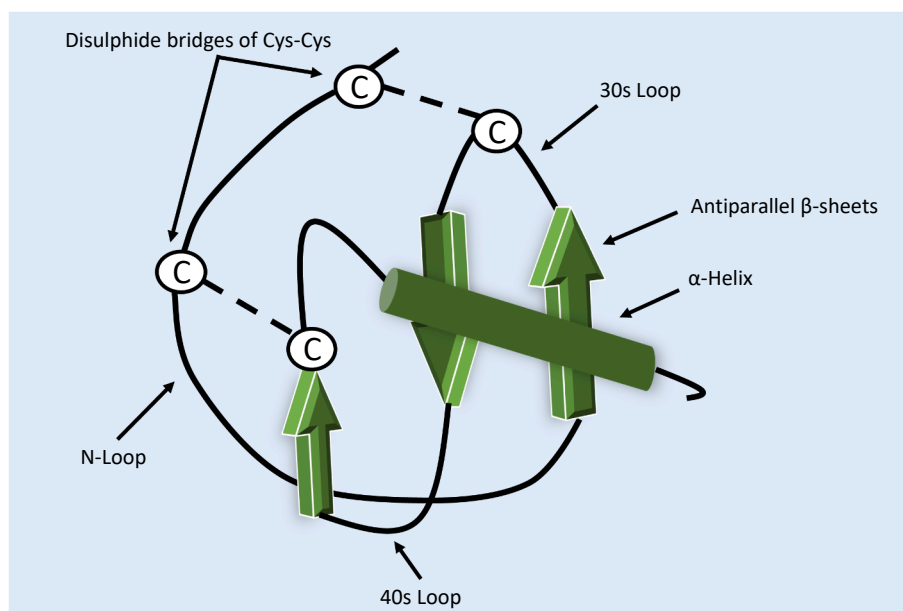


Fig. 1. Structure of chemokines.

meta-analysis [28]. The MCP-1 A-2518G polymorphism is not involved in the development of Alzheimer's disease [29]. MCP-1 polymorphism is also associated with systemic lupus erythematosus (SLE), in Mexican population there is a moderate association of MCP-1-2518 with the genetic susceptibility to SLE while in Indian SLE patients it has been correlated with renal disorders [30,31].

5. MCP-1 in ulcer and bowel disease

In early phase of inflammation in gastric ulceration, the expression of MCP-1 is induced by tumor necrosis factor- α (TNF- α) which further regulates the leukocyte recruitment, thus playing key role in the ulceration [32]. The neutrophil and macrophage infiltration are facilitated in interstitial space by increased expression of MCP-1 by ulcer wound. Gastric epithelial cells are stimulated during gastric mucosa infection by *Helicobacter pylori* and release MCP-1, which elicits enhanced COX-2 expression in T cells [33]. Another study has also shown that in ethanol induced ulcer the level of MCP-1 is increased along with others cytokines and the treatment leads to decreased MCP-1 level as well as inhibition of neutrophil recruitment at the site of injury [34].

In inflammatory bowel disease (IBD), the expression of MCP-1 is elevated which attracts monocytes to the lesion in mucosa [35]. The serum level of MCP-1 was elevated in IBD patients in comparison to healthy controls in a study that also suggested the MCP-1's involvement in intestinal inflammation [36]. In European population, but not in Asian and African patients, MCP-1 -A2518G gene polymorphism has been suggested to be a protective factor for IBD [37]. Another study has reported that after infection with the IBD-associated bacteria, the Engulfment and cell motility protein-1 (ELMO1) enhances the expression of MCP-1 in epithelium which results in the recruitment and activation of monocytes to infection site. It also kills bacteria and thus aids in controlling high bacterial load [38]. Increased levels of MCP-1 as proinflammatory mediators have been seen in patients of Irritable bowel syndrome (IBS) also which is one of the gastrointestinal sickness [39].

