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DNA Mutation Induced Toxicity

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Abstract
Mutation are hereditary changes in genetic information, resulting from spontaneous or xenobiotic induced DNA damage. The number of proto-oncogenes that must be activated to convert a normal cell into a malignant cell is unknown at present. Point mutation and frame shift mutations were examined. Phosphorylation is the most important in the synthesis of purine and pyrimidine nucleosides and DNA damage. Impact of toxic effects to phosphorylation reactions modifications and xenobiotic inducing was studied. In this paper a normal cell into a malignant cell transformation was considered

Keywords: Mutation, genes, DNA bases, chromosomes, metabolism.

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. In this paper point mutation was studied.

The structure and function of the purines and pyrimidines and their nucleosides and nucleotides were studied in numerous literature[1]-[3]. Synthetic analogs of naturally occurring nucleotides find application in cancer chemotherapy as enzyme inhibitors and can replace the naturally occurring nucleotides in nucleic acids.

Therapeutic attempts to inhibit the growth of cancer cells or certain viruses have often employed administration of analogs of bases, nucleosides, or nucleotides that inhibit the synthesis of either *DNA* or *RNA*. Allopurinol, a purine analog, is widely used in the treatment of gout.

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2 Nucleotides and nucleosides

The nucleotides participate in a wide variety of biochemical processes. Perhaps the best known role of purine and pyrmidine nucleotides is to serve as the monomeric precursors of *RNA* and *DNA* [4],[5]. However, the purine ribonucleotides serve also as the ubiquitous high energy source, *ATP*, as regulatory signals (cycle *AMP* [*cAMP*] and *GMP* [*cGMP*]), and as components of the coenzymes and of the methyl group donor S adenosil methionine. The pyrimidine nucleotides in addition to providing monomeric precursors for nucleic acid synthesis, also serve as high energy intermediates, such as UDP - glucose and UDP-galactose in carbohydrate metabolism and CDP-acylglycerol in lipid synthesis.

The heterocyclic bases purine and pyrimidine are the parent molecules of nucleosides and nucleotides. Nucleotides are ubiquitous in living cells, where they perform numerous key functions. Examples include incorporation, as their ribose (*RNA*) or deoxyribose (*DNA*) monophosfates, into nucleic acids, energy transduction (*ATP*), parts of coenzymes (*AMP*) acceptors for oxidative phosphorylation (*ADP*) allosteric regulators of enzyme activity, and second messengers (*cAMP*), (*cGMP*).

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Biomedical important it neither nucleotides nor their parent purine and pyrimidine bases in the diet are incorporated into human tissue nucleic acids or into purine or pyrimidine coenzymes. Even when a diet rich in nucleoproteins is ingested, human subjects form the constituents of tissue nucleic acids from amphibolic intermediates. This de novo synthesis permits purine and pyrimidine analogs with potential as anticancer drugs to be incorporated into *DNA*. The rates of synthesis of purine and pyrimidine oxy- and deoxyribonucleotides are subject to precise regulation. Mechanisms have evolved to ensure production of these compounds in quantities and at times appropriate to meet varying physiologic demand.

In addition to de novo synthesis, these include "salvage" pathways for reutilization of purine or pyrimidine bases released by degradation of nucleic acids in vivo. Human diseases that involve abnormalities in purine or pyrimidine metabolism include gout, Lesch-Nyhan syndrome, Reye's syndrome, adenosine deaminase deficiency, and purine nucleoside phosphorylase deficiency.

3. De novo synthesis

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 (Jones,1980). For the thymidne nucleotides and for all purine nucleotides, tetrahydrofolate derivates are also necessary. There is one striking difference between the syntesis of pyrimidine nucleotides and that of purine nucleotides, namely, that the synthesis of the purine nucleotides commences with ribose phosphate as an integral part of the earliest precursor molecule whereas the pyrimidine base is formed and attachment of the ribose phosphate moiety delayed until the later steps of the pathway.

