

Targeted Gene Therapy of Cancer: Second Amendment toward Holistic Therapy

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SUMMARY

It seems solid tumors are developing smart organs with specialized cells creating specified bio-territory, the so called "tumor microenvironment (TME)", in which there is reciprocal crosstalk among cancer cells, immune system cells and stromal cells. TME as an intricate milieu also consists of cancer stem cells (CSCs) that can resist against chemotherapies. In solid tumors, metabolism and vascularization appears to be aberrant and tumor interstitial fluid (TIF) functions as physiologic barrier. Thus, chemotherapy, immunotherapy and gene therapy often fail to provide cogent clinical outcomes. It looms that it is the time to accept the fact that initiation of cancer could be generation of another form of life that involves a cluster of thousands of genes, while we have failed to observe all aspects of it. Hence, the current treatment modalities need to be re-visited to cover all key aspects of disease using combination therapy based on the condition of patients. Perhaps personalized cluster of genes need to be simultaneously targeted.

Thus far, standard chemotherapy alone or in combination with immunotherapy and ionizing radiation modalities have been used to destroy dividing aberrant cells in various tumors, while morbid statistics of cancer therapy show limited clinical successes. Given the fact that malignant cells proliferate more rapidly than normal cells, damage to the cancer cells is anticipated to be markedly greater than normal cells. However, cancer cells generate chemoresistance mechanisms, while undesired toxicity occurs within the normal cells. Therefore, necessity for development and advancement of more effective modalities is perceptible to achieve successful cancer treatment and cure. In cancer development, the origination of cancer is an intricate biological process, in which molecular changes at genomic/epigenomic levels play a central role. These molecular alterations can equip cancerous cells with unique molecular bio-structures that play crucial roles in survival, progression and invasion of cancer cells. Such genomic alterations (e.g., changes in gene expression, mutations, gene deletion, DNA methylation) have directed scientists to devise genomedicines to fix the genomic defects. It should be evoked that, unlike treatment strategies for genetic defects that need permanent expression of the corrected genes, cancer gene therapy is based on temporary and locally limited

stimulation/suppression effects on desired gene(s). Further, malignant cells display specific gene markers that are different in nature or magnitude compared to the normal cells. These characteristics of cancer cells are deemed to provide a robust platform for specific targeted gene therapy that provides major advantages over current chemotherapy and immunotherapy modalities.^{1, 2} Recent vibrant progressions regarding diverse molecular events of the pathogenesis of malignancies have highlighted pivotal roles of the genomic and/or epigenomic elements. Accordingly, specific targeting of designated gene(s) in the context of cancer gene therapy appears to be largely dependent upon global genomic/epigenomic reprogramming of the target cell to make a clear picture from this intriguing puzzle. Until now, a number of studies (in vitro, ex vivo and in vivo animal models) have resulted in effective impacts; hence, a number of cancer gene therapy strategies have been progressed to the clinical applications or are in transitional trajectory to be implemented into the clinical uses. Thus far, more than 65% of the gene therapy trials have been devoted to the cancer diseases using various vectors (retrovirus (20%), adenovirus (18%), adeno-associated virus (5%), lipofection (6%)) and naked/plasmid DNA (18.5%),³ while less than 3% of these trials have been progressed toward phase II/III and

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only two trials in phase IV. It seems that our next steps will be exploiting not only the tumor cells, but also all other elements of tumor microenvironment, stromal cells and tumor associated cells. More importantly, CSCs that are a small population of progenitor cells need to be targeted. In fact, the gene therapy approaches are going to be redirected towards not only the malignant cells but also CECs, tumor vasculature endothelial cells and tumor associated cells. This new directionality of gene therapy needs targeting more than ever to impose dramatic inhibitory impacts, specifically on the survival, progression and invasion of tumor cells. Of many cancer therapy endeavors, cancer gene therapy has granted great hopes even though it is in its developmental trajectory. The main basis of gene therapy is to fix the genomic defects; nonetheless the gene therapy concept is going to be revolutionized by illumination of epigenomics and targeted genomeditines. Up until now, some domains of cancer gene therapy have been devoted greater attention, including:

