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Monocyte Chemoattractant Protein 1 (MCP-1) in Obesity and Diabetes

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Abstract

Monocyte chemoattractant protein-1 (MCP-1) is the first discovered and most extensively studied CC chemokine, and the amount of studies on its role in the etiologies of obesity- and diabetes-related diseases have increased exponentially during the past 2 decades. This review attempted to provide a panoramic perspective of the history, regulatory mechanisms, functions, and therapeutic strategies of this chemokine. The highlights of this review include the roles of MCP-1 in the development of obesity, diabetes, cardiovascular diseases, insulitis, diabetic nephropathy, and diabetic retinopathy. Therapies that specifically or non-specifically inhibit MCP-1 overproduction have been summarized.

Keywords

MCP-1; inflammation; obesity; diabetes; diabetic complications

1. HISTORICAL PERSPECTIVES OF MONOCYTE CHEMOATTRACTANT PROTEIN-1

1989 witnessed the birth of Monocyte Chemoattractant Protein-1 (MCP-1) into the light of scientific investigation at the National Cancer Institute, Maryland, USA. This protein was initially identified from the conditioned media of human myelomonocytic cell line as the monocyte chemotactic factor (MCF) [1]. It was further named as monocyte chemotactic and activating factor (MCAF), which was found to be rapidly produced in normal human dermal fibroblasts in response to the stimuli of interleukin 1 (IL-1) or tumor necrosis factor (TNF) [2]. Using glioma cells [3, 4] and stimulated mononuclear leukocytes [5], this protein was sequenced and cloned, and was found to consist of 76 amino acids and four cysteine residues [6], and named as MCP-1 for the first time [3]. It is worth pointing out that in the same year this protein was also cloned and sequenced in Japan under the name of MCAF [7].

Due to its high abundance and ubiquitous production, MCP-1 is the first discovered and most extensively studied human CC chemokine, which is characterized by the conserved

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position of four cysteine residues (with the first two adjacent to each other) forming intra-molecular disulphide bridges to stabilize peptide folding [8]. Therefore this protein is also known as Chemokine (C-C motif) ligand 2 (CCL2). Human MCP-1 is located on chromosome 17 (chr.17, q11.2) [9], with a putative molecular weight of 8,685 Da [8]. Mouse JE/mouse MCP-1 is thought to be the homologue of human MCP-1, with 49 more amino acids at the carboxy-terminal end, increasing its putative molecular weight to 13,848 Da [8]. Glycosylation of MCP-1 resulted in higher molecular weight and slightly reduced the chemotactic potency [10]. The main receptor used by MCP-1 is CCR2, consisting of two isoforms, CRR2A and CCR2B, derived from a single gene via alternative splicing, and differ in their terminal carboxyl tails [11]. CCR2B is the predominate form in human monocytes, and the gene expression levels of both CCR2A and CCR2B decreases as the monocytes differentiated into macrophages [12].

2. TRANSCRIPTIONAL REGULATION OF MCP-1

Expression of MCP-1 is ubiquitous in various cell types and is upregulated by a wide variety of stimuli. The list of MCP-1-producing cell types grew rapidly after the aforementioned pioneer studies in 1989 [13-18]. A summary of MCP-1-producing cell types and stimuli can be found in Table 3 in a review by Van Collie et al. [8]. In addition, adipocytes have been recognized as an important source of MCP-1[19, 20].

Human MCP-1 gene consists of 3 exons of 145, 118 and 478 bp in length, and 2 introns of 800 and 385 bp in length. In 1990 Shyy et al. reported two phorbol ester responsive elements (TRE) 129 and 157 bp upstream from the translation initiation site, and the upregulation of MCP-1 expression in cultured endothelial cell after phorbol ester treatment [21]. Subsequently Ueda et al. [22] identified two remote kappa B binding sites known as A1 (−2640/−2632) and A2 (−2612/−2603). A2 was found to be important for enhancer activity induced by IL-1β, TNF-α, and 2-O-tetradecanoylphorbol 13-acetate (TPA). One GC box (−64/−59) was also found important for the maintenance of basal transcriptional activity, and can possibly be controlled by Sp1. A graphical summary of the transcriptional regulatory elements of human MCP-1 gene is shown in Figure 1. Further studies by Ueda et al. [23] revealed that lipopolysaccharide (LPS) stimulation induces the binding of p65/p65, c-Rel/p65, p50/p65, and p50/cRel to the A2 probe and increase of MCP-1 mRNA in human acute monocytic leukemia THP-1 cells, while TPA treatment on this cell line only resulted in the binding of p65/p50 to A2 probe, but not increase of MCP-1 mRNA. However, TPA treatment on other human cell lines such as cervical carcinoma HeLa, osteosarcoma HOS, and glioblastoma A172 cells induced both binding of p65/p65 and cRel/p65 to A2 probe, and elevated MCP-1 mRNA levels. Co-transfection of p65 or p65/cRel with hMCP-1 showed trans-activation. Thus stimulus-specific and tissue-specific regulation on human MCP-1 gene has been emphasized [22, 23].

In rat JE gene, the −141/−88 promoter region is reportedly responsive to the phorbol ester TPA, and the −70/−38 promoter region is essential for basal activity. The later region harbors the sequence TGACTCC, resembling the consensus site for AP-1 binding TGACTCA. The JE AP-1 site and the consensus AP-1 site have an overlapping but not identical binding spectrum for AP-1 proteins [24]. Hanazawa et al. reported that TNF-α induces JE expression via c-fos and c-jun genes following protein kinase C activation in mouse osteoblastic MC3T3-E1 cells, and curcumin, a specific inhibitor of c-jun/AP-1, markedly inhibited JE gene expression induced by the cytokine [25]. Ping et al. further reported that TNF regulates the occupancy of both distal and proximal regulatory regions of murine JE gene, and demonstrated a multi-step model involving chromatin accessibility, transcription factor complex assembly, and protein phosphorylation [26]. In a subsequent report from Ping et al. [27] it was shown that two distal kappa B sites, a novel

dimethylsulfate-hypersensitive sequence, and a promoter proximal Sp1 site were required for TNF induction, and illustrated a crucial role of p65 in the assembly of a NFκB dependent enhancer in vivo.