6. MCP-1 in diabetes

Monocyte chemoattractant protein-1 plays a key role in insulin resistance, diabetes and its complications such as diabetic nephropathy, retinopathy. The level of circulating MCP-1 is significantly increased in type 1 and type 2 diabetes. MCP is an adipokine whose increased

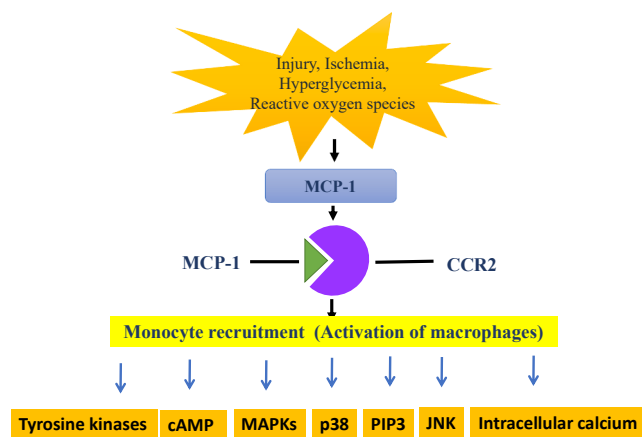


Fig. 3. Pathway for MCP-1 activation and subsequent signaling cascades involved.

expression by adipose tissue can induce insulin resistance and infiltration of macrophages into adipose tissue [40]. The insulin resistance due to obesity is a risk factor for type 2 diabetes [T2DM] which causes inflammation of adipose tissue mediated by the production of MCP-1 by adipocytes which results in recruitment of monocytes and activation of macrophages [41]. The polymorphisms of MCP-1 have been correlated with type 1 diabetes mellitus [T1DM] and the complications associated with it [42]. The serum level of MCP-1 was found to be higher in patients with type 1 diabetes mellitus than in healthy controls [43]. Another study has suggested the dual role of MCP-1 in T1DM where it was seen to be playing protective role against progression of T1DM with higher serum level in healthy controls than T1DM patients while in the same study diabetic complications were correlated with elevated MCP-1 serum levels [44]. MCP-1 has been associated with the renal tubular damage which is increased by heavy proteinuria thus contributing in progression of diabetic nephropathy [45]. There is elevation of MCP-1 serum level in diabetic nephropathy patients and has been suggested as biomarker for the same [46]. The urinary level of MCP-1 increases with progression of renal impairment in patients of T2DM [47]. Retinal neurons are the source of MCP-1 which activates retinal microglia implicating link to the pathogenesis of diabetes. In a diabetic retinopathy rodent model, it was found that the MCP-1 is upregulated in early

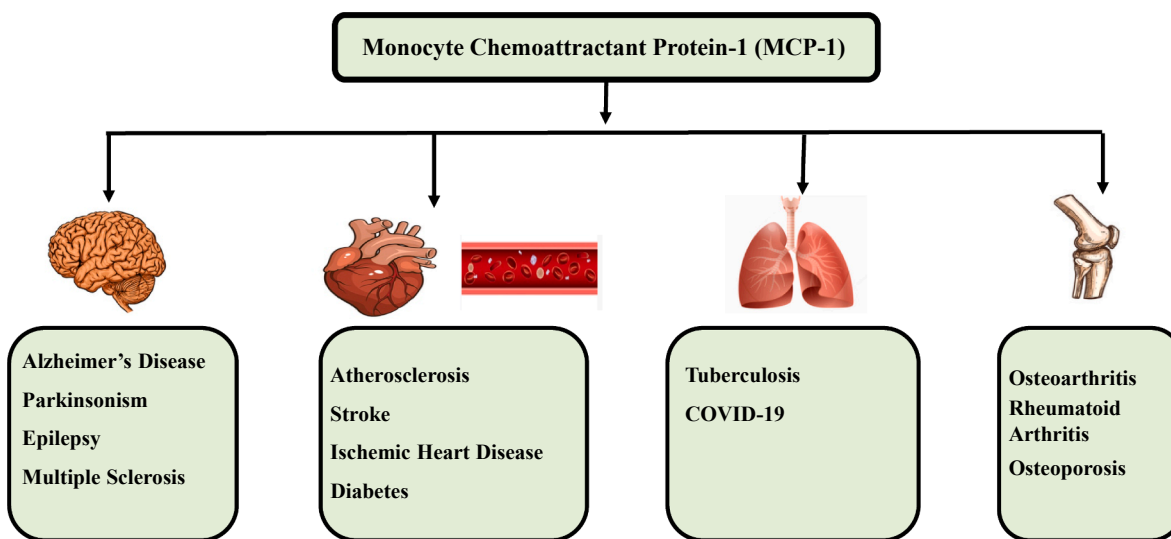


Fig. 2. Role of MCP-1 in disease. Over expressed MCP-1 causes dysfunction of microglia and astrocytes lead to brain disorders, Elevated amount of MCP-1 lead to activation of Th1 cell in Covid-19, MCP-1 regulate monocyte recruitment in inflammatory sites of joint disorders, furthermore MCP-1 is responsible for the migration of monocytes induces endothelial activation and dysfunction.

