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GENE THERAPY FOR CANCER- A REVIEW

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ABSTRACT

Gene therapy is useful for cancer which is associated with altered expression of genes. With advancing knowledge, more and more genes are identified. The exact role in preventing and curing cancer with gene therapy is still at a primitive stage in certain cases. There is no doubt that chemo- gene therapy, which is a combination of gene transfer and chemo therapy, will play an important role in advanced cancer. Several gene therapy trials are underway worldwide. Based upon the results of these trials, gene therapy may be used as a sole therapy or as an adjuvant to other modalities of treatment.

KEYWORDS: Oncology, Germline therapy, Adenovirus (Ad), coxsackie -Ad receptor (CAR), couth ‘replication- competent oncolytic agents (CRADS), tissue specific promoter (TSP), Bax gene, herpes simplex virus (HSV).

INTRODUCTION

The study of cancer called Oncology is the work of countless doctors and scientists around the world whose discoveries in anatomy, physiology, chemistry, epidemiology, and other related fields made oncology what it is today.

Cancer begins when cells in a part of the body start to grow out of control. Cancer is the second leading cause of death in United States. About one half of all men and one third of all women in the US develops cancer during their lifetime.[1,2]

Development of modern knowledge about cancer causes

1. Viral and chemical carcinogens.
2. Oncogenes and tumor suppressor genes.

History of cancer screening and early detection

The first screening test to be widely used for cancer was the pap test. Modern monograph methods were developed late in the 1960s and first officially recommended by the American Cancer Society (ACS) current ACS guidelines include methods for early detection of cancer of the cervix, breast, colon and rectum lung, prostate.

Gene therapy attempts to treat genetic diseases by correcting what is wrong with defective genes.

GENE THERAPY

Gene therapy is the therapeutic delivery of nucleic acid polymers in to a patient's cells as a drug to treat diseases.

The origins of gene therapy can be traced back to the first live attenuated vaccines in the 1950s. Although attenuated vaccines do not alter extant human genes, viruses are RNA polymers with their own genetic code that acts upon human cells, thus live vaccines can be considered a primitive from of gene therapy, albeit not in the sense that is generally implied today.[4]

TYPES OF GENE THERAPY

There are two basic types of gene therapy

1. Germline therapy
2. Somatic gene therapy

GERMLINE THERAPY

This therapy involves the modification of the genes inside germ cells. During reproduction these gamete cells fuse to form a zygote, which would divide and pass on the modified gene in to all other cells of the body during the development of offspring.[5]

SOMATIC GENE THERAPY

It involves the insertion of therapeutic DNA in to body cells and not the germ cells or gametes. This means any effects of the therapy are confined to the individual being treated and are not inherited by future offspring.[6]

Mechanism of Therapy

Three regions of the viral genome can accept insertions or substitution of DNA to generate an independent therapeutic virus vector:

The regions are E1, E3, and a short region between E4 and end of the genome. In first-generation vectors, the E1region was removed and replaced with a therapeutic transgenic; although vectors were directed to tumor cells, they displayed inhibited viral replication within those cells. Viral transcription of remaining viral genes still occurred, resulting in early innate host cytokine transcription and antigen immune responses. The immune response limited time allotted for gene expression, due to cell mediated destruction of the transduced cells.

Adenovirus is key vector: Benefits and Risk factors.

Serotypes in Ad, infection are mediated by the binding of the fiber-knob region to a receptor of target cell, known as coxsackie -Ad receptor (CAR). CAR binding is most commonly observed in serotype 5 in humans.

Life cycle of Ad is separated by DNA replication process

The early and late phase, Responses are due to both Ad vector and already disease-infected cells. Ad presentation activates the immune system and enlists a natural response to combat tumor antigens however, using Ad as a vector is risky in that too high a dose will result in acute toxicity and autoimmunity.

Alternative Approaches

Two strategies have been used to restrict viral replication to target tumor cells and spare normal tissue. The first method involves genetic complementation couth ‘replication-competent oncolytic agents ‘or conditionally explicative Ad, CRADS. These CARDS have a mutation in immediate early E1A or E1B Ad genome region, which is complemented in tumor cells and not in normal cells. Therefore, location of growth is localized to tumor/ tissue specific promoters. There are 2 known types of CRADS.

A prototype of type 1 CRADS is ONYX- 015. It contain 2 mutation in the gene encoding for E1B55K and inactivates protein for motion .under normal conditions, E1B55K protein binds and inactivates the tumor –suppressor protein P53 in humans.