The regulation of MCP-1 gene expression in pancreatic islets has been extensively studied due to its clinical relevance (refer to Section 7). Reported regulatory factors include primary inflammatory cytokines (i.e. IL-1β, TNFα), lipopolysaccharide, ERK1/2 and p38 MAPK, but not glucose or nitric oxide [28, 29]. An IL-1β-responsive enhancer region has been identified between −2180 bp and −2478 bp of the MCP-1 gene in rat β-cells, which contains two NF κB sites binding to p65/p50 heterodimers and p65 homodimer. Mutation of either NFκB sites present in this region abrogated IL-1 β-induced MCP-1 promoter activity. Therefore NFκB plays an important role for MCP-1 expression in β-cells [30]. The lack of expression of the transcriptional repressor B-cell lymphoma-6 (BCL-6), which inhibits MCP-1 gene expression and NF κB activity, may render β cells particularly susceptible to propagating inflammation [31]. The primary cytokines reportedly induce the expression of I κB isoforms and MCP-1 several fold higher in rat INS-1E cells than in fibroblasts 208F cells, and correlate with a proapoptotic outcome [32]. Angiotensin II (AngII) is another factor regulating the expression of MCP-1 in rat RINm5F β-cell line and activating MCP-1 promoter, possibly through a MAPK signaling mechanism [33].

Role of hypoxia in MCP-1 expression in brain, cardiovascular system, and adipocytes has been reported. Human MCP-1 was found regulated by hypoxia-inducible factor −1 (HIF-1) in astrocytes [34], and upregulation of MCP-1 expression in neurons induced by hypoxic preconditioning protected mice from stroke [35]. Chronic intermittent hypoxia also upregulated MCP-1 expression in the carotid body in rats [36]. Controversial results were documented regarding the responses of adipocytes to hypoxic condition. For example, Yu et al. [37] showed upregulation of MCP-1 mRNA and protein expression in mouse 3T3-L1 adipocytes under 1% O_2 atmosphere. In contrast, Famulla et al. [38] reported that the same hypoxic condition reduced the secretion of MCP-1 from human primary adipocytes.

Other than transcriptional regulation, glucocorticoids have been reported to trigger the specific binding of glucocorticoid receptor to MCP-1 mRNA, facilitating the mRNA degradation [39]. Multiple studies have reported parallel increases of mRNA, protein, and monocyte chemotactic activity of MCP-1 [14, 15, 17].

3. MCP-1 AND OBESITY

A Pubmed keyword-guided literature search showed a linear increase of the number of publications related to “MCP-1” during the period of 1989 - 2010, while an exponential increase of the percentages of these publications pertaining to either “obesity” or “diabetes”, implicating a rapidly growing interest in the pathological role of this chemokine under obese and diabetic conditions.

Obesity is a result of expansion in both number and size of adipocytes. The gene expression of CC chemokines and their receptors (such as MCP-1 and CCR2) was found higher in the visceral and subcutaneous adipose tissues of obese patients compared to lean controls [19]. Furthermore, MCP-1 protein expression was higher in omental fat than in subcutaneous fat in severely obese patients, which was paralleled by elevated macrophage infiltration into omental fat [20]. The plasma level of MCP-1 has been generally found increased in obese adults [40] and obese children [41] compared to lean controls. It correlated with the number and volume of omental adipocytes in baboos [42], and was similarly affected by visceral adiposity in human [43]. The high levels of circulating MCP-1 in obese patients were further increased by fructose consumption [44], reduced by low-glycemic index diet [45], and mediated by parathyroid hormone [46]. In addition, 1α, 25-dihydroxycholecalciferol, the

hormonally active form of vitamin D, was reported to attenuate MCP-1 production in human adipocytes [47]. Similarly, plasma MCP-1 was found high in obese mice in comparison to lean controls [18, 48], and this increase was suppressed by COX2 inhibitors [49]. Systemic administration of MCP-1 in mice induced insulin resistance, and this adverse effect was ameliorated by a CCR2 antagonist without affecting macrophage infiltration into adipose tissue [50].

Furthermore, MCP-1 signaling has a direct role in the development of obesity. For example, Younce et al. reproted that MCP-1-induced protein (MCPIP, a zinc finger protein) induced adipogenesis in 3T3-L1 cells independent of PPARgamma activation [51]. Mice with CCR2 deficiency had attenuated deposition of visceral fat and insulin resistance when challenged with a high fat diet [52]. Moreover, MCP-1 had angiogenic effect on endothelial cells [53], and therefore it can contribute to the expansion and remodeling of adipose tissues.

Efforts have been exerted to inhibit MCP-1 over-production and ameliorate obesity-related syndromes, such as insulin resistance and type 2 diabetes. As summarized in Table 1, a significant portion of the studies was on plant-based extracts and compounds; other studies also included bacterial-derived compounds, trace elements, antioxidants, synthetic ligands and commercial drugs.

4. MCP-1 AND TYPE 2 DIABETES

Type 2 diabetes comprises 95% of diabetic cases and its etiology is closely related to obesity and insulin resistance. Circulating MCP-1 has been found significantly increased in patients with type 2 diabetes [80-84].