phase and increases with progression of disease [48]. Retinal resident cells (endothelial cells, Muller's cells, microglial cells) via production of MCP-1 have been suggested to be involved in inflammatory responses in vitreous and aqueous humor of diabetic retinopathy patients [49]. MCP-1 have been demonstrated in the treatment of diabetic wound healing by the restoration of macrophage response [50].

7. MCP-1 in immune responses

MCP-1 on binding to its receptors CCR2 activates cells such as monocytes and other immune cells that promote inflammation. It directs the leukocyte infiltration as well as effect proliferation of T cells and immune function. Unlike other chemokines which triggers Th1 phenotype, MCP-1 act as regulator in the polarization of Th0 cells toward a Th2 phenotype [4]. T1 and T2 both responses can be promoted by MCP-1 *in-vivo* which depends on some additional factors (MCP-1 induction timing, tissue site, type of pathogen) as reported in a study [51]. MCP-1 regulates the differentiation of monocytes into dendritic cells. It modulates Th1 immune response by selectively suppressing naïve T cells differentiation into Th1 effector cells by regulating IL-12 releasing ability of dendritic cells [52]. MCP-1 is involved in cytokine production by naïve Th cell. IL-4 production by T cells is augmented as MCP-1 can activate IL-4 promoter, which results in the enhancement of type 2 immune response [53]. MCP-1 produced by neutrophils in a Th1 microenvironment has been suggested to be involved in Th1 adaptive responses [54].

8. MCP-1 in cancer

Both tumor cells and stromal cells produce MCP-1 which recruits the macrophages to the tumor microenvironment in various cancers. In primary breast tumors, the TAM accumulation has been associated with MCP-1 expression which produces various angiogenic factors and promotes angiogenesis [55]. The expression of MCP-1 by stromal elements and parenchymal cells in human invasive ductal breast carcinoma has been demonstrated *in-vivo* [56]. The 4T1 cells can upregulate MCP-1 production by macrophages by the release of GM-CSF along with other mechanisms in tumor microenvironment [57]. The non-tumor stromal cell derived MCP-1 aids the lung metastasis of 4T1 breast cancer cells [58]. It has been shown that MCP-1 secreted by primary breast tumors stimulates the migration of mesenchymal stem cells [59]. The overexpression of MCP-1 induces cell invasion and metastasis leading to disease progression in triple negative breast cancer (TNBC) [60]. The MCP-1 deficient mice have shown the delayed mammary tumorigenesis, and decreased localized inflammation in TNBC model [61]. In TN- Inflammatory breast cancer MCP-1 is overexpressed and regulates the proteolytic activity by activating Src and Erk1/2 signalling pathways which leads to the invasion and metastasis [62].

MCP-1 induces invasion, migration and adhesion of SKOV-3 ovarian cancer cells. In primary ovarian cancer, there is elevated serum level of MCP-1 which also serves as a differentiation marker from benign ovarian cysts. MCP-1 act as an autocrine and paracrine factor in the proliferation and invasion of prostate cancer. It plays role in the prostate cancer growth by regulating macrophage infiltration and increased angiogenesis [63]. In another study, MCP-1 serves as a mediator along with increased NF- κ B activity in the monocyte-induced prostate cancer cell invasion [64]. Although MCP-1 expression and NF- κ B activity are correlated because of which they both are involved in mediating the prostate cancer cell invasion. Prostate cancer growth in bone is also promoted by the MCP-1/CCR2 axis activation where the MCP-1 serum level is elevated [65]. Even the MCP-1 derived from adipocytes has shown to promote prostate cancer cell progression [66]. MCP-1 deficient mice have lower metastasis in Lewis lung carcinoma which was fed high fat diet indicating the contribution of adipose-derived MCP-1 [67].

