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Review

Current strategies in cancer gene therapy

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Abstract

Cancer gene therapy is the most studied application of gene therapy. Many genetic alterations are involved in the transformation of a normal cell into a neoplastic one. The two main gene groups involved in cancer development are oncogenes and tumor suppressor genes. While the latter eliminates cancerous cells via apoptosis, the former enhances cell proliferation. Therefore, apoptotic genes and anti-oncogenes are widely used in cancer gene therapy. In addition to oncogenes and tumor suppressor genes, chemotherapy and gene therapy can be combined through suicide gene strategy. A suicide gene encodes for a non-mammalian enzyme; this enzyme is used to convert a non-toxic prodrug into its active cytotoxic metabolite within the cancerous cells. Tumor suppressor genes, anti-oncogenes and suicide genes target cancer cells on the molecular level. On the other hand, cancer is immunogenic in nature; therefore, it can also be targeted on the immunological level. Boosting the immune response against cancerous cells is usually achieved via genes encoding for cytokines. Interleukin-12 gene, for example, is one of the most studied cytokine genes for cancer gene therapy applications. DNA vaccines are also used after conventional treatments to eliminate remnant malignant cells. All these therapeutic strategies and other strategies namely anti-angiogenesis and drug resistant genes are briefly reviewed and highlighted in this article.

Keywords: Cancer gene therapy; Anti-oncogene; Suicide gene; *p53* gene; DNA vaccine; Cytokine gene

1. Introduction

Gene therapy includes the treatment of both genetically based and infectious diseases by introducing genetic materials which have therapeutic effects (Anderson, 1998; Crystal, 1995; Miller, 1992). In its simplest terms, a wild type gene (which is non-functional in the cell leading to disease development) is introduced into the somatic cell lacking this gene to restore the cell's normal gene function. Many gene therapy strategies, however, utilize genes to destroy specific cells. Such strategy is widely encountered in cancer gene therapy (Fillat et al., 2003; Zeh and Bartlett, 2002). Another gene therapy strategy is found in the diseases of the nervous system where the genetic basis is very complicated or not well understood. Therapeutic genes in this case encode for a protein which is missing in the neuro-cells. The loss of dopaminergic neurons, for example, plays a major role in the development of Parkinson's disease (Lindvall et al., 1990). Therefore, genes that can enhance dopamine production will have therapeutic effects (Latchman and Coffin, 2001). Genes can also boost the body defense system against foreign infectious microorganisms. Gene therapy for human immunodeficiency virus (HIV), which relies on boosting T-cell immunity, for instance, has entered clinical trails phase I (Clayton, 2002).

During the past 15 years, intensive research in the area of gene therapy has conducted worldwide with the first approved gene therapy clinical trail in 1990. In this study, adenosine deaminase (ADA) gene was transferred into T-cells of two children with severe combined immunodeficiency (ADA-SCID) (Blaese et al., 1995). After a decade, there are more than 400 clinical studies in gene therapy. Almost 70% of these studies are in the area of cancer gene therapy (Breyer et al., 2001).

Gene therapy for cancer can provide a new treatment option for this fatal disease. Over 2,500,000 cancer patients

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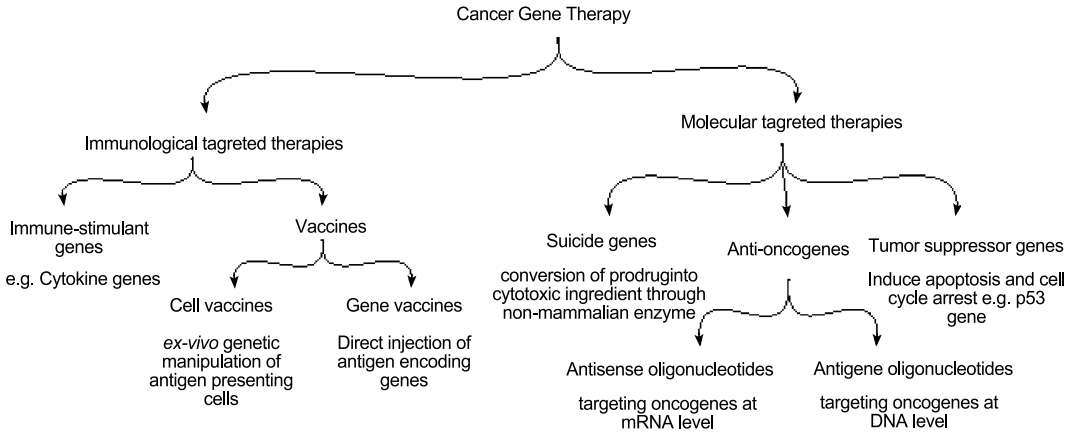

