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 benezene molecule, (benzol-pyrene) the shape is such that it fits into the major grove of a DNA double helix. Once their; negatively charged region of benzene can disrupt the binding of the DNA's sugar phosphate backbone causing cleavage, hence mutation. Irradiated hematopoetic cells could provide higher levels of inflammatory cytokines and the transplanted irradiation induced senescene 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 TSG_S 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 TSG_S.

It downregulates some TSG_S by bringing about high incidence of single base mutation on RASSFI and RBSP3 located in chromosome 3 P21.3 region, LUCA and AP 20 respectively. This is possible when the chemicals from the agents mixes 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 RASSFIA expression is due to presence of tumor acquired promoter methylation and occurring missense mutation in RASSFIA, thereby reducing growth inhibitory activity (decrease in growth suppressor activity) [15].

Note:

Cytidine- is from the family of induced deamination gene.

RASSFIA- Ras association domain family 1 codes for cyclin D_1.

They also lead to loss of Heterozygosity. The short arm of human chromosome 3 contains TSG_S. TSG_S 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 G_1 (The first gap in the normal cell cycle is called G_1 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 G_1 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 TSG_S 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 IIH, TF IIH.
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 freshpiece 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 G_2 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 DSB_S 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 DSB_S [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 malfunctional 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.*
$\overline{R}_T$ = *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:

$$\frac{dT}{dt}\Big|_{OM} = a_0T + a_1E_T + a_2V_T + a_3R_T + a_4\overline{R}_T \text{ ----------} (1)$$

$$\frac{dT}{dt}\Big|_{AOM} = b_0T - b_1E_T - b_2V_T - b_3R_T - b_4\overline{R}_T \text{ ----------} (2)$$

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

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

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

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

where E_T, V_T, R_T are given as

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

And

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

SOLUTIONS TO THE MODEL EQUATIONS

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

Solution

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

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

where $\mu_1 = c_0 + c_1 + c_2 + c_3.$

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

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

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

where $\mu_2 = d_0 + d_1 + d_2.$

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

Solution

At $t = 0,\quad R_T(0) = R_0$ and let the effect of R_0 be minimal at $t = 0,$ so that for a real biological system we have, $\quad R_T = R_0 e^{\mu_3 t}\quad$ where $\quad \mu_3 = e_0 + e_1 + e_2$

4. $\dfrac{d\overline{R}_T}{dt}\ f_0 \overline{R}_T + f_1 \overline{R}_T + f_2 \overline{R}_T + f_3 \overline{R}_T = (f_0 + f_1 + f_2 + f_3) \overline{R}_T$

Solution

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

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

where $\mu_4 = f_0 + f_1 + f_2 + f_3.$

For AOM:

1. $\frac{dE_T}{dt} = k_0E_T - k_1E_T - k_2E_T - k_3E_T = (k_0 - k_1 - k_2 - k_3)E_T$

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

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

2. $\frac{dV_T}{dt} = m_0V_T - m_1V_T = (m_0 - m_1)V_T$

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

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

3. $\frac{dR_T}{dt} = n_0R_T - n_1R_T - n_2R_T - n_3R_T = (n_0 - n_1 - n_2 - n_3)R_T$

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

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

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

Solution

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

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

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

$$\frac{dT}{dt}\Big|_{OM} = a_0T + a_1E_0e^{\mu_1 t} + a_2V_0e^{\mu_2 t} + a_3R_0e^{\mu_3 t} + a_4\overline{R}_0e^{\mu_4 t}$$

$$\frac{dT}{dt}\Big|_{AOM} = b_0T - b_1E_0e^{\lambda_1 t} - b_2V_0e^{\lambda_2 t} - b_3R_0e^{\lambda_3 t} - b_4\overline{R}_0e^{\lambda_4 t}$$

But, $\frac{dT}{dt} = \frac{dT}{dt}\Big|_{OM} + \frac{dT}{dt}\Big|_{AOM}$

so that

$$\frac{dT}{dt} = z_0T + a_1E_0e^{\mu_1 t} + a_2V_0e^{\mu_2 t} + a_3R_0e^{\mu_3 t} + a_4\overline{R}_0e^{\mu_4 t} - b_1E_0e^{\lambda_1 t} - b_2V_0e^{\lambda_2 t} - b_3R_0e^{\lambda_3 t} - b_4\overline{R}_0e^{\lambda_4 t} \quad ---(*)$$

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

Solving (*), we obtain

$$\frac{dT}{dt} - z_0T = a_1E_0e^{\mu_1 t} + a_2V_0e^{\mu_2 t} + a_3R_0e^{\mu_3 t} + a_4\overline{R}_0e^{\mu_4 t} - b_1E_0e^{\lambda_1 t} - b_2V_0e^{\lambda_2 t} - b_3R_0e^{\lambda_3 t} - b_4\overline{R}_0e^{\lambda_4 t}$$