MCP-1 participates in tumor angiogenesis in esophageal squamous cell carcinoma and has been related to venous invasion, distant

metastasis or lymph node metastasis [68]. The pro survival signaling pathways comprising Akt, ERK, and/or STAT3 in the advancement of head and neck squamous cell carcinoma are modulated by MCP-1 [69]. In osteosarcoma, cancer cell migration and invasion are enhanced by MCP-1 through activation of MAPK, c-Jun, c-Raf, AP-1 pathway and upregulating production of matrix metalloproteinase-9 (MMP-9), suggesting prognostic value of this chemokine [70]. In a study done for pancreatic cell cancer showed different result from other cancers. This study reported that MCP-1 act as a negative regulator of the cancer progression where it opposed proliferation and increased pancreatic cancer apoptosis. Higher survival rates were seen in patients with high circulating MCP-1 levels than with low MCP-1 producers [71].

9. MCP-1 in respiratory tract infection

Novel Coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was originated from Wuhan, China. It was declared as pandemic by World Health Organization and has affected people globally. The current hallmark of this disease is "Cytokine storm" which reflects the elevated level pro-inflammatory cytokines and chemokines that may lead to other complications and may even also result in death. The role of MCP-1 has been seen in recent studies of COVID-19 where its serum level was elevated along with other inflammatory mediators. IL-6, IL-7, IL-8, IL-10, IL-18, G-CSF, M-CSF, MCP-1, MCP-3, IP-10, TNF α , IFN γ and MIP-1 α serum levels have been associated with the severity of the disease although in other study the serum level of MCP-1 and IP-10 was greater in critically ill patients of COVID-19 than that of severe patients [72]. The mediators of IL-1 pathway IL-18, MCP-1 and VEGF-A were upregulated in critically-ill patients [73]. The patients infected with novel coronavirus have elevated amount of IFN γ , IP10, and MCP-1 which may lead to activation of T-helper-1 (Th1) cell responses [74]. IL-6 *trans*-signalling enhances production of IL-6, IL-8, MCP-1 and IL-10 in cytokine release syndrome (CRS). Although serum level of MCP-1 and others is relatively lower in COVID-19 mediated CRS than in bacterial CRS [75]. Acute kidney injury development in critically ill COVID-19 patients has been associated with raised levels of IL-6, IL-8, IL-17a, IP-10 and MCP-1 [76]. Elevated IL-6, MCP-1, IP-10 and IL-1ra have been correlated with respiratory failure in COVID-19 [77]. COVID-19 cases with an unfavourable evolution have significantly higher expression of MCP-1, suggesting its predictive value as marker [78]. The elevated level of this chemokine has been detected in COVID-19 patients and proven to be a biomarker associated with the extremity of disease and death risk along with IP-10 [72].

In comparison to healthy control subjects, bronchoalveolar lavage fluid from patients with active pulmonary tuberculosis contained elevated levels of RANTES, MCP-1 and IL-8 indicating their participation in host response to Mycobacterium tuberculosis (MTB) infection [79,80]. Multiple chemokines can therefore be involved in recruiting cells for the formation of granuloma in tuberculosis [79]. In a recent study, MCP-1 was among the cytokines which exhibited substantial variation between healthy controls and patients of active tuberculosis [81]. MCP-1 expression is elevated in the blood and at the site of human tuberculosis disease. Macrophages are the predominant source of MCP-1 [82]. The data from another study indicate that expression of MCP-1 in patients with TB is not exceptionally augmented systemically, while production of MCP-1 may be enhanced by monocytes in the chronic stage of TB or with local pleural infection [83]. A study reported that reduced immune function in spinal tuberculosis is correlated with greater expressions of MCP-1 and NF- κ B [84]. CCL2 has been suggested to be a helpful adjunct marker of tuberculosis severity [85]. MCP-1 is a biomarker with high diagnostic efficacy which can reflect variation in different stages of MTB infection. In active tuberculosis, better diagnostic performance of MCP-1 in peripheral blood has been observed and therefore suggested as ancillary diagnostic target of active tuberculosis. It can be also diagnosed and differentiated from latent tuberculosis by

MCP-1 [86,87].

