OPEN ACCESS
Global Journal of Research in Medical Sciences
ISSN: 2583-3960 (Online)
Volume 04 | Issue 06 | Nov.-Dec. | 2024
Journal homepage: https://gjrpublication.com/gjrms/
Research Article

Why normal cells transform into malignant cells

[1]Jelenka Savkovic-Stevanovic* and [2]Radmila M. Stevanović

[1] Department of Chemical Engineering, Faculty of Technology and Metallurgy, The University of Belgrade, 11000 Belgrade, Karnegijeva 4, Serbia.
[2] Srbisim"-Belgrade, 11000 Belgrade, Serbia.

DOI: 10.5281/zenodo.14563130 **Submission Date: 15 Nov. 2024 | Published Date: 27 Dec. 2024**

***Corresponding author: Jelenka Savkovic-Stevanovic**
Department of Chemical Engineering, Faculty of Technology and Metallurgy, The University of Belgrade, 11000 Belgrade, Karnegijeva 4, Serbia.

Abstract

In this paper malignant mutation was studied. Malignant transformation is a multistage process which manipulated with point mutation. Gene activation and tumor suppressor gene inactivation induced by mutations provide strong evidence for the involvement of harmful mechanisms in tumor formation. In the next stage promotion finally resulting in tumor formation. The number of genes that must be activated to convert a normal cell into a malignant cell is unknown at present. In this paper mechanisms a normal cell into a malignant cell transformation were studied by equations which describe genes motion and transition state.

Keywords: *Mutation, mechanism, DNA repair, promotion, malignant.*

1. Introduction

The term mutation can be applied to point mutations, which are qualitative changes involving one or a few bases within one gene, as well as to larger changes involving parts of chromosome detectable by light microscopy or even whole chromosomes and thus many thousend of genes.

The structure and function of the purines and pyrimidines and their nucleosides and nucleotides were studied in numerous literature [1]-[6]. Synthetic analogs of naturally occurring nucleotides find application in cancer chemotherapy as enzyme inhibitors and can replace the naturally occurring nucleotides in nucleic acids.

Although the pyramidine nucleus is simpler and its synthetic pathway briefer than that of the purine structure, the share several common precursors. PRPP, glutamine, CO_2, and aspartate are required for the synthesis of all pyramidine and purine nucleotides. For the thymidine nucleotides and for all purine nucleotides, tetrahydrofolate derivates are also necessary.

Mammals and most lower vertebrates are prototrophic for purines and pyrimidines, i.e., they synthesize purine and pyrimidine nucleotides de novo.

In human and other mammals, purine nucleotides are synthesized to meet the needs of the organism for the monomeric precursors of nucleic acids and for those other functions.

At neutral *pH*, guanine is the least soluble of the bases, followed in the respect xanthine. Although uric acid as urate is relatively soluble at a neutral *pH*, it is highly insoluble in solutions with a lower *pH*, such as urine. Guanine is not a normal constituent of human urine, but xanthine and uric acid do occur in human urine.

In this paper enzyme inhibition in cancer cell growing was studied.

2. Mutation

Point mutation is occurred when one base is substituted for another (substitution) or when base pair are deleted or inserted (deletions/insertions). Substitution of another purine for a purine base or of another pyrimidine for a pyrimidine base is called a transition. Substitution of purine for pyrimidine or pyrimidine for purine is called a transversion. Very slight alterations in the chemical structure of the DNA bases may be sufficient for a base pair substitution to occur. Guanine for example, normally pairs with cytosine, while O^6 -methylguanine, frequent DNA modification seen with methylating agents such as dymethylnitrosamine, pairs with thymine, resulting in a hereditary change of the genetic information.

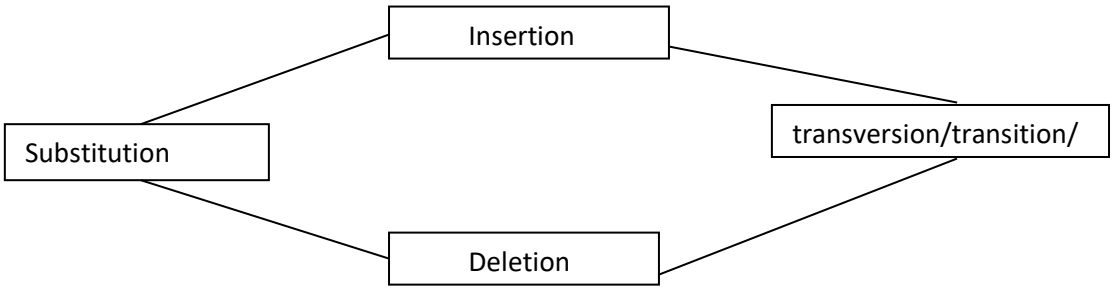


Fig. 1 Activities during manipulation

It has long been known that, the double helical structure of DNA is disrupted into single stranded random coils by heat, alkali, and other denaturing agents.