Scheme 1. Summary of the most common current cancer gene therapy approaches.

died in the United States alone between the years of 1976 and 1996 (Ries et al., 1999). The transformation of normal cells into neoplastic ones is associated with multi-mutational alterations on the genetic level of these cells (Bertram, 2000). Due to the complex nature of cancer, cancer gene therapy includes many therapeutic strategies. These strategies can be categorized into two main avenues: immunologic and molecular (Heo, 2002; Brand, 2000). Scheme 1 summarizes different gene therapy approaches reviewed in this article.

2. Immunologic approaches in cancer gene therapy

There are two arms for the immune system to encounter foreign antigens. One arm includes antibodies which are secreted by B cells after being activated through membrane immunoglobulin (B cell receptors)-antigen binding. Antibodies are soluble proteins that circulate in the blood to reach their targets of soluble antigens. On the other hand, T cells, the second arm of the immune system, do not secrete antibodies and interact directly with antigens. These antigens can be synthesized ones presented at the cell surface through major histocompatibility complex. T cells can then mediate multiple immune reactions including cytotoxic effects (Benjamini et al., 2000).

Cancer cells are immunogenic in nature with cancer antigens being intracellular molecules (Oettgen and Old, 1991). Therefore, cellular immunity (T-cell mediated) is more prominent than humoral immunity (B-cell mediated) (Ostrand-Rosenberg et al., 1999). The regular immune response, however, is not enough to eradicate tumor cells. The ability of cancer cells to escape the immune system is related to the secretion of immunosuppressive factors, (Cochran et al., 2001) down-regulation of antigen expression (Kurnick et al., 2001; Uyttenhove et al., 1983) or major histocompatibility complex molecules (Cabrera et al., 2003; Hui et al., 1984), and the lack of co-stimulation (Pardoll, 1998; Galea-Lauri et al., 1996). In fact, the antigen is presented by the tumor cell itself rather than the antigen presenting cells capable of co-stimulants secretion. Genetic immunotherapy can be utilized mainly to boost T-cell mediated immune response against cancer.

One of the frequently encountered genetic immunotherapy strategies involves the transfer of the genes of the immune-stimulant molecules such as cytokines. Intensive research has focused on the transfection with Interleukin-12 gene. Complete tumor regression in rat animal models was observed in hepatocellular carcinoma and adenocarcinoma after successful Interleukin-12 gene transfection into the cancer cells (Shi et al., 2002; Barajas et al., 2001). The production of Interleukin-12 by tumor cells mediates the immune response by the activation of many components in the immune system, in particular cytotoxic T lymphocytes and natural killer cells (Saudemont et al., 2002; Caruso et al., 1996).

Another genetic immunotherapy approach includes the in vitro manipulation of antigen presenting cells to enable them of active tumor antigen presentation. Dendritic cells are the most powerful antigen presenting cells. Engineered dendritic cells, for example, expressing α-fetoprotein (AFP), a hepatocellular carcinoma antigen, was able to provoke a strong immune response against the cancerous cells (Vollmer et al., 1999). Acute leukemic cells can also boost body immunity after being modified ex vivo into functional antigen presenting cells (Stripecke et al., 2002). These strategies of in vitro manipulation are very efficient in treating minimal disease status observed after conventional chemo- and radiotherapies (i.e. cell vaccines).

