The genomic guardian: A boon for cancer survival
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Abstract
Oral cancer is an alarming health problem globally, with 300,000 cases being newly diagnosed annually. Despite research being aimed to improve treatment with conventional methods such as surgery, radiotherapy, and chemotherapy; there is severe morbidity associated with this malignancy. This presents an emerging need to develop advanced treatment options. Recent advances in molecular biology and technology have provided us with unique possibilities for studying aberrations at the genetic level and hence provided the basis for possible treatments such as gene therapy. The definition of gene therapy hence is given as the “alteration or insertion of genetic material into an organism to replace or repair a defect to correct or prevent disease.” Employing human tumor suppressor p53 as the target of gene therapy demonstrates great potential in curing squamous cell carcinomas. The functions of tumor suppressor genes can be reinstated with the incorporation of the therapeutic p53 gene into tumor cells. The treatment results are also greatly improved when it is administered with various vectors, most commonly adenoviral delivery. Combination therapy with p53 and chemotherapy provides a synergistic benefit toward the tumor growth suppression and apoptosis and also emphasizes the superiority of intra-arterial administration of this combination as compared to other routes. Thus, the purpose of this article is to review and emphasize the use and purpose of intra-arterial infusion of chemotherapeutics in combination with p53 gene therapy.

Introduction
In the recent years, cancer is considered as one of the deadliest diseases with frequently fatal complications. The diagnosis of almost 300,000 new cases of oral cancer annually proffers an important worldwide health problem. It is one of the mainly encountered malignant lesions of the oral cavity and the 6th most common cancer in the world. It constitutes approximately 5% of all cancers globally, with about 0.7 million new cases being diagnosed annually in India. Of the 0.3 million annual cancer-related deaths in India, nearly 33% arise from tobacco-related cancers. Oral cancer is associated with gene mutations involving cell growth and apoptosis leading to uncontrolled proliferation of tumor cells as a consequence of exposure to chemical carcinogens. Hence, gene therapy replacing defective gene with a therapeutic one has emerged promisingly in the field of bio-medicine, to improve treatment effect and overall survival rate.

Gene therapy as defined by Cusack and Tanabe in 1998 is the “alteration or insertion of genetic material into an organism to replace or repair a defect to correct or prevent disease.” This embraces both the tweaking of the previous and the transfer of new genetic material.

One promising treatment option in this arena is the use of wild-type variant of human tumor suppressor p53 (wt-p53) protein. The introduction of p53 gene into tumor cells helps reinstate tumor suppressor functions and enhance treatment results. Certain delivery viral vectors can be used to introduce this wt-p53 is into tumor matter. Adenoviral DNA is used most routinely for epithelium of upper aerodigestive tract. The benefits of selective intra-arterial administration of chemotherapy agents for head and neck cancers have been evaluated by several studies and they concluded modestly better responses or at least certain superiority.

Thus, the purpose of this article is to review and emphasize the synergistic benefit toward tumor growth suppression and
apoptosis caused by the combination therapy of intra-arterial infusion of chemotherapy with p53 gene.

**Understanding the use of p53 in Cancer Therapy**

Advances in molecular biology have made it possible to fathom fresh intervention for cancer therapeutics. As reported damage in the p53 pathway is the most common alteration identified in carcinogenesis. Approximately, 50% of common epithelial cancers have p53 mutations. Loss of p53 function may also be linked to resistance to existing DNA-damaging therapies that require a working cellular apoptotic mechanism to achieve cell death.

Tumors with defective p53 pathway might be refractory to usual chemotherapy or radiation. The wt-p53 appears to take over the mutant pathway when transduced into cells. This led to the contemplation of strategies intended to deliver wt-p53 into mutant tumor cells. The p53 protein oversees the damage to the cell and constituent DNA, either causing growth arrest to facilitate DNA repair or inducing apoptosis if DNA damage is extensive. The p53 gene is central in the processes of apoptosis, repair to various cell stresses, and the regulation of the cell cycle; thus, it is referred to as the "guardian of the genome." Hence, it stands to reason that the p53 molecular pathway is disabled in the majority of cancer cells through mutations, gene deletions, or escalated protein destruction.

Thus, the p53 gene is a vital component in the apoptotic cascade, and any mutation reduces the ability of a cell to undergo apoptosis. Alterations in p53 protein can occur early on during carcinogenesis and can be preserved till a full-scale headway to malignancy takes place. This leads to the development of drug resistance in most epithelial origin tumors.

The proposed mechanism of action for p53 gene therapy has been listed in Table 1.

