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CCL2/CCR2 signaling pathway in glioblastoma multiforme

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ABSTRACT

Glioblastoma multiform (GBM) is described as one of the most frequent primary brain tumors. These types of malignancies constitute only 15% of all primary brain tumors. Despite, extensive developments on effective therapeutic methods during the 20th century as well as the first decade of the present century (21st), the median survival rate for patients suffering from GBM is only approximately 15 months, even in response to multi-modal therapy. numerous types of reticuloendothelial system cells such as macrophages and microglial cells occupied within both GBM and also normal surrounding tissues. These immune cells acquire an otherwise activated phenotype with potent tumor-tropic functions that contribute to the glioma growth and invasion. The CC chemokine, CCL2 (previously named MCP-1) is of the most important CC chemokines family member involving in regulation of oriented migration and penetrative infiltration of mainly reticuloendothelial system cells specifically monocyte/macrophage phenotypes. Fundamental parts are played by CCL2 and its related receptor (the CCR2) in brain tumors and obviously in migration of monocytes from the bloodstream through the vascular endothelium. Therefore, CCL2/CCR2 axis is required for the routine immunological surveillance of tissues, in accordance with response to inflammation. Briefly, in this review, we have tried our best to collect the latest, straightened and summarize literature reports exist within data base regarding the interaction between microglia/macrophages and CCL2/CCR2 axis in GBM. We aimed to discuss potential application of this chemokine/receptor interaction axis for the expansion of future anti-glioma therapies as well.

Contents

1. Introduction

Malignant gliomas are identified and fitted within the most proliferative and invasive tumors which extremely develop inside the central nerves system (CNS). Genetic variations, amplified

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signaling pathways, and their exploitation of surrounding non-transformed brain cells for molecules are essential for the glioma growth, invasiveness, and tumorigenicity (Huse and Holland, 2010; Charles et al., 2011). In more recent investigations, especial attentions are paid to chemokine/receptor network functions in pathogenesis and pathophysiology of neuroinflammatory disorders (Vazirinejad et al., 2014; Khorramdelazad et al., 2016; Kothur et al., 2016). Chemokines are members of a subfamily of the wider family of cytokines with pro-migratory properties and act as recruiters and/or chemo attractive factors for a broad spectrum of cell types for regulation of their oriented locomotion. Cells which are targeted by these mediators respond chemokine ligands and then express appropriate trans-membrane G protein chemokine receptors (Aminzadeh et al., 2012; Derakhshan et al., 2012; Hassanshahi et al., 2013; Ahmadi et al., 2016; Khorramdelazad et al., 2016). According, on the basis of the position of conserved cysteine amino acid motifs within their biochemical structure, chemokines are further subdivided into C, CC, CX3C and CXC sub divisions(Aminzadeh et al., 2012; Ahmadi et al., 2013; Ostadebrahimi et al., 2013; Ahmadi et al., 2016).Several members of the CC and CXC chemokines including CCL2, CXCL8and CXCL12are generated by glioma cells (Oh et al., 1999; Kielian et al., 2002; Salmaggi et al., 2004; Bajetto et al., 2006; Terasaki et al., 2011). Glioma cells generate chemokines and express chemokine receptors and regardingly are involved in various biological aspects of glial tumors such as invasiveness, survival, angiogenesis, and proliferation (Proudfoot, 2002; Sciumè et al., 2010; Terasaki et al., 2011). For instance, we have previously reported that CXCL12 was increasing patients suffering from glioblastoma (Moosavi et al., 2013). however, there exist some evidences to report that expression of chemokines by glioma cells, the exact function(s) of these proteins in glioma biology and pathogenesis has yet to completely defined, (particularly their possible roles in the glioma microenvironment) (Rutar and Provis, 2016).In addition to the stromal CNS-intrinsic cell types, such as astrocytes and microglia in the neighboring tissues of glioma cells, inflammatory cells including lymphocytes, macrophages and neutrophils (which are infiltrated into the tumor from the circulation)are also observed (Carvalho da Fonseca and Badie, 2013). In spite of the fact that initially these infiltrated immune cells are responsible for the tumor growth and progression, much more evidences pointed to the fact that tumor also in turn capable of neutralizing the immune cells (von Hanwehr et al., 1984; Hussain et al., 2006; Ben-Neriah and Karin, 2011). Moreover, glioma recruit and attract neural and immune cell types into its microenvironment for growth progression, invasiveness and for facilitating of the phenomenon of angiogenesis (Le et al., 2003; Charles et al., 2011).Briefly, in this review, we collected a straightened and summarize the latest literature reports present within the database regarding the interaction between microglia/macrophages and CCL2/CCR2 axis in GBM. We also tried our best to discuss potential application of this chemokine/receptor interaction axis for the expansion of future anti glioma therapies.