These changes in certain codons may cause insertion of the wrong amino acid into a relevant polypeptide. In this case, the changes are called missense mutation. Such proteins may have dramatically altered properties if the new amino acid is close to the active centre of an enzyme or affects for three dimensional structure of an enzyme or a structural protein.

Hence, the alternations may result in marked changes in the differentiations and proliferative characteristics of the affected cells. A base substitution can also result in the formation of a new inappropriate stop (or nonsense codon). The results of nonsense mutations are the formation of a shorter and, most likely, inactive protein. Owing to the redundancy of the genetic code, about a quarter of all possible base substitutions will not result in amino acid replacement and will be silent mutations.

Bases can be also deleted or added to a gene. Because each gene has a precisely defined length, these changes, if they involve a number of bases that is not a multiple of three, result in a change in the reading frame of the DNA sequence and are known as frame shift mutations. Such mutations often have a dramatic effect on the polypeptide coded by the affected gene, because most amino acids will differ from the point of the insertion or deletion of bases in the DNA strand onward.

What happen during manipulation can analysis by equation (1) and (2) [7]-[10]:

$$\int_V \{\frac{\partial \psi_c}{\partial t} + v_x \frac{\partial \psi_c}{\partial x} + v_y \frac{\partial \psi_c}{\partial y} + v_z \frac{\partial \psi_c}{\partial z} + \sum_{i=1}^{n} \frac{\partial (v_i \psi_c)}{\partial \xi_i} - D_f (\frac{\partial^2 \psi_c}{\partial x^2} + \frac{\partial^2 \psi_c}{\partial y^2} + \frac{\partial^2 \psi_c}{\partial z^2}) + (r) - D\} dV = 0 \quad (1)$$

Changes can occur by the following mechanisms: mixing, diffusion, hybridization and denaturation. These changes can control by particular mechanism effect. How can influence to the denaturation?

From pure physical or physicochemical points of view, melting of DNA is still an intriguing theme. Fine comparison discloses noticeable discrepancies between experimental and theoretical profiles, which must be solved by refinement of the theoretical model and parameter values.

Heat generation in eq. (2) can be melting effect.

$$\int_V \{\rho C_p (\frac{\partial \psi_T}{\partial t} + v_x \frac{\partial \psi_T}{\partial x} + v_y \frac{\partial \psi_T}{\partial y} + v_z \frac{\partial \psi_T}{\partial z} + \sum_{i=1}^{n} \frac{\partial (v_i \psi_T)}{\partial \xi_i}) - \lambda (\frac{\partial^2 \psi_T}{\partial x^2} + \frac{\partial^2 \psi_T}{\partial y^2} + \frac{\partial^2 \psi}{\partial z^2}) + S_r\} dV = 0 \quad (2)$$

where t-time, x, y and z, - space, ξ - some atribute, v - геометријска брзина, ψ_c - concentration, D_f - diffusion coefficient, r - hybridization reaction, D - denaturation, ψ_T - temperature, λ - coefficient of heat conductivity, S_r - generation heat, and V - volume. Stochastic variables can be generated by probability distribution.

3. Malignant transformation

Mutations are hereditary changes in genetic information, resulting from spontaneous or xenobiotic induced *DNA* damage. The term mutation can be applied to point mutations, which are qualitative changes involving one or a few bases within one gene, as well as to larger changes involving parts of the chromosome detectable by light microscopy or even whole chromosomes and thus many thousands of genes as shown in Table 1.

Table 1. Types of mutation

Gene mutations	Base pair substitution, deletions, insertion, gene rearrangements, gene amplifications
Chromosomal mutations	
Structural	breaks, translocations
Numerical	Loss or gain of an entire chromosome

Very slight alterations in the chemical structure of the *DNA* bases may be sufficient for a base pair substitution to occur. Guanine for example, normally pairs with cytosine, while O^6-methyl guanine (a frequent *DNA* modification seen with methylating agents such as dimethyl nitrosamine) pairs with thymine as shown in Fig. 2, Fig.3 and Fig.4 [11]-[14].