Type 2 CRADS include a tissue specific promoter (TSP), for specific target cells. Promoter fragments with specific activity in type 2 CRADS are rare as structure- function relationship

of promoter regions have not been well characterized TSPs have only been observed empirically yet hold strong promise for functional therapies.

Gene therapy for brain tumors

Basic developments and clinical implementation

Glioblastoma multiform (GBM) is the most common and dead list of adult primary brain tumors. The resistance of GBM against chemotherapy and radiotherapy necessitate the development of novel the treatment of brain tumors Simplex Type 1 Thymidine kinase (T K) and the power full Dc growth factor. Combined delivery of these vectors elicits tumor cell death and an anti – tumor adaptive immune response that regives TLR2 activation. Combined cytotoxic and immune -therapeutic strategies are effective to combat deadly brain tumors and warrant their implementation in human phase 1 clinical trials for GBM.[7,8]

BREAST CANCER

Gene therapy targets metastasis to stop breast cancer.

Brest cancer remains the leading cancer diagnosis in women and over all, the second –leading cause of cancer. Brest cancer stimulates metastasis by taking over a process known as epithelial mesenchymal transition. This process encourages cells to break apart from the tumor and travel through the body to new location, usually another organ. To keep the epithelial – mesenchymal transition going, breast cancer cells turn on a gene known as Twist 1 to produce high levels of twist 1 protein.

The research team focused on controlling twist 1 expression as a means to control metastasis of breast cancer cells. The Twist 1 gene is considered as a good target because it isn't active in most normal, healthy situations. To turn Twist 1 gene researchers developed a gene therapy that uses short interfering RNA. Because one limitation of RNA- based gene therapies is the ability to make a significant change, the team attached the short – interfering RNA to molecules known as dendrimers to ensure sufficient delivery. They then tested the effects on 2 slightly highly invasive breast cancer cell lines, with positive results.[9]

Gastric cancer

Gastric cancer is the fourth most common on malignancy world-wide. There are different ways to modulate tumor growth by gene therapy strategies.

These include

- Direct destruction of tumor cells
- Inhibition of tumor angiogenesis
- Tumor cell spread inhibition.

Tumor suppressor genes

The most obvious way to target growth regulation in cancer cells is to introduce tumor suppressors that may be in activated in tumors. Introduction of the p 53 gene via recombinant adenoviruses has been shown to inhibit the growth of gastric cancer cells with mutated p 53 in vitro and in-vivo, consequently Bax gene may serve as a good alternative top 53 for cancer gene therapy. All these signaling molecules work through a common pathway involving activation of the effectors caspase. Thus a recombinant expression of caspase 3 leads to the induction of apoptosis in gastric cancer cells. Finally a replacement of this tumor suppressor often inactivated in gastric cancer, decrease sensitivity to carcinogens and induces apoptosis in gastric tumor cell in vivo.[12]

Suicide gene

This strategy relies on the conversion of pro drugs in to physiologically active agents by means of non- mammalian enzymes. These suicide enzymes are over –expressed in neoplastic cells as a result of successful transfect ion with their genes. The most widely used suicide gene or pro drug system is the herpes simplex virus (HSV) timeline kinase (HSV-tk) that can convert the pro drug GCV in to phosphorylated GCV. The phosphorylated GCV inhibits cellular DNA synthesis and leads to the killing of cancer cells via appropriate and non- appropriate mechanisms.[11]

Anti –angio genesis therapy

Tumor angiogenesis plays an important role in the growth of solid tumors and the formation of metastases in contrast to other, genetic treatments, anti-antigenic gene therapy does not necessarily require direct and selective Trans duct ion around the tumor to create an anti – antigenic environment. This advantage helps to overcome the limitations of the currently available vector systems, which often lack adequate transduction efficiency in cancer cells. Several studies were undertaken to evaluate the potential of anti – antigenic gene therapy in gastric cancer.

ADENOVIRAL GENE THERAPY FOR OVARIAN CANCER

Adenoviral gene therapy is an attractive modality for the treatment of ovarian cancer because ovarian cancer tends to remain localized in the peritoneal cavity, allowing for regional delivery of the vector or virus in the setting of ovarian cancer, ad21 was among the first clinically evaluated adenoviral gene therapy approaches, Ad21encodes an ER localized anti-erb B2single chain intra body it was hypothesized that the expressed intra body traps a cancer associated receptor erbB2 to ER, and therefore, down regulates the cell surface expression of otherwise over expressed protein this approach resulted in induction of apoptosis and ovarian cancer cytotoxicity in vitro, and enhanced, anti –tumor activity and survival in ovarian cancer animal models.[3]

Alvarez analyzed the feasibility of the strategy in phase I ovarian cancer trial the treatment was well tolerated without dose limiting toxicity. Importantly, PCR and RT-PCR analyses from ascites samples demonstrated the presence of vector and expression of transgene, however, there was no data identifying the infected cells. Further, there were no responses detected. The major disadvantage of this kind of approach is a requirement of infecting all cancer cells.

