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Genistein enhances proteasomal degradation of the short isoform of FLIP in malignant glioma cells and thereby augments TRAIL-mediated apoptosis.

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Abstract

Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) is a promising cancer drug. One obstacle in TRAIL-based therapies is that many cancer cells, including gliomas, are resistant towards TRAIL. In this study one glioblastoma cell line, one human short-term glioblastoma culture and human astrocytes were treated with genistein, tumour necrosis factor-related apoptosis-inducing ligand or the combination of both. Single treatment with genistein or TRAIL does not induce cytotoxicity in malignant glioma cells. However, treatment with genistein in combination with TRAIL induces rapid apoptosis in TRAIL-resistant glioma cells. Notably, normal human astrocytes were not affected by the combination treatment consisting of genistein and TRAIL. Genistein enhanced proteasomal degradation of the short isoform of c-FLIP. Importantly, over-expression of only the short isoform of c-FLIP attenuated genistein TRAIL-mediated cytotoxicity. Taken together, we gave evidence that genistein facilitated TRAIL-mediated apoptosis at the level of the extrinsic apoptotic pathways in malignant glioma cells.

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