Viruses as Therapeutic Agents Against Malignant Disease of the Central Nervous System

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Viruses have gained attention in experimental approaches toward antineoplastic therapy. Many of these approaches are directed against malignant glioma, by far the most common malignancy of the central nervous system (CNS). Malignant glioma is almost invariably refractory to available treatment options and hence is associated with exceedingly poor prognosis. The urgent need for novel experimental treatments has rendered malignant glioma a prime target for the development of treatment strategies involving animal viruses.

These strategies use viruses either as mere delivery vehicles for heterologous genetic material ("gene therapy") or as infectious agents with inherent cytotoxic activity ("viral oncolysis"). Oncolytic viruses based on adenovirus (1), herpesvirus (2), vesicular stomatitis virus (3), and poliovirus (4) have been described, and the article by Wilcox et al. (5) in this issue of the Journal extends findings documented for oncolytic reoviruses (6).

Successful applications employing these agents depend on efficient control of inherent pathogenic properties to eliminate the possibility of collateral damage to nonmalignant tissue. The mechanism and extent of virus-mediated oncolysis are dictated by the pathogenic properties of these virus species, which determine spread, host cell targeting, immune evasion, and replication within the target. Not only is the antineoplastic activity of an oncolytic agent determined by its direct interaction with cancer cells, but also it is subject to the intricacies of the agent's relationship with the human host organism.

All too often, proposed therapeutic applications involving viruses preceded crucial analyses of the molecular mechanisms governing tissue tropism, virulence, and pathogenicity. Host cell tropism, obviously a key factor determining the effectiveness of virus-based therapeutics, appears to be a major limitation. Discrepancies of target specificity in cell culture or in animal experiments with those observed in clinical studies may simply be due to failure to invade tumor tissue and to bind to the intended target cell. Preclinical assays for oncolysis are typically carried out in tissue culture and in experimental animals with the use of clonal tumor cell lines. Expression profiles for many classes of viral receptors in clonal cell lines are not representative of those in real tumors. Thus, experimental evidence for virus-mediated oncolysis obtained with tumor cell lines does not necessarily imply similar responses in actual tumor tissue. Any clinical application of therapeutic viral agents should await comprehensive expression analyses of critical determinants of host cell tropism and specificity in biopsy samples of the intended target tissues.

The proposed use of reoviruses as therapeutic agents is not exempt from problems stemming from a lack of information on the basic mechanisms of host cell target tropism and specificity. The authors’ concept of a ubiquitous reovirus receptor (terminally sialylated cellular glycoproteins) to mediate universal susceptibility of glioma cells (5) may be simplifying a more complex process, involving multiple cellular surface recognition molecules interacting with various epitopes on the viral particle’s exterior. Recently, junction adhesion molecule (JAM) was found to mediate reovirus infectivity (7). JAM is not the sole determinant for reovirus cell and tissue tropism, and JAM-independent entry via sialic acid can occur in tissue culture. Studies of the association of this molecule with malignant glioma to elucidate the relative contributions of sialylated receptors versus JAM toward host cell specificity could help to predict the ability of reovirus-based therapeutic agents to target and enter malignant glioma cells. Identification of the nature of the interaction of reovirus with its multiple cellular binding molecules is all the more relevant to the proposed strategy, since reovirus-induced intracellular signaling events appear to be linked to JAM binding (6).

A difficulty in extrapolating experimental evidence obtained in tissue culture to the situation in patients similarly affects the proposed mechanism of reovirus virulence responsible for selective tumor cell killing. Unison activation of the ras pathway in all cells within a given clonal cell line, the basis for their selective susceptibility to reovirus oncolysis, is unlikely to occur in glioblastoma multiforme. These tumors, epitomized as “multiforme,” are exceedingly heterogeneous in composition, containing diverse cell populations that can display widely variant phenotypes. Specific biochemical abnormalities associated with malignancy commonly affect only parts of glial neoplasms. Unfortunately, because of the absence of a suitable animal model mimicking the heterogeneous nature of glial neoplastic lesions, experimental studies addressing the variable composition of glioblastomas are exceedingly difficult to conduct at this time.

Although immunity to reovirus is almost universal, suggesting widespread infection, these agents cannot be linked to clinical manifestations of disease. (The acronym reo [i.e., respiratory enteric orphan] indicates the absence of clinically overt disease associated with reovirus infection.) While the absence of disease symptoms with infection may recommend reoviruses for therapeutic use in humans, it leaves some uncertainty regarding the long-term effects of administering reovirus intracerebrally to humans. There is justified concern that intracerebral inoculation of reovirus preparations in humans may either unleash unknown properties of these agents or provide a suitable milieu promoting adaptation events that give rise to altered pathogens with new properties. Other oncolytic agents with activity against malignant glioma are based on known human CNS pathogens, such as...
herpes simplex virus or poliovirus, whose interactions with the primate CNS have been under intense scrutiny and are well documented. Furthermore, it may be expected that human CNS pathogens would exhibit properties useful in glioma therapy, e.g., the ability to penetrate CNS parenchyma from the site of inoculation and to reach distant tumor microsatellites.

The authors’ proposed strategy to treat malignant gliomas with reovirus (5) has produced very encouraging results in tumor xenograft experiments in laboratory animals and in cultured glioma cells. The idea to exploit a signaling pathway selectively active in tumors is convincing and may yield sufficient specificity for malignant cell types. Nevertheless, the precedent of successful viral oncolysis in animal tumor models, which could not be replicated in patients, reminds us to view promising preclinical results as encouragement for further basic studies of the molecular biology of viral pathogenesis. Many virus species will replicate within and destroy malignant cells, a property that has allowed us to establish convenient cell culture propagation systems. The original notion to treat tumors through viral infection is intuitively obvious, and first published applications date back to the beginning of the 20th century. Innovation stems from new strategies based on the understanding of the molecular principles of viral pathogenesis and how they can be exploited to selectively target malignancy. The success of these strategies will ultimately depend on our insight into the numerous factors determining spread, tropism, virulence, persistence, and immunity as well as on our ability to manipulate viruses to harness them for therapeutic purposes.

REFERENCES