EDITORIAL

Viruses as Oncolytic Agents: a New Age for "Therapeutic" Viruses?

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Since the discovery of microbial organisms, scientists have speculated about harnessing pathogens for therapeutics. However, as illustrated by the fate of the fictional Sinclair Lewis character Arrowsmith[1] (who attempted to use bacteriophage to cure infections), the use of microorganisms in patients can be fraught with hazard. This issue of the Journal has two papers (*1,2*) that illustrate the potential use of viruses to lyse human cancer cells. The results from these and other studies are exciting and raise the possibility that the time may be near for controlled trials to determine whether cytolytic viruses can be used to treat some human cancers. However, there is also the fear that infection of extremely ill patients with live viruses will result in "runaway" viral infection.

The concept of using viruses to treat human cancer dates to early in this century [reviewed in (*3*)]. In the 1950s, it was noted that, in tissue culture, many viruses can infect and lyse tumor cells more efficiently than they can infect and lyse normal cells (*3*). Subsequently, virally induced immunologic effects have also surfaced as a mechanism by which certain viral infections can cause tumor lysis (*3,4*). In vivo, viral infections of tumor cells may enhance the presentation or recognition of tumor cell antigens. In addition, viruses can induce the production of cytokines, mobilizing an immune response to tumor cells (*4*).

Viruses proposed as potential oncolytic agents have included mumps (*5*) and measles (*6*) viruses, bovine enterovirus (*7*), Newcastle disease virus (NDV) (*4,8-11*), and attenuated herpes simplex virus (HSV) (*12-14*), among others. The human mumps virus (which is related to the avian NDV) was reported to have an oncolytic effect on sarcomas in rats (*15*). Subsequently, in an uncontrolled trial, inoculation of wild-type live mumps virus into 90 terminally ill cancer patients reportedly produced a "very good" or "good" response in 79 of the patients, without causing ill effects (*5*). In addition, some association between measles infection and remission of human leukemia has been reported (*6*). However, rigorously controlled trials using oncolytic viruses to treat specific human tumors have not been performed.

Two of the viruses that may have the most promise for this purpose are NDV and HSV. Each has advantages and disadvantages as a potential therapeutic agent. NDV has the advantage of relative safety. Experience with farmers and laboratory workers infected with NDV suggests that even the wild-type form of this chicken paramyxovirus produces minimal disease, mainly mild conjunctivitis and laryngitis. NDV strain 73-T, used in the study by Lorence et al. (*1*) reported in this issue of the Journal, has been attenuated by multiple passages through mouse tumor cells and has been injected into numerous patients with melanoma and colon cancer without harmful aftermath (*10,11*). In contrast to other oncolytic viruses, NDV 73-T appears to be almost uniquely lacking in neurotoxicity (*8*).

Another advantage of NDV as an oncolytic agent is its apparent ability to induce tumor lysis through different mechanisms. In vitro, NDV 73-T, while not significantly affecting normal human fibroblasts, can infect and directly lyse a variety of human tumor cells (*4*). Whether this discrimination in culture is due to cell type or is specific for tumor cells is not entirely clear. In addition, NDV can induce tumor necrosis factor-α (TNF-α) production in human mononuclear cells. Furthermore, infection of tumor cells by NDV appears to enhance their sensitivity to the cytolytic effects of TNF-α (*9*). The ability of "oncolysate" vaccines (i.e., vaccines containing melanoma cells lysed in vitro by NDV) to prolong survival in patients with malignant melanoma (*10*) may reflect such an enhancement phenomenon.

Important hurdles remain in developing NDV 73-T as a clinically useful oncolytic agent. With NDV, certain key molecular and pathogenetic mechanisms are obscure. The mutations that confer oncolytic activity on the NDV 73-T strain have yet to be identified, and the mechanisms responsible for specific tumor cell killing are unexplored. The potential of NDV 73-T to mutate into a more virulent strain is unknown. Finally, there are no antiviral agents as yet to treat NDV infection, should symptoms occur.