Direct genetic vaccination by the antigen-encoding genes can also induce the desired immune reaction against cancer cells. When injected by subcutaneous or intramuscular routes, DNA enters local cells (fibroblasts or myocytes) which can then produce and secrete the antigen. Antigen presenting cells will capture the new antigen and migrate to the lymphoid organs initiating the desired immune response (Ribas et al., 2000). AFP-expressing tumors, for instance, were rejected by at least 60% of tested mice after being vaccinated with AFP-expressing gene. The life span in the treated animals was also significantly prolonged (Hanke et

al., 2002; Grimm et al., 2000). Similarly, immunization of monkeys by carcino-embryonic antigen gene resulted in both humoral and lymphoproliferative immune responses (Conry et al., 1998).

3. Molecular approaches in cancer gene therapy

Upregulation or downregulation of some genes is the basis of tumor initiation and progression. The underlying mechanism of gene dysfunction includes many mutations on the genetic level. Many genes are involved in the development of cancerous cell (Bertram, 2000). The two gene groups believed to be mainly involved in cancer development are oncogenes and tumor suppressor genes. Oncogenes are growth promoting while tumor suppressor genes are growth inhibiting. Tumor suppressor genes have been widely used in cancer treatments. On the other hand, oligonucleotides, which bind and subsequently inhibit oncogenes (i.e. antioncogenes), can also be utilized in cancer therapy. In either case, the aim is to induce cell cycle arrest or better apoptosis (programmed cell death) in cancer cells.

Suicide genes which also target cancer cells on the molecular levels are considered as another molecular approach in cancer gene therapy.

3.1. Suicide genes

This strategy relies on the conversion of non-toxic substances (prodrugs) into physiologically active agents by means of non-mammalians enzymes. These enzymes were over-expressed in the neoplastic cells as a result of a successful transfection with their genes (Kirn et al., 2002; Mullen, 1994).

One of the most investigated suicide gene/prodrug systems is the herpes simplex virus thymidine kinase (HSV-tk)/ganciclovir (GCV) system. The idea of utilizing HSV-tk for therapy is rooted from the pioneer studies which observed cellular growth inhibition in cells treated with attenuated HSV after exposure to acyclovir (Nishiyama and Rapp, 1979; Elion, 1980) or GCV (Oliver et al., 1985) and from the discovery of the viral tk gene (Colbere-Garapin et al., 1979) HSV-tk was subsequently used to investigate its killing ability associated with GCV treatment in various cancerous lesions (Moolten, 1986; Moolten and Wells, 1990; Culver et al., 1992; Oldfield et al., 1993).

HSV-tk is a herpetic enzyme that catalyzes the phosphorylation of nucleoside analogs such as the antiviral drug GCV (Fillat et al., 2003; Dubowchik and Walker, 1999). The phosphorylated GCV mediates the killing of cancer cells via apoptotic (Wei et al., 1998; Hamel et al., 1996) and non-apoptotic mechanisms (Kwon et al., 2003; Link et al., 1997). GCV and its phosphorylated form are shown in Fig. 1. Apoptosis is characterized by chromatin condensation, cell shrinkage, and the formation of apoptotic vesicles

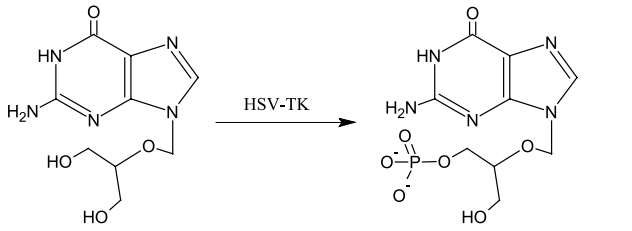

Fig. 1. Activation of GCV by HSV-tk.

(apoptotic bodies) (Gschwind and Huber, 1997) which are phagocytosed by adjunct cells. Following the treatment with GCV, apoptotic bodies were detected in HSV-tk negative colon cancer cells which were co-cultured with HSV-tk positive cells (Freeman et al., 1993).