These changes in certain codons may cause insertion of the wrong amino acid into a relevant polypeptide. In this case, the changes are called *missense mutations*. Such proteins may have dramatically altered properties if the new amino acid is close to the active center of an enzyme or affects the three-dimensional structure of an enzyme or a structural protein. Hence, the alterations may result in marked changes in the differentiation and proliferative characteristics of the affected cells. A base substitution can also result in the formation of a new inappropriate stop or nonsense codon. The result of nonsense mutations is the formation of a shorter and, most likely, inactive protein.

Owing to the redundancy of the genetic code, about a quarter of all possible base substitutions will not result in amino acid replacement and will be silent mutations. Bases can be also deleted or added to a gene Because each gene has a precisely defined length, these changes, if they involve a number of bases that is not a multiple of three, result in a change in the reading frame of *DNA* sequence and are known as *frameshift mutations*. Such mutations often have dramatic effect on the polypeptide coded by the affected gene, because most will differ from the point of the insertion or deletion of bases in the *DNA* strand onward.

Some forms of unrepaired alkylated bases are lethal, due to interference with *DNA* replication. Others such as O^6-methyl guanine led to mutations, if unrepaired. These differences indicate that not all *DNA* adducts are of equivalent importance. In fact, some adducts appear not to interfere with normal *DNA* functions or to be rapidly repaired, others are mutagenic, and yet others are lethal. The most vulnerable base is guanine, which can form adducts at several of its atoms, e.g. N-7, C-8, O-6, and exocyclic N-2.

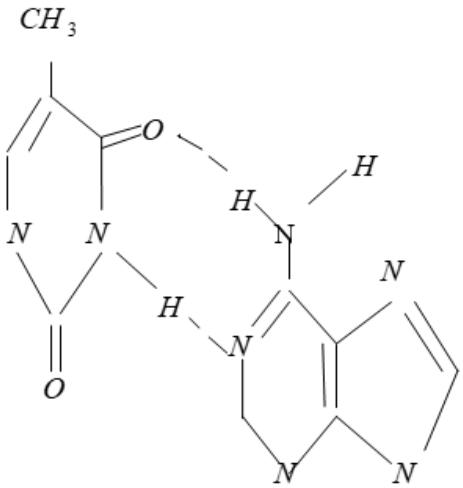
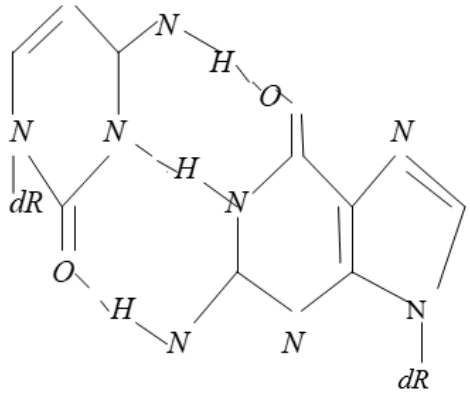


Fig. 2. Formation of a base substitution thymine with adenine



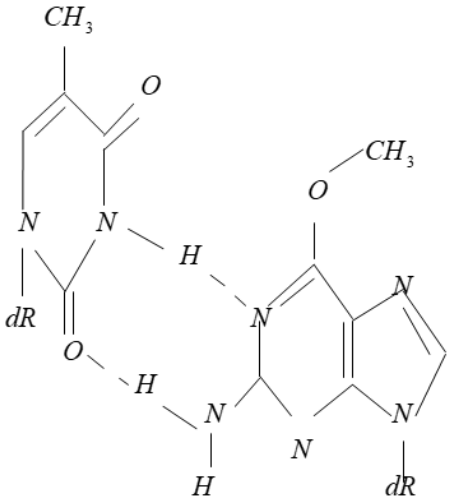
dR-deoxyribose

Fig. 3 Formation of a base substitution cytosine with guanine

4. Genetic information flow

A series of nucleoside analogs with antivirial activities has been studied for several years, one 5-iododeoxyuridine, is effective in the local treatment of herpetic keratitis, an infection of the cornea by herpesvirus.

Numerous analogs of purine and pyrimidine ribonucleotides have been synthesized so as to generate nonhydrolyzable di- or triphosphates for use in vitro. These analogs allow the investigator to determine whether given biochemical effects of nucleoside di- or triphosphates require hydrolysis or whether their effects are mediated by occupying specific nucleotide binding sites on enzymes or regulatory proteins.



dR-deoxyribose

Fig.4 Formation of a base substitution thymine with O^6-methyl guanine

The reduction of the ribonucleoside diphosphates to deoxyribonucleoside diphosphates is subject to complex regulation. DNA is a complex biopolymer that is organized as a double helix The fundamental organizational element is the sequence of purine (adenine or guanine and pyrimidine cytosine or thymine bases. These bases are attached to the C-1' position of the sugar deoxyribose, and the bases are linked together through joining of the sugar moieties at their 3'- and 5 -'positions via a phosphodiester bond. The alternating deoxyribose phosphate groups form the backbone of the double helix. These 3'-5'- linkages also define the orientation of a given strand of the DNA molecule, and since the 2-strands run in opposite directions, they are said to be antiparallel.