In contrast, there is a wealth of information on the molecular biology, pathogenesis, and antiviral treatment of HSV infection. A widespread, sometimes lethal human pathogen, HSV has been the target for intensive study and development of antiviral

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drugs. The viral thymidine kinase (tk) gene is not needed for viral replication in most cell types. However, several years ago, reports (*12*,*13*) appeared that HSV-1 mutants lacking the viral tk gene (deleted through genetic engineering) were unable to replicate efficiently in nondividing cells (including normal neuronal cells), whereas they were still able to lyse dividing cells (including human tumor cell lines). It is presumed that, under these conditions, host cell tk generated in rapidly dividing cells can substitute for the viral tk and promote viral replication. Thus, tk-deleted HSV-1 is less neurovirulent than wild-type virus but still infects (and lyses) glioblastoma cells in culture. Furthermore, several animal studies (*13*,*14*) have now confirmed that direct intracranial inoculation of tk-deleted HSV-1 can cure glioblastomas in vivo. The study by Jia et al. (*2*) reported in this issue of the Journal is the first to show the effectiveness of such therapy in an immunocompetent animal host. Jia et al. report no neurotoxicity after intracranial injection of tk-deleted HSV-1 into normal rats.

Although these results are promising, more extensive study is certainly needed before such HSV mutants can be used to treat human glioblastomas. The tk-deleted HSV-1 did not induce encephalitis in normal rats (*2*); however, in nude mice that were long-term survivors after inoculation with glioblastoma cells (*12*), encephalitis ensued after exposure to a similar HSV-1 mutant. Furthermore, infection in humans with attenuated HSV-1 mutants might produce impairment of cognitive functions without encephalitis. Since the popular drugs acyclovir and ganciclovir both require phosphorylation by the HSV-encoded tk for conversion into active antiviral agents, tk-deleted HSV mutants will be resistant to treatment with these potent agents. However, tk-deleted HSV mutants are still susceptible to the antiviral drug foscarnet.

If HSV mutants are to be used to treat glioblastomas, the development of even less neurovirulent HSV strains that can still lyse glioblastoma cells is called for. Certain HSV mutants (containing mutations in the gamma-1 34.5 gene) may be less neurovirulent than tk-deleted mutants, while retaining their antitumor activity against glioblastomas in nude mice (*14*). Furthermore, these mutants retain susceptiblity to acyclovir. However, to reduce the risk that such strains could revert to virulent forms after infection in vivo, the safest approach will require the construction of viruses containing multiple, large deletions. The use of tk-deficient HSV mutants stands in contrast to an entirely different approach, in which the HSV tk gene is itself exploited by specific delivery of the viral gene to cancer cells (using gene therapy vectors), so that these cells can then be selectively killed by administration of ganciclovir (*16*).

Are we about to revive Arrowsmith's obsession and enter a new age of viral therapeutics for human cancer? Our ability to uncover the complex interactions between viruses and their host cells in culture is unbounded. Whether viruses can be harnessed for the treatment of cancer in humans requires another level of understanding of virus infection, coupled with a cautious empiric approach now beginning to be outlined.

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Notes

[1]Lewis S: Arrowsmith. New York: Harcourt Brace, 1925.

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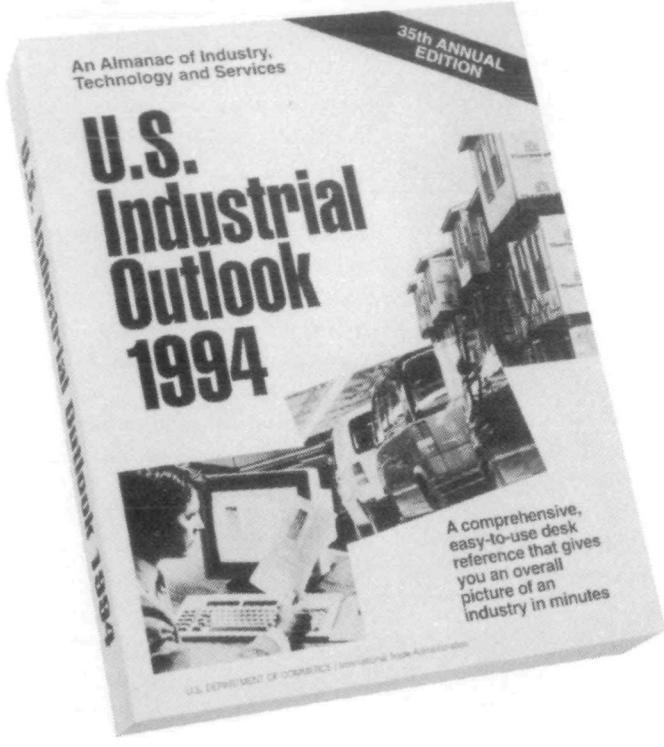

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