



MATHEMATICAL MODEL ON DNA MUTATION AND TUMOR FORMATION

Chukwudi OKOYE^a, Stephen Ekwueme ANIAKU^b, Sunday Ifeanyi ONAH^c, and Godwin Christopher Ezike MBAH^d.

^a Department of Mathematics,
University of Nigeria, Nsukka
Enugu State, Nigeria.

E-mail: chukwudi.okoye@unn.edu.ng

^b Department of Mathematics,
University of Nigeria, Nsukka.
Enugu State, Nigeria.

E-mail: stephen.aniaku@unn.edu.ng

^c Department of Mathematics,
University of Nigeria, Nsukka
Enugu State, Nigeria.

E-mail: sunday.ifeanyi@unn.edu.ng

^d Department of Mathematics,
University of Nigeria, Nsukka
Enugu State, Nigeria.

E-mail: godwin.mbah@unn.edu.ng

ABSTRACT

Several abnormal growths which endanger life, springs up at different times in different regions of the human system. This work studies causes of Tumour formation due to DNA mutation. System of differential equations which describes the various contributors to DNA mutation that causes tumour formation is modeled. These equations were solved and the various impacts of these factors were demonstrated using graphs drawn using MATLAB software. It was shown in the analysis that reduction in these factors can reduce DNA Mutation and thus tumour formations.

1. INTRODUCTION

Obviously the gene is the major block of all happenings in human system. It spearheads growth, differentiation, and diseases. The latter as a result of external influences that charges the gene with making wrong interpretation. As a result endangers human system to being susceptible to various degrees of illness; in vivo and in vitro. The gene is contained in an 'X' shaped structure known as the DNA which in turn is embedded in the chromosome.

It has been observed that the number of cells existing in a region in order to maintain equilibrium (proper health) varies at times due to influences that battle with the gene thereby disrupting its normal plan forcing it to misunderstand and misinterpret information to be passed across.

Tumor is one of the diseased conditions that occur as a result of gene overexpression or underexpression. Various kinds of Tumors ranging from; lung, esophageal, tracheal, breast etc has directly or indirectly been associated with gene stretching (overexpression and underexpression).

One of the core causes of gene error is DNA Mutation which in turn leads to spontaneous/unregulated cell division, chunking out many more cells in the region by doubling, tripling etc the exact number of cells that should be in the region to maintain balance.

Relatively, this paper is carved out so as to see, know and understand the contribution of DNA Mutation in Tumor formation via two major genes; namely; one that stimulates cell division (the proto-oncogene) and the other that stalls/inhibits cell division (Tumor suppressor gene).

There are two main types of tumor; Benign and Malignant tumor. A benign tumor notwithstanding the size remains localized to the part from which it originates. It is not an infiltrating growth, that is to say it does not eat its way into its surrounding tissues, but rather pushes them aside, and so may be said to be "expansive" [4].

Moreover, it is separated from them by a thin but usually well-marked layer of fibrous tissue known as the "capsule" of the tumor, which seems to be formed as a result of slight inflammation that the presence of the tumor growth always causes among healthy tissues surrounding it, and may be viewed as a protest on their part against the invasion of the tumor.

Non-Malignant tumors are not of themselves dangerous to life. They may however cause a great deal of pain and even death, when situated in some delicate organs. For instance, a small tumor may cause intense pain by pressing on a nerve or dropsical swelling of a limb by obstructing a vein or death from suffocating by blocking the larynx. Nevertheless, it remains true that any disastrous effect are not due to the nature of the tumor, but to its situations, whereas once it becomes cancerous can lead to death despite its position. They (Benign) do not have the capacity to reproduce themselves in distant parts of the body. More than one may be present in the same individual, but each occurs independently, and the widespread dissemination so typical of a cancerous growth is never seen. The boundaries of the growth are so well defined that complete removal is usually easy, and the processes (operation) is a simple and satisfactory procedure [4].

On the other hand, malignant tumors are cancerous. They emerge out of the cavity, by breaking out through the basal membrane and then metastasizing into extra-cellular matrix. Its ability to metastasize is based on the process called “ANGIOGENESIS-the arterial nerves grows into the tumor allowing the passage of nutrients and thus, the tumor fluid been carried to other parts of the body” [11]. Their boundaries of growth are not well defined, hence complicating removal at times. They make their way in all directions into the surrounding parts. They are of two kinds: Sarcomata-evolving from the connective tissues and Carcinomata-emanating from the epithelial tissues. They can spread to lymph nodes through the lymphatic vessels by producing growth factors that stimulate lymphatic vessel growth and spread directly or indirectly. It actively invades and destroys surrounding tissues and also gives rise to cells which often spread to produce foci of growth at distant sites [4].

CAUSES OF DNA MUTATION

DNA mutation is a change in the base sequence of the DNA. These mutations in DNA sequences generally occur through one of four processes:

- DNA damages from environmental agents such as ionizing radiation, alcohol, smoke and other chemicals. This involves the following:

Modifying nucleotide bases- Environmental mutagens can damage DNA by altering nucleotide bases so that they look like others. When the DNA strands are separated and copied, the altered base will pair with an incorrect base and cause a mutation.

Breaking the phosphate backbone- They can damage DNA by breaking the bonds between oxygen (o) and phosphate group (p). This creates a mutated form of the gene. Possibly the mutated gene will produce a protein that functions differently. Cells with broken DNA will attempt to fix the broken ends by joining free ends to other pieces of DNA within the cell.

- Mistakes that occur when a cell copies its DNA in preparation for/during cell division (DNA REPLICATION).