**Considerations for Routes of Administration for p53**

**Viral vector delivery**

The delivery of p53 into the tumor mass is made possible by conjugating them with viral vectors which consist of synthetic virus particles devoid of pathogenic function. These are incapable of replication, contain a therapeutic gene incorporated within the viral genome, and deliver this gene to the host cells by infection. Recombinant adenovirus p53 (rAd-p53) and oncolytic virus are the promising therapeutic products.

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**Figure 1:** Role of p53 "guardian of genome"
Recombinant adenovirus p53 (Ad-p53)
Human adenovirus vector systems cater to a larger variety of hosts and are comparatively less pathogenic to humans.[36] They also show binding affinity for epithelium,[37] which is especially useful in epithelial origin tumors. The E1 region of adenovirus has been identified as a sub-region of the viral genome present in transformed cells and is the integral part responsible for transformation.[38]

Recombinant human adenoviruses fabricated with the E1 molecular region replaced by exogenous DNA are known to replicate defectively and produce low degree of acute toxic symptoms.[39] They can cause inhibition of tumor growth in vivo and in vitro, suggesting the involvement of an underlying anti-angiogenic mechanism.[40] All of these mechanisms eventually result in robust wt-p53 expression in tissues and minimal hematopoietic toxicity.[32]

Oncolytic virus
This is an adenovirus mutant capable of destroying tumor cells deficient in p53 or containing abnormal p53 (due to mutation or deletion). It replicates 100 times less efficient in normal human epithelial and endothelial cells with intact p53 functioning.[39] ONYX-015 is a prototype and can replicate only in wt-p53 deficient cells.[41]

The two kinds of viruses and their characteristics are compared [Table 2] and a schematic representation is depicted in Figure 3.

Mode of infusion
P53 can be introduced via intraarterial, intratumoral perfusion, or intravenous infusion routes. Intra-arterial injection has proven to provide better or similar responses. Advantages of intra-arterial infusion may include:

i. Accurate drug delivery to target organ.[42]

ii. Possibly more extensive distribution in the tumor mass than with intratumoral injection.[42]

iii. Better response and a suitable palliative alternative to other radical modalities in elderly patients.[42]

iv. An elevated concentration of rAd-p53 injected directly into an oral tumor produces relatively fewer side effects.[32]

v. The feeding arteries to the tumor may be more anatomically apparent as compared to healthy tissue. This eases the administration of drug to the target cells.[32]

Currently, two techniques of injection are employed to perform intra-arterial infusion therapy for head and neck cancer, namely, insertion of a catheter into the target artery through the femoral artery and the superficial temporal artery. The latter is easier, and it enables the drugs to be administered into several arteries.[43-46]

Clinical Data Pertaining to p53 Therapy
Roth in 1996 clinical trial used a retroviral vector expressing wt-p53 with beta-actin promoter for the replacement of faulty p53 gene. This combination was introduced into nine patients

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**Figure 2:** Basic molecular functions of p53

**Table 1:** Mechanism of action for p53 gene therapy

| Author          | Mechanism                                                                 | Reference |
|-----------------|---------------------------------------------------------------------------|-----------|
| Roth et al., 2006 | Increasing the sensitivity of tumor cells to radiotherapy and chemotherapy | [25]      |
| Guan et al., 2007 | Downregulation of the expression of genes involved in angiogenesis through the angiogenesis-inhibiting properties of the wt-p53 protein | [34]      |
| Liu et al., 2007  | Adenovirus-mediated p53 gene transfer promotes G1-phase arrest and cell apoptosis | [35]      |

**Table 2:** Comparison of several characteristics of rAd-p53 with oncolytic virus products

| Products          | Characteristics                                                                 |
|-------------------|---------------------------------------------------------------------------------|
| rAd-p53           | p53 gene is transfected into HCC cells with recombinant adenoviral vector expressing wt-p53 |
| Adyexin           | Larger host range, low pathogenicity to human, replication-impaired adenoviral vector carrying the p53 gene |
| Gendicine         | The first commercial gene therapy product in the world approved by SFDA         |
| SCH58500          | Replication-deficient type 5 adenovirus vector expressing human wt-p53 under control of cytomegalovirus promoter |
| Oncoptic viruses  | Incapable of replicating in normal cells but selectively replicating in p53 - defective tumor cells to lyse them |
| ONYX-015          | Tumor-selective replicating virus, the prototype for oncolytic adenoviral therapy |
| CNHK300-mE        | Replication-competent with advantages of both gene and virus therapies          |

HCC: Human hepatocellular carcinoma
suffering from non-small cell lung cancer (NSCLC) resistant to other interventions. Three of the nine patients demonstrated antitumor activity with no toxicity arising due to the viral vector, thus proving the viability of gene therapy. Another study in 1998 used Ad-p53 for gene substitution in 33 patients suffering from head and neck squamous cell carcinoma (HNSCC). The trial concluded that transfer of the Ad-p53 caused little toxicity and showed significant clinical response in 9 out of 18 patients.

