Immunological studies with human gliomas

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In 1936, Siris prepared an alcohol extract of glioblastoma multiforme tissue with which he immunized rabbits and collected the sera for complement fixation testing against alcohol extracts of glioblastoma, normal brain, liver, and meningioma. The antibody titer was quite high, but the sera reacted better with normal brain antigen than with the original glioblastoma antigen. The antisera did not react with meningioma or liver antigens; preabsorption of the antisera into normal brain extracts removed all antibodies that would react with glioblastoma extracts. More recently Hass reported an antiserum against the soluble portion of a glioblastoma homogenate which, after plasma absorption, reacted with identical antigen in glioblastoma, normal brain, liver, spleen, and metastatic carcinoma cyst fluid. In the intervening 30 years between these reports of Siris and Hass, there has been no confirmation by in vitro techniques of glioma-specific antigens.

In vivo investigations generally have involved attempts to produce active immunity by antigen inoculation or to demonstrate the presence of autoantibodies within the host serum. In 1960, the autogenous implantation of glial tumor was described by Bloom and associates. The tumor implants grew, but there was no immunological reaction on the part of the sera. At the time of the patient’s death, the subcutaneous implants appeared histologically similar to the intracranial lesions, and regional lymphatics were involved. One year later Grace, et al., using similar assay methods reported no immunologic activity in the sera of two patients with successful autogenous glioma implants.

In an effort to demonstrate autoantibodies occurring spontaneously which might influence glioma growth, other investigators have exposed the sera from patients with gliomas to tissue culture explants of the autogenous gliomas. Conflicting results have indicated that autogenous sera both inhibit and stimulate explant growth. In our own laboratory, autogenous serum globulins were labeled with radioiodine and injected intravenously 3 to 30 days prior to surgical removal of recurrent glioma tissue, which was homogenized and separated into subcellular fractions by zonal centrifugation. A significantly high concentration of radioactive globulin was found in the middle peak fraction of this tissue which has subsequently been found to be myelin-rich. These experiences with autogenous sera are of interest, and the search for autogenous antitumor antibodies, even if only in trace quantities, still bears consideration, particularly in these unusual cases of spontaneous tumor regression.

In 1963, studies were begun in our laboratories to elucidate the antigenic potential of human gliomas and to determine the feasibility of producing heterologous antiglioma “carrier” antibodies capable of preferential glioma localization in vivo. Glioma tissue fresh from the operating room was homogenized, rabbits were immunized with subcutaneous injections of individual glioma sediments, and the rabbit sera were collected for globulin precipitation. \(^{125}\text{I}\) was attached to the globulin, which in most cases was then partially purified for antibody in vitro by absorption and elution methods. When a patient whose tumor had been used for antibody preparation was hospitalized later be-
Immunological studies with human gliomas

due to recurrence and was considered a candidate for a second operation, the operation was preceded several days by a radioantibody infusion via the ipsilateral internal carotid artery. The amount of rabbit antiserum antibody infused was never over 50 μg but carried as much as a millicurie (mCi) of $^{131}$I. Frequently, albumin or autogenous globulins labeled with $^{131}$I were simultaneously infused as a control for any nonspecific localization of proteins within the recurrent glioma. External brain scans revealed localization of the radioantibody within the area of recurrent glioma. Tissue removed at surgery was separated into tumor and adjacent brain and counted directly for the presence of antibody and control protein.

Preferential localization within tumor tissue as compared with normal brain was found in the majority of cases. Antibody localized in tumor and also brain tissue to a greater degree than did control protein. In several cases, C$^{14}$-labeled Cytoxan was infused along with the antiglioma antibody and control protein. The tumor to normal brain ratio was significantly greater for antibody than for Cytoxan in five of seven such cases. Radioautographs revealed antibody localized heavily within the tumor cells and the blood vessel walls within the tumor tissue. There was also some radio-antibody present in adjacent brain tissue in the nuclei of normal neurons and the blood vessel walls. Radioantibody was still present in tumor cells at the time of autopsy of three patients, 2, 4, and 6 months following antibody infusion. This pilot study with human gliomas was performed with trace quantities of heterologous antiglioma globulin for the purpose of assaying the tissue-localizing potential of the antibody preparation in patients whose hospitalization was necessitated by recurrent tumor and not with definitive serotherapy in mind.

There has been no proof to date of specific glioma antigens or specific antiglioma antibody production, autogenous or heterologous, despite the continuing interest in utilizing antibodies in the treatment of tumors either by direct antigen-antibody action or as carriers of therapeutic agents.

References


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