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Editorial Comment

Tumour viruses—could they be an Achilles' heel of cancer?

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1. Viruses and human cancer

Cancer is not an infectious disease, but it has become clear that certain types of human cancer have a viral component to their aetiology (see Table 1). For Hepatitis B virus and primary liver cancer, immunisation against the virus has started to reduce the incidence of the cancer, proving the causative link [1]. Together the virus-associated cancers account for approximately 16% of all human cancer worldwide so viruses make a major contribution to carcinogenesis in humans [2].

Immune surveillance is important in the control of viral infection, so it is not surprising that some virus-associated cancers are more frequent in immunosuppressed people, for example transplant recipients or AIDS patients. In spite of this and the large numbers of AIDS cases worldwide, most virus-associated cancers still occur in immunologically-competent people.

Table 1
Viruses associated with human cancer

Human papillomavirus 16, 18	Cervical carcinoma
Hepatitis B, C	Primary hepatocellular carcinoma
Epstein–Barr virus	Endemic Burkitt's lymphoma Nasopharyngeal carcinoma Hodgkin's disease Gastric carcinoma Immunoblastic lymphoma
Kaposi's sarcoma herpesvirus (HHV8)	Kaposi's sarcoma Castelman's disease Primary effusion lymphoma
HTLV1	Acquired T cell lymphoma leukaemia
SV40	Mesothelioma (controversial)

SV40, Simian Virus 40; HTLV1, human T cell leukaemia virus type-1.

2. Cancer therapy strategy

The general problem in cancer therapy is to devise a procedure that distinguishes cancer cells from normal cells. Conventional chemotherapy and radiotherapy are thought to work primarily by causing apoptosis in cancer cells. The relatively low specificity of the treatments for cancer cells results in the severe side-effects and general toxicity associated with most cancer therapies. The differences between cancer cells and normal cells are often very subtle and it is difficult to identify agents which are specific for cancer cells.

In the virus-associated cancers, the presence of the virus in the tumour cells could provide an alternative way to obtain specificity of treatment for cancer cells. This would work best if there were a very low number of normal cells infected by the virus, but every tumour cell were infected. In that situation, killing virus infected cells would be equivalent to killing cancer cells. The Epstein–Barr virus (EBV)-associated cancers would be a good model for such an approach because the number of EBV infected cells in normal carriers of the virus is very low, but most of the malignant cells contain the virus in an EBV-positive tumour. Examples of such tumours include undifferentiated nasopharyngeal carcinomas and EBV-positive tumours of Hodgkin's Disease, gastric carcinomas and Burkitt's lymphoma. EBV also causes immunoblastic lymphomas in immunocompromised patients, for example, transplant recipients.

3. EBV as an example

EBV-associated cancers have a latent infection with EBV so the antiherpes drug acyclovir (which inhibits virus lytic replication) is not effective against the virus in these diseases. There are several obvious ways in which

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the presence of latent virus could theoretically be used to therapeutic advantage.

For the tumour to have developed in an imunocompetent patient, it must have avoided immune surveillance. If immune recognition could be boosted by immunisation or if the virus could be induced to express other viral antigens that are normally silenced in latency, the tumour cells would most likely become a target for the immune system. Attempts are being made to boost the immune response to latent cycle EBV antigens in nasopharyngeal carcinoma patients using components of the EBV latent membrane protein (LMP) proteins, which are expressed in the tumour cells. EBV infected immunoblastic lymphoma cells have already been treated by infusion of cytotoxic T lymphocytes specific for latent cycle EBV antigens [3].

Another approach would be to identify drugs which reactivate the latent virus within tumour cells to commence lytic replication. The early proteins of EBV are highly antigenic and would presumably make the tumour cells targets for immune surveillance. An extension of this approach that has recently been found to be effective in animal models has taken advantage of reactivation of the latent EBV in tumour cells by cisplatin, 5-fluorouracil (5-FU) or paclitaxel (taxol). Kenney's group found that co-administration of the acyclovir analogue gancyclovir (GCV) resulted in conversion of the gancyclovir prodrug to its active form and significantly enhanced the ability of 5-FU and cisplatin to kill EBV-positive, but not EBV-negative, gastric carcinoma cells *in vitro* [4]. The combination of GCV and 5-FU (or GCV and cisplatin) was much more effective in the treatment of EBV-positive nasopharyngeal carcinomas passaged in nude mice than either agent alone.

Other strategies being proposed utilise the unique features of the viral replication system in latent infection [5]. For episomal EBV to persist in tumour cells, the virus has to express EBNA1, which binds to the viral origin of replication oriP to allow maintenance replication of the episomal viral DNA in tumour cells by the cell DNA polymerase. It appears that the continued presence of the viral genome contributes to the tumour phenotype, at least in the lymphoma cells that have been tested [6]. Agents which selectively interfere with the function of EBNA1 or oriP would result in eventual loss of the virus and remove the contribution of EBV to tumour growth (currently proposed to be mediated by the small viral RNAs called EBER RNAs [6]). Sixbey's group used hydroxyurea to cause progressive loss of the EBV episome as an approach to therapy of central nervous system (CNS) lymphoma in AIDS patients [7]. A recent discovery by Lieberman's group that the human telomere associated TRF2 protein also binds to part of the EBV origin and is required for the efficient function of oriP provides yet another potential angle on this approach [8]. Inhibitors of TRF2's cooperative binding with EBNA1 to oriP could be effective antiviral agents and thus potential antitumour agents.

4. Conclusion

Cancers are often heterogeneous mixtures of cells. It might be that strategies which are designed to kill virus infected cells would just result in the selection of virus-negative tumours. However, the strategies based on the presence of virus work by quite different mechanisms from the induction of apoptosis via DNA damage that is the basis for most conventional radiotherapy and chemotherapy. The combination is likely to provide powerful synergies if suitable agents can be targeted at the tumour viruses.

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