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A viral strategy to ambush tumors

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Abstract

A new combinatorial approach harnesses the power of immuno- and virotherapy in a vesicular stomatitis virus (VSV) vector carrying a cDNA library that expresses normal human prostate antigens, thus providing proof of principle that this vaccine can induce prostate tumor rejection in mice (pages 854–859). This strategy might bypass many of the issues associated with conventional cancer immuno- or virotherapy.

Both cancer immunotherapy and virotherapy have generated mixed results in clinical trials and face a series of obstacles that must be overcome to achieve clinical success. One of the pressing issues facing virotherapy researchers is the role of host immunity. For instance, complement, preimmune immunoglobulin M (IgM) and antiviral cellular mediators have been shown to hinder viral oncolysis¹. In contrast, numerous reports suggest that antitumor immunity is either essential for or at least synergizes with virotherapy². While the field of oncolytic viral therapy tackles these pressing issues, the immunotherapy field struggles to identify robust tumor-associated antigens that can be adequately targeted across various types of tumors³. Moreover, cancer genomes are associated with a high mutation rate, leading to immune escape⁴. This results in a lack of effective therapies to treat recurrent tumors that are resistant to initial therapy.

To circumvent some of the limitations of these individual therapeutic approaches, in this issue of *Nature Medicine*, Kottke *et al.*⁵ propose a strategy that incorporates elements of virotherapy and immunotherapy. They describe how a VSV-based cDNA library expressing self epitopes from normal human prostate specifically induces rejection of mouse prostate tumors in the absence of detectable autoimmunity⁵. Moreover, if tumors escape immune selection and recur with a new phenotype, they can be ‘ambushed’ with a second-line therapy in which the VSV vector expresses a set of antigens derived from the recurrent tumor itself (Fig. 1). This vaccination approach may therefore hold promise for overcoming the issue of tumor resistance; furthermore, the principles outlined in this work may be used to design vaccines for other tumor types without the need for previous knowledge of tumor-associated antigens.

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The rationale for this new study came from previous work from the same group showing that the induced killing of normal cells released a broad spectrum of unidentified self antigens that can subsequently be used in a T cell–dependent manner to break tolerance and reject tumors of the same histological type as the parental normal cells^{6,7}. Building on these results, the authors argued that we have insufficient knowledge to predict the types of tumor-associated antigens that could be presented by different tumors and, consequently, they propose using a known, immunogenic viral backbone to express a large repertoire of cDNAs made from normal or tumor tissue⁵. Kottke *et al.*⁵ suggest that this approach provides the immune system with an opportunity to resample self epitopes in a highly immunostimulatory environment.

Kottke *et al.*⁵ selected VSV as an oncolytic viral backbone on the basis of its ability to replicate to high titers in tumor cells, its relative nonpathogenicity in humans, its immunostimulatory properties and its ability to mediate T cell immunity toward virally encoded trans-genes. Although the authors showed that VSV is a modestly efficacious oncolytic viral vector in the treatment of established mouse prostate tumors caused by subcutaneous injection of mouse TC2 cells, tumor eradication was dramatically enhanced when VSV encoded a cDNA library from normal human prostate⁵. Kottke *et al.*⁵ therefore concluded that tumor clearance seemed to derive primarily from a T cell–mediated mechanism rather than from direct viral oncolysis. Importantly, the authors also did an elegant series of experiments in which VSV encoding cDNA from normal prostate was effective against TC2 prostate tumors but not B16 melanoma; conversely, VSV encoding a pooled cDNA library from two melanoma cell lines was effective against B16 melanoma but not TC2 prostate tumors. These findings demonstrate that the VSV vaccine elicits an immune response directed toward tissue- specific antigens encoded within the cDNA library and not toward xenogeneic variants of normal household proteins.

Despite the ability of the vaccine to induce tumor regression, Kottke *et al.*⁵ found that recurrent TC2 (TC2R) tumors occurred with sub-optimal dosing. These recurrent tumors were aggressive, histologically distinct from parental TC2 tumors, adopted the expression of genes associated with an epithelial-mesenchymal transition and were resistant to treatment with the initial VSV-cDNA library. Notably, this tumor phenotype has been associated with tumor recurrence in other tumor models and is frequently resistant to initial therapy^{8–10}. To ambush the recurrent tumors, Kottke *et al.*⁵ created a second VSV library encoding cDNA from three TC2R tumors. Using this approach in mice immune to VSV, they found that TC2 tumors were very sensitive to intravenous (i.v.) treatment with sequential vaccinations of VSV encoding cDNA from normal human prostate followed by VSV encoding cDNA from TC2R tumors. Importantly, they achieved this successful outcome only when VSV containing the initial prostate cDNA library was first loaded onto antigen-nonspecific peripheral blood leukocytes to protect against neutralizing antibodies produced in response to the initial VSV infection^{5,11}.

These findings are important for many reasons. First, the authors show that tumor-associated antigens do not have to be known a priori for their vaccine to elicit an effective antitumor immune response⁵. It will be interesting to see whether future studies can differentially select cDNA libraries to enrich for tissue-specific cDNAs that are the key ingredients of

tumors, and whether vaccines expressing these cDNAs alter the rate of tumor recurrence, the histology of recurrent tumors and their susceptibility to second-line therapy. One point of caution with this approach pertains to the potential for autoimmunity and whether the use of antigens from normal cells may lead to undesirable side effects. The authors show a lack of such autoimmunity in mice⁵, but whether this will translate to humans is not known. In addition, autoimmunity with normal prostate antigens may not be as severe as that with antigens from other tissues (for example, from the central nervous system).

Second, this approach suggests a feasible approach for treating escape variants with a second cDNA library. This targeted ambush is a unique adaptation of current oncolytic viral therapies and should be explored with other oncolytic viruses that are replication competent or replication defective. Additionally, it will be important to understand the nature of viral infection in this process, such as whether efficacy is dependent on the localization of the virus within both the lymph node and the target tumor-bearing tissue.

Although barriers to i.v. administration of oncolytic viruses have been well documented¹², this route is also essential for the treatment of disseminated metastatic disease. Although Kottke *et al.*⁵ focused on a subcutaneous prostate model, the authors showed that i.v. administration is the optimal route of delivery. Future studies are required to understand the mechanism of action, but it is likely that i.v.-mediated viral localization to lymph nodes stimulates priming of antigen presenting cells, thus leading to downstream T cell activation. Moreover, systemic VSV administration may help the virus to circumvent the immunosuppressive tumor microenvironment that is encountered with intratumoral inoculation.

One limitation of the study by Kottke *et al.*⁵ is that the established cancer cell lines used to induce tumors in the mouse models they describe have substantial differences from the original tumors from which the cells were derived. It will thus be important to extend the approaches outlined in this paper to both spontaneous tumor models and primary prostate cancers.

Kottke *et al.*⁵ have spanned the realms of immunotherapy and oncolytic virotherapy to present the best of both worlds. As researchers continue to understand this new approach, uncover the nature of the key ingredients that elicit tumor immunity in the cDNA library and examine the ability of this method to treat other types of recurrent tumors, perhaps this vaccine strategy will provide clinicians with an eagerly awaited tool to combat cancer.

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Figure 1.

Kottke *et al.*⁵ propose a model in which murine TC2 prostate cancer can be treated *in vivo* by the intravenous administration of oncolytic VSV encoding a cDNA library derived from normal human prostate. When histologically distinct, recurrent TC2 tumors arose, they were effectively ambushed by inoculation with VSV encoding a cDNA library from mouse TC2R prostate cancer.