- a) Suppression of cancer cells by introducing genes into tumor cells to lead cells toward apoptosis (e.g., herpes simplex virus thymidine kinase, cytosine deaminase)
- b) Inhibition of growth of cancer cells
- c) Enhancement of cancer cells' chemosensitivity (p53, Bax)
- d) Stimulation of the host's immune response against the cancer cells specifically (tumor antigen, DNA vaccines, cytokine genes) by introducing the relevant genes into tumor cells or dendritic cells

Although use of genomeditines (e.g., antisense RNA, siRNA, ribozymes, DNzyme and aptamers) have shown positive outcomes, their combination with other cancer therapy modalities including chemotherapy and immunotherapy can open other avenues for cancer therapy.⁴⁻⁶ In addition, immune gene therapies (e.g., targeted DNA vaccine) exploit the lymphocytes and dendritic cell potentials, activating the immune system harmful mechanisms against cancer cells. DNA vaccines possess intrinsic ability to activate multiple pathways of innate immunity and to provide a unique opportunity to guide defined antigens, accompanied by specific activator molecules, through a patient's compromised immune system.⁷ Further, suicide gene therapy tackles to deliver genes to the cancer cells, upon which cancer cells convert nontoxic prodrugs into active chemotherapeutics. In this approach, cancerous cells containing suicide genes are solely targeted through a systemic administration of prodrug. The suicide gene therapy is deemed to provide maximal inhibitory effects in cancer cells, but minimal toxic effects in normal cells.⁸

Other than these strategies, antisense oligodeoxynucleotides (AS-ODNs) as a new class of molecularly targeted agents are in transitional trajectory from the laboratory into the clinic. A number of very imperative transcriptomic elements (VEGF, Ang-1, MDM2, protein kinase C- α , c-myc, integrin subunit β 3, PKA-I, H-ras, bcl-2, c-raf, R1/R2 subunits of ribonucleotide reductase) have successfully been targeted by AS-ODNs.⁹ In contrast to AS-ODNs technology, the mechanism of silencing an endogenous gene through a homologous double-stranded RNA (dsRNA), which is termed post-transcriptional gene silencing (PTGS) or RNA interference (RNAi), is a natural mechanism by which mammalian cells regulate expansion of genes. Short interfering RNA (siRNA) is currently the fastest growing sector of the gene therapy field for target validation and therapeutic.¹⁰ Nevertheless, these genomeditines need delivery systems (either viral or non-viral vectors) even though these vectors may impose some inadvertent side effects.¹¹⁻¹⁴

Given the fact that cancer cells escape from immune system within the TME,¹⁵ immune targeted gene therapy may provide an effective tactic for activation of immune systems in such intricate microenvironment whereby targeted gene therapy of angiogenesis and lymph angiogenesis bestow another possibility.¹⁶

Despite these approaches, still, there exist some striking questions. How confident are we regarding current gene therapy approaches? Is it a wise strategy to target a single gene and hope to suppress an intricate malignancy? How can we get the desired genomeditines to the target sites? Would not be wise to simultaneously target the key genes of all involved pathways?

If we consider cancer as a developing smart organ with specialized cells creating specified bio-territory, in which cells are cooperating and performing TIF functions as barrier, then the initiation of cancer could be considered as an emergence of another form of life that we have failed to perceive all aspects of it. More recently, exploiting genetic screening technology, scientists have started unraveling exactly how contact with the microenvironment can alter the cancer cells' genetic program.¹⁷ Besides, there exist more factors (such as chromatin remodeling and epigenetic changes) to the genetic causes of cancer than sequence mutations, which are beyond genetic alterations and bring much complexity in terms of cancer gene therapy.¹⁸ This raises some other questions such how can we reprogram the cancer cells epigenetically? And, is it going to affect the genomic materials and cellular response? These facts seem to redirect us toward a holistic view.

Further, both viral vectors and non-viral vectors used as gene delivery systems (GDSs) have been shown to induce undesired immunologic and toxicogenic

impacts.^{12,14,19-23} Hence, GDSs need to be improved for successful delivery of genomedicines and effective targeting of the gene(s) of interest.

Despite continuously increasing translational attempts and/or clinical trials of cancer gene therapy,²⁴ the rate of success is low and the outcomes are limited. It appears that we need to consider a second amendment in cancer therapy strategies by looking at the entire entity of cancer (epigenomic, genomic, metabolomic and bio-organizations within tumor microenvironment) and find a way to reprogram the genomic/epigenomic defects using targeted genocenticals.

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Competing interests

The authors declare no competing interests.

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