Synthesis of the pyrimidine ring commences with the formation of carbamoyl phosphate from glutamine, ATP, and CO_2, in a reaction catalyzed by the carbamoyl phosphate synthase in the cytosol. The carbamoyl phosphate synthase enzyme responsible for the early steps in urea synthesis resides in the mitochondria.

The first step uniquely committed to the biosynthesis of pyrimidines is the formation of carbamoyl aspartate by the condensation of carbamoyl phosphate and aspartate, a reaction catalyzed by the enzyme aspartate transcarbamoylase.

A ring structure can then be formed from carbamoyl aspartate by loss of H_2O catalyzed by the enzyme dihydroorotase.

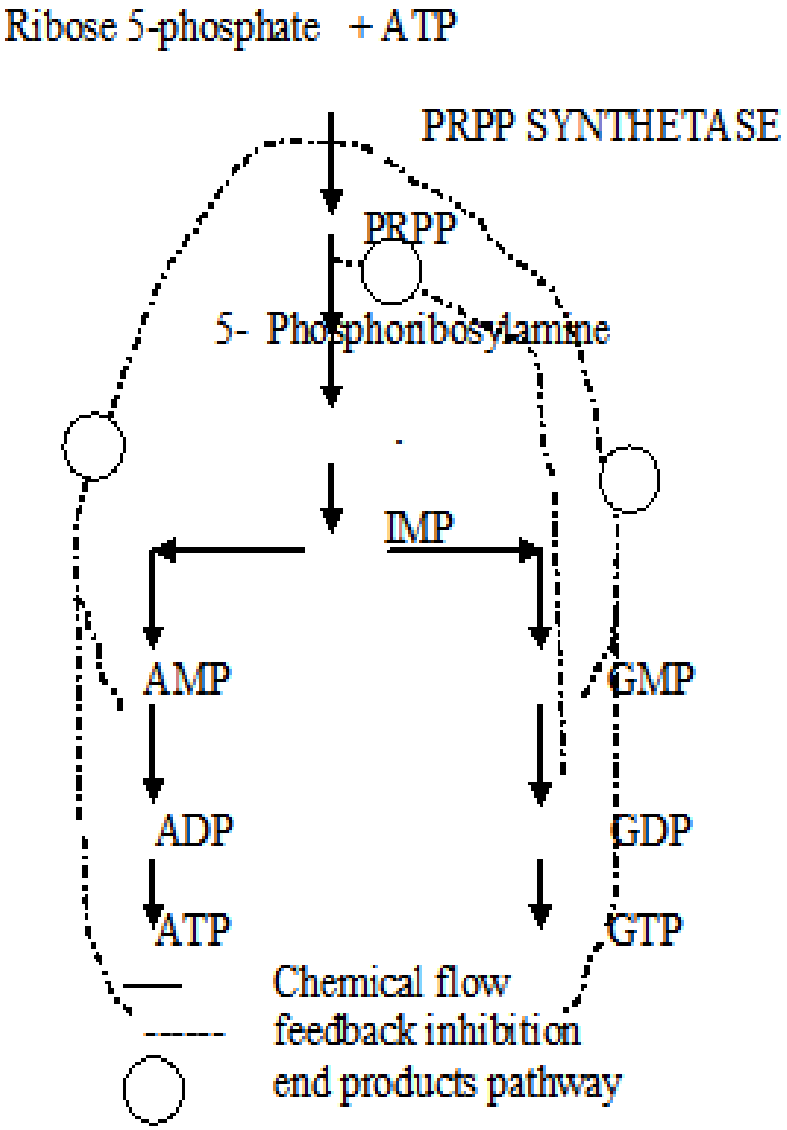

Fig. 1. De novo synthesis purine control

5. Metabolism

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.

