

Elevated levels of proinflammatory cytokines in cerebrospinal fluid of multiple sclerosis patients

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Abstract

© 2017 Khaibullin, Ivanova, Martynova, Cherepnev, Khabirov, Granatov, Rizvanov and Khaiboullina. Multiple sclerosis (MS) is an autoimmune neurodegenerative disease characterized by chronic brain inflammation. Leukocyte infiltration of brain tissue causes inflammation, demyelination, and the subsequent formation of sclerotic plaques, which are a hallmark of MS. Activation of proinflammatory cytokines is essential for regulation of lymphocyte migration across the blood-brain barrier. We demonstrate increased levels of many cytokines, including IL-2RA, CCL5, CCL11, MIF, CXCL1, CXCL10, IFN γ , SCF, and TRAIL, were upregulated in cerebrospinal fluid (CSF), whereas IL-17, CCL2, CCL3, CCL4, and IL-12(p40) were activated in MS serum. Interaction analysis of cytokines in CSF demonstrated a connection between IFN γ and CCL5 as well as MIF. Many cells can contribute to production of these cytokines including CD8 and Th1 lymphocytes and astrocytes. Therefore, we suggest that IFN γ released by Th1 lymphocytes can activate astrocytes, which then produce chemoattractants, including CCL5 and MIF. These chemokines promote an inflammatory milieu and interact with multiple chemokines including CCL27 and CXCL1. Of special note, upregulation of CCL27 was found in CSF of MS cases. This observation is the first to demonstrate CCL27 as a potential contributor of brain pathology in MS. Our data suggest that CCL27 may be involved in activation and migration of autoreactive encephalitogenic immune effectors in the brain. Further, our data support the role of Th1 lymphocytes in the pathogenesis of brain inflammation in MS, with several cytokines playing a central role.

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Keywords

C-C motive ligand, C-X-C motive ligand, Cerebrospinal fluid, Interferon, Interleukin, Multiple sclerosis

References

- [1] Lassmann H, van Horssen J, Mahad D. Progressive multiple sclerosis: pathology and pathogenesis. *Nat Rev Neurol* (2012) 8(11):647-56. doi: 10.1038/nrneurol.2012.168
- [2] Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Ann Neurol* (2000) 47(6):707-17. doi:10.1002/1531-8249(200006)47:6<707::AID-ANA3>3.0.CO;2-Q

