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Curcumin as a natural regulator of monocyte chemoattractant protein-1

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ABSTRACT

Monocyte chemoattractant/chemotactic protein-1 (MCP-1), a member of the CC chemokine family, is one of the key chemokines that regulate migration and tissue infiltration of monocytes/macrophages. Its role in the pathophysiology of several inflammatory diseases has been widely recognized, thus making MCP-1 a possible target for anti-inflammatory treatments. Curcumin (diferuloylmethane) is a natural polyphenol derived from the rhizomes of Curcuma Longa L. (turmeric). Anti-inflammatory action underlies numerous pharmacological effects of curcumin in the control and prevention of several diseases. The purpose of this review is to evaluate the effects of curcumin on the regulation of MCP-1 as a key mediator of chemotaxis and inflammation, and the biological consequences thereof. *In vitro* studies have shown that curcumin can decrease MCP-1 production in various cell lines. Animal studies have also revealed that curcumin can attenuate MCP-1 expression and improve a range of inflammatory diseases through multiple molecular targets and mechanisms of action. There is limited data from human clinical trials showing the decreasing effect of curcumin on MCP-1 concentrations and improvement of the course of inflammatory diseases. Most of the *in vitro* and animal studies confirm that curcumin exert its MCP-1-lowering and anti-inflammatory effects by down-regulating the mitogen-activated protein kinase (MAPK) and NF-κB signaling pathway. As yet, there is limited data from human clinical trials showing the effect of curcumin on MCP-1 levels and improvement of the course of inflammatory diseases. More evidence, especially from human studies, is needed to better assess the effects of curcumin on circulating MCP-1 in different human diseases and the role of this modulatory effect in the putative anti-inflammatory properties of curcumin.

Contents

Abbreviations: LDL-c, low density lipoprotein cholesterol; HDL-c, high density lipoprotein cholesterol; Apo A-1, apolipoprotein A-1; PON, paraoxonase; MCP-1, monocyte chemoattractant/chemotactic protein-1; MIP-1β, macrophage inflammatory protein-1β; LPS, lipopolysaccharide; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; IL, interleukin; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factors; CRP, C-reactive protein; CNS, central nervous system; Ang, angiotensin; AP-1, activator protein 1; Ox-LDL, oxidized-LDL; MAPK, Mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; MS, Multiple sclerosis; CVD, cardiovascular disease; ROS, reactive oxygen species; NFκB, Nuclear factor kappa B; CCR2, chemokine receptor type 2; HUVEC, human umbilical vein endothelial cell; VSMC, vascular smooth muscle cell; OASF, osteoarthritis synovial fibroblast.

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1. The pivotal role of chemotaxis in inflammation

A relationship between systemic inflammation and the course of several diseases (*e.g.*, autoimmune and cardiovascular diseases) is widely recognized [1–4]. Systemic inflammation is sustained through a heightened secretion of pro-inflammatory cytokines from immune cells. Among inflammatory cells, monocytes, by migrating from the circulation across the vascular endothelium, play a key role in routine immunological surveillance of tissues and in response to inflammation [5]. Tethering and adhesion of monocytes to the apical surface of the endothelium is promoted by different chemokines, which are able to employ also neutrophil and lymphocyte cells [6]. Induction of chemotaxis by chemokines is exerted by activating G-protein-coupled receptors (GPCRs) [7]. Upon binding of chemokines to their specific receptors, the GPCR forms a ternary complex with a heterotrimeric G protein; this event starts the cascade of downstream signaling proteins ultimately resulting in the migration of inflammatory cells to the chemokine source [8]. Chemokines consist of a large family of peptides, including at least 50 human chemokines. They have been categorized into four subfamilies: CC, CXC, CX_3C, and C [6]. Chemokine family members compete for binding to the receptors on target cells [8]. Finally, different chemokines may target the same cell line by acting on distinct receptors. In this regard, monocyte chemoattractant/chemotactic protein-1 (MCP-1) and macrophage inflammatory protein-1β (MIP-1β) are chemotactic for monocytes but they exert their function by distinct receptors [9].

2. MCP-1: an overview of its activities

MCP-1 is known as a member of CC chemokine family which has chemotactic activity for monocytes, basophils and T lymphocytes [6,10,11]. MCP-1 can regulate leukocyte trafficking by affecting their chemotactic activity, activating inflammatory cells and modulating interactions between leukocytes and endothelial cells [12]. Once believed to act specifically on monocytes, MCP-1 is now known to recruit memory T cells and dendritic cells to the inflammation sites [13]. It has been shown that MCP-1 is synthesized and released from cardiac, vascular, and renal cells in response to hemodynamic (*e.g.* blood flow, shear stress and oxidative stress) and humoral (*e.g.* angiotensin II [Ang II] and endothelin-1) stimuli [14].

