

**GENE THERAPY AND CARCINOMA PROSTATE**Raj Kumar Goel¹, Pratap Shankar^{2*}, Sanjay Khanna¹, Rakesh Kumar Dixit², Amod Kumar Sachan²¹Department of Pharmacology, Hind Institute of Medical Sciences, Safedabad, Barabanki, U.P., India²Department of Pharmacology & Therapeutics, King George's Medical University, Lucknow, U.P., India**ABSTRACT**

Despite recent advances in early detection and treatment, prostate cancer is the most common cancer and the second leading cause of cancer-related deaths in developed countries. Prostate cancer patients having a limited number of treatment options such as radiotherapy, cytotoxic chemotherapy etc. Although results of all approaches are showing beneficial effects, but without long term survival benefit. A recent development in the field of cancer treatment named as gene therapy comes in existence with promise of prostate cancer treatment. It is an emerging field against not only prostate cancer but for all types of cancers. With advancement of basic research and gene therapy technology, no doubt it may be the best future cancer treatment with the use of genetic engineering and clinical trials. In this review we tried to conclude the importance of the gene therapy in prostate cancer with novel and unique characteristics and with promise to cure as the hope for management of the prostate cancer.

KEYWORDS: Gene Therapy, Carcinoma Prostate, Gene Transfer, Immunotherapy, Oncolytic Virotherapy.

INTRODUCTION:

Experiments on animals are still necessary for explanation of fundamental mechanism of the malignancy and to find out the improved methods to prevent, diagnose and treat cancer (1). Despite recent advances in early detection and treatment, prostate cancer is the most common cancer and the second leading cause of cancer-related deaths in developed countries (2,3). Prostate cancer patients having a limited number of treatment options such as radiotherapy, cytotoxic chemotherapy etc. Although results of all approaches are showing beneficial effects, but without long term survival benefit (4-6). Unfortunately, with all possible treatments of the prostate cancer, the patients become non-responsive towards treatment with high mortality due to uncontrolled death. Regarding this issue it is necessary to develop and use some new more effective therapeutic approaches. Present treatments often showing long term negative side effects (7). In addition, Chemotherapy causes long-term side effects, including an increased risk of developing other types of cancers (6,8). In case of metastatic prostate cancer treatment, on one hand treatment prolonging life and on the other hand causes negative side effects like: hot flashes, impotence, incontinence, an increased risk of bone fractures etc. (9). Therefore, it is a need for new treatment option to reduce the death due to prostate cancer.

One new therapy named as gene therapy comes in existence with promise of prostate cancer treatment (10-12). The emerging field of cancer treatment "gene therapy" offers a number of exciting potential treatments (13). Wide range of treatment options occurs with use of genetic material either in vitro or in vivo to cure the prostate

cancer in gene therapy (13). Under this therapeutic approach potential therapeutic gene injected directly in to tumor. These genes directly act on the target genes resulting monitored disease progression. Recently, several gene therapy strategies have generated provocative results in early-stage clinical trials, raising the possibility that gene therapy may have the potential to affect both localized and metastatic disease (14). This disease progression monitored by measuring prostate-specific antigen (PSA) (10-12,15-16). Prostate cancer is amenable in nature, relatively slow-growing disease. With a plus point, due to amenable and slow-growing nature, multiple gene therapies can be used to for the prostate cancer treatment (17-19).

In this review we tried to conclude the importance of the gene therapy in prostate cancer with novel and unique characteristics and with promise to cure as the hope for management of the prostate cancer.

GENE THERAPY:

Lack of significant efficacy is a major limitation of human cancer gene therapy (20). Gene therapy is a broad field with a dedicated promise for cure and prevention of deaths due to prostate cancer. Gene therapy comprises by means three types of techniques; Immunotherapy, Oncolytic Virotherapy and Gene Transfer. These all techniques are used independently for the treatment of the prostate cancer. We hope, with more research in the field of gene therapy, all the techniques may be used in combination for treatment of not even the prostate cancer but all type of prostate cancers (21). We cannot ignore the importance of the Adenovirus in the gene therapy because

these are the most common vehicle for the gene therapy approaches (10,12,22). In recent time, in search of novel and safer prostate cancer treatment, gene therapy delivery agents have been created and a number of prostate cancer patients globally have participated in gene therapy trials with remarkably few treatment side effects (23,24). The most frequent side effects are fever and symptoms that resemble a cold. If the agent is injected, there is often localized swelling and inflammation at the site of the injection (23, 25-27). If we see the comparative results of side effects, other treatments and treatment benefits by gene therapy, side effects are less than the benefits. So we can recommend gene therapy as a conventional treatment (21). Three major issues i.e. systemic delivery, specific introduction, and specific expression of the target gene are to be focused to develop a clinically relevant treatment strategy (20).

With reference to the Genetic Modification Clinical Research Information System (<http://www4.od.nih.gov/oba/RAC/GeMCRIS/GeMCRIS.htm>), more than about 70 gene therapy protocols have been reviewed by the Recombinant DNA Advisory Committee of the National Institutes of Health, targeting with the prostate cancer till 2007. It is not a surprise regarding few proceeded towards the clinic and even one or two have shown results (14). Question arises regarding what is the main cause of this failure? The answer is very logical i.e. because of lack of resources, regulatory barriers, etc. (28). Both approaches in vivo as well as ex vivo, regarding the gene therapy trials reported till date for the prostate cancer treatment may be an attractive target for the further research. This is because of the various strategies required to promise for localized and metastatic disease. This discussion regarding the localized versus metastatic prostate cancer treatment strategies can be discussed separately.