The biosynthetic pathway for the synthesis of purine nucleotides can be summarized in the following steps. The first step in the synthesis of purine nucleotides is the formation of 5'-phosphoribosyl-1'-pyrophosphate *(PRPP*). The conversion of ribose 5-posphate and *ATP* to *AMP* +*PRPP* is not however unique to the synthesis of purine nucleotides. *PRPP* also serves as a precursors of the pyrimidine nucleotides and required for the synthesis of *NAD* and *NADP*, 2-coenzymes derived from niacin.

PRPP then react with glutamine in a reaction catalyzed by phosphor ribosylpyrophosphate amidotransferase to form 5'-phosphoribosyl amine. The reaction is accompanied by the displacement of pyrophosphate and the formation of glutamate. Although other mechanism have been proposed for the synthesis of 5'-phosphoribosylamine, the physiological important reaction in mammalian tissues is that catalyzed by the amidotransferase. 5'- phosphoribosylamine, then reacts with glycine to produce glycinamide ribosylphosphate. Synthesis of purine and

pyramidine deoxyribonucleotides occurs by direct reduction at the 2'-carbon in the ribose moiety of the corresponding nucleotide, not by synthesis of the entire nucleotide utilizing 2'-deoxy analog of *PRPP*.

Several antimetabolites that are glutamine analogs are effective inhibitors of purine biosynthesis.

Conversion of *AMP* and *GMP* to their respective nucleoside diphosphates and nucleoside triphosphates occurs in 2 successive steps. The successive transfers of phosphate groups from *ATP* are catalysed by nucleoside monophosphate kinase and nucleoside diphosphate kinase, respectively. The enzyme that phosphorylates adenalyte is also called myokinase.

The pharmacologic approach has been to use an analog in which either the heterocyclic ring structure of the sugar moiety has been altered in such a way as to induce toxic effects when the analog becomes incorporated into various cellular constituents. Many of these effects results from inhibition by the drug of specific enzyme activities necessary for nucleic acids synthesis or from the incorporation of metabolites of the drug into the nucleic acids where they alter the base pairing essential to accurate transfer of information.

6. DNA and RNA

The metabolism of the purines and pyrimidines and their nucleosides and nucleotides have examined. The regulatory mechanisms of purine and pyrimidine biosynthesis and the oligonucleotides hybridization and stacking interactions were examined [6]-[10].

Purine and pyrimidine bases that occur in the nucleotides are derived by substitution on the ring structures of the parent substances, purine and pyrimidine (Fig.2 –Fig.4).

The three major pyrimidine bases present in the nucleotides of both procaryotes and eukaryotes are cytosine, thymine, and uracil (Fig.4). The purine bases adenine and guanine are the two major purines found in living organisms. Two other purine bases, hypoxanthine and xanthine, occur as intermediates in the metabolism of adenine and guanine (Fig.2). In humans, a completely oxidizes purine base, uric acid, is formed as the end product catabolism.

In natural materials, unusual bases occur in the addition to the 5 major described bases. Some of these unusual substituted bases are present only in the nucleic acids of bacteria and viruses, but many are also found in the *DNA* and transfer *RNA*s of both prokaryotes and eukaryotes. For example, both bacterial and human DNA contain significant quantities of 5-methylcytosine, bacteriophages contain 5- hydroxyl-methyl-cytosine. Unusual bases presenting the messenger *RNA* molecules of mammalian cells include N^6, N^6-dimethyladenine, and N^7-methylguanine. An uracil modified at the N_3 position by the attachment of an α-amino, α-carboxyl-propyl group has also been detected in bacteria.

In plants, a series of purine bases containing methyl substituents occurs. Many have pharmacologic properties. Examples are coffee, which contains caffeine (1,3,7 –tri-methyl-xanthine), tea, which contains theophylline (1,3-di-methyl-xanthine).

Because of keto-enol tautomerism, theses aromatic molecules can exist in a lactim or lactam form, the latter is by far the predominant tautomer of guanine or thymine under physiologic conditions.

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.