Prior to cell division, each cell must duplicate its entire DNA sequence. This process is called DNA replication. It begins with a protein called DNA helicase which separates the DNA molecule into two strands. Next, a protein called DNA polymerase copies each strand of DNA to create two double-stranded molecule. Any mistake made by the DNA polymerase becomes a mutation.

- Certain viruses.
- Error during DNA repair.

(<http://learn.genetics.utah.edu/archive/sloozeworm/mutationbg.html>)

EFFECTS OF THE LISTED FACTORS ON THE GENES

ENVIRONMENTAL AGENTS ON GENE THAT STIMULATES AND INHIBITS CELL DIVISION RESPECTIVELY.

PROTO-ONCOGENE MUTATION

The effect of the environmental agents may not be to kill the cell, but to alter its DNA code in a way that leave the cell alive, but with an error in the DNA blueprint that eventually leads to loss of concentration of cell division and cell begins to divide uncontrollably. Alcohol as a carcinogen yields acetaldehyde when ethanol is broken down in the liver. The liver does its best to eliminate 99% of the acetaldehyde but studies have shown that heavy drinkers are exposed to more acetaldehyde than normal through a defect in the gene for alcohol dehydrogenase. It induces cytochrome P450 2E1 and associated oxidative stress and conversion of pro-carcinogens to carcinogens [6]. It also depletes 5- adenosyl methionine and consequently, induction of global DNA hypomethylation which serves as a tumor promoter by binding with the proto-oncogene to form oncogenic mutation (by overexpressing certain genes).

Furthermore, as a result of the above binding it brings about induction of increased production of inhibitory guanine nucleotide regulatory proteins and component of extracellular signal regulated kinase-mitogen – activated protein kinase signaling [6].

One of smoke carcinogen is a benzene molecule, (benzo(a)-pyrene) the shape is such that it fits into the major groove of a DNA double helix. Once there; negatively charged region of benzene can disrupt the binding of the DNA's sugar phosphate backbone causing cleavage, hence mutation. Irradiated hematopoietic cells could provide higher levels of inflammatory cytokines and the transplanted irradiation induced senescence of fibroblasts boosts cytokine production which promotes tumorigenesis by selectively impairing the fitness of non initiated cell [7].

It also induces polycyclic aromatic hydrocarbon (PAH) and nitrosamine (4-methyl-nitrosamino)-1-(3-pyridyl)-1-butanone which acts as a reactive oxygen species (ROS) and Nitrogen species (NOS) to alter longlasting adaptive landscape (either by increasing or decreasing selective effect of particular oncogenic mistake). The induced ROS also brings about a decline in fitness of hematopoietic stem cell and inhibiting clonal expansion [7].

ANTI-ONCOGENIC/TUMOR SUPPRESSOR GENE MUTATION

The high level of acetaldehyde in heavy drinkers inactivates some TSGs such as BRCA1 (makes it not to function) and increase estrogen responsiveness. Also this is supported by aberrant tumor acquired DNA promoter region methylation that constitutes important mechanism in carcinogenesis and represents the main mechanism for inactivation of several TSGs.

It downregulates some TSGs by bringing about high incidence of single base mutation on RASSF1 and RBSP3 located in chromosome 3 P21.3 region, LUCA and AP 20 respectively. This is possible when the chemicals from the agents mix with enzyme cytidine to form the mutation by diminishing the ability of corresponding transgene to suppress cell and tumour growth implying a loss of function. The loss of RASSF1A expression is due to presence of tumor acquired promoter methylation and occurring missense mutation in RASSF1A, thereby reducing growth inhibitory activity (decrease in growth suppressor activity) [15].

Note:

Cytidine- is from the family of induced deamination gene.

RASSF1A- Ras association domain family 1 codes for cyclin D₁.

They also lead to loss of Heterozygosity. The short arm of human chromosome 3 contains TSGs. TSGs are recessive i.e. they contain one normal cell and one allele (mutated) cell.

Loss of Heterozygosity occurs as a result of alteration of chromosome 3p. The activation of tumor promoter DNA methylation as epigenetic mechanism for inactivation of the expression of the gene plus direct role of smoking leads to allele loss resulting from mitotic recombination and oxidative damage.

EFFECT OF VIRUS ON PROTO-ONCOGENE AND TUMOR SUPPRESSOR GENE

Viruses are involved in uncontrolled cell growth because they can carry either a copy of one of these genes or can alter expression of the cells copy of one of these genes.

There are two classes of tumor viruses

DNA tumor Viruses

RNA tumor viruses

They have different ways of reproducing themselves but they often have one aspect of their cycle in common. The ability to integrate their own genome into that of the host cell, though not a prerequisite for tumor formation.

PROTO-ONCOGENE MUTATION

If a virus takes up residence in a cell and alters the properties of that cell, the cell is said to be transformed. Transformation by a virus is the change in the biological properties of a cell that results from the regulation of the cell by viral genes that confer on the infected cells certain properties of neoplasia.

The virus carries its own proto-oncogene called **an oncogene (a gene that codes for a protein that potentially can transform a normal cell into a malignant cell)** and binds with a gene stimulating cell division bringing about loss of growth control by causing the host cell to take a new property. They (viruses) also activate cellular proto-oncogene by picking up a cellular gene during its evolution and making the gene altered. Normally, the cellular proto-oncogenes are not expressed in quiescent cell since they are not involved in growth and development or they are expressed under strict control by the cell. However, they may become aberrantly expressed when the cell is infected by tumor viruses that do not themselves carry a viral oncogene. A typical

example of oncogene are Tumor antigens. The presence of virus elicits the formation of antibodies against the tumor antigen.

