Adenovirus Gene Therapy for Ovarian Cancer

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Ovarian cancer is the leading cause of death from gynecologic malignancies and, although conventional chemotherapy provides some initial positive response, drug resistance can often occur within months. Thus, it is not surprising that other strategies are sought, and a number of groups have used virus gene therapy as one possible route to supplement conventional chemotherapy.

Adenovirus vectors have been used extensively for gene therapy because of their high infection efficiency in dividing and nondividing cells and the wide prevalence of the coxsackievirus-adenovirus receptors (CARs) in a variety of cells and tissues (1). For cancer gene therapy, three principal targets have been explored: repairing defects in tumor suppressor genes, such as defects in the p53 and phosphatidylinositol-3-kinase (PI-3/Akt) pathways; inducing and promoting specific antitumor cell immunity; and inducing tumor cell cytotoxicity with oncolytic adenoviruses—often in association with the gene for herpesvirus thymidine kinase—and treating with sensitizing drugs (referred to as suicide gene delivery). Although some encouraging results have been achieved using the latter concept [e.g., using the ONYX vectors for solid tumors such as those of head and neck (2,3)], on the whole, progress has been disappointing. One of the factors responsible for this disappointment appears to be the lack of CARs (4) in primary tumor tissues, leading to poor virus uptake and gene expression. However, a number of strategies have been developed to circumvent the CAR gateway to infection. One of these involves introducing another ligand (RGD) into the virus attachment protein (referred to as the fiber) so that the oncolytic virus can target the more ubiquitous integrins as a portal of entry. In this issue of the Journal, Hemminki et al. (5) demonstrate the success of this modification in targeting ovarian cancer in vivo in animal models. Moreover, by introducing an additional somatostatin receptor into the virus, they were able to carry out noninvasive imaging using a 99mTc-somatostatin analogue to trace the progress of the virus after injection. The Hemminki article extends their primary studies (6,7), assessing the efficacies of the vector and the imaging techniques, and represents a valuable approach to easier assessment of the safety and efficacy of a gene therapy approach. There was only a modest response in an in vivo orthotopic mouse model. However, this effect is encouraging because no previous studies using this extremely treatment-resistant model had reported any amelioration.

Another inhibition to the success of adenovirus gene therapies has been the rapid development of an immune response against the vector (1). Hemminki et al. (5) claim that the vector used in their experiments (where the fiber has been modified by the attachment of ligand) will partially ablate neutralization of the virus. This is especially important in ovarian cancers, in which malignant ascites, often a characteristic clinical feature of the disease, can contain substantial levels of adenovirus neutralizing antibodies (8). The presence of neutralizing antibodies may be one reason for the modest success noted but, because neutralization of virus can occur via other routes, it is anticipated that the growth inhibitory effect will be transient. Moreover, the role of cell-mediated immune responses to the virus will come into play to complicate the picture. Other studies have sought to address this immunological problem, and one of these seems to offer some promise. In this strategy (9), the adenovirus vector is covalently coated with a multivalent hydrophilic polymer PHPMA (poly[N-(2-hydroxypropyl)methacrylamide]), which can be modified by other ligands to redirect the virus to other receptors. By coating all the structural viral antigens, the initial neutralizing responses should be delayed.

In analyzing the specific pathways that seem to be important in ovarian cancers, Reles et al. (10) reported that 99 (56%) of 178 ovarian carcinomas had defects in p53 and, moreover, that the p53 alterations were associated with resistance to chemotherapy, early relapses, and shorter overall survival. However, attempts to rectify p53 defects using a recombinant adenovirus with a wild-type p53 insert (11) indicated that expression of p53 was short-lived, presumably because of an effective antibody response.

Other approaches to adenoviral vector therapy have sought to interfere with the PI-3/Akt pathway, which appears to be overactive in ovarian cancer cells (12). This pathway is normally controlled by the tumor suppressor PTEN, which encodes a phosphatidylinositol phosphatase and PTEN is often defective in ovarian cancer. An adenovirus vector that expressed PTEN was assayed in nine human ovarian cancer cell lines and was found to cause biologically significant effects in six of them (13). The PTEN adenoviral vector had not been modified to reduce the antibody responses as described above, but it may be well worth re-examining this with the use of some of the improved vector methodologies.

One of the major complications in attempting to repair specific defects in tumor suppressor pathways is that, because ovarian cancer is such a heterogeneous disease (14), effective therapy would seem to necessitate a molecular analysis of every patient. Other gene therapy strategies, such as specific targeting of virus vectors to receptors on ovarian cancer cells (15), immunotherapy (16), and using alternative adenovirus serotypes to bypass CAR entry (17,18) have also been explored.

In this rather complex situation, there is considerable attraction in attempting the direct oncolysis of tumor cells (19), such as described by Hemminki et al. (5). However, one should note, with caution, the results obtained (20) using the ONYX vector in a series of defined drug-resistant human ovarian tumor cell lines. Here, it was demonstrated that differing effects could be obtained depending on the p53 status of the cells, which influenced apoptosis and the spread and cytolytic activity of the vector.

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does offer a variety of routes to improved therapy, but further progress will depend, to a large extent, on our ability to modulate the immune responses to the vector and its transgenes.

REFERENCES