10. MCP-1 in other infection

Regardless of the dual role of MCP-1 in infectious disease, our comprehension of how the chemokine is controlled throughout infection is limited. High MCP-1 serum levels are identified during the intense period of the infection in humans and laboratory animals and correspond with the viremic period [88]. It has been recently proposed that IFN β -stimulated the increment of MCP-1 can add to the MCP-1-mediated inhibition of the CCR2 expression and subsequently decrease the responsiveness of monocytes to this chemokine [89]. The antibacterial impacts of MCP-1 appeared to be mediated through regulation of IFN-g production, just as by stimulating monocyte and DC recruitment to the airways. Furthermore, MCP-1 and CCR2 were discovered to be significant for controlling the scattering of *B. mallei* from the lungs to extrapulmonary destinations following beginning pneumonic contamination [90]. During one examination related to research part of MCP-1 in improvement of Hapten-induced colitis has insufficient MCP-1. This was associated with a down regulation of myeloperoxidase activity, IL-1, IL-12p40, and IFN- α production and macrophages in the colonic mucosa. Likewise, the outcomes noticed altogether lower quantities of 5-HT-expressing EC cells in the colon of MCP-1-deficient mice compared with those in wild-type mice after dinitrobenzene sulfonic acid. These outcomes give proof of the critical role of MCP-1 in the development of colonic inflammation in this model in the context of immune and enteric endocrine cells. Hyperoxia-mediated lung infection and septic peritonitis models has revealed that treatment with anti-MCP-1 antibody diminishes leukocyte penetration in the lungs and peritoneum independently. Till now studies have suggested that anti-MCP-1 treatments is essentially diminished penetration of macrophages into the lungs after influenza virus infection. Blocking MCP-1 diminishes neutrophil population and MPO level in bronchoalveolar lavage. Besides, MCP-1 encourages the pulmonary recruitment of CD81T cells that are essential in host defense against viral infection. Thus, diminished MCP-1-dependent CD81 T cell recruitment may likewise add to the observed pathologic effects [91].

11. MCP-1 in brain disorders

Over the years, MCP-1 has emerged as an important chemokine playing pivotal role in many CNS disorders specially in those which involves inflammation. Chronic inflammation has a key function in the onset and progression of neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), and Multiple Sclerosis (MS) [92]. The progressive neurodegenerative disease in elderly, Alzheimer's disease (AD) is distinguished by the presence of amyloid plaques and neurofibrillary tangles in brain. There is upregulation of chemokines, which are associated with pathogenesis of Alzheimer's disease. MCP-1 is found in senile plaques and reactive microglia in AD [93]. MCP-1 serum levels are elevated in mild cognitive impairment (MCI) and mild AD, which lowers during progression of disease [94]. Although another study suggested somewhat different result from this where elevated plasma MCP-1 levels were correlated with the faster cognitive decline and greater severity of the disease [95]. MCP-1 is a reliable predictor of AD and plays a major role in chronic inflammation in disease process [96]. Cerebrospinal fluid (CSF) levels of MCP-1 are significantly higher in AD patients and it is positively correlated to p-tau, β -amyloid levels in CSF [97]. The CSF MCP-1 levels are also linked to the brain atrophy and cognitive impairment in AD where its overexpression leads to aggregation of β -amyloid and senile plaques have been suggested [98]. The interaction of MCP-1 and another chemokine eotaxin-1 elevated level have been negatively associated with verbal and visual memory in MCI and AD [99]. In a study with asymptomatic older adults, verbal episodic memory declined with time due to increase in longitudinal MCP-1 levels [100]. A recent finding suggested the role of MCP-1

in AD and other tauopathies due to the overexpression of MCP-1 in brain, which enhances glial activation and expedites tau pathology with elevated levels of tau in hippocampus [101]. The urinary MCP-1 has can be used as a potential biomarker of AD as it can differentiate patients with AD and amnesic MCI from normal subjects [102].

The neurodegenerative disorder with characterization of progressive loss of neurons in substantia nigra and other regions of brain is known as Parkinson's disease (PD). The neuroinflammation is associated with PD and various pro-inflammatory cytokines play role in this process. MCP-1 has been correlated with the PD progression and maybe used for predicting motor dysfunction in the disorder [103]. MCP-1 levels have been found to be elevated in the CSF in studies for PD suggesting its role in the progression. MCP-1 is a marker for microglia activation and was associated negatively with the disease duration [104]. One study has found the correlation between MCP-1 and non-motor symptoms especially with severe symptoms of depression [105]. Another study reported there is increase of monocytes in the blood of PD patients along with increase in MCP-1 level [106]. MCP-1 has been suggested to be a potential biomarker for the PD progression [107].