- [3] Frischer JM, Bramow S, Dal-Bianco A, Lucchinetti CF, Rauschka H, Schmidbauer M, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. *Brain* (2009) 132(Pt 5):1175-89. doi:10.1093/brain/awp070
- [4] Stadelmann C, Wegner C, Bruck W. Inflammation, demyelination, and degeneration - recent insights from MS pathology. *Biochim Biophys Acta* (2011) 1812(2):275-82. doi:10.1016/j.bbadis.2010.07.007
- [5] Whitaker JN, Gupta M, Smith OF. Epitopes of immunoreactive myelin basic protein in human cerebrospinal fluid. *Ann Neurol* (1986) 20(3):329-36. doi:10.1002/ana.410200310
- [6] Halawa I, Lolli F, Link H. Terminal component of complement C9 in CSF and plasma of patients with MS and aseptic meningitis. *Acta Neurol Scand* (1989) 80(2):130-5. doi:10.1111/j.1600-0404.1989.tb03854.x
- [7] Fainardi E, Castellazzi M, Bellini T, Manfrinato MC, Baldi E, Casetta I, et al. Cerebrospinal fluid and serum levels and intrathecal production of active matrix metalloproteinase-9 (MMP-9) as markers of disease activity in patients with multiple sclerosis. *Mult Scler* (2006) 12(3):294-301. doi:10.1191/135248506ms12740a
- [8] Maimone D, Gregory S, Arnason BG, Reder AT. Cytokine levels in the cerebrospinal fluid and serum of patients with multiple sclerosis. *J Neuroimmunol* (1991) 32(1):67-74. doi:10.1016/0165-5728(91)90073-G
- [9] Burman J, Svensson E, Fransson M, Loskog AS, Zetterberg H, Raininko R, et al. The cerebrospinal fluid cytokine signature of multiple sclerosis: a homogenous response that does not conform to the Th1/Th2/Th17 convention. *J Neuroimmunol* (2014) 277(1-2):153-9. doi:10.1016/j.jneuroim.2014.10.005
- [10] Kothur K, Wienholt L, Brilot F, Dale RC. CSF cytokines/chemokines as biomarkers in neuroinflammatory CNS disorders: a systematic review. *Cytokine* (2016) 77:227-37. doi:10.1016/j.cyto.2015.10.001
- [11] Hauser SL, Doolittle TH, Lincoln R, Brown RH, Dinarello CA. Cytokine accumulations in CSF of multiple sclerosis patients: frequent detection of interleukin-1 and tumor necrosis factor but not interleukin-6. *Neurology* (1990) 40(11):1735-9. doi:10.1212/WNL.40.11.1735
- [12] Rodríguez-Sáinz Mdel C, Sánchez-Ramón S, de Andrés C, Rodríguez-Mahou M, Muñoz-Fernández MA. Th1/Th2 cytokine balance and nitric oxide in cerebrospinal fluid and serum from patients with multiple sclerosis. *Eur Cytokine Netw* (2002) 13(1):110-4
- [13] Khaiboullina SF, Gumerova AR, Khafizova IF, Martynova EV, Lombardi VC, Bellusci S, et al. CCL27: novel cytokine with potential role in pathogenesis of multiple sclerosis. *Biomed Res Int* (2015) 2015:189638. doi:10.1155/2015/189638