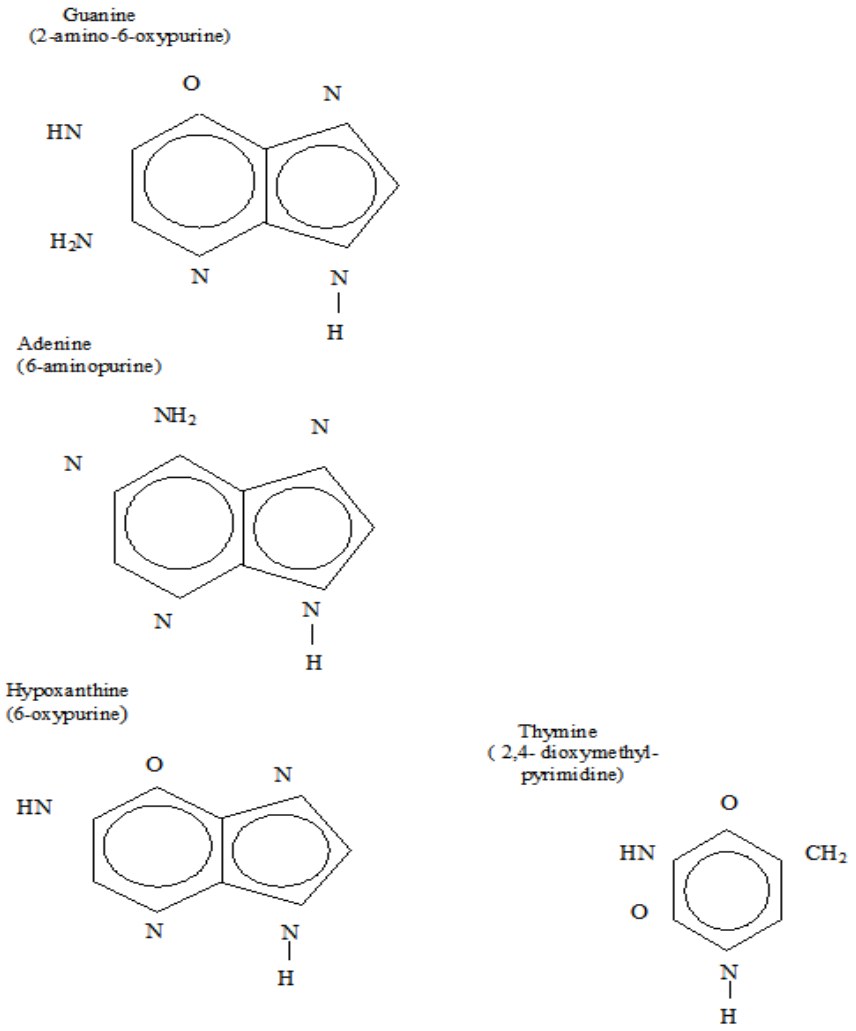

Fig. 2 The major purine bases adenine, guanine, and hypoxanthine present in nucleotides

