CCR4

Hematoma is a crucial factor leading to poor prognosis after intracerebral hemorrhage (ICH). Promoting microglial phagocytosis to enhance hematoma resolution may be an important therapeutic target for recovery after ICH. C-C chemokine receptor 4 (CCR4) is important for regulating immune balance in the central nervous system. However, whether CCR4 activation can attenuate hematoma after ICH remains unknown. Deng et al. aimed to evaluate whether CCL17 (a specific ligand of CCR4) treatment can promote hematoma resolution through CCR4/ERK/Nrf2/CD163 pathway after ICH. A total of 261 adult male CD1 mice were used. Mice were subjected to intrastriatal injection of autologous blood to induce ICH and randomly assigned to receive recombinant CCL17 (rCCL17) or vehicle which was administered intranasally at 1 h after ICH. To elucidate the underlying mechanism, C021, a selective inhibitor of CCR4 and ML385 and a selective inhibitor of Nrf2 were administered 1 h prior to ICH induction. Clustered regularly interspaced short palindromic repeats (CRISPR) knockout for CD163 was administered by intracerebroventricular injection at 48 h before ICH. Brain edema, short- and long-term neurobehavior evaluation, hematoma volume, hemoglobin content, western blot, and immunofluorescence staining were performed. Endogenous CCL17, CCR4, and CD163 expression increased and peaked at 72 h after ICH. CCR4 was expressed by microglia. CCR4 activation with rCCL17 significantly improved neurobehavioral scores and reduced hematoma volume and brain edema compared with vehicle. Moreover, rCCL17 treatment significantly promoted phosphorylation of ERK1/2, increased the expression Nrf2, and upregulated CD163 expression after ICH. The protective effects of rCCL17 were abolished by administration of C021, ML385, and CD163 CRISPR knockout. This study demonstrated that CCR4 activation with rCCL17 promoted hematoma resolution by increasing CD163 expression and CCR4/ERK/Nrf2 pathway activation after ICH, thereby reducing brain edema and improving neurological function. Overall, our study suggests that CCR4 activation may be a potential therapeutic strategy to attenuate hematoma in early brain injury after ICH [1)].

Machine learning analyses demonstrated that the genes and subject factors CCR4, IFNA2, IL-9, CXCL3, Age, T2DM, IL-7, CCL4, BMI, IL-5, CCR3, TNFα, and IL-27 predicted infarct volume. The genes and subject factor IFNA2, IL-5, CCL11, IL-17C, CCR4, IL-9, IL-7, CCR3, IL-27, T2DM, and CSF2 predicted edema volume. The overlap of genes CCR4, IFNA2, IL-9, IL-7, IL-5, CCR3, and IL-27 with T2DM predicted both infarct and edema volumes. These genes relate to a microenvironment for chemoattraction and proliferation of autoimmune cells, particularly Th2 cells and neutrophils. Conclusions: Machine learning algorithms can be employed to develop prognostic predictive biomarkers for stroke outcomes in ischemic stroke patients, particularly in regard to identifying acute gene expression changes that occur during stroke [2)].

Mogamulizumab is a defucosylated humanized anti-CC chemokine receptor type 4 (CCR4) antibody that exerts an anti-tumor immune effect against various tumors through a suppressive effect on regulatory T-cells. We herein report a patient with peripheral T-cell lymphoma who developed Epstein-Barr virus (EBV)-related primary diffuse large B-cell lymphoma of the central nervous system (CNS DLBCL) after mogamulizumab therapy. Our experience should alert physicians to the possibility of the development of EBV-related CNS DLBCL in patients treated for primary lymphoma and suggests that the anti-tumor immune effect of mogamulizumab is ineffective for the prophylaxis of EBV-related lymphomas [3)].

Chang et al. reported that macrophages and microglia within the glioma microenvironment produce CCL2, a chemokine that is critical for recruiting both CCR4+ Treg and CCR2+Ly-6C+ monocytic MDSCs in this disease setting. In murine gliomas, they established novel roles for tumor-derived CCL20 and osteoprotegerin in inducing CCL2 production from macrophages and microglia. Tumors grown in CCL2-deficient mice failed to maximally accrue Tregs and monocytic MDSCs. In mixed-bone marrow chimera assays, we found that CCR4-deficient Treg and CCR2-deficient monocytic MDSCs were defective in glioma accumulation. Furthermore, administration of a small-molecule antagonist of CCR4 improved median survival in the model. In clinical specimens of glioblastoma multiforme, elevated levels of CCL2 expression correlated with reduced overall survival of patients. Finally, we found that CD163-positive infiltrating macrophages were a major source of CCL2 in glioblastoma multiforme patients. Collectively, our findings show how glioma cells influence the tumor microenvironment to recruit potent effectors of immunosuppression that drive progression [4].

Despite the immunogenicity of glioblastoma multiforme (GBM), immune-mediated eradication of these tumors remains deficient. Regulatory T cells (Tregs) in the blood and within the tumor microenvironment of GBM patients are known to contribute to their dismal immune responses. Here, we determined which chemokine secreted by gliomas can preferentially induce Treg recruitment and migration. In the malignant human glioma cell lines D-54, U-87, U-251, and LN-229, the chemokines CCL22 and CCL2 were detected by intracellular cytokine analysis. Furthermore, tumor cells from eight patients with GBM had a similar chemokine expression profile. However, only CCL2 was detected by enzyme-linked immunosorbent assay, indicating that CCL2 may be the principal chemokine for Treg migration in GBM patients. Interestingly, the Tregs from GBM patients had significantly higher expression levels of the CCL2 receptor CCR4 than did Tregs from healthy controls. Glioma supernatants and the recombinant human chemokines CCL2 and CCL22 induced Treg migration and were blocked by antibodies to the chemokine receptors. Production of CCL2 by glioma cells could also be mitigated by the chemotherapeutic agents temozolomide and carmustine [3-bis (2-chloroethyl)-1-nitrosourea]. Our results indicate that gliomas augment immunosuppression by selective chemokine-mediated recruitment of Tregs into the tumor microenvironment and that modulating this interaction with chemotherapy could facilitate the development of novel immunotherapeutics to malignant gliomas. [5].

CXCR3 and CCR4 thus appear to be available as markers for Th1/Th2 subsets in the synovia of AA rats. Using these markers, it became clear that the percentage of Th1 cells to total Th cells was higher than that of Th2 cells in axotomized AA rats at weeks 2-4, whereas in sham-operated AA rats, the percentage of Th1 cells to total Th cells was higher than that of Th2 cells at week 2 and the latter exceeded the former at week 4. Our observations strongly suggested the presence of the anti-inflammatory action of sensory nerves in rats with adjuvant arthritis [6].

1)
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