

Mathematical Model of P53 Gene in Gene Therapy Treatment for Lung Cancer

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Abstract— The TP53 gene, which encodes p53, is one of the most frequently mutated genes in human cancers. It is reported that approximately half of all cancers have inactivated p53 [1]. The p53 protein has broad range of biological functions, including regulation of the cell cycle, apoptosis, senescence, DNA metabolism, angiogenesis, cellular differentiation, and the immune response. Gene therapy is the insertion of a functional gene into the cells of a patient to correct an inborn error of metabolism, to alter or repair an acquired genetic abnormality, and to provide a new function to a cell. Gene therapy for the treatment of cancer has a wide variety of potential uses. Gene therapy is an experimental treatment currently being tested in clinical trials that involves introducing additional genetic material (either DNA or RNA) into cells to fight cancer in a few different ways.

Key words: Metabolism, Chromosomes, DNA, Apoptosis

I. INTRODUCTION

Chromosomes contain the recipe for making a living thing. They are found in almost every cell's nucleus and are made from strands of DNA. Segments of DNA called "genes" are the ingredients, and chromosomes are the structures that contain all the genes. Genes are located on chromosomes inside all of our cells and are made of DNA. Each gene adds a specific protein to the recipe. Proteins build, regulate and maintain your body. For instance, they build bones, they enable muscles to move, they control digestion, and they keep your heart beating. It is thought that we have about 20,000 genes in our cells that code for all of our traits. Your genes make you what are, they decide virtually everything about you. Your genes are passed from one generation to the next via your children. We have 46 chromosomes in total; each child receives 23 chromosomes from its mother and 23 from its father. Unfortunately, genes can become damaged, we can suffer illness or even pass this illness to the next generation.

Cancer is a major cause of death worldwide, resulting from the uncontrolled growth of abnormal cells in the body. Cells are the body's building blocks, and cancer starts from normal cells. Normal cells divide to grow in order to maintain cell population equilibrium, balancing cell death. Cancer occurs when unbounded growth of cells in the body happens fast. It can also occur when cells lose their ability to die. There are many different kinds of cancers, which can develop in almost any organ or tissue, such as lung, colon, breast, skin, bones, or nerve tissue. There are many known causes of cancers that have been documented to date including exposure to chemicals, drinking excess alcohol, excessive sunlight exposure, and genetic differences. However, the cause of many cancers still remains unknown. The most common cause of cancer-

related death is lung cancer[1]. Cellular cancer therapy currently largely involve the infusion of immune cells designed to either (i) replace most of the patient's own immune system to enhance the immune response to cancer cells, (ii) activate the patient's own immune system (T cells or Natural Killer cells) to kill cancer cells, or (iii) to directly find and kill the cancer cells. Moreover, genetic approaches to modify cellular activity further alter endogenous immune responsiveness against cancer.

II. GENE THERAPY FOR CANCER

Humans have approximately 35,000 genes. The first p53-based gene therapy was reported in 1996. A retroviral vector containing the wild-type p53 gene under the control of an actin promoter was injected directly into tumors of non-small cell lung cancer patients. After development of a replication-defective recombinant p53 virus (Ad5CMV-p53), many clinical trials have been performed, including one in esophageal cancer patients. The science of genetic manipulation has opened the possibility for doctors to treat and prevent cancer by altering a patient's genes. This experimental treatment is known as "Gene therapy" [4].

First, scientists are attempting to use gene therapy to replace missing or mutated genes with healthy genes (for example, p53). Second, scientists are attempting to put genes into tumors that act like suicide bombs once they are turned on by drugs that are administered to the patient. Similar to the suicide genes, a third approach is to insert genes that make tumors more susceptible to treatments such as chemotherapy and radiotherapy. And finally, gene therapy is being used to improve the immune response to cancers by enhancing the ability of immune cells, such as T cells, to fight cancer cells[1]. Several methods such as surgery, radiation, and chemotherapy have been used to treat cancers. The cancer patients who are not helped by these therapies may be treated by gene therapy. Gene therapy is the insertion of a functional gene into the cells of a patient to correct an inborn error of metabolism, to alter or repair an acquired genetic abnormality, and to provide a new function to a cell[4].

Gene therapy for the treatment of cancer has a wide variety of potential uses. There are several potential strategies for gene therapy in the treatment of cancer. Strategies of gene therapy for cancer enhancing the immunogenicity of the tumor, for example by introducing genes that encode foreign antigens[2].