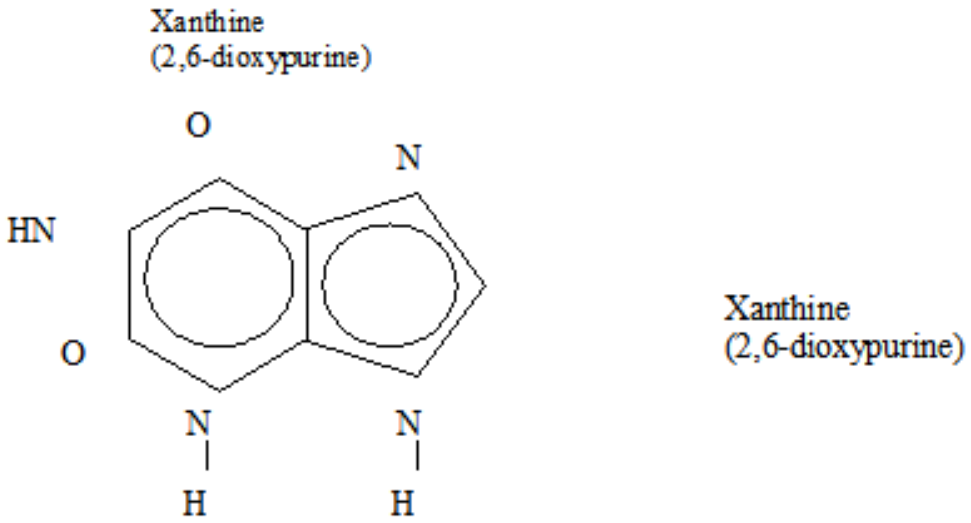

Fig. 3 The major purine base present in nucleotides xanthine (2,6-dioxypurine)

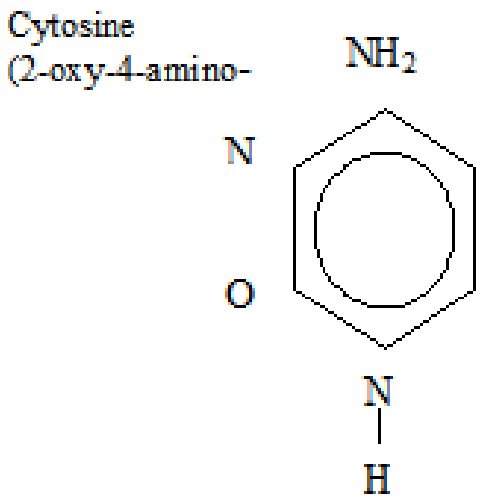

Fig. 4 The major pyrimidine bases cytosine thymine present in nucleotides

These latter 2 purines frequently occur as constituents of urinary tract stones.

The free bases are much less abundant in nature than are their nucleosides and nucleotides. The nucleoside is composed of a purine or a pyramidine base to which a sugar (usually either D-ribose or 2-deoxyribose) is attached in β – linkage at N_9 or N_1, respectively. Thus, the adenine ribonucleside adenosine consists of adenine with D-ribose attached at N_9. Guanosine consists of guanine with D-ribose attached at N_9. Utidine is cytosine with ribose attached at its N_1 position. Uridine consists of ribose attached at the position of uracil.

The 2'-deoxyribonucleosides consist of 2-deoxyribose attached to purine or pyrimidine bases. Attachment of the ribose or 2-deoxyribose to the ring structures is through an glycosidic bond, which is relatively acid labile. Although, theoretically, free rotation of the sugar moiety and the purine or pyrimidine.

Ring structure occurs about this N-glycosidic bond, steric hindrance in fact hinders free rotation. The anti form is necessary for the proper positioning of the complementary purine and pyrimidine bases in the double stranded β-form of deoxyribonucleic acid.

Nucleotides are nucleosides phosphotylated on one or more of the hydroxyl groups of the sugar (ribose or deoxyribose). Thus, adenosine monophosphate (*AMP* or adenylate) is adenine + ribose + phosphate. 2'-deoxyadenosine mono-phosphate (*dAMP* or deoxyadenylate) consists of 2-deoxyribose + phosphate. The only sugar commonly found attached to uracil is ribose, and that commonly found attached to thymine is 2-deoxyribose. Therefore, thymidic acid (*TMP*) is thymine +2-deoxyribose + phosphate, and uridylic acid *(UMP*) is uracil +phosphate. *DNA* is a polymer of thymidilic acid, 2'-deoxycytidilic acid, 2'-deoxyadenylic acid, and 2'-deoxyguanylic acid. *RNA* is a polymer containing uridylate, citydilate, adenylate, and guanylate.

There are expectations to the above structures of nucleotides. For example, in *tRNA* ribose occasionally attached to uracil at the 5' position, establishing a carbon-to-carbon linkage instead of the usual nitrogen - to - carbon linkage. This unusually compound is called pseudo uridine (ψ). *tRNA* molecules contain another unusual nucleotide structure, i.e. thymine attached to ribose monophosphate. Pseudourydilic acid (ψMP) is similarly rearranged from urydilic acid after the tRNA molecule has been synthesized.

