Chapter 4
Gene Therapy and Gene Editing for Cancer Therapeutics

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ABSTRACT

Over the past two decades, developments in human genomics have shown that cancer in the host genome is caused by somatic aberration. This discovery has inspired interest among cancer researchers; many are now using genetic engineering therapeutic methods to improve the cancer regression and seeking a possible cure for the disease. The large gene therapy sector offers a variety of therapies which are likely to become effective in preventing cancer deaths. The latest clinical trials of third generation vaccines for a wide variety of cancers have produced promising results. Cancer virotherapy, which uses viral particles replicating within the cancer cell, is an emerging method of treatment which shows great promise. The latest developments in gene editing techniques, such as CRISPR, Cas9, TALENs, and ZFNs, are being used to help to make cancer a manageable condition. Gene therapy is expected to play a significant role in potential cancer therapy as a part of a multi-modality procedure.

INTRODUCTION OF GENE THERAPY

Gene therapy means an approach aimed at altering, removing or replacing anomalous gene(s) at a target cell (High KA & Roncarolo MG, 2019). These target cells may be primary malignant or metastatic nodules, circulating tumour cells or inactive stem cells, and unique cells like T-cell lymphocytes or dendritic cells. With the presence of more than 20,000 active genes in human cells exposed to multiple causes, whether inherited, environmental, infectious or random, infinite possibilities for gene mutation, aberration, deficiency or deletion have been expected, leading to clinical presentation of various medical disorders, including cancer (Dulbecco, 1986; Lander ES et al., 2001).

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A clear and succinct concept of gene therapy (there are many) is the use of any of a set of human disease treatment strategies that rely on the transfer of genetic material based on DNA into an organism (fda.gov). Gene delivery can be achieved in vivo by injecting the packaged gene directly into the blood, tissue, or cell. Additionally, the packaged DNA can be indirectly administered via ex vivo laboratory techniques. Somatic gene therapy which targets nongermline cells (nonegg and non-sperm cells) is currently consistent with the extension of biomedical science and medical therapy in which treatment does not go beyond the patient. Gene therapy can correct the basic pathophysiology of the disease in altering the genetic material of somatic cells. In addition to posing particular ethical problems, therapy of human germline cells, thus changing the genetic makeup of an offspring will represent a deviation from current medical practices (Strachan and Read, 1999).

In a subset of cancer patients and in paediatric cases, the main neoplastic events are germline mutations of the tumour suppressor or DNA repair genes. Germline mutations cause all of an individual's cells to become at risk for the development of cancer and are thus not appropriate for somatic cell gene therapy. Yet clonal selection of variant cells results in a population of cells with increasingly violent growth properties, in both somatic and germline mutations (Miller,1992).

In individuals with only somatic gene mutations, the insertion of a gene (such as a tumour suppressor gene) would alter the phenotype of a malignant cell only if the mutation is not dominant. In addition, both the degree of corrective cell therapy (possibly as high as 100 percent correction of all tumour cells) and the question of gene therapy in distal metastasis will need to be decided. Therefore, significant biological obstacles in the application of gene therapy to other types of cancer remain to be resolved. Indirect approaches were suggested, based on these formidable problems. These include: gene transfer of cytokines or other immune mediators to improve host immune responses, genetic alteration of neoplastic cells to promote immunogenicity, treatment of localized cancers with viral or bacterial enzyme encoding genes that transform prodrugs into toxic metabolites, or transfer of genes to provide enhanced resistance to traditional chemotherapy (Weichselbaum and Kufe, 1997).

HISTORY OF GENE THERAPY

The tradition of cancer therapy goes back to the 18th century, when surgery was the main treatment for early cancer stages, and patients experienced regular recurrences (DeVita *et al.,* 2012). The patients were treated with herbal remedies, castor oil, or arsenic until the disease spread. Radiation therapy was invented in 1895, which brought few cures (Curie and Curie, 1898). Many cases of spontaneous cancer regression after bacterial infection have been documented at that time (Lage, 2013). Following an erysipelas infection, a patient with soft tissue sarcoma went into remission in 1868 but this relapse lasted only a short time Nitrogen mustard was used in the treatment of lymphoma patients in 1943, and folic acid antagonists in childhood leukaemia contributed to temporary remission in 1948 (Goodman *et al*., 1946; Faber and Diamond, 1948; Hemminiki and Hemminki,2013). Chemotherapy care for cancer has also been making dramatic strides (DeVita, 2012).

In animal models, too, and subsequently in humans in 1956, viruses were found to be effective in regulating malignancies. Especially adenoviruses were studied more intensively in humans, with the subsequent development of gene therapy (Kelly and Russell, 2007; Atasheva et al., 2019; Atasheva S & Shayakhmetov DM et al., 2016). In 1987, immunotherapy was implemented in the treatment of lymphoma patients with subsequent FDA approval of the rituximab antibodies (1997) (Maloney *et al*., 1997).