The double – helical DNA is packaged into a more compact structure by a number of proteins, most notably the basic proteins called *histones*. The DNA presents within nucleus of a cell, if simply extended, would be about a meter long. The chromosomal proteins compact this long length of DNA so that it can be packaged into a nucleus with a volume of a few cubic microns.

4. Causal link between mutation and cancer

The change from cells undergoing normal controlled cell division and differentiation to cells that are transformed, dividing without control, and undifferentiated or abnormally differentiated does not occur as a single step. Evidence for the involvement of multistage comes from in vitro studies, animals models, and epidemiological observations. In humans, the latent period between exposure to a chemical carcinogen and the operations of a tumor in the target tissue is approximately 10-25 years.

Modern molecular biology techniques enable thorough investigation of the genome of malignant cells compared to the genome of their normal counter parts. These studies clearly show that a single mutation is not sufficient to induce malignant transformation. The number of genetic changes varies between two and seven in different tumor types. Also, several types of mutations are usually formed in a malignant transformed cell, e.g. base pair substitutions, gene rearrgements, chromosomal breaks, and deletions [15]- [22].

5. Tumor suppressor genes

Oncogenes were originally discovered in the genome of transforming retroviruses and were therefore named v-oncogenes. Subsequent studies showed that these viral genes were originally derived from the mammalian genome. In the normal cell, these proto-oncogenes have important functions in signal transduction pathways. Proto-oncogenes are expressed in the course of physiological growth processes, such as organ formation during embryogenesis in the maternal organism, regeneration of damaged tissues, and stimulation of cell division by growth factors in the adolescent and adult organism. Activation of cellular proto-oncogenes into c-oncogenes in spontaneously and chemically induced tumors results in qualitatively (altered protein) or quantitatively, too much, at the wrong time altered gene expression. Oncogenes can be activated by several types of genetic damage such as point mutations, gene amplifications, and chromosomal translocations.

A substantial number of human tumors 10-15% contain activated *ras* oncogenes. In all cases so far examined, activation relies on a point mutation in codon 12, 13, 59, or 61 of one of the *ras* proto-oncogenes. The p21 protein coded by the *ras* genes exerts GTPase (GTP hydrolase) activity and is membrane bound. The physiological function of p21 is not precisely known; the protein is bound to the inner surface of the plasma membrane; therefore, it may have a function in transducing signals from growth factors receptors across the cytoplasm to the nucleus. The point mutations described above change the properties of the p21 protein and often result in reduced GTPase activity. Since this activity is also responsible for inactivation of the p21 protein itself, reduction of GTPase activity by point mutation results in prolongation of the *ras* signal transduction pathway.

Point mutations resulting in activation of *ras* proto-oncogenes have also been described in several chemically induced rodent tumors. In the majority of mammary tumors induced by nitro-somethylurea, the *ras* oncogene is mutated at codon 12. Similar activation of H-*ras* at codon 61 is detected in mammary and skin tumors induced by 7, 12-dimethylbenzanthracene. Nitro-somethylurea is an alkylating agent that induces the formation of O^6 -methylguanine in *DNA* which is consistent with the type of point mutation (G transition) observed at the 12^{th} codon of H-*ras*. The mutation at codon 61 in dimethylbenzanthracene-induced tumor cells (mainly A T transversion /transition) is consistent with the formation of adenine adducts, resulting from dimethylbenzanthracene metabolites binding to adenine residues.

7. Conclusion

This paper mutation and malignant transformation have been studied The equations which define mechanisms of gene motion and transition state were discussed.

Normal control of cell division and differentiation is now generally accepted to base on the interplay of two sets of genes, the proto-oncogenes and the tumor suppressor genes. Abnormal activation of proto-oncogenes or inactivation of tumor suppressor genes eventually leads to malignant transformation.

Causal link between mutation and cancer was studied. Tumor suppressor genes code for proteins that negatively regulate cell proliferation and inhibit neoplastic transformation. Oncogenes act in a dominant manner, i.e. activation of one copy of the gene can result in perturbation of normal cell proliferation or diferentation.