A common A/G polymorphism located at position –2518 in the distal regulatory region regulates MCP-1 expression [85]. In a large cohort of German Caucasians, the MCP-1 G-2518 gene variant was found significantly and negatively correlated with plasma MCP-1 levels and the prevalence of insulin resistance and type 2 diabetes [84]. Similarly, reports from Turkey and China also documented decreased prevalence of type 2 diabetes in populations with MCP-1 G-2518 genotype [86, 87]. A study in Japan reported that there was no association between this single-nucleotide polymorphisms (SNP) and type 2 diabetes, but Japanese obese diabetic −2518AA carriers had a higher MCP-1 concentration and increased insulin resistance than obese diabetic −2518G carriers [88]. In contrast, another Germany-based study reported that the genotype frequencies were similar in diabetic and non-diabetic subjects and were not related to MCP-1 levels [83]. Interestingly, the MCP-1 −2518 AG + GG polymorphisms were found positively associated with the prevalence of diabetic retinopathy [89] and the risk of developing carotid atherosclerosis [90]. The role of A-2518G polymorphism in diabetic nephropathy is under debate. For example, Ahluwalia et al. reported that −2518GG in co-occurrence with CCR5 (DD) and MMP9 (279Gln/Gln) conferred a tenfold increased risk of nephropathy among type 2 diabetics in Indian population [91]. In contrast, Moon et al. found that carriage of A allele significantly associated with increased diabetic kidney failure in Korean patients [92]. While another study carried out in Korea reported that there were no association of MCP-1 promoter SNP with diabetic end-stage renal disease [93].

5. DIABETIC COMPLICATION - CARDIOVASCULAR DISEASE

Diabetes is associated with accelerated rates of atherosclerosis. MCP-1 attracts monocytes to the inflammatory sites of vascular subendothelial space, initiating migration of monocytes into the arterial wall to form excessive macrophage-derived foam cells. Large population-based studies showed significant correlation between circulating MCP-1 and other traditional risk factor for atherosclerosis, such as serum high-sensitivity C-reactive protein

(hsCRP), plasma fibrinogen, and combined carotid artery intimal-medial thickness [81, 94, 95]. High level of MCP-1 mRNA was observed in epicardial adipose stores in patients with critical coronary artery disease (CAD) [96]. Elevated MCP-1 was also found to correlate with atherosclerosis-associated complications, including ischemic stroke [97], myocardial infarction [95, 97], and cardiovascular disease mortality [81]. The correlations appear to be stronger in obese individuals [81, 98] than in those of normal body weight [99]. High levels of plasma MCP-1 have been found to independently associate with mortality after acute coronary syndromes [100], and adverse outcome in advanced heart failure [101], and therefore can be potentially considered as a prognostic marker.

A transgenic mouse study demonstrated that cardiac-specific expression of MCP-1 caused transcriptional activation of a cluster of ER stress-related genes during the development of ischemic heart disease [102]. In another study, cardiomyocyte-targeted expression of MCP-1 was found in the nuclei of apoptotic cells and caused heart failure in mice [103]. The apoptotic effect of MCP-1 was attributed to MCPIP, which induced the expression of apoptotic gene families and activate caspase-3 [103].

5.1 High glucose concentrations and MCP-1

Hyperglycemia is the major cause of diabetic angiopathy. High glucose treatment on endothelial cells isolated from diabetic subjects resulted in a 40-70% increase of MCP-1 release, and a 10-20% increase of the basal expression of vascular cell adhesion molecule-1 (VCAM-1), indicating synergistic enhancement on the monocyte-endothelial cell interaction [104]. Similarly, high glucose treatment on human aortic smooth muscle cells (SMC) upregulated the expression of MCP-1 and fractalkine leading to increased monocyte-SMC adhesive interactions by a mechanism involving activation of MAPK, AP-1 and NFκB [105]. Up to 7 days of chronic incubation of human umbilical vein endothelial cells (HUVEC) with high glucose increased mRNA expression and production rate of MCP-1 in a time- and concentration (10-35 mM)-dependent manner, through upregulation of reactive oxygen species (ROS) generation and subsequent activation of p38 MAPK [106]. Consistent with previous reports, exposure of human endothelial ECV304 cells to high glucose for 24 h caused an increase of MCP-1 and intercellular adhesion molecule-1 (ICAM-1), and promoted cell adhesion between monocyte and ECV304 cells [107]. Furthermore, high glucose treatment on human acute monocytic leukemia THP-1 cells increased both mRNA and protein levels of MCP-1, enhanced the adhesion of THP-1 cells to endothelial cells, and the pathways reportedly involved oxidative stress, protein kinase C, ERK1/2, and p38 MAPK [108]. Other than interact with endothelial cells, high glucose concentrations can also induce cardiomyocyte death. Exposure of H9c2 cardiomyoblasts and primary rat cardiomyocytes to a high glucose concentration resulted in elevated MCP-1 production and MCPIP expression, and subsequently led to ROS production, endoplasmic reticulum (ER) stress, autophagy, and cell death [109].

5.2 Low-density lipoprotein (LDL) and MCP-1

The progression of diabetic atherosclerosis entails complex interactions between the modified low-density lipoproteins (LDL) and the cells of the arterial wall. LDL and intermediate density lipoprotein (IDL) isolated from type 2 diabetic subjects induced the mRNA expression of MCP-1 in cultured human endothelial cells, possibly through the activation of NFκB pathway. The increment of MCP-1 mRNA content was positively correlated with haemoglobin A1C (HbA1c, a biomarker of hyperglycemia) and lysophosphatidylcholine (LPC, potential atherogenic molecular species [110]) content in the lipoprotein, negatively correlated with diene formation lag time (a marker of oxidizability of the lipoprotein), and inhibited by antioxidants probucol, alpha-tocopherol, and

deferoxamine. These data indicate that oxidatively modified lipoproteins found in diabetic plasma stimulate MCP-1 gene expression in endothelial cells [111].

