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Invited critical review

MCP-1: Chemoattractant with a role beyond immunity: A review

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ABSTRACT

Background: Monocyte Chemoattractant Protein (MCP)-1, a potent monocyte attractant, is a member of the CC chemokine subfamily. MCP-1 exerts its effects through binding to G-protein-coupled receptors on the surface of leukocytes targeted for activation and migration. Role of MCP-1 and its receptor CCR2 in monocyte recruitment during infection or under other inflammatory conditions is well known.
Method: A comprehensive literature search was conducted from the websites of the National Library of Medicine (http://www.ncbl.nlm.nih.gov) and Pubmed Central, the US National Library of Medicine's digital archive of life sciences literature (http://www.pubmedcentral.nih.gov/). The data was assessed from books and journals that published relevant articles in this field.
Result: Recent and ongoing research indicates the role of MCP-1 in various allergic conditions, immunodeficiency diseases, bone remodelling, and permeability of blood - brain barrier, atherosclerosis, nephropathies and tumors.
Conclusion: MCP-1 plays an important role in pathogenesis of various disease states and hence MCP-1 inhibition may have beneficial effects in such conditions.

Contents

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1. Introduction

Chemokines include a superfamily of small, secreted proteins that play a central role in many homeostatic and pathological processes in human body. Though initial research identified these molecules as regulators of leukocyte trafficking [1], subsequent research has pointed to its involvement in other aspects of the inflammatory process, such as fibrosis, tissue remodelling and angiogenesis [2]. Chemokines control the migration of neutrophils, lymphocytes, antigen-presenting cells, including dendritic cells and cells of monocyte/macrophage lineage [3]. In response to an inflammatory insult, chemokines coordinate the recruitment, activation and homing of leukocytes during the different phases of both innate and adaptive inflammatory responses [4]. During inflammation, sentinel cells at the inflammatory focus release chemokines and generate a chemotactic gradient to surrounding blood vessels. Migrating cells tend to move towards high local concentration of chemokines [5]. Presentation of chemokines on endothelial cells induces rolling and transendothelial migration of leucocytes. The differences in the concentration of chemokines induce accumulation of intracellular signalling molecules at the leading edge of migrating cells, whereas the chemokine receptors themselves remain uniformly distributed over the plasma membrane during migration [6]. Functionally, chemokines may be grouped into two main subfamilies: inflammatory and homeostatic chemokines. Inflammatory cytokines control the recruitment of leukocytes in inflammation and tissue injury, whereas homeostatic chemokines fulfil housekeeping functions such as navigating leukocytes to secondary leukocytes to secondary lymphoid organs, bone marrow and thymus during hematopoiesis [7].

Thus an alteration of chemokine expression or function might lead to the persistence of an inflammatory reaction well beyond its original purpose thereby creating a key pathogenetic event for the establishment of chronic inflammation [8]. Chemokines have multiple actions and functions and thus play a major role in various vascular, neoplastic and infectious conditions as well as allergic disorders, transplant rejections and auto-immune diseases [8,9].

2. Structure of chemokines

Chemokines are a family of small molecules with a molecular weight of 8–14 kDa. To date approximately 50 human chemokines and 20 G-protein-coupled chemokine receptors have been identified. Most chemokines also have at least four cysteines in highly conserved positions and three distinct domains: A highly flexible N-terminal domain is anchored to the rest of the molecule by disulfide bonds involving the two N-terminal domain cysteines. This is followed by an extended loop that leads into three antiparallel β-pleated sheets (a so-called Greek key) which provide a flat base over which the C-terminal α helix extends (Fig. 1) [10]. Based on their genetic organization and the position of two highly conserved cysteine residues at the N-terminus, chemokines can be divided into four subgroups, the CC, CXC, C and CX_3C families [11]. In the CXC chemokine family, the two N-terminal cysteine residues are separated by a variable amino acid (Fig. 2). Genes from this family are clustered at human chromosome 14q12-21. Chemokines of the CC family have adjacent cysteines close to the N-terminus, and their genes cluster—with some exceptions—at 17q11.2-12 [12]. As a general rule, members of the CC family are primarily targeting monocytes and T-cells, whereas CXC chemokines affect mainly neutrophils. Five members of the family of monocyte chemoattractant proteins have been identified so far. MCP-1 (CCL2), MCP-2 (CCL8), MCP-3 (CCL7), MCP-4 (CCL13) and MCP-5 (CCL12) constitute a subfamily within the CC chemokines [13].