- 1) Enhancing immune cells to increase anti-tumor activity, for example by introducing genes that encode cytokines.
- 2) Inserting a "sensitivity" or suicide' gene into the tumor, for example by introducing the gene that encodes HSVtk.

- 3) Blocking the expression of on cogenies, for example by introducing the gene that encodes antisense K-RAS message.
- 4) Inserting a wild-type tumor suppressor gene, for example P53 or the gene involved in Wilm' tumor.
- 5) Protecting stem cells from the toxic effects of chemotherapy, for example by introducing the gene that confers MDR-1.
- 6) Blocking the mechanisms by which tumors evade immunological destruction, for example by introducing the gene that encodes antisense IGF-1 message.
- 7) Killing tumor cells by inserting toxin genes under the control of a tumor-specific promoter, for example the gene that encodes diphtheria A chain.

One of the most promising approaches to emerge from the improved understanding of cancer at the molecular level is the possibility of using gene therapy to selectively target and destroy tumor cells, for example, the loss of tumor suppressor genes (e.g. the P53 gene) and the over expression of oncogenes (e.g. K-RAS) that have been identified in a number of malignancies. It may be possible to correct an abnormality in a tumor suppressor gene such as P53 by inserting a copy of the wild-type gene; in fact, insertion of the wild-type P53 gene into P53-deficient tumor cells has been shown to result in the death of tumor cells[4]. This has significant implications, since P53 alterations are the most common genetic abnormalities in human cancers. Gene therapy for the treatment of cancer has a wide variety of potential uses. Gene therapy is tumor-based p53 therapy, an approach that is showing great potential for the management of lung cancer. The anti-growth, p53, pathway is activated in the case of DNA. This is particularly relevant during irradiation. p53 pathway activation can block the cell cycle and induce apoptosis[1]. Different types of gene therapy are shown in the fig.

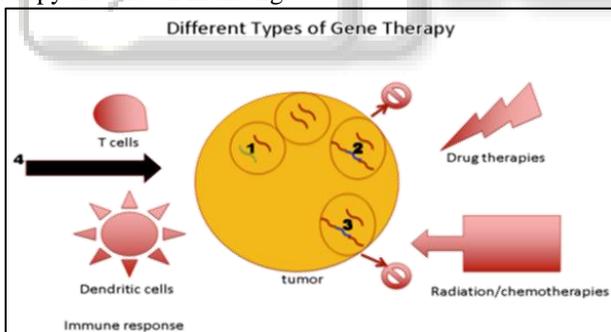


Fig. 1: Gene therapy and immunotherapy treatment

- 1) Replace missing or mutated genes with healthy genes.
- 2) Insert genes into tumors that act like suicide bombs by drugs
- 3) Insert genes that make tumors more susceptible by chemotherapy/ radiotherapy
- 4) By enhancing the ability of immune cells to fight cancer cells.

At the heart of tumor-based p53 therapy is the p53 gene. Often described as “the guardian of the genome,” p53 plays a central role in blocking the formation of tumors. Tobacco smoke often damage cell DNA, and these genetic changes can trigger the development of lung cancer. To prevent cancerous cells from dividing uncontrollably, the p53 gene activates proteins that arrest cell division and repair corrupted DNA. In cases where the damage done is

irreparable, p53 initiates a process called apoptosis that destroys the tainted cells. The p53 gene can also limit blood flow to tumors which prevents growth and alerts nearby immune cells to attack cancerous cells.

III. GENE THERAPY FOR LUNG CANCER

A mutation of the p53 gene is the most common abnormality observed in tumors. And that's not just for cancers of the lung, but all human cancers. Filled with high concentrations of p53, viral vectors are injected directly into malignant tumors [5]. As the virus releases the contained genetic material, the effects of the cancerous genes are reversed. Damaged cells are either destroyed or replaced with p53, which stops the tumor from growing or spreading. The first p53-based gene therapy was reported in 1996. A retroviral vector containing the wild-type p53 gene under the control of an actin promoter was injected directly into tumors of non-small cell lung cancer patients [4]. The broad field of gene therapy promises a number of innovative treatments that are likely to become important in preventing deaths from cancer. Recently, p53-based gene therapy has been developing in China. One notable example of gene therapy is tumor-based p53 therapy, an approach that is showing great potential for the management of lung cancer[6]. Researchers continue to recruit lung cancer patients for tumor-based p53 therapy clinical trials, and a diagnostic test was developed to detect specific changes to the p53 gene. By determining exactly how the p53 gene is expressed in an individual, doctors may soon be able to identify patients that will respond best to gene therapy. Only through ongoing trials will researchers be able to unlock the true potential of tumor-based p53 gene therapies[5].

