17-AAG sensitized malignant glioma cells to death-receptor mediated apoptosis

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Abstract

17-AAG is a selective HSP90-inhibitor that exhibited therapeutic activity in cancer. In this study three glioblastoma cell lines (U87, LN229 and U251) were treated with 17-AAG, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) or the combination of both. Treatment with subtoxic doses of 17-AAG in combination with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induces rapid apoptosis in TRAIL-resistant glioma cells, suggesting that this combined treatment may offer an attractive strategy for treating gliomas. 17-AAG treatment down-regulated survivin through proteasomal degradation. In addition, over-expression of survivin attenuated cytotoxicity induced by the combination of 17-AAG and TRAIL. In summary, survivin is a key regulator of TRAIL–17-AAG mediated cell death in malignant glioma.
Keywords: Glioma; TRAIL/Apo2L; Survivin; HSP90; 17-AAG; Proteasome

Abbreviations: TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; IAP, Inhibitor of Apoptosis proteins; 17-AAG, 17-Allylamino geldanamycin; XIAP, X-linked Inhibitor of Apoptosis Protein; HSP90, heat-shock-protein 90; ph–Akt, phosphorylated Akt

Article Outline

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  17-AAG sensitized U87, LN229 and U251 to TRAIL-induced apoptosis
  17-AAG augments TRAIL-induced apoptosis through caspase activation
  Down-regulation of survivin, XIAP, ph–Akt and Akt by 17-AAG
  17-AAG enhances proteasomal degradation of survivin
  Survivin-specific siRNA sensitizes U87 for TRAIL-induced cytotoxicity
  Over-expression of survivin attenuates TRAIL–17-AAG mediated cytotoxicity
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