In another neurodegenerative disorder, Multiple Sclerosis (MS) the role of MCP-1 has been seen but the results varied in different studies. A study suggested that MCP-1, adipokines and adiponectin play role in the progression of MS and are potential biomarker for the same [108]. With different subtypes of the MS, the MCP-1 can get modified. This study reported that the level of MCP-1 was lower in CSF and serum of MS patients [109]. In primary progressive MS (PPMS), the intrathecal synthesis and the concentration of MCP-1 is elevated which implicates its role in pathogenesis [110]. The astrocytes and microglia expressed MCP-1 and its receptor at the rim of lesion with ongoing demyelination in the brain of secondary progressive MS (SPMS) patients in a study suggesting its contribution in the neurodegeneration of the disease [111].

Epilepsy is a chronic neurological disorder characterized by the recurrence of seizures. During increased seizure frequency there is upregulation of MCP-1 [112]. After status epilepticus, the CCL2-CCR2 signalling causes neurodegeneration through STAT3 activation and IL-1 production. The seizure induced neurodegeneration in the hippocampal region was reduced in CCL2/CCR2 deficient mice [113]. The MCP-1 and CCR2 contributes in the pathogenesis and progression of intractable epilepsy as their expression is upregulated in neurons and glia in epileptogenic zone [114]. In a recent *in-vivo* study of ischemic stroke, the MCP-1 was seen to be upregulated in rats while its down-regulation reduced the neurological impairments, inflammatory response, and ischemic infarct area indicating the contribution of MCP-1-chemokine signalling pathway in ischemic stroke progression [115]. MCP-1 plasma level has been suggested as biomarker as early predictors of cerebral ischemic stroke which is usually elevated in patients of ischemic stroke [116]. In secondary brain injury after Intracerebral Haemorrhage (ICH), chemokine MCP-1 and its receptor CCR2 play a significant role [117]. It leads to disruption of blood brain barrier by mediating the p38 MAPK signalling pathway [118].

12. MCP-1 in joint and bone disorders

Osteoarthritis (OA) is a most common form of arthritis which is a joint disorder. The patients of OA have higher level of MCP-1 in synovial fluid [119]. During OA pathogenesis, MCP-1 is the principal regulator of monocyte recruitment into inflammatory sites [120]. A study demonstrated that monocytes recruited by MCP-1/CCR2 are responsible for tissue damage and inflammation in OA [119]. Another study for knee osteoarthritis reported that the ligand-receptor axis of MCP-1-CCR2 plays a distinctive role in the induction and advancement of OA pathology [121]. The MCP-1 and its receptor have been found to be expressed in both normal and OA chondrocytes whose production is regulated by IL-1b and TNF- α , which may contribute in the cartilage degradation of OA [122]. Adipokine Resistin was seen increasing the production of MCP-1 in human synovial fibroblasts and encouraging

migration of monocytes [120]. In a study, MCP-1 and RANTES were expressed by synovium at elevated amounts compared to meniscus cultured, in both early and end-stage OA patients [123]. The pain associated with experimental osteoarthritis is mediated by the CCL2-CCR2 pathway while the TGF- α -CCL2 axis is involved in progression of experimental post traumatic osteoarthritis [124,125].

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by the pain and inflammation of the joints. The levels of MCP-1, IL-6 and IL-1 β in RA are substantially higher, suggesting that people with RA have a chronic inflammatory immune status [126]. MCP-1 is produced by the synovium of various inflammatory joint disorders. The findings of a study revealed that synovial release of MCP-1 can play an important role in the recruitment of monocytes during RA-associated inflammation and that the dominant source of this cytokine is synovial tissue macrophages [127]. Later another study confirmed that MCP-1 and other proinflammatory cytokines released by rheumatoid synovium contribute to the immunopathogenesis of RA [128]. In serum of RA patients with follicular synovitis (FS), the concentrations of IL-8, RANTES, and MCP-1 were relatively higher than those with diffuse synovitis confirming greater disease activity in FS [129]. The chemokine signalling pathway (CCL4/CCR5/c-Jun and c-Fos/CCL2) is involved in CCL2 expression, which may lead to RA-associated chronic inflammation [130].

