Role of CCR5 receptor on microglia-glioma interaction

E. Laudati, P.Navarra, L. Lisi

Institute of Pharmacology, Catholic University Medical School

Malignant glioma belong to the most aggressive neoplasms in humans with no successful treatment available. Patients suffering from glioblastoma multiforme (GBM), the highest-grade glioma, have an average survival time of only around one year after diagnosis. Microglia and peripheral macrophages accumulate within and around glioma, but fail to exert effective antitumor activity and even support tumor growth. Tumor cell proliferation and invasion are critically regulated by chemokines and their receptors. Recent studies have shown that the chemokine CCL5 and its receptor CCR5 play important roles in tumor invasion and metastasis. Nonetheless, the roles of the CCR5 in GBM still remain unclear.
In the present project, for the first time we show that Maraviroc (MRC), a small molecule CCR5 antagonist, is able to reduce proliferation and viability of rat C6 glioma cells determined by BrdU incorporation assay and MTT assay, at different concentration and different time of exposure. Furthermore, we analyzed the interaction and the tumor-invasion of microglia in GBM. We already characterized the influence of glioma-soluble factors on microglial function, comparing the effects of media harvested under basal conditions (control conditioned media C-CM) with those of media obtained after inducing a pro-inflammatory activation state in glioma cells (LPS-IFNγ conditioned media LI-CM) (Lisi L, Laudati E et al 2014). After microglia cells were stimulated with C-CM or LI-CM , cell proliferation and invasion (BrdU assay and MTT assay) were significantly enhanced, and this effect was modified in 3 days by treatment with 100nM - 1μM MRC. In addition we studied the invasion of microglia by transwell assay.
Finally by RT-PCR analyses and measurement of Nitrites (M1 marker) and Urea (M2 marker) we studied the different polarization phenotype (M1 versus M2 phenotype)of microglia in presence of C-CM and MRC or LI-CM and MRC. In particular we provide the evidence that the chemokine receptor promotes different microglia polarization, suggesting that small molecule inhibitors of CCR5 might be exploited for their anticancer potential, targeting both glioma and microglia cells.

Lisi L, Laudati E, Navarra P, Dello Russo C. The mTOR kinase inhibitors polarize glioma-activated microglia to express a M1 phenotype. J Neuroinflammation. 2014 Jul 23;11:125.