A virus such as SV40 integrates part of its genome into the chromosomes of the host cell and is transcribed into mRNA and this is the region that encodes the early function of the viral replication cycle [2].

TUMOR SUPPRESSOR GENE MUTATION

Many DNA virus have early and late function. The early function are the result of the expression of protein that prime the cell for virus production and are involved in viral DNA replication. These proteins are expressed before genome replication and do not usually end up in the mature virus particle. Late function forms the mature virus. They are expressed during and after the process of DNA replication

The presence of virus can mimic mutation and take the tumor suppressor gene out of action by complexing it in an active form that cannot bind to the specific site on DNA.

SV40 expresses two proteins, the antigens (large T and small T antigens). The large T antigen acts as a cis-regulatory element at the level of viral DNA replication by binding to the origin of replication and stimulating transcription. It can also bind to and modulate the activity of host cell DNA polymerase alpha. DNA replication in the cell is controlled by suppressor protein (Rb and P53). SV40 large T antigen can bind directly to these proteins and inactivate them thereby inducing the cells to go from G₁ (The first gap in the normal cell cycle is called G₁ and is the period when the necessary proteins for DNA replication are synthesized. However, this phase of the cell cycle is not only characterized by synthesis of replication machinery. During this period the cell must monitor both the internal and external environments to ensure that all the preparations for DNA synthesis have been completed and that the overall conditions for cell division are favourable) to S phase (The duplication of the cellular content of DNA occurs during S-phase, so-called because this is the phase when DNA is synthesized. This phase of the cell cycle is the longest taking 10-12 hours of a typical 24hr eukaryotic cell cycle).

ERROR DURING CELL COPYING ON PROTO-ONCOGENE AND TSG

PROTO-ONCOGENE MUTATION

Mitosis is one of the cell cycle phases. During cell copying, the c-MYC protein which plays an important role in regulation of cell replication begins to produce their product in excess, possibly causing promoters and/ or enhancers to be mutated. This is as a result of increased rate of mitosis within the region (Mary M, et al 2003).

Also, error during DNA replication inhibits apoptosis- suicide of damaged cell. This promotes the formation of cancer. For example, BCL-2; the product of this gene inhibits apoptosis, over expression of the gene is a hallmark of B-cell cancer.

ANTI-ONCOGENIC(TSG) MUTATION

The normal Rb (retinoblastoma) gene controls the cell cycle. It interprets the signals reaching the cell to determine whether it is safe for cell to complete the passage from G₁ of the cell cycle to mitosis [1]. The unphosphorylated Rb proteins prevents cell from entering S phase of the cell cycle. It does them by binding to transcription factors called E2F. This inturn prevents the E2F's from binding to the promoters of such proto-oncogenes as c-MYC and C- fos. Based on these, when Rb gene fails to function, chromosome begins to break because mutation of the remaining Rb locus that are non-dividing and should not enter the cell cycle completely removes the inhibition produced by the Rb-protein and the affected cells grow into tumor [13].

P53 gene monitors sequence of cell division and if damaged automatically halts cell division until the damage is repaired (minor damage) when damage is major, cells are copied as such through replication line thus triggering apoptosis [14].

Finally, any observed mismatch in DNA leads to homozygous deletion of some TSGs such as P16 and P15. The P16 at trade off (as its level rises) in adult stem cell and progenitor cells their ability to reproduce and thus replace lost or damaged tissue diminishes thereby resulting to tumor cells as certain unscrupulous enzymes begins to take advantage of their frailty [15].

Note: Aneuploidy is the abnormality involving a chromosome number that is not an exact multiple of the haploid number (one set is incomplete).

ERROR DURING DNA REPAIR ON PROTO-ONCOGENE AND TSG.

There are two main methods of repairing damaged bases

By (i) Direct chemical reversal of the damage

(ii) Excision repair in which the damaged base or bases are removed and then replicated with the correct ones in a localized burst of DNA synthesis. There are three modes of excision repair. Each of which employs specialized sets of enzymes

1. Base excision repair (BER)
2. Nucleotide excision repair (NER)
3. MisMatch repair (MMR)

Direct chemical reversal

Perhaps most of frequent cause of point mutation is the spontaneous addition of a methyl group (CH₃-) (an example alkylation) to C_s followed by deamination to a T. Fortunately, most of these changes are repaired by enzymes called glycosylases, that remove the mismatched T restoring the correct C. This is done without the need to break the DNA backbone.

BASE EXCISION REPAIR- Steps and some key players

- Removal of the damaged base (estimated to reoccur 20, 000 times a day in each cell in our body) by a DNA glycosylase. There are at least eight genes encoding different DNA glycosylases each enzyme responsible for identifying and removing a specific kind of base damage.
- Removal of its deoxyribose phosphate in the backbone, producing a gap, there are two genes encoding enzymes with this function.
- Replacement with the correct nucleotide. This relies on DNA polymerases beta, one of at least 11 DNA polymerases encoded by our genes.
- Ligation of the break in the strand. Two enzymes are known that can do this; both require ATP to provide the needed energy.

NUCLEOTIDE EXCISION REPAIR (NER)

- It uses different enzymes.
- Even though there may be only a single ‘bad’ base to correct, its nucleotide is removed along with many other adjacent nucleotides, that is, **NER** removes a large ‘‘ patch’’ around the damage.