2. Biostructure and biological functions of CCL2

The CCL2 fit within the C-C chemokine subfamily which is mainly involved in oriented locomotion of monocytes toward pathologic locations. The CCL gene locus exists on chromosome 17 (Chr. 17, q11. 2) (Feng et al., 2012). The CCL2 in human is the mouse homologue of JE, a gene which shown to be up-regulated by platelet-derived growth factor (PDGF) in mouse fibroblasts (Cochran et al., 1983). In other words, the human homologue that best characterized as CCL2 was originally purified from human cell lines with regard to its monocyte chemoattractant properties and was initially called Monocyte Chemoattractant Protein-1 (MCP-1) and is a protein with 13 kD in size and contains 76 amino acids (Van Coillie, et al., 1999). The CC chemokine, branch of MCP proteins are accommodating at least four members, including MCP-1, 2, 3, and 4. There exist high levels of sequence homology between CCL2 and other MCP members, varying from 71% for CCL7 to61% for CCL4 and CCL8 (Uguccioni, et al., 1995; Van Coillie, et al., 1999). The main protein structure of human CCL2 was initially characterized through employing purified natural material(Liu et al., 1996).

In response to the induction in by several stimuli and conditions such as cytokines, oxidative stress, or growth factors a wide variety of cell types including, endothelial, fibroblasts, epithelial cells, smooth muscle cells, mesangial cells, astrocytices, monocytices, and microglial cells generate CCL2. However, monocytes/macrophages are not the unique CCL2 producers but are considered as the major source of CCL2 (Deshmane et al., 2009). These cells are important during antiviral immune responses which occur in the peripheral circulation and within various tissues. Two different locates of the CCL2 primary structure are critical for its biological functions (Beall et al., 1996). The first region is consists of a sequence from Thr-10 to Tyr-13, and the second region which appears to be functionally important contains residues of 34 and 35. The CCL2 bio functions decrease following mutation in either residue 10 or 13 (Ebisawa et al., 1994). Two gene variations in the second region of the molecule are important, one of which introducing a proline between Ser-34 and Lys-35, and another one is a substitution of those two residues with the sequence Gly-Pro-His. Both of these mutations strictly reduce CCL2 activity. In addition to above polymorphisms, it has also been claimed that cell-type specificity of CCL2 was affected by mutation of residues 28 and 30, but not by residue 30 alone (Beall et al., 1996). The activity of CCL2 can also be lost, when a deletion occurs within residues at its N-terminal domain (Gong and Clark-Lewis, 1995) and some of these N-terminus deletion mutants serve as CCL2 antagonists (Gong et al., 1997).

Structural analysis by NMR techniques and asymmetrically labeling of CCL2, showed that the solution structure of the CCL2 is in dimer form (Handel and Domaille, 1996).The secondary structure of CCL2 contains four regions of β-sheet. These regions consist of residues 9–11 (β0), 27–31 (β1), 40–45 (β2), and 51–54 (β3). In addition to the four strands of sheet, CCL2 also consists of two helical regions. A long helix extends from approximately residue 58 to residue 69, nonetheless, residues 6–16 are involved in the dimerization interface of CCL2 (Zhang and Rollins, 1995). The functional residues that involved in the interface include Asn6, Ala7, Val9, Cys11, Tyr13, Asn 14, Phe15, and Thr16 near by the N-terminus, and Glu 50, Ile51, and Cys 52. It is likely that the quaternary structures of CCL2 monomers and dimers resemble them macrophage inflammatory protein-1β (MIP-1β) and CCL5 (Meunier et al., 1997). The protein complex appears to be extended with the two monomers and oriented to give an equally large pocket. Two crystal forms(I and P forms) are in structures of monomeric and dimeric CCL2 (Lubkowski et al., 1997). Antibody blocking studies and to determination of the structures of CCL2 (Reid et al., 2006). Furthermore, CCL2 form a dimer with a nonfunctional mutated form which is possibly decreasing the function of CCL2. As an example, it has been well established that7ND as a dominant-negative inhibitor of CCL2 inhibits the CCL2/CCR2 signal pathway *in vivo*, via blocking the activation of N-terminal amino acids of 2–8 (Kitamoto and Egashira, 2003). Additionally, it has been revealed that this CCL2 mutant (e.g7ND) in accompanying with wild-type CCL2 form a heterodimer, which binds to the CCL2 receptor (CCR2) and entirely constrains CCL2-mediated monocyte chemotaxis *in vitro* (Zhang and Rollins, 1995). Consistent with these facts, in a study transgenic mice expressing 7ND gene were found to inhibit CCL2 pathway and subsequently inhibit the formation of