One of the powerful features in these systems is the bystander effect. It is the mechanism by which the toxic metabolites are transferred from transduced cells to neighboring cancerous cells via gap junctions and/or apoptotic vesicles described below (Tanaka et al., 2001; Freeman et al., 1993). It has been shown that the treatment with GCV for cancer cells with as few as 10% of the cells expressing the HSV-tk gene in vitro or 50% in vivo will lead to the same degree of cell death and tumor regression as that obtained with 100% cell transfection (Freeman et al., 1993; Takamiya et al., 1993; Culver et al., 1992).

Gap junctions (also known as metabolic cooperation) are cylindrical structures in the cellular membrane; these structures combine the cytoplasm of two adjunct cells. They are composed mainly of connexin32 (Cx32) protein (Ladish et al., 2000). These cellular communicating units enable cells to transfer ionic and low molecular weight substances (i.e. <2000 Da) between each other (Ladish et al., 2000). The relationship between gap junctions and HSV-tk/CGV system is well established (Asklund et al., 2003; Nicholas et al., 2003; Marconi et al., 1996; Touraine et al., 1998).

This two-step approach in cancer gene therapy, however, may affect the surrounding non-cancerous cells. Normal tissue damage was reported when rat hepatoma was treated with the HSV-tk/GCV system (Bustos et al., 2000).

In addition to HSV-tk/GCV system, there are many other systems which are under investigation. These systems include, but are not limited to, cytosine deaminase (CD)/5-fluorocytosine (Yoshimura et al., 2001; Li et al., 1997), cytochrome P450/cyclophosphamide (Chen et al., 1996; Wei et al., 1995), and carboxypeptidase/4-[2-chloroethyl 2-mesyloxyethel-0-amino] bensoyl-L-glutamic acid (CMDA) (Marais et al., 1996).

3.2. Anti-oncogenes

The biological activity of oncogenes can be modulated and suppressed either on the RNA or the DNA levels.

Anti-oncogenes are oligonucleotides (short nucleic acid segments) that can bind to a specific sequence of the RNA (antisense oligonucleotides) or the DNA (antigene oligonucleotides) resulting in the inhibition of the oncogene activity (Zhang and Roth, 1994; Helene, 1994).

3.2.1. Antisense oligonucleotides

Antisense oligonucleotides bind to mRNA through Watson–Crick base pairing inhibiting the translation step of protein synthesis (Kibler-Herzog et al., 1990). One of the most prominent oncogenes is *bcl-2* gene, a prototypical inhibitor of apoptosis (Gross et al., 1999). Over-expression of *bcl-2* also increases resistance to chemo- and radiotherapies in cancer cells (Reed, 1999). Expression of *bcl-2* in vitro was significantly reduced after treatment with the liposomal solutions of the antisense oligonucleotide G3139 (Hu et al., 2001; Duggan et al., 2001). The intravenous infusion of the short oligonucleotide G3139 in patients with solid tumors, however, did not show antitumor effects (Morris et al., 2002). In contrast, the combination with chemotherapy revealed encouraging therapeutic results for leukemic patients (Marcucci et al., 2003).

Other important targets for antisense therapy are *c-myc* (Potter and Marcu, 1997) and *ras* family oncogenes (Scharovsky et al., 2000). For example, retardation in cell growth rate was observed in melanoma cells treated with antisense oligonucleotide targeting the *c-myc* gene (Chana et al., 2002). In addition, in vivo treatment showed significant reduction in tumor growth in adenocarcinoma-implanted rats only when combined with the chemotherapeutic agent Carboplatin. The latter was not effective when used alone (Walker et al., 2002). Oncogenes seem to play a central role in cancer resistance against chemotherapy.

It is also possible to include cleavage capable fragment in the oligonucleotides (i.e. ribozymes) (James, 1999). This strategy will lead to the destruction of the targeted RNA. Point mutation in codon 12 of the *K-ras* oncogene was utilized successfully to design a site-specific antisense ribozyme (Kijima and Scanlon, 2000). Apoptosis and tumor growth suppression were observed both in vitro and in vivo when colon cancer cells were treated with the *K-ras* antisense (Tokunaga et al., 2000).