Abrreviation

DNA - deoxyribonucleic acid

RNA – ribonucleic acid

GTP - guanine triphosphate

References

1. J.Savkovic Stevanovic, Mutation by base pair substitution, *Advances in Nanomedicine and Nanotechnology Research*, 2 (2) 122-125, 2020 , ISSN2699-5476.
2. J. Savkovic-Stevanovic, DNA combination and recombination state, *10the International Conference on Mathematics and Computers in Biology and Chemistry*, ID632-188, Iashi, 11-12 June, 2010.
3. J.Savkovic Stevanovic J., Biopolymers helix-coil structure, *International Journal of Biology and Biomedicine*, www.iaras.org, 7, 34-39, 2 July, 2022.
4. J. Savkovic-Stevanovic, Djurovic J., Pharamceutical drugs formation modelling,*4th International Conference on Drug Discovery and Therapy*, Dubai, UAE, 12-15 Feb., 2012.
5. J. Savkovic-Stevanovic, Helix stability of the double to single strands oligonucleotides transition, *HSBS'12- Health Science and Biomedical Systems*, ID 67910-006, Naun, Romania, Iashi, June 13-15, 2012.
6. J. Savkovic-Stevanovic, Vilendecic-Grkinic Lj., Siler-Marinkovic S., Molecular modeling of the helix structure formation in biopolymers, *WCCE9- 9th World Congress of Chemical Engineering*, P-01-136, Coex, Seoul, Korea, August, 18-23, 2013.
7. J. Savkovic Stevanovic, Modeling and simulation of the biological system, Proceedings of the *MESM2000-2nd Middle –East Simulation Conference, Modelling and Simulation for Medical Applications*, Philadelphia University, Ammam, Jordan, p. 6, August 28-30, 2000.
8. J. Savkovic Stevanovic, DNA sequences simulation, *Proceedings of the MESM2001-3nd Middle - East Simulation Conference, Modelling and Simulation for Medical Applications*, Philadelphia University, Ammam, Jordan, p. 5, September 1-5, 2001.
9. Savkovic Stevanovic J., Using recombinant DNA technology against viruses and bacterias, *Journal of Genetic Engineering and Biotechnology Research*, vol.2 (2) 1-6, 2020, ISSN 2690-912X.
10. J. Savkovic Stevanovic, Biotransformation transfer for product formation, *Innovat International Journal of Medical & Pharmaceutical Sciences*, vol. 8(1) 1-4, 2023.
11. J. Savković Stevanović and R. Stevanović, DNA strand transition state, *Comput. Ecol. Eng. Q.*, 20(3) 85-91, 2024, ISSN 1452-0729
12. P. Lawley, *Mutat. Res*., vol.213, 1989, p. 3-26.
13. J. M. Bishop, *Science* (Washington DC 1883), vol. 235, 1987, p. 305-311.
14. J. Savkovic-Stevanovic, Nucleotides recombination, states, *Trasaction on Biology and Biomedicine*, vol.7 (3) 253-262 (2010) ISSN 1109-9518.
15. F. P. Guengerich, *J. Biol. Chem.*, vol. 266, p.10019-10022 (1991).
16. J. L. Cmarik, et. al., *Cancer Res*., vol. 50, p. 2747-2752 (1990).
17. D. M. Ziegler, *Drug, Metab.Rev.*, vol. 19, 1988, p. 1-32 (1988).
18. R. N. Hines, et.al., *Toxicol. Appl. Pharmacol.*, vol.125, p. 1-6 (1994).
19. M. Blum et al., DNA *Cell Biol*., vol. 9, p. 193-203 (1990).
20. J.M. Bishop, Cell, vol. 64, p. 235-248 (1991).
21. J. Savković Stevanović, Gene degeneration changes, *Comput. Ecol. Eng.Q.*, 18 (4) 145-153, 2022, ISSN 1452-0729.
22. J. Savkovic Stevanovic, R. Stevanović, Purine and pyrimidine nucleotide biosynthesis, *Global Journal of Research in Medical Sciences (Global J Res Med Sci)*, Vol. 4 (4) 5-11 (2024) ISSN2583-3960 https://doi.org/10.5281/zenodo.12689400, IF5.47.

CITATION

J. Savkovic-Stevanovic, & R. M. Stevanović. (2024). Why normal cells transform into malignant cells. In Global Journal of Research in Medical Sciences (Vol. 4, Number 6, pp. 72–77). https://doi.org/10.5281/zenodo.14563130