Cytomegalovirus

Human cytomegalovirus (HCMV) is a beta herpes virus that is trophic for glial cells and infects 50% to 90% of the adult human population. HCMV-mediated disease in immunosuppressed patients has highlighted the possible role of this virus in the development of other diseases, particularly inflammatory diseases such as vascular diseases, autoimmune diseases, and certain malignancies. Sensitive detection of viral DNA, mRNA, and antigens in tumor tissues, as well as seroepidemiologic evidence, suggest a link between HCMV and several human malignancies.

HCMV gene products are proposed to dysregulate multiple cellular pathways involved in oncogenesis, such as cell cycle regulation, apoptosis, migration, and angiogenesis. These theories, currently being researched, suggest that HCMV acts as an oncomodulator in malignancies.

Human seroprevalence is approximately 80%, and in most cases, is associated with asymptomatic infection. HCMV may be an important agent in the initiation, promotion and/or progression of tumorigenesis. Regardless of a possible etiologic role in GBM, interest has centered on exploiting this association for development of immunomodulatory therapies [1].

Glioblastoma

see Glioblastoma immunotherapy.

The presence of HCMV in high-grade gliomas was first reported by Cobbs et al in 2002. Immunohistochemistry (IHC) of formalin-fixed paraffin-embedded tissue showed staining with antibodies against HCMV-encoded proteins immediate early antigen-1 (IE1; 72 kDa), pp65 tegument protein, and p52/76-kDa early DNA-binding protein and early protein (IE/EA). This signal was present both in the cytoplasm and in the nuclei of tumor cells, but not in areas of vascular proliferation, necrosis, or normal brain tissue. Characteristic nuclear inclusions were not identified, and special optimization of IHC conditions was reported to be necessary for detecting low levels of proteins. In situ hybridization (ISH) yielded positive results for HCMV messenger RNA and DNA in gliomas, but not in normal brain or in other neurologic disorders. Electron microscopy showed pp65-positive particles. Based on these results, Cobbs et al hypothesized that HCMV plays a role in GBM pathogenesis, although they believed that there was insufficient evidence to conclude that viral activity was caused by either primary infection or reactivation in the context of local immunosuppression [2].

One of the more polarized ongoing debates in the brain tumor field over recent years has centered on the association of cytomegalovirus (CMV) with glioblastoma. Several laboratories have reported the presence of CMV antigens in glioblastoma patient specimens, whereas others have failed to detect them. CMV genomic DNA and mRNAs have been detected by PCR, but not in next-generation sequencing studies. CMV promotes high grade glioma progression in a mouse genetic model, and many CMV proteins promote cancer hallmarks in vitro, but actively replicating virus has not been isolated from tumor samples. A consensus is gradually emerging in which the presence of CMV antigens in glioblastoma is increasingly accepted. However, it remains challenging to understand this mechanistically due to the low levels of CMV nucleic acids and the absence of viral replication observed in tumors thus far. Nonetheless, these observations have inspired the development of novel therapeutic approaches based on anti-viral drugs and immunotherapy.

The potential benefit of valganciclovir in glioblastoma has generated great interest, but efficacy remains to be established in a randomized trial. Also, early stage immunotherapy trials targeting CMV

have shown promise. In the near future we will know more answers to these questions, and although areas of controversy may remain, and the mechanisms and roles of CMV in tumor growth are yet to be clearly defined, this widespread virus may have created important new therapeutic concepts and opportunities for the treatment of glioblastoma [3].

Priel et al, investigated the association between HCMV infection and reactivation, and malignant gliomas. An open, matched case-control, parallel group pilot study was performed in a tertiary referral center. The HCMV viral load in peripheral blood and tumor samples of 19 patients newly diagnosed with glioblastoma multiforme was compared with a matched control cohort comprising 19 patients newly diagnosed with non-malignant brain tumors. There was no significant correlation between peripheral blood and tumor tissue HCMV viral load in patients with glioblastoma multiforme compared to the control cohort. The findings of the present study did not support an oncomodulatory role for HCMV in malignant gliomas [4]

1)
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