When total LDL obtained from type 1 diabetic subjects was subfractionated into electropositive LDL(+) and electronegative LDL(−) by anion exchange chromatography, LDL(−) increased the release of MCP-1 and interleukin 8 (IL-8) in endothelial cells by two folds, suggesting an inflammatory role [112]. In comparison to LDL(+), LDL(−) had higher triglyceride, non-esterified fatty acids, apoE, apoC-III and platelet-activating factor acetylhydrolase (PAF-AH), as well as lower apoB relative content, but no evidence of increased oxidation. When LDL(−) was studied in type 2 diabetic patients, it was found that the proportion of LDL(−) was increased in plasma from these patients compared to control subjects and was not modified after glycemic optimization. LDL(−) from the patients presented low binding affinity to the low-density lipoprotein receptor (LDLr) in cultured fibroblasts compared to LDL(+), and 2-3 folds of increased ability to release MCP-1 and interleukin-8 (IL-8) in endothelial cells [113].

In comparison to native LDL, glycoxidized LDL and LDL modified by phospholipase A2 (PLA2) have higher contents of lysophosphatidylcholine (lyso-PC), and induce upregulation of MCP-1 mRNA expression through NFκB activation in HUVEC. In both in vitro and human studies, palmitoyl- and stearoyl-lyso-PC contents correlated with MCP-1 expression and NFκ B activity [114, 115]. Moreover, LDL isolated from diabetics contained more lyso-PC than that from nondiabetic subjects, and induced higher MCP-1 mRNA expression and NFκ B activity in HUVEC [115].

Hyperglycemia and the associated formation of advanced glycation end-products (AGE) and AGE-modified low-density lipoproteins (AGE-LDL) can directly affect the cells of the vascular wall. Exposure of human vascular smooth muscle cells (hSMC) to AGE-LDL, in comparison to native LDL, induced increased MCP-1 gene expression (+160%) and protein secretion (+300%), increased NADPH oxidase activity (+30%) and ROS production (+28%) by up-regulation of NOX1, NOX4, p22phox and p67phox expression [116]. Similar effects were observed in human endothelial cells (HEC): AGE-LDL induced an oxidative stress and increased MCP-1 mRNA and protein [117]. Microarray and reverse transcription real-time PCR analyses revealed that AGE-LDL significantly increased levels of CCR2 mRNA in human macrophages compared with native LDL, an effect accompanied by increased levels of CCR2 protein, mediated by the receptor for AGE (RAGE). Exposure of THP-1 cells to AGE-LDL increased MCP-1-medicated chemotaxis by up to 3 folds in comparison to native LDL treatment [118].

5.3 12/15-Lipoxygenase and MCP-1

12/15-lipoxygenase (12/15-LO) and its products are associated with LDL oxidation, cellular migration, adhesion, and inflammatory gene expression. MCP-1 mRNA were increased in Plox-86 cells, a J774A.1 cell line stably overexpresses leukocyte-type 12/15-LO [119]. The 12/15-LO product of linoleic acid, 13-hydroperoxyocta decadienoic acid (13-HPODE), can transcriptionally upregulate the expression of MCP-1 in vascular smooth muscle cell (VSMC) [120]. shRNA-mediated 12/15-LO knockdown resulted in reduced expression of MCP-1, and attenuated oxidative stress and expression of vascular cell adhesion molecule-1 and IL-6 in a differentiated mouse monocytic cell line [121]. Knocking out 12/15-LO in mice resulted in reduced activation of NFκB and expression of MCP-1 in VSMC, in comparison to wild type controls [120].

5.4 Treatments on MCP-1 over-production and arteriosclerosis

Table 2 summarizes studies that have utilized therapies to ameliorate MCP-1 over-production and relieve arteriosclerotic development under diabetic condition. The investigated compounds/products include: ligands to the PPARs (such as the thiazolidinediones and fibrates) and the statins that inhibit cholesterol production, gliclazide stimulate insulin secretion from pancreatic β cells, anti-hypertensive drugs, plant extracts, and traditional Chinese medicine.

6. DIABETIC NEPHROPATHY

Diabetic nephropathy is a kidney disease that develops gradually over a period of 15–20 years after the onset of diabetes, affects ~40% of diabetic patients, and is the primary cause of dialysis [138]. The pathologic abnormalities related to this diabetic complication include mesangial expansion, glomerular basement membrane thickening, and glomerular sclerosis [139]. The significant role of MCP-1 in the development of diabetic nephropathy has been implicated by several studies using MCP-1 knockout mice. For example, in MCP-1(−/−) db/db mice kidney macrophage accumulation and the progression of diabetic renal injury were substantially reduced compared to MCP-1(+/+) db/db mice with equivalent diabetes [140]. Similar results were reported when diabetic condition was induced in MCP-1(−/−) mice by streptozotocin treatment [141].

Locally produced MCP-1 has been reported to contribute to the development of advanced diabetic nephropathy through monocytes/macrophages recruitment and activation [142, 143]. A strong upregulation of MCP-1 was observed in tubular cells in biopsy specimens from patients with type 2 diabetes and overt nephropathy, correlating with NFκB activation in the same cells [144]. Urinary MCP-1 levels were found significantly elevated in patients with diabetic nephrotic syndrome [145-147], and well correlated with the number of CD68-positive infiltrating cells in the interstitium [145]. An in vitro study showed that MCP-1 directly increased extracellular matrix (ECM) protein, and therefore may contribute to ECM accumulation in diabetic nephropathy [148].

