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Basic and Translational Investigations

Tumor-growthpromoting cyclooxygenase-2 prostaglandin E₂ pathway provides medulloblastoma therapeutic targets

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► Abstract

Prostaglandin E₂ (PGE₂) has been shown to play important roles in several aspects of tumor development and progression. PGE₂ is synthesized from arachidonic acid by cyclooxygenases (COX) and prostaglandin E synthases (PGES) and mediates its biological activity through binding to the four prostanoid receptors EP₁ through EP₄. In this study, we show for the first time that medulloblastoma (MB), the most common malignant childhood brain tumor, expresses high levels of COX-2, microsomal prostaglandin E synthase-1, and

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EP₁ through EP₄ and secretes PGE₂. PGE₂ and the EP₂ receptor agonist butaprost stimulated MB cell proliferation. Treatment of MB cells with COX inhibitors suppressed PGE₂ production and induced caspase-dependent apoptosis. Similarly, specific COX-2 silencing by small interfering RNA inhibited MB cell growth. EP₁ and EP₃ receptor antagonists ONO-8713 and ONO-AE3-240, but not the EP₄ antagonists ONO-AE3-208 and AH 23848, inhibited tumor cell proliferation, indicating the significance of EP1 and EP3 but not EP4 for MB growth. Administration of COX inhibitors at clinically achievable nontoxic concentrations significantly inhibited growth of established human MB xenografts. Apoptosis was increased, proliferation was reduced, and angiogenesis was inhibited in MBs treated with COX inhibitors. This study suggests that PGE₂ is important for MB growth and that therapies targeting the prostanoid metabolic pathway are potentially beneficial and should be tested in clinical settings for treatment of children with MB.

Key Words: angiogenesis, apoptosis, cyclooxygenase-2, in vivo treatment, medulloblastoma, microsomal prostaglandin E synthase-1, primitive neuroectodermal tumors, proliferation, prostaglandin E₂, prostanoid receptors

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