Role of herpesvirus infections in brain tumor development

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Current knowledge

Malignant gliomas are the most common primary brain tumors in adults, have no known etiology, and are generally rapidly fatal despite current therapies. Several studies have linked these tumors to virus infections (SV40, JC-virus, herpesviruses). The association with SV40 and polyomaviruses is controversial and recent investigations render it rather unlikely. Human herpesviruses that establish lifelong latent infections are implicated in the pathogenesis of several human cancers, and viral reactivation is believed to occur after years of latency and to lead to malignancy (Howley et al., 2001). On the other hand, infection with some herpesviruses (notably varizella-zoster virus, VZV) may counteract glioma development: an inverse correlation with serum antibodies against VZV was observed (Wrensch et al., 2001). This is in line with findings that previous infections in general, may reduce the risk for brain tumors (Schlehofer et al., 1999), possibly due to stimulation of the immune system. Most recently, it has been reported that a high percentage of malignant glioma tissue (but not meningiomas) are infected by the human cytomegalovirus (HCMV, a herpesvirus) and multiple HCMV gene products are expressed in these tumors suggesting that HCMV may play an active role in glioma pathogenesis, most likely as a tumor promotion factor (Cobbs et al., 2002).

HCMV is a ß-herpesvirus trophic for glial cells (Fritschy et al., 1996) that persistently infects 50-90% of the population (Britt et al., 1996). It can cause devastating encephalitis in fetuses and – through reactivation from its latent state – in immunocompromised adults. HCMV gene transcription can be activated by inflammatory stimuli, and transcriptionally active HCMV can induce malignant transformation. HCMV gene products can also transactivate other oncogenic viruses that are associated with malignant gliomas such as JC virus (Winklhofer et al., 2000, Del Valle et al., 2001), and may synergize with such viruses to promote oncogenesis. It is interesting to note, that in immunosuppressed patients (e.g., organ transplanted, HIV-infected, chemotherapy-treated), reactivation of HCMV is one of the most feared complications and that lymphomas and brain tumors occur rather frequently in these individuals. Exogenous factors can also trigger herpesvirus reactivation, such as stress or sunlight. Inconsistent reports discuss an association of glioma with exposure to animals (Menegoz et al., 2002; Yeni-Komshian & Holly, 2000), and possibly such contacts may transmit factors contributing to rescue human herpesviruses from latency.

Aim

1. In this project, the possible role of herpesvirus infections in the pathogenesis of brain tumors will be evaluated. Extending the recent small study suggesting an active role of HCMV in glioma development (Cobbs et al., 2002), the presence of HCMV DNA, RNA and proteins in brain tumor (glioma, meningioma) material and non-tumorous tissue of the same individuals will be analyzed, in a substantially higher number of patients (~200). In addition, serum of these patients will be tested for antibodies against several herpesviruses (herpes simplex viruses [HSV], HCMV, Epstein-Barr virus [EBV], VZV) to evaluate the role of previous infections on the development of brain tumors, as suggested by serological studies (Wrensch et al., 2001).

2. In addition, information from the patients will be gathered using a questionnaire, to assess the possible role of factors susceptible to contribute to reactivation of HCMV and other herpesviruses, e.g., immunosuppression, previous infections, and exposure to animals.
Study design

1. From September 2002, all incident gliomas and meningiomas in adults (Neurosurgical University Hospital of Heidelberg, cooperation with Dr. K. Geletneky) will be collected during two years, together with non-tumorous tissue ("internal controls"; cf., below) and blood samples of the same patients. These biopsies will be analyzed for the presence of HCMV macromolecules (using PCR, RT-PCR, immunofluorescence, see below), and patients' sera will be tested for herpesvirus antibodies. In addition, clinical, biographical and demographical data of the patients will be gathered to get information on other than viral risk factors.

The student will establish and validate virological methods by testing an existing collection of brain tumor biopsies and non-tumorous material (blood, muscle, tumor-adjacent tissue) from the same patients (about 120 samples [75 gliomas, 35 meningiomas, and some other types], stored [at −196°C] in the laboratory of the virological collaborator [J.R.Schlehofer]) for HCMV DNA and RNA, using nested PCR and RT-PCR, respectively. In addition, to distinguish tumor cells from non-tumorous tissue, an in situ hybridization technique will be established detecting viral nucleic acids in single cells of cryosections. Furthermore, an immunofluorescence method of detection of HCMV-specific proteins (e.g., IE 1-72, pp65, p52/76kd) in cryosections will be developed.

2. In an extension of an existing questionnaire used in an international study on brain tumor risks ("Interphone Study", in which all supposed brain tumor risk factors are asked), information on the participants' exposure to animals, previous herpesvirus infections, factors susceptible to be involved in herpesvirus reactivation, and confounders (with respect to molecular and serological results) will be obtained.

3. Cross-sectional Analysis will assess association of brain tumors with herpesvirus infections by taking into account additional factors concerning reactivation of herpesviruses.

Title of the Thesis (preliminary):
Role of herpesvirus infections in glioma pathogenesis.

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Cooperations
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References