Steps and some key players

1. The damage is recognized by one or more protein factors that assemble the location.
2. The DNA is unwound producing a “bubble”, the enzyme system that does this is transcription factors ITH, TF ITH.
3. Cuts are made on both the 3' side and the 5' side of the damaged area so that tract containing the change can be removed.
4. A fresh burst of DNA synthesis- using the (opposite) strand as a template fills in the correct nucleotides. The DNA polymerases responsible are designated polymerase delta and epsilon.
5. A DNA ligase covalently inserts the fresh piece into the backbone

MISMATCH REPAIR (MMR)

This deals with correcting mismatch of the normal bases, which is failures to maintain normal Watson-crick base pairing (A-T, C-G).

It can enlist the aid of enzymes involved in both base excision repair (BER) and nucleotide excision repair (NER) as well as using enzymes specialized for this function

- Recognition of a mismatch repair requires several different proteins including one encoded by MSH2.
- Cutting the mismatch out also requires several protein including one encoded by MLHI

In repairing strand breaks, breaks in a single strand of the DNA molecule are repaired using the same enzymes systems that are used in BER, whereas double strand breaks (DSB_S) are repaired in two ways

- ❖ Direct joining of the broken ends- this requires proteins that recognize and bind to the exposed ends and bring them together for ligating. They would prefer to see some complementary nucleotides but can proceed without them. This type is also known on **Non homologous end-joining (NHEJ)**. A protein called ku is essential for NHEJ. It is a heterodimer of the subunits ku70 and ku80.
- ❖ Homologous recombination: Here the broken ends are repaired using the information on the intact sister chromatid (available in G₂ after chromosome duplication) or on the

homologous chromosome (in G_1 , that is before each chromosome has been duplicated). This requires searching around in the nucleus for the homolog- a task sufficiently uncertain that G_1 cells usually prefer to mend their DSBs by NHEJ or the same chromosome if there are duplicated copies of the gene on the chromosome oriented in opposite directions (head to head or back to back). Two of the proteins used in homologous recombination are encoded in the gene BRCA 1 and BRCA 2 [16].

PROTO-ONCOGENE MUTATION

During NHEJ, the system fails to encode kinases that are regulated by Ras and mediate cellular response to growth signals.

Also, MAX is a type of gene that controls the access of c-MYC protein in their physiological DNA recognition sequence. In the course of repair, the proto-oncogene becomes mutated due to loss of binding as a result of failure to bind to MAX and consequently transactivation function of c-MYC.

Finally, gene amplification occurs from chromosomal instability as a result of error in the direct joining method of repairing DSBs [3].

Note:

Kinases are enzymes that attach phosphate group to other proteins.

Ras –This is a molecule that turns on kinases. They reside in the plasma membrane where they serve to link receptor activation to downstream kinases.

ANTI-ONCOGENIC (TSG) MUTATION

Tumor is inevitable as a result of suppressor gene mutation resulting from the following

Loss of mismatch: Non recognition of MM (mismatch encoded by MSH2 and MLH1). The inactivation of these mismatch repair genes forces the formation of heterodimers with MSH3 and MSH6 which bind to mismatches and insertion in DNA as well as certain DNA adducts, such as those induced by the malfunctioning alkylating agent. This binding thus leads to strand-specific MMR [13].

Loss of Heterozygosity/Reduction to homozygosity: This occurs from loss of the chromosome containing the normal allele followed by duplication of the chromosome containing the normal allele followed by, mitotic recombination (crossing over with genetic recombination). The resulting cell now carries two copies of the “bad gene” leading to a reduction to homozygosity. A heterozygote at the Rb allele still has normal Rb and tumors can still be suppressed but homozygote has no functional Rb and tumor cannot be suppressed [15].

ASSUMPTIONS AND THE MODEL EQUATIONS

Cells in a region grows/remains as supposed if namely:

The proto-oncogenes are properly functioning (stimulating cell division)

The Anti-oncogenes (Tumor suppressor genes) are also not short changed in their job (inhibiting cell division)

Using the following factors based on our research/knowledge on how the number of cells in a region increases to formulate the required models.

- ✓ *Influence of environmental agents (ionizing radiation, smoke, Alcohol, Hormone, certain drugs etc.*
- ✓ *Effect of virus (DNA Virus)*
- ✓ *Error during DNA replication without repair (cell copying)*
- ✓ *Error in course of DNA repair (Mismatch repair)*

So let

T = Number of cells in a region

E_T = Effect/influence of environmental agents on cell multiplication.

V_T = Effect of DNA virus on cell multiplication.

R_T = Effect of error during DNA replication without repair on cell multiplication.

\bar{R}_T = Effect of error during DNA repair on cell multiplication.

Combining the factors, we obtain a system model equations describing change in number of cells in a region with respect to Proto-oncogene mutation (OM) and Anti-oncogenic (Tumor suppressor gene) mutation (AOM) respectively, with time which are given as:

$$\left. \frac{dT}{dt} \right|_{OM} = a_0 T + a_1 E_T + a_2 V_T + a_3 R_T + a_4 \bar{R}_T \text{------(1)}$$

$$\left. \frac{dT}{dt} \right|_{AOM} = b_0 T - b_1 E_T - b_2 V_T - b_3 R_T - b_4 \bar{R}_T \text{------(2)}$$

$$\frac{dT}{dt} = \text{equation (1)} + \text{equation (2)} \text{------(3)}$$

Where a_0 is a model parameter that estimates the exact number of cells that maintain balance in a region through, OM, a_1 measures the increase in the number of cells produced due to the effect

of environmental agents on the cells in a region, a_2 measures the increase in the number of cells due to interception by a DNA Virus, a_3 measures additional increase in the number of cells due to cell copying error, a_4 estimate additional increase in the number of cells due to mismatch repair error.

b_0, b_1, b_2, b_3 , and b_4 are same as above but with respect to AOM.

