

Abstract 4919: Ablation of neuropilin 1 from glioma-associated microglia and macrophages slows tumor progression

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Abstract

Gliomas are the most commonly diagnosed primary tumors of the central nervous system (CNS). Median times of survival are dismal regardless of the treatment approach, underlying the need to develop more effective therapies. Modulation of the immune system is a promising strategy as innate and adaptive immunity play important roles in cancer progression. Glioma associated microglia and macrophages (GAMs) can comprise over 30% of the cells in glioma biopsies. Gliomas secrete cytokines that suppress the anti-tumorigenic properties of GAMs, causing them to secrete factors that support the tumor's spread and growth. Neuropilin 1 (Nrp1) is a transmembrane receptor that in mice both amplifies pro-angiogenic signaling in the tumor microenvironment and affects behavior of innate immune cells. Using a Cre-lox system, we generated mice that lack expression of Nrp1 in GAMs. We demonstrate, using an in vivo orthotopic glioma model, that tumors in mice with Nrp1-deficient GAMs exhibit less vascularity, grow at a slower pace, and are populated by increased numbers of anti-tumorigenic GAMs. Moreover, glioma survival times in mice with Nrp1-deficient GAMs were significantly longer. Treating wild-type mice with a small molecule inhibitor of Nrp1's b1 domain, EG00229, which we show here is selective for Nrp1 over Nrp2, yielded an identical outcome. Moreover, transplanting bone marrow from mice with Nrp1-deficient macrophages to wild type recipient mice led to reductions in tumor growth, albeit not to the extent seen in knockout mice. Nrp1-deficient or EG00229-treated wild-type microglia exhibited a shift towards anti-tumorigenicity as evident by altered inflammatory marker profiles in vivo and decreased SMAD2/3 activation when conditioned in the presence of glioma-derived factors. These results provide support for the proposal that pharmacological inhibition of Nrp1 constitutes a potential strategy for suppressing glioma progression.

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