The abbreviations *A*, *G*, *C*, *T*, and *U* may be used to designate the nucleosides that contain adenine, guanine, cytosine thymine, or uracil, respectively (Fig.2 - Fig. 4).

Because the phosphate are in the acid anhydride form a low entropy situation-the phosphates are

said to be high energy ones, i.e., high potential energy. The hydrolysis of

1 mol *ATP* to *ADP* releases about 7 x 4,16 KJ of potential energy.

Free nucleotides also perform important functions in tissues.

The functional moieties of many vitamins are coenzyme nucleotides with structures analogous to purine and pyramidine nucleotides.

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

Hypoxanthine ribonucleotide, usually called inosinic acid *IMP* or inosinate in the salt form, is a precursor of all purine ribonucleotides synthesized de novo.

Inosinate can also be formed by the deamination of *AMP*, a reaction which occurs particularly in muscle as part of the purine nucleotide cycle. Inosinate, derived from *AM*, when reconverted to *AMP* results in the net production of ammonia from aspartate. Removal of the phosphate group from IMP forms the nucleoside inosine (hypoxanthine riboside), an intermediate in another cycle referred to as the purine salvage cycle.

Inosine diphosphate *IDP* and inosine triphosphate *ITP*, analogs of *ADP* and *ATP* in which the purine nucleoside derivative is inosine rather than adenosine, occasionally participate in phosphorylation reactions.

Uridine nucleotide derivatives are important coenzymes in reactions involving the metabolism of hexoses and the polymerization of sugars to form starch and the oligosaccharide moieties of glycoproteins and proteoglycans. In these reactions, the substrates are uridine diphospho-sugars. For example uridine diphosphate glucose is the precursor of glycogen. Another uridine nucleotide coenzyme, uridine diphosphoglucuronic acid serves as the active glucuronide for conjugation reactions such as the formation of bilirubin glucuronide.

Uracil also participates in the formation of high energy phosphate compounds analogous to *ATP*, *GTP*, or *ITP*. Uridine triphosphate, *UTP* is utilized for example, in the reactions involving conversion of galactose to glucose in which uridine diphosphate glucose and uridine diphosphate galactose also are formed. *UTP* is a precursor for the polymerization of uridine nucleotides into *RNA*.

7. 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 dymethyl nitrosamine, pairs with tymine, resulting in a hereditary change of the genetic information.

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 results 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 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 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.

Some forms of unrepaired alkylated bases are lethal, due interference with DNA replication. Others, such as O^6-methylguanine leads to mutations if unrepared. 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 (N-7, C-8, O-6, and ecocyclic N-2).

8. Conclusion

In this paper toxic effect to the regulatory mechanism of the oligonucleotides synthesis were studied. Errors in substitution, deletion/insertion, transition, and transfersion in mutations were examined. DNA modification may cause insertion of the wrong amino acid into a relevant polypeptide and these changes are called missense mutation.

Mutation and malignant transformation were investigated. The major purine and pyrimidine bases present in nucleotides have considered and the most vulnerable base is guanine, which can affected gene damage.

Abbreviation

AMP- adenine monophosphate

ADP- adenine diphosphate

ATP- adenine triphosphate

CTP- cytosine triphosphate

DP-diphosphate

GDP- guanine diphosphate

GMP-guanine monophosphate

GTP- guanine triphosphate

HGPRT-ase-hypoxanthine-guanine

phosphoribosyl- transferase

IMP- inosine monophosphate

MP-monnophosphate

NADPH-cofactor

OMP- orotidine monophosphate

PRPP- phosphoribosyl-pyrophosphate

TMP-thymidine monophosphate

TP- triphosphate

UMP- uridine monophosphate

UTP- uridine triphosphate

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