$$\frac{dT}{dt} = a_0T + a_1E_T + a_2V_T + a_3R_T + a_4\bar{R}_T + b_0T - b_1E_T - b_2V_T - b_3R_T - b_4\bar{R}_T$$

and $a_0 + b_0 = z_0$ (since we are working on same region)

where E_T, V_T, R_T are given as

$$\left. \begin{aligned} (i) \quad & \frac{dE_T}{dt} = c_0E_T + c_1E_T + c_2E_T + c_3E_T \\ (ii) \quad & \frac{dV_T}{dt} = d_0V_T + d_1V_T + d_2V_T \\ (iii) \quad & \frac{dR_T}{dt} = e_0R_T + e_1R_T + e_2R_T \\ (iv) \quad & \frac{d\bar{R}_T}{dt} = f_0\bar{R}_T + f_1\bar{R}_T + f_2\bar{R}_T + f_3\bar{R}_T \end{aligned} \right\} OM$$

And

$$\left. \begin{aligned} (v) \quad & \frac{dE_T}{dt} = k_0E_T - k_1E_T - k_2E_T - k_3E_T \\ (vi) \quad & \frac{dV_T}{dt} = m_0V_T - m_1V_T \\ (vii) \quad & \frac{dR_T}{dt} = n_0R_T - n_1R_T - n_2R_T - n_3R_T \\ (viii) \quad & \frac{d\bar{R}_T}{dt} = p_0\bar{R}_T - p_1\bar{R}_T - p_2\bar{R}_T \end{aligned} \right\} AOM$$

SOLUTIONS TO THE MODEL EQUATIONS

$$1. \quad \frac{dE_T}{dt} = c_0E_T + c_1E_T + c_2E_T + c_3E_T = (c_0 + c_1 + c_2 + c_3)E_T$$

Solution

At $t = 0$, $E_T(0) = E_0$ and let the effect of E_0 be minimal at $t = 0$, so that for a real biological system we have

$$E_T = E_0 e^{\mu_1 t}$$

$$\text{where } \mu_1 = c_0 + c_1 + c_2 + c_3.$$

$$2. \quad \frac{dV_T}{dt} = d_0 V_T + d_1 V_T + d_2 V_T = (d_0 + d_1 + d_2) V_T$$

Solution

At $t = 0$, $V_T(0) = V_0$ and let the effect of V_0 be minimal at $t = 0$, so that for a real biological system we have

$$V_T = V_0 e^{\mu_2 t}$$

$$\text{where } \mu_2 = d_0 + d_1 + d_2.$$

$$3. \quad \frac{dR_T}{dt} = e_0 R_T + e_1 R_T + e_2 R_T = (e_0 + e_1 + e_2) R_T$$

Solution

At $t = 0$, $R_T(0) = R_0$ and let the effect of R_0 be minimal at $t = 0$, so that for a real biological system we have,

$$R_T = R_0 e^{\mu_3 t} \quad \text{where } \mu_3 = e_0 + e_1 + e_2$$

$$4. \quad \frac{d\bar{R}_T}{dt} = f_0 \bar{R}_T + f_1 \bar{R}_T + f_2 \bar{R}_T + f_3 \bar{R}_T = (f_0 + f_1 + f_2 + f_3) \bar{R}_T$$

Solution

At $t = 0$, $\bar{R}_T(0) = \bar{R}_0$ and let the effect of \bar{R}_0 be minimal at $t = 0$, so that for a real biological system we have

$$\bar{R}_T = \bar{R}_0 e^{\mu_4 t}$$

$$\text{where } \mu_4 = f_0 + f_1 + f_2 + f_3.$$

For AOM:

$$1. \quad \frac{dE_T}{dt} = k_0 E_T - k_1 E_T - k_2 E_T - k_3 E_T = (k_0 - k_1 - k_2 - k_3) E_T$$

At $t = 0$, $E_T(0) = E_0$ and let the effect of E_0 be minimal at $t = 0$, so that for a real life biological system, we have

$$E_T = E_0 e^{\lambda_1 t}, \quad \text{where } \lambda_1 = k_0 - k_1 - k_2 - k_3$$

$$2. \quad \frac{dV_T}{dt} = m_0 V_T - m_1 V_T = (m_0 - m_1) V_T$$

At $t = 0$, $V_T(0) = V_0$ and let the effect of V_0 be minimal at $t = 0$, so that for a real life biological system, we have

$$V_T = V_0 e^{\lambda_2 t}, \quad \text{where } \lambda_2 = m_0 - m_1$$

$$3. \quad \frac{dR_T}{dt} = n_0 R_T - n_1 R_T - n_2 R_T - n_3 R_T = (n_0 - n_1 - n_2 - n_3) R_T$$

Solution

At $t = 0$, $R_T(0) = R_0$ and let the effect of R_0 be minimal at $t = 0$, so that for a real life biological system, we have

$$R_T = R_0 e^{\lambda_3 t} \quad \text{where } \lambda_3 = n_0 - n_1 - n_2 - n_3$$

$$4. \quad \frac{d\bar{R}_T}{dt} = p_0 \bar{R}_T - p_1 \bar{R}_T - p_2 \bar{R}_T = (p_0 - p_1 - p_2) \bar{R}_T$$

Solution

At $t = 0$, $\bar{R}_T(0) = \bar{R}_0$ and let the effect of \bar{R}_0 be minimal at $t = 0$, so that for a real life biological system, we have

$$\bar{R}_T = \bar{R}_0 e^{\lambda_4 t}, \quad \text{where } \lambda_4 = p_0 - p_1 - p_2$$