Another disorder in which MCP-1 plays a role in osteoporosis, a prevalent condition that is characterized by reduction in bone mineral density (BMD) and greater fracture risk. The MCP-1 serum levels are inversely associated with the bone mass density. It may be clinically important along with CXCL1 for early detection and prevention of osteoporosis as it can predict early bone loss [131]. By impacting the development and activation of OCs, MCP-1 plays a significant role in bone remodelling as it was demonstrated in a study done on MCP-1-KO mice who had higher bone mass than the wild type mice [132]. In cancer-induced bone pain in rats, the production of MCP-1 is regulated by NF- κ B signaling pathway [133].

13. MCP-1 in endothelial dysfunction

The endothelial function is essential for the homeostasis of the body and its dysfunction is correlated with several pathophysiological conditions, including atherosclerosis, hypertension and diabetes. Endothelial cells control cellular adhesion, thromboresistance, proliferation of smooth muscle cells, and inflammation of the vessel wall by generating a broad variety of factors. The disrupted bioavailability of NO is the characteristic of endothelial dysfunction [134]. Vascular endothelium injury contributes to the inflammation by secretion of cytokines and chemokines (MCP-1) and to the expression of adhesion molecules by endothelium damage. MCP-1 activation of CCR2 has been observed to be responsible for vascular endothelium renewal after injury, angiogenesis, and collateral formation [135]. The MCP-1 is responsible for the migration of monocytes to the sub-endothelium and attracting leucocytes to the site of injury, thus facilitating atherogenic and thromboembolic potential. The monocytes get matured as macrophages, releasing cytokines, and combine with the accumulated oxidized LDL to form foam cells. The smooth muscle cells also proliferate and migrate to the sub-endothelial space due to the effect of proinflammatory cytokines and growth factors interaction [136]. There is formation of fatty streak which eventually leads to atherosclerotic plaque. The MCP-1 level in human atherosclerosis have been correlated with plaque vulnerability [137]. Recently, MCP-1 was seen to be involved in the endothelial dysfunction associated with COVID-19 [138].

14. MCP-1 in liver diseases

MCP-1 is involved in various hepatic disorders and impairments include hepatic fibrosis, liver cirrhosis, hepatitis, hepatic steatosis, liver cancer associated fibroblast and other liver diseases. Chemokines (MCP-

1/CCL2) and chemokines receptor (CCR2) meditates the inflammatory cells results in the recruitment of extra hepatic cells which causes hepatic fibrosis. Hepatic stellate cells (HSCs) are activated due to the up regulation of MCP-1 which initiates the progression of chronic liver injury. Liver cell necrosis, deposition of fibrins and DNA alterations are induced by chemokines system (MCP-1) through expression of CD4, CD8 cells, TH cells and NK cells leads to the hepatic tumour progression and hepatocarcinogenesis [139]. Whether selective elimination or pharmacological inhibition of CCR2 leads to lower immune cell activation and decreased liver fibrosis in mouse models of liver cirrhosis. In addition, the enhanced proportion of MCP-1/CCR2 macrophages in visceral adipose tissue in obese patients is correlated with the histological disease severity of non-alcoholic steatohepatitis. Other very significant potential causes of hepatocellular carcinoma include chronic liver disease and cirrhosis associated with viral hepatitis and excessive alcohol consumption. There is an expectation that after the hepatitis C virus infection, the amount of MCP-1/CCL2 would be increased to induce immunity against viral proteins, therefore CCL2 should begin to be operated by mir122 (predominant liver specific miRNA), which will be regulated by the virus as per its genetic variant [140]. A primary occurrence associated with liver damage caused by viruses and other inflammatory agents is fibrosis. These were characterized by intense accumulation into Dese of extra-cellular matrix components including collagens, fibronectin and proteoglycan and decreased amounts of metalloproteinase tissue inhibitor, extracellular matrix eliminating metalloproteinase matrix [141].

