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Commentary

Immunology of Human Brain Tumors

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INTRODUCTION

IN THE treatment of primary malignant brain tumours conventional therapy, consisting of surgery and irradiation, has made little impact on survival. Results have been particularly discouraging in patients with high-grade gliomas [1], and this has led to the examination of other therapeutic approaches, including the theoretically attractive concept of immunotherapy. Human brain tumour immunology has received increasing attention over the past 10 yr and it would seem appropriate to review progress, particularly since the development of monoclonal antibodies [2].

THE EXISTENCE OF GLIOMA-ASSOCIATED ANTIGENS

The evidence for antigens totally specific for brain tumour cells has yet to be presented and, possibly, never will. However, a number of operationally useful glioma-associated antigens have been defined by a variety of serological systems and, more recently, by monoclonal antibodies. Early studies employed highly absorbed rabbit sera or non-human primate sera raised against glioma cultures, which defined antigens common to astrocytomas [3, 4] or were shared by gliomas and foetal brain [5–7]. Concurrent studies of glioma patient sera indicated the presence of neuroectodermal tumour antigens shown by allogeneic testing on a well-characterised glioma cell line [8]. More detailed analysis of autologous human sera revealed a category of glioma surface antigens shared by other neuroectodermally derived tumours and also foetal brain [9, 10]. This antigenic system appears fundamental and has now been repeatedly demonstrated by monoclonal antibodies (MABs) generated against foetal brain [11–13], melanoma [14–16] and glioma [17].

Certain neuroectodermal antigens are widely distributed throughout tissues and tumours of this germ layer [18], whilst others are restricted to subsets of neuroectodermally derived cells [12]. These may represent differentiation antigens expressed at different stages of maturity.

So far, the monoclonal antibodies thought to be most glioma-specific have, on further testing, been found to bind reactive glia and may recognise determinants which are related with intermediate-filaments. It is becoming apparent that extensive histological screening is necessary before specificity can be assigned to a new monoclonal antibody. This is most effectively achieved by immunohistological techniques rather than binding assays on cell cultures, the reason for this being that monoclonal antibodies can show unexpected cross-reactivities with subsets of cells in unrelated tissues and these can only be identified by careful histological review [19, 20].

EVIDENCE FOR A HUMORAL RESPONSE TO GLIOMAS

It is now known that immunological privilege of brain tissues is only relative [21] and that, in addition, the blood–brain barrier is disrupted by the presence of a tumour [22]. This means that systemically produced antibodies have access to

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glioma cells, as indicated by Mahaley's work with [^{125}I]-rabbit antibody conjugate [23]. Moreover, the recent production of human hybridomas derived from intratumoral lymphocytes provides strong evidence for functioning B cells within gliomas [24].

Circulating anti-glioma IgG and IgM which fix rabbit or guinea-pig complement have been found in patients' sera [8, 25] and, using a sensitive allogeneic assay, are detected in up to 82% of patients harbouring a glioma [26]. This incidence corresponds to the 79% of glioma patient sera found to precipitate allogeneically with a solubilised glioma membrane preparation [27]. When cytotoxicity experiments are performed with fractionated sera IgM is more effective than IgG which, in some patients, can inhibit IgM cytotoxicity [25]. Autologous cytotoxic activity has recently been found to correlate highly with survival in 44 high-grade glioma patients [28], but the significance of this interesting observation remains to be determined. It is salutary to bear in mind that human complement seems relatively ineffective in mediating autologous cytotoxicity against glioma cultures [29].

EVIDENCE FOR CELL-MEDIATED IMMUNITY

This evidence is much less compelling than that for a humoral response. The original observation of lymphocyte infiltration in gliomas [30] has been well substantiated and perivascular cuffing may relate to improved survival [31]. Studies with monoclonal antibody subset markers (Leu series, Becton Dickinson) show the majority of cells to be T lymphocytes with a high proportion of cytotoxic/suppressor cells and very scanty B cells (unpublished observations). A significant number of infiltrating macrophages have also been demonstrated [32].

All this has led to numerous attempts to demonstrate specific responses *in vivo* by skin testing for delayed hypersensitivity [33, 34] and *in vitro* by lymphocyte-microcytotoxicity assays [35–37]. Interpretation of these *in vitro* results has been complicated, particularly by the unknown participation of alloantigens and of NK cells. Carefully controlled autologous studies have now shown the *in vitro* cytotoxic T lymphocyte response to be minimal [29, 38], and no significant antibody-dependent cell-mediated cytotoxicity can be demonstrated [39].

In view of the substantial evidence for glioma-associated antigens which can stimulate autologous antibody, we are led to ask why the cell-mediated response is apparently unsuccessful.

HOW GLIOMAS EVADE IMMUNE ATTACK

It is now well established that glioma patients have a marked *generalised* impairment of immune competence in the absence of cachexia, which is seldom seen. There is a reduced number of circulating lymphocytes, particularly T cells, a paucity of skin-test reactions to common antigens and impaired blastogenesis of blood lymphocytes [40, 41]. The reasons for this are not clearly understood, but one interesting hypothesis proposes that sequestered brain proteins are released by tumour invasion and these induce immunosuppression to 'protect against allergic encephalitis', perhaps by the production of serum blocking factors or stimulation of suppressor cells [41]. In addition, the increasing list of antigens shared by brain and lymphoid cells, defined by monoclonal antibodies [42], suggests the possibility of a complex disturbance of immunoregulation brought about by release of such antigens.

The therapeutic use of corticosteroids and phenytoin may also contribute to generalised immunosuppression [43]. It is also possible that glioma cells possess defences against immune attack such as decreased immunogenicity, a protective mucopolysaccharide coat and the production of immunosuppressive macromolecules [44]. In this respect, there is interesting new evidence that C6 glioma cells elaborate non-specific factors that modulate T cell proliferation (Fontana, personal communication). Finally, there may be tumour-specific immune blockade, suggested by the recent finding of absent *autologous* cytotoxic antibody activity in patients who possess an intact *allogeneic* response against glioma cells [28]. Since the serum of such patients can contain an IgG fraction which inhibits cytotoxicity, it is conceivable that this indicates the presence of a 'personal blocking' anti-idiotype antibody in such cases.

IMMUNOTHERAPY

Our incomplete understanding of the complex immune system has contributed to the failure of attempted glioma immunotherapy by active immunisation [34, 45] or with locally infused leukocytes [46–48]. However, the development of monoclonal antibodies has revitalised the idea of specific targeted therapy with immunotoxins [49] or monovalent antibody [50]. Monoclonal antibody conjugated with locally destructive isotopes is a strong possibility and the technique of neutron capture therapy with ^{10}B-labelled antibody should be reconsidered [51]. The successful development of human tumour radioimmunodetection using monoclonal antibodies provides a stimulus to investigate all these possibilities [52].

A number of anti-neuroectodermal monoclonal antibodies have already proved useful in immunohistological diagnosis [53] but the ideal *in vivo* targeting agents are still being sought. Present experience suggests that (1) monoclonal antibodies directed against 'oncofoetal' antigens are suitable candidates, and (2) it may be necessary to use cocktails of monospecific antibodies in order to overcome heterogeneity of antigenic expression by tumour cells [54]. Finally, the development of monoclonal antibodies reactive with experimental animal brain tumours will be invaluable in developing *in vivo* diagnostic or therapeutic targeting systems.

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