6.1 Hyperglycemia, advanced glycation end products and MCP-1

It has been shown that high concentration of glucose directly increased MCP-1 expression in human mesangial cells (MCs) [149], and hyperglycemic condition stimulated MCP-1 production and excretion into the urine [146, 150]. Furthermore, elevated blood glucose level was associated with enhanced generation of advanced glycation end products (AGE), which stimulated the secretion of MCP-1 in MCs either alone, or synergistically combined with high concentrations of glucose [151, 152]. Significant correlations between the levels of serum glycated albumin and urinary MCP-1 have been reported [152]. Interaction between AGE and their receptor (RAGE) may also activate PPARγ and induce oxidative stress, which is another pathway contributing to diabetic nephropathy [153].

6.2 proteinuria and MCP-1

Proteinuria is a result of increased leakage of plasma protein from glomerular capillary to the tubular fluid. Glomerular ultrafiltration of bioactive proteins, such as transforming growth factor beta (TGF-β) and hepatocyte growth factor (HGF), has been reported to cause increased expression and basolateral secretion of MCP-1 in proximal tubular and collecting duct cells [154, 155]. Urinary MCP-1 level from type 2 diabetic patients with macroalbuminuria was found over 2-fold higher than those from normo- and micro-albuminuria [142]. Significant correlations between urinary MCP-1 and the extent of proteinuria were also reported in several other studies [144, 152, 156], implicating that

MCP-1 produced in renal tubular cells is released into urine in proportion to the degree of proteinuria.

6.3 Treatments on MCP-1 over-production and diabetic nephropathy

The treatments documented to inhibit MCP-1 production and benefit diabetic nephropathy are summarized in Table 3. The investigated compounds/products include: thiazolidinediones and statins, anti-hypertensive drugs, immunosuppressants, vitamins, polyunsaturated acids, compound/extracts from plants, and trace element.

7. DIABETIC RETINOPATHY

Diabetic retinopathy is a diabetic complication that can cause blindness. The incidence of this disease is approximately 60% after 10 years with type 1 diabetes and after 20 years with type 2 diabetes [192]. Reportedly myofibroblasts and vascular endothelial cells are the major cell types expressing MCP-1 in epiretinal membranes (ERM), caused by changes in the vitreous humor in diabetic eyes [193]. When ERM were collected from patients with proliferative diabetic retinopathy (PDR), MCP-1 mRNA level was found significantly higher in comparison to that in idiopathic ERM, and MCP-1 protein was co-localized with active form of NFκB p50 [194]. The concentrations of MCP-1 in the vitreous samples from patients with proliferative vitreoretinal disorders, including PDR, were higher than in the cadaveric controls, implicating the role of MCP-1 in the recruitment of macrophages and monocytes into the vitreous of eyes [195]. Furthermore, vitreous MCP-1 levels were found positively correlated with the degree of proliferative membrane in PDR eyes, and negatively associated with the extent of preoperative retinal photocoagulation, indicating that MCP-1 may play a role in the development of the proliferative phase of PDR [196]. Other studies also reported that vitreous MCP-1 levels correlated with PDR activity[197], and the clinical stage of diabetic retinopathy[198, 199]. The causative role of MCP-1 in diabetic retinopathy was further supported by other studies documenting that the concentrations of MCP-1 in the vitreous samples from patients with diabetic retinopathy were significantly higher than those in controls [200-203]. Reportedly increased serum level of MCP-1 may also act as a regulator of diabetic retinopathy [204]. An in vitro study showed that glycated albumin or high glucose induced NFκB activation followed by up-regulation of MCP-1 promoter activity and protein production in Müller glial cells, demonstrating that MCP-1 overproduction in the eye is a response to the hyperglycemic condition [194].

8. INSULITIS AND ISLET TRANSPLANTATION

Insulitis is an inflammatory status in pancreatic islets, signified by mononuclear cell infiltration and destruction of insulin-producing β cells. It is a causative factor of insulin dependence in both type 1 and type 2 diabetes [205]. In non-obese diabetic (NOD) mice, MCP-1 mRNA expression was found to increase with age and peak at the early phases of insulitis, and therefore the production of MCP-1 by β cells could contribute to the recruitment of mononuclear cells into pancreatic islets [29]. While in a similar study, MCP-1 expression in islets and exocrine macrophages was found to increase during the later stages of diabetes in NOD mice as well [206].

In clinical islet transplantation, high levels of donor-derived MCP-1 have been associated with poor islet allograft outcome in patients with type 1 diabetes [207]. Transplantation of islets with elevated levels of MCP-1into syngeneic recipients led to a significantly greater influx of CCR2(+) cells and higher expression of monocyte/macrophage-associated inflammatory cytokines compared with low MCP-1 donor islets. The level of pre-transplantation MCP-1 inversely correlated with isograft function, while this correlation did not present in CCR2−/− recipients [208].

Under nonphysiologic state, MCP-1 expression was found significantly elevated in the islets from brain death donors (the major tissue source of allograft), which is a causative factor for early loss and poor long-term function of the grafts [209]. When adult porcine islets (APIs) were used to substitute human donor tissues, MCP-1 secreted by APIs was suggested to contribute to both instant blood-mediated inflammatory reaction (IBMIR) and rejection by attracting monocytes into the islet [210].

9. MCP-1-SPECIFIC TREATMENTS

Due to the pathological significance of MCP-1, efforts have been exerted to specifically target the signaling pathway of this chemokine. Several studies have attempted to decrease MCP-1 level in the circulation or block CCR2 activity by antibody administration. Such a neutralization of MCP-1 ameliorated glomerular crescent formation and development of interstitial fibrosis in mice [211]. However, when a MCP-1 monoclonal antibody was tested in patients with rheumatoid arthritis, the treatment did not show any beneficial effects, and the highest dose even aggravated the symptoms, which may relate to the dramatic increases of antibody-complexed MCP-1 levels in peripheral blood [212].