In another clinical trial with similar gene substitution with Ad-p53 in more than 200 recalcitrant HNSCC patients resulted in complete or partial responses in about 10% of patients. Some antitumor activity was observed in 60% of these patients.

Twenty-four NSCLC cases which were unresponsive to conventional treatment were given p53 in combination with cisplatin. Intravenous cisplatin was given in six-month courses; each followed with an intratumoral injection of Ad-p53. A total of 17 patients remained stable for ≥2 months, 2 patients achieved partial response, and 4 continued to exhibit progressive disease. Biopsy of tumor sites showed an increase in apoptotic cells in 79% of cases.

A Phase II clinical trial was conducted on metastatic lesions in NSCLC patients where either three rounds of carboplatin plus paclitaxel or three rounds of cisplatin plus vinorelbine were administered for all the patients, and then Ad-p53 was injected directly into the lesion. This trial revealed no overall increase in chemotherapy-related adverse effects with minimal vector-related toxicity.

Buller et al. used intraperitoneal Ad-p53 in single- and multiple-dose along with platinum chemotherapy in refractory ovarian cancer patients and successfully demonstrated the safety and tolerance profile of the same. Follow-up of these patients over years indicated that those receiving Ad-p53 with chemotherapy had a better mean survival rate than those treated with a single dose of Ad-p53.

An in vitro study conducted by Xie et al. observed the early therapeutic effectiveness of rAd/p53 or in combination with iodinated oil or 5-fluorouracil (5-FU) for the treatment of SW480 human colon carcinoma in a nude mouse model. The expression of p53 and consequent tumor necrosis were much higher in the therapeutic groups. The authors concluded that the anticancer effect of rAd/p53 is increased with the combination of 5-FU and iodized oil and that this particular combination may act via a synergistic route.

In another study by Li et al., the results of rAd-p53 gene therapy with intra-arterial injection of chemotherapeutic agents were evaluated for oral squamous cell carcinoma. Ninety-nine patients with end-stage oral carcinoma who were ineligible for surgical correction were enrolled in a placebo-controlled, Phase III, double-blind, and randomized trial. They were assigned to three groups with rAd-p53 and chemotherapy administration in one, and either of the two agents was replaced by placebo in the remaining two groups, respectively. During follow-up, Group I (48.5%) had better response rates than Groups II (16.7%) and Group III (17.2%). The number of patients with no response was significantly lower in Group I than in Groups II and III. The survival rate was also significantly better in Group I than in Group III.

Combination Therapy with p53 and Chemotherapy

Weinrib et al. proposed that the combination of rAd-p53 and cisplatin act in a synergistic manner to kill tumor cells. The risk of integration of the adenovirus DNA into the genome is not increased by the DNA damage in somatic cells brought about by chemotherapy. However, this non-specific DNA damage results in activation of the wt-p53 protein provided by rAd-p53 thereby harnessing a synergistic effect between the two.

The theorized mechanisms via which wt-p53 protein reduces the toxicity involved with chemotherapy are:

1. p53 protein communication with DNA helicase enzyme
2. Ribonucleotide reductase up-regulation by p5
3. Exhibited 3′→ 5′ exonuclease activity of p53 protein.
However, additional research is indispensable to explore and confirm these mechanisms.\[^{[32]}\]

**Conclusion**

Positive results obtained from ongoing research in the therapeutic role of tumor suppressor genes imply that aiming to continue to develop new strategies or to expand existing ones to correct the defect in apoptosis initiation can help us to treat tumors which are resistant to conventional radiation and chemotherapy and also minimize the toxicity caused by these modalities. This may help us in early diagnosis and treatment of oral cancer. Numerous clinical trials constantly prove that gene therapy is, in fact, a feasible and beneficial therapeutic approach to oral cancer treatment, especially in resistant and refractory cases. As advancements occur in understanding the molecular basis of cancer, it will serve to expand our knowledge of defining genetic targets for tumor treatment and slowly fill the gaps which need explanation.

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