IV. MATHEMATICAL MODEL IN LUNG CANCER

Cigarette smoking kills over 1,000,000 people each year in the world by causing lung cancer as well as many other cancers. Tobacco smoke contains over 3500 different chemicals, and 60 of them have been classified as “carcinogenic to humans” by the International Agency for Research on Cancer (Lyon, France). Many pieces of evidence demonstrate the role of tobacco smoke in causing lung cancers. One of the central pieces of DNA that is often damaged in cancer cells is the p53 gene. This gene works as cellular policemen that halt the abnormal proliferation of cancer cells. Thus, if p53 is damaged, the cell can go wild, escape control and proceed down the road that leads to malignant cancer. In contrast, as long as p53 works well, cells are relatively protected against becoming cancerous.

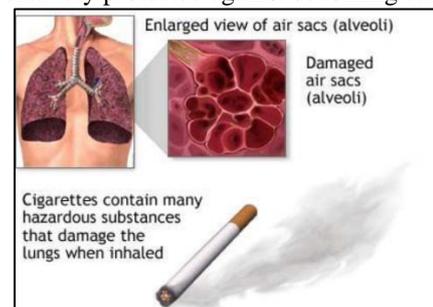


Fig. 2: Tobacco Carcinogens

Lung cancer has become one of the most common malignancies worldwide and in India. It is the leading cause

of cancer-related deaths. Majority of lung cancer patients are diagnosed as non-small cell type including squamous cell, adenocarcinoma and large cell lung carcinoma as the three major subtypes. Exposure to smoke and environmental derived pro-carcinogens are the established risk factors for lung cancer wherein smoking accounts for 80% to 90% of cases among men and 55% to 80% of cases among women. Occupational exposures in industrial facilities account for an additional 9% to 15% of lung cancer cases. However, only a small fraction of smokers and workers in high-risk occupations develop this disease. This suggests that other causes, including genetic susceptibility, may contribute to the variation in individual lung cancer risk. Despite the development of new chemotherapeutic drugs and multimodal treatment strategies, the survival rate of non-small cell lung cancer remains unchanged and poor. Identification of new prognostic markers for the characterization of lung cancer biology may be helpful, as they could serve as a basis for predicting response to therapy at a molecular level [6].

In this model, how can the lung cancer patient can be treated by using p53 gene through the Birth and death process[7].

V. BIRTH AND DEATH PROCESS

Consider a population whose members are cells. Suppose the members can give birth (by splitting or mutation) to new members or mutated cells but cannot die, it will be cancer cells. We assume that in an interval of length h each cell has a probability $\lambda_n + o(h)$ of giving birth to a new cell. Then if n individuals are present at time t, the probability that there will be one birth between t and t+h is $\lambda_n + o(h)$. If N(t) denotes the total number of cells by epoch t and $P_n(t) = \Pr\{N(t)=n\}$, then by putting

$$\lambda_n = n\lambda,$$

We get the following equations,

$$P_n'(t) = -n\lambda P_n(t) + (n-1)\lambda P_{n-1}(t), n \geq 1 \quad (1)$$

$$P_0'(t) = 0 \quad (2)$$

If the initial conditions are given, explicit expression for $p_n(t)$ can be obtained.

Suppose that the initial conditions are given, explicit expressions for $P_1(0)=1, p_i(0) = 0$ for $i \neq 1$ the process started with only one cell at time t=0. The solution can be obtained by the method of induction as follows:

For n=1, we have $P_1'(t) = -\lambda P_1(t)$ whose solution is $P_1(t) = e^{-\lambda t}$ and putting $P_1(0) = 1$ we have $c_1 = 1$ so that $P_1(t) = e^{-\lambda t}$

For n=2, we have $P_2'(t) = -2\lambda P_2(t) + \lambda P_1(t)$

$$P_2'(t) + 2\lambda P_2(t) = \lambda P_1(t)$$

This linear equation has the integration factor $e^{2\lambda t}$ and therefore

$$P_2'(t) + 2\lambda P_2(t) = \lambda P_1(t)$$

$$e^{2\lambda t} P_2(t) = \int \lambda e^{2\lambda t - \lambda t} dt = e^{\lambda t} + c_2$$

