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Gamma-linolenic acid inhibits both tumour cell cycle progression and angiogenesis in the orthotopic C6 glioma model through changes in VEGF, Flt1, ERK1/2, MMP2, cyclin D1, pRb, p53 and p27 protein expression.

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Abstract

BACKGROUND: Gamma-linolenic acid is a known inhibitor of tumour cell proliferation and migration in both in vitro and in vivo conditions. The aim of the present study was to determine the mechanisms by which gamma-linolenic acid (GLA) osmotic pump infusion alters glioma cell proliferation, and whether it affects cell cycle control and angiogenesis in the C6 glioma in vivo.

METHODS: Established C6 rat gliomas were treated for 14 days with 5 mM GLA in CSF or CSF alone. Tumour size was estimated, microvessel density (MVD) counted and protein and mRNA expression measured by immunohistochemistry, western blotting and RT-PCR.

RESULTS: GLA caused a significant decrease in tumour size (75 +/- 8.8%) and reduced MVD by 44 +/- 5.4%. These changes were associated with reduced expression of vascular endothelial growth factor (VEGF) (71 +/- 16%) and the VEGF receptor Flt1 (57 +/- 5.8%) but not Flk1. Expression of ERK1/2 was also reduced by 27 +/- 7.7% and 31 +/- 8.7% respectively. mRNA expression of matrix metalloproteinase-2 (MMP2) was reduced by 35 +/- 6.8% and zymography showed MMP2 proteolytic activity was reduced by 32 +/- 8.5%. GLA altered the expression of several proteins involved in cell cycle control. pRb protein expression was decreased (62 +/- 18%) while E2F1 remained unchanged. Cyclin D1 protein expression was increased by 42 +/- 12% in the presence of GLA. The cyclin dependent kinase inhibitors p21 and p27 responded differently to GLA, p27 expression was increased (27 +/- 7.3%) while p21 remained unchanged. The expression of p53 was increased (44 +/- 16%) by GLA. Finally, the BrdU incorporation studies found a significant inhibition (32 +/- 11%) of BrdU incorporation into the tumour in vivo.

CONCLUSION: Overall the findings reported in the present study lend further support to the potential of GLA as an inhibitor of glioma cell proliferation in vivo and show it has direct effects upon cell cycle control and angiogenesis. These effects involve changes in protein expression of VEGF, Flt1, ERK1, ERK2, MMP2, Cyclin D1, pRb, p53 and p27. Combination therapy using drugs with other, complementary targets and GLA could lead to gains in treatment efficacy in this notoriously difficult to treat tumour.

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