PUMA

Replacement of the p53 tumor suppressor gene is a rational approach to the management of malignant gliomas because p53 is frequently mutated or inactivated in these cancers. Major weaknesses of this approach are that malignant gliomas are mixtures of cells with wild-type and mutant p53, and that tumor cells exhibiting wildtype p53 are resistant to p53 gene transfer. An effective alternative is needed to overcome these difficulties. p53-upregulated modulator of apoptosis (PUMA) was identified as a p53-inducible proapoptotic molecule. Our purpose was to elucidate a role for PUMA in p53 gene therapy and to investigate whether PUMA is an efficient substitute for p53 in cancer therapy. We demonstrated that PUMA was upregulated in mutant p53 malignant glioma cells (U373-MG and T98G) undergoing apoptosis but was not upregulated in apoptosis-resistant wild-type p53 malignant glioma cells (U87-MG and D54) after adenoviral transfer of p53. Overexpression of PUMA resulted in massive apoptosis associated with mitochondrial damage and caspase-3 activation in all tumor cells tested. Use of the human telomerase reverse transcriptase (hTERT) promoter system induced apoptosis only in malignant glioma cells with telomerase activity, while sparing normal cells lacking telomerase. The ability of PUMA to induce apoptosis was greater than that of caspase-6 or caspase-8 transfer, using the same system. Moreover, exogenous expression of PUMA under the hTERT promoter system significantly suppressed the growth of subcutaneous U87-MG tumors in nude mice and did not induce apoptosis in surrounding nontumor tissues. These results indicate that PUMA, which is regulated under a tumor-specific expression system such as the hTERT promoter, may be better than p53 as a therapeutic tool for malignant gliomas [1].

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Ito H, Kanzawa T, Miyoshi T, Hirohata S, Kyo S, Iwamaru A, Aoki H, Kondo Y, Kondo S. Therapeutic efficacy of PUMA for malignant glioma cells regardless of p53 status. Hum Gene Ther. 2005 Jun;16(6):685-98. PubMed PMID: 15960600; PubMed Central PMCID: PMC1387050.