Antibody neutralization of CCR2 inhibited restenosis in primates [213]. When a similar strategy was tested in mice with collagen-induced arthritis, early stage treatment improved clinical signs, which was in contrast to the disease aggravation caused by a later stage treatment [214]. Furthermore, a selective small molecule antagonist of mouse CCR2, namely INCB3344, reduced multiple sclerosis and inflammatory arthritis in mice [215].

Another strategy to interfere the binding of MCP-1 to CCR2 was truncating the NH2-terminal residues of MCP-1 [216]. Such antagonists, especially MCP-1(9-76), were found to prevent the onset and ameliorate the symptoms of arthritis in MRL-lpr mice [217], to reduce in-stent restenosis in cynomolgus monkeys fed a high cholesterol diet [218], and to decrease vein graft thickening due to intimal hyperplasia and accelerated atherosclerosis in mice [219].

Further studies attempted to abrogate oligomerization of MCP-1 in order to inhibit its in vivo activity[220]. An obligate monomer mutant form, documented as CCL2(P8A), was found unable to recruit leukocytes into the peritoneal cavity and into lungs of ovalbumin-sensitized mice [221].

The interaction between MCP-1 and glycosaminoglycans (GAGs) of the extracellular matrix and endothelial cell surfaces has long been known to mediate the chemotaxis process [222], and contribute to MCP-1 oligomerization [223]. Recent molecular engineering was able to increase the binding affinity to GAG and decrease that to CCR2 in antagonistic MCP-1 mutants. Such examples include MCP-1(PA508), which reduced inflammatory monocyte recruitment, limited neointimal hyperplasia, and attenuated myocardial ischemia/reperfusion injury in mice [224]; and MCP-1(Y13A/S21K/Q23R), which had a mild ameliorating effect on experimental autoimmune uveitis in rats [225].

In summary, this article reviews the history, regulation, and function of chemokine MCP-1, with emphases on its pathological role in the development of obesity, type 2 diabetes, and diabetic complications. Tables 1-3 summarize studies that aimed to ameliorate obesity-associated metabolic syndromes, diabetes-related cardiovascular diseases, and diabetic nephropathy. In these studies the downregulation of MCP-1 production was found to co-occur with the improvement of the symptoms. Although these studies did not confirm the etiological role of MCP-1, they implicated a close relationship between MCP-1 and the status of these diseases. The significance of MCP-1 in the development of obesity, diabetes and diabetic complications was highlighted in the studies specifically targeting MCP-1, such

as the MCP-1 and CCR2 knockout animals, MCP-1 SNP, and MCP-1 antagonistic treatments. The promising results obtained from these studies implicate that MCP-1 is a viable therapeutic target.

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HIGHLIGHTS

- Historic perspectives of the pioneer studies on MCP-1
- Role of MCP-1 in obesity-related metabolic syndrome
- Role of MCP-1 in type 2 diabetes and diabetic complications
- Treatments on MCP-1 over-production and inhibition of MCP-1 signaling

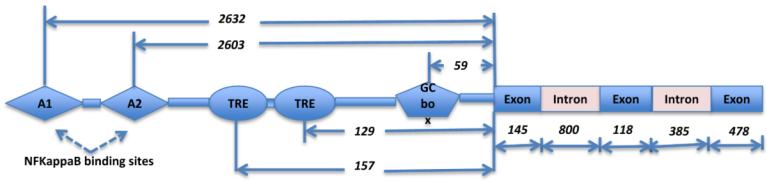

Figure 1.
A graphical summary of the transcriptional regulatory elements in human MCP-1 gene. TRE, phorbol ester responsive elements. The numbers indicate length in base pair. The schematic illustration is not proportional to the length of the DNA.

Table 1

Treatments that have been reported to inhibit MCP-1 over-production and ameliorate obesity-related metabolic syndromes.

Treatment	Comment	Experimental model	Result	Ref.
Methanolic extract from unripe kiwi fruit (*Actinidia deliciosa*)		3T3-L1 cells	MCP-1↓, NFκB activation ↓, cell differentiation ↑ glucose uptake ↑, adiponectin↑	[54]
Ethanolic extract from leaves of bamboo *Phyllostachys edulis*	Raw plant extracts	Obese mice 3T3-L1, hepa6, C2C12 cells	Serum MCP-1 ↓ MCP-1 secretion under lipotoxic condition↓	[48] [55]
Mulberry (*Morus Alba L.*) leaf		ApoE(-/-) mice	MCP-1↓, macrophage infiltration in adipose tissue↓, adiponectin↑	[56]
Dehydroabietic acid	Diterpene from rosin, ligand for PPARs	Obese diabetic mice	MCP-1↓, macrophage infiltration in adipose tissues↓, adiponectin↑	[57]
		Co-culture of RAW 264 macrophages and 3T3-L1 adipocytes	MCP-1↓, TNFα↓, nitric oxide ↓	[58]
Capsaicin	Spicy component of hot peppers	Obese mice	MCP-1↓, fasting glucose ↓, insulin↓, hepatic triglyceride content ↓	[59]
			MCP-1↓, NFκB activation ↓, macrophage migration and activation↓, adiponectin ↑, PPARγ activation↑	[60]
Curcumin	Component of spice turmeric	Diabetic rats	MCP-1↓, glucose↓, oxidative stress↓	[61]
Diallyl disulfide, allyl isothiocyanate, piperine, zingerone, curcumin	Spice-derived components	Adipose tissue and Raw 264.7 macrophages	MCP-1↓, macrophage migration ↓	[62]
Procyanidins	Flavonoids from grape seeds	Human adipocytes and THP-1 cells	MCP-1↓, NFκB nuclear translocation ↓, adiponectin↑	[63]
Berberine	Isoquinolone alkaloid from plants	Obese db/db mice	MCP-1↓, other inflammatory factors (TNFα, IL-1β, IL-6, iNOS, and COX-2) ↓	[64]
Resveratrol	Stilbenoid in red grape skin and other fruits	TNFα -stimulated cells	MCP-1↓, NFκB activation ↓	[65]
Acarbose	Microbial product, α-glucosidase inhibitor	Fructose-fed rats	MCP-1 expression ↓	[66]
Propagermanium	Trace element	Obese db/db mice	CCR2 activity↓, body weight gain↓, macrophage accumulation in adipose tissue↓, insulin resistance↓	[67]
Chromium niacinate		U937 monocytes	MCP-1↓, oxidative stress↓	[68]
L-cysteine	Antioxidant	Zucker diabetic fatty rats	MCP-1↓, NFκB activation ↓, insulin resistance↓, glucose↓	[69]
Troglitazone	Thiazolidinedione drugs, PPAR ligands	Mononuclear cells of nondiabetic obese patients	Plasma MCP-1 and insulin ↓, ROS generation ↓, NFκB↓, IκBα↑, IL-10↑ atherosclerosis↓	[70]
Rosiglitazone		Obese humans subjects	Plasma MCP-1 ↓	[71]
Troglitazone, rosiglitazone		Human acute monocytic leukemia THP-1 cells	MCP-1-induced migration↓	[72]
Atorvastatin	Type 2 statin	Human subjects	Serum MCP-1 ↓	[73]
Dilazep; fenofibric acid	PPARα ligands, hypocholesterolemic	Human endothelial cells	MCP-1 mRNA↑, glycoxidized LDL↓	[74]