Since $P_2(0) = 0$; we have $c_2 = -1$

$$P_2(t) = e^{-2\lambda t} (e^{-\lambda t} - 1) = e^{-\lambda t} (1 - e^{-\lambda t})$$

Proceeding in this way it can be shown that

$$P_n(t) = e^{-n\lambda t} (1 - e^{-\lambda t})^{n-1}, n \geq 1$$

Solving the equation, we get $P_0(t) = 0$ we get

$$P_0(t) = 0$$

The distribution is of the geometric form its p.g.f is

$$p(s,t) = \sum \{e^{-\lambda t} (1 - e^{-\lambda t})^{n-1}\} s^n$$

$$= \frac{se^{-\lambda t}}{1 - s(1 - e^{-\lambda t})}$$

The mean of this process is given by

$$E[N(t)] = e^{\lambda t}$$

And variance is given by

$$Var [(t)] = e^{\lambda t} (e^{\lambda t} - 1)$$

VI. RESULT

From NSCLC patients, we take 160 patients were taken from North Indians .The cause of lung cancer is smoking of cigarette, Bidi, Huka, age factor, family history of cancer. The level of lung cancer is given in the following table.

Cause of lung cancer	Patients Affected (%)
Smoking Cigarette	29.2
Bidi	14.2
Huka	23.9
Cigarette + Bidi	13.3
Cigaretta + Huka	19.5
<u>Age factor</u>	
Less than 45 yrs ≤≤	20.0
Greater than 45 yrs	80.0
Family significant of cancer	11.9
<u>Smoking lelvel</u>	
Mild	15.9
Moderate	43.4

Table 1: Result

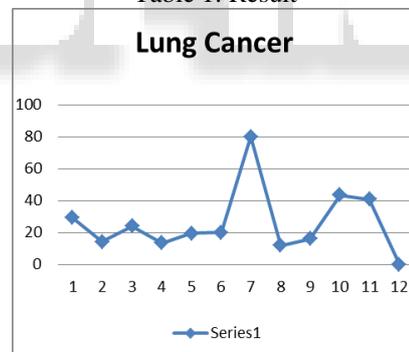


Fig. 3: Lung cancer with various causes

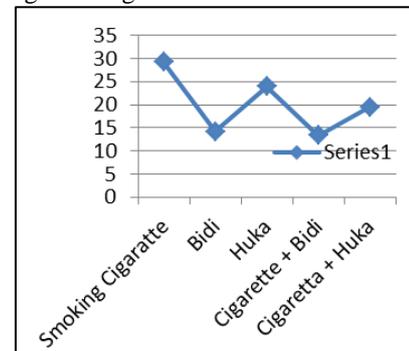


Fig. 4: Lung cancer for smoking
Here N(t) = 160, The mean and variance value for smoking causes for lung cancer is

$$\text{Mean} = E[N(t)] = e^{\lambda t} = 22.6,$$

$$\text{Variance} = Var [(t)] = e^{\lambda t} (e^{\lambda t} - 1) = 57.3$$

VII. CONCLUSION

By using this Birth and Death process, we can conclude that the p53 gene stimulates the cells for proliferating uncontrollably and prevents lung cancer, the cells go to the process of apoptosis. The genetic function of the p53 gene is to prevent cell division of cells with damaged DNA. Damaged DNA could contain genetic changes that promote uncontrolled cell growth related to the birth process and apoptosis related to the death process. Therefore, preventing cell division until damaged DNA is repaired is one mechanism of preventing the onset of cancer. There has been a substantial growth in gene therapy, especially in the field of oncology. The best outcome of human gene therapy for cancer would be a single treatment that would correct enough cells to provide a permanent cure for the patient's cancer. Cancer gene therapy includes three main strategies: the insertion of a normal gene into cancer cells to replace a mutated (or otherwise altered) gene, genetic modification to silence a mutated gene, and genetic approaches to directly kill the cancer cells. Change in expression and mutations of the p53 gene cause variations of cellular p53 protein concentration. Higher cellular protein p53 levels are associated with increased protein transfer to the extracellular liquid and to blood. It has been observed that increased blood serum protein p53 concentrations may have a prognostic value in early diagnosis of lung cancer.

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