3.2.2. Antigene oligonucleotides

Antigene oligonucleotides bind to the DNA through Hoogsteen hydrogen bonding forming a non-functional triple helical structure (Helene et al., 1992). In this strategy, gene expression is blocked at the transcription stage. The main benefit of this approach over the antisense strategy is the limited targets for the therapeutic oligonucleotides (two targets per cell versus hundreds to thousands of mRNA for the antisense oligonucleotides). For example, the combined radiotherapy, via ^{99m}technetium (^{99m}Tc), and *bcl-2* antigene treatment, for example, was illustrated in vitro through the use of ^{99m}Tc-conjugated *bcl-2* antigene resulting in successful transcriptional cessation of the *bcl-2* gene (Shen et al., 2003).

In addition, the combination of more than one antigene can result in synergistic effects. Dual treatment with *c-myc* and *c-erbB2* (also known as *HER/neu*) antigenes, for example, showed 80% efficiency in cell growth inhibition in ovarian cancer cells in comparison to 60% efficiency observed with individual antigene treatments (Fei and Shaoyang, 2002).

3.3. Tumor suppressor genes

Tumor suppressor genes constrain unusual cell proliferation (Weinberg, 1991). These genes induce apoptosis and/or cell cycle arrest in malignant cells (Opalka et al., 2002). The main representative gene of this family is the *p53* gene which is responsible for the detection of DNA damage followed by repair initiation or apoptosis induction (Sager, 1989). *p53* protein interfere in the biochemical pathways of many gene groups which regulate cell growth and differentiation namely, Bcl-2, Caspase, and IAP gene families (reviewed in Shen and White, 2001).

Mutational alterations in the *p53* gene occur in almost 40% of all tumors (Greenblatt et al., 1994). Despite that wild type *p53* (*wt p53*) belongs to tumor suppressor gene family, some of its mutant forms can act as oncogenes (Marshall, 1991; Lane and Benchimol, 1990). Therefore, successful transfection of the *wt p53* into cancerous cells will have therapeutic outcomes. It is well documented that *p53* gene induces apoptosis and cell cycle arrest in cultured cells (Sauter et al., 2002; Roy et al., 2002; Mitry et al., 1997). Similarly, tumor growth inhibition and tumor regression in animal models were observed after *p53* transfection (Dolivet et al., 2002; Anderson et al., 1998; Hsiao et al., 1997).

p53 treatment has found its way into clinical stages. Intratumoral injections of adenovirus mediated transfection of *p53* (Ad-*p53*) for 28 patients diagnosed with non-small cell lung cancer (NSCLC) resulted in disease stabilisation in 16 patients (64%) and more than 50% tumour size reduction in two patients (Swisher et al., 1999). More promising outcomes were reported when Ad-*p53* treatment was combined with chemotherapy (Cisplatin) (Nemunaitis et al., 2000) or radiation (Swisher et al., 2003). In the later combination, no viable tumor was observed in 63% of patients after three month of the completion of the therapy. Fig. 2 summarizes the subsequent steps for *p53* treatment and its effects via apoptosis induction within malignant cell.

3.4. Other molecular approaches in cancer gene therapy

Cancer tissue proliferation is associated with vasculature growth from existing blood vessels (i.e. angiogenesis) (Folkman, 1990). Angiogenesis provides cancerous cells with the necessary nutrients; therefore, interfering with this process in the tumor can produce therapeutic effects. The