Substituting the respective sub-solutions into the main equation, we obtain the separate equations:

$$\left. \frac{dT}{dt} \right|_{OM} = a_0 T + a_1 E_0 e^{\mu_1 t} + a_2 V_0 e^{\mu_2 t} + a_3 R_0 e^{\mu_3 t} + a_4 \bar{R}_0 e^{\mu_4 t}$$

$$\left. \frac{dT}{dt} \right|_{AOM} = b_0 T - b_1 E_0 e^{\lambda_1 t} - b_2 V_0 e^{\lambda_2 t} - b_3 R_0 e^{\lambda_3 t} - b_4 \bar{R}_0 e^{\lambda_4 t}$$

But, $\frac{dT}{dt} = \left. \frac{dT}{dt} \right|_{OM} + \left. \frac{dT}{dt} \right|_{AOM}$

so that

$$\frac{dT}{dt} = z_0 T + a_1 E_0 e^{\mu_1 t} + a_2 V_0 e^{\mu_2 t} + a_3 R_0 e^{\mu_3 t} + a_4 \bar{R}_0 e^{\mu_4 t} - b_1 E_0 e^{\lambda_1 t} - b_2 V_0 e^{\lambda_2 t} - b_3 R_0 e^{\lambda_3 t} - b_4 \bar{R}_0 e^{\lambda_4 t} \dots (*)$$

where $z_0 = a_0 + b_0$ since the number of cell is for same region.

Solving (*), we obtain

$$\frac{dT}{dt} - z_0 T = a_1 E_0 e^{\mu_1 t} + a_2 V_0 e^{\mu_2 t} + a_3 R_0 e^{\mu_3 t} + a_4 \bar{R}_0 e^{\mu_4 t} - b_1 E_0 e^{\lambda_1 t} - b_2 V_0 e^{\lambda_2 t} - b_3 R_0 e^{\lambda_3 t} - b_4 \bar{R}_0 e^{\lambda_4 t}$$

By integrating factor method.

$$\begin{aligned} (e^{-z_0 t} T)' &= e^{-z_0 t} [a_1 E_0 e^{\mu_1 t} + a_2 V_0 e^{\mu_2 t} + a_3 R_0 e^{\mu_3 t} + a_4 \bar{R}_0 e^{\mu_4 t} - b_1 E_0 e^{\lambda_1 t} - b_2 V_0 e^{\lambda_2 t} - b_3 R_0 e^{\lambda_3 t} - b_4 \bar{R}_0 e^{\lambda_4 t}] \\ &= a_1 E_0 e^{(\mu_1 - z_0)t} + a_2 V_0 e^{(\mu_2 - z_0)t} + a_3 R_0 e^{(\mu_3 - z_0)t} + a_4 \bar{R}_0 e^{(\mu_4 - z_0)t} - b_1 E_0 e^{(\lambda_1 - z_0)t} - b_2 V_0 e^{(\lambda_2 - z_0)t} \\ &\quad - b_3 R_0 e^{(\lambda_3 - z_0)t} - b_4 \bar{R}_0 e^{(\lambda_4 - z_0)t} \\ \therefore (e^{-z_0 t} T) &= \left[\frac{a_1 E_0 e^{(\mu_1 - z_0)t}}{\mu_1 - z_0} + \frac{a_2 V_0 e^{(\mu_2 - z_0)t}}{\mu_2 - z_0} + \frac{a_3 R_0 e^{(\mu_3 - z_0)t}}{\mu_3 - z_0} + \frac{a_4 \bar{R}_0 e^{(\mu_4 - z_0)t}}{\mu_4 - z_0} - \frac{b_1 E_0 e^{(\lambda_1 - z_0)t}}{\lambda_1 - z_0} \right. \\ &\quad \left. - \frac{b_2 V_0 e^{(\lambda_2 - z_0)t}}{\lambda_2 - z_0} - \frac{b_3 R_0 e^{(\lambda_3 - z_0)t}}{\lambda_3 - z_0} - \frac{b_4 \bar{R}_0 e^{(\lambda_4 - z_0)t}}{\lambda_4 - z_0} + A \right] \\ \Rightarrow T &= e^{z_0 t} \left[\frac{a_1 E_0 e^{(\mu_1 - z_0)t}}{\mu_1 - z_0} + \frac{a_2 V_0 e^{(\mu_2 - z_0)t}}{\mu_2 - z_0} + \frac{a_3 R_0 e^{(\mu_3 - z_0)t}}{\mu_3 - z_0} + \frac{a_4 \bar{R}_0 e^{(\mu_4 - z_0)t}}{\mu_4 - z_0} - \frac{b_1 E_0 e^{(\lambda_1 - z_0)t}}{\lambda_1 - z_0} \right. \\ &\quad \left. - \frac{b_2 V_0 e^{(\lambda_2 - z_0)t}}{\lambda_2 - z_0} - \frac{b_3 R_0 e^{(\lambda_3 - z_0)t}}{\lambda_3 - z_0} - \frac{b_4 \bar{R}_0 e^{(\lambda_4 - z_0)t}}{\lambda_4 - z_0} + A \right] \end{aligned}$$

$$i.e. \quad T = \frac{a_1 E_0 e^{\mu_1 t}}{\mu_1 - z_0} + \frac{a_2 V_0 e^{\mu_2 t}}{\mu_2 - z_0} + \frac{a_3 R_0 e^{\mu_3 t}}{\mu_3 - z_0} + \frac{a_4 \bar{R}_0 e^{\mu_4 t}}{\mu_4 - z_0} - \frac{b_1 E_0 e^{\lambda_1 t}}{\lambda_1 - z_0} - \frac{b_2 V_0 e^{\lambda_2 t}}{\lambda_2 - z_0} - \frac{b_3 R_0 e^{\lambda_3 t}}{\lambda_3 - z_0} - \frac{b_4 \bar{R}_0 e^{\lambda_4 t}}{\lambda_4 - z_0} + A e^{z_0 t}.$$

