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*Cancer Research* 68, 6978-6986, September 1, 2008. doi: 10.1158/0008-5472.CAN-07-5675

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## Cell, Tumor, and Stem Cell Biology

# Nonsteroidal Anti-inflammatory Drugs Suppress Glioma via 15- Hydroxyprostaglandin Dehydrogenase

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**Key Words:** prostaglandin dehydrogenase • cyclooxygenase • glioblastoma • nonsteroidal antiinflammatory drug

Studies have conjectured that nonsteroidal anti-inflammatory drugs (NSAID) inhibit growth of various malignancies by inhibiting cyclooxygenase-2 (COX-2) enzyme activity. Yet, several lines of evidence indicate that a COX-2-independent mechanism may also be involved in their antitumor effects. Here, we report that NSAIDs may inhibit the growth of glioblastoma multiforme (GBM) cells through COX-2-independent mechanisms, including up-regulation of both 15-hydroxyprostaglandin dehydrogenase (15-PGDH, the key prostaglandin catabolic enzyme) and the cell cycle inhibitor p21. Using Western blot and real-time PCR analysis in various GBM cell lines,

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we observed up-regulation of 15-PGDH and p21 after NSAIDs treatment. To elucidate the role of 15-PGDH in GBM, transfection assays were conducted using the T98G GBM cell line. Overexpression of 15-PGDH suppressed cell growth and was associated with increased expression of p21. In an attempt to investigate the roles of COX-2, 15-PGDH, and p21 in the inhibition of growth of GBM, small interfering RNA (siRNA) against each of these proteins was transfected into T98G cells. Inhibition of growth mediated by NSAIDs was partially reversed after knockdown of either 15-PGDH or p21, but not after COX-2 knockdown. Moreover, expression level of p21 was not affected in COX-2 siRNA transfected cells. Our studies provide evidence that the up-regulation of 15-PGDH induced by NSAIDs has the potential to inhibit growth of GBM, in part, by up-regulation of p21 possibly independent from COX-2 enzymatic function. [Cancer Res 2008;68(17):6978–86]

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