Treatment	Comment	Experimental model	Result	Ref.
HE3286	Synthetic adrenal steroid	Obese/ diabetic mice	MCP-1& CCR2↓, NF-κB activation↓, hyperglycemia↓, insulin resistance↓	[75]
TEI-K03134	CCR2 antagonist	Obese mice	MCP-1 and CCR2 ↓, insulin resistance↓	[76]
ARB L158809	Angiotensin receptor inhibitor	Fatty rats	MCP-1 expression↓, blood glucose, cholesterol, triglyceride↓, epididymal fat↓, lipid peroxidation↓, insulin resistance↓, adiponectin↑, small differentiated adipocytes number ↑	[77]
Bypass surgery	Physical treatments	Obese human subjects	MCP-1↓, number of macrophages in adipose tissue ↓	[78]
Exercise		Human subjects with metabolic syndrome	Plasma MCP-1 ↓, IL-8 and visceral fat↓	[79]

Table 2

Treatments that have been reported to inhibit MCP-1 over-production and improve diabetic vascular conditions.

Treatment	Comment	Experimental model	Result	Ref.
Troglitazone	Thiazolidinedione drugs, PPAR ligands	TNFα-treated HUVECs	MCP-1 mRNA and protein secretion ↓	[122]
Rosiglitazone		Streptozotocin-induced diabetes mice	MCP-1 expression ↓, leukocyte adhesion↓, macrophage infiltration↓	[123]
		Human subjects	MCP-1↓, glucose↓, insulin ↓, LDL/HDL↓, HDL↑, adiponectin ↑ PPARγ activation ↑	[124]
		Arteriosclerotic rats	CCR2 expression in lesional and circulating monocytes↓	[125]
Aspirin; fenofibrate and clofibrate	Anti-inflammatory drug; PPAR activators	Human endothelial cells	High glucose-increased MCP-1 expression↓, ROS↓, activation of NFκB and AP-1↓	[126]
Simvastatin	Statins, hypocholesterolemic via inhibiting HMG-CoA reductase	Diabetic rats	Serum MCP-1↓, ICAM-1↓	[127]
Atorvastatin		Human subjects with high cardiovascular risk	Plasma MCP-1↓, ICAM-1↓	[128]
Pravastatin		Fatty rats	MCP-1↓, TGF-β1↓, endothelial nitric oxide synthase (eNOS)↑	[129]
Gliclazide	Hypoglycemic, sulfonylurea receptor ligand leading to insulin release in β cells	Human aortic vascular smooth muscle cells (HASMCs)	MCP-1↓, oxLDL-induced monocyte adhesion↓ oxLDL-induced MCP-1↓	[130] [131]
Irbesartan	Anti-hypertensive	ApoE-null mice	Aorta MCP-1↓, atherosclerosis↓, collagen content↓, cellular proliferation↓, macrophage infiltration↓	[132]
Doxazosin		Human monocytes	MCP-1-directed monocyte migration↓	[133]
D-psicose	Naturally occurred, ultralow-energy monosaccharide	Human umbilical vein endothelial cells (HUVECs)	High glucose-induced MCP-1 expression↓	[134]
Erigeron multiradiatus (Lindl.) Benth	Plant extracts	Human endothelial cells; alloxan-induced diabetic mice	High glucose-induced MCP-1↓, NFκB activation↓, serum MCP-1↓	[107]
Aqueous extract of Buddleja officinalis		Human umbilical vein endothelial cells (HUVEC)	High glucose-induced MCP-1↓, hydrogen peroxide production↓	[135]
Danggui-Buxue-Tang	Traditional Chinese medicine	Diabetic rats	Aorta MCP-1↓, ICAM-1↓	[136]
Shenqi compound recipe			Aorta MCP-1↓, PPARγ↑	[137]

Table 3

Treatments that have been reported to inhibit MCP-1 over-production and improve diabetic nephropathy conditions.