By integrating factor method.

$$\begin{aligned}\left(e^{-z_0t}T\right)' &= e^{-z_0t}\left[a_1E_0e^{\mu_1 t} + a_2V_0e^{\mu_2 t} + a_3R_0e^{\mu_3 t} + a_4\overline{R}_0e^{\mu_4 t} - b_1E_0e^{\lambda_1 t} - b_2V_0e^{\lambda_2 t} - b_3R_0e^{\lambda_3 t} - b_4\overline{R}_0e^{\lambda_4 t}\right] \\ &= a_1E_0e^{(\mu_1 - z_0)t} + a_2V_0e^{(\mu_2 - z_0)t} + a_3R_0e^{(\mu_3 - z_0)t} + a_4\overline{R}_0e^{(\mu_4 - z_0)t} - b_1E_0e^{(\lambda_1 - z_0)t} - b_2V_0e^{(\lambda_2 - z_0)t} \\ &\quad - b_3R_0e^{(\lambda_3 - z_0)t} - b_4\overline{R}_0e^{(\lambda_4 - z_0)t}\end{aligned}$$

$$\therefore \quad \left(e^{-z_0t}T\right) = \left[\begin{array}{l}\dfrac{a_1E_0e^{(\mu_1 - z_0)t}}{\mu_1 - z_0} + \dfrac{a_2V_0e^{(\mu_2 - z_0)t}}{\mu_2 - z_0} + \dfrac{a_3R_0e^{(\mu_3 - z_0)t}}{\mu_3 - z_0} + \dfrac{a_4\overline{R}_0e^{(\mu_4 - z_0)t}}{\mu_4 - z_0} - \dfrac{b_1E_0e^{(\lambda_1 - z_0)t}}{\lambda_1 - z_0} \\ -\dfrac{b_2V_0e^{(\lambda_2 - z_0)t}}{\lambda_2 - z_0} - \dfrac{b_3R_0e^{(\lambda_3 = z_0)t}}{\lambda_3 - z_0} - \dfrac{b_4\overline{R}_0e^{(\lambda_4 - z_0)t}}{\lambda_4 - z_0} + A\end{array}\right]$$

$$\Rightarrow \quad T = e^{z_0t}\left[\begin{array}{l}\dfrac{a_1E_0e^{(\mu_1 - z_0)t}}{\mu_1 - z_0} + \dfrac{a_2V_0e^{(\mu_2 - z_0)t}}{\mu_2 - z_0} + \dfrac{a_3R_0e^{(\mu_3 - z_0)t}}{\mu_3 - z_0} + \dfrac{a_4\overline{R}_0e^{(\mu_4 - z_0)t}}{\mu_4 - z_0} - \dfrac{b_1E_0e^{(\lambda_1 - z_0)t}}{\lambda_1 - z_0} \\ -\dfrac{b_2V_0e^{(\lambda_2 - z_0)t}}{\lambda_2 - z_0} - \dfrac{b_3R_0e^{(\lambda_3 = z_0)t}}{\lambda_3 - z_0} - \dfrac{b_4\overline{R}_0e^{(\lambda_4 - z_0)t}}{\lambda_4 - z_0} + A\end{array}\right]$$

i.e. $T = \dfrac{a_1E_0e^{\mu_1 t}}{\mu_1 - z_0} + \dfrac{a_2V_0e^{\mu_2 t}}{\mu_2 - z_0} + \dfrac{a_3R_0e^{\mu_3 t}}{\mu_3 - z_0} + \dfrac{a_4\overline{R}_0e^{\mu_4 t}}{\mu_4 - z_0} - \dfrac{b_1E_0e^{\lambda_1 t}}{\lambda_1 - z_0} - \dfrac{b_2V_0e^{\lambda_2 t}}{\lambda_2 - z_0} - \dfrac{b_3R_0e^{\lambda_3 t}}{\lambda_3 - z_0} - \dfrac{b_4\overline{R}_0e^{\lambda_4 t}}{\lambda_4 - z_0} + Ae^{z_0t}$.

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

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

Where

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

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

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).

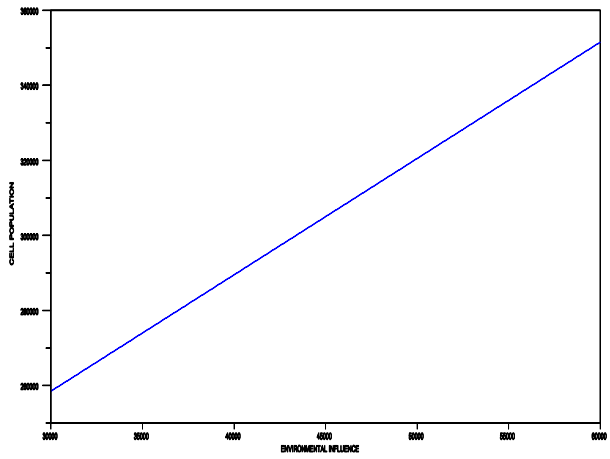

Figure 1: Graph of cell population against Environmental influence

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.