At $t = 0$, $T(0) = T_0 \Rightarrow A = T_0 - \sigma_1 - \sigma_2 - \sigma_3 - \sigma_4 + \sigma_5 + \sigma_6 + \sigma_7 + \sigma_8$ so that

$$T = (T_0 - \sigma_1 - \sigma_2 - \sigma_3 - \sigma_4 + \sigma_5 + \sigma_6 + \sigma_7 + \sigma_8)e^{z_0 t} + \sigma_1 e^{\mu_1 t} + \sigma_2 e^{\mu_2 t} + \sigma_3 e^{\mu_3 t} + \sigma_4 e^{\mu_4 t} - \sigma_5 e^{\lambda_1 t} - \sigma_6 e^{\lambda_2 t} - \sigma_7 e^{\lambda_3 t} - \sigma_8 e^{\lambda_4 t}$$

$$\sigma_1 = \frac{a_1 E_0}{\mu_1 - z_0}; \sigma_2 = \frac{a_2 V_0}{\mu_2 - z_0}; \sigma_3 = \frac{a_3 R_0}{\mu_3 - z_0}; \sigma_4 = \frac{a_4 \bar{R}_0}{\mu_4 - z_0}$$

Where

$$\sigma_5 = \frac{b_1 E_0}{\lambda_1 - z_0}; \sigma_6 = \frac{b_2 V_0}{\lambda_2 - z_0}; \sigma_7 = \frac{b_3 R_0}{\lambda_3 - z_0}; \sigma_8 = \frac{b_4 \bar{R}_0}{\lambda_4 - z_0};$$

On conditions that for

$\mu_i - z_0$ and $\lambda_i - z_0$; $i = 1, 2, 3, 4$, $\mu_i \neq z_0$ and $\lambda_i \neq z_0$, $\mu_i \neq 0$ and $\lambda_i \neq 0$ simultaneously

Reasons for this assumption are:

Original/ initial number of cells cannot equal that produced by oncogene and tumor suppressor gene processes. Due to the nature of biological system at any point in time, at least one cell must be produced or inhibited as a result of varying system actions, [17].

DISCUSSION OF RESULT

From the obtained expression for T in the model solution, it could be seen that linear summation of the influence of the subject matters (factors that leads to gene mutation and subsequently tumor) yields increased number of cells in a region. Below are the simulations for different cases {graph of number of cells/cell population in a region against each factor varying, other parameters remain constant}.

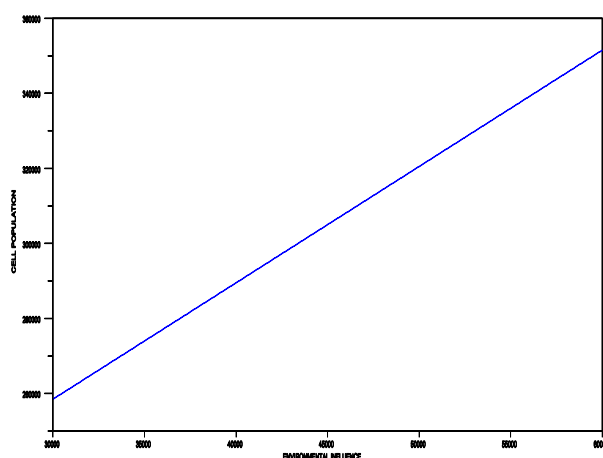


Figure 1: Graph of cell population against Environmental influence

By this graph, it can be seen that increase in the environmental influences (smoking, alcohol, ionizing radiation etc), increases cell population by having much impact on the anti-oncogene as found out from the expression used for the simulation. This also shows that the effect of environmental agents on cell multiplication cannot be undermined considering the sharp upward movement.

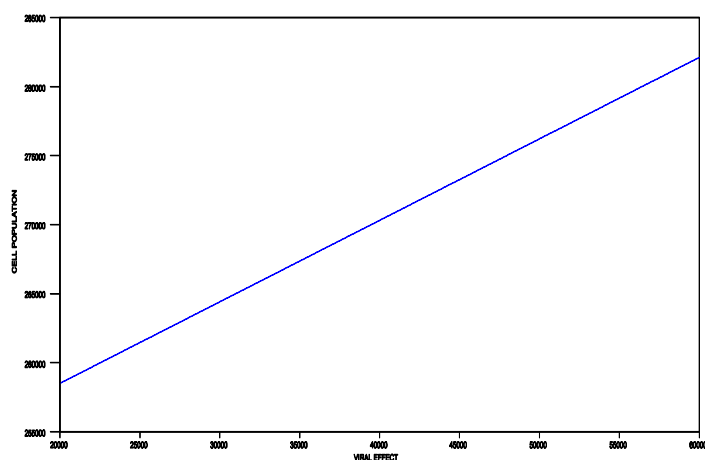


Figure 2: Graph of Cell population against viral effect

The DNA virus takes a very tough toll on the cell population viewing from the graph. Viral onslaught brings about increased level of damage on the system, disjoining the proto-oncogene and anti-oncogene (TSG) functions, thus, a rise in number of cells. This increase may not be as fast as seen in the impact of the environmental agents but, it equally contributes significantly to change in cell population..

