

PubMed

U.S. National Library of Medicine
National Institutes of Health



Display Settings: Abstract

[Cancer Res.](#) 2011 Feb 15. [Epub ahead of print]

COX-2 blockade suppresses gliomagenesis by inhibiting myeloid-derived suppressor cells.

Fujita M, Kohanbash G, Fellows-Mayle W, Hamilton RL, Komohara Y, Decker SA, Ohlfest JR, Okada H.
Neurological Surgery, Brain Tumor Program, University of Pittsburgh.

Abstract

Epidemiological studies have highlighted associations between the regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) and reduced glioma risks in humans. Most NSAIDs function as cyclooxygenase-2 (COX-2) inhibitors that prevent production of prostaglandin E2 (PGE2). Since PGE2 induces expansion of myeloid-derived suppressor cells (MDSCs), we hypothesized that COX-2 blockade would suppress gliomagenesis by inhibiting MDSC development and accumulation in the tumor microenvironment (TME). In mouse models of glioma, treatment with the COX-2 inhibitors acetylsalicylic acid (ASA) or celecoxib inhibited systemic PGE2 production and delayed glioma development. ASA treatment also reduced the MDSC-attracting chemokine CCL2 in the TME along with numbers of CD11b+Ly6GhiLy6Clo granulocytic MDSCs in both the bone marrow and TME. In support of this evidence that COX-2 blockade blocked systemic development of MDSCs and their CCL2-mediated accumulation in the TME, there were defects in these processes in glioma-bearing Cox2-deficient and Ccl2-deficient mice. Conversely, these mice or ASA-treated wild-type mice displayed enhanced expression of CXCL10 and infiltration of cytotoxic T lymphocytes (CTL) in the TME, consistent with a relief of MDSC-mediated immune suppression. Antibody-mediated depletion of MDSCs delayed glioma growth in association with an increase in CXCL10 and CTLs in the TME, underscoring a critical role for MDSCs in glioma development. Lastly, Cxcl10-deficient mice exhibited reduced CTL infiltration of tumors, establishing that CXCL10 limited this pathway of immune suppression. Taken together, our findings show that the COX-2 pathway promotes gliomagenesis by directly supporting systemic development of MDSC and their accumulation in the TME, where they limit CTL infiltration.

PMID: 21324923 [PubMed - as supplied by publisher]

[LinkOut - more resources](#)