SPLIT IMMUNITY: IMMUNE INHIBITION OF RAT GLIOMAS BY SUBCUTANEOUS EXPOSURE TO UNMODIFIED LIVE TUMOR CELLS.

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ABSTRACT

Gliomas, which appear to grow uninhibited in the brain, almost never metastasize outside the CNS. The rare occurrences of extracranial metastasis are usually associated with an immune compromised status of the host. This observation raises the possibility that some gliomas might not grow outside the CNS due to an inherent immune response.

We now report that the highly malignant F98 Fischer rat undifferentiated glioma, which grows aggressively in the brain, spontaneously regresses when injected live subcutaneously (sc). We found that this regression is immune-mediated and that it markedly enhances the survival, or cures rats challenged with the same tumor intracranially (ic) either before or after the sc live-cell inoculation.

Adoptive transfer experiments showed the effect was immune-mediated, and that the CD8 T-cell fraction, which exhibited direct tumor cytotoxicity, was more effective than the CD4 T-cell fraction in mediating resistance to intracranial challenge of naïve rats.

The results in the F98 model were corroborated also in the Lewis rat CNS-1 astrocytoma model. In both tumor models the unprecedented survival results using live-cell immunization were significantly better than those achieved using immunization with irradiated cells.

We propose here a location-based immunotherapeutic phenomenon we term '*Split immunity*': a tumor that thrives in an immune privileged site may be inhibited by injecting live unmodified tumor cells in a site that is not privileged, generating protective immunity that spreads back to the privileged site. Split immunity could explain several long-standing paradoxes regarding the lack of overt extracranial metastasis in patients with primary brain tumors.

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