Spotlight

By Gina Kirchweger

Arming Stem Cells to Fight Brain Cancer

Chang *et al*.
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Despite advances in surgical, radiation, pharmacologic, and gene therapy, the prognosis for gliomas, the most common primary tumors of the central nervous system, is dismal. Current therapies are limited by their inability to reach widely disseminated tumor cells that become dispersed within normal brain structures. To overcome this major obstacle to effective treatment of gliomas, Chang *et al*. took advantage of the fact that mesenchymal stem cells (MSCs) are irresistibly drawn to brain tumor cells, which makes them efficient tools for delivering suicide genes to otherwise intractable gliomas.

They armed MSCs with cytosine deaminase (CD), a bacterial enzyme that converts the nontoxic prodrug 5-flourocytosine (5-FC) to 5-flourouracil (5-FU), which has been widely used as an anticancer drug for more than 40 years. When co-cultured with C6 glioma cells, CD-expressing MSCs efficiently converted 5-FC to 5-FU and exerted a strong bystander effect that directly correlated with the level of CD activity. Similarly, CD-expressing MSCs transplanted in the contralateral hemisphere of glioma-bearing animals migrated to the site of early stage tumors and reduced tumor mass in proportion to 5-FC dosages. Later stage tumors, however, required multiple transplantations to successfully repress tumor growth.

Although it had been shown that 5-FU has an antitumor effect on brain tumor cells, most clinical studies administering 5-FU alone indicated no value for the treatment of patients with malignant gliomas. Using bone marrow-derived MSCs as cellular vehicles to deliver high local concentrations of CD, or any other suicide gene for that matter, could overcome the primary limitation of systemic chemotherapy—its low therapeutic index—while minimizing systemic side effects.

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Fig. 6

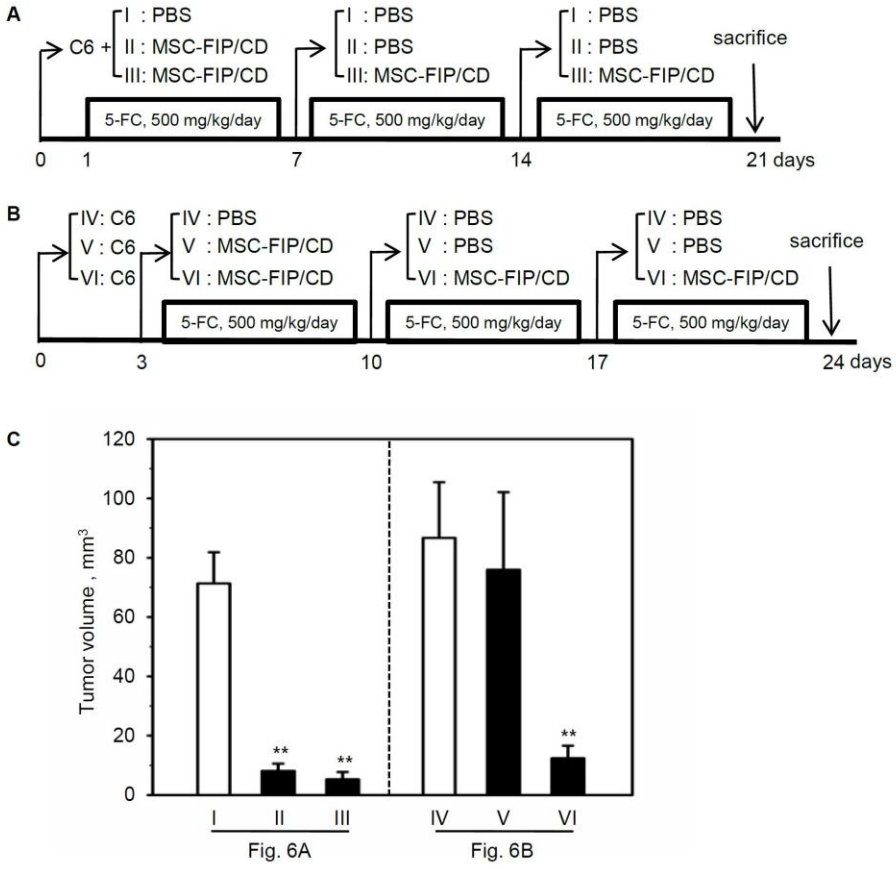

Figure 6: Correlation of *in vitro* bystander activities with *in vivo* anti-tumoral efficacy. (A) 5-FC (500 mg/kg) was administered daily for 13 days starting 1 day after sequential transplantation of C6/LacZ and CD-expressing cells at day 0. PBS and MSCs were used as negative controls. (B) X-gal positive tumor area was measured in each brain slice. Tumor volumes from at least 8 animals are presented as the mean ±S.E. (**$p<0.01$ compared to PBS; ANOVA). The difference between PBS and MSCs groups was significant. (C) The Most representative brain slice from each group each shown.