The Bax gene as a competitor in the marathon towards licensed cancer gene therapy

Intrapерitoneal spread of gastrointestinal malignancies is a significant clinical problem and contributes to an incidence of distant relapse as high as 30% in gastric cancer. Local dissemination of tumour cells into the peritoneal cavity determines the outcome in advanced gastric cancer and diffuse-type carcinoma, and patients with negative peritoneal washings have a more favourable prognosis. Extensive lymph node dissection has been shown (by quantitative reverse transcription-polymerase chain reaction for carcinoembryonic antigen and cytokeratin 20 combined with extensive intraperitoneal peritoneal lavage) to open lymphatic channels and spread viable cancer cells into the peritoneal cavity. Hence, patient subpopulations that might benefit from intraperitoneal therapy regimens may be identified.

Malignant disease localised within the abdominal cavity has been a target for the staged development of clinical gene therapy approaches because of the smaller doses of experimental agent and increased safety margins over systemic administration. There has been extensive—and safe—experience of p53 gene therapy which culminated in a randomised phase III trial in which women with p53 null or p53 mutant ovarian cancer were randomised to chemotherapy alone or chemotherapy plus intraperitoneal Ad p53 following optimum debulking primary surgery. However, the first interim analysis indicated that not only did Ad p53 fail to improve effectiveness but it was also associated with increased toxicity. As a result, the study has been abandoned (reported in Zeimet and Marth). Two broad possibilities exist to explain why the trials were relatively unsuccessful. Firstly, there is the perennial problem of suboptimal gene transfer. Secondly, there is the possibility that p53 is the "wrong" transgene. Although p53 mutations are found in many malignancies and defective p53 function may be causally linked to chemotherapy resistance, many aspects of p53 biology remain obscure, especially factors involved in the decision that determines whether cells undergo apoptosis or cell cycle arrest in response to p53 activation. There is some evidence that low level p53 expression, in the range likely after adenosine gene transfer, causes cell cycle arrest rather than cell death. Also, the proapoptotic function of p53 depends on transactivation of genes such as Bax, Apaf-1, Fas, and PTEN whose own expression or activity may be abnormal in tumour cells. Mutant p53 can act as a dominant negative in p53 tetramers, which could abrogate the effect of exogenous wild-type protein encoded by the transgene. Finally, polymorphisms of the p53 gene (especially codon 72 arg) can determine the responsiveness of tumours to chemotherapeutic drugs by influencing inhibition of p73. Hence while p53 gene replacement was the early leader, it is likely to be overtaken by more robust competitors in the marathon towards a successful and licensed cancer gene therapy.

The work reported by Tsunemitsu and colleagues in this issue of Gut focuses on the potential of the Bax gene as a strong inducer of apoptosis, targeting gastric cancer growing as solid tissue deposits and as intraperitoneal disease [see page 554]. They show that a replication defective adenosaviral vector expressing human Bax as a transgene could induce death even of p53 resistant gastric cancer. Interestingly, treatment with a "control" virus expressing the reporter gene lac-Z was also observed to extend survival, a phenomenon that has been previously reported in the treatment of pancreatic cancer. However, it was evident that penetration of tumour deposits was only superficial after intraperitoneal instillation and, even though survival of treated animals was extended, cure was not achieved. Thus it appears that while Bax may be a more effective transgene than p53 for cancer gene therapy, its application might be restricted to lavgation at the time of surgical dissection rather than the treatment of established bulk disease.

What further developments are on the horizon for the gene therapy of gastrointestinal cancers? We believe that advances will come from both improved gene delivery technologies and more powerful transgene combinations.

Replicating biological agents are the most promising means to improve the delivery kinetics in solid tumours, and both viruses and bacteria are being exploited for this purpose. The adenovirus E1B 55 kDa protein suppresses p53 function in infected cells and E1B 53K deleted adenoviral vectors replicate within and cause cytolysis of tumours with defective p53 function. In the past two years, six separate phase I/II trials of such a virus (variously known as d1520, Onyx-015, and CI-1042) have been published, in a range of tumour types, including colorectal, ovarian, and pancreatic carcinomas, and in patients with liver metastases from gastrointestinal malignancies. In combination with chemotherapy, some responses were seen; with 5-fluorouracil, eight patients with colorectal liver metastases demonstrated either partial or minor responses, at least five of whom had previously been refractory to 5-fluorouracil. A second generation of selectively replicating adenosaviral vectors specifically targeting retinoblastoma (Rb) function are approaching clinical trial. DNA tumour viruses such as adenovirus can infect and replicate in quiescent cells because viral proteins induce S phase entry. The G1-S phase cell cycle checkpoint is regulated by pRb and its related family members (p107, p130), and efficient progression from G1 to S phase requires binding and inactivation of the pRb family of proteins by the adenovirus E1A early viral protein. This interaction requires amino acids 121-127 of the E1A protein conserved region 2. Components of the G1 checkpoint, including Rb protein, cyclin D and p16INK4a, are commonly altered in human malignancies, abrogating cell cycle control. Two similar adenovirus mutants have been described recently: d922/947 is deleted in amino acids 122-129 and Δ24 is deleted in amino acids 121-128. Both have been assessed in in vitro and in vivo models of cancer, and d922/947 is capable of replicating with much greater efficiency within a panel of tumour cell lines (including gastrointestinal) than d1520, with minimal S phase induction in quiescent non-immortalised cells. Transcriptional targeting of viral replication is also possible (overexpression of cyclooxygenase 2 (COX-2) in gastrointestinal and pancreatic cancers has stimulated the construction and preclinical validation of selectively replicating adenoviruses incorporating the COX-2 promoter to drive expression of...
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References


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