GLIOMA-MICROGLIA COMMUNICATION: FROM MECHANISMS TO THERAPEUTIC TARGETING

ABSTRACT

Glioma cells produce factors attracting and polarizing microglia and peripheral macrophages into pro-invasive, immunosuppressive cells, which support tumor progression and contribute to therapy resistance. Tumor-microglia interactions create an immunosuppressive milieu and inhibit responses of infiltrating T cells. We identified major microglia-activating factors as granulocyte macrophage colony factor (CSF2) and tumor-processed osteopontin/SPP1. Osteopontin is a small glycoprotein, interacting via a RGD motif with integrin receptors on immune cells. Tumor-processed Spp1 induces the pro-invasive re-programming of microglia in vitro. Knockdown of Spp1 in experimental rat C6 glioma inhibited growth of intracranial gliomas and reduced the number of pro-invasive microglia/macrophages expressing Arg1 and CD163. Moreover, T lymphocytes infiltrating Spp1-depleted gliomas showed signs of restoration of antitumor activity. Using a series of Spp1 mutants we discriminated if protumorigenic effects of Spp1 depends on its contribution to self-renewal or glioma stem cells or interactions with microenvironment. We found that only re-expression of the RGD mutated Spp1 did not restore tumor growth in vivo suggesting that interactions with microglia is vital for tumor growth. We designed a short RGD peptide interfering with osteopontin binding and the peptide blocked efficiently migration, phagocytosis and tumor-evoked integrin signaling in cultured microglia. While osteopontin was critical for microglia polarization, CSF2 interacting with its receptor on microglia was essential for microglia infiltration and survival. We developed and tested in vitro short peptides targeting CSF2 or osteopontin and provided an evidence for anti-tumor activity of CSF2 targeting peptides delivered intra-cranially to human U87 gliomas growing in nude mice. Our results show that targeting glioma-microglia interactions with short interfering peptides could be a novel therapeutic strategy.