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Gene therapy developments for pancreatic cancer

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Treatment options for pancreatic cancer have limited success and it is therefore an appropriate target for the development of new strategies, including gene therapy. Gene therapy approaches include inhibition of activated oncogenes (KRAS, LSM1) with antisense and RNA interference strategies, replacement of inactivated tumour suppressor genes (TP53, CDKN2A, CDKN1A), targeting of cell signalling pathways, gene-directed prodrug-activation therapies and the use of replication-competent oncolytic viruses. Angiogenesis and apoptosis have also been targeted for gene therapy.
Clinical trials of gene therapy have shown only moderate anti-tumour effects. As there are many genetic abnormalities in pancreatic cancer, strategies combining different targets or indeed different modalities of treatment, may be more successful. Identification of new targets and improvements in delivery and targeting may further improve the efficacy of gene therapy in pancreatic cancer.

Keywords: gene therapy; pancreatic cancer; oncolytic adenoviruses; replication-competent; antisense; tumour suppressor genes; apoptosis; anti-angiogenesis; siRNA.

Pancreatic cancer is the fourth commonest cause of cancer-related death in men and women.[1] Despite advances in diagnostic techniques, early stage disease detection is poor. Most patients present with locally advanced or metastatic disease and therefore, only a low proportion of patients are suitable candidates for surgical resection.

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The prognosis of pancreatic cancer remains poor, with an overall 5-year survival rate from the time of diagnosis of less than 5%.[2]

Chemotherapy has been demonstrated to be active in the palliative treatment of pancreatic cancer although the overall outcome is poor. Gemcitabine has been demonstrated to be superior to 5-fluorouracil in palliating the symptoms of pancreatic cancer[3] and therefore, it remains the standard therapy in pancreatic cancer despite a low median survival of 5.4 months.

Advances in the knowledge of the genetics of pancreatic cancer provide new opportunities for the application of gene therapy. Cancer-associated genes, characteristic gene expression profiles and mutations in cancer cells have been identified. Gene therapy based on the exploitation of these genetic targets is being actively developed in several centres as a novel therapeutic strategy to be used alone or in combination with conventional cytotoxic chemotherapy in pancreatic cancer.

This article aims to review the principles behind the use of gene therapy in pancreatic cancer and to review the approaches that have been investigated in pancreatic cancer to date, including in vitro, in vivo and clinical studies.

GENE THERAPY

Gene therapy is based on the transfer of genetic material into the cells of a patient with disease. The genetic material is packaged into vectors, either viral or non-viral, for delivery into the cells. In order to achieve expression of the gene by the cell, the gene must be linked to regulatory DNA sequences. Transgene expression may occur constitutively in every cell transfected, or expression may be targeted selectively to cells containing particular activated transcription factors, which interact with conditional (tissue-selective or tumour-selective) promoter/enhancer elements.

Strategies for gene therapy include antisense and RNA interference strategies whereby the function of activated oncogenes is inhibited, or strategies to restore the function of tumour suppressor genes, gene-directed prodrug activation therapy and the use of replication-selective oncolytic viruses.

Transfer of genetic material by non-viral means can be direct with naked DNA, attached to ligands, or via liposomes. However, the highest efficiencies of gene transfers to date have been achieved with viral vectors and adenoviruses (especially serotypes 2 and 5), retroviruses (including lentiviruses), adeno-associated viruses, herpes virus and vaccinia viruses have all been used as gene therapy vectors.

Most of the developments in pancreatic cancer gene therapy are in the pre-clinical stage and will be discussed in this review. A few agents have progressed to early phase clinical trials.

GENETIC TARGETS IN PANCREATIC CANCER

Pancreatic cancer occurs as a result of accumulated genetic alterations and has more mutations identified than any other common tumour type (Table 1). The most frequently mutated genes are CDKN2A (p16), which is inactivated in nearly all cases[4,5], and KRAS, which is activated by mutation in over 90% of cases.[6]