GENE THERAPY FOR LOCALIZED PROSTATE CANCER:

Gene therapy for localized prostate cancer initiated from replication-defective adenoviruses containing a single therapeutic gene to replication-competent oncolytic adenoviruses containing multiple therapeutic genes (29-37). Freytag and colleagues in 2007 evaluated in the setting of locally recurrent and newly diagnosed disease, and as single agents or in combination with radiation therapy (14). In all, low toxicity in humans has demonstrated. Freytag et al. were the first to “arm” a replication-competent adenovirus with a therapeutic gene and propose combining gene therapy and oncolytic viral therapy with radiotherapy (38-41). In a study by the Freytag, primary results increase the possibility that replication-competent adenovirus-mediated suicide gene therapy may have the potential to

improve local tumor control of conformal radiotherapy in select patient groups (42).

GENE THERAPY FOR METASTATIC PROSTATE CANCER:

Previously both in vivo and ex vivo gene therapy strategies targeting metastatic prostate cancer have been evaluated in the clinic. Kubo and colleagues were among the first to evaluate an in vivo adenovirus-mediated gene therapy strategy targeting metastatic prostate cancer (43). Simon and colleagues were among the first to evaluate an ex vivo gene therapy strategy targeting metastatic prostate cancer (44). Their strategy utilized an autologous granulocyte-monocyte colony stimulating factor –secreting cancer cell vaccine to treat men who were found to have metastatic prostate cancer at the time of surgery. The rationale for using granulocyte-monocyte colony stimulating factor as a cancer therapy is well founded scientifically and stems from the fact that it has demonstrated the greatest ability to induce durable tumoricidal anti-tumor immune responses in preclinical models (45) Although not a study endpoint, all subjects demonstrated significant declines in serum PSA, which is expected after prostate resection. However, all subjects exhibited disease progression (14). The main factor for the prostate cancer bone metastasis is epithelial and stromal interactions (46). After the metastasis to bone prostate cancer cells begin to express bone specific proteins such as OC, osteopontin, and bone sialoprotein (47). All above gene expressions are controlled by the many factors. These properties are known as osteomimetic properties, which can be a golden opportunity to target bony metastases of prostate cancer (48-54).

IMMUNOTHERAPY:

In this type of gene therapy, genetically modified cells and viral particles are usually used for immune system stimulation resulting cancer cells destruction (21). The main purpose of the immunotherapy is to boost the immune system targeting and destruction of cancer cells (55). Currently there are many new researches going on in the field of gene therapy to create recombinant cancer vaccines (56). It is favorite modality, has proved itself better therapeutically under clinical investigations (12,57). It is described under three common approaches (i) tumor cell vaccines, (ii) vector-based vaccines, and (iii) dendritic cell (DC)-based vaccines (20).

Vaccine models showing positive results for prostate cancer treatment in preclinical trials. For example: in a prostate cancer vaccine trial, a patient who achieved normal prostate specific antigen (PSA) levels for the year of the trial, developed rising PSA levels after vaccination was stopped. His PSA levels were stabilized again only with re-

initiation of the vaccine therapy. (58-59). These results, while not entirely positive, have given scientists a better understanding of the immune reaction to cancer and have led to the development of the next generation of cancer vaccines (21).

ONCOLYTIC VIROTHERAPY:

It is an emerging treatment approach that uses replication-competent viruses to destroy cancers. (60) Under oncolytic virotherapy, viral particles are used for replication inside the cancer cell resulting cell death. This is an emerging treatment modality with great promise for treatment of the metastatic prostate cancer (21). As with many current treatment regimens for cancer, gene therapy utilized as a monotherapy may not be the sole solution. A multimodal approach combining virus based gene therapy with chemotherapy and/or radiotherapy may be necessary for more complete tumor eradication (61). Although the majority of our work to date has utilized the prostate cancer model, researchers have also demonstrated the utility of gene therapy in vitro and/or in vivo for several other tumor models, including breast, pancreas, colon, medullary thyroid, ovarian carcinomas (62-63), and in multiple myeloma (64).

GENE TRANSFER:

This is a recent treatment modality in which new genes introduction takes place into a cancerous cell to cause the cell death or slow down the cancer cells growth. It is a very flexible cancer treatment technique with the help of wide range of genes and vectors used for positive results against the prostate cancer treatment (21). Gene therapy for treatment of cancer is generally substratified into four strategies based on the molecular target of gene transfer (65):

1. Tumor suppressor gene therapy
2. Suicide gene therapy
3. Immune modulatory gene therapy
4. Antioncogene therapy

ROLE IN PROSTATE CANCER TREATMENT:

In recent days there is gradual increase in incidence and mortality of prostate cancer (66). Management of localized prostate cancer is possible with surgery or radiation (67-69). Unfortunately, these treatment types are less effective against more aggressive forms of the disease (Stage XT2b or Gleason score X7 or PSA 410 ng/mL), and many of these patients relapse. Because prostate cancer is usually hormone-dependent at this point, patients with a rising prostate-specific antigen (PSA) following definitive therapy are typically treated with salvage androgen suppression therapy (AST).

Despite of these some therapies challenging sure treatment of the prostate cancer, there is no effective curable approach for prostate cancer in an androgen independent state or aggressive state (70-71). To overcome the present problem of prostate cancer it is a very urgent need to search, invent and develop new and effective therapies (71). With respect to all the therapies present for the prostate cancer treatment, gene therapy is seems to be a ray of therapeutic hope for the prostate cancer treatment (71-72).

CONCLUSION:

Gene therapy is emerging field against not only prostate cancer but for all types of cancers. By the advancement of basic research and gene therapy technology, no doubt it may be the best future cancer treatment with the use of genetic engineering and clinical trials. But many hurdles have to be crossed to reach towards the effective gene therapy. Gene therapy can be the best in future treatment of the cancer with few concerns regarding the safety and benefits.

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