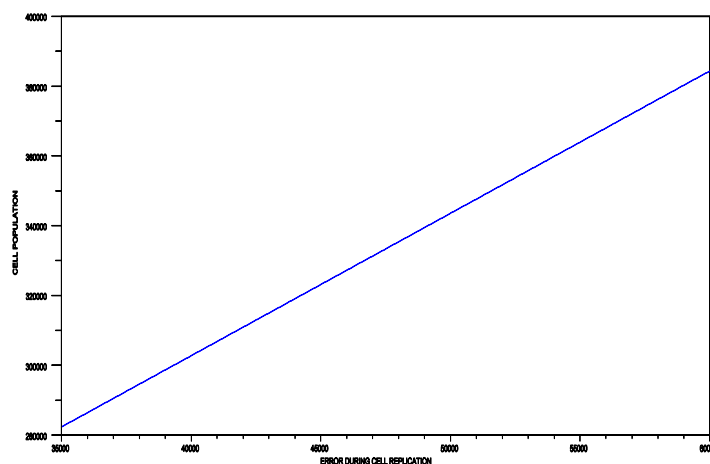


Figure 3: Relationship between cell population and effect of error during cell replication.

At the early stage of the replication error without repair, it is easy to see that the change in the cell population is minimal, but gets flying so high subsequently. The higher the error during cell division, the stronger the damage on proto-oncogene and tumor suppressor gene, hence; the cell population increasing rapidly. This is one of the major factors that contribute to tumor formation as shown by the number of cells it yield when it varies. Also comparing its contribution to cell population with other factors, it can be observed to be a major gun on cell multiplication leading to tumorigenesis.

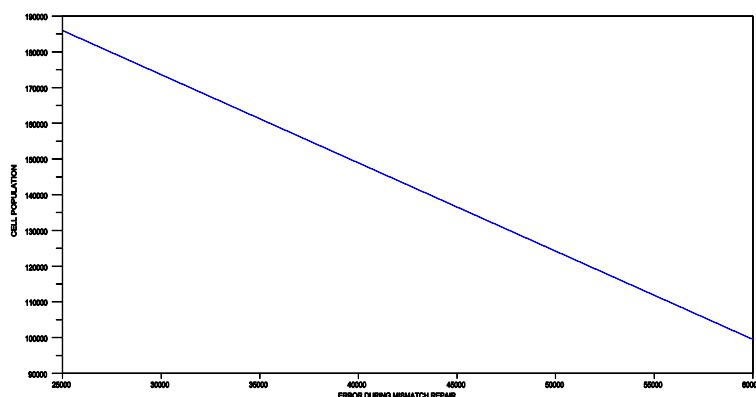


Figure 4: Graph showing number of cells versus error during mismatch repair.

The downward movement in the graph depicts a decline. This shows that increase in the effect of error during mismatch repair decreases cell population and vice-versa. It also confirms that

indeed error occurs during repair of damaged genes but the repair scheme may necessarily not be mismatch and even if, the higher the effect gets, many of the produced cells commit apoptosis and inturn are quickly removed, hence the surviving cells are far smaller than initially obtained.

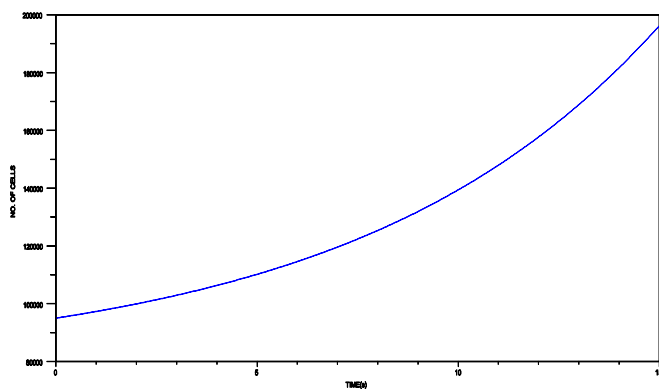


Figure 5: Changes in the number of cells with time based on the contribution of all the aforementioned influences with time, $\{0 \leq t \leq 15 (t \text{ in years})\}$.

Figure 5 is a true picture of how cells behave in a region with time when mistakes as a result of mutation lead to misinterpretation of sent information in proto-oncogene and tumor suppressor gene respectively. This increase in the curve indicates that cells are churned out above the normal/expected level. The Tumor suppressor gene fails to put a check on the proto-oncogene because it is acting abnormally, likewise the proto-oncogene veers off control pattern due to belated understanding and subsequent interpretation of instructions. Hence the accumulation of cells leading to tumor origination in the region.

CONCLUSION

It is evident that uncontrolled cell growth occurs when genes are mutated, specifically, the genes in charge of cell growth. Mutation is a very serious action that may hang human life on the balance if not checked. Its permanent nature tends to disrupt the coded order of events just as have been discovered. Gene(s) are rendered ineffective or alternatively considered loss in function due to mutation effect. The study shows that effect of environmental agents-smoking, alcohol, ultraviolet rays etc, DNA virus, error during cell replication and error during mismatch repair which are all mutation induced, contributes noticeably to increase in cell .production over time, thus manifesting into tumors of various degrees.

RECOMMENDATION

The fact that tumor occurs from uncontrolled cell growth basically due to DNA mutation is to a large extent beyond human control but effort can be made to reduce mutation. Supported by the stability analysis in this work, the study showed that the influence of environmental agents on the DNA awakens mutation, hence, disorganizing the already stated programme of the system. It is important that we stay away from cigarette smoking and the likes and alcohol intake as these sends very fast signals to the system, damaging normal protein synthesis, transfer, etc.

In general we must try to stay healthy by eating good meal as to keep the immune system very functional in order to wage war against viral intrusion.

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