15. MCP-1 as a diagnostic marker

With potential involvement of MCP-1 in various pathological conditions many research also indicate that MCP-1 can be a tool for diagnosis of level of inflammation in many diseases. MCP-1 acts a diagnostic marker in urinary diseases, such as lupus nephritis where the level of urinary MCP-1 becomes elevated as compared to the control subjects. Determination of concentration of urinary MCP-1 is reliable and non-invasive method for lupus nephritis due to its inflammatory activity [142]. The ratio of MCP-4/MCP-1 in plasma is also a circadian diagnostic biomarker for the chronic post-traumatic stress disorder because hypothesis suggests that proinflammatory cytokines and chemokines in plasma might be mediators of psychophysiological mechanisms relating changes in behaviour and mental health disorder and medical morbidity [143]. MCP-1 also acts as a diagnostic marker in the liver fibrosis associated with transient myeloproliferative disorder in Down syndrome [144].

16. Conclusion

In summary, MCP-1 is an important chemokine which plays a crucial role in a number of pathological conditions such as cardiovascular diseases, brain pathologies, bone and joint disorders, respiratory infections, cancer, and endothelial dysfunction. The contribution of MCP-1 has been seen in the recent novel corona virus disease (COVID-19) also, which claimed millions of lives. The role of this chemokine is pivotal in inflammation, the MCP-1 binds to its receptor CCR2 and thus activating the signalling pathways which regulates the migration of cells (Fig. 4). By fostering leukocyte recruitment, MCP-1 is involved in protective immune responses during infections [145-147]. MCP-1 influence the activity of NF- κ B pathway, Akt signalling pathway, ERK pathway and several others that affect the development and progression of diseases specially in cancer. It has been suggested as a potential prognostic and diagnostic biomarker with appropriate levels of MCP-1 in numerous disorders thus emphasizing on its significance. While the involvement of the MCP-1/CCL2-CCR2 axis in the pathogenesis of various diseases has been demonstrated in multiple studies, there are lot of clinically available drugs targeting this axis. The drugs designed for manipulating the expression of MCP-1 or CCR2 to achieve the beneficial effects have to be

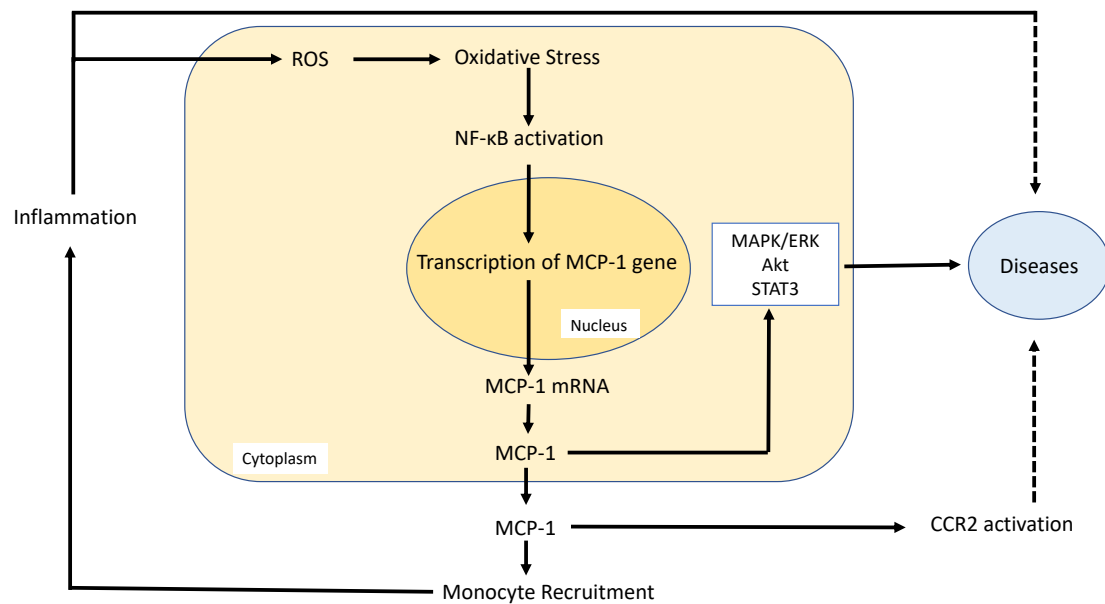


Fig. 4. Expression of MCP-1 mediated by oxidative stress and NF-κB activation. MCP-1 promotes monocyte recruitment to the site of inflammation in diseases. It is involved in progression of various disorders by activating its receptor CCR2 and signalling pathways which promotes migration of cells.

closely controlled due to its role in immunity and health maintenance.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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