Treatment	Comment	Experimental model	Result	Ref.
Rosiglitazone	Thiazolidinedione drugs, PPAR ligands	STZ-induced diabetic rats	Renal & urinary MCP-1↓	[157]
			MCP-1↓, ROS↓, NFκB activation↓	[158]
		Stretched human mesangial cells	MCP-1↓ NFkB activation↓, monocyte chemotaxis ↓	[159]
Troglitazone		Cultured human mesangial cells	TNFα-induced MCP-1↓	[160]
Pioglitazone		Type 2 diabetic rats; cultured mesangial cells	MCP-1 gene expression↓, urinary MCP-1& albumin ↓, glomerulosclerosis↓	[161]
Pravastatin	Satins	Human subjects	Serum MCP-1↓	[162]
Cerivastatin		Spontaneously hypertensive rats	MCP-1↓, albuminuria, glomerular hyperfiltration, mesangial expansion, and loss of charge barrier↓	[163]
Olmesartan medoxomil	Anti-hypertensive drugs	Zucker Diabetic Fatty rats; tubular epithelial cells	MCP-1 in tubular cells↓, proteinuria↓	[164]
Valsartan; PD123319; pyrrolidine dithiocarbamate		Diabetic animals	MCP-1 expression↓, macrophage infiltration↓, p65 activation↓	[165]
Telmisartan		Cultured mesangial cells	MCP-1 expression↓, RAGE gene expression ↓, oxidative stress↓, PPAR-γ activation↑	[153]
Enalapril; candesartan		Diabetic rats	MCP-1 expression↓, proteinuria↓, glomerular macrophage number↓	[166]
Enalapril; mycophenolate mofetil		Diabetic rats	Renal MCP-1 overexpression↓, macrophage recruitment ↓	[167]
Lisinopril		Patients with type 1 and type 2 diabetes	Urinary MCP-1↑, proteinuria↓	[168]
Spironolactone		Type 2 diabetic rats; cultured mesangial and proximal tubular cells	Renal and urinary MCP-1↓, macrophage infiltration↓, NFκB activation↓	[169]
		Type 2 diabetic patients with nephropathy	Urinary MCP-1↓, oxidative stress↓	[170]
		OLETF rats; cultured cells	Urinary MCP-1↓, urinary albumin↓, NFκB activity↓	[171]
Mycophenolate mofetil	Immunosuppressant	STZ-induced diabetic rats	MCP-1↓, podocytes loss↓	[172]
			Renal MCP-1↓, early renal injury↓, oxidative stress↓	[173]
Mizoribine		Fatty rats	Tubules and glomeruli MCP-1↓	[174]
LY333531	Protein kinase C-β isoform inhibitor	STZ-induced diabetic rats	MCP-1↓, urinary albumin↓, glomerular volume and tubulointerstitial injury↓ lipid peroxidation↓, macrophages recruitment↓ antioxidant enzyme activities↑	[175]
Cilostazol	Type 3 phosphodiesterase inhibitor	Diabetic rats	Kidney MCP-1↓, glomeruli hypertrophy↓, NFκB	[176]

Treatment	Comment	Experimental model	Result	Ref.
			activation↓, inflammatory cell infiltration ↓	
Colestimide	Hypolipidemic drug	Human patients	Urinary MCP-1↓, urinary oxidative stress marker ↓	[177]
Insulin	Hormone	Type 2 diabetic patients with microalbuminuria	Urinary MCP-1 excretion↓	[142]
Propagermanium	Trace element	Diabetic mice	CCR2 antagonist, Mesangial matrix expansion↓, macrophage infiltration↓	[178]
Triptolide	A constituent of immunosuppressive Chinese herbal medicine	Patients with diabetic nephropathy	Urinary MCP-1 ↓	[179]
Lithospermic acid B	Active component in Salvia miltiorrhizae	Fatty rats	Renal MCP-1 expression ↓, albuminuria↓, glomerular hypertrophy↓, mesangial expansion↓, extracellular matrix expansion↓, lipid peroxidation↓	[180]
Breviscapine	Flavonoid from the Chinese herb Erigeron breviscapus	Diabetic rats	MCP-1 production in glomeruli and tubulointerstitium ↓, albuminuria↓, glomeruli hypertrophy↓, tubulointerstitial injury↓, lipid peroxidation↓, antioxidant enzyme activities ↑	[181]
Azuki bean (Vigna angularis) seed coats	Contain polyphenols	STZ-induced diabetic rats	MCP-1 expression ↓, macrophages infiltration ↓, glomerular expansion↓	[182]
Colchicine	Compound from plants of the genus Colchicum	STZ-induced diabetic rats	MCP-1 expression ↓, inflammatory cell infiltration ↓	[183]
Retinoic acid	Vitamin A	Diabetic rats; cultured podocytes	Urinary MCP-1↓, intrarenal MCP-1 protein synthesis↓, high glucose-induced MCP-1↓	[184]
1,25-Dihydroxycholecalciferol	Vitamin D, hormonally-active form	Mesangial cells from vitamin D receptor knockout animals	NFκB activation↓, hyperglycemia-induced renal injury ↓	[185]
Vitamin E	Vitamin E	Type 1 diabetic patients	MCP-1↓	[186]
Astaxanthin	carotenoid	Mesangial cells challenged with high glucose medium	MCP-1 ↓, ROS ↓, NFκB activation↓	[187]
Eicosapentaenoic acid	An omega-3 fatty acid	Diabetic mice	MCP-1 expression↓, ERK1/2 and p38 ↓	[188]
Canola oil	Contain n-3 poly unsaturated fatty acid	STZ-induced diabetic rats	MCP-1 expression↓	[189]
Kremezin (AST-120)	Uremic toxin adsorptive carbon	Fatty rats	Renal MCP-1↓, tubulointerstitial injury ↓	[190]
Low-dose radiation	Physical treatment	STZ-treated mice	Serum and renal MCP-1↓	[191]