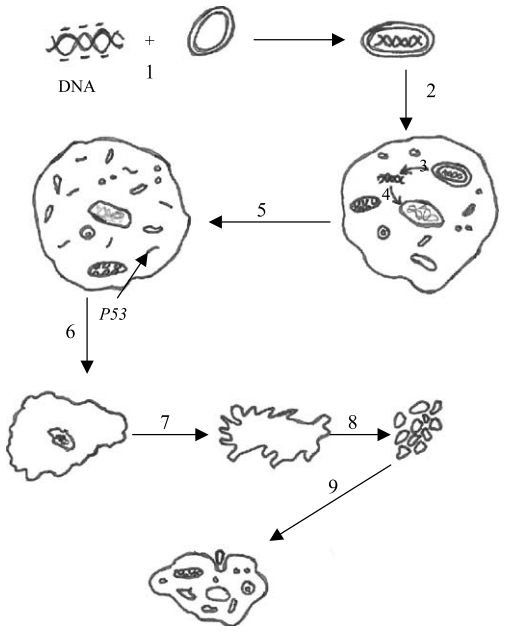

Fig. 2. Schematic representation of *p53* transfection and consequent apoptosis induction in targeted cancerous cells. (1) Encapsulation of *p53* DNA in suitable gene carrier, (2) Uptake of DNA/carrier complex by targeted cells, (3) DNA release in the cytoplasm, (4) DNA uptake by the nucleus, (5) *p53* protein production, (6) Cell shrinkage and chromosome condensation, (7) Membrane bubbling, (8) Apoptotic bodies formation, (9) phagocytosis and digestion of apoptotic bodies by neighbouring cells.

main targets for anti-angiogenesis cancer therapy includes inhibiting angiogenic inducers (namely, vascular endothelial growth factor and angiopoietine) or introducing angiogenic inhibitors such as angiostatine, endostatine, Interleukin-12, and p53 (Chen et al., 2001). For example, tumor growth of implanted hepatocellular carcinoma cells in athymic mice was proportional to the percentage of cells transfected with angiostatin gene. No tumor growth was observed when 90–100% of cells were transfected with the antiangiogenesis gene (Ishikawa et al., 2003). It was also illustrated that significant tumor regression was achieved when only 5% of human breast cancer cells were transduced with the apoptotic gene *p53* (Xu et al., 1997). This tumor regression was associated with 60% reduction in the number of the blood vessels (i.e. anti-angiogenesis effect). The main advantages of this cancer therapy strategy are the easy accessibility to the endothelial cells of the blood vessels and its applicability to different cancer types.

Another cancer gene therapy approach includes the prevention of toxic side effects, mainly myelosuppression, of antineoplastic agents. This can be achieved by transferring the drug resistance genes such as multiple drug resistance gene-1 (MDR-1) into the hematopoietic progenitors (Licht and Peschel, 2002; Koc et al., 1999). MDR-1 gene encodes for P-glycoprotein, a cell membrane transporter which effluxes many hydrophobic and amphipathic substances (Gottesman et al., 1995). The main advantage of this strategy is overcoming the dose-limiting toxicity of traditional chemotherapy.

4. Closing remarks

The potential therapeutic outcomes and the possible revolutionary treatments through cancer gene therapy will encourage researchers to increasingly explore this area of the health sciences. It will advance via multidisciplinary efforts to establish effective strategies capable of eliminating cancerous lesions. A potential therapeutic gene for cancer should first be successfully encapsulated in suitable, non-toxic and preferably targeted gene carriers which may be viral or non viral vectors (reviewed recently by El-Aneed, 2004) followed by efficient gene transfer and expression within the cancerous tissue. These events should eventually lead to cancer cell elimination.

Tremendous possible gene therapy strategies are currently investigated within animal models (Shen et al., 2003; Kanazawa et al., 2003; Pang et al., 2001). However, many cancer gene therapy protocols have passed animal trails and have proceeded to clinical trails in humans (Germano et al., 2003; Khorana et al., 2003; Nemunaitis et al., 2000; Blaese et al., 1995). These advances are clear indicative to the sustained developments in this area of cancer therapy.

Whether targeting cancerous cells on the immunological or molecular levels, gene therapy will eventually serve as a new weapon in fighting one of the most lethal diseases in the world. It is expected, however, that successful cancer treatments will combine traditional therapies such as surgery, chemotherapy, and/or radiotherapy along with single or multiple gene treatments. The ultimate goal of these treatments is to eradicate cancer via various methods of effective therapies.

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