Chemokine (C-C motif) ligand 5 (also CCL5) is a protein which in humans is encoded by the CCL5 gene.

It is also known as RANTES (regulated on activation, normal T cell expressed and secreted).

CCL5 is an 8kDa protein classified as a chemotactic cytokine or chemokine. CCL5 is chemotactic for T cells, eosinophils, and basophils, and plays an active role in recruiting leukocytes into inflammatory sites. With the help of particular cytokines (i.e., IL-2 and IFN-γ) that are released by T cells, CCL5 also induces the proliferation and activation of certain natural-killer (NK) cells to form CHAK (CC-Chemokine-activated killer) cells.

It is also an HIV-suppressive factor released from CD8+ T cells. This chemokine has been localized to chromosome 17 in humans.

RANTES was first identified in a search for genes expressed “late” (3–5 days) after T cell activation. It was subsequently determined to be a CC chemokine and expressed in more than 100 human diseases. RANTES expression is regulated in T lymphocytes by Kruppel like factor 13 (KLF13).

RANTES, along with the related chemokines MIP-1alpha and MIP-1beta, has been identified as a natural HIV-suppressive factor secreted by activated CD8+ T cells and other immune cells.

Recently, the RANTES protein has been engineered for in vivo production by Lactobacillus bacteria, and this solution is being developed into a possible HIV entry-inhibiting topical microbicide.

CCL5 has been shown to interact with CCR3, CCR5 and CCR1.

CCL5 also activates the G-protein coupled receptor GPR75.

CCL2 (MCP-1) and CCL5 (RANTES) are pro-inflammatory chemokines that mediate neuroimmune responses to acute insults, and aspects of brain injury and neurodegenerative diseases; however, a blood-to-brain transport system has not been evaluated for either chemokine in vivo. Therefore, Quaranta et al. determined whether CCL2 and CCL5 in blood can cross the intact BBB and enter the brain. Using CD-1 mice, they found that 125I-labeled CCL2 and CCL5 crossed the BBB, and entered the brain parenchyma. They next aimed to identify the mechanisms of 125I-CCL2 and 125I-CCL5 transport in an in-situ brain perfusion model. They found that both heparin and eprodisate inhibited brain uptake of 125I-CCL2 and 125I-CCL5 in situ, whereas antagonists of their receptors, CCR2 or CCR5 respectively, did not, suggesting that heparan sulfates at the endothelial surface mediate BBB transport. Finally, they showed that CCL2 and CCL5 transport across the BBB increased following a single injection of 0.3mg/kg lipopolysaccharide. These data demonstrate that CCL2 and CCL5 in the brain can derive, in part, from the circulation, especially during systemic inflammation. Further, binding to the BBB-associated heparan sulfate is a mechanism by which both chemokines can cross the intact BBB, highlighting a novel therapeutic target for treating neuroinflammation.The work demonstrates that CCL2 and CCL5 can cross the intact BBB, and that transport is robustly increased during inflammation. These data suggest that circulating CCL2 and CCL5 can contribute to brain levels of each chemokine. They further showed that the transport of both chemokines is inhibited by heparin and eprodisate, suggesting that CCL2/CCL5-heparan sulfate interactions could be therapeutically targeted to limit accumulation of these chemokines in the brain [1)].

Pro-inflammatory chemokines CCL5 and CXCL6 are released by induced degenerative discs, and CCL5 has been associated with discogenic back pain. A case-control study was performed, based on the Hong Kong Disc Degeneration Population-Based Cohort of Southern Chinese, to investigate if systemic levels of CCL5 and CXCL6 were elevated in subjects with disc degeneration compared to non-degenerated individuals. Eighty subjects were selected, 40 with no disc degeneration (control group; DDD score 0) and 40 with moderate/severe disc degeneration (disc degeneration group; DDD score ≥5) as noted on MRI. Subjects were matched for age, sex, body mass index and workload. Blood plasma samples were obtained from each individual, and levels of CCL5 and CXCL6 were measured. Secondary phenotypes of lumbar disc displacement and cervical disc changes were also assessed. CCL5 concentrations were significantly increased in the disc degeneration (mean: 19.8 ng/mL) compared to the control group (mean: 12.8 ng/mL) ($p = 0.015$). The degeneration group demonstrated higher levels of CXCL6 (mean: 56.9 pg/mL) compared to the control group (mean: 43.4 pg/mL) ($p = 0.010$). There was a trend towards elevated CCL5 levels with disc displacement in the degeneration group ($p = 0.073$). Cervical disc degeneration was not associated with elevated chemokine levels ($p > 0.05$). This is the first study to note that elevated systemic CCL5 and CXCL6 were associated with moderate/severe lumbar disc degeneration, further corroborating tissue studies of painful discs. These chemokines may be systemic biomarkers for the diagnosis and monitoring of disc degeneration [2].

1)
Quaranta DV, Weaver RR, Baumann KK, Fujimoto T, Williams LM, Kim HC, Logsdon AF, Omer M, Reed MJ, Banks WA, Erickson MA. Transport of the pro-inflammatory chemokines CCL2 (MCP-1) and CCL5 (RANTES) across the intact mouse blood-brain barrier is inhibited by heparin and eprodisate and increased with systemic inflammation. J Pharmacol Exp Ther. 2022 Oct 30:JPET-AR-2022-001380. doi: 10.1124/jpet.122.001380. Epub ahead of print. PMID: 36310035.

2)
Grad S, Bow C, Karppinen J, Luk KD, Cheung KM, Alini M, Samartzis D. Systemic blood plasma CCL5 and CXCL6: Potential biomarkers for human lumbar disc degeneration. Eur Cell Mater. 2016 Jan 5;30:1-10. PubMed PMID: 26728495.