Intralesional Injection with PV-10 Induces a Systemic Anti-tumor Immune Response in Murine Models of Breast Cancer and Melanoma

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Introduction

Rose Bengal is a water-soluble xanthene dye that had been previously used in liver function studies and is still in use by ophthalmologists. PV-10 is a 10% solution of Rose Bengal formulated for intralesional (IL) injection. In initial clinical trials, IL PV-10 therapy induced regression of both injected lesions and un.injected bystander lesions in patients with melanoma. Relatively little is known about the mechanism by which PV-10 can induce resolution of bystander lesions. However, an immune-mediated process is likely as responses in untreated lesions occur only when there is a response in injected lesions, and regression of bystander lesions typically occurs in a delayed fashion compared to regression of injected lesions. This study was undertaken to determine whether IL PV-10 therapy leads to a systemic anti-tumor immune response.

Methods

Two models were used to investigate the systemic effects of PV-10. In the first model, BALB/c mice were injected subcutaneously (s.c.) in the bilateral flanks with MT-901 breast cancer cells. The right tumor was injected with PV-10 or PBS on day 7. Tumor sizes were measured for both the right (treated) and left (untreated/bystander) tumors. In the second model, mice received B16 melanoma cells s.c. to establish a solitary flank tumor and intravenous cells to establish multiple lung metastases. On day 7, the s.c. tumor was treated with IL PV-10. PBS was used in control mice. Lungs were collected on day 21. Splenocytes were collected on day 7 after PV-10 injection for functional assays. For adoptive transfer experiments, mice bearing B16 tumor were treated with 600 rad of total body irradiation on day 3 after tumor injection. One day later, mice received 1e7 T cells purified from the spleens of B16 bearing mice treated with IL PV-10. Tumor size was measured.

Results

Balb/c mice with bilateral MT-901 flank tumors had a significant regression of tumors injected with PV-10 and in the untreated bystander flank tumor.

MT-901 bearing BALB/c mice treated with PV-10 demonstrated enhanced survival (p<0.01 compared to PBS treated mice)

BALB/c mice treated with PV-10 demonstrated enhanced production of IFN-gamma in response to MT-901.

C57BL/6 were injected s.c. and i.v. with B16 cells to establish a single subcutaneous tumor and multiple lung lesions. The s.c. tumor was injected IL with PBS or PV-10. Mice treated with PV-10 had significantly smaller s.c. lesions and fewer lung metastases than mice treated with PBS.

Splenocytes from PV-10 treated mice demonstrated enhanced (A) IFN-gamma production and (B) cytotoxicity against B16. (C) Adoptive transfer of T cells from PV-10 treated mice led to reduced tumor growth in B16-bearing mice.

Conclusions

These murine studies confirm that PV-10 chemoablation results in both a direct effect on injected lesions as well as a systemic response that leads to regression of un injected subcutaneous and lung lesions. Intralesional PV-10 treatment leads to the induction of tumor-specific immunity.

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