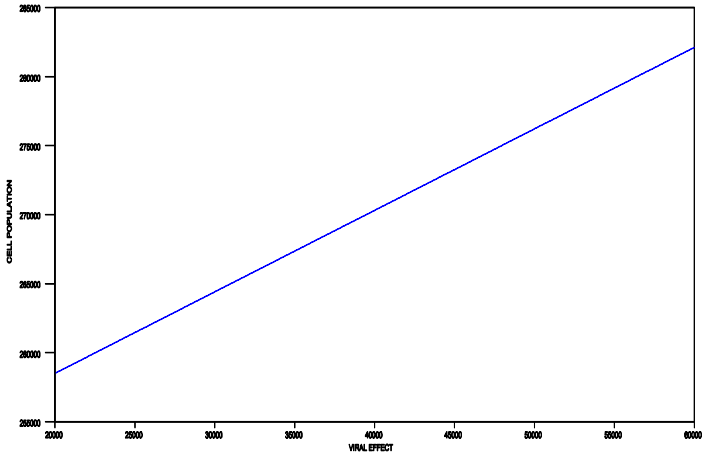

Figure 2: Graph of Cell population against viral effect

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, disjointing 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..

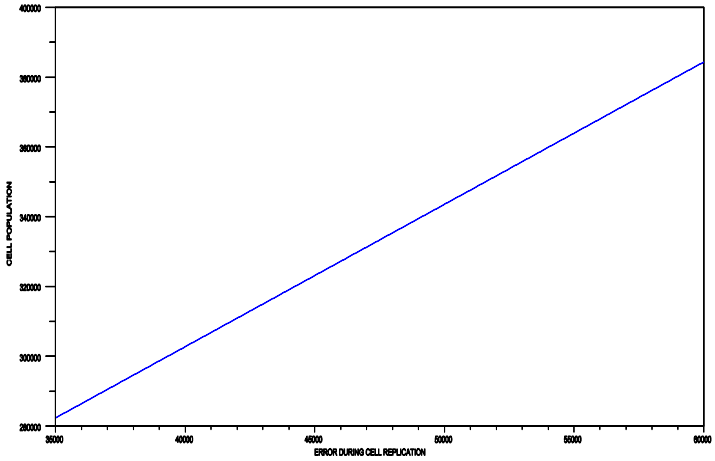

Figure 3: Relationship between cell population and effect of error during cell replication.

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.

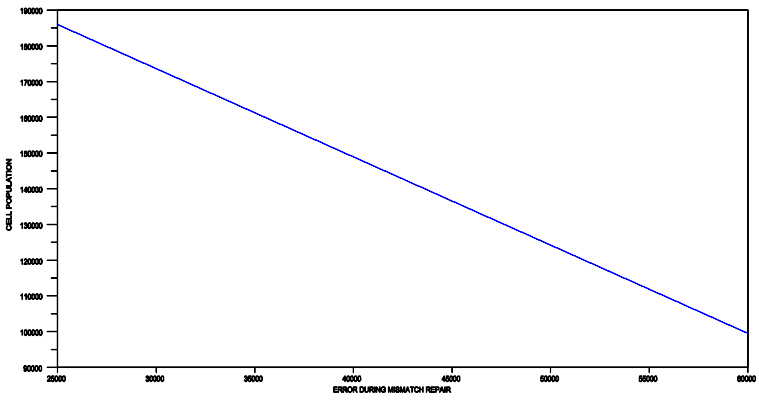

Figure 4: Graph showing number of cells versus error during mismatch repair.

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.

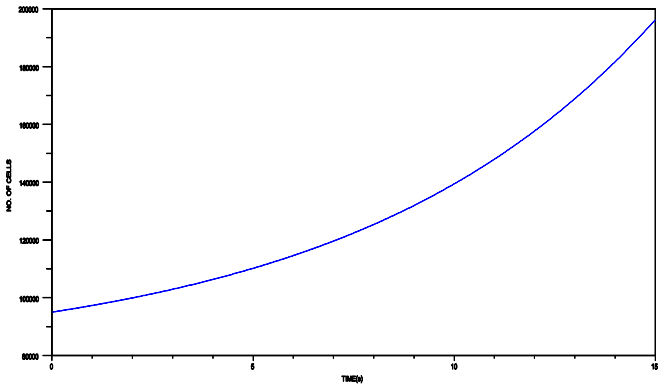

Figure 5: Changes in the number of cells with time based on the contribution of all the aforementioned influences with time, $\{0 \leq t \leq 15\ (t\ in\ years)\}$.

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 inorder to wage war against viral intrusion.

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