Importantly, none of the studies above were randomized. Further there were no clinical complete responses It might be necessary to target adenovirus to non- CAR receptors to achieve reasonable transduction levels in clinical setting various strategies to retarget adenovirus binding or transgene expression in ovarian cancer cells have been analyzed in vitro- in vivo. A clinical trial for treatment of ovarian cancer patients with peritoneal disseminated disease with this virus will soon start enrolling patients.[10]

Adenovirus –based gene therapy: A promising novel cancer therapy

Adenovirus (Ad) based cancer gene therapy is a common from of the treatment, as the Ad vector is second to lent virus vectors in gene based therapy. Treatment has been used as an alternative in clinical trials today and proved to be effective, it is also commonly co-administered with other anti – tumor drugs, Known as " cocktail" drug therapy.

Ad is unique in its viral structure; it is a medium sized (90-100 mm), non enveloped icosahedra, which includes a nucleocapsid. It is the largest of the non – enveloped viruses and contain a single double stranded (ds) DNA genome. About 57 serotypes exist in humans and cause 5-10/ of upper respiratory infections in children, it is also highly prevalent among

adults, Ad infects various species of vertebrates and was first found and isolated in human adenoids, pharyngeal tonsil or nasopharyngeal tonsil tissue, in the middle of 1950's Ad is an extremely durable virus, ubiquitous in human and animal populations as it can survive long periods of time out of the host and is endemic year round.

Merits of Gene Therapy

1) Giving an advantage to someone who has born with a genetic disease by replacing nonfunctional gene with a functional One. This may give someone a chance of normal life.
2) A cancer patient can also get advantage of this technique by insertion of genetically altered vectors in to human genome.

Demerits of Gene Therapy

1) Before going to perform gene therapy, defective genes are searched and to find these genes, it is obligatory to perform genetic tests or genetic screening to see whether a defective gene that causes for example, cancer is present or not. But because of this genetic testing some issues or legal problems stood up.
2) For the diagnosis of disease in a fetus or embryo before it is born prenatal testing is performed. If an unborn carries any defective gene then their parent's definitely want to abort this child this may increase number of abortions, This is braggy disadvantage of gene the therapy. This creates many ethical problems.

Applications

1. Gene corrections

Cancer may result when there is an imbalance between proto – on genes and tumor suppressor gene. TP53 is the most commonly intuited gene or inactivating- proto- ontogeny by antisense method. Tumor suppressor gene TP53 is the most commonly mutated gene in human cancer. TP53 normally regulates the cell cycle and repairs abnormal DNAs.

2. Immune –gene therapy

Immunological mechanisms are important for the elimination of cancer by the human body. Individuals with immune deficiency, such as HIV infection, are at a high risk of developing cancers cancer cells are destroyed by deactivating CD8+ cytotoxic T cells and natural killer cells but many cancers cells escape this immune mediated cancer cells escape this immune mediated destruction by exhibiting loss of HLA Class I antigens.

3. Drug resistance gene therapy

The main limiting factor for patients undergoing chemotherapy is bone marrow toxicity there is a gene celled multiple drug resistance gene (MDR) which may confer the bone marrow resistance to Vinca alkaloids, Anthrocyclins and paclitaxel. This gene therapy is still in an experimental stage.

4. Chemo –Gene Therapy

The susceptibility of cancer cells to chemotherapy is enhanced by combining them both gene therapy which is known as chemo gene therapy. It means administering a chemotherapeutic agent such as 5FU in conjunction with a gene such as FLT3L to have a hematopoietic factor which stimulates immune cells which may kill cancer cells The synegism which results from the combined gene therapy and chemotherapy is much more efficient and may eradicate the tumor.[13]

CONCLUSION

Gene therapy is useful for cancer which is associated with altered expression of genes. With advancing knowledge, more and more genes are identified. The exact role in preventing and curing cancer with gene therapy is still at a primitive stage in certain cases. There is no doubt that chemo- gene therapy, which is a combination of gene transfer and chemo therapy, will play an important role in advanced cancer. Several gene therapy trials are underway worldwide. Based upon the results of these trials, gene therapy may be used as a sole therapy or as an adjuvant to other modalities of treatment.

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