Activator protein 1 (AP-1) and NF-κB have key roles in regulating the MCP-1 gene expression. Previous studies have shown that the 5′-flanking region in the MCP-1 gene has binding sites for the above-mentioned transcription factors [15]. Also, the renin-angiotensin system (RAS) activation can trigger an inflammatory response and induce several transcription factors, cytokines and chemokines [16]. Conversely, NF-κB and AP-1 can activate Ang III that induces MCP-1 expression in mesangial renal cells [17].

It has been reported that MCP-1 expression is also stimulated by oxidized-LDL (ox-LDL) in endothelial cells [18], macrophages [19], and vascular smooth muscle cells [20]. Ox-LDL can induce MCP-1 release from macrophages in a time- and concentration-dependent manner [21]. Because MCP-1 has a key role in the migration of monocytes into the sub-endothelial space [22], it is believed to trigger the early stage of atherosclerotic plaque formation.

Mitogen-activated protein kinase (MAPK) pathways can regulate several processes and inflammation as well. MAPK pathways, including extracellular signal regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 MAPK pathways [23], can modulate MCP-1 expression in numerous kidney diseases [24–27]. In addition, MAPK pathways can mediate the production of MCP-1 and other inflammatory factors in macrophage cell lines [28,29]. Also, it has been reported that JNK pathway has a key role in the regulation of MCP-1 expression [22].

Tesch reviewed MCP-1 as a possible diagnostic marker for renal injury in diabetic nephropathy. Accordingly, urinary MCP-1 concentration is known as a marker of diabetic renal inflammation [30]. MCP-1 has been suggested also as a therapeutic target in patients with myocardial infarction and ischemic cardiomyopathy [31]. Finally, because of its important role in the recruitment of monocytes into the arterial wall in vascular atherosclerotic disease, it can be an important target for developing specific anti-atherogenic treatments.

3. The health benefits of curcumin

Turmeric, a yellow spice, is widely used by people in the Southeast Asia and India. Curcumin (diferuloylmethane) is a natural polyphenol derived from the rhizomes of the turmeric plant (*Curcuma longa* L.) [32]. It has several biological and pharmacological activities including anti-inflammatory [33–35], anti-oxidant [36–41], anti-tumor [42–48], hepatoprotective [49], lipid-modifying [50–54], anti-ischemic [55], hypouricaemic [56], anti-prutitic [57], analgesic [58], anti-dyspeptic [59], anti-anxiety and anti-depressant [60,61], immunoregulatory [62–64], anti-arthritic [65], and cognition-enhancing [66,67] effects, therefore, can improve several diseases in which these processes are overrepresented (*e.g.*, rheumatisms, sinusitis, inflammatory skin ailments, trauma, asthma, allergies, ulcers, diabetes) [32].

Curcumin can affect several molecular targets including growth factors, cytokines, transcription factors, cell adhesion molecules, protein kinases, redox state enzymes, and receptors [68,69]. Curcumin is also an inhibitor of the mitogen-activated protein kinases (MAPKs) and NF-κB [20,70], which have key roles in the regulation of proinflammatory cytokine gene expression and for the maintenance of chronic pain [71,72]. Some *in vitro* studies have demonstrated that curcumin can inhibit proinflammatory cytokines including interleukin-1β (IL-1β), tumor necrosis factor- α (TNF-α), and chemokines such as MCP-1 that are induced by lipopolysaccharide (LPS) in monocytes, astrocytes or alveolar macrophages [73,74]. Also, it has been shown that curcumin can prevent the production of interleukins 1, 2, 6, 8 and 12. The anti-inflammatory effects of curcumin are also exerted by its effects on lipoxygenase, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) enzymes activities [32].

It has been demonstrated that curcumin has no dose-limiting toxicity in phase I clinical trials [75], and can be effective in the prevention and treatment of several inflammatory diseases [69]. It has analgesic effects on both acute inflammatory pain and chronic neuropathic pain [76,77]. Curcumin can also decrease inflammation and improve quality of life in solid tumors patients [45]. Curcumin supplementation can reduce circulating levels of IL-8 and Hs-CRP and also quality of life in patients with sulphur