The amino acid sequences of chemokine are so similar that their secondary and tertiary structures are also similar. Studies on structure–function relationship have revealed that N-terminal region is important for receptor binding and activation [14]. So far, all structural analyses

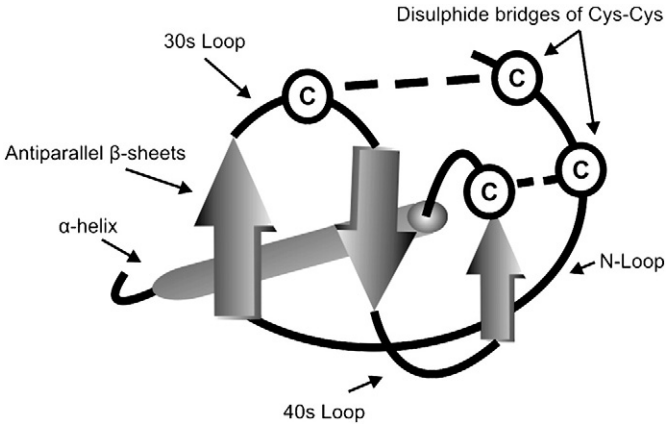

Fig. 1. Structure of MCP-1.

show that chemokines are multimers under conditions required for crystallization or NMR study [15]. In the case of CC chemokines, such as MCP-1, the dimer interface forms primarily by involvement of antiparallel β-sheet with cysteine residues near the N-terminal domain (CC chemokine) or the two α- helices (CXC chemokine) [16–18]. Most chemokines bind to cell-surface or connective-tissue components such as glycosaminoglycans and the association with these molecules may favor dimerization [19].

3. Chemokine receptors

Chemokine receptors are seven-transmembrane-domain receptors, which are coupled to heterotrimeric G-proteins [20]. To induce migration of target cells along a chemotactic gradient, the release of the βγ subunits from the heterotrimeric G-protein is required. The βγ subunits then directly activate phosphoinositide-specific phospholipase C (PLC) isoenzymes leading to the formation of inositol-1,4,5-trisphosphate and a rise of the intracellular calcium concentration. It is noteworthy that the chemokine/chemokine receptor system is highly redundant, in that most chemokine receptors bind several different chemokines and most chemokines bind to several different receptors. The signals mediated by chemokine receptors (except CXCR 4) are short and transient. The rapid termination of receptor activity is achieved by phosphorylation at multiple sites of the cytoplasmic C-terminus, homologous and heterologous desensitization and subsequent internalization [20].

4. Monocyte Chemoattractant Protein-1 (MCP-1)

MCP-1 (CCL2), a potent monocyte attractant, is a member of the CC subfamily [21]. It was the first discovered human CC chemokine. It was originally isolated from mouse 3T3 fibroblasts [22]. The human

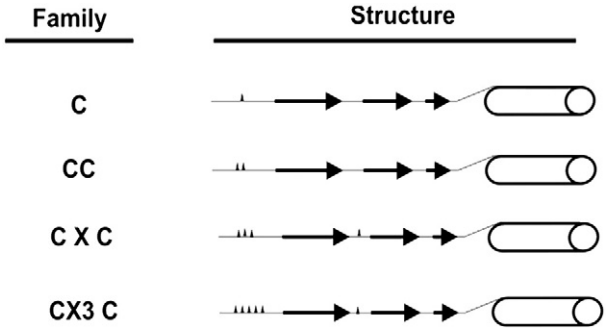

Fig. 2. Structure of chemokine family. Bold arrow shows β-plated and cylinder shows α-helical structure. Structure of all the chemokine is similar, except the four conserved cysteine residue.