- [14] Franceschini A, Szklarczyk D, Frankild S, Kuhn M, Simonovic M, Roth A, et al. STRING v9.1: protein-protein interaction networks, with increased coverage and integration. *Nucleic Acids Res* (2013) 41(Database issue):D808-15. doi:10.1093/nar/gks1094
- [15] Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* (2011) 69(2):292-302. doi:10.1002/ana.22366
- [16] Kuenz B, Lutterotti A, Ehling R, Gneiss C, Haemmerle M, Rainer C, et al. Cerebrospinal fluid B cells correlate with early brain inflammation in multiple sclerosis. *PLoS One* (2008) 3(7):e2559. doi:10.1371/journal.pone.0002559
- [17] Olsson T, Zhi WW, Höjeberg B, Kostulas V, Jiang YP, Anderson G, et al. Autoreactive T lymphocytes in multiple sclerosis determined by antigen-induced secretion of interferon-gamma. *J Clin Invest* (1990) 86(3):981-5. doi:10.1172/JCI114800
- [18] Sun JB, Olsson T, Wang WZ, Xiao BG, Kostulas V, Fredrikson S, et al. Autoreactive T and B cells responding to myelin proteolipid protein in multiple sclerosis and controls. *Eur J Immunol* (1991) 21(6):1461-8. doi:10.1002/eji.1830210620
- [19] Pelfrey CM, Rudick RA, Cotleur AC, Lee JC, Tary-Lehmann M, Lehmann PV. Quantification of self-recognition in multiple sclerosis by single-cell analysis of cytokine production. *J Immunol* (2000) 165(3):1641-51. doi:10.4049/jimmunol.165.3.1641
- [20] Brucklacher-Waldert V, Stuermer K, Kolster M, Wolthausen J, Tolosa E. Phenotypical and functional characterization of T helper 17 cells in multiple sclerosis. *Brain* (2009) 132(Pt 12):3329-41. doi:10.1093/brain/awp289
- [21] Kebir H, Ifergan I, Alvarez JI, Bernard M, Poirier J, Arbour N, et al. Preferential recruitment of interferon-gamma-expressing TH17 cells in multiple sclerosis. *Ann Neurol* (2009) 66(3):390-402. doi:10.1002/ana.21748
- [22] Ouyang W, Kolls JK, Zheng Y. The biological functions of T helper 17 cell effector cytokines in inflammation. *Immunity* (2008) 28(4):454-67. doi:10.1016/j.immuni.2008.03.004
- [23] Lees JR, Golumbek PT, Sim J, Dorsey D, Russell JH. Regional CNS responses to IFN-gamma determine lesion localization patterns during EAE pathogenesis. *J Exp Med* (2008) 205(11):2633-42. doi:10.1084/jem.20080155
- [24] Panitch HS, Hirsch RL, Haley AS, Johnson KP. Exacerbations of multiple sclerosis in patients treated with gamma interferon. *Lancet* (1987) 1(8538):893-5. doi:10.1016/S0140-6736(87)92863-7
- [25] Maxeiner HG, Marion Schneider E, Kurfiss ST, Brettschneider J, Tumani H, Bechter K. Cerebrospinal fluid and serum cytokine profiling to detect immune control of infectious and inflammatory neurological and psychiatric diseases. *Cytokine* (2014) 69(1):62-7. doi:10.1016/j.cyto.2014.05.008

- [26] Li QQ, Bever CT. Mechanisms underlying the synergistic effect of Th1 cytokines on RANTES chemokine production by human glial cells. *Int J Mol Med* (2001) 7(2):187-95. doi:10.3892/ijmm.7.2.187
- [27] Bakht M, Tjernlund A, Mousa A, Gad A, Strömlund S, Kuziel WA, et al. RANTES promotes growth and survival of human first-trimester forebrain astrocytes. *Nat Cell Biol* (2001) 3(2):150-7. doi:10.1038/35055057
- [28] Dong Y, Benveniste EN. Immune function of astrocytes. *Glia* (2001) 36(2):180-90. doi:10.1002/glia.1107
- [29] Tan LJ, Vanderlugt CL, McRae BL, Miller SD. Regulation of the effector stages of experimental autoimmune encephalomyelitis via neuroantigen-specific tolerance induction. III. A role for anergy/deletion. *Autoimmunity* (1998) 27(1):13-28. doi:10.3109/08916939809008034
- [30] Kort JJ, Kawamura K, Fugger L, Weissert R, Forsthuber TG. Efficient presentation of myelin oligodendrocyte glycoprotein peptides but not protein by astrocytes from HLA-DR2 and HLA-DR4 transgenic mice. *J Neuroimmunol* (2006) 173(1-2):23-34. doi:10.1016/j.jneuroim.2005.11.014
- [31] Stüve O, Youssef S, Slavin AJ, King CL, Patarroyo JC, Hirschberg DL, et al. The role of the MHC class II transactivator in class II expression and antigen presentation by astrocytes and in susceptibility to central nervous system autoimmune disease. *J Immunol* (2002) 169(12):6720-32. doi:10.4049/jimmunol.169.12.6720
- [32] van Veen T, Nielsen J, Berkhof J, Barkhof F, Kamphorst W, Bö L, et al. CCL5 and CCR5 genotypes modify clinical, radiological and pathological features of multiple sclerosis. *J Neuroimmunol* (2007) 190(1-2):157-64. doi:10.1016/j.jneuroim.2007.08.005
- [33] Bartosik-Psujek H, Stelmasiak Z. Correlations between IL-4, IL-12 levels and CCL2, CCL5 levels in serum and cerebrospinal fluid of multiple sclerosis patients. *J Neural Transm (Vienna)* (2005) 112(6):797-803. doi:10.1007/s00702-004-0225-9
- [34] Szczucinski A, Losy J. CCL5, CXCL10 and CXCL11 chemokines in patients with active and stable relapsing-remitting multiple sclerosis. *Neuroimmunomodulation* (2011) 18(1):67-72. doi:10.1159/000317394
- [35] Bernhagen J, Calandra T, Bucala R. Regulation of the immune response by macrophage migration inhibitory factor: biological and structural features. *J Mol Med (Berl)* (1998) 76(3-4):151-61. doi:10.1007/s001090050204
- [36] Bacher M, Meinhardt A, Lan HY, Mu W, Metz CN, Chesney JA, et al. Migration inhibitory factor expression in experimentally induced endotoxemia. *Am J Pathol* (1997) 150(1):235-46
- [37] Heyland DK, Rocker GM, Dodek PM, Kutsogiannis DJ, Konopad E, Cook DJ, et al. Family satisfaction with care in the intensive care unit: results of a multiple center study. *Crit Care Med* (2002) 30(7):1413-8. doi:10.1097/00003246-200207000-00002
- [38] Choi SS, Lee HJ, Lim I, Satoh J, Kim SU. Human astrocytes: secretome profiles of cytokines and chemokines. *PLoS One* (2014) 9(4):e92325. doi:10.1371/journal.pone.0092325
- [39] Niino M, Ogata A, Kikuchi S, Tashiro K, Nishihira J. Macrophage migration inhibitory factor in the cerebrospinal fluid of patients with conventional and optic-spinal forms of multiple sclerosis and neuro-Behcet's disease. *J Neurol Sci* (2000) 179(S 1-2):127-31. doi:10.1016/S0022-510X(00)00397-X
- [40] Cox GM, Kithcart AP, Pitt D, Guan Z, Alexander J, Williams JL, et al. Macrophage migration inhibitory factor potentiates autoimmune-mediated neuroinflammation. *J Immunol* (2013) 191(3):1043-54. doi:10.4049/jimmunol.1200485
- [41] Castaneda Moreno VA, Muñoz-Valle JF, Torres Carrillo N, Gonzalez Perez OP, Macias Islas MA, Ruiz Sandoval JL, et al. A case-control study on the association of MIF-794 CATT5-8 and-173 G > C polymorphisms and its serum levels and the clinical severity of multiple sclerosis in Mexican patients. *Front Immunol* (2015). doi:10.3389/conf.fimmu.2015.05.00227
- [42] Akcali A, Pehlivan S, Pehlivan M, Sever T, Neyal M. Association of macrophage migration inhibitory factor gene promoter polymorphisms with multiple sclerosis in Turkish patients. *J Int Med Res* (2010) 38(1):69-77. doi:10.1177/147323001003800108
- [43] Reiss Y, Proudfoot AE, Power CA, Campbell JJ, Butcher EC. CC chemokine receptor (CCR)4 and the CCR10 ligand cutaneous T cell-attracting chemokine (CTACK) in lymphocyte trafficking to inflamed skin. *J Exp Med* (2001) 194(10):1541-7. doi:10.1084/jem.194.10.1541
- [44] Gunsolly C, Nicholson JD, Listwak SJ, Ledee D, Zelenka P, Verthelyi D, et al. Expression and regulation in the brain of the chemokine CCL27 gene locus. *J Neuroimmunol* (2010) 225(1-2):82-90. doi:10.1016/j.jneuroim.2010.04.019
- [45] Dorf ME, Berman MA, Tanabe S, Heesen M, Luo Y. Astrocytes express functional chemokine receptors. *J Neuroimmunol* (2000) 111(1-2):109-21. doi:10.1016/S0165-5728(00)00371-4
- [46] Cartier L, Hartley O, Dubois-Dauphin M, Krause KH. Chemokine receptors in the central nervous system: role in brain inflammation and neurodegenerative diseases. *Brain Res Brain Res Rev* (2005) 48(1):16-42. doi:10.1016/j.brainresrev.2004.07.021
- [47] Homey B, Alenius H, Müller A, Soto H, Bowman EP, Yuan W, et al. CCL27-CCR10 interactions regulate T cell-mediated skin inflammation. *Nat Med* (2002) 8(2):157-65. doi:10.1038/nm0202-157