Is Cytomegalovirus a Therapeutic Target in Glioblastoma?

John H. Sampson and Duane A. Mitchell

Several investigators have now demonstrated the expression of genes unique to cytomegalovirus (CMV) in malignant gliomas. Many of these genes promote oncogenesis, alter tumor microenvironment, and serve as immunologic targets. Is the level of CMV infection within tumor cells sufficient to drive important oncogenic or immunosuppressive processes? Can CMV serve as a target for therapeutic intervention?

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have reported a failure to detect the presence of CMV within these tumors (9, 10). This discrepancy is likely attributable to methodologic differences, as we and others have demonstrated that sensitive and optimized protocols are required to detect the very low levels of CMV likely present within these tumors. This observation raises the following questions: (i) is the level of CMV infection within tumor cells sufficient to drive important oncogenic or immunosuppressive processes, and (ii) is CMV a clinically relevant target within these tumors for therapeutic intervention?

Koch’s postulates are a stringent set of criteria that are used to determine whether an infectious agent causes a disease. However, these strict criteria are not often met in cases of virally induced cancers (11). The long latency between infection and cancer diagnosis, and the fact that only a small minority of individuals exposed to a cancer-promoting virus (i.e., human papillomavirus or hepatitis B) ever develop a malignancy associated with the viral infection, clearly implicates multiple factors in addition to the infectious insult in the oncogenic process. In the majority of cancers caused by viral infections, the viral DNA is present in very small copy number, usually less than 1 DNA copy per 10 tumor cells. Furthermore, it is now clear that chronic infections can facilitate oncogenesis through indirect mechanisms without coding for transforming genes themselves, such as Helicobacter pylori promotion of gastric cancer and gastric lymphoma, providing several mechanisms by which infections may promote cancer formation. Finally, microbial genomes within cancer cells are often altered such that viable infectious pathogens are not recoverable from tumor cells and thus fail to fulfill the major criteria for Koch’s postulates. Future experiments that can demonstrate true modulation of the oncogenic phenotype via physiologic levels of infection with CMV-associated tumors will be pivotal for assessing any direct or indirect causality between CMV and oncogenesis.
The immunologic impact of CMV as reported by Dziurzynski and colleagues (1) raises a question: Would the levels of CMV viral IL-10 produced by \textit{in vivo} gCSCs be sufficient to drive the immunosuppressive changes described within TAMs? If so, treatments targeting viral IL-10 could constitute novel and highly relevant therapeutic modalities. Similarly, evidence already exists that low levels of CMV viral gene expression may be sufficient for immunologic targeting (5), and it has also been demonstrated that killing by cytotoxic T lymphocytes can occur with presentation of as few as 3 antigenic peptides upon the surface of the target cell (12). Furthermore, if gCSCs do preferentially express CMV antigens \textit{in vivo}, CMV-targeted therapies may profoundly inhibit malignant growth through eradication of this tumor-propagating population. The work of Dziurzynski and colleagues exemplifies that the continued characterization of biologically relevant levels of CMV infection as related to malignant progression and examination of CMV antigens as